Plant-based Diet on Cardiovascular Disease

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A thesis submitted in fulfilment of the requirements for the degree of
Doctor of Philosophy in Medicine and Health

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Co-supervisors: Dr Cynthia M Kroeger, Dr Sophie Cassidy, Dr Rosilene V Ribeiro

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Statement of originality

I certify that all intellectual content of this thesis is the product of my own work. I have not accepted unauthorized aid on this work. The sources, collaboration and assistance received in preparing this thesis have been acknowledged.

Presented in Chapter 5 is the published work of which I am a co-author. This contains an endorsement statement signed by all other authors of this paper.

This thesis has not been submitted for any other degree or purpose.

Tian WANG

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RESEARCH OUTPUTS

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MANUSCRIPTS

4. **T. Wang,** A. Masedunkas, W.C. Willett, L. Fontana. Vegetarian and vegan diets: benefits and drawbacks, European Heart Journal, 2023; ehad436, https://doi.org/10.1093/eurheartj/ehad436 **IF 39.3**
3. **T. Wang,** C. M. Kroeger, S. Cassidy, S. Mitra, R. Ribeiro, S. Jose, A. Masedunskas, L. Fontana. Vegetarian Dietary Patterns and Cardiometabolic Risk in People With or at High Risk of Cardiovascular Disease: A Systematic Review and Meta-analysis. JAMA Netw Open. 2023;6(7):e2325658. doi:10.1001/jamanetworkopen.2023 **IF 13.8**
2. **T. Wang,** A. Nova, S. Cassidy, T. Fazia, S. Mitra, C. M. Kroeger, A. Masedunskas, L. Bernardinelli, W.C. Willett, L. Fontana. Association of a healthy plant-based heart-protective diet with reduced cardiovascular disease incidence and mortality: findings from the UK Biobank Study. [Manuscript under revision by European Heart Journal]
1. S. Cassidy, C.M. Kroeger, **T. Wang**, S. Mitra, C. Liu, R.V. Ribeiro, A. Dai, J. Lau, R. Huang, A. Masedunkas, S. Jose, N. Liu, L. Avery, J. Yang, M. McGrady, S.N. Lo, J. George, P.A. Cistulli, L. Khor, R. Kozor, M. Ugander, I. Wilcox, I. Hunyor, L. Fontana. Impact of an Intensive Lifestyle Program on Low Attenuation Plaque and Myocardial Perfusion in Coronary Heart Disease: A Randomised Clinical Trial Protocol. Nutrition and Healthy Aging, 2022: 9-22, DOI: 10.3233/NHA-210146 **IF 1.3** Citations: 1

CONFERENCE PRESENTATIONS AND INVITED TALKS

6. **T. Wang**, A. Nova, S. Cassidy, C.M. Kroeger, S. Mitra, A. Masedunkas, T. Fazia, L. Bernardinelli, L. Fontana. Heart-protective Diet Scores, Cardiometabolic Risk and Cardiovascular Disease Incidence and Mortality: A Prospective Study from UK Biobank. [Conference abstract presented at American Society for Nutrition (ASN) conference 2023]
5. **T. Wang**, S. Cassidy, C.M. Kroeger, S. Mitra, R.V. Ribeiro, A. Masedunkas, R. Huang, L. Fontana. Impact of an Intensive Lifestyle Program on Low Attenuation Plaque and Myocardial Perfusion in Coronary Heart Disease: A Randomised Clinical Trial Protocol. [Conference abstract presented at ASN conference 2023]
4. **T. Wang**, A. Nova, S. Cassidy, C.M. Kroeger, S. Mitra, A. Masedunkas, T. Fazia, L. Bernardinelli, L. Fontana. Heart-protective Diet Scores, Cardiometabolic Risk and Cardiovascular Disease Incidence and Mortality: A Prospective Study from UK Biobank. [Oral presentation at Royal Prince Alfred Hospital Research Showcase 2023]
3. **T. Wang**, S. Cassidy, C.M. Kroeger, S. Mitra, R.V. Ribeiro, A. Masedunkas, R. Huang, L. Fontana. Vegetarian Dietary Patterns and Cardiometabolic Risk in People With or at High Risk of Cardiovascular Disease: A Systematic Review and Meta-analysis. [Oral presentation at Royal Prince Alfred Hospital Research Showcase 2023]
2. **T. Wang**, C. Kroeger, S. Cassidy, S. Mitra, R. Ribeiro, S. Jose, A. Masedunskas, L. Fontana. How vegetarian diets affect people with or at high risk of cardiovascular diseases: A meta-analysis [Conference abstract presented at Dietitians Australia (DA) conference 2022]
1. **T. Wang**, C. Kroeger, S. Cassidy, S. Mitra, R. Ribeiro, S. Jose, A. Masedunskas, L. Fontana. The Effect of Different Vegetarian Diets on Cardiometabolic Profile in People With or At High Risk of Cardiovascular Diseases: A Systematic Review and Meta-Analysis [Conference abstract presented at ASN conference 2022 and **awarded 'Emerging Leaders in Nutrition Science Abstract Recognition Award' and 'Winner of Student Interest Group Three-Minute Thesis Competition'**]

ABSTRACT PUBLICATIONS

3. **T. Wang**, A. Nova, S. Cassidy, C.M. Kroeger, S. Mitra, A. Masedunkas, T. Fazia, L. Bernardinelli, L. Fontana. P23-079-23 Heart-Protective Diet Scores, Cardiometabolic Risk and Cardiovascular Disease Incidence and Mortality: A Prospective Study From UK Biobank. Current Developments in Nutrition. Volume 7, Supplement 1, 2023, 100187, ISSN 2475-2991, https://doi.org/10.1016/j.cdnut.2023.100187
2. **T. Wang**, S. Cassidy, C.M. Kroeger, S. Mitra, R. Ribeiro, A. Masedunkas, R. Huang, L. Fontana. P23-080-23 Impact of an Intensive Lifestyle Program on Low Attenuation Plaque and Myocardial Perfusion in Coronary Heart Disease: A Randomised Clinical Trial Protocol. Current Developments in Nutrition. Volume 7, Supplement 1, 2023, 100188, ISSN 2475-2991, https://doi.org/10.1016/j.cdnut.2023.100188
1. **Wang T**, Kroeger C, Cassidy S, Mitra S, Ribeiro R, Jose S, Masedunskas A, Fontana L. The Effect of Different Vegetarian Diets on Cardiometabolic Profile in People With or At High Risk of Cardiovascular Diseases: A Systematic Review and Meta-Analysis. Curr Dev Nutr. 2022 Jun 14;6(Suppl 1):53. doi:10.1093/cdn/nzac047.053

OPEN DATA AND ANALYSIS CODE REPOSITORIES

3. **T. Wang**. R scripts and datasets for the LIVEPLUS chapters (Chapter 6 and Chapter 7) of Tian WANG's PhD Thesis entitled "Plant-based Diet on Cardiovascular Disease". Zenodo. 2023. DOI: 10.5281/zenodo.83717492.
2. **T. Wang**, A. M. Senior, S. Jose, A. Masedunskas, C.M. Kroeger. Data and R scripts analysis code for manuscript entitled "Vegetarian Dietary Patterns and Cardiometabolic Risk in People With or At High Risk of Cardiovascular Disease: A Systematic Review and Meta-analysis". Zenodo. 2023. DOI: 10.5281/zenodo.8017027
1. **T. Wang**, A. Nova. R scripts analysis code for manuscript entitled "Adherence to a plant-based heart-protective diet reduces cardiovascular disease incidence and mortality in the UK Biobank study". Zenodo. 2023. DOI: 10.5281/zenodo.8115595

PREREGISTERED PROTOCOLS AND STATISTICAL ANALYSIS PLANS

1. **Wang T**, Cassidy S, Kroeger CM, Ribeiro R, Mitra S, Fontana L. The effect of plant-based diets on cardiometabolic profile in people with cardiovascular disease or individuals at risk of cardiovascular disease: A systematic review and meta-analysis. PROSPERO 2021 CRD42021218348

COMMUNITY ENGAGEMENT AND SELECTED MEDIA

20.	**News Medical Life Sciences:** S. Cheriyedath. Do vegetarian diets improve the cardiometabolic profile of people with or at high risk of cardiovascular diseases?	Aug 2023
19.	**VegNews:** A. Starostinetskaya. 20 Cardiovascular Disease Studies Link Plant-Based Diet to Reducing Your Risk	Aug 2023
18.	**tctMD:** C. E. Cox. Vegetarian Diets May Curb Cardiometabolic Risk: Meta-analysis	Aug 2023
17.	**Endocrinology Advisor:** Vegetarian Diet Aids Outcomes in Patients With or at High Risk for CVD	Aug 2023
16.	**aponet.de:** Gesünder und leichter bei vegetarischer Ernährung	Aug 2023
15.	**Brisbane Times:** S. Berry. Giving up meat can lower your risk of cardiovascular disease	Aug 2023
14.	**Medisite:** L. Geffray. Régime végétarien : il réduit le risque cardiovasculaire	Aug 2023
13.	**Renal & Urology News:** Vegetarian Diet Aids Outcomes in Patients With or at High Risk for CVD	Aug 2023
12.	**Nieuws voor diëtisten:** S. Luderer. Vegetarisch eten en het risico op harten vaatziekten	Aug 2023

11.	**Deutsches Ärzteblatt**: Ernährung: Vegetarische Kost senkt Cholesterin, HbA1c und Körpergewicht nur leicht	Aug 2023
10.	**WedMD:** N.A. Melville. Going Vegetarian May Help Your Heart and Lower Diabetes Risk	July 2023
9.	**U.S. News & World Report:** A Mozes. Vegetarian Diet May Be the Best Bet for Those at High Risk for Heart Disease.	July 2023
8.	**Medscape:** N.A. Melville. Vegetarian Diets Can Improve High-Risk Cardiovascular Disease	July 2023
7.	**Daily Journal:** L. Solomon. Vegetarian Diet Aids Outcomes in Patients With or at High Risk for CVD	July 2023
6.	**Medical Xpress:** J. Jackson. Meta-analysis finds vegetarian diets effective in lowering cholesterol, glucose and weight	July 2023
5.	**Medical Professionals Reference:** Vegetarian Diet Aids Outcomes in Patients With or at High Risk for CVD	July 2023
4.	**Pourquoi Docteur:** D. Cacciarella. Cholestérol, poids, glucose : les bienfaits du régime végétarien confirmés	July 2023
3.	**Deutsche Apotheker Zeitung:** J. Russ. Hohes kardiovaskuläres Risiko – vegetarische Ernährung könnte helfen	July 2023
2.	**Auburn Citizen:** L. Solomon. Vegetarian Diet Aids Outcomes in Patients With or at High Risk for CVD.	July 2023
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MANUSCRIPTS

13. **T. Wang,** A. Ravier, C. Forsyth, S. Mitra, C. M. Kroeger, R. Ribeiro, A. Masedunskas, S. Cassidy, L. Fontana. Effect of Time Restricted Eating on the cardiometabolic health of patients at heightened risk of cardiovascular disease: a systematic review of randomised controlled trials. [Manuscript under revision by American Journal of Clinical Nutrition]
12. S. Mitra, C.M. Kroeger, J. Xu, L. Avery, A. Masedunkas, S. Cassidy, **T. Wang**, R. Huang, B. Chakraborty, L. Fontana. Testing the effects of app-based motivational messages on physical activity and resting heart rate via smartphone app compliance in patients with vulnerable coronary artery plaques: Protocol for a micro-randomized trial. JMIR Preprints. 13/03/2023:46082 **IF 7.4**
11. **T. Wang,** G. Siopis, H. Y. Wong, M. Allman-Farinelli. Poor quality of dietary assessment methods and reporting in randomised controlled trials of nutritional interventions for type 2 diabetes may impact outcome conclusions: a systematic review and meta-analysis. *Nutrition*, 2021, vol. 94, 111498, ISSN 0899-9007, https://doi.org/10.1016/j.nut.2021.111498 **IF 4.9** Citations: 3
10. **T. Wang,** A. Grech, H. U. Dissanayake, S. Boylan, M. Skilton. Modeling the Effect of Environmentally Sustainable Food Swaps on Nutrient Intake in Pregnant Women. *Nutrients*. 2021; 13(10):3355. https://doi.org/10.3390/nu13103355 **IF 5.7**
9. S. R. Partridge, A. A. Gibson, R. Roy, J. A. Malloy, R. Raeside, S. S. Jia, A. C. Singleton, M. Mandoh, A. R. Todd, **T. Wang**, N. K. Halim, K. Hyun, J. Redfern. Junk Food on Demand: A Cross-Sectional Analysis of the Nutritional Quality of Popular Online Food Delivery Outlets in Australia and New Zealand. *Nutrients*. 2020; 12: 10. **IF 5.7** Citations: 67
8. C. M. Kroeger, **T. Wang**, J. F. Trepanowski, A. Barnosky, K.K. Hoddy, K. Gabel, C. Lyu, S. Dickinson, K. A. Varady. Alternate Day Fasting versus Calorie Restriction for Health Behavior: Randomized Clinical Trial. [Manuscript under revision by American Journal of Clinical Nutrition]
7. S. Mitra, C. M. Kroeger, **T. Wang**, A. Masedunkas, S. Cassidy, R. Huang, L. Fontana, N. Liu. Gamified Smartphone-App Interventions on Behaviour and Metabolic Profile in Patients at Risk of Cardiovascular Disease: A Systematic Review and Meta-analysis [Manuscript under revision by The Lancet Digital Health]
6. G. Rajakumar, M.L. Cagigas, **T. Wang**, A.Y. Pan, T. Pelaia, S. Fuller*, L. Fontana*. Effect of the ketogenic diet on IGF-1 levels and other metabolic parameters in healthy adults and various disease subsets: A systematic review and meta-analysis. *Equal contribution. [Manuscript under revision by Annual Review of Nutrition]
5. C. M. Kroeger, S. Cassidy, **T. Wang,** R. Ribeiro, S. Jose, A. Y. X. Dai, L. Fontana. Clinically testing nutrition, physical activity, and stress reduction interventions for healthy longevity: Key metabolic and molecular pathways to target and biomarkers to measure. [Manuscript in preparation to be submitted to Lancet Healthy Longevity]
4. R. Ribeiro, A Kanjrawia, Alistair M Senior, **T. Wang**, David Le Couteur, Stephen J. Simpson. The effect of high protein intake on parameter of cardiometabolic health in older individuals: a systematic review and meta-analysis. [Manuscript under revision by Nature Aging]
3. A. Masedunkas, **T. Wang**, R.H. Henchman, Q. Liang, I. De Ciutiis, S. Mitra, L. Fontana. Prolonged Fasting Intervention for Diseases of Aging: Metabolic and Molecular Mechanisms. [Manuscript under preparation]
2. Q. Liang, A. Masedunkas, **T. Wang**, S. Mitra, I. De Ciutiis, C.M. Kroeger, L. Fontana. Impact of Exogenous Ketone Bodies on Cardiovascular Function in Healthy Adults and Patients with Heart Failure: A Systematic Review and Meta- analysis. [Manuscript under preparation]
1. C.M. Kroeger, J. Dymock, H. Chen, **T. Wang**, A. Nova, P. Hooijenga, R. Kishore, L. Fontana. Relationship between childhood maltreatment exposure and cardio-metabolic risk biomarkers in adulthood: A UK Biobank study. [Manuscript under preparation]

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6. **T. Wang**, G. Siopis, H. Y. Wong, M. Allman-Farinelli. The efficacy of nutritional interventions trials for type 2 diabetes: a systematic review and meta-analysis [Conference abstract presented at DA conference 2021]
5. **T. Wang**, A. Grech, H. U. Dissanayake, S. Boylan, M. Skilton. Modelling the effect of environmentally sustainable food substitutions on nutrient intake in pregnant women [Conference abstract presented at DA conference 2021 and **awarded 'The 2021 New Conference Presenter Award' and 'The 2021 New Researcher Award'**]
4. **T. Wang**, G. Siopis, H. Y. Wong, M. Allman-Farinelli. Poor quality of dietary assessment in randomised controlled trials of nutritional interventions for type 2 diabetes may impact outcome conclusions: a systematic review. [Conference abstract presented at ASN conference 2021]
3. **T. Wang**, A. Grech, H. U. Dissanayake, S. Boylan, M. Skilton. Modelling the effect of environmentally sustainable food substitutions on nutrient intake in pregnant women [Conference abstract presented at ASN conference 2021]
2. S. Mitra, C. M. Kroeger, **T. Wang**, A. Masedunkas, S. Cassidy, R. Huang, L. Fontana, N. Liu. Gamified Smartphone-App Interventions on Behaviour and Metabolic Profile in Patients at Risk of Cardiovascular Disease: A Systematic Review and Meta-analysis [Conference abstract presented in MedInfo23 Conference]
1. C.M. Kroeger, J. Dymock, H. Chen, **T. Wang**, A. Nova, P. Hooijenga, R. Kishore, L. Fontana. Relationship between childhood maltreatment exposure and cardio-metabolic risk biomarkers in adulthood: A UK Biobank study. [Abstract accepted by 9th Annual CPC EMCR Symposium 2023]

ABSTRACT PUBLICATIONS

2. **T. Wang**, A. Grech, H. Dissanayake, S. Boylan, M. Skilton. Modelling the Effect of Environmentally Sustainable Food Substitutions on Nutrient Intake in Pregnant Women. Current Developments in Nutrition, Volume 5, Supplement 2, 2021, Page 91, ISSN 2475-2991, https://doi.org/10.1093/cdn/nzab060_009
1. **T. Wang**, G. Siopis, H. Y. Wong, M. Allman-Farinelli. Poor Quality of Dietary Assessment in Randomised Controlled Trials of Nutritional Interventions for Type 2 Diabetes May Impact Outcome Conclusions: A Systematic Review. Current Developments in Nutrition, Volume 5, Supplement 2, 2021, Page 64, ISSN 2475-2991. https://doi.org/10.1093/cdn/nzab033_064

PREREGISTERED PROTOCOLS AND STATISTICAL ANALYSIS PLANS

5. **T. Wang,** A. Ravier, C. Forsyth, S. Mitra, S. Cassidy, C. M. Kroeger, R. Ribeiro, A. Masedunskas, L. Fontana. Effect of Time Restricted Eating on Cardiometabolic Health in individuals with or at high risk of cardiovascular disease: a systematic review and meta-analysis. PROSPERO 2023 CRD42023411472
4. G. Rajakumar, M. L. Cagigas, **T. Wang**, L. Fontana, S. Fuller. Effect of the ketogenic diet on IGF-1 levels in healthy adults and various disease subsets: A systematic review and meta-analysis. PROSPERO 2022 CRD42022334648
3. Q. Liang, A. Masedunkas, S. Mitra, **T. Wang**, C.M. Kroeger, L. Fontana. Impact of Exogenous Ketone Bodies on Cardiovascular Function in Adults: a systematic review and meta-analysis. PROSPERO 2023 CRD42023432574
2. Sayan M, Cassidy S, Kroeger CM, **Wang T**, Huang R, Fontana L, Liu N. A systematic review of gamification app-based content to modify behaviour change towards a healthier lifestyle and metabolic profile in cardiovascular patients. PROSPERO 2021 CRD42021239220
1. R. V. Ribeiro, A. Kanjrawi, S. J. Simpson, D. L. Couteur, A. M. Senior, **T. Wang**, M. Cooper. The effect of high protein intake on parameter of cardiometabolic health in older individuals: a systematic review and meta-analysis. PROSPERO 2022 CRD42022289317

List of Abbreviations

AHA	American Heart Association
BMI	Body mass index
CHD	Coronary heart disease
CVD	Cardiovascular disease
HbA1c	Hemoglobin A1c
LDL-c	Low-density lipoprotein cholesterol
SBP	Systolic blood pressure
T2DM	Type 2 Diabetes Mellitus

Authorship Attribution

CHAPTER 2 of this thesis is published as an original research article in the European Heart Journal. I was involved in the conceptualization, literature search, study screening, data extraction, creation of figures, and writing of the original draft.

> **T. Wang**, A. Masedunkas, W.C. Willett, L. Fontana. Vegetarian and vegan diets: benefits and drawbacks, European Heart Journal, 2023; ehad436, https://doi.org/10.1093/eurheartj/ehad436

CHAPTER 3 of this thesis is published as an original research article in the JAMA Network Open. I was involved in the conceptualization and design, literature search, study screening, acquisition, analysis and interpretation of data, creation of figures, and writing of the original draft.

> **T. Wang**, C. M. Kroeger, S. Cassidy, S. Mitra, R. Ribeiro, S. Jose, A. Masedunskas, L. Fontana. Vegetarian Dietary Patterns and Cardiometabolic Risk in People With or at High Risk of Cardiovascular Disease: A Systematic Review and Meta-analysis. JAMA Netwwork Open. 2023;6(7):e2325658. doi:10.1001/jamanetworkopen.2023

CHAPTER 5 of this thesis is published as a study protocol in the Journal of Nutrition and Health Aging. I was involved in the design and drafting of the manuscript.

> S. Cassidy, C.M. Kroeger, **T. Wang**, S. Mitra, C. Liu, R.V. Ribeiro, A. Dai, J. Lau, R. Huang, A. Masedunkas, S. Jose, N. Liu, L. Avery, J. Yang, M. McGrady, S.N. Lo, J. George, P.A. Cistulli, L. Khor, R. Kozor, M. Ugander, I. Wilcox, I. Hunyor, L. Fontana. Impact of an Intensive Lifestyle Program on Low Attenuation Plaque and Myocardial Perfusion in Coronary Heart Disease: A Randomised Clinical Trial Protocol. Nutrition and Healthy Aging, 2022: 9-22, DOI: 10.3233/NHA-210146

CHAPTER 4 of this thesis is currently under review by the European Heart Journal for publication as an original research article. I was involved in the conceptualization and design, development of the heart-protective diet score, statistical analysis and interpretation of data, and writing of the original draft. I was responsible as corresponding author for submitting the manuscript.

> **T. Wang,** A. Nova, S. Cassidy, T. Fazia, S. Mitra, C. M. Kroeger, A. Masedunskas, L. Bernardinelli, W.C. Willett, L. Fontana. Association of a healthy plant-based heart-protective diet with reduced cardiovascular disease incidence and mortality: findings from the UK Biobank Study. [Manuscript under revision by European Heart Journal]

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Sydney, 26/9/2023

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Sydney, 26/9/2023



Overview Abstract

Cardiovascular diseases (CVDs) remain the leading cause of disease burden and premature death globally, despite major advancements in therapeutic interventions over the past decades. This enduring prevalence can be partially attributed to the insufficient attention given to modifiable lifestyle risk factors in individuals at high risk. Past research has demonstrated that poor diet is mechanistically linked to an elevated risk of CVD morbidity and mortality. In contrast, a high-quality plant-based diet, emphasizing nutrient-dense foods, including minimally processed plant-based foods, supplemented with fish and seafood, while minimizing the consumption of energy-dense nutrient-poor foods, has been demonstrated to exert a strong protective influence against cardiovascular risks. In particular, plant-based diets have gained extensive attention in recent years. However, most current evidence of plant-based diets on CVD health, especially vegetarian diets, is based on observational studies with mixed findings. Present data from clinical randomized trials and meta-analyses of randomized controlled trials (RCTs) of vegetarian diets primarily focus on general populations but not individuals with CVD. Moreover, the effects of different vegetarian diets on cardiometabolic outcomes have not been investigated thoroughly. Overall, there is a paucity of data of plant-based diets on the secondary prevention of CVD.

To explore these mixed findings and potentially identify novel dietary patterns for the primary and secondary prevention of CVD, the aim of this thesis is to employ a mixed approach to investigate the associations between plant-based diets and cardiovascular health, with a particular focus on individuals with or at high risk of CVD. A systematic review and meta-analysis (20 RCTs) of vegetarian diets in populations with or at high risk of CVDs (n=1878, mean age: 28-64 years) illustrates that consuming a vegetarian diet for at least six months modestly but significantly improves cardiometabolic outcomes (significant reductions in low-density lipoprotein cholesterol by 0.18mmol/L, hemoglobin A1c by 0.25%, and body weight by 3.4 kg) beyond standard pharmacological therapy, highlighting the potential protective and synergistic effects of vegetarian diets for the primary prevention of CVD. From the meta-analysis, these research gaps were identified: a) most clinical trials failed to document detailed dietary intake; b) the duration of most included studies was less than six months; c) there is a paucity of data of plant-based diets and lifestyle interventions in secondary prevention of CVD. To address this, we designed and developed a heart-protective diet score, taking into account the quality of diet and tested it in the UK Biobank cohort (n=192274, mean age: 56.3±7.9 years, 43.3% male). We demonstrated that individuals who consumed a high-quality plant-based diet, rich in whole grains, non-starchy vegetables, fruits, legumes and beans, with fish and seafood, experienced a significantly lower risk of CVD events (HR: 0.92, 95% CI: 0.88 to 0.95) and mortality (HR: 0.72, 95% CI: 0.61 to 0.86). Finally, we further addressed research gaps identified in the meta-analysis by designing and delivering the LIVEPLUS trial, aiming to evaluate the clinical effects of an intensive lifestyle program (ILP: combining a 5:2 pesco-vegetarian diet, individualized exercise sessions and stress reduction) in patients with stable coronary heart disease (CHD). The preliminary findings (n=9) show that all patients have suboptimal cardiometabolic profiles at baseline and their baseline diet is characterized by an excessive intake of saturated fats (12.7%E) and sodium (2227.4mg/d), with insufficient intake of vegetables (4.1 serves/d), fruits (1.2 serves/d) and dietary fibre (24.1g/d). After one-month of intervention, patients significantly reduced body weight and BMI. This intervention caused an improvement in blood pressure (systolic blood pressure: -12.1mmHg; diastolic blood pressure: -8.1mmHg) but the time effect is not significant yet. Our findings reinforce the clinical benefits of intensive lifestyle programs in the secondary prevention of cardiovascular disease.

Overall, we demonstrate the protective effects of a high-quality plant-based diet and regular fish consumption on cardiovascular health, both in primary and secondary prevention of cardiovascular disease. Our findings contribute significantly to the development of current guidelines in lifestyle prevention and management of cardiovascular diseases. We highlight a research gap concerning the role of diet in the secondary prevention of CVD, primarily due to an existing oversight in acknowledging the importance of diet quality. Looking ahead, high-quality nutrition clinical trials with comprehensive dietary data and long-term follow-up periods are warranted to confirm the effectiveness of such diets in individuals with CVDs.

CHAPTER 1: Introduction

1.1 Cardiovascular Disease and Modifiable Risk Factors

Cardiovascular diseases (CVDs) encompass a broad spectrum of conditions involving the heart and circulation, including coronary heart disease (CHD), atrial fibrillation (AF), myocardial infarction (MI), heart failure (HF), stroke and other conditions affecting the cardiovascular system [1]. CVDs remain the leading cause of disease burden and premature death globally, despite major advancements in CVDs therapies over the past decades [2]. According to the World Health Organization, approximately 18 million people died from CVDs in 2019, contributing to 32% of all global deaths [3]. Coronary heart disease (CHD), the most common type of heart disease, is caused by atherosclerosis——the accumulation of plaque on the walls of the arteries, resulting in a narrowing or blockage of the small blood vessels that deliver blood and oxygen to the heart muscle [4]. CHD is the leading single cause of death in Australia and the United States [4, 5]. The Australian Institute of Health and Welfare reported 17,300 deaths from CHD in 2021, representing 10% of all deaths and 41% of CVD deaths [6], despite it being largely preventable by addressing modifiable risk factors in individuals at high risk [7]. In fact, researchers reported that most US residents who experienced a myocardial infarction presented at least one suboptimal CVD risk factor before the CVD event [8].

Major modifiable CVD risk factors include overweight and obesity, elevated blood pressure, diabetes, suboptimal lipid profile, and smoking, which greatly elevate the risk of CVD events and mortality. Researchers found that individuals with type 2 diabetes (T2DM) experience greater than two times the risk of developing CVD and four times the risk of having MI and strokes than people with normal blood glucose level [9]. Elevated blood cholesterol is a primary cause of atherosclerosis and subsequent CVD events [10]. A recent study published in the Lancet found that for every 1.0mmol/L increase in LDL-cholesterol, the risk of MI and atherosclerotic CVD significantly increased by 34% (hazard ratio (HR): 1.34, 95%CI [1.27, 1.41]) and 16% (HR: 1.16, 95%CI [1.12, 1.21]), respectively [11]. Another meta-analysis [12] published in the Lancet combined data from 123 studies with more than 600,000 participants and found a significant protective effect of blood pressure lowering in the prevention of CVD events and deaths: for every 10mmHg reduction in systolic blood pressure (SBP), the risk of major CVD events, CHD, stroke and HF significantly decreased by 20% (relative risk (RR): 0.80, 95%CI [0.77, 0.83]), 17% (RR: 0.83, 95%CI [0.78, 0.88]), 27% (RR: 0.73, 95%CI [0.68, 0.77]) and 28% (RR: 0.72, 95%CI [0.67, 0.78]), respectively. Furthermore, being overweight or obese is closely linked to dyslipidemia, T2DM, hypertension and chronic inflammation [13].

Unhealthy lifestyle practices including excessive energy intake, poor quality diets, physical inactivity, excessive alcohol consumption, tobacco smoking and chronic stress are strongly associated with suboptimal cardiometabolic profiles and the risk of subsequent CVD events [2]. According to the Global Burden of Disease Study 2017 published in the Lancet [14], there were estimates of 11 million deaths and 255 million disability-adjusted life-years (DALYs) attributable to dietary risk factors, and CVD was the leading cause of diet-related deaths (10 million), followed by cancers (>0.9 million) and T2DM (>0.3 million). Poor nutrition is mechanistically linked to an increased risk of CVD morbidity and mortality [2]. A high-quality nutritious diet, however, has been demonstrated to provide beneficial effects on cardiometabolic health and lower the risk of CVD.

1.2 Plant-based Diet and Cardiovascular Health

In recent years, plant-based diets have gained extensive attention due to their purported health benefits and positive environmental impacts outlined by the EAT-Lancet Commission [15], aligning with the global sustainable development goals proposed by the United Nations [16]. The World Health Organization and the Food and Agriculture Organization of the United Nations promote a predominantly plant-based sustainable healthy diet, which emphasizes a variety of fruits and vegetables, wholegrains, legumes and nuts, with a moderate consumption of fish and seafood, poultry, eggs and dairy products, and a small amounts of red meats [17]. Hence, plant-based diets can be broadly defined as any dietary patterns that mostly composed of plant-based products, with a small amount of foods of animal origins [18].

Past research has demonstrated the protective effects of plant-based diets on cardiometabolic health and subsequent CVD events and deaths. In a large multicenter trial (the PREDIMED study) [19], 7447 individuals with high CVD risk at baseline were randomly assigned to a Mediterranean diet and a low-fat diet. The Mediterranean diet prioritized minimally processed plant-based foods, such as fresh fruits and vegetables, legumes, and placed emphasis on either olive oil or nut consumption, depending on the group allocation. It also encouraged replacing red meat with white meat, and promoted fish and seafood consumption. After a median follow-up of 4.8 years, a primary end-point event—comprising major CVD events, including MI, stroke and cardiovascular-related mortality—was observed in 288 participants. After adjusting for baseline demographics (e.g. age), clinical characteristics (e.g. diabetes or hypertension at baseline) and propensity scores, individuals assigned to a Mediterranean diet experienced a significant 30% lower risk (HR: 0.70, 95%CI [0.55, 0.89]) of CVD events and death compared to the control group.

Well-balanced vegetarian diets, are promoted by diabetes organizations, in line with the vast evidence supporting their protective effects in lowering blood glucose levels, and preventing T2DM and some of its clinical complications [20-22]. The beneficial effects of vegetarian diets on cardiometabolic outcomes (including body weight, blood pressure, blood lipids, and blood glucose) in the general population and individuals with diabetes are demonstrated by meta-analyses of randomized clinical trials (RCTs) [23-26]. The 2021 Dietary Guidance by the American Heart Association (AHA) [27], the Nutrition Position Statements by the Australian Heart Foundation (HF) [28], together with the 2019 European Society of Cardiology (ESC)/ European Atherosclerosis Society (EAS) guidelines for the management of dyslipidemias[29], underscore the importance of plant-based heart-protective dietary patterns, rich in diverse fruits and vegetables, wholegrain cereals, and predominantly plant-derived sources of protein from beans and legumes, nuts and seeds, with regular inclusion of fish and seafood, healthy fats (from nuts and seeds, avocados and olives), and low-fat dairy products, and a minimal intake of red meat. These guidelines also emphasized the consumption of minimally processed foods to promote optimal cardiometabolic health.

1.3 Research Gaps

Importance of a thorough evaluation of diet quality

Most current evidence of plant-based diets on CVD health, in particular vegetarian diets, is based on observational studies [30, 31] with mixed findings. For example, some studies observed a protective effect against CVD in individuals following the pesco-vegetarian diet [32, 33], while others reported no significant difference or even an increased risk of CVD events among lacto-ovo-vegetarians and pesco-vegetarians, respectively [34, 35]. These studies utilized food frequency questionnaires (FFQ) to categorize individuals into various diet groups (e.g. meat-eaters, vegetarians) and some of them relied on simplistic questionnaires with only four questions to determine individuals' vegetarian status. The quality of diet, which is a critical factor to influence cardiometabolic health, is overlooked by these studies. Observational studies provide critical descriptive data and play a crucial role in examining the effect of long-term exposure to plant-based diets on cardiovascular health in a large population. This is often not achievable in clinical trials. Thus, a high-quality observational study exploring the quality of plant-based diets in at-risk populations is warranted.

Diet quality indices are commonly used by researchers in observational studies to assess the quality of plant-based diets [36]. Marchese et al. [36] recently reviewed 35 plant-based diet quality indices, of which 19, 9 and 5 indices were developed based on FFQ, semi-FFQ and 24hr recall, respectively. Both FFQ and 24hr recall are commonly used dietary assessment approaches in observational studies to reflect participants' dietary patterns. However, as highlighted by Nutritools and Dietary Assessment Guidelines [37], short FFQs are not reliable for evaluating total diet and FFQ in general is prone to inaccurate or subjective reporting, which may explain the mixed findings by forementioned studies. Instead, 24hr recall generates detailed dietary data, and multiple 24hr recalls are suitable to assess the usual intakes of individuals, with the flexibility in evaluating dietary intake to answer a variety of research questions by numerous types of analysis [37].

Thus, to allow a thorough evaluation of diet quality and potentially resolve the mixed findings by previous literature, detailed dietary data generated by 24hr recall is needed to reflect individuals' adherence to a plant-based diet. **Table 1.1** summarizes the current main five plant-based diet quality indices utilizing data from 24hr recall. Among them, only three indices (Comprehensive Diet Quality Index (cDQI) [38], Diet Quality Index Associated to the Digital Food Guide (DQI-DFG) [39], and Global Diet Quality Score (GDQS) [40]) consider healthiness of both animal-based and plant-based foods. Discrepancies in categorization of food groups among these scores are identified in red meats, eggs, processed meats, full-fat dairy products, tubers and roots, refined carbohydrates and sugars and sweets. For example, red meats, refined grains and sweets are included as 'moderation components' groups by DQI-DFG, and all dairy products including full-fat dairy and cream are categorized as 'adequacy components'; cDQI considers 'eggs' as unhealthful animal groups while the other two scores put 'eggs' in healthy food groups. Yet, none of these scores fully reflect the diet recommended by AHA, HF and ESC/EAS guidelines [28, 29, 41] for the prevention and management of cardiovascular disease. To address the current research gaps in plant-based diets and cardiovascular events, a new score designed specifically for cardiovascular health incorporating current guidelines recommendations is warranted.

Generating strong evidence from RCT and meta-analysis of RCTs

In addition, researchers found the current evidence from epidemiological studies of plant-based diets is likely to be influenced by confounders. A large meta-analysis [30] combined evidence from seven cohort studies including 197,737 participants and found a protective effect of following vegetarian diets on CVD mortality, with the evidence graded as very low due to indirectness and imprecision in results. Several other observational studies [31, 42] have suggested that the observed benefits from vegetarian diets might be attributed to the health-conscious behaviours of included cohorts. These individuals may opt for a vegetarian diet based on perceived health benefits, leading them to adopt overall healthier lifestyles, including being more physically active, and greater likelihood of abstaining from smoking and excessive alcohol consumption.

Overall, findings from observational studies could be influenced by potential confounders and a causal relationship cannot be established [30, 31, 43, 44]. Moreover, present data from clinical randomized trials and meta-analyses of RCTs primarily focused on general populations [2]. The effects of different vegetarian diets (e.g. pesco-vegetarian, lacto-vegetarian) on cardiometabolic outcomes have not been investigated thoroughly [23, 24, 42, 45, 46], and the impact of key confounders such as energy restriction [24-26], physical activity [24, 25] and medication changes [23, 24] have not been addressed. Overall, there is a paucity of data of plant-based diets in individuals with or at elevated risk of CVD.

Table 1.1 A summary of the main five plant-based diet quality indices

Index name	Country	Food groups	Calculation
Animal-based diet quality index (aDQI) [38]	U.S.	6 food groups Healthy animal groups: fish/seafood, poultry and dairy products Unhealthful animal groups: red meats, eggs and processed meats	Dietary intake of each food component is adjusted for total energy intake (EI) using density method, divided into sex-specific quintile cut offs, and each quintile scored from 0 to 5. Intake of each food group adjusted for total EI using density method. EI adjusted in analysis models.
Comprehensive Diet Quality Index (cDQI) [38]	U.S.	17 food groups Healthy plant groups: wholegrains, vegetables (excluding white potatoes), whole fruits, nuts/seeds/legumes, vegetable oils, and coffee/tea. Unhealthful plant group: refined grains, fruit juices, white potatoes, sugar-sweetened beverages (SSBs), and sweets/desserts Healthy animal groups: fish/seafood, poultry and dairy products. Unhealthful animal groups: red meats, eggs and processed meats	Same as aDQI. Healthy animal and plant foods positively scored; unhealthy animal and plant foods reverse scored. EI adjusted in analysis models.
Diet Quality Index Associated to the Digital Food Guide (DQI-DFG) [39]	Brazil	11 food groups Moderation components: sugars and sweets; meats: beef, pork and processed meat; refined cereals, and processed fats Adequacy components: poultry, fish and eggs, whole cereals, tubers and roots, fruits, vegetables, legumes and oilseeds, milk and dairy products, and oils and fats	All food groups scored a maximum of 5 or 10, on the basis of portion per 1,000 kcal. Dichotomous scoring for moderation components, where the maximum score is awarded for being within the recommended intake range or scored 0 when this range exceeded. For adequacy components, increasing score for higher intake with the maximum score awarded for being within or above the recommended intake range. For whole cereals, tubers

			and roots, fruits, and milk and dairy products with intake above the recommendation, decreasing scores were given for intake that is twice the upper limit, and no points for intake above twice the upper limit
Global Diet Quality Score (GDQS) [40]	African countries, China, India, Mexico, US	25 food groups Healthy food groups: citrus fruits, deep orange fruits, other fruits, dark green leafy vegetables, cruciferous vegetables, deep orange vegetables, other vegetables, deep orange tubers, legumes, nuts and seeds, whole grains, liquid oils, fish and shellfish, poultry and game meat, low-fat dairy, and eggs. Unhealthy groups when consumed in excess: high-fat dairy and red meat. Unhealthy food groups: processed meat, refined grains and baked goods, sweets and ice cream, SSBs, juice, white roots and tubers, and purchased deep fried foods	All foods ranked into 3 categories of consumed amounts (g/d) (apart from high-fat dairy which has 4 categories). The categories of consumption are specific for each food group and points are assigned on the basis of these categories. Healthy foods have higher scores for higher consumption. Unhealthy when consumed in excess foods are scored in increasing points until specific amounts are consumed. Unhealthy foods are given more points for lower consumption. All groups scored from 0 to 2 points, apart from: cruciferous vegetables, deep orange vegetables, other vegetables, and deep orange tubers (0–0.5 points); red meat (0–1 point); dark green leafy vegetables, legumes, nuts and seeds (4 points). EI adjusted in some analysis models.
Plant-based Diet Quality Index (pDQI) [47]	U.S.	11 food groups Healthy plant group: whole grains, vegetables (excluding white potatoes), whole fruits, nuts/seeds/legumes, vegetable oils, and coffee/tea Unhealthful plant group: refined grains, fruit juices, white potatoes, SSBs, and sweets/desserts	Dietary intake of each food component was adjusted for total EI using density method, divided into sex-specific quintile cut offs, and each quintile scored from 0 to 5. Healthy plant foods positively scored, and unhealthy plant foods reverse scored. EI adjusted in analysis models.

1.4 Aims and Overview

To address the above research gaps, explore the reasons for the aforementioned mixed findings, and potentially identify a promising dietary pattern in primary and secondary prevention of CVD, the aim of this thesis is to employ a mixed approach to investigate the associations between plant-based diets and cardiovascular health, with a particular focus on individuals with or at high risk of CVD.

Figure 1.1 illustrates the overview of this thesis structure. To gain an understanding of current evidence and identify the research gaps, **CHAPTER 2** is a narrative literature review [48] that: a) discusses the current literature around vegetarian diets and cardiovascular health from clinical trials and large prospective studies; b) outlines the potential mechanisms of its proposed beneficial effects; 3) identifies research gaps from current evidence. Following the research gap identified in **CHAPTER 2, CHAPTER 3** is a systematic review and meta-analysis [2] of vegetarian diets on cardiometabolic profiles in populations with or at high risk of CVDs, combining the data from all RCTs published to date (by the last date of database searches for this systematic review). From **CHAPTER 3,** we found: **a)** most current clinical trials failed to document detailed dietary intake for us to thoroughly evaluate the diet quality of vegetarian diets; **b)** the duration of most included studies was less than six months; **c)** there is a paucity of data of plant-based diets and lifestyle interventions in secondary prevention of CVD. We therefore, in **CHAPTER 4,** designed and developed our own heart-protective diet score, taking into account the quality of diet and incorporating fish and seafood into our score, following the dietary guidelines by the AHA, Australian HF and ESC/EAS [28, 29, 41]. To evaluate the long-term exposure to a high-quality pesco-vegetarian diet on the risk of cardiovascular events in a large sample size, we tested our developed score in the UK Biobank cohort. We demonstrated that individuals who consumed a high-quality plant-based diet, rich in whole grains, non-starchy vegetables, fruits, legumes and beans, with fish and seafood, experienced a significantly lower risk of CVD events and mortality. We further addressed research gaps identified in **CHAPTER 2 and CHAPTER 3** by designing and delivering the LIVEPLUS trial (**CHAPTER 5-7**) in patients with stable CHD, aiming to compare an intensive lifestyle program (combining a 5:2 pesco-vegetarian diet, individualized exercise sessions and stress reduction) with lifestyle recommendations by the AHA. Finally, **CHAPTER 8** discusses the main findings from this thesis, highlights the contribution of this thesis to the current field and gives directions to future studies.

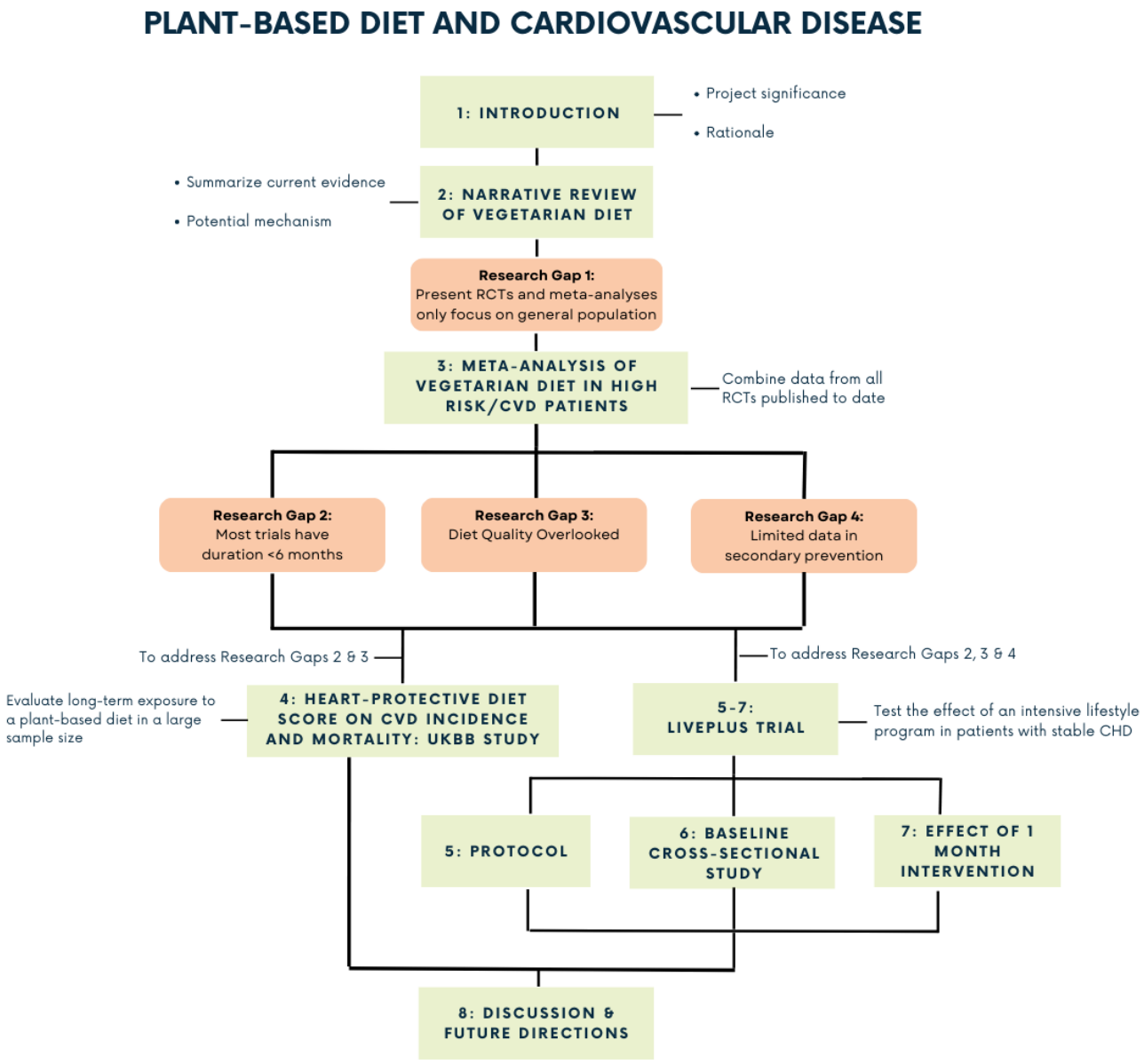


Figure 1.1. The overview of this thesis structure

CHAPTER 2: Vegetarian and Vegan Diets: Benefits and Drawbacks

Plant-based diets have gained extensive attention in recent years thanks to their purported health benefits and positive environmental impacts outlined by the EAT-Lancet Commission [15]. The aim of this chapter was to: a) discuss the current literature around vegetarian diets and cardiovascular health from clinical trials and large prospective studies; and b) outline the potential mechanisms of its proposed beneficial effects. Following this narrative review, these research gaps were identified: 1) most current evidence of plant-based diets on cardiovascular health, especially vegetarian diets, is based on observational studies with mixed findings. These findings could be influenced by potential confounders and a causal relationship cannot be established; 2) present data from clinical randomized trials and meta-analyses of randomized controlled trials primarily focus on general populations and primary prevention of cardiovascular disease; 3). The effects of different vegetarian diets (e.g. pesco-vegetarian, lacto-vegetarian) on cardiometabolic outcomes have not been investigated thoroughly, and the impact of key confounders such as energy restriction, physical activity and medication changes have not been addressed.

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I have won the **'Best Researcher Award in 2023'** with this publication at the International Research Awards on Cardiology and Cardiovascular Medicine.

ESC European Society of Cardiology

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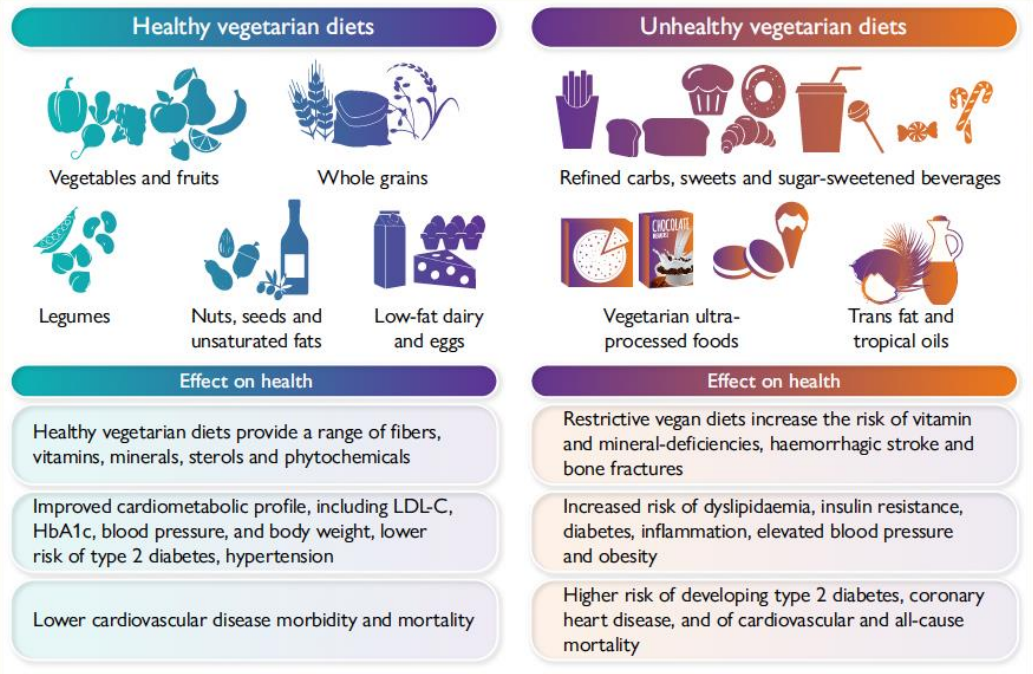
Vegetarian and vegan diets: benefits and drawbacks

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Graphical Abstract



A comparison of healthy vegetarian diets vs. unhealthy vegetarian diets. HbA1c, glycosylated haemoglobin; LDL-C, low-density lipoprotein cholesterol.

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Abstract

Plant-based diets have become increasingly popular thanks to their purported health benefits and more recently for their positive environmental impact. Prospective studies suggest that consuming vegetarian diets is associated with a reduced risk of developing cardiovascular disease (CVD), diabetes, hypertension, dementia, and cancer. Data from randomized clinical trials have confirmed a protective effect of vegetarian diets for the prevention of diabetes and reductions in weight, blood pressure, glycosylated haemoglobin and low-density lipoprotein cholesterol, but to date, no data are available for cardiovascular event rates and cognitive impairment, and there are very limited data for cancer. Moreover, not all plant-based foods are equally healthy. Unhealthy vegetarian diets poor in specific nutrients (vitamin B12, iron, zinc, and calcium) and/or rich in highly processed and refined foods increase morbidity and mortality. Further mechanistic studies are desirable to understand whether the advantages of healthy, minimally processed vegetarian diets represent an all-or-nothing phenomenon and whether consuming primarily plant-based diets containing small quantities of animal products (e.g. pesco-vegetarian or Mediterranean diets) has beneficial, detrimental, or neutral effects on cardiometabolic health outcomes. Further, mechanistic studies are warranted to enhance our understanding about healthy plant-based food patterns and the biological mechanisms linking dietary factors, CVD, and other metabolic diseases.

Keywords Nutrition • Plant-based diets • Vegetarian • Vegan • Cardiovascular disease • Diabetes • Hypertension • Obesity • Dementia • Cancer

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Introduction

Plant-based diets have become increasingly popular thanks to their purported health benefits and more recently for their positive environmental impact.[1] There are different types of plant-based diets, but in this review, we will focus our attention primarily on vegan (100% plant-based), lacto-ovo vegetarian (i.e. plant-based except for dairy products and/or eggs), and pesco-vegetarian or pescatarian (i.e. plant-based except for fish and seafood with or without eggs and dairy) diets. All vegetarian diets exclude meat (e.g. beef, pork, lamb, venison, chicken, and other fowl) and related meat products.

According to the American and Canadian Dietetic Associations, appropriately planned and supplemented vegan and lacto-ovo vegetarian diets are nutritionally adequate and suitable for individuals in all stages of the life cycle and may provide health benefits in disease prevention and treatment.[2,3] These statements are supported mainly by cross-sectional and prospective studies with accumulating data from a limited number of clinical randomized trials. Moreover, not all plant-based foods are equally healthy. Vegetarian diets rich in refined flours, hydrogenated oils, high-fructose corn syrup (HFCS), sucrose, artificial sweeteners, salt, and preservatives have been shown to increase morbidity and mortality (*Figure 1*).[4–6] The purpose of this article is to review succinctly the current knowledge on the effects of vegetarian diets on the risk of developing some of the most common and costly chronic diseases, including cardiovascular disease (CVD), obesity, type 2 diabetes mellitus (T2DM), hypertension, dementia, and cancer, and to discuss what is known about its metabolic and molecular adaptations and effects.

Evidence acquisition

We searched EMBASE, MEDLINE, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL), and PubMed, from inception until 20 September 2022. Hand searches of reference lists of reviews, protocols, and clinical trial registries (ClinicalTrials.gov) were performed to supplement searches. Search terms included *diet*, *plant-based*, *vegetarian*, *vegan*, *cardiovascular*, *cardiovascular diseases*, *diabetes*, *T2DM*, *hypertension*, *cancer*, *dementia*, and *cognitive function*. The authors of the ongoing trials were contacted to retrieve preliminary findings and full manuscripts. Both basic science and clinical research studies were reviewed. The published clinical reports that we reviewed included epidemiologic studies, case-control studies, and randomized controlled trials. Quality of data was assessed by taking into account publication in a peer-reviewed journal, number of individuals studied, objectivity of measurements, and techniques used to minimize bias.

Metabolic and molecular mechanisms associated with vegetarian diets

The precise mechanisms by which well-designed and balanced vegetarian or vegan diets may exert their beneficial effects in lowering the risk of coronary heart disease (CHD) and possibly cancer and dementia are under scrutiny. Many factors have been hypothesized to play a role, including (i) lipid-lowering effect; (ii) glucose-lowering, insulin sensitizing, and hormonal effects; (iii) protection against oxidative stress, inflammation, and hypertension, and (iv) production of intestinal microbial metabolites influencing metabolic and immune health (*Figure 2*).

Lipid-lowering effect

Several factors can explain why vegetarians have significantly lower levels of plasma cholesterol, especially when they consume minimally processed plant foods. Vegetarians do not consume meat, and vegans also avoid milk, butter, and dairy. Beef, lamb, and pork contain high levels of saturated fat and cholesterol and minimal amounts of polyunsaturated fats; even lean cuts of beef may contain up to 4.5 g of saturated fat per 100 g serving. One-cup serving of whole milk contains 4.5 g of saturated fat, and one tablespoon of butter contains 102 kcal and 7 g of saturated fat. In contrast, one tablespoon of olive oil contains 119 kcal and only 1.9 g of saturated fatty acids. Epidemiological studies have shown a strong linear relationship between saturated fat intake, plasma cholesterol levels, and CHD.[7,8] Substituting 5% of energy intake from saturated fatty acids with a similar quantity of energy from polyunsaturated fats, monounsaturated fats, or carbohydrates from whole grains is associated with a 25%, 15%, and 9% lower risk of CHD,

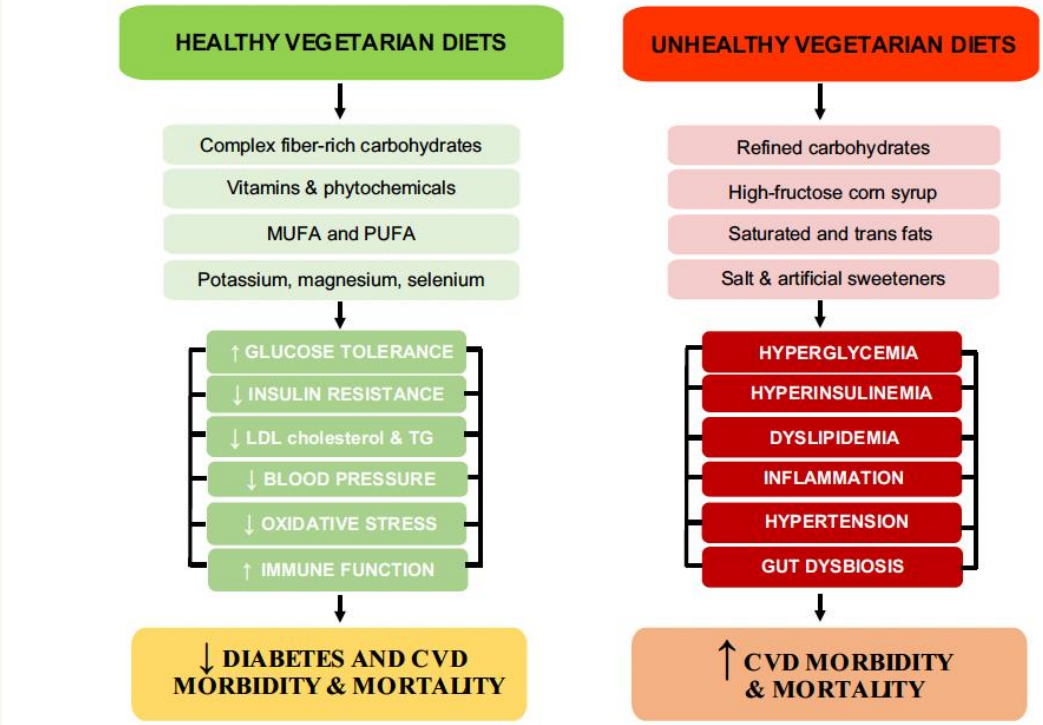


Figure 1 Metabolic effects of healthy and unhealthy vegetarian diets. MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

respectively. However, when saturated fats are replaced with carbohydrates from refined carbohydrates, the risk of developing CHD increases substantially.[9] Data from randomized clinical trials have demonstrated a cause–effect relationship;[10–12] replacing saturated fat with vegetable polyunsaturated fats decreases CHD by 30% that is similar to the reduction induced by statin therapy.[13] Seeds and nuts are excellent sources of polyunsaturated fatty acids and contain soluble and insoluble fibres and sterols that are known to lower cholesterol.[14] Epidemiological studies suggest that frequent nut consumption can reduce the risk of CHD by 40%–60%.[15] Data from randomized clinical trials confirm that consuming a diet rich in nuts, viscous fibres from oats, barley, psyllium, and plant sterol ester–enriched margarine can reduce plasma low-density lipoprotein (LDL) cholesterol by 13%.[16] Moreover, vegetarian diets rich in whole grains, legumes, nuts, and dried fruits can provide ~15 g of dietary fibre per 1000 kcal. In a 4 month weight loss double-blind, placebo-controlled clinical trial, overweight or obese men and women who received a daily supplement of soluble fibre (3 g *Plantago ovata* husk and 1 g glucomannan) experienced a significant greater drop in LDL cholesterol than those in the placebo group.[17] Dietary fibres and phytosterols reduce the (re)absorption of cholesterol and bile acids in the small intestine, thus resulting in an increased LDL uptake by the liver.[18,19] Moreover, foods rich in dietary fibre and with low glycaemic index can lower insulin production and increase the levels of short-chain fatty acids produced by fibre fermentation, which have both been shown to inhibit cholesterol synthesis.[19]

Glucose-lowering, insulin sensitizing, and hormonal effects

Vegetarians, and especially vegans, tend to have lower body weights than omnivores. In a survey of the American Adventists population, average body mass index (BMI) in omnivores, semi-vegetarians, lacto-ovo vegetarians, and vegans was 28.3, 27.3, 26.1, and 24.1 kg/m^2, respectively.[20] Although consuming a vegetarian diet does not require counting calories, results from clinical trials demonstrate that people randomized to a vegetarian diet tend to lose more weight than those consuming Western diets.[21,22] Preclinical, epidemiological, and clinical studies suggest that distinct dietary interventions may promote atherogenic and metabolic fat depot mobilization differently.[23] The high-fibre and water content and lower energy density of vegetables, legumes, and whole grains may in part explain this effect. Consumption of diets rich in dietary fibre induces gastric distention, delays gastric emptying, and prevents large fluctuations in postprandial blood glucose.[24] Short-chain fatty acids produced by the intestinal microbial metabolism of resistant starch and oligosaccharides of minimally refined plant foods induce satiety by inhibiting gastric emptying through incretins such as peptide-YY and glucagon like peptide-1 that markedly reduce blood glucose and body weight in randomized clinical trials.[25–27] Moreover, whole-food vegan and vegetarian diets may result in fewer bioavailable calories, and it is well known that calorie restriction with adequate nutrition in humans exert a powerful effect in improving glucose tolerance, insulin sensitivity, and many other cardiometabolic,

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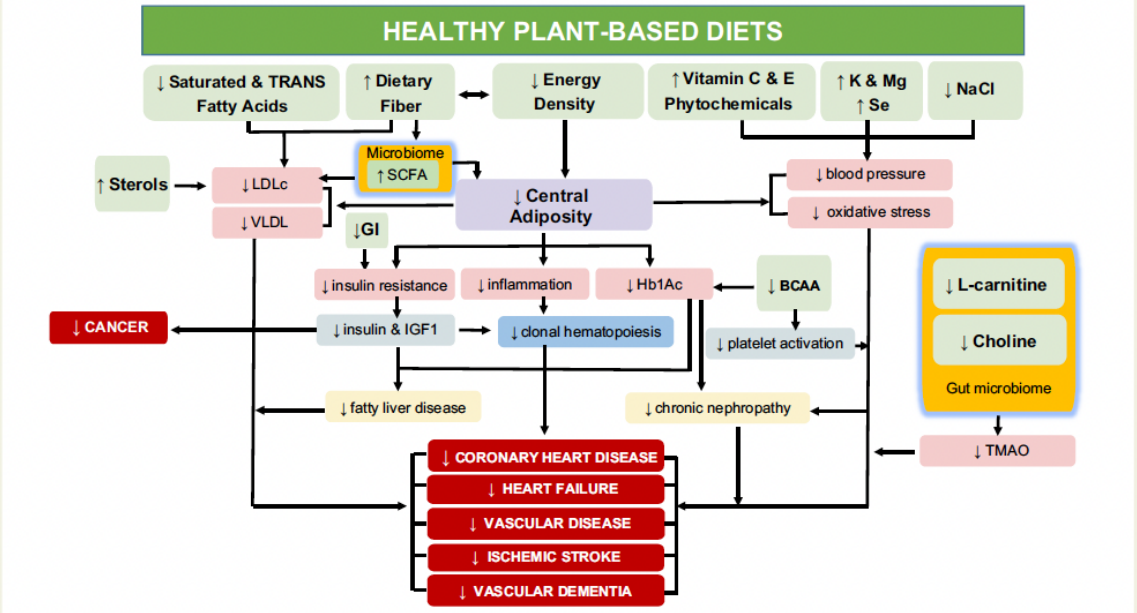


Figure 2 Cardioprotective mechanisms of healthy vegetarian diets. Multiple nutritional effectors of a healthy vegetarian diet modulate important metabolic, hormonal, and immune factors associated with the development of cardio- and cerebrovascular diseases. K, potassium; Mg, magnesium; Se, selenium; NaCl, sodium chloride; SCFA, short-chain fatty acids; LDL-C, low-density lipoprotein cholesterol; VLDL, very-low-density lipoprotein; GI, glycaemic index; BCAA, branched-chain amino acid; TMAO, trimethylamine *N*-oxide.

inflammatory, and hormonal factors implicated in the pathogenesis of CVD and cancer.[28–30] As reviewed elsewhere,[28,31] excessive (central) adiposity causes insulin resistance, dysregulation of sex hormones and insulin-like growth factor-1 (IGF-1) signalling, low-grade chronic inflammation, and immune dysregulation of natural killer cells and stromal tumour-infiltrating lymphocytes, limiting antitumour responses. Compensatory hyperinsulinaemia together with increased bioavailability of oestradiol, testosterone, and IGF-1 promotes cell proliferation and genomic instability through activation of the PI3K/AKT and $p66^{shc}$ pathways, which have been associated with increased risk of multiple cancers, including breast, endometrial, prostate, and colon cancer.[28,31]

Additional mechanisms mediating the insulin sensitizing and glucose-lowering effects of healthful minimally processed vegetarian diets are the low glycaemic index/load and the lower intake of protein, especially of sulphur and branched-chain amino acids. Estimated daily protein intake for omnivores in Western societies is ~90–100 g of which ~70%–85% is animal proteins rich in methionine, valine, leucine, and isoleucine. Results from both population and randomized experimental diet interventions show that high protein intake, especially of branched-chain amino acids, is associated with an increased prevalence and risk of developing pre-diabetes and T2DM.[32] Diabetes risk increases by 20%–40% for every 10 g of protein consumed in excess of 64 g per day.[33,34] Interestingly, in some studies, high intake of animal protein, but not of plant protein, was associated with the higher risk of developing T2DM.[32,34,35] In weight loss trials of obese women, high protein intake (1.3 g kg^{-1} per day including two servings of a whey protein isolate) completely prevented the markedly improved insulin sensitivity observed in women consuming a normal protein diet (0.8 g kg^{-1} per day) who lost the same amount of body weight and visceral and liver fat.[36] Furthermore, dietary branched-chain amino acid (BCAA) restriction in mice recapitulates many of the beneficial effects of protein restriction observed in rodents and humans, including reduced adiposity, increased glucose tolerance, and increased energy expenditure, but not increased FGF21 levels.[37] In contrast, high dietary intake of BCAA increases platelet activation and arterial thrombosis risk by enhancing tropomodulin-3 propionylation.[38] Consistently, data from two trials demonstrated that consuming high-protein diets (comprising dairy and meat products and whey protein supplements) cause a reduction in insulin sensitivity and an associated increase in blood insulin levels.[39,40] In an another trial of patients with T2DM, high consumption of chicken, fish, eggs, low-fat milk, and cheeses prevented the expected improvements in glucose metabolism and insulin sensitivity induced by a 2 month weight loss intervention.[41] High-protein diets, particularly those rich in leucine, can also play a role in promoting atherosclerosis and plaque instability in mice by exacerbating macrophage apoptosis induced by atherogenic lipids, via mTORC1-dependent inhibition of mitophagy and accumulation of dysfunctional mitochondria.[42]

Protection against oxidative stress, inflammation, and hypertension

Well-designed vegetarian diets rich in vegetables, whole grains, legumes, nuts, seeds, and fruits provide a wide range of vitamins (vitamin C, vitamin E, and beta-carotene), minerals (selenium), and phytochemicals (tannins, phenols, alkaloids, and flavonoids) with xenohormetic

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effects.[43] Numerous large observational studies suggest that an inverse relationship exists between antioxidant and polyphenol intake and the risk of developing diabetes, CVDs, cancer, and possibly dementia.[44] High intake of dietary antioxidants and phytochemicals may reduce the risk of developing atherosclerotic plaques because it triggers adaptive modulations of stress-response enzymes and receptors that prevent lipoprotein oxidation, endothelial dysfunction, and immune activation.[45,46] Findings from large prospective studies suggest that dietary patterns with higher inflammatory potential are significantly associated with higher level of systemic and vascular inflammation, an unfavourable lipid profile, and ultimately with a higher incidence of CHD and stroke.[47] Dietary patterns with lower inflammatory potential are those that favour foods rich in dietary antioxidants and vegetable fibre (e.g. green leafy and dark yellow vegetables, whole grains, fruit, tea, and coffee) and avoid red and processed meat and refined liquid and solid carbohydrates.[48–52]

Diets rich in vegetable fibre, potassium, and magnesium and low in sodium, especially when associated with a healthy body weight and regular endurance exercise training, markedly lower systolic and diastolic blood pressure,[53–56] which is a powerful risk factor for the development of CHD, heart failure, stroke (both ischaemic and haemorrhagic), and dementia. Indeed, data from epidemiological and genetic causal inference studies show that elevated systolic blood pressure, insulin resistance, and excess adiposity at midlife are important risk factors for developing cognitive impairment and Alzheimer's disease because they cause endothelial dysfunction and vascular damage to the brain, particularly at the level of perforating cerebral arteries and neurovascular units.[57,58] In contrast, reduction of systolic blood pressure prevents and/or slows progression of cognitive impairment to dementia.[59]

Modulation of gut microbiome function and effect on human metabolic state

Diet composition has a pervasive effect in modulating systemic microbiome biology. Metagenomic data show that specific nutrients, especially insoluble fibre, and protein intake deeply influence gut microbiota structure and function and the production of a growing list of metabolically active molecules.[60,61] For instance, unlike vegetarians diets, Western diets rich in red meat, eggs, and cheese contain higher concentrations of nutrients such as choline and L-carnitine that increase the microbial production of trimethylamine *N*-oxide (TMAO).[62,63] Animal and human studies have shown that higher levels of circulating TMAO increase the risk of developing CVD, independent of traditional cardiometabolic risk factors, by inducing vascular inflammation and platelet activation.[64,65] In contrast, healthful plant-based diets rich in whole grains, legumes, and nuts can markedly increase the intake of dietary fibres, key fermentable substrates for the proliferation of Bacteroidetes and the production of short-chain fatty acids such as acetate, propionate, and butyrate.[66,67] Experimental animal data indicate that these microbial metabolites exert powerful blood pressure–lowering and immune-modulating effects, via activation of specific G-protein–coupled receptors expressed on enteroendocrine and intestinal immune cells.[61,68] Long-term consumption of vegetarian diets has also been associated with more phylogenetic biodiversity of stool microbiota; in contrast, multigenerational exposure to Western diets poor in 'microbiota-accessible carbohydrates' causes an extinction of specific bacterial lineages, which impairs immune function and maturation, and increases the risk of developing a range of metabolic, inflammatory, allergic, and autoimmune diseases.[69,70] Interestingly, data from the DIRECT-PLUS trial show that a calorie-restricted and (almost) red-meat-free version of the Mediterranean diet enriched in plant-based proteins (Green-MED diet) is superior to the classical Mediterranean diet in improving the 10-year Framingham risk score and in lowering waist circumference, intrahepatic fat, LDL cholesterol, diastolic blood pressure, C-reactive protein, and HOMA insulin resistance.[71] These cardiometabolic beneficial effects were partially mediated by a major shift in the composition and function of the gut microbiome, including enrichments in the genus Prevotella and reductions in the genus Bifidobacterium with associated inhibition in BCAA biosynthesis and up-regulation of BCAA degradation enzymatic pathways.[72] This is crucial because a growing body of evidence show that reprogramming microbial functions through long-term adherence to healthier plant-rich diets has profound effects in shaping physiologic response to specific nutrients, to calorie restriction, and to other features of host biology that are instrumental in promoting health and longevity.[73,74]

Evidence from prospective studies

Prospective epidemiological studies have suggested that consuming vegetarian diets might have protective effects against the development of obesity, diabetes, hypertension, CHD, several type of cancers, and, most recently, cognitive decline. Whether these associations are causal deserves careful consideration of all available evidence, including data from other types of studies.

Hypertension

Findings from observational studies suggest that people consuming vegetarian and vegan diets have lower blood pressure than people eating Western diets, even after adjusting for age, sex, and BMI.[75] Compared with Seventh-day Adventist who are omnivores, those who follow a vegetarian diet have lower blood pressure and a reduced incidence of hypertension, independent of body weight and sodium intake.[76] Data from multiple observational studies including three large prospective American cohort studies suggest that consuming red meat and poultry is associated with an increased risk of hypertension, independent of vegetable, whole grain, and fruit intake.[77]

Type 2 diabetes mellitus

Several studies suggest protective effects of vegetarian diets in the prevention of T2DM. Findings from the Adventist Health Study-2 (41 387 participants free of diabetes followed for 2 years) found that, even after controlling for multiple confounding factors, vegetarians had a significantly lower risk of T2DM than omnivores.[78] The most apparent protective effect was for vegan diets with a 62% risk reduction, followed by semi-vegetarian (51% reduction) and lacto-ovo vegetarian (38% reduction) diets. The Adventist Mortality Study and Adventist Health Study followed a cohort of 8401 individuals for more than 17 years.[79] After controlling for weight and weight change, long-term adherence to a diet incorporating weekly meat intake was associated with a 38% higher risk of T2DM compared with a vegetarian diet with no meat intake. This finding are supported by data from a joint analysis of three large cohort studies (the Health Professionals Follow-up Study, $n = 26,357$; the Nurses' Health Study, $n = 48,709$; and the Nurses' Health Study II, $n = 74,077$) confirming a statistically significant association between red meat consumption and an increased risk of T2DM ($P < .001$ for all studies).[80] After adjusting for initial BMI and concurrent weight gain, a daily increase of > 0.5 servings of red meat was linked with a

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30% higher risk of T2DM. In contrast, reducing red meat intake by > 0.5 servings/day was associated with a 14% lower risk of T2DM.

Cardiovascular disease

A joint analysis of five prospective studies including 76 172 individuals has shown a lower CHD mortality in vegetarians than in omnivores: 34% less in lacto-ovo vegetarians and pesco-vegetarians and 26% lower in vegans.[81] Another meta-analysis of 7 studies (124 706 participants) report a 29% decreased mortality from CHD in vegetarians than omnivores.[82] The EPIC-Oxford cohort study (44 561 participants) showed a 32% risk reduction of CHD in vegetarians than non-vegetarians.[83] However, subsequent studies suggest that the protective effect against CHD of vegetarian diets seems to be almost exclusively limited to the Seventh-day Adventists, who don't smoke, don't drink alcohol, do regular physical activity, and are very religious and socially connected.[84] Indeed, data from epidemiological studies of English and German vegetarians show only a modest protective effect against cardiovascular and overall mortality.[85–87] A German prospective study of 1225 vegetarians and 679 health-conscious non-vegetarians has shown that there is no difference in mortality among vegetarians and this control group of health-conscious individuals consuming meat three to four times per month.[88] Cigarette smoking, obesity, alcohol intake, and exercise patterns seem to explain most of the differences in cardiovascular mortality among these different groups. Another potential problem is diet quality, which can vary greatly among both vegetarian and non-vegetarians.[4,5,89]

The effects of vegetarian diets on major cardiometabolic risk factors (i.e. hypercholesterolaemia, dyslipidaemia, hypertension, T2DM, and obesity) are more consistent. Well-educated vegetarians who consume balanced diets tend to have a lower body weight than non-vegetarians[21] together with lower levels of cholesterol, glucose, and blood pressure.[90] A recent umbrella review integrated evidence from 20 meta-analyses and found that people following vegetarian diets had significantly lower total cholesterol and LDL cholesterol than people consuming Western diets.[91] On average, total and HDL cholesterol are ~0.36 and 0.10 mmol/L, respectively, lower in vegetarians than in omnivores.[92]

Cancer

A meta-analysis of 7 epidemiological studies (124 706 participants) found an 18% lower cancer incidence in vegetarians than omnivores {relative risk [RR]: 0.82 [95% confidence interval (CI): 0.67, 0.97]}.[82] Results from the EPIC-Oxford study on a cohort of 65 000 men and women found that the overall cancer risk was 10% lower in vegetarians and 18% lower in vegans than in meat-eaters.[93] However, after correcting for multiple confounding factors, only stomach and haematological cancers were significantly lower, while cervical cancer was 90% higher in vegetarians. Recent data from the UK Biobank prospective study on 409 110 participants show that compared with omnivores, vegetarians had a 13% and pescatarians a 7% lower overall cancer risk, respectively. In this study, vegetarians had a lower risk of colorectal and prostate cancer, and pescatarians had a lower risk of melanoma. However, when these data were pooled with eight previously published studies in a meta-analysis, only the association with colorectal cancer persisted.[94] These findings suggest that other factors beyond vegetarian diets may explain these associations. The incidence of lung cancer, for example, is lower in vegetarians than in people consuming typical Western diets, but this seems due primarily to the reduced smoking habit of vegetarians. No difference has been reported for lung cancer risk for vegetarians in maximally adjusted models.[95–97] The incidence of colon cancer is reduced by 22% among Seventh-day Adventist vegetarians, but not in British vegetarians. In the latter group, for example, it seems that vegans have an even higher risk of colon cancer, while in pesco-vegetarians, there is a 33% reduction, even after correcting for body weight.[95] The quality of diet probably plays a major role. Indeed, unhealthy plant-based diets rich in refined and processed carbohydrates and unhealthy fats are associated with higher risk of colon cancer, but healthy plant-based diets enriched in whole grains, legumes, and vegetables are associated with lower incidence of colorectal cancer, especially KRAS-wildtype subtype.[6] The risk of developing breast cancer is no different between vegetarian and non-vegetarian women in most studies, and some epidemiological data in Adventist and British women suggest vegans, but not lacto-ovo vegetarians, may have an increased risk.[98] The same is true for prostate cancer, with the risk no different among lacto-ovo vegetarians and omnivores but 34% lower in the Adventists vegans.[99] A lower intake of dairy products may explain this association because milk consumption increases serum IGF-1 levels, a risk factor for prostate cancer, breast, and colon cancer.[100]

Dementia

Very little is known about the effects of vegetarian diets on cognitive function and dementia risk. A recent systematic review and meta-analysis suggests that vegetarian diets are not associated with any significant improvement in memory when compared with omnivorous diets, but heterogeneity among studies was very high.[101] Findings from a small prospective study (5710 participants with 121 incident cases) conducted in Taiwan suggest that vegetarians might have a lower risk of dementia than non-vegetarians.[102]

Evidence from randomized clinical trials

Hypertension

Data from a meta-analysis of 7 clinical trials including 311 participants show that consuming a vegetarian diet is associated with a reduction of mean systolic [−4.8 mmHg (−6.6 to −3.1)] and diastolic [−2.2 mmHg (−3.5 to −1.0)] blood pressure compared with non-vegetarian diets.[103] A meta-analysis of 11 trials and 983 participants showed that strict plant-based (vegan) diets seem less effective than less restrictive diets and reduced systolic [−4.10 mmHg (−8.14 to −0.06)] and diastolic [−4.01 mmHg (−5.97 to −2.05)] blood pressure only in patients with a baseline systolic blood pressure (SBP) ≥130 mmHg.[104] A recent meta-analysis of randomized trials show that the lacto-ovo vegetarian diet is as effective as other healthy diets containing some animal products [Dietary Approaches to Stop Hypertension (DASH) and healthy Nordic diet] at reducing blood pressure. In contrast, vegan diets did not significantly reduce blood pressure unless caloric restrictions was also prescribed,[105] suggesting that complete elimination of animal food is not required for lowering blood pressure and might even increase haemorrhagic stroke risk, possibly due to very low intake of saturated fat.[93] Other factors such as calorie restriction and weight loss,[30,54,106] lower dietary sodium and high potassium and magnesium intake,[53,55] and regular endurance exercise training[56] are important factors beyond fibre-rich plant food consumption. Moreover, findings from a meta-analysis of 15 randomized trials show that reduced alcohol consumption dose-dependently lowers systolic and blood pressure in both in non-hypertensive and hypertensive individuals.[107]

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Type 2 diabetes mellitus

The results of a recent meta-analysis of nine randomized clinical trials provide evidence that vegetarian diets can significantly reduce fasting glucose (range 0.1–1.0 mmol/L) and glycosylated haemoglobin (HbA1c) (range 0.12%–0.45%) together with LDL cholesterol (range 0.04–0.2 mmol/L) and body weight (range 1.3–3.0 kg) in T2DM patients.[108] Interestingly, one randomized clinical trial comparing a low-fat vegan diet with the American Diabetes Association (ADA) diet demonstrated that both diets caused significant improvements in HbA1c, body weight, plasma lipid concentrations, and urinary albumin excretion in individuals with T2DM.[109] Forty-three percent of patients randomized to the vegan group and 26% of those allocated to the ADA group reduced the use of glucose-lowering drugs. Moreover, among medication-stable patients, the effects of the low-fat vegan diet on HbA1c, weight, waist circumference, and LDL cholesterol were significantly greater than in the control group. Similar improvements in HbA1c levels have been found in a population of Korean men and women affected by T2DM.[110] Thus, these trials suggest that low-fat vegan diets might be more effective than conventional diabetic diets in glycaemic control, but more studies with long-term follow-up are needed to confirm these findings. *Table 1* summarizes the ongoing clinical trials with vegetarian diet interventions in people with T2DM.

Cardiovascular disease

Randomized clinical trials are usually considered gold standard studies for evaluating the cause–effect relationship of health interventions, although misleading conclusions can easily occur due to low adherence to the intervention or inadequate follow-up time. To the best of our knowledge, there are no randomized clinical trials that have tested the effects of vegetarian diets alone on CHD event rates. The Lifestyle Heart Trial was designed to investigate the effects of an intensive lifestyle programme comprising a 10% fat whole foods vegetarian diet together with aerobic exercise, stress management training, smoking cessation, and group psychosocial support in 48 patients with moderate to severe CHD.[119] Only 20 of the 28 patients randomized to the experimental group completed the 5-year follow-up and experienced a small but significant regression of coronary atherosclerosis (a 7.9% relative improvement) and a decrease in symptomatic and scintigraphic myocardial ischaemia.[119,120] In contrast, patients randomized to the usual care control group who completed the study ($n = 15$) experienced a 27.7% relative worsening of the average percent diameter stenosis. However, this was a very small, under-powered study that does not allow to differentiate the effects of the vegetarian regimen from those induced by the very low-fat diet, regular aerobic exercise, smoking cessation, and stress reduction programme.

Many randomized clinical trials have tested the effects of different forms of vegetarian diets on cardiometabolic risk factors. Recent meta-analyses reported that vegetarian diets significantly improve several risk factors, including body weight (1.2–2.8 kg reduction),[121] SBP (3.3–7.6 mmHg reduction),[103,105] total cholesterol (0.32–0.76 mmol/L reduction), LDL cholesterol (0.32–0.59 mmol/L reduction), high-density lipoprotein (HDL) cholesterol (0.088–0.093 mmol/L reduction),[122] and HbA1c (0.15%–0.65% reduction).[123] A crossover randomized trial showed that a vegetarian diet was as effective as the Mediterranean diet in reducing body weight and fat mass, but the former resulted in significantly lower LDL cholesterol levels in middle-aged men and women.[22] However, many of these meta-analyses were focused on relatively healthy populations or did not stratify patients for gender and disease status. Evidence of the metabolic effects of plant-based diets in people with CVD is limited. *Table 2* summarizes the ongoing clinical trials with vegetarian diet interventions in people with CVD.

Cancer

To our knowledge, only one randomized clinical trial to date has investigated the effects of a vegan diet on cancer outcomes, and preliminary data show a significant reduction in body weight and cholesterol at 8 weeks.[130] *Table 3* summarizes the ongoing interventional clinical trials on the effects of vegetarian diets in people with cancer.

Dementia

To the best of our knowledge, no randomized clinical trials to date have investigated the effects of vegetarian or vegan diets on cognitive impairment or dementia outcomes. Our search of ongoing randomized clinical trials identified only one study testing the effects of a low-fat vegan diet on dementia (NCT04606420).

Potential health risks of vegan and vegetarian diets

Accumulating evidence indicate that some vegetarians, especially vegans who are consuming restrictive diets, are at greater risk of developing haemorrhagic stroke, bone fractures, and a range of vitamin and mineral deficiencies that are particularly dangerous for growing children and pregnant and breastfeeding women.[136,137] Vitamin B12, for example, is an essential vitamin produced by specific strains of soil bacteria that animals ingest when grazing grass. During digestion, large amounts of vitamin B12 are formed and incorporated in the animal's meat, milk, and eggs. Fish and shellfish also contain considerable amount of vitamin B12; for instance, 100 g of clams contain up to 49 µg of vitamin B12. People following strict vegan diets must take a vitamin B12 supplement and/or consume foods supplemented with vitamin B12, including vitamin B12–fortified nutritional yeast, to avoid developing megaloblastic anaemia, a potentially irreversible form of neuropathy, and impaired bone formation. Vitamin B12 in spirulina or other algae is not bioavailable and may even inhibit vitamin B12 metabolism,[136] but vitamin B12 in duckweed is bioavailable.[138] Other potential deficiencies that vegetarians may develop are those from iron and zinc and occasionally riboflavin.[139] These deficiencies are especially important in vegan children, pregnant/breastfeeding women, and those with menorrhagia. Many plant foods contain iron and zinc, but their bioavailability is limited due plant anti-nutrients, such as phytates, tannins, lectins, and oxalates. Cooking, sprouting, fermenting, and processing plant foods with vitamin C rich foods can increase iron and zinc absorption.[140] Dietary calcium deficiency especially when coupled with protein restriction and excessive sodium intake can increase the risk of bone fractures in ethical vegans who do not consume healthy diets rich in calcium- and protein-rich plant foods.[93,137,141–143] Many plants contain calcium, and in some of these, its bioavailability is very high. For instance, 40%–60% of the calcium contained in cabbage, broccoli, or broccoli sprouts is absorbed because of their low oxalate content, against only 31%–32% of the calcium in cow's milk.[144] Legumes, soy products (especially tofu made with calcium sulphate), and figs are also excellent sources of dietary calcium and protein. Regular exercise training, adequate sun exposure, and vitamin D supplementation are also important to promote bone health and prevent fractures[145] and may play a key role in the protection against certain autoimmune diseases and advanced (metastatic) cancers.[146,147]

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Table 1 Study characteristics of completed and ongoing clinical trials in people with type 2 diabetes mellitus

Author, year, country	Study design; intervention duration	Registration number; status	Study arms, sample size	Population condition, gender, mean age (years)	Diet description		Relevant biomarkers [MD (95% CI)]
					Intervention	Comparison	
Barnard *et al.*, 2006,[109] USA	22 weeks, randomized, controlled trial, parallel arm; 52 weeks follow-up	NCT00276939; completed trial	(1) The LF vegan Diet (49) (2) The ADA diet (50)	T2DM and being overweight (BMI ≥ 25 kg/m^2); gender: (1) 27 F, 22 M; (2) 33 F, 17 M; mean age (range): (1) 57 (35–82); (2) 55 (27–80)	The LF, vegan diet: no animal products and added fats; consisted of F & V, grains, and legumes, favour low-GI foods; vitamin B12 supplement (100 mcg) taken every other day	The ADA diet: participants (with BMI >25 kg/m^2) were prescribed 500–1000 kcal energy deficits; vitamin B12 supplement (100 mcg) to be taken every other day	LDL: −0.02 [−0.31, 0.27] mmol/L; HbA1c: −0.40 [−0.85, 0.05]%; SBP: −0.2 [−5.4; 5.0] mmHg
Barnard *et al.*, 2018,[111] USA	20 weeks, randomized, controlled trial, parallel arm	NCT01222429; completed trial	(1) The LF vegan diet (22) (2) The portion-controlled eating plan (23)	T2DM (HbA1c 6.5%–10.5%) and overweight (BMI ≥ 25 kg/m^2); gender: (1) 13 F, 9 M; (2) 11 F, 12 M; mean (range): (1) 62 (41–79); (2) 61 (30–75)	The LF, low-GI, vegan diet: consisted of whole grains, F & V, and legumes; no animal products and added oils; no restrictions on energy or carbohydrate intake	The portion-controlled eating plan: energy limits when needed for weight loss (calorie-restricted −500 kcal/d) and guidance on portion sizes	LDL: 0.06 [−0.01, 0.13] mmol/L; SBP: 5.5 [2.7, 8.3] mmHg
Bunner *et al.*, 2015,[112] USA	20 weeks randomized, parallel arm, controlled trial	NCT01690962; completed trial	(1) The LF vegan diet + B12 supplement (17) (2) No intervention + B12 supplement (17)	T2DM with painful diabetic neuropathy for ≥6 months; gender: (1) 11 F, 6 M; (2) 8 F, 9 M; mean age: (1) 57 ± 6; (2) 58 ± 6	The LF, vegan diet first: no animal products; focused on grains, F & V, and legumes; limited fat to 20–30 g/d; favoured low-GI foods; daily vitamin B12 (1000 mcg)	No dietary change except for daily vitamin B12 supplement (1000 mcg)	LDL: −0.21 [−0.65, 0.23] mmol/L; HbA1c: −0.80 [−1.51, −0.09] %; SBP: −7.2 [−20.1, 5.7] mmHg
Kahleova *et al.*, 2011,[113] Czech Republic	24 weeks RCT, open, parallel arm. The second 12 weeks were combined with aerobic exercise.	NCT00883038; completed trial	(1) The lacto-vegetarian diet (37) (2) Conventional diabetic diet (37)	T2DM (HbA1c 6%–11%) and being overweight (BMI 25–53 kg/m^2); gender: (1) 20 F, 17 M; (2) 19 F, 18 M; mean age (years): (1) 55 ± 7.8; (2) 58 ± 4.9	The lacto-vegetarian diet: consisted of grains, F & V, and legumes; animal products limited to ≤1 portion of LF yogurt/d; vegetarian meals provided in vegetarian restaurants; calorie-restricted (−500 kcal/d); daily vitamin B12 supplement (50 mcg)	The conventional diabetic diet: follow dietary guidelines of the DNSG or the EASD; meals provided; calorie-restricted (−500 kcal/d); daily vitamin B12 supplement (50 mcg)	LDL: −0.04 [−0.28, 0.20] mmol/L; HbA1c: −0.09 [−0.49, 0.31]%

Continued

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Table 1 *Continued*

Author, year, country	Study design; Intervention duration	Registration number; status	Study arms, sample size	Population condition, gender, mean age (years)	Diet description		Relevant biomarkers (MD[95%CI])
					Intervention	Comparison	
Lee *et al.*, 2016,[114] Korea	12 weeks, randomized, controlled trial, parallel arm	CRiS KCT0001771; completed trial	(1) The vegan diet + brown rice (53) (2) The conventional diabetic diet (53)	T2DM (HbA1c 6.0%–11.0%); gender: (1) 40 F, 6 M; (2) 35 F, 12 M; mean age: (1) 57.5 ± 7.7 (2) 58.3 ± 7.0	The vegan diet + brown rice: consisted of F & V, whole grains, and legumes; no animal products, white rice, and processed food made of rice/wheat flour; have brown rice; favour low-GI foods; energy intake, and portion sizes not restricted	The conventional diabetic diet: followed the treatment guidelines by the Korean Diabetes Association (2011); restrict individualized daily energy intake based on weight, physical activity, need for weight control, and compliance	LDL: −0.04 [−0.29, 0.21] mmol/L; HbA1c: −0.30 [−0.61, 0.01] %; SBP: 2.5 [−4.4, 9.4] mmHg
Nicholson *et al.*, 1999,[115] USA	12 weeks randomized controlled trial, parallel arm	Completed trial	(1) The LF vegan diet (7) (2) The conventional LF diet (6)	T2DM; gender: (1) 3 F, 4 M; (2) 2 F, 2 M; mean (range): (1) 51 (34–62); (2) 60 (51–74)	The LF vegan diet: no animal products, added oils, and refined carbohydrates; consisted of F & V, whole grains, and legumes; the diet was adequate in all nutrients except vitamin B12	The LF diet: emphasized fish and poultry, rather than red meat	HbA1c −0.40 [−2.00, 1.20] %; SBP: 8.5 [−9.1, 26.1] mmHg

Author, year, country	Study design; Intervention duration	Study name/registration number; status	Study arms, sample size	Population condition, gender, mean age (years)	Diet description	
					Intervention	Comparison
Campbell *et al.* 2018,[116] USA	RCT, crossover design, each for 2 weeks with a 4–6 week washout	NCT 05414851; not yet recruiting	(1) WFPB diet (20) (2) Low-carbohydrate diet (20)	Aged >50y with diagnosis of: hypertension or hyperlipidaemia or pre-diabetes or diabetes or obesity	The WFPB diet: exclude animal foods, oils, and solid fats	The low-carbohydrate diet: 'nut' carbs <50 g/d
Kahleova *et al.*, 2019,[117] USA	22 weeks, RCT, crossover design	NCT04088981; not yet recruiting	(1) The LF vegan diet (30) (2) The portion-controlled diet (30)	Individuals aged ≥ 18 years with T2DM and BMI 26–40 kg/m^2	The LF, vegan diet: no animal products and added oils; no restriction on energy intake	The portion-controlled diet: an individualized diet; reduce 500 kcal/d for overweight participants
Sangeetha *et al.*, 2018, India	Randomized, parallel arm trial	CTRI/2018/10/015896; NI on recruitment	(1) Vegetarian diet (2) Mixed diet	T2DM	Vegetarian diet: consume the prescribed vegan, pesco-, and ovo-lacto-vegetarian diet	Diabetics on mixed diet: the prescribed non-vegetarian diet
Wright *et al.*, 2017,[118] New Zealand	10 weeks RCT, parallel arm; 42 weeks follow-up	ACTRN12617000541303; results not published yet	(1) WFPB diet (24) (2) Usual care (24)	Obese (BMI ≥ 30 kg/m^2) and T2DM/pre-diabetes	WFPB approach: avoid animal products; no energy restriction; daily 50 mcg vitamin B12 supplement	Usual care

ADA, American Diabetes Association; CI, confidence interval; F & V, fruits and vegetables; HbA1c, haemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; LF, low-fat; LOV, lacto-ovo vegetarian diet; MD, mean differences; SBP, systolic blood pressure; DNSG, Diabetes and Nutrition Study Group; EASD, European Association for the Study of Diabetes; NA, not applicable; RR, relative risk; F, females; M, males; NI, no information; OR, odds ratio; RCT, randomized controlled trial; IQR, interquartile range; M, males; WFPB, whole foods plant-based.

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Table 2 Study characteristics of completed and ongoing clinical trials in people with cardiovascular diseases

Author, year, country	Study design; intervention duration	Study name/ registration number; status	Study arms, sample size	Population condition, gender, mean age (years)	Diet description		Relevant biomarkers [MD (95%CI)]
					The vegetarian diet	Comparison	
Aldana *et al.*, 2007,[124] USA	1 year RCT, parallel arm	Completed trial	(1) The Dr. Ornish Programme (46) (2) Traditional cardiac rehabilitation (47)	CHD; males: (1) 47.8%; (2) 64.6%; mean age: (1) 60.9 ± 9.7; (2) 62.2 ± 8.9	The very LF, LOV diet: no animal proteins except for non-fat dairy and egg whites; liberal consumption of F & V, whole grains, and legumes; one serve of soy food/day; a multivitamin and a flax source of omega-3-fatty acids	No dietary intervention: traditional cardiac rehabilitation	LDL-C: −0.07 (−0.39, 0.25) mmol/L; SBP: 0.6 (−6.8, 7.9) mmHg
Ornish *et al.*, 1990,[119,125] USA	Initially 1 year RCT, but extended the study for an additional 4 years, parallel arm	Completed trial	(1) The LF LOV diet (53) (2) Usual care (40)	CHD; gender: (1) 1 F, 21 M; (2) 4 F, 15 M; mean age: (1) 56.1 ± 7.5; (2) 59.8 ± 9.1	The LF (10% energy from fat), LOV diet: consisted of F & V, grains, legumes, and soybean products; no animal proteins except for non-fat dairy and egg whites; vitamin B12 supplemented; no calorie restriction; salt restricted for hypertensive patients; caffeine eliminated, alcohol limited to ≤2 units/d	Usual care: not asked to make lifestyle changes	SBP: 2.0 (−10.2, 14.2) mmHg

Author, year, country	Study design; Intervention duration	Study name/registration number; status	Study arms, sample size	Population condition, gender, mean age (years)	Diet description		Relevant biomarkers (MD[95%CI])
					The vegetarian diet	Comparison	
Shah *et al.*, 2018,[126,127] USA	8 weeks RCT, open-label, blinded, parallel arm	NCT02135939; completed trial	(1) The vegan diet (50) (2) The AHA diet (50)	CHD: > 3/4 had dyslipidaemia. gender: (1) 57 F, 43 M; (2) 58 F, 42 M; median age (IQR): (1) 63.0 (57.0–68.0); (2) 59.5 (53.0–67.0)	The vegan diet: whole-food plant-based diet with no processed foods; no animal products; vitamin B12–fortified soy milk; given the cookbooks *Simply Vegan* (Baltimore: Vegetarian Resource Group, 2012)	The AHA diet: given the AHA LF, *Low-Cholesterol Cookbook* (New York: Clarkson Potter, 2008)	LDL-C: −0.09 (−0.27, 0.09) mmol/L; HbA1c: 0.00 (−0.13, 0.13) %
Toobert *et al.*, 2000,[128] USA	2 years, RCT, parallel arm	Completed trial	(1) Prime Time programme: very LF, LOV diet (17) (2) Usual care (11)	Women with CHD; mean age: (1) 64 ± 10; (2) 63 ± 11	The reversal diet (very LF, LOV diet): no animal products other than egg whites and non-fat yogurt; no added oils or other concentrated fats; < 10% calories from fat	Usual care	LDL-C: −0.12 (−0.72, 0.48) mmol/L; SBP: −9.0 (−27.7, 9.7) mmHg

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Table 2 *Continued*

Author, year, country	Study design; Intervention duration	Study name/registration number; status	Study arms, sample size	Population condition, gender, mean age (years)	Diet description		Relevant biomarkers (MD[95%CI])
					The vegetarian diet	Comparison	
Cassidy *et al.*, 2022,[129] Australia	1 year, RCT, parallel arm	ACTRN12620001151921; recruiting	(1) Intensive lifestyle programme (75) (2) AHA diet (75)	Individuals with CHD aged 18–80 years	The 5:2 pesco-vegetarian diet: no animal foods other than fish, egg and dairy products; 2 non-consecutive fasting days per week	The AHA diet: general dietary guidelines from the AHA	NA

CI, confidence interval; CHD, coronary heart disease; CR, calorie-restricted; F& V, fruits and vegetables; LDL-C, low-density lipoprotein cholesterol; LF, low-fat; LOV, lacto-ovo vegetarian diet; MD, mean differences; RCT, randomized controlled trial; SBP, systolic blood pressure; AHA, American Heart Association; HbA1c, haemoglobin A1c; IQR, interquartile range; NA, not applicable.

The importance of consuming healthy vegetarian diets

Vegetarians should pay close attention to the quality and composition of their diets. Data from epidemiological studies suggest that men and women consuming plant-based diets rich in healthier plant foods (fresh vegetables, legumes, minimally processed whole grains, fruits, nuts, monounsaturated-rich vegetable oils, tea, and coffee) have lower risks of CHD and overall mortality with regular fish intake providing additionally health benefits.[4,87,148–150] In contrast, people eating 'unhealthy' plant-based diets that emphasize refined grains, potatoes, high-sodium preserved vegetables, fried goods, sweets, juices, and sweetened beverages experienced higher risk of CHD and mortality.[4,5] Similar results have been found for T2DM.[5] Plant-based food products marketed as vegetarian and/or vegan can be rich in refined starch, added sugar, HFCS, salt, partially hydrogenated (*trans*) fat, and saturated fatty acids from tropical oils (e.g. one tablespoon of coconut oil contains 12 grams of saturated fat). Consumption of ultra-processed foods rich in sucrose and in HFCS, even if labelled as 'vegetarian' or 'vegan', promotes the development of insulin resistance, cardiometabolic syndrome, fatty liver disease, CVD, and cancer.[151,152] High salt intake not only increases the risk of developing hypertension, CHD, and stroke,[55,153] but it also triggers inflammation by increasing monocyte CCR2 expression.[154] *Trans*-fatty acids from partially hydrogenated oils have markedly adverse effects on serum lipids, systemic inflammation, endothelial function, and ultimately on the risk of developing T2DM and CVD.[155] However, naturally occurring *trans*-fatty acids found in milk and meat of ruminant animals have also similar adverse effects on LDL cholesterol, total cholesterol to HDL cholesterol ratio, and apolipoprotein B levels as do industrially produced *trans*-fatty acids.[156] Finally, people consuming unhealthy vegetarian diets rich in refined carbohydrates might also be at risk of protein malnutrition. Plant foods contain all the nine essential amino acids but in different proportions. Legumes, for instance, are high in lysine, but low in tryptophan and methionine. In contrast, whole grains are low in lysine but high in tryptophan and methionine. Therefore, it is essential to consume every day a mixture of whole grains, beans and nuts, and/or protein-rich plant foods (e.g. tofu and mankai, a cultivated strain of the *Wolffia globosa* aquatic plant) to provide adequate amounts of all the essential and non-essential amino acids.

Conclusions

Consuming vegetarian diets rich in minimally processed plant foods has been associated with a reduced risk of developing multiple chronic diseases including CVD, diabetes, hypertension, cancer, and dementia. Data from randomized clinic trials have confirmed a protective effect of vegetarian diets for the prevention of diabetes, hypercholesterolaemia, hypertension, and overweight, but to date, no data are available for acute coronary syndrome, heart failure, stroke, cognitive impairment, and dementia, and there are very limited data for cancer. However, since many individuals commonly and increasingly adopt vegetarian diets worldwide for ideological, cultural, environmental, and personal factors, it is of paramount importance to define which vegetarian dietary compositions provide better health outcomes and which components are detrimental to human health (*Graphical Abstract*).

New randomized trials are needed to understand whether the advantages of healthy plant-based diets represent an all-or-nothing phenomenon and if consuming less strict plant-based diets containing small

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Table 3 Study characteristics of clinical trials in people with cancer

Author, year, country	Study design; intervention duration	Registration number; status	Study arms, sample size	Population condition, gender, mean age (years)	Diet description		Relevant biomarkers (MD)
					The vegetarian diet	Comparison	
Campbell *et al.*, 2022,[130] USA	Randomized trial, parallel arms; 8 weeks	NCT03045289	(1) WFPBD + multivitamin (19) (2) Usual diet + multivitamin (9)	Women age ≥18 years with metastatic breast cancer	A WHPBD: provide 3 meals/d; no animal products, refined flours; encourage fruits and vegetables	A usual diet + daily multivitamin	Final value (adjusted for baseline): weight (kg): (1) 73; (2) 77; $P < .01$ LDL-C (mmol/L): (1) 2.1; (2) 2.76; $P < .01$ SBP (mmHg): (1) 108.5; (2) 114.8; $P = .06$ CA 27.29 (U/mL): (1) 24.4; (2) 27.7; $P = .09$
Gulley *et al.*, 2021,[131] USA	RCT, parallel arms; 16 weeks	NCT04866810; recruiting	(1) High-fibre PBD + exercise prescription (40) (2) Standard diet + exercise guidelines (40)	Age ≥18 years with histologically or cytologically confirmed unresectable melanoma	A high-fibre PBD: ideally a vegan diet, provided a sample meal plan and vegan recipes; ≥30 g fibre/d	Standard diet from healthy eating guidelines	NA

Author, year, country	Study design; Intervention duration	Registration number; status	Study arms, sample size	Population condition, gender, mean age (years)	Diet description	
					The vegetarian diet	Comparison
Jeppsen *et al.*, 2022,[132] USA, India	Randomized trial, parallel arms; 12 weeks	NCT05410002; active, not recruiting	(1) Vegetarian + N-111 (2) Non-vegetarian + N-111 (3) Vegetarian + placebo (4) Non-vegetarian + placebo (5) Vegetarian control (6) Non-vegetarian control	Age ≥ 25, < 80 years with positive diagnosis of breast or prostate cancer	Vegetarian diet	Usual diet
Iyengar *et al.*, 2020,[133] USA	Randomized trial, parallel arms; 8 weeks	NCT04298086; recruiting	(1) CR vegetarian diet (31) (2) Nutrition + physical activity counselling (31)	Overweight post-menopausal women with breast cancer	A vegetarian diet: provide lunch + dinner for 6 d/week; no animal products; structured exercise	A home-based, physical activity programme and nutrition counselling
Avivi *et al.*, 2021,[134] Israel	Single-arm clinical trial; 3 years	NCT04957693; recruiting	Vegan diet and lifestyle changes (40)	Age ≥18 years with diagnosis of indolent lymphoma	Specifically designed vegan nutrition, physical activity (mostly aerobic), and stress reduction	Not applicable

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Table 3 *Continued*

Author, year, country	Study design; Intervention duration	Registration number; status	Study arms, sample size	Population condition, gender, mean age (years)	Diet description	
					The vegetarian diet	Comparison
Shah *et al.*, 2021,[135] USA	Single-arm clinical trial; 24 weeks	NCT04920084; recruiting	WFPBD (20)	Age ≥18 years with smoldering multiple myeloma or MGUS	A WHPBD: provide lunch + dinner for 6 d/ week; no/minimal animal products; access to a coach daily	Not applicable

LDL-C, low-density lipoprotein cholesterol; MD, mean differences; NA, not applicable; SBP, systolic blood pressure; WFPBD, whole-food plant-based diet; CR, calorie-restricted; MGUS, monoclonal gammopathy of undetermined significance; N-111, nutraceutical supplement, ingredients unspecified.

quantities of animal products (e.g. pescatarian or traditional Mediterranean diets) has beneficial or detrimental effect on specific health outcomes, including the prevention of haemorrhagic stroke and bone fracture. Further, mechanistic studies are warranted to enhance our understanding about healthy plant-based food patterns and the biological mechanisms linking dietary factors and chronic diseases.

Recommendations for clinicians and allied health practitioners

For overweight men and women seeking weight loss and cardiometabolic improvement as means of primary and secondary prevention of T2DM, hypertension, and CVD, well-balanced and supplemented vegetarian diets rich in minimally processed plant foods may be an option, especially when coupled with calorie restriction and regular exercise training as recommended in the 2018 Physical Activity Guidelines Advisory Committee Scientific Report.[28,157] Regular fish intake can provide additional cardiovascular health benefits.[158] Additional trials are warranted to determine whether patients with CVD will ultimately benefit from consuming vegetarian and vegan diets and, if so, in what ways. As with any potential therapeutic strategy, the risks and benefits of vegetarian diets must be discussed with patients. There is evidence to suggest that some vegetarians, particularly those who follow restrictive diets such as vegans, may be at greater risk of haemorrhagic stroke and bone fractures if they do not carefully plan their diets and consume fortified plant-based foods or supplements. In addition, vegans and some vegetarians may be at risk of deficiencies in vitamins and minerals such as vitamin B12, riboflavin, iron, zinc, calcium, and omega-3 fatty acids. This can be particularly dangerous for pregnant and breastfeeding women and growing children, as these nutrients are crucial for foetal and child development. It is recommended that anyone considering a vegetarian or vegan diet consult with a registered dietitian or healthcare provider to ensure that their diet is nutritionally adequate. Consuming vegetarian diets rich in refined grains, potatoes, high-sodium preserved vegetables, fried goods, sweets, juices, and sweetened beverages can increase the risk of developing T2DM and CVD morbidity and mortality. Finally, in the case of vegetarian diets and cancer, the benefits and risks are not well defined. As a weight loss strategy, this may be an option for some cancer patients, but there are currently no data to suggest that vegetarian or vegan diets in the absence of weight loss and/or changes in physical activity patterns will have a positive impact on cancer outcomes, including either recurrence or the development of metastatic cancers.

Supplementary data

Supplementary data are not available at *European Heart Journal* online.

Declarations

Disclosure of Interest

All authors declare no conflict of interest for this contribution.

Data Availability

Most extracted data and study materials are available from previously published research. Additional data extracted from the corresponding author of included studies will be shared upon reasonable request.

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References

1. Willett W, Rockstrom J, Loken B, Springmann M, Lang T, Vermeulen S, *et al.* Food in the anthropocene: the EAT-Lancet Commission on healthy diets from sustainable food systems. *Lancet* 2019;**393**:447–92. https://doi.org/10.1016/S0140-6736(18)31788-4
2. Sievenpiper JL, Chan CB, Dworatzek PD, Freeze C, Williams SL. Nutrition therapy. *Can J Diabetes* 2018;**42**:S64–79. https://doi.org/10.1016/j.jcjd.2017.10.009
3. Melina V, Craig W, Levin S. Position of the academy of nutrition and dietetics: vegetarian diets. *J Acad Nutr Diet* 2016;**116**:1970–80. https://doi.org/10.1016/j.jand.2016.09.025
4. Satija A, Bhupathiraju SN, Spiegelman D, Chiuve SE, Manson JE, Willett W, *et al.* Healthful and unhealthful plant-based diets and the risk of coronary heart disease in U.S. adults. *J Am Coll Cardiol* 2017;**70**:411–22. https://doi.org/10.1016/j.jacc.2017.05.047
5. Satija A, Bhupathiraju SN, Rimm EB, Spiegelman D, Chiuve SE, Borgi L, *et al.* Plant-based dietary patterns and incidence of type 2 diabetes in US men and women: results from three prospective cohort studies. *PLoS Med* 2016;**13**:e1002039. https://doi.org/10.1371/journal.pmed.1002039
6. Wang F, Ugai T, Haruki K, Wan Y, Akimoto N, Arima K, *et al.* Healthy and unhealthy plant-based diets in relation to the incidence of colorectal cancer overall and by molecular subtypes. *Clin Transl Med* 2022;**12**:e893. https://doi.org/10.1002/ctm2.893
7. Sacks FM, Lichtenstein AH, Wu JHY, Appel LJ, Creager MA, Kris-Etherton PM, *et al.* Dietary fats and cardiovascular disease: a presidential advisory from the American Heart Association. *Circulation* 2017;**136**:e1–e23. https://doi.org/10.1161/CIR.0000000000000510

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8. Mensink RP, Zock PL, Kester AD, Katan MB. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. *Am J Clin Nutr* 2003;**77**:1146–55. https://doi.org/10.1093/ajcn/77.5.1146
9. Li Y, Hruby A, Bernstein AM, Ley SH, Wang DD, Chiuve SE, *et al.* Saturated fats compared with unsaturated fats and sources of carbohydrates in relation to risk of coronary heart disease: a prospective cohort study. *J Am Coll Cardiol* 2015;**66**:1538–48. https://doi.org/10.1016/j.jacc.2015.07.055
10. Dayton S, Pearce ML, Goldman H, Harnish A, Plotkin D, Shickman M, *et al.* Controlled trial of a diet high in unsaturated fat for prevention of atherosclerotic complications. *Lancet* 1968;**2**:1060–2. https://doi.org/10.1016/S0140-6736(68)91531-6
11. Leren P. The Oslo diet-heart study. Eleven-year report. *Circulation* 1970;**42**:935–42. https://doi.org/10.1161/01.CIR.42.5.935
12. Turpeinen O. Effect of cholesterol-lowering diet on mortality from coronary heart disease and other causes. *Circulation* 1979;**59**:1–7. https://doi.org/10.1161/01.CIR.59.1.1
13. Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, Barnes EH, *et al.* The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* 2012;**380**:581–90. https://doi.org/10.1016/S0140-6736(12)60367-5
14. Kris-Etherton PM, Hecker KD, Bonanome A, Coval SM, Binkoski AE, Hilpert KF, *et al.* Bioactive compounds in foods: their role in the prevention of cardiovascular disease and cancer. *Am J Med* 2002;**113**:71s–88s. https://doi.org/10.1016/S0002-9343(01)00995-0
15. Hu FB, Stampfer MJ, Manson JE, Rimm EB, Colditz GA, Rosner BA, *et al.* Frequent nut consumption and risk of coronary heart disease in women: prospective cohort study. *BMJ* 1998;**317**:1341–5. https://doi.org/10.1136/bmj.317.7169.1341
16. Jenkins DJ, Jones PJ, Lamarche B, Kendall CW, Faulkner D, Cermakova L, *et al.* Effect of a dietary portfolio of cholesterol-lowering foods given at 2 levels of intensity of dietary advice on serum lipids in hyperlipidemia: a randomized controlled trial. *JAMA* 2011;**306**:831–9. https://doi.org/10.1001/jama.2011.1202
17. Salas-Salvado J, Farres X, Luque X, Narejos S, Borrell M, Basora J, *et al.* Effect of two doses of a mixture of soluble fibres on body weight and metabolic variables in overweight or obese patients: a randomised trial. *Br J Nutr* 2008;**99**:1380–7. https://doi.org/10.1017/S0007114507868528
18. Abumweis SS, Barake R, Jones PJ. Plant sterols/stanols as cholesterol lowering agents: a meta-analysis of randomized controlled trials. *Food Nutr Res* 2008;**52**. https://doi.org/10.3402/fnr.v52i0.1811
19. Theuwissen E, Mensink RP. Water-soluble dietary fibers and cardiovascular disease. *Physiol Behav* 2008;**94**:285–92. https://doi.org/10.1016/j.physbeh.2008.01.001
20. Orlich MJ, Fraser GE. Vegetarian diets in the Adventist Health Study 2: a review of initial published findings. *Am J Clin Nutr* 2014;**100**:353S–8S. https://doi.org/10.3945/ajcn.113.071233
21. Key T, Davey G. Prevalence of obesity is low in people who do not eat meat. *BMJ* 1996;**313**:816–7. https://doi.org/10.1136/bmj.313.7060.816
22. Sofi F, Dinu M, Pagliai G, Cesari F, Gori AM, Sereni A, *et al.* Low-calorie vegetarian versus Mediterranean diets for reducing body weight and improving cardiovascular risk profile: CARDIVEG Study (Cardiovascular Prevention With Vegetarian Diet). *Circulation* 2018;**137**:1103–13. https://doi.org/10.1161/CIRCULATIONAHA.117.030088
23. Gepner Y, Shelef I, Schwarzfuchs D, Zelicha H, Tene L, Yaskolka Meir A, *et al.* Effect of distinct lifestyle interventions on mobilization of fat storage pools: CENTRAL Magnetic Resonance Imaging Randomized Controlled Trial. *Circulation* 2018;**137**:1143–57. https://doi.org/10.1161/CIRCULATIONAHA.117.030501
24. Müller M, Canfora EE, Blaak EE. Gastrointestinal transit time, glucose homeostasis and metabolic health: modulation by dietary fibers. *Nutrients* 2018;**10**:275. https://doi.org/10.3390/nu10030275
25. Cani PD, Delzenne NM. The role of the gut microbiota in energy metabolism and metabolic disease. *Curr Pharm Des* 2009;**15**:1546–58. https://doi.org/10.2174/138161209788168164
26. Alkhezi OS, Alahmed AA, Alfayez OM, Alzuman OA, Almutairi AR, Almohammed OA. Comparative effectiveness of glucagon-like peptide-1 receptor agonists for the management of obesity in adults without diabetes: a network meta-analysis of randomized clinical trials. *Obes Rev* 2023;**24**:e13543. https://doi.org/10.1111/obr.13543
27. Marx N, Husain M, Lehrke M, Verma S, Sattar N. GLP-1 receptor agonists for the reduction of atherosclerotic cardiovascular risk in patients with type 2 diabetes. *Circulation* 2022;**146**:1882–94. https://doi.org/10.1161/CIRCULATIONAHA.122.059595
28. Green CL, Lamming DW, Fontana L. Molecular mechanisms of dietary restriction promoting health and longevity. *Nat Rev Mol Cell Biol* 2022;**23**:56–73. https://doi.org/10.1038/s41580-021-00411-4
29. Weiss EP, Racette SB, Villareal DT, Fontana L, Steger-May K, Schechtman KB, *et al.* Improvements in glucose tolerance and insulin action induced by increasing energy expenditure or decreasing energy intake: a randomized controlled trial. *Am J Clin Nutr* 2006;**84**:1033–42. https://doi.org/10.1093/ajcn/84.5.1033
30. Kraus WE, Bhapkar M, Huffman KM, Pieper CF, Krupa Das S, Redman LM, *et al.* 2 years of calorie restriction and cardiometabolic risk (CALERIE): exploratory outcomes of a multicentre, phase 2, randomised controlled trial. *Lancet Diabetes Endocrinol* 2019;**7**:673–83. https://doi.org/10.1016/S2213-8587(19)30151-2
31. Clifton KK, Ma CX, Fontana L, Peterson LL. Intermittent fasting in the prevention and treatment of cancer. *CA Cancer J Clin* 2021;**71**:527–46. https://doi.org/10.3322/caac.21694
32. Mittendorfer B, Klein S, Fontana L. A word of caution against excessive protein intake. *Nat Rev Endocrinol* 2020;**16**:59–66. https://doi.org/10.1038/s41574-019-0274-7
33. Tinker LF, Sarto GE, Howard BV, Huang Y, Neuhouser ML, Mossavar-Rahmani Y, *et al.* Biomarker-calibrated dietary energy and protein intake associations with diabetes risk among postmenopausal women from the Women's Health Initiative. *Am J Clin Nutr* 2011;**94**:1600–6. https://doi.org/10.3945/ajcn.111.018648
34. Sluijs I, Beulens JW, van der A DL, Spijkerman AM, Grobbee DE, van der Schouw YT. Dietary intake of total, animal, and vegetable protein and risk of type 2 diabetes in the European Prospective Investigation into Cancer and Nutrition (EPIC)-NL study. *Diabetes Care* 2010;**33**:43–8. https://doi.org/10.2337/dc09-1321
35. Malik VS, Li Y, Tobias DK, Pan A, Hu FB. Dietary protein intake and risk of type 2 diabetes in US men and women. *Am J Epidemiol* 2016;**183**:715–28. https://doi.org/10.1093/aje/kwv268
36. Smith GI, Yoshino J, Kelly SC, Reeds DN, Okunade A, Patterson BW, *et al.* High-protein intake during weight loss therapy eliminates the weight-loss-induced improvement in insulin action in obese postmenopausal women. *Cell Rep* 2016;**17**:849–61. https://doi.org/10.1016/j.celrep.2016.09.047
37. Fontana L, Cummings NE, Apelo SIA, Neuman JC, Kasza I, Schmidt BA, *et al.* Decreased consumption of branched-chain amino acids improves metabolic health. *Cell Rep* 2016;**16**:520–30. https://doi.org/10.1016/j.celrep.2016.05.092
38. Xu Y, Jiang H, Li L, Chen F, Liu Y, Zhou M, *et al.* Branched-chain amino acid catabolism promotes thrombosis risk by enhancing tropomodulin-3 propionylation in platelets. *Circulation* 2020;**142**:49–64. https://doi.org/10.1161/CIRCULATIONAHA.119.043581
39. Weickert MO, Roden M, Isken F, Hoffmann D, Nowotny P, Osterhoff M, *et al.* Effects of supplemented isoenergetic diets differing in cereal fiber and protein content on insulin sensitivity in overweight humans. *Am J Clin Nutr* 2011;**94**:459–71. https://doi.org/10.3945/ajcn.110.004374
40. Hattersley JG, Pfeiffer AF, Roden M, Petzke KJ, Hoffmann D, Rudovich NN, *et al.* Modulation of amino acid metabolic signatures by supplemented isoenergetic diets differing in protein and cereal fiber content. *J Clin Endocrinol Metab* 2014;**99**:E2599–609. https://doi.org/10.1210/jc.2014-2302
41. Sargrad KR, Homko C, Mozzoli M, Boden G. Effect of high protein vs high carbohydrate intake on insulin sensitivity, body weight, hemoglobin A1c, and blood pressure in patients with type 2 diabetes mellitus. *J Am Diet Assoc* 2005;**105**:573–80. https://doi.org/10.1016/j.jada.2005.01.009
42. Zhang X, Sergin I, Evans TD, Jeong SJ, Rodriguez-Velez A, Kapoor D, *et al.* High-protein diets increase cardiovascular risk by activating macrophage mTOR to suppress mitophagy. *Nat Metab* 2020;**2**:110–25. https://doi.org/10.1038/s42255-019-0162-4
43. Howitz KT, Sinclair DA. Xenohormesis: sensing the chemical cues of other species. *Cell* 2008;**133**:387–91. https://doi.org/10.1016/j.cell.2008.04.019
44. Liguori I, Russo G, Curcio F, Bulli G, Aran L, Della-Morte D, *et al.* Oxidative stress, aging, and diseases. *Clin Interv Aging* 2018;**13**:757–72. https://doi.org/10.2147/CIA.S158513
45. Fito M, Guxens M, Corella D, Saez G, Estruch R, de la Torre R, *et al.* Effect of a traditional Mediterranean diet on lipoprotein oxidation: a randomized controlled trial. *Arch Intern Med* 2007;**167**:1195–203. https://doi.org/10.1001/archinte.167.11.1195
46. Björkegren JLM, Lusis AJ. Atherosclerosis: recent developments. *Cell* 2022;**185**:1630–45. https://doi.org/10.1016/j.cell.2022.04.004
47. Li J, Lee DH, Hu J, Tabung FK, Li Y, Bhupathiraju SN, *et al.* Dietary inflammatory potential and risk of cardiovascular disease among men and women in the U.S. *J Am Coll Cardiol* 2020;**76**:2181–93. https://doi.org/10.1016/j.jacc.2020.09.535
48. Hajihashemi P, Haghighatdoost F. Effects of whole-grain consumption on selected biomarkers of systematic inflammation: a systematic review and meta-analysis of randomized controlled trials. *J Am Coll Nutr* 2019;**38**:275–85. https://doi.org/10.1080/07315724.2018.1490935
49. Hosseini B, Berthon BS, Saedisomeolia A, Starkey MR, Collison A, Wark PAB, *et al.* Effects of fruit and vegetable consumption on inflammatory biomarkers and immune cell populations: a systematic literature review and meta-analysis. *Am J Clin Nutr* 2018;**108**:136–55. https://doi.org/10.1093/ajcn/nqy082
50. Hosseinpour-Niazi S, Mirmiran P, Fallah-Ghohroudi A, Azizi F. Non-soya legume-based therapeutic lifestyle change diet reduces inflammatory status in diabetic patients: a randomised cross-over clinical trial. *Br J Nutr* 2015;**114**:213–9. https://doi.org/10.1017/S0007114515001725
51. Aeberli I, Gerber PA, Hochuli M, Kohler S, Haile SR, Gouni-Berthold I, *et al.* Low to moderate sugar-sweetened beverage consumption impairs glucose and lipid metabolism and promotes inflammation in healthy young men: a randomized controlled trial. *Am J Clin Nutr* 2011;**94**:479–85. https://doi.org/10.3945/ajcn.111.013540
52. Hematdar Z, Ghasemifard N, Phishdad G, Faghih S. Substitution of red meat with soybean but not non- soy legumes improves inflammation in patients with type 2 diabetes;

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a randomized clinical trial. *J Diabetes Metab Disord* 2018;**17**:111–6. https://doi.org/10.1007/s40200-018-0346-6
53. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, *et al.* Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N Engl J Med* 2001;**344**:3–10. https://doi.org/10.1056/NEJM200101043440101
54. Neter JE, Stam BE, Kok FJ, Grobbee DE, Geleijnse JM. Influence of weight reduction on blood pressure: a meta-analysis of randomized controlled trials. *Hypertension* 2003;**42**:878–84. https://doi.org/10.1161/01.HYP.0000094221.86888.AE
55. Neal B, Wu Y, Feng X, Zhang R, Zhang Y, Shi J, *et al.* Effect of salt substitution on cardiovascular events and death. *N Engl J Med* 2021;**385**:1067–77. https://doi.org/10.1056/NEJMoa2105675
56. Whelton SP, Chin A, Xin X, He J. Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. *Ann Intern Med* 2002;**136**:493–503. https://doi.org/10.7326/0003-4819-136-7-200204020-00006
57. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, *et al.* Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet* 2020;**396**:413–46. https://doi.org/10.1016/S0140-6736(20)30367-6
58. Schiffrin EL, Engert JC. Hypertension, brain imaging phenotypes, and cognitive impairment: lessons from Mendelian randomization. *Eur Heart J* 2023;**44**:2126–8. https://doi.org/10.1093/eurheartj/ehad187
59. Hughes D, Judge C, Murphy R, Loughlin E, Costello M, Whiteley W, *et al.* Association of blood pressure lowering with incident dementia or cognitive impairment: a systematic review and meta-analysis. *JAMA* 2020;**323**:1934–44. https://doi.org/10.1001/jama.2020.4249
60. Muegge BD, Kuczynski J, Knights D, Clemente JC, González A, Fontana L, *et al.* Diet drives convergence in gut microbiome functions across mammalian phylogeny and within humans. *Science* 2011;**332**:970–4. https://doi.org/10.1126/science.1198719
61. Thorburn AN, Macia L, Mackay CR. Diet, metabolites, and "western-lifestyle" inflammatory diseases. *Immunity* 2014;**40**:833–42. https://doi.org/10.1016/j.immuni.2014.05.014
62. Wang Z, Bergeron N, Levison BS, Li XS, Chiu S, Jia X, *et al.* Impact of chronic dietary red meat, white meat, or non-meat protein on trimethylamine N-oxide metabolism and renal excretion in healthy men and women. *Eur Heart J* 2018;**40**:583–94. https://doi.org/10.1093/eurheartj/ehy799
63. Koeth RA, Lam-Galvez BR, Kirsop J, Wang Z, Levison BS, Gu X, *et al.* l-Carnitine in omnivorous diets induces an atherogenic gut microbial pathway in humans. *J Clin Invest* 2019;**129**:373–87. https://doi.org/10.1172/JCI94601
64. Tang WH, Wang Z, Levison BS, Koeth RA, Britt EB, Fu X, *et al.* Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. *N Engl J Med* 2013;**368**:1575–84. https://doi.org/10.1056/NEJMoa1109400
65. Li XS, Obeid S, Klingenberg R, Gencer B, Mach F, Räber L, *et al.* Gut microbiota-dependent trimethylamine N-oxide in acute coronary syndromes: a prognostic marker for incident cardiovascular events beyond traditional risk factors. *Eur Heart J* 2017;**38**:814–24. https://doi.org/10.1093/eurheartj/ehw582
66. Dietrich S, Trefflich I, Ueland PM, Menzel J, Penczynski KJ, Abraham K, *et al.* Amino acid intake and plasma concentrations and their interplay with gut microbiota in vegans and omnivores in Germany. *Eur J Nutr* 2022;**61**:2103–14. https://doi.org/10.1007/s00394-021-02790-y
67. Losno EA, Sieferle K, Perez-Cueto FJA, Ritz C. Vegan diet and the gut microbiota composition in healthy adults. *Nutrients* 2021;**13**:2402. https://doi.org/10.3390/nu13072402
68. Kasahara K, Krautkramer KA, Org E, Romano KA, Kerby RL, Vivas EI, *et al.* Interactions between *Roseburia intestinalis* and diet modulate atherogenesis in a murine model. *Nat Microbiol* 2018;**3**:1461–71. https://doi.org/10.1038/s41564-018-0272-x
69. Sonnenburg ED, Smits SA, Tikhonov M, Higginbottom SK, Wingreen NS, Sonnenburg JL. Diet-induced extinctions in the gut microbiota compound over generations. *Nature* 2016;**529**:212–5. https://doi.org/10.1038/nature16504
70. Mazmanian SK, Liu CH, Tzianabos AO, Kasper DL. An immunomodulatory molecule of symbiotic bacteria directs maturation of the host immune system. *Cell* 2005;**122**:107–18. https://doi.org/10.1016/j.cell.2005.05.007
71. Tsaban G, Yaskolka Meir A, Rinott E, Zelicha H, Kaplan A, Shalev A, *et al.* The effect of green Mediterranean diet on cardiometabolic risk; a randomised controlled trial. *Heart* 2020;**107**:heartjnl-2020-317802. https://doi.org/10.1136/heartjnl-2020-317802
72. Rinott E, Meir AY, Tsaban G, Zelicha H, Kaplan A, Knights D, *et al.* The effects of the green-Mediterranean diet on cardiometabolic health are linked to gut microbiome modifications: a randomized controlled trial. *Genome Med* 2022;**14**:29. https://doi.org/10.1186/s13073-022-01015-z
73. Griffin NW, Ahern PP, Cheng J, Heath AC, Ilkayeva O, Newgard CB, *et al.* Prior dietary practices and connections to a human gut microbial metacommunity alter responses to diet interventions. *Cell Host Microbe* 2017;**21**:84–96. https://doi.org/10.1016/j.chom.2016.12.006
74. Dey N, Wagner VE, Blanton LV, Cheng J, Fontana L, Haque R, *et al.* Regulators of gut motility revealed by a gnotobiotic model of diet-microbiome interactions related to travel. *Cell* 2015;**163**:95–107. https://doi.org/10.1016/j.cell.2015.08.059
75. Sacks FM, Kass EH. Low blood pressure in vegetarians: effects of specific foods and nutrients. *Am J Clin Nutr* 1988;**48**:795–800. https://doi.org/10.1093/ajcn/48.3.795
76. Beilin LJ, Rouse IL, Armstrong BK, Margetts BM, Vandongen R. Vegetarian diet and blood pressure levels: incidental or causal association? *Am J Clin Nutr* 1988;**48**:806–10. https://doi.org/10.1093/ajcn/48.3.806
77. Borgi L, Curhan GC, Willett WC, Hu FB, Satija A, Forman JP. Long-term intake of animal flesh and risk of developing hypertension in three prospective cohort studies. *J Hypertension* 2015;**33**:2231–8. https://doi.org/10.1097/HJH.0000000000000722
78. Tonstad S, Stewart K, Oda K, Batech M, Herring RP, Fraser GE. Vegetarian diets and incidence of diabetes in the Adventist Health Study-2. *Nutr Metab Cardiovasc Dis* 2013;**23**:292–9. https://doi.org/10.1016/j.numecd.2011.07.004
79. Vang A, Singh PN, Lee JW, Haddad EH, Brinegar CH. Meats, processed meats, obesity, weight gain and occurrence of diabetes among adults: findings from Adventist health studies. *Ann Nutr Metab* 2008;**52**:96–104. https://doi.org/10.1159/000121365
80. Pan A, Sun Q, Bernstein AM, Manson JE, Willett WC, Hu FB. Changes in red meat consumption and subsequent risk of type 2 diabetes mellitus: three cohorts of US men and women. *JAMA Intern Med* 2013;**173**:1328–35. https://doi.org/10.1001/jamainternmed.2013.6633
81. Key TJ, Fraser GE, Thorogood M, Appleby PN, Beral V, Reeves G, *et al.* Mortality in vegetarians and nonvegetarians: detailed findings from a collaborative analysis of 5 prospective studies. *Am J Clin Nutr* 1999;**70**:516S–24S. https://doi.org/10.1093/ajcn/70.3.516s
82. Huang T, Yang B, Zheng J, Li G, Wahlqvist ML, Li D. Cardiovascular disease mortality and cancer incidence in vegetarians: a meta-analysis and systematic review. *Ann Nutr Metab* 2012;**60**:233–40. https://doi.org/10.1159/000337301
83. Crowe FL, Appleby PN, Travis RC, Key TJ. Risk of hospitalization or death from ischemic heart disease among British vegetarians and nonvegetarians: results from the EPIC-Oxford cohort study. *Am J Clin Nutr* 2013;**97**:597–603. https://doi.org/10.3945/ajcn.112.044073
84. Kwok CS, Umar S, Myint PK, Mamas MA, Loke YK. Vegetarian diet, Seventh Day Adventists and risk of cardiovascular mortality: a systematic review and meta-analysis. *Int J Cardiol* 2014;**176**:680–6. https://doi.org/10.1016/j.ijcard.2014.07.080
85. Key TJ, Appleby PN, Spencer EA, Travis RC, Roddam AW, Allen NE. Mortality in British vegetarians: results from the European Prospective Investigation into Cancer and Nutrition (EPIC-Oxford). *Am J Clin Nutr* 2009;**89**:S1613–S9. https://doi.org/10.3945/ajcn.2009.26736L
86. Appleby PN, Crowe FL, Bradbury KE, Travis RC, Key TJ. Mortality in vegetarians and comparable nonvegetarians in the United Kingdom. *Am J Clin Nutr* 2016;**103**:218–30. https://doi.org/10.3945/ajcn.115.119461
87. Petermann-Rocha F, Parra-Soto S, Gray S, Anderson J, Welsh P, Gill J, *et al.* Vegetarians, fish, poultry, and meat-eaters: who has higher risk of cardiovascular disease incidence and mortality? A prospective study from UK Biobank. *Eur Heart J* 2020;**42**:1136–43. https://doi.org/10.1093/eurheartj/ehaa939
88. Chang-Claude J, Hermann S, Eilber U, Steindorf K. Lifestyle determinants and mortality in German vegetarians and health-conscious persons: results of a 21-year follow-up. *Cancer Epidemiol Biomarkers Prev* 2005;**14**:963–8. https://doi.org/10.1158/1055-9965.EPI-04-0696
89. Baden MY, Liu G, Satija A, Li Y, Sun Q, Fung TT, *et al.* Changes in plant-based diet quality and total and cause-specific mortality. *Circulation* 2019;**140**:979–91. https://doi.org/10.1161/CIRCULATIONAHA.119.041014
90. Appel LJ, Brands MW, Daniels SR, Karanja N, Elmer PJ, Sacks FM. Dietary approaches to prevent and treat hypertension: a scientific statement from the American Heart Association. *Hypertension* 2006;**47**:296–308. https://doi.org/10.1161/01.HYP.0000202568.01167.B6
91. Oussalah A, Levy J, Berthezène C, Alpers DH, Guéant JL. Health outcomes associated with vegetarian diets: an umbrella review of systematic reviews and meta-analyses. *Clin Nutr* 2020;**39**:3283–307. https://doi.org/10.1016/j.clnu.2020.02.037
92. Wang F, Zheng J, Yang B, Jiang J, Fu Y, Li D. Effects of vegetarian diets on blood lipids: a systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc* 2015;**4**:e002408. https://doi.org/10.1161/JAHA.115.002408
93. Key TJ, Papier K, Tong TYN. Plant-based diets and long-term health: findings from the EPIC-Oxford study. *Proc Nutr Soc* 2022;**81**:190–8. https://doi.org/10.1017/S0029665121003748
94. Parra-Soto S, Ahumada D, Petermann-Rocha F, Boonpoor J, Gallegos JL, Anderson J, *et al.* Association of meat, vegetarian, pescatarian and fish-poultry diets with risk of 19 cancer sites and all cancer: findings from the UK Biobank prospective cohort study and meta-analysis. *BMC Med* 2022;**20**:79. https://doi.org/10.1186/s12916-022-02257-9
95. Key TJ, Appleby PN, Crowe FL, Bradbury KE, Schmidt JA, Travis RC. Cancer in British vegetarians: updated analyses of 4998 incident cancers in a cohort of 32,491 meat eaters, 8612 fish eaters, 18,298 vegetarians, and 2246 vegans. *Am J Clin Nutr* 2014;**100**:378S–85S. https://doi.org/10.3945/ajcn.113.071266
96. Gilsing AM, Weijenberg MP, Goldbohm RA, Dagnelie PC, van den Brandt PA, Schouten LJ. Vegetarianism, low meat consumption and the risk of lung, postmenopausal breast and prostate cancer in a population-based cohort study. *Eur J Clin Nutr* 2016;**70**:723–9. https://doi.org/10.1038/ejcn.2016.25

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97. Cade JE, Taylor EF, Burley VJ, Greenwood DC. Common dietary patterns and risk of breast cancer: analysis from the United Kingdom Women's Cohort Study. *Nutr Cancer* 2010;**62**:300–6. https://doi.org/10.1080/01635580903441246
98. Penniecook-Sawyers JA, Jaceldo-Siegl K, Fan J, Beeson L, Knutsen S, Herring P, *et al.* Vegetarian dietary patterns and the risk of breast cancer in a low-risk population. *Br J Nutr* 2016;**115**:1790–7. https://doi.org/10.1017/S0007114516000751
99. Tantamango-Bartley Y, Knutsen SF, Knutsen R, Jacobsen BK, Fan J, Beeson WL, *et al.* Are strict vegetarians protected against prostate cancer? *Am J Clin Nutr* 2016;**103**:153–60. https://doi.org/10.3945/ajcn.114.106450
100. Heaney RP, McCarron DA, Dawson-Hughes B, Oparil S, Berga SL, Stern JS, *et al.* Dietary changes favorably affect bone remodeling in older adults. *J Am Diet Assoc* 1999;**99**:1228–33. https://doi.org/10.1016/S0002-8223(99)00302-8
101. Iguacel I, Huybrechts I, Moreno LA, Michels N. Vegetarianism and veganism compared with mental health and cognitive outcomes: a systematic review and meta-analysis. *Nutr Rev* 2021;**79**:361–81. https://doi.org/10.1093/nutrit/nuaa030
102. Tsai JH, Huang CF, Lin MN, Chang CE, Chang CC, Lin CL. Taiwanese vegetarians are associated with lower dementia risk: a prospective cohort study. *Nutrients* 2022;**14**:588. https://doi.org/10.3390/nu14030588
103. Yokoyama Y, Nishimura K, Barnard ND, Takegami M, Watanabe M, Sekikawa A, *et al.* Vegetarian diets and blood pressure: a meta-analysis. *JAMA Int Med* 2014;**174**:577–87. https://doi.org/10.1001/jamainternmed.2013.14547
104. Lopez PD, Cativo EH, Atlas SA, Rosendorff C. The effect of vegan diets on blood pressure in adults: a meta-analysis of randomized controlled trials. *Am J Med* 2019;**132**:875–83.e7. https://doi.org/10.1016/j.amjmed.2019.01.044
105. Gibbs J, Gaskin E, Ji C, Miller MA, Cappuccio FP. The effect of plant-based dietary patterns on blood pressure: a systematic review and meta-analysis of controlled intervention trials. *J Hypertension* 2021;**39**:23–37. https://doi.org/10.1097/HJH.0000000000002604
106. Meyer TE, Kovács SJ, Ehsani AA, Klein S, Holloszy JO, Fontana L. Long-term caloric restriction ameliorates the decline in diastolic function in humans. *J Am Coll Cardiol* 2006;**47**:398–402. https://doi.org/10.1016/j.jacc.2005.08.069
107. Xin X, He J, Frontini MG, Ogden LG, Motsamai OI, Whelton PK. Effects of alcohol reduction on blood pressure: a meta-analysis of randomized controlled trials. *Hypertension* 2001;**38**:1112–7. https://doi.org/10.1161/hy1101.093424
108. Viguiliouk E, Kendall CW, Kahleová H, Rahelić D, Salas-Salvadó J, Choo VL, *et al.* Effect of vegetarian dietary patterns on cardiometabolic risk factors in diabetes: a systematic review and meta-analysis of randomized controlled trials. *Clin Nutr* 2019;**38**:1133–45. https://doi.org/10.1016/j.clnu.2018.05.032
109. Barnard ND, Cohen J, Jenkins DJ, Turner-McGrievy G, Gloede L, Jaster B, *et al.* A low-fat vegan diet improves glycemic control and cardiovascular risk factors in a randomized clinical trial in individuals with type 2 diabetes. *Diabetes Care* 2006;**29**:1777–83. https://doi.org/10.2337/dc06-0606
110. Lee YM, Kim SA, Lee IK, Kim JG, Park KG, Jeong JY, *et al.* Effect of a brown rice based vegan diet and conventional diabetic diet on glycemic control of patients with type 2 diabetes: a 12-week randomized clinical trial. *PLoS One* 2016;**11**:e0155918. https://doi.org/10.1371/journal.pone.0155918
111. Barnard ND, Levin SM, Gloede L, Flores R. Turning the waiting room into a classroom: weekly classes using a vegan or a portion-controlled eating plan improve diabetes control in a randomized translational study. *J Acad Nutr Diet* 2018;**118**:1072–9. https://doi.org/10.1016/j.jand.2017.11.017
112. Bunner AE, Wells CL, Gonzales J, Agarwal U, Bayat E, Barnard ND. A dietary intervention for chronic diabetic neuropathy pain: a randomized controlled pilot study. *Nutr Diabetes* 2015;**5**:e158. https://doi.org/10.1038/nutd.2015.8
113. Kahleova H, Matoulek M, Malinska H, Oliyarnik O, Kazdova L, Neskudla T, *et al.* Vegetarian diet improves insulin resistance and oxidative stress markers more than conventional diet in subjects with type 2 diabetes. *Diabet Med* 2011;**28**:549–59. https://doi.org/10.1111/j.1464-5491.2010.03209.x
114. Lee YM, Kim SA, Lee IK, Kim JG, Park KG, Jeong JY, *et al.* Effect of a brown rice based vegan diet and conventional diabetic diet on glycemic control of patients with type 2 diabetes: a 12-week randomized clinical trial. *PLoS One* 2016;**11**:e0155918. https://doi.org/10.1371/journal.pone.0155918
115. Nicholson AS, Sklar M, Barnard ND, Gore S, Sullivan R, Browning S. Toward improved management of NIDDM: a randomized, controlled, pilot intervention using a lowfat, vegetarian diet. *Prev Med* 1999;**29**:87–91. https://doi.org/10.1006/pmed.1999.0529
116. Campbell TM. *Whole-Food, Plant-Based Nutrition Among Women With Metastatic Breast Cancer: A Pilot Study of Recruitment, Retention, and Preliminary Changes in Biomarkers and Symptoms*: University of Rochester; 2018.
117. Kahleova H. Effect of a dietary intervention on intracellular lipid, insulin sensitivity, and glycemic control in type 2 diabetes. https://clinicaltrialsgov/show/NCT04088981. 2019.
118. Wright N. The EDGe (End Diabetes Gisborne) trial. Using the whole-foods, plant-based diet in a community programme for people with obesity and diabetes. 2017. https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=372452&isReview=true.
119. Ornish D, Scherwitz LW, Billings JH, Brown SE, Gould KL, Merritt TA, *et al.* Intensive lifestyle changes for reversal of coronary heart disease. *JAMA* 1998;**280**:2001–7. https://doi.org/10.1001/jama.280.23.2001
120. Gould KL, Ornish D, Scherwitz L, Brown S, Edens RP, Hess MJ, *et al.* Changes in myocardial perfusion abnormalities by positron emission tomography after long-term, intense risk factor modification. *JAMA* 1995;**274**:894–901. https://doi.org/10.1001/jama.1995.03530110056036
121. Huang RY, Huang CC, Hu FB, Chavarro JE. Vegetarian diets and weight reduction: a meta-analysis of randomized controlled trials. *J Gen Intern Med* 2016;**31**:109–16. https://doi.org/10.1007/s11606-015-3390-7
122. Yokoyama Y, Levin SM, Barnard ND. Association between plant-based diets and plasma lipids: a systematic review and meta-analysis. *Nutr Rev* 2017;**75**:683–98. https://doi.org/10.1093/nutrit/nux030
123. Yokoyama Y, Barnard ND, Levin SM, Watanabe M. Vegetarian diets and glycemic control in diabetes: a systematic review and meta-analysis. *Cardiovasc Diagn Ther* 2014;**4**:373–82. https://doi.org/10.3978/j.issn.2223-3652.2014.10.04
124. Aldana SG, Greenlaw R, Salberg A, Merrill RM, Hager R, Jorgensen RB. The effects of an intensive lifestyle modification program on carotid artery intima-media thickness: a randomized trial. *Am J Health Promot* 2007;**21**:510–6. https://doi.org/10.4278/0890-1171-21.6.510
125. Ornish D, Brown SE, Scherwitz LW, Billings JH, Armstrong WT, Ports TA, *et al.* Can lifestyle changes reverse coronary heart disease? The Lifestyle Heart Trial. *Lancet* 1990;**336**:129–33. https://doi.org/10.1016/0140-6736(90)91656-U
126. Shah B, Ganguzza L, Slater J, Newman JD, Allen N, Fisher E, *et al.* The effect of a vegan versus AHA DiEt in coronary artery disease (EVADE CAD) trial: study design and rationale. *Contemp Clin Trials Commun* 2017;**8**:90–8. https://doi.org/10.1016/j.conctc.2017.09.003
127. Shah B, Newman JD, Woolf K, Ganguzza L, Guo Y, Allen N, *et al.* Anti-inflammatory effects of a vegan diet versus the American Heart Association-recommended diet in coronary artery disease trial. *J Am Heart Assoc* 2018;**7**:e011367. https://doi.org/10.1161/JAHA.118.011367
128. Toobert DJ, Glasgow RE, Radcliffe JL. Physiologic and related behavioral outcomes from the Women's Lifestyle Heart Trial. *Ann Behav Med* 2000;**22**:1–9. https://doi.org/10.1007/BF02895162
129. Cassidy S, Kroeger CM, Wang T, Mitra S, Liu C, Ribeiro RV, *et al.* Impact of an intensive lifestyle program on low attenuation plaque and myocardial perfusion in coronary heart disease: a randomised clinical trial protocol. *Nutr Heal Aging* 2022;**7**:9–22. https://doi.org/10.3233/NHA-210146
130. Campbell T, Campbell E, Culakova E, Janelsins MC, Mustian KM, Kamen CS, *et al.* A whole-food, plant-based (WFPB) dietary intervention to improve cancer-related and cardiometabolic outcomes in metastatic breast cancer patients. *J Clin Oncol* 2022;**40**:e24116. https://doi.org/10.1200/JCO.2022.40.16_suppl.e24116
131. Gulley JL. *The Effect of Diet and Exercise on ImmuNotherapy and the Microbiome (EDEN)*: National Cancer Institute (NCI); 2023.
132. Jeppsen E. *A Study on the Effect Diet Has Affecting the Response of Patients Taking N-111 Who Are on a Vegetarian Diet vs a Non-Vegetarian Diet or a Placebo*: Optimal Health Research; 2022.
133. Iyengar N. *Pharmacodynamic Response to Exercise Treatment and Plant-Based Diet in Overweight/Obese Postmenopausal Women With Primary Hormone Receptor Positive Breast Cancer: A Phase 2 Randomized Control Trial*; 2020.
134. Avivi I. *Effect of Vegan Diet and Lifestyle Changes on Indolent Lymphoma During Controlled Waiting Period*: Tel-Aviv Sourasky Medical Center; 2021.
135. Shah U. *A Study of a Plant-Based Diet in People With Monoclonal Gammopathy of Undetermined Significance (MGUS) or Smoldering Multiple Myeloma (SMM)*; 2021.
136. Donaldson MS. Metabolic vitamin B12 status on a mostly raw vegan diet with follow-up using tablets, nutritional yeast, or probiotic supplements. *Ann Nutr Metab* 2000;**44**:229–34. https://doi.org/10.1159/000046689
137. Appleby P, Roddam A, Allen N, Key T. Comparative fracture risk in vegetarians and nonvegetarians in EPIC-Oxford. *Eur J Clin Nutr* 2007;**61**:1400–6. https://doi.org/10.1038/sj.ejcn.1602659
138. Sela I, Yaskolka Meir A, Brandis A, Krajmalnik-Brown R, Zeibich L, Chang D, *et al.* *Wolffia globosa*-mankai plant-based protein contains bioactive vitamin B(12) and is well absorbed in humans. *Nutrients* 2020;**12**:3067. https://doi.org/10.3390/nu12103067
139. Savva SC, Kafatos A. Is red meat required for the prevention of iron deficiency among children and adolescents? *Curr Pediatr Rev* 2014;**10**:177–83. https://doi.org/10.2174/157339631130900008
140. Manary MJ, Krebs NF, Gibson RS, Broadhead RL, Hambidge KM. Community-based dietary phytate reduction and its effect on iron status in Malawian children. *Ann Trop Paediatr* 2002;**22**:133–6. https://doi.org/10.1179/027249302125000850
141. Matkovic V, Ilich JZ, Andon MB, Hsieh LC, Tzagournis MA, Lagger BJ, *et al.* Urinary calcium, sodium, and bone mass of young females. *Am J Clin Nutr* 1995;**62**:417–25. https://doi.org/10.1093/ajcn/62.2.417
142. Tesar R, Notelovitz M, Shim E, Kauwell G, Brown J. Axial and peripheral bone density and nutrient intakes of postmenopausal vegetarian and omnivorous women. *Am J Clin Nutr* 1992;**56**:699–704. https://doi.org/10.1093/ajcn/56.4.699

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143. Itoh R, Suyama Y. Sodium excretion in relation to calcium and hydroxyproline excretion in a healthy Japanese population. *Am J Clin Nutr* 1996;**63**:735–40. https://doi.org/10.1093/ajcn/63.5.735
144. Weaver CM, Proulx WR, Heaney R. Choices for achieving adequate dietary calcium with a vegetarian diet. *Am J Clin Nutr* 1999;**70**:543S–8S. https://doi.org/10.1093/ajcn/70.3.543s
145. Holick MF. Sunlight, UV radiation, vitamin D, and skin cancer: how much sunlight do we need? *Adv Exp Med Biol* 2020;**1268**:19–36. https://doi.org/10.1007/978-3-030-46227-7_2
146. Hahn J, Cook NR, Alexander EK, Friedman S, Walter J, Bubes V, *et al.* Vitamin D and marine omega 3 fatty acid supplementation and incident autoimmune disease: VITAL randomized controlled trial. *BMJ* 2022;**376**:e066452. https://doi.org/10.1136/bmj-2021-066452
147. Chandler PD, Chen WY, Ajala ON, Hazra A, Cook N, Bubes V, *et al.* Effect of vitamin D3 supplements on development of advanced cancer: a secondary analysis of the VITAL randomized clinical trial. *JAMA Netw Open* 2020;**3**:e2025850. https://doi.org/10.1001/jamanetworkopen.2020.25850
148. Chen H, Shen J, Xuan J, Zhu A, Ji JS, Liu X, *et al.* Plant-based dietary patterns in relation to mortality among older adults in China. *Nat Aging* 2022;**2**:224–30. https://doi.org/10.1038/s43587-022-00180-5
149. Kim J, Kim H, Giovannucci EL. Plant-based diet quality and the risk of total and disease-specific mortality: a population-based prospective study. *Clin Nutr* 2021;**40**:5718–25. https://doi.org/10.1016/j.clnu.2021.10.013
150. Thompson AS, Tresserra-Rimbau A, Karavasiloglou N, Jennings A, Cantwell M, Hill C, *et al.* Association of healthful plant-based diet adherence with risk of mortality and major chronic diseases among adults in the UK. *JAMA Netw Open* 2023;**6**:e234714. https://doi.org/10.1001/jamanetworkopen.2023.4714
151. Mirtschink P, Jang C, Arany Z, Krek W. Fructose metabolism, cardiometabolic risk, and the epidemic of coronary artery disease. *Eur Heart J* 2017;**39**:2497–505. https://doi.org/10.1093/eurheartj/ehx518
152. Taylor SR, Ramsamooj S, Liang RJ, Katti A, Pozovskiy R, Vasan N, *et al.* Dietary fructose improves intestinal cell survival and nutrient absorption. *Nature* 2021;**597**:263–7. https://doi.org/10.1038/s41586-021-03827-2
153. O'Donnell M, Mente A, Alderman MH, Brady AJB, Diaz R, Gupta R, *et al.* Salt and cardiovascular disease: insufficient evidence to recommend low sodium intake. *Eur Heart J* 2020;**41**:3363–73. https://doi.org/10.1093/eurheartj/ehaa586
154. Wenstedt EF, Verberk SG, Kroon J, Neele AE, Baardman J, Claessen N, *et al.* Salt increases monocyte CCR2 expression and inflammatory responses in humans. *JCI Insight* 2019;**4**:e130508. https://doi.org/10.1172/jci.insight.130508
155. Mozaffarian D, Katan MB, Ascherio A, Stampfer MJ, Willett WC. Trans fatty acids and cardiovascular disease. *N Engl J Med* 2006;**354**:1601–13. https://doi.org/10.1056/NEJMra054035
156. Gebauer SK, Destaillats F, Dionisi F, Krauss RM, Baer DJ. Vaccenic acid and trans fatty acid isomers from partially hydrogenated oil both adversely affect LDL cholesterol: a double-blind, randomized controlled trial. *Am J Clin Nutr* 2015;**102**:1339–46. https://doi.org/10.3945/ajcn.115.116129
157. Piercy KL, Troiano RP, Ballard RM, Carlson SA, Fulton JE, Galuska DA, *et al.* The physical activity guidelines for Americans. *Jama* 2018;**320**:2020–8. https://doi.org/10.1001/jama.2018.14854
158. Hu Y, Hu FB, Manson JE. Marine omega-3 supplementation and cardiovascular disease: an updated meta-analysis of 13 randomized controlled trials involving 127 477 participants. *J Am Heart Assoc* 2019;**8**:e013543. https://doi.org/10.1161/JAHA.119.013543

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CHAPTER 3: Vegetarian Dietary Patterns and Cardiometabolic Risk in People With or At High Risk of Cardiovascular Disease: A Systematic Review and Meta-analysis

Following the research gaps identified in CHAPTER 2, the aim of this chapter was to perform a systematic review and meta-analysis of randomized controlled trials (RCTs) published to date (by the last date of database searches for this systematic review) to: 1) evaluate the effect of vegetarian diets on cardiometabolic outcomes in individuals with or at high risk of cardiovascular diseases (CVDs); and 2) perform subgroup analyses and assess the effect of different vegetarian diets, different control diets, energy restriction, physical activity, medication changes, and analysis methods (intention-to-treat versus completers approaches). In this work, we combined data from 20 RCTs (n=1878, mean age: 28-64 years) and found that consuming a vegetarian diet for at least six months modestly but significantly improves cardiometabolic outcomes (significant reductions in low-density lipoprotein cholesterol by 0.18mmol/L, hemoglobin A1c by 0.25%, and body weight by 3.4 kg) beyond standard pharmacological therapy, highlighting the potential protective and synergistic effects of vegetarian diets for the primary prevention of CVD. From this study, we identified the following research gaps: 1) most clinical trials failed to document detailed dietary intake; 2) the duration of most included studies was less than six months; 3) there is a paucity of data of plant-based diets and lifestyle interventions in secondary prevention of CVD.

This work has been presented at the American Society for Nutrition (ASN) conference 2022 and I have won two prizes with this presentation:

- Emerging Leaders in Nutrition Science Abstract Recognition Award in 2022
- Winner of Student Interest Group Three-Minute Thesis Competition $300 (US dollars) in 2022

This work has also been presented at the Dietitians Australia (DA) conference 2022.

The abstract of this work has been published in the Current Developments in Nutrition:

> **Wang T**, Kroeger C, Cassidy S, Mitra S, Ribeiro R, Jose S, Masedunskas A, Fontana L. The Effect of Different Vegetarian Diets on Cardiometabolic Profile in People With or At High Risk of Cardiovascular Diseases: A Systematic Review and Meta-Analysis. Curr Dev Nutr. 2022 Jun 14; 6(Suppl 1):53. doi:10.1093/cdn/nzac047.053

The paper of this work has been published in the JAMA Network Open:

> **T. Wang**, C. M. Kroeger, S. Cassidy, S. Mitra, R. Ribeiro, S. Jose, A. Masedunskas, L. Fontana. Vegetarian Dietary Patterns and Cardiometabolic Risk in People With or at High Risk of Cardiovascular Disease: A Systematic Review and Meta-analysis. JAMA Netwwork Open. 2023;6(7):e2325658. doi:10.1001/jamanetworkopen.2023

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The Effect of Different Vegetarian Diets on Cardiometabolic Profile in People With or At High Risk of Cardiovascular Diseases: A Systematic Review and Meta-Analysis

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Abstract

Objectives

This systematic review and meta-analysis assesses the effect of various vegetarian diets on cardiometabolic risk factors (systolic blood pressure (SBP), low-density lipoprotein cholesterol (LDL-C), hemoglobin A1c (HbA1c)) in people with cardiovascular diseases (CVDs) or people with at least two risk factors of CVDs.

Methods

We performed systematic searches in EMBASE, MEDLINE, CINAHL and CENTRAL, from inception until 31st July 2021 for randomised controlled trials of vegetarian diet interventions in people with CVDs or people with at least two risk factors (e.g. being overweight, high blood pressure, high total cholesterol/LDL-C, high blood glucose) of CVDs. Trials had to use a non-vegetarian diet as the comparison diet and measure at least one of these outcomes: LDL-C, HbA1c and SBP. We extracted demographics, study design, sample size, and diet description of intervention and control group from included studies. We assessed the risk of bias of studies using the Cochrane Risk of Bias Assessment Tool 2.0. A random-effects model was used to assess mean changes in LDL-C, HbA1c, SBP and body weight. We evaluated the overall certainty of evidence using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) tool.

Results

Of the 7871 records screened, 29 (20 studies) met our inclusion criteria. Four studies targeted people with CVD, seven focused on people with type 2 diabetes mellitus and the remaining included people with at least two risk factors of CVDs. Meta-analyses showed that consuming vegetarian diets for at least 12 weeks significantly decreased LDL-C, HbA1c, and weight, by 6.8mg/dL (95%CI: −10.7, −3.0), 0.25% (95%CI: −0.43, −0.06), 3.4kg (95%CI: −4.6, −2.2), respectively, but the effect on SBP was not significant (−0.1 mmHg, 95%CI: −2.8, 2.6). The GRADE assessment showed a moderate level of evidence for LDL-C and HbA1c reduction.

Conclusions

Consuming vegetarian diets causes a moderate improvement of LDL-C, HbA1c and body weight in people at high risk of CVD, highlighting the protective effects of vegetarian diets in the primary prevention of CVD. Additional high-quality clinical trials are warranted to further explore the effect of this diet in people with CVD.

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Vegetarian Dietary Patterns and Cardiometabolic Risk in People With or at High Risk of Cardiovascular Disease

A Systematic Review and Meta-analysis

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Abstract

IMPORTANCE Plant-based diets are known to improve cardiometabolic risk in the general population, but their effects on people at high risk of cardiovascular diseases (CVDs) remain inconclusive.

OBJECTIVE To assess the association of vegetarian diets with major cardiometabolic risk factors, including low-density lipoprotein cholesterol (LDL-C), hemoglobin A_{1c} (HbA_{1c}), systolic blood pressure (SBP), and body weight in people with or at high risk of CVDs.

DATA SOURCES This meta-analysis was registered before the study was conducted. Systematic searches performed included Embase, MEDLINE, CINAHL, and CENTRAL from inception until July 31, 2021.

STUDY SELECTION Eligible randomized clinical trials (RCTs) that delivered vegetarian diets in adults with or at high risk of CVDs and measured LDL-C, HbA_{1c} or SBP were included. Of the 7871 records screened, 29 (0.4%; 20 studies) met inclusion criteria.

DATA EXTRACTION AND SYNTHESIS Two reviewers independently extracted data including demographics, study design, sample size, and diet description, and performed risk of bias assessment. A random-effects model was used to assess mean changes in LDL-C, HbA_{1c}, SBP, and body weight. The overall certainty of evidence was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) tool.

MAIN OUTCOMES AND MEASURES Mean differences between groups in changes (preintervention vs postintervention) of LDL-C, HbA_{1c}, and SBP; secondary outcomes were changes in body weight and energy intake.

RESULTS Twenty RCTs involving 1878 participants (range of mean age, 28-64 years) were included, and mean duration of intervention was 25.4 weeks (range, 2 to 24 months). Four studies targeted people with CVDs, 7 focused on diabetes, and 9 included people with at least 2 CVD risk factors. Overall, relative to all comparison diets, meta-analyses showed that consuming vegetarian diets for an average of 6 months was associated with decreased LDL-C, HbA_{1c}, and body weight by 6.6 mg/dL (95% CI, −10.1 to −3.1), 0.24% (95% CI, −0.40 to −0.07), and 3.4 kg (95% CI, −4.9 to −2.0), respectively, but the association with SBP was not significant (−0.1 mm Hg; 95% CI, −2.8 to 2.6). The GRADE assessment showed a moderate level of evidence for LDL-C and HbA_{1c} reduction.

(continued)

Key Points

Question Do vegetarian diets improve the cardiometabolic profile of people with or at high risk of cardiovascular diseases (CVDs)?

Findings In this meta-analysis of 20 randomized clinical trials (with 1878 participants) with an average 6 months of intervention, vegetarian diets were associated with significant improvements in low-density lipoprotein cholesterol by 6.8 mg/dL, hemoglobin A_{1c} by 0.25%, and body weight by 3.4 kg. The GRADE assessment showed a moderate level of evidence for low-density lipoprotein cholesterol and hemoglobin A_{1c} reduction.

Meaning These results suggest that consuming a vegetarian diet may modestly but significantly improve cardiometabolic outcomes beyond standard pharmacological therapy in individuals at high risk of CVDs, highlighting the potential protective and synergistic effects of vegetarian diets for the primary prevention of CVD.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

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Abstract (continued)

CONCLUSIONS AND RELEVANCE In this study, consuming a vegetarian diet was associated with significant improvements in LDL-C, HbA_{1c} and body weight beyond standard therapy in individuals at high risk of CVDs. Additional high-quality trials are warranted to further elucidate the effects of healthy plant-based diets in people with CVDs.

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Introduction

Despite major therapeutic advancements, cardiovascular diseases (CVDs) remain the leading cause of disease burden and escalating health care costs worldwide. Much of this is attributable to the failed implementation of prevention strategies to comprehensively address modifiable risk factors in individuals at risk.[1] In fact, researchers found that most US residents who experienced a myocardial infarction had at least 1 suboptimal CVD risk factor before the event.[2,3] Thus, identifying any practical intervention that can improve cardiometabolic profiles beyond standard therapy in high-risk individuals is critical in CVD prevention and should be one of the main focuses of clinicians, health practitioners, and researchers.

Poor diet is mechanistically linked to an elevated risk of CVD morbidity and mortality.[4] The 2021 dietary guidelines of the American Heart Association emphasize the importance of dietary patterns rich in minimally processed plant foods, fish and seafood, and low-fat dairy products.[5] Different forms of vegetarian diets, which exclude meat and sometimes also eggs and dairy, are becoming increasingly popular because of their health and environmental benefits.[6] Diabetes organizations recommend the consumption of well-balanced vegetarian diets in line with the vast evidence supporting their beneficial effects in preventing type 2 diabetes and some of its metabolic complications.[7-9]

Accumulating data from meta-analyses of randomized clinical trials (RCTs) suggest a role of vegetarian diets in the primary prevention of CVDs in the general population,[10,11] but little is known on their effectiveness in patients with or at high risk of CVDs. Moreover, metabolic outcomes among different vegetarian diets (eg, vegan vs lacto-ovo-vegetarian diets) were not investigated thoroughly,[10-14] with little control for key confounders, such as energy restriction,[12,15,16] physical activity,[12,15] and medication changes.[10,12]

To the best of our knowledge, no meta-analysis of RCTs has been conducted to investigate the association of vegetarian diets with outcomes among people with CVD—indeed, research here has primarily focused on observational studies.[17,18] For example, Glenn et al[17] combined evidence from 7 cohort studies and found that a vegetarian diet was not associated with CVD mortality, with the evidence graded as very low due to indirectness and imprecision. An observational study found that individuals may choose to follow vegetarian diets because of perceived health benefits; these individuals may also present fewer adverse health behaviors (eg, smoking, excessive alcohol intake), and the findings can be affected by these confounders.[18] In general, findings from observational studies provide less strength of evidence, as they cannot rule out residual confounding, and a causal relationship cannot be established.[14,17-19] Thus, our meta-analysis aims to fill in this gap, with subgroup analyses controlling for energy restriction, physical activity, medication use, and the type of control diet.

Methods

This systematic review and meta-analysis was registered with PROSPERO (CRD42021218348) before the study was conducted. Institutional review board approval and informed consent were not required as this was a secondary analysis of deidentified data. We followed the Preferred Reporting

Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline and the AMSTAR-2 checklist[20] for this study.

Search Strategy and Selection Criteria

Search strategy was informed by PICOS criteria (Population, Intervention, Comparator, Outcome, Study design) (eTable 1 in Supplement 1). We performed systematic searches in Embase, MEDLINE, CINAHL and CENTRAL (Cochrane Central Register of Controlled Trials), from inception until July 31, 2021 (eTable 2 in Supplement 1). Hand searches of reference lists of reviews, protocols, abstracts, and gray literature (eg, websites mentioning relevant studies) were performed to supplement searches. The authors of the ongoing trials and abstracts were contacted at least 3 times to retrieve preliminary findings and full manuscripts.

Eligible RCTs delivered vegetarian diets in adults with or at high risk of CVDs and measured low-density lipoprotein cholesterol (LDL-C), hemoglobin A_{1c} (HbA_{1c}), or systolic blood pressure (SBP) were included. Of the 7871 records screened, 29 (0.4%; 20 studies) met inclusion criteria. Two reviewers (T. W. and one of C. K., S. C., A. M., S. M., or R. R.) independently extracted data including demographics, study design, sample size, and diet description, and performed risk of bias assessment.

Statistical Analysis

The primary outcomes are the mean differences between groups in changes (preintervention vs postintervention) in LDL-C, HbA_{1c}, and SBP. The secondary outcomes are changes in body weight, and energy intake. The meta package of R version 1.4.1717 (R Project for Statistical Computing)[21] was used to perform meta-analysis and meta-regression.[22] A random-effects model was used, implemented using the metacont function for mean differences. We estimated the overall pooled effect size based on inverse-variance weighting using a restricted maximum likelihood estimator for the among-study heterogeneity.[23] Confidence intervals are at the 95% level and estimated based on a standard-normal distribution (ie, default method in the meta package). The total heterogeneity was quantified as τ^2 (ie, variance among effect sizes not attributable to sampling). The statistical significance for heterogeneity was assessed by a modified *Q* test, which used the Farebrother method to obtain the distribution of *Q* values, as recommended for mean differences by Kulinskaya et al.[24] We evaluated the overall certainty of evidence using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) tool.

Results

Characteristics of Included Studies

Of the 7871 records screened, 29 articles (20 RCTs; 1878 total participants) were included (**Figure 1**). Reasons for exclusion at the full-text stage are presented in Figure 1 and eTable 3 in Supplement 1. Seven ongoing trials were identified (eTable 4 in Supplement 1); however, preliminary results were not yet available. RCTs were mostly parallel-group trials, except for 2 crossover design studies (**Table**).[31,49] Studies were conducted in the US,[25,26,30-33,38,41,42,44,45,47,51,52] Asia,[36,39,40] Europe,[37,49] or New Zealand,[53] and all published between 1990 and 2021. Sample size ranged from 13 to 291 participants (mean age, 28 to 64 years), and mean duration of intervention was 25.4 weeks (range, 2-24 months).

Of included trials, 4 targeted people with CVDs[25,45,47,52] of which 3 applied the Ornish diet.[25,45,52] This diet is a very low-fat (less than 10% energy from fat), lacto-ovo-vegetarian diet that excludes all animal proteins except for nonfat dairy products and egg whites (Table). Seven studies[26,30,32,37,39,42,44] focused on individuals with type 2 diabetes, and most[26,30,32,39,42,44] delivered a low-fat, vegan diet. This diet excludes all animal products, with vitamin B12 supplemented in some studies[26,32,42,44] to balance nutrient intake. Different vegetarian diets were

delivered in individuals with at least 2 risk factors for CVDs, including vegan diets,[31,38,40,53] lacto-ovo-vegetarian diets[33,36,41,49] and a lacto-vegetarian diet.[51] Energy restrictions were prescribed in several studies[33,36,40,41,49,51] to promote weight loss. Overall, the most commonly prescribed diets were vegan diets,[26,30-32,38-40,42,44,47,53] followed by lacto-ovo-vegetarian diets,[25,33,36,41,45,49,52] and lacto-vegetarian diets.[37,51]

Effects of Vegetarian Diets on LDL-C, HbA_{1c}, SBP, Weight, Energy Intake, and Medication Use

Nineteen studies (1661 participants; trial duration, 8 weeks to 2 years)[25,26,30-33,36-42,45,47,49,51-53] were included in the meta-analysis of LDL-C (**Figure 2**; eFigures 1-14 in Supplement 1). Compared with control diets, consuming a vegetarian diet was associated with significantly decreased LDL-C by 6.6 mg/dL (95% CI, −10.1 to −3.1 mg/dL) in a mean of 6 months of intervention beyond that achieved with standard therapy (to convert LDL-C to millimoles per liter, multiply by 0.0259). However, a moderate but statistically significant among-study heterogeneity was noted (Q = 20788.2; P = .04). We therefore conducted a sensitivity analysis excluding Ornish et al[45] and the effect size remained statistically significant (−5.4 mg/dL; 95% CI, −8.4 to −2.3 mg/dL) (eFigure 1 in Supplement 1). Baseline LDL-C levels were associated with responsiveness to dietary intervention, with greater reductions detected in studies with higher baseline values. Baseline values explained 100% of among-study heterogeneity (P < .001) (eFigure 15 in Supplement 1). The most consistent reduction was observed in people at high risk of CVDs (−9.1 mg/dL; 95% CI, −12.7 to −5.5 mg/dL) (Figure 2). Among all different vegetarian diets, lacto-ovo vegetarian diets were associated with the greatest reduction in LDL-C (−14.1 mg/dL; 95% CI, −24.5 to −3.6 mg/dL) (eFigure 2 in Supplement 1); however, 4 out of 5 trials[33,36,41,49] restricted energy intake. Compared with usual diet, vegetarian diets lowered LDL-C by 12.9 mg/dL (95% CI, −21.4 to −4.5 mg/dL), and this reduction is clinically significant (eFigure 3 in Supplement 1). However, the association of vegetarian diets with LDL-C levels was not significant when compared with active controls (eg, diabetic diet). Vegetarian diets were associated with similar LDL-C reduction in studies with (−7.2 mg/dL; 95% CI, −10.8 to −3.5 mg/dL) and without energy restriction (−6.8 mg/dL; 95% CI, −12.1 to −1.6 mg/dL) (eFigure 4 in Supplement 1). Furthermore, vegetarian diets were associated with lowered LDL-C (−5.9 mg/dL; 95% CI, −10.1 to −1.7 mg/dL) in studies with no physical activity intervention (eFigure 5 in Supplement 1). The association of vegetarian diets with LDL-C was similar among individuals with (−6.1 mg/dL; 95% CI, −10.3 to −2.0 mg/dL) and without (−6.2 mg/dL; 95% CI, −11.0 to −1.4 mg/dL) changes of lipid-lowering medication

Figure 1. Flow Diagram of Study Selection

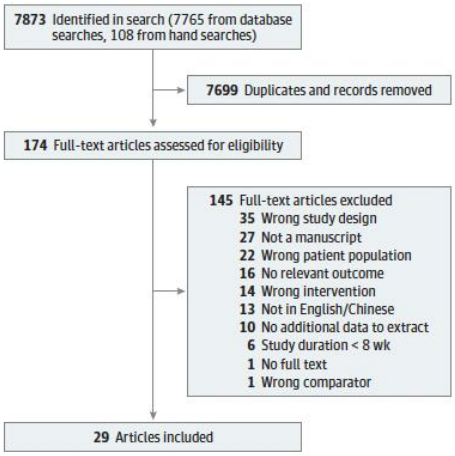


Table. Study Characteristics of Included Randomized Clinical Trials

Source	Country	Study groups (No. randomized)	Participants (intervention/control)			Diet description	Study length and design
			Population condition	Gender	Age, mean (SD), y		
Aldana et al,[25] 2006	US	Dr Ornish Program (46)	CHD	47.8% male	60.9 (9.7)	Very LF, LOV diet (no animal proteins except for nonfat dairy and egg whites); recommend liberal consumption of fruits and vegetables, whole grains, and legumes; daily serving of soy food	1 y, RCT, parallel group
		Traditional cardiac rehabilitation (47)		64.6% male	62.2 (8.9)	No dietary intervention (traditional cardiac rehabilitation)	
Barnard et al,[26-29] 2006	US	LF vegan diet (49)	Type 2 diabetes and being overweight (BMI ≥25)	27 female; 22 male	56.7 (range, 35-82)	No animal products and added fats; fruits and vegetables, grains, and legumes, favor low-GI foods; vitamin B12 supplement (100 µg) every other day	22 wk, RCT, parallel group; 52 wk follow-up
		ADA diet (50)		33 female; 17 male	54.6 (range, 27-80)	Participants with a BMI >25 were prescribed energy deficits of 500-1000 kcal; vitamin B12 supplement (100 µg) every other day	
Barnard et al,[30] 2018	US	LF vegan diet (22)	Type 2 diabetes (HbA_{1c}, 6.5%-10.5%) and being overweight (BMI ≥25)	13 female; 9 male	62 (range, 41-79)	Whole grains, fruits and vegetables, legumes; no animal products and added oils; no restrictions on energy or carbohydrate intake	20 wk RCT, parallel group
		Portion-controlled eating plan (23)		11 female; 12 male	61 (range, 30-75)	Energy limits when needed for weight loss (calorie restricted −500 kcal/d)) and guidance on portion sizes	
Barnard et al, 2021[31]	US	LF vegan diet first (31)	Overweight (BMI, 28-40) and high LDL cholesterol (>100 mg/dL)	22 female; 8 male	58.3 (8.4)	Grains, fruits and vegetables, legumes; no animal products and added oils; daily vitamin B12 supplement (500 mcg) during the vegan phase	16 wk, randomized, crossover trial; 4 wk washout period
		Mediterranean diet first (31)		26 female; 6 male	56.6 (10.9)	Select white meats (with visible fat removed) instead of red meats; use extra virgin olive oil instead of other fats or oils; daily food servings: vegetables ≥2, fresh fruits ≥2-3; weekly food servings: legumes ≥3, fish or shellfish ≥3, nuts or seeds ≥3	
Bunner et al,[32] 2015	US	LF vegan diet + B12 supplement (17)	Type 2 diabetes with painful diabetic neuropathy for ≥6 mo	11 female; 6 male	57 (6)	No animal products; focused on grains, fruits and vegetables, legumes; limited fat intake to 20-30 g/d; favored low-GI foods; daily vitamin B12 supplement (1000 mcg)	20 wk randomized, parallel group, clinical trial
		No intervention + B12 supplement (17)		8 female; 9 male	58 (6)	No dietary change except for daily vitamin B12 supplement (1000 mcg)	
Burke et al,[33-35] 2006	US	SBT + LOV (participant preferred, 36; participant not preferred, 48)	Overweight (BMI, 27-43) and high LDL cholesterol (>100 mg/dL)	73 female (86.9)	45.0 (8.2)	No animal flesh foods; restrict consumption of calories (1200-1500 for women and 1500-1800 for men) and fat (25% of total calories)	12 mo, randomized, parallel group, clinical trial; 6 mo follow up
		SBT (participant preferred, 63[a]; participant not preferred, 50)		86 female (87.8)	43.4 (8.9)	SBT: restrict calories (1200-1500 for women and 1500-1800 for men) and fat (25% of total calories)	
Garousi et al, 2021[36]	Iran	LOV (40)	Overweight (BMI ≥25) and high LDL cholesterol (>100 mg/dL)	13 male; 13 female	43.51 (9.85)	Included protein sources from egg (24%), dairy (19%), gluten (26%), soy (16%), nuts (8%), vegetables, and fruits (7%); no animal flesh foods; calorie restricted (−500 kcal/d)	3 mo (12 wk), randomized, parallel group, clinical trial
		Standard weight loss diet (40)		14 male; 12 female	42.84 (9.85)	Approximately 18% of protein sources from meat and meat products, poultry, fish and seafood, and flesh of any other animal; calorie restricted (−500 kcal/d)	
Kahleova et al,[37] 2010	Czech Republic	Lacto-vegetarian diet (37)	Type 2 diabetes (HbA_{1c}, 6%-11%) and being overweight (BMI, 25-53)	20 female; 17 male	54.6 (7.8)	Grains, fruits and vegetables, legumes; animal products limited to ≤1 portion of LF yogurt/d; vegetarian meals provided in 2 vegetarian restaurants; calorie-restricted (−500 kcal/d); daily vitamin B12 supplement (50 µg).	24 wk, randomized, open, parallel clinical trial; second 12 wk diet were combined with aerobic exercise
		Conventional diabetic diet (37)		19 female; 18 male	57.7 (4.9)	Following dietary guidelines of the Diabetes and Nutrition Study Group of the European Association for the Study of Diabetes; meals were provided; calorie-restricted (−500 kcal/d); daily vitamin B12 supplement (50 µg)	

(continued)

Table. Study Characteristics of Included Randomized Clinical Trials (continued)

Source	Country	Study groups (No. randomized)	Participants (intervention/control)			Diet description	Study length and design
			Population condition	Gender	Age, mean (SD), y		
Kahleova et al,[38] 2020	US	LF vegan diet (122)	Overweight (BMI, 28-40) and high LDL cholesterol (>100 mg/dL)	105 female; 17 male	53 (10)	No animal products or added fats; daily vitamin B12 supplement (500 µg); consisted of fruits and vegetables, grains, legumes	16 wk, RCT using a single-center, open parallel design
		No dietary change (122)		106 female; 16 male	57 (13)	No dietary changes	
Lee et al,[39] 2016	Korea	Vegan diet + brown rice (53)	Type 2 diabetes (HbA_{1c} level, 6.0%-10.0%)	40 female; 6 male	57.5 (7.7) [32-70]	Fruits and vegetables, whole grains, legumes; no animal products, polished rice (white rice) and processed food made of rice or wheat flour; have unpolished rice (brown rice)	3 mo (12 wk), RCT, parallel group
		Conventional diabetic diet (53)		35 female; 12 male	58.3 (7.0) [range, 40-69]	Followed 2011 treatment guidelines by the KDA; restrict individualized daily energy intake based on body weight, physical activity, need for weight control, and compliance	
Liao et al,[40] 2007	Republic of China	Soy low-calorie diet (15)	Overweight (BMI, >26) and high LDL cholesterol (>100 mg/dL)	3 male; 12 female	28.8 (9.1)	Soy protein as the only protein source; provided various soy foods, including drinks, miso, tofu, and vegetarian meat substitutes from markets; 1200 kcal/d	8 wk, RCT, parallel group
		Traditional low-calorie diet (15)		3 male; 12 female	38.0 (11.1)	Two-thirds of total protein consumed was animal protein; 1200 kcal/d	
Mahon et al,[41] 2007	US	LOV plus carbohydrates	Overweight (BMI >25) and high LDL cholesterol (>100 mg/dL)	61 female	58 (2)	1250 kcal/d-1000 kcal/d LOV diet and provided 250 kcal/d portioned nonmeat carbohydrate (shortbread cookies and sugar-coated chocolates)	11-wk protocol: a 2-wk weight maintenance period, followed by a 9-wk period of dietary intervention and energy restriction. RCT, parallel group
		LOV plus beef					
		LOV plus chicken					
		Control				Habitual diet	
Mishra et al,[42,43] 2013	US	LF vegan diet (142)	Overweight (BMI >25) and/or previous diagnosis of type 2 diabetes	110 female; 32 male	44.3 (15.3)	No animal products; minimize added oils; vitamin B12 supplement/d; consisted of fruits and vegetables, whole grains, legumes; no energy restriction; LF vegan menu options made available	18 wk cluster RCT, parallel group
		Usual diet (149)		132 female; 18 male	46.1 (13.6)	No dietary changes; no dietary guidance	
Nicholson et al,[44] 1999	US	LF vegan diet (7)	Noninsulin-dependent diabetes	3 female; 4 male	51 (range, 34-62)	No animal products, added oils and refined carbohydrates; consisted of fruits and vegetables, whole grains, legumes; the diet was adequate in all nutrients except vitamin B12	12 wk RCT, parallel group
		Conventional LF diet (6)		2 female; 2 male	60 (range, 51-74)	Emphasized fish and poultry, rather than red meat	
Ornish et al,[45,46] 1990	US	LF LOV diet (53)	CHD	1 female; 21 male	56.1 (7.5)	Fruits and vegetables, grains, legumes and soybean products; no animal proteins except for nonfat dairy and egg whites; vitamin B12 supplemented	Initially 1 y RCT, but extended the study for an additional 4 y, parallel group
		Usual care (40)		4 female; 15 male	59.8 (9.1)	No lifestyle changes	
Shah et al,[47,48] 2018	US	Vegan diet (50)	CHD; >3/4 with dyslipidemia; >1/2 with hypertension	57 female; 43 male	Median (IQR), 63.0 (57.0-68.0)	The vegan diet: whole-food plant-based diet with no processed foods; no animal products; vitamin B12 fortified soy milk; given vegan cookbook	8 wk randomized, open-label, masked clinical trial, parallel group
		AHA diet (50)		58 female; 42 male	Median (IQR), 59.5 (53.0-67.0)	Given AHA LF, low-cholesterol cookbook	
Sofi et al,[49,50] 2018	Italy	LOV (60)	Overweight (BMI ≥25) and presence of ≥1 of: TC >190 mg/dL; LDL >115 mg/dL, TG >150 mg/dL, glucose levels 110-126 mg/dL	49 female; 11 male	Median, 49.5 (range, 24-70)	No animal products except for eggs and dairy products; included all the other food groups; hypocaloric with respect to the energy requirements of the participants, but completely isocaloric with the Mediterranean diet	6-mo randomized, open, crossover trial with no washout period.
		Mediterranean diet (58)		43 female; 15 male	Median, 52 (range, 21-75)	Consumption of all food groups, including animal flesh foods; hypocaloric with respect to the energy requirements of the participants	3 mo for each intervention.

(continued)

Table. Study Characteristics of Included Randomized Clinical Trials (continued)

Source	Country	Study groups (No. randomized)	Participants (intervention/control)			Diet description	Study length and design
			Population condition	Gender	Age, mean (SD), y		
Tang et al,[51] 2013	US	Normal protein: the lacto-vegetarian diet	Overweight (BMI 25.0-39.9) and high LDL cholesterol (>100 mg/dL)	45 total participants (all male)	44.8 (3.6); Median, 43 (range, 24-75)	No animal flesh foods and egg products; portioned quantities of milk comprising 13% of total protein intake; 0.8 g protein/kg/d	12 wk RCT, parallel group
		High protein: omnivorous			51.0 (2.6); Median, 52 (24-69)	Portioned quantities of cooked lean pork and egg products comprising 40% of total protein intake (25% from pork, 15% from eggs); 1.4 g protein kg/d	
Toobert et al,[52] 2000	US	Prime Time program: very LF, LOV diet (17)	CHD	Female	64 (10)	No animal products other than egg whites and nonfat yogurt; no added oils or other concentrated fats; <10% calories from fat	2 y RCT, parallel group
		Usual care (11)			63 (11)	Usual care	
Wright et al,[53] 2017	New Zealand	Whole food plant-based diet + normal care (33)	Overweight (BMI ≥25) with a diagnosis of type 2 diabetes, CHD, orhypertension, or hypercholesterolemia	22 female; 11 male	56 (9.9)	Fruits and vegetables, whole grains, legumes; no animal products and refined oil; discouraged high-fat plant foods (eg, nuts and avocados), and highly processed foods	6-mo 2-group, parallel RCT
		Normal care (32)		17 female; 15 male	56 (9.5)	Normal care	

Abbreviations: ADA, American Diabetes Associations; AHA, American Heart Associations; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CHD, coronary heart disease; GI, glycemic index; HbA_{1c}, hemoglobin A_{1c}; KDA, Korean Diabetes Association; LDL, low-density lipoprotein cholesterol; LF, low-fat; LOV, lacto-ovo-vegetarian diet; RCT, randomized clinical trial; SBT, standard calorie- and fat-restricted weight loss diet; TC, total cholesterol; TG, triglyceride.

To convert glucose to millimoles per liter, multiply by 0.0555; HbA_{1c} to proportion of total hemoglobin, 0.01; LDL cholesterol to millimoles per liter, 0.0259; total cholesterol to millimoles per liter, 0.0259.

[a] Results for 15 participants discarded.

dosage (eFigure 6 in Supplement 1). Finally, a greater decrease in LDL-C was observed in trials reporting only data of completers (−11.3 mg/dL; 95% CI, −17.0 to −5.6 mg/dL) compared with those that used the intention-to-treat analysis (−5.1 mg/dL; 95% CI, −8.1 to −2.2 mg/dL) (eFigure 7 in Supplement 1). Funnel plot of LDL-C was symmetrical indicating low risk of publication bias (eFigure 16 in Supplement 1).

Ten studies (778 participants; trial duration, 8 weeks to 6 months)[26,31,32,37-39,42,44,47,53] were included in the HbA_{1c} meta-analysis (**Figure 3**, eFigures 17-29 in Supplement 1). Overall, consuming vegetarian diets was associated with decreased HbA_{1c} by 0.24% (95% CI, −0.40 to −0.07) in a mean 6 months of intervention (to convert HbA_{1c} to proportion of total hemoglobin, multiply by 0.01), and the heterogeneity was not statistically significant (Q = 9.22; P = .15), with greater effect observed in studies of people with type 2 diabetes (−0.36%; 95% CI, −0.53 to −0.18) (Figure 3; eFigure 30 in Supplement 1). A reduction in HbA_{1c} (−0.26%; 95% CI, −0.44 to −0.08) was observed in people following a vegan diet[26,31,32,38,39,42,44,47,53] even without energy restriction (eFigures 17 and 18 in Supplement 1). Improvements in HbA_{1c} were also observed when vegetarian diets were compared with both usual (−0.39%; 95% CI, −0.69 to −0.10) and the conventional energy-restricted diabetic diet (−0.26%; 95% CI, −0.48 to −0.05) (eFigure 19 in Supplement 1).[26,37,39] Furthermore, vegetarian diets were associated with improved HbA_{1c} (−0.21%; 95% CI, −0.38 to −0.05) in studies with no physical activity prescription (eFigure 20 in Supplement 1). Finally, the improvement in HbA_{1c} remained significant (−0.27%; 95% CI, −0.49 to −0.05) in studies that used the intention-to-treat analysis (eFigure 21 in Supplement 1). Funnel plot of HbA_{1c} were symmetrical suggesting low risk of publication bias (eFigure 31 in Supplement 1).

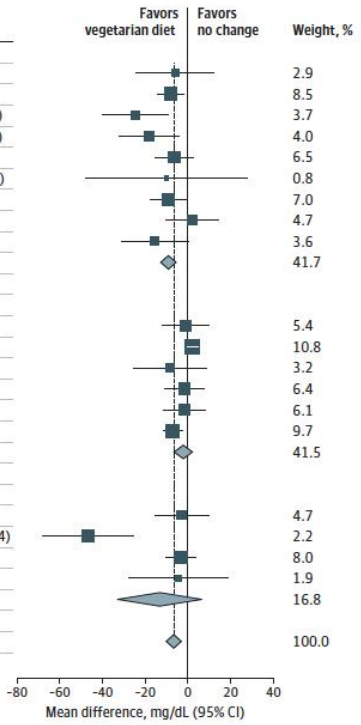
Fourteen studies (955 participants; trial duration, 8 weeks to 2 years)[25,26,30-32,36,39,40,42,44,45,51-53] were included in the meta-analysis of SBP, and the pooled effect size of vegetarian diets was not statistically significant (−0.1 mm Hg; 95% CI, −2.8 to 2.6 mm Hg) (**Figure 4**; eFigures 32-44 in Supplement 1). Among-study heterogeneity was not statistically significant (Q = 3520.37, P = .29) (eFigure 45 in Supplement 1). Funnel plot of SBP was symmetrical, indicating low risk of publication bias (eFigure 46 in Supplement 1).

Sixteen RCTs (1395 participants; trial duration, 8 weeks to 1 year)[25,26,30-33,36,38,40-42,44,45,49,51,53] were included in the meta-analysis of body weight (eFigures 47-52 in Supplement 1). Overall, body weight decreased by 3.4 kg in a mean 6 months of intervention (95% CI, −4.9 to −2.0 kg) in individuals randomized to vegetarian diets (eFigure 47 in Supplement 1). Among-study heterogeneity was very high (Q = 2795.31, df = 15, P < .001) (eFigure 53 in Supplement 1). The greatest reduction was observed in people at high risk of CVD (−3.6 kg; 95% CI, −5.8 to −1.4 kg), followed by people with type 2 diabetes (−2.8 kg; 95% CI, −4.2 to −1.4 kg). Paradoxically, a greater reduction was observed in interventions without energy restriction (−4.7 kg; 95% CI, −6.6 to −2.7 kg) when compared with energy-restricted vegetarian diets (−1.8 kg; 95% CI, −3.3 to −0.2 kg) (eFigure 48 in Supplement 1). However, it is important to note that 6 out of 10 studies[25,32,38,42,45,53] of vegetarian diets without energy restriction used usual diet as the comparison group; whereas in 5 out of 6 trials[33,36,40,49,51] of energy-restricted vegetarian diets, omnivorous energy-restricted interventional diet (eg, diabetic diet) were the comparison group. This was consistent with our results that showed how vegetarian diets were associated with greater weight reduction compared with usual diets (−5.5 kg; 95% CI, −7.7 to −3.2 kg) than with energy-restricted interventional diet (−1.4 kg; 95% CI, −2.4 to −0.4 kg) (eFigure 49 in Supplement 1). Funnel plot of weight was symmetrical indicating low risk of publication bias (eFigure 54 in Supplement 1).

Finally, individuals on energy-unrestricted vegetarian diets[38,42,45,52] significantly reduced energy intake compared with the usual diet (−275.7 kcal; 95% CI, −376.5 to −175.0 kcal) (eFigures 55 and 56 in Supplement 1). Funnel plot of energy intake was symmetrical, suggesting low risk of publication bias (eFigure 57 in Supplement 1).

Figure 2. Random Effects Model Meta-Analysis for Changes in Low-Density Lipoprotein-Cholesterol Concentrations Comparing Vegetarian Diets Intervention and All Comparison Diets, Grouped by Disease Status of Participants

Source	Experimental: Total participants	Experimental: Mean (SD), mg/dL	Control: Total participants	Control: Mean (SD), mg/dL	Mean difference, mg/dL (95% CI)	Weight, %
CVD risk						
Barnard et al,[31] 2021	24	-11.8 (27.1)	28	-5.9 (39.3)	-5.9 (-24.1 to 12.3)	2.9
Burke et al,[34] 2006	84	-6.2 (20.9)	98	1.9 (21.3)	-8.1 (-14.3 to -2.0)	8.5
Garousi et al,[36] 2021	37	-21.2 (24.3)	38	3.4 (40.8)	-24.6 (-39.8 to -9.4)	3.7
Kahleova et al,[38] 2020	117	-15.5 (74.6)	106	2.7 (22.4)	-18.2 (-32.4 to -4.0)	4.0
Liao et al,[40] 2007	15	-15.4 (7.7)	15	-9.0 (16.5)	-6.4 (-15.6 to 2.8)	6.5
Mahon et al,[41] 2007	14	-20.0 (50.0)	11	-10.0 (46.0)	-10.0 (-47.7 to 27.7)	0.8
Sofi et al,[49] 2018	54	-7.0 (22.9)	53	2.1 (20.8)	-9.1 (-17.4 to -0.8)	7.0
Tang et al,[51] 2013	21	-20.0 (22.9)	22	-22.0 (18.8)	2.0 (-10.5 to 14.5)	4.7
Wright et al,[53] 2017	25	-30.9 (28.2)	24	-15.5 (27.5)	-15.5 (-31.1 to 0.1)	3.6
Random effects model	391		395		-9.1 (-12.7 to -5.5)	41.7
Heterogeneity: τ^2 = 0						
Type 2 diabetes						
Barnard et al,[26] 2006	49	-16.4 (30.6)	48	-15.4 (25.1)	-1.0 (-12.1 to 10.1)	5.4
Barnard et al,[30] 2018	14	-11.2 (3.7)	15	-13.4 (3.7)	2.2 (-0.5 to 4.9)	10.8
Bunner et al,[32] 2015	17	-7.8 (28.9)	17	0.4 (21.0)	-8.2 (-25.2 to 8.8)	3.2
Kahleova et al,[37] 2010	37	-7.7 (22.0)	37	-6.2 (18.6)	-1.5 (-10.8 to 7.7)	6.4
Lee et al,[39] 2016	46	-2.8 (17.8)	47	-1.0 (29.3)	-1.8 (-11.6 to 8.0)	6.1
Mishra et al,[43] 2013	142	-8.1 (21.4)	149	-0.9 (17.1)	-7.2 (-11.7 to -2.7)	9.7
Random effects model	305		313		-2.2 (-6.5 to 2.1)	41.5
Heterogeneity: τ^2 = 13.3						
CVD						
Aldana et al,[25] 2006	46	5.5 (38.1)	47	8.3 (21.2)	-2.8 (-15.3 to 9.8)	4.7
Ornish et al,[45] 1990	21	-56.5 (38.6)	18	-9.7 (29.5)	-46.8 (-68.2 to -25.4)	2.2
Shah et al,[47] 2018	50	-6.1 (18.6)	50	-2.7 (16.8)	-3.4 (-10.3 to 3.5)	8.0
Toobert et al,[52] 2000	14	-10.9 (23.9)	11	-6.3 (33.1)	-4.6 (-27.8 to 18.6)	1.9
Random effects model	131		126		-13.2 (-33.0 to 6.6)	16.8
Heterogeneity: τ^2 = 336.8						
Random effects model	827		834		-6.6 (-10.1 to -3.1)	100.0
Heterogeneity: τ^2 = 28.37						
Test for subgroup differences: χ^2_2 = 6.33, df = 2 (P = .04)						



CVD indicates cardiovascular disease.

It should be noted that most participants included in the studies (14 total studies)[25,26,30-33,37-39,42,44,47,52,53] were taking medication for management of suboptimal cardiometabolic profiles at enrollment (eTable 5 in Supplement 1). Eight RCTs[26,30-33,37,44,53] found a reduction in medication dose for hyperglycemia, dyslipidemia, and/or hypertension, although their improvements in LDL-C and HbA_{1c} did not reach clinical significance. In contrast, 2 RCTs[36,49] excluded patients on medications that could influence cardiometabolic outcomes; these studies significantly improved SBP and LDL-C.

Diet Quality and Adherence of Trials

Thirteen studies[25,26,30-32,37-39,42,44,45,47,53] emphasized the consumption of plant-based whole foods (Table). eTable 6 in Supplement 1 shows comprehensive dietary data of all included trials. Most studies[26,30,31,33,36-42,44,45,47,49,52,53] used a 3-day food record or validated 24-hour recall to collect dietary data. However, key macronutrients intake was not assessed thoroughly, and this limits the capacity to evaluate diet quality and adherence. More than one-third of included studies[25,32,33,38,40,41,51-53] did not report saturated fat intake and/or total cholesterol intake; nearly half of the trials[25,30,32,33,45,49,51-53] did not report dietary fiber intake; only 2 studies[26,47] reported trans fatty acid intake; finally, only 1 trial[31] reported alcohol intake. In most of the trials that carefully measured these macronutrients, a significant improvement in saturated fat, total cholesterol, and dietary fiber intake was found.

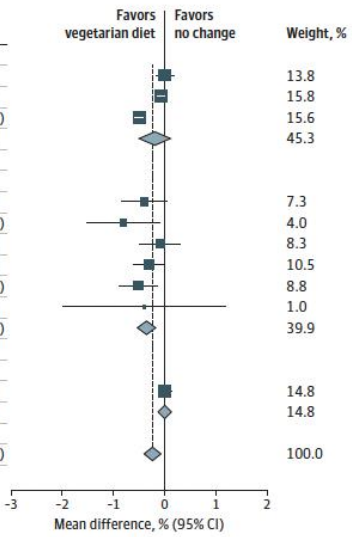
Risk of Bias Assessment and GRADE Quality Rating

eFigure 58 in Supplement 1 shows the risk of bias assessment (the detailed descriptions can be found in eTable 7 in Supplement 1). Only 8 trials[26,30,31,37,38] clearly described the randomization process; 12 studies[25,30,31,36,37,39,41,44,47,49,51,52] failed to present any deviations from the intended intervention; 6 studies[25,31,36,41,44,52] raised bias concern in missing outcome data and all studies performed well in terms of outcome measurement. Indeed, our primary outcomes were objective measurements that are unlikely to be influenced by assessors' knowledge of group allocation. Finally, 11

Figure 3. Random Effects Model Meta-Analysis for Changes in Hemoglobin A_{1c} Comparing Vegetarian Diets Intervention and All Comparison Diets, Grouped by Disease Status of Participants

Source	Experimental: Total participants	Experimental: Mean (SD, %)	Control: Total participants	Control: Mean (SD), %	Mean difference, % (95% CI)	Weight, %
CVD risk						
Barnard et al,[31] 2021	24	-0.10 (0.2)	28	-0.10 (0.4)	0.00 (-0.17 to 0.17	13.8
Kahleova et al,[38] 2020	117	-00.6 (0.3)	106	0.01 (0.2)	-0.07 (-0.15 to 0.01)	15.8
Wright et al,[53] 2017	25	-0.30 (0.2)	24	0.20 (0.1)	-0.50 (-0.59 to -0.41)	15.6
Random effects model	166		158		-0.19 (-0.50 to 0.11)	45.3
Heterogeneity: $\tau^2 = 0.07$						
Type 2 diabetes						
Barnard et al,[26] 2006	49	-1.00 (1.2)	50	-0.60 (1.1)	-0.40 (-0.85 to 0.05)	7.3
Bunner et al,[32] 2015	17	-0.80 (1.2)	17	0.00 (0.9)	-0.80 (-1.51 to -0.09)	4.0
Kahleova et al,[37] 2010	37	-0.68 (0.9)	37	-0.59 (0.9)	-0.09 (-0.49 to 0.31)	8.3
Lee et al,[39] 2016	46	-0.50 (0.8)	47	-0.20 (0.7)	-0.30 (-0.61 to 0.01)	10.5
Mishra et al,[43] 2013	21	-0.60 (0.8)	22	-0.08 (0.4)	-0.52 (-0.90 to -0.14)	8.8
Nicholson et al,[44] 1999	7	-1.40 (1.7)	4	-1.00 (1.0)	-0.40 (-2.00 to 1.20)	1.0
Random effects model	177		177		-0.36 (-0.53 to -0.18)	39.9
Heterogeneity: $\tau^2 = 0$						
CVD						
Shah et al,[25] 2018	50	-0.17 (0.3)	50	-0.17 (0.4)	00.0 (-0.13 to 0.13)	14.8
Random effects model	50		50		00.0 (-0.13 to 0.13)	14.8
Heterogeneity: NA						
Random effects model	393		385		-0.24 (-0.40 to -0.07)	100.0

Heterogeneity: $\tau^2 = 0.04$
Test for subgroup differences: $\chi^2_2 = 10.12$, $df = 2$ ($P < .01$)



CVD indicates cardiovascular disease; NA, not applicable.

studies[25,30-33,37,41,44,47,49,51] selectively reported outcomes. Overall, only 3 studies[26,38,53] rated as having a low risk of bias, and the majority[25,30,31,33,36,37,41,44,47,49,51,52] rated as having a high risk of bias.

eTables 8-11 in Supplement 1 show the GRADE assessment for outcomes by different populations. We did not rate down studies for lack of masking because it is impossible to mask participants in nutritional trials targeting whole dietary patterns. Overall, the level of evidence was rated moderate for LDL-C and HbA_{1c} reduction, and low for SBP and weight reduction (eTable 12 in Supplement 1). However, a high level of evidence for LDL-C reduction was found in people at high risk of CVD, with the mean difference close to clinical significance (cut point of 10 mg/dL). In contrast, in this group, the evidence of reduction in HbA_{1c}, SBP, and weight was rated very low due to inconsistency (high heterogeneity) and imprecision (sample size under 400 and mean difference includes zero). In individuals with type 2 diabetes, the certainty of the evidence was rated moderate for a reduction in HbA_{1c} and an increase in SBP. Note that 4 of 6 studies[26,30,39,44] included in the GRADE assessment of SBP used active control as the comparison diet. We found low evidence for LDL-C and weight reduction in people with type 2 diabetes. Finally, in people with CVD, the certainty of the evidence was low in LDL-C and SBP reduction. The outcomes and funding sources of included studies are described in eTable 13 and eTable 14 in Supplement 1.

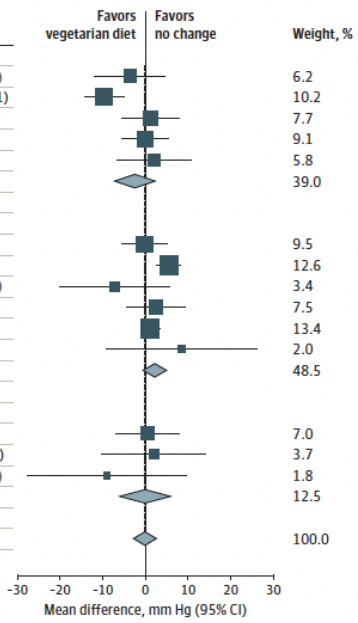
Discussion

Findings from pharmacological randomized trials of statins, antidiabetic, and antihypertensive drugs have clearly shown that lowering cholesterol, glucose, and blood pressure levels exerts major antiatherosclerotic and nephro-protective effects.[54,55] The results of this meta-analysis demonstrate that consuming a vegetarian diet exerts a modest but significant effect in concomitantly reducing

Figure 4. Random Effects Model Meta-Analysis for Changes in Systolic Blood Pressure Comparing Vegetarian Diets Intervention and All Comparison Diets, Grouped by Disease Status of Participants

Source	Experimental: Total participants	Experimental: Mean (SD), mm Hg	Control: Total participants	Control: Mean (SD), mm Hg	Mean difference, mm Hg (95% CI)	Weight, %
CVD risk						
Barnard et al,[31] 2021	24	-10.8 (15.2)	28	-7.2 (15.1)	-3.6 (-11.8 to 4.6)	6.2
Garousi et al,[36] 2021	37	-6.6 (10.6)	38	3.1 (9.9)	-9.7 (-14.3 to -5.1)	10.2
Liao et al,[40] 2007	15	2.9 (6.1)	15	1.6 (11.7)	1.3 (-5.4 to 8.0)	7.7
Tang et al,[51] 2013	21	-11.0 (9.2)	22	-11.0 (9.4)	0.0 (-5.5 to 5.5)	9.1
Wright et al,[53] 2017	25	-2.0 (14.5)	24	-4.0 (16.6)	2.0 (-6.7 to 10.7)	5.8
Random effects model	122		127		-2.5 (-7.2 to 2.3)	39.0
Heterogeneity: $\tau^2 = 18.0$						
Type 2 diabetes						
Barnard et al,[26] 2006	48	-3.8 (12.6)	50	-3.6 (13.7)	-0.2 (-5.4 to 5.0)	9.5
Barnard et al,[30] 2018	9	-1.6 (2.9)	13	-7.1 (3.9)	5.5 (2.7 to 8.3)	12.6
Bunner et al,[32] 2015	17	-11.5 (22.5)	17	-4.3 (15.0)	-7.2 (-20.1 to 5.7)	3.4
Lee et al,[39] 2016	46	1.0 (14.9)	47	-1.5 (18.7)	2.5 (-4.4 to 9.4)	7.5
Mishra et al,[43] 2013	142	-1.7 (8.3)	149	-2.8 (11.0)	1.1 (-1.1 to 3.3)	13.4
Nicholson et al,[44] 1999	7	-10.4 (10.8)	4	-18.9 (15.9)	8.5 (-9.1 to 26.1)	2.0
Random effects model	269		280		2.2 (-0.6 to 5.0)	48.5
Heterogeneity: $\tau^2 = 4.48$						
CVD						
Aldana et al,[25] 2006	46	-5.0 (18.6)	47	-5.5 (17.6)	0.6 (-6.8 to 7.9)	7.0
Ornish et al,[45] 1990	21	-7.0 (13.0)	18	-9.0 (23.6)	2.0 (-10.2 to 14.2)	3.7
Toobert et al,[52] 2000	14	-7.0 (21.5)	11	2.0 (25.2)	-9.0 (-27.7 to 9.7)	1.8
Random effects model	81		76		-0.1 (-6.1 to 5.9)	12.5
Heterogeneity: $\tau^2 = 0$						
Random effects model	472		483		-0.1 (-2.8 to 2.6)	100.0
Heterogeneity: $\tau^2 = 12.9$						

Test for subgroup differences: $\chi^2_2 = 2.85$, $df = 2$ ($P = .24$)



CVD indicates cardiovascular disease.

multiple key risk factors, including LDL-C, HbA_{1c}, and body weight, especially in high-risk patients. In population-stratified analysis, the greatest reduction in LDL-C was observed in individuals at high risk of CVD. Vegetarian diets were most effective in glycemic control among people with type 2 diabetes, and led to favorable changes in weight in people at high risk of CVD and in those with type 2 diabetes, suggesting that vegetarian diets might have a synergistic (or at least nonantagonistic) use in potentiating the effects of optimal drug therapy in the prevention and treatment of a range of cardiometabolic diseases.

To the best of our knowledge, this meta-analysis is the first that generates evidence from RCTs to assess the association of vegetarian diets with outcomes in people affected by CVDs. Previous meta-analyses of RCTs reported a favorable association of vegetarian diets with LDL-C (−12.2 mg/dL; 95% CI, −17.7 to −6.7 mg/dL),[56] HbA_{1c} (−0.29%; 95% CI, −0.45 to −0.12%),[16] SBP (−2.5 mm Hg; 95% CI, −3.6 to −1.4 mm Hg),[12] and body weight (−2.2 kg; 95% CI, −2.8 to −1.2 kg),[10] which is consistent with our findings in terms of LDL-C, HbA_{1c}, and body weight improvement. However, most prior meta-analyses did not stratify populations by disease status,[10,56] type of vegetarian diet,[16] nor comparison diet.[10,12,16,56] Moreover, important confounders such as energy restriction,[12,15,16,56] physical activity,[12,15,16,56] or changes in medication use[10,12,16] were not controlled for. For instance, Yoko et al[56] reported a greater improvement in LDL-C, but 7 out of the 17 studies targeted general population, and 5 studies had a duration of less than 8 weeks. To fill in this research gap, our meta-analysis only included mid- to long-term trials (ie, longer than 8 weeks) of patients with or at high risk of CVD.

Interestingly, we did not observe a significant change in SBP, consistent with the findings of previous meta-analyses,[57,58] suggesting that diet quality plays a major role in lowering blood pressure, independent of animal food consumption, as the DASH diet trial demonstrated.[59] Different from the general population, most patients included in our study[25,26,30-33,37-39,42,44,47,52,53] took medications to manage their hypertension, hyperglycemia, and/or dyslipidemia at trial enrollment. Eight RCTs[26,30-33,37,44,53] reported a decrease in medication dose due to intervention effect. Although our results show an overall improvement in LDL-C, HbA_{1c}, and weight, independent of energy restriction, the changes in LDL-C and HbA_{1c} did not reach the clinically significance as per cutoff target. In fact, the use of glucose, lipid, and blood pressure-lowering drugs, and the reduction in medication dosage, may obscure the favorable effect on cardiometabolic outcomes induced by vegetarian diets, implying a larger actual effect size. This hypothesis is supported by 2 RCTs[36,49] in our meta-analysis that required patients not to take medication that could influence cardiometabolic outcomes; these studies significantly improved SBP and LDL-C.

Potential Mechanisms

There are different forms of vegetarian diets: pesco-vegetarian diets eliminate animal products except for fish and seafood; lacto-ovo-vegetarians exclude meat and fish but not dairy products and eggs; vegans eliminate all animal food including honey. Well-balanced and adequately supplemented vegetarian (and vegan) diets can have multiple health benefits, including lower intake of: saturated fat,[60] L-carnitine and choline (precursors of the atherogenic TMAO),[61] and branch chain amino acids (promoters of insulin resistance[62,63] and platelet activation via tropomodulin-3 propionylation).[64] In our meta-analysis, 12 studies emphasized low-fat content, which may in part contribute to the observed improvement in LDL-C. Depending on their design, these diets may also be high in dietary fiber, sterols, mono- and polyunsaturated fatty acids, potassium, magnesium, phytochemicals, and have lower energy density and lower scores on the glycemic index.[7,65,66] Indeed, not all vegetarian diets could be considered healthy. For instance, more than one-third of the studies included in our meta-analysis did not emphasize the importance of consuming minimally processed plant-based whole foods. Vegetarian diets, particularly those practiced for ethical reasons or focused on convenience, may contain high levels of so-called empty calories, refined carbohydrates, hydrogenated oils, high-fructose corn syrup, sucrose or artificial sweeteners and salt. We were unable to perform a thorough evaluation of diet quality and adherence for the studies included in our

meta-analysis because of limited dietary data (eTable 6 in Supplement 1). Therefore, it is possible that some diets were of poor quality, which could explain the modest reductions in body weight and HbA_{1c}, and no significant change in SBP. Furthermore, consumption of plant-based diets that emphasize energy-dense high–glycemic index refined carbohydrates, deep-fried foods rich in trans fatty acids and salty take-away meals are associated with a 32% higher risk of coronary heart disease[67] as well as high risk of type 2 diabetes.[68]

Strengths and Limitations

The strengths of this study included: (1) to our knowledge, this is the first meta-analysis generating evidence of vegetarian diets from RCTs in people with CVDs; (2) we strictly followed a prespecified protocol; (3) we conducted a rigorous search using 4 databases, including trials registries, supplemented by hand searches; (4) we performed comprehensive subgroup analyses to examine people with different disease status and the effect of different vegetarian diets, control diets, energy restriction, physical activity, medication, and analyses method; (5) we contacted authors of included studies to extract unpublished data, and to improve the accuracy of meta-analysis calculations; (6) we used the GRADE approach to assess the overall certainty of the evidence for each cardiometabolic outcome in people with different disease status; and (7) we published the R script for meta-analysis and shared the data set, hence our findings are transparent and reproducible (eAppendix in Supplement 2).

This article had several limitations. Only 4 trials (each of them with 100 participants or less) investigated vegetarian diets in patients with CVDs, of which 3 required SD imputation as these could not be obtained from authors. Second, although we conducted comprehensive subgroup analyses, the results could be limited by the relatively small sample sizes (200 participants or less) of the subgroups as reflected by the GRADE assessment. Furthermore, these subgroup analyses did not reach the required sample size to draw solid conclusions, and some of them had high heterogeneity in the pooled estimate. Third, we were not able to assess adherence and diet quality thoroughly due to limited dietary data. Future research should fully document dietary data including energy, macronutrients, micronutrients, and ideally food groups and other relevant information (eg, cooking methods) to allow for a thorough assessment of adherence and diet quality. Fourth, many of the studies included in this meta-analysis emphasized a low-fat diet, and data on the effectiveness of vegetarianism combined with higher or moderate fat intake on cardiometabolic health are limited. Fifth, most of included studies were conducted in Western countries (17 studies) and mostly in the US (14 studies), which could limit the generalizability of our findings to other populations. Past research revealed that the quality of vegetarian diets varied between South Asian and American with vegetarians in the US consistently consuming healthier food groups than South Asian vegetarians.[69] Thus, our findings should be cautiously interpreted when applied to other populations. Sixth, most included studies had a trial duration between 8 weeks to 6 months, and there is a lack of studies investigating long-term adherence (ie, beyond 6 months) to vegetarian diets on cardiometabolic health in individuals at high risk of CVD. Seventh, although the detected publication bias was low and we conducted a rigorous search, we cannot rule out the possibility of missing unpublished data. Eighth, only studies published in English and Chinese were included, and trials published in other languages were likely to have been missed (eTable 12 in Supplement 1).

Conclusions

In summary, our findings contribute important information to the development of clinical guidelines in cardiometabolic risk factors management as they demonstrate that consuming a vegetarian diet was associated with significant reductions in LDL-C, HbA_{1c} and body weight, beyond standard therapy, in patients with or at high risk of CVDs. The greatest improvements in HbA_{1c} and LDL-C were observed in individuals with type 2 diabetes and people at high risk of CVD, highlighting the potential

protective and synergistic effects of vegetarian diets for the primary prevention of CVD. Well-designed nutrition clinical trials with comprehensive dietary information are warranted to investigate the full effect of high-quality vegetarian diets in combination with optimal pharmacological therapy in people with CVDs.

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REFERENCES

1. Timmis A, Vardas P, Townsend N, et al; Atlas Writing Group, European Society of Cardiology. European Society of Cardiology: cardiovascular disease statistics 2021. *Eur Heart J*. 2022;43(8):716-799. doi:10.1093/eurheartj/ehab892

2. Greenland P, Knoll MD, Stamler J, et al. Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. *JAMA*. 2003;290(7):891-897. doi:10.1001/jama.290.7.891

3. Lloyd-Jones DM, Leip EP, Larson MG, et al. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. *Circulation*. 2006;113(6):791-798. doi:10.1161/CIRCULATIONAHA.105.548206

4. Visseren FLJ, Mach F, Smulders YM, et al; ESC National Cardiac Societies; ESC Scientific Document Group. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J*. 2021;42(34):3227-3337. doi:10.1093/eurheartj/ehab484

5. Lichtenstein AH, Appel LJ, Vadiveloo M, et al. 2021 dietary guidance to improve cardiovascular health: a scientific statement from the American Heart Association. *Circulation*. 2021;144(23):e472-e487. doi:10.1161/CIR.0000000000001031

6. Willett W, Rockström J, Loken B, et al. Food in the Anthropocene: the EAT-Lancet Commission on healthy diets from sustainable food systems. *Lancet*. 2019;393(10170):447-492. doi:10.1016/S0140-6736(18)31788-4

7. Craig WJ, Mangels AR; American Dietetic Association. Position of the American Dietetic Association: vegetarian diets. *J Am Diet Assoc*. 2009;109(7):1266-1282. doi:10.1016/j.jada.2009.05.027

8. Dyson PA, Twenefour D, Breen C, et al. Diabetes UK evidence-based nutrition guidelines for the prevention and management of diabetes. *Diabet Med*. 2018;35(5):541-547. doi:10.1111/dme.13603

9. Sievenpiper JL, Chan CB, Dworatzek PD, Freeze C, Williams SL; Diabetes Canada Clinical Practice Guidelines Expert Committee. Nutrition therapy. *Can J Diabetes*. 2018;42(suppl 1):S64-S79. doi:10.1016/j.jcjd.2017.10.009

10. Huang R-Y, Huang C-C, Hu FB, Chavarro JE. Vegetarian diets and weight reduction: a meta-analysis of randomized controlled trials. *J Gen Intern Med*. 2016;31(1):109-116. doi:10.1007/s11606-015-3390-7

11. Kwok CS, Umar S, Myint PK, Mamas MA, Loke YK. Vegetarian diet, Seventh Day Adventists and risk of cardiovascular mortality: a systematic review and meta-analysis. *Int J Cardiol*. 2014;176(3):680-686. doi:10.1016/j.ijcard.2014.07.080

12. Lee KW, Loh HC, Ching SM, Devaraj NK, Hoo FK. Effects of vegetarian diets on blood pressure lowering: a systematic review with meta-analysis and trial sequential analysis. *Nutrients*. 2020;12(6):1604. doi:10.3390/nu12061604

13. Schwingshackl L, Chaimani A, Schwedhelm C, et al. Comparative effects of different dietary approaches on blood pressure in hypertensive and pre-hypertensive patients: a systematic review and network meta-analysis. *Crit Rev Food Sci Nutr*. 2019;59(16):2674-2687. doi:10.1080/10408398.2018.1463967

14. Huang T, Yang B, Zheng J, Li G, Wahlqvist ML, Li D. Cardiovascular disease mortality and cancer incidence in vegetarians: a meta-analysis and systematic review. *Ann Nutr Metab*. 2012;60(4):233-240. doi:10.1159/000337301

15. Wang F, Zheng J, Yang B, Jiang J, Fu Y, Li D. Effects of vegetarian diets on blood lipids: a systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc*. 2015;4(10):e002408. doi:10.1161/JAHA.115.002408

16. Viguiliouk E, Kendall CWC, Kahleová H, et al. Effect of vegetarian dietary patterns on cardiometabolic risk factors in diabetes: a systematic review and meta-analysis of randomized controlled trials. *Clin Nutr*. 2019;38(3):1133-1145. doi:10.1016/j.clnu.2018.05.032

17. Glenn AJ, Viguiliouk E, Seider M, et al. Relation of vegetarian dietary patterns with major cardiovascular outcomes: a systematic review and meta-analysis of prospective cohort studies. *Front Nutr*. 2019;6:80. doi:10.3389/fnut.2019.00080

18. Benatar JR, Stewart RAH. Cardiometabolic risk factors in vegans; a meta-analysis of observational studies. *PLoS One*. 2018;13(12):e0209086. doi:10.1371/journal.pone.0209086

19. Jabri A, Kumar A, Verghese E, et al. Meta-analysis of effect of vegetarian diet on ischemic heart disease and all-cause mortality. *Am J Prev Cardiol*. 2021;7:100182. doi:10.1016/j.ajpc.2021.100182

20. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ*. 2017;358:j4008. doi:10.1136/bmj.j4008

21. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. *Evid Based Ment Health*. 2019;22(4):153-160. doi:10.1136/ebmental-2019-300117

22. Wang T, Kroeger CM, Cassidy S, Mitra S, et al. Veg_CVD_JAMA-Network-Open Repository. June 8, 2023. Accessed June 8, 2023. https://github.com/sylviawt/Veg_CVD_JAMA-Network-Open

23. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188. doi:10.1016/0197-2456(86)90046-2

24. Kulinskaya E, Hoaglin DC, Bakbergenuly I, Newman J. A Q statistic with constant weights for assessing heterogeneity in meta-analysis. *Res Synth Methods*. 2021;12(6):711-730. doi:10.1002/jrsm.1491

25. Aldana SG, Greenlaw R, Salberg A, Merrill RM, Hager R, Jorgensen RB. The effects of an intensive lifestyle modification program on carotid artery intima-media thickness: a randomized trial. *Am J Health Promot*. 2007;21(6):510-516. doi:10.4278/0890-1171-21.6.510

26. Barnard ND, Cohen J, Jenkins DJ, et al. A low-fat vegan diet improves glycemic control and cardiovascular risk factors in a randomized clinical trial in individuals with type 2 diabetes. *Diabetes Care*. 2006;29(8):1777-1783. doi:10.2337/dc06-0606

27. Barnard ND, Cohen J, Jenkins DJ, et al. A low-fat vegan diet and a conventional diabetes diet in the treatment of type 2 diabetes: a randomized, controlled, 74-wk clinical trial. *Am J Clin Nutr*. 2009;89(5):1588S-1596S. doi:10.3945/ajcn.2009.26736H

28. Barnard ND, Gloede L, Cohen J, et al. A low-fat vegan diet elicits greater macronutrient changes, but is comparable in adherence and acceptability, compared with a more conventional diabetes diet among individuals with type 2 diabetes. *J Am Diet Assoc*. 2009;109(2):263-272. doi:10.1016/j.jada.2008.10.049

29. Turner-McGrievy GM, Barnard ND, Cohen J, Jenkins DJ, Gloede L, Green AA. Changes in nutrient intake and dietary quality among participants with type 2 diabetes following a low-fat vegan diet or a conventional diabetes diet for 22 weeks. *J Am Diet Assoc*. 2008;108(10):1636-1645. doi:10.1016/j.jada.2008.07.015

30. Barnard ND, Levin SM, Gloede L, Flores R. Turning the waiting room into a classroom: weekly classes using a vegan or a portion-controlled eating plan improve diabetes control in a randomized translational study. *J Acad Nutr Diet*. 2018;118(6):1072-1079. doi:10.1016/j.jand.2017.11.017

31. Barnard ND, Alwarith J, Rembert E, et al. A Mediterranean diet and low-fat vegan diet to improve body weight and cardiometabolic risk factors: a randomized, cross-over trial. *J Am Coll Nutr*. 2021;41(2):127-139.

32. Bunner AE, Wells CL, Gonzales J, Agarwal U, Bayat E, Barnard ND. A dietary intervention for chronic diabetic neuropathy pain: a randomized controlled pilot study. *Nutr Diabetes*. 2015;5(5):e158. doi:10.1038/nutd.2015.8

33. Burke LE, Styn MA, Steenkiste AR, Music E, Warziski M, Choo J. A randomized clinical trial testing treatment preference and two dietary options in behavioral weight management: preliminary results of the impact of diet at 6 months–PREFER study. *Obesity (Silver Spring)*. 2006;14(11):2007-2017. doi:10.1038/oby.2006.235

34. Burke LE, Choo J, Music E, et al. PREFER study: a randomized clinical trial testing treatment preference and two dietary options in behavioral weight management–rationale, design and baseline characteristics. *Contemp Clin Trials*. 2006;27(1):34-48. doi:10.1016/j.cct.2005.08.002

35. Burke LE, Warziski M, Styn MA, Music E, Hudson AG, Sereika SM. A randomized clinical trial of a standard versus vegetarian diet for weight loss: the impact of treatment preference. *Int J Obes (Lond)*. 2008;32(1):166-176. doi:10.1038/sj.ijo.0803706

36. Garousi N, Tamizifar B, Pourmasoumi M, et al. Effects of lacto-ovo-vegetarian diet *vs*. standard-weight-loss diet on obese and overweight adults with non-alcoholic fatty liver disease: a randomised clinical trial. *Arch Physiol Biochem*. Published online March 9, 2021. doi:10.1080/13813455.2021.1890128

37. Kahleova H, Matoulek M, Malinska H, et al. Vegetarian diet improves insulin resistance and oxidative stress markers more than conventional diet in subjects with Type 2 diabetes. *Diabet Med*. 2011;28(5):549-559. doi:10.1111/j.1464-5491.2010.03209.x

38. Kahleova H, Petersen KF, Shulman GI, et al. Effect of a low-fat vegan diet on body weight, insulin sensitivity, postprandial metabolism, and intramyocellular and hepatocellular lipid levels in overweight adults: a randomized clinical trial. *JAMA Netw Open*. 2020;3(11):e2025454. doi:10.1001/jamanetworkopen.2020.25454

39. Lee YM, Kim SA, Lee IK, et al. Effect of a brown rice based vegan diet and conventional diabetic diet on glycemic control of patients with type 2 diabetes: a 12-week randomized clinical trial. *PLoS One*. 2016;11(6):e0155918. doi:10.1371/journal.pone.0155918

40. Liao F-H, Shieh M-J, Yang S-C, Lin S-H, Chien Y-W. Effectiveness of a soy-based compared with a traditional low-calorie diet on weight loss and lipid levels in overweight adults. *Nutrition*. 2007;23(7-8):551-556. doi:10.1016/j.nut.2007.05.003

41. Mahon AK, Flynn MG, Stewart LK, et al. Protein intake during energy restriction: effects on body composition and markers of metabolic and cardiovascular health in postmenopausal women. *J Am Coll Nutr*. 2007;26(2):182-189. doi:10.1080/07315724.2007.10719600

42. Mishra S, Xu J, Agarwal U, Gonzales J, Levin S, Barnard ND. A multicenter randomized controlled trial of a plant-based nutrition program to reduce body weight and cardiovascular risk in the corporate setting: the GEICO study. *Eur J Clin Nutr*. 2013;67(7):718-724. doi:10.1038/ejcn.2013.92

43. Mishra S, Barnard ND, Gonzales J, Xu J, Agarwal U, Levin S. Nutrient intake in the GEICO multicenter trial: the effects of a multicomponent worksite intervention. *Eur J Clin Nutr*. 2013;67(10):1066-1071. doi:10.1038/ejcn.2013.149

44. Nicholson AS, Sklar M, Barnard ND, Gore S, Sullivan R, Browning S. Toward improved management of NIDDM: a randomized, controlled, pilot intervention using a lowfat, vegetarian diet. *Prev Med*. 1999;29(2):87-91. doi:10.1006/pmed.1999.0529

45. Ornish D, Brown SE, Scherwitz LW, et al. Can lifestyle changes reverse coronary heart disease? the Lifestyle Heart Trial. *Lancet*. 1990;336(8708):129-133. doi:10.1016/0140-6736(90)91656-U

46. Ornish D, Scherwitz LW, Billings JH, et al. Intensive lifestyle changes for reversal of coronary heart disease. *JAMA*. 1998;280(23):2001-2007. doi:10.1001/jama.280.23.2001

47. Shah B, Newman JD, Woolf K, et al. Anti-inflammatory effects of a vegan diet versus the American Heart Association-recommended diet in coronary artery disease trial. *J Am Heart Assoc*. 2018;7(23):e011367. doi:10.1161/JAHA.118.011367

48. Shah B, Ganguzza L, Slater J, et al. The effect of a vegan versus AHA DiEt in coronary artery disease (EVADE CAD) trial: study design and rationale. *Contemp Clin Trials Commun*. 2017;8:90-98. doi:10.1016/j.conctc.2017.09.003

49. Sofi F, Dinu M, Pagliai G, et al. Low-calorie vegetarian versus mediterranean diets for reducing body weight and improving cardiovascular risk profile: CARDIVEG Study (Cardiovascular Prevention With Vegetarian Diet). *Circulation*. 2018;137(11):1103-1113. doi:10.1161/CIRCULATIONAHA.117.030088

50. Sofi F, Dinu M, Pagliai G, Cesari F, Marcucci R, Casini A. Mediterranean versus vegetarian diet for cardiovascular disease prevention (the CARDIVEG study): study protocol for a randomized controlled trial. *Trials*. 2016;17(1):233. doi:10.1186/s13063-016-1353-x

51. Tang M, Armstrong CLH, Leidy HJ, Campbell WW. Normal vs. high-protein weight loss diets in men: effects on body composition and indices of metabolic syndrome. *Obesity (Silver Spring)*. 2013;21(3):E204-E210. doi:10.1002/oby.20078

52. Toobert DJ, Glasgow RE, Radcliffe JL. Physiologic and related behavioral outcomes from the Women's Lifestyle Heart Trial. *Ann Behav Med*. 2000;22(1):1-9. doi:10.1007/BF02895162

53. Wright N, Wilson L, Smith M, Duncan B, McHugh P. The BROAD study: a randomised controlled trial using a whole food plant-based diet in the community for obesity, ischaemic heart disease or diabetes. *Nutr Diabetes*. 2017;7(3):e256. doi:10.1038/nutd.2017.3

54. Tokgozoglu L, Orringer C, Ginsberg HN, Catapano AL. The year in cardiovascular medicine 2021: dyslipidaemia. *Eur Heart J*. 2022;43(8):807-817. doi:10.1093/eurheartj/ehab875

55. Cosentino F, Ceriello A, Baeres FMM, et al. Addressing cardiovascular risk in type 2 diabetes mellitus: a report from the European Society of Cardiology Cardiovascular Roundtable. *Eur Heart J*. 2019;40(34):2907-2919. doi:10.1093/eurheartj/ehy677

56. Yokoyama Y, Levin SM, Barnard ND. Association between plant-based diets and plasma lipids: a systematic review and meta-analysis. *Nutr Rev*. 2017;75(9):683-698. doi:10.1093/nutrit/nux030

57. Gibbs J, Gaskin E, Ji C, Miller M, Cappuccio F. The effect of plant-based diets on blood pressure: a systematic review and meta-analysis of controlled clinical trials. *J Hypertens*. 2021;39:e322. doi:10.1097/01.hjh.0000748212.53272.08

58. Lopez PD, Cativo EH, Atlas SA, Rosendorff C. The effect of vegan diets on blood pressure in adults: a meta-analysis of randomized controlled trials. *Am J Med*. 2019;132(7):875-883.e7. doi:10.1016/j.amjmed.2019.01.044

59. Sacks FM, Svetkey LP, Vollmer WM, et al; DASH-Sodium Collaborative Research Group. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. *N Engl J Med*. 2001;344(1):3-10. doi:10.1056/NEJM200101043440101

60. Mensink R. *Effects of Saturated Fatty Acids on Serum Lipids and Lipoproteins: A Systematic Review and Regression Analysis*. World Health Organization; 2016.

61. Tang WH, Wang Z, Levison BS, et al. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. *N Engl J Med*. 2013;368(17):1575-1584. doi:10.1056/NEJMoa1109400

62. Green CL, Lamming DW, Fontana L. Molecular mechanisms of dietary restriction promoting health and longevity. *Nat Rev Mol Cell Biol*. 2022;23(1):56-73. doi:10.1038/s41580-021-00411-4

63. Mittendorfer B, Klein S, Fontana L. A word of caution against excessive protein intake. *Nat Rev Endocrinol*. 2020;16(1):59-66. doi:10.1038/s41574-019-0274-7

64. Xu Y, Jiang H, Li L, et al. Branched-chain amino acid catabolism promotes thrombosis risk by enhancing tropomodulin-3 propionylation in platelets. *Circulation*. 2020;142(1):49-64. doi:10.1161/CIRCULATIONAHA.119.043581

65. Threapleton DE, Greenwood DC, Evans CE, et al. Dietary fibre intake and risk of cardiovascular disease: systematic review and meta-analysis. *BMJ*. 2013;347:f6879. doi:10.1136/bmj.f6879

66. Tosti V, Bertozzi B, Fontana L. Health benefits of the Mediterranean diet: metabolic and molecular mechanisms. *J Gerontol A Biol Sci Med Sci*. 2018;73(3):318-326. doi:10.1093/gerona/glx227

67. Satija A, Bhupathiraju SN, Spiegelman D, et al. Healthful and unhealthful plant-based diets and the risk of coronary heart disease in U.S. adults. *J Am Coll Cardiol*. 2017;70(4):411-422. doi:10.1016/j.jacc.2017.05.047

68. Satija A, Bhupathiraju SN, Rimm EB, et al. Plant-based dietary patterns and incidence of type 2 diabetes in US men and women: results from three prospective cohort studies. *PLoS Med*. 2016;13(6):e1002039. doi:10.1371/journal.pmed.1002039

69. Jaacks LM, Kapoor D, Singh K, et al. Vegetarianism and cardiometabolic disease risk factors: differences between South Asian and US adults. *Nutrition*. 2016;32(9):975-984. doi:10.1016/j.nut.2016.02.011

SUPPLEMENT 1.

eMethods.
eTable 1. Description of PICOS Criteria
eTable 2. Complete Search Strategies for Different Databases
eTable 3. Inclusion and Exclusion Criteria of Included Studies
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SUPPLEMENT 2.
eAppendix. Data Set (Separate File)

SUPPLEMENT 3.
Data Sharing Statement

CHAPTER 4: Plant-Based Heart-Protective Diets, Cardiometabolic Risk and Cardiovascular Disease Incidence and Mortality in the UK Biobank Study

To address the research gaps identified in CHAPTER 3, we designed and developed a heart-protective diet score, taking into account the quality of diet. In this chapter, we tested this score in a large sample size (the UK Biobank cohort, n=192274, mean age: 56.3±7.9 years, 43.3% male) with a long duration of follow-up (12.3 years). We demonstrated that individuals who consumed a high-quality plant-based diet, rich in whole grains, non-starchy vegetables, fruits, legumes and beans, with fish and seafood, experienced a significantly lower risk of CVD events (HR: 0.92, 95% CI: 0.88 to 0.95) and mortality (HR: 0.72, 95% CI: 0.61 to 0.86).

This work has been presented at the American Society for Nutrition (ASN) conference 2023.

The abstract of this work has been published in the Current Developments in Nutrition:

T. Wang, A. Nova, S. Cassidy, C.M. Kroeger, S. Mitra, A. Masedunkas, T. Fazia, L. Bernardinelli, L. Fontana. P23-079-23 Heart-Protective Diet Scores, Cardiometabolic Risk and Cardiovascular Disease Incidence and Mortality: A Prospective Study From UK Biobank. Current Developments in Nutrition. Volume 7, Supplement 1, 2023, 100187, ISSN 2475-2991, https://doi.org/10.1016/j.cdnut.2023.100187

The paper of this work has been submitted to the European Heart Journal:

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oral gavage for 8 weeks. After euthanasia, mouse aorta were collected for further analysis.

Results: The endothelium-dependent relaxation (EDR) induced by the addition of acetylcholine (ACh) was impaired in the db/db control mouse compared to the db/m^+ counterparts. After 8-week oral gavage treatment, the ISL treatment group showed improved EDR in db/db mice aortae, while did not show significant effect in db/m^+ mouse aortae. The total endothelium-independent relaxation induced by sodium nitroprusside (SNP) was found comparable among all groups. ROS levels were increased in db/db mouse aortic rings as compared to db/m^+ and were lowered by ISL. What's more, pro-inflammatory cytokines TNF-α, MCP-1, IL-6 were up-regulated while the anti-inflammatory cytokine IL-10 was down-regulated in db/db mouse aortae, and ISL could rescue such effects. Besides, the expression level of NOX2 and iNOS, which were 2 important source of ROS, were found to be up-regulated in db/db mouse aortae and were reduced by ISL. The antioxidant genes SOD-1, SOD-2 and SOD-3 were found to be down-regulated in db/db mouse aortae and were increased by ISL. In addition, the nuclear factor erythroid 2–related factor 2 (Nrf2) and its downstream heme oxygenase-1 (HO-1), were also found to be down-regulated in db/db control mouse aortae and were increased by ISL.

Conclusions: Isoliquiritigenin could alleviate endothelial dysfunction via attenuating inflammation and oxidative stress in type II diabetes, which was possibly through regulating Nrf2/HO-1 signaling pathway.

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P23-079-23 Heart-Protective Diet Scores, Cardiometabolic Risk and Cardiovascular Disease Incidence and Mortality: A Prospective Study From UK Biobank

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Objectives: To investigate whether adherence to a plant-based heart-protective diet might attenuate risks of cardiovascular events in the UK Biobank (UKBB) population.

Methods: This study included 192,274 individuals (mean age: 56.3 ± 7.9 years, 43.3% males) in UKBB who: (1) were free of cardiovascular diseases (CVDs) at baseline; and (2) performed at least one 24-h dietary measurement between 2009 and 2012. Using dietary data collected by the Oxford WebQ, we developed a heart-protective diet score (HPDS) based on 22 food groups. The adherence to an HPDS was divided into quartiles, where Q1 (reference group) and Q4 represented the lowest and the highest adherence, respectively. Associations between adherence to a heart-protective diet and cardiovascular outcomes were examined using Cox proportional hazard models.

Results: After a median (IQR) follow-up of 12.3 (11.7, 13.2) years, compared to Q1, participants who had the highest HPDS (Q4) had an 8% decreased risk of CVD incidence (HR: 0.92 [0.88,0.95]), 12% decreased risk in ischemic heart disease incidence (IHD; HR: 0.88 [0.83,0.93]), 18% decreased risk in myocardial infarction (MI; HR: 0.82 [0.74,0.90]), and 4% decreased risk in heart failure (HF; HR: 0.86 [0.78,0.95]), respectively, adjusting for age (timescale), sex, ethnicity, Townsend deprivation index, socioeconomic status, lifestyle factors (e.g. physical activity, sleep, smoke habits), and history of cancer and hyperglycemia/type 2 diabetes diagnosis. In addition, we observed a more pronounced protective effect in CVD mortality in individuals with the highest HPDS (Q4), with a 28% decreased risk of overall CVD mortality (HR: 0.72 [0.61,0.86]), 32% decreased risk in IHD mortality (HR: 0.68 [0.52,0.89]), 35% decreased risk in MI mortality (HR: 0.65 [0.46,0.91]), and 49% decrease risk in HF mortality (HR: 0.51 [0.30,0.85]).

Conclusions: Adherence to a plant-based heart-protective diet is associated with a significant attenuation of cardiovascular disease incidence and mortality.

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P23-080-23 Impact of an Intensive Lifestyle Program on Low Attenuation Plaque and Myocardial Perfusion in Coronary Heart Disease: A Randomised Clinical Trial Protocol

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Objectives: To conduct a randomised controlled trial (RCT) to determine the impact of a 12-month intensive lifestyle intervention program (ILIP) versus a standard clinical recommendations program (SCRP) on low-attenuation plaque (LAP) volume and structure, stress myocardial perfusion, and diastolic function (LIVEPLUS trial).

Methods: This is a single-centre, parallel-group, RCT (Trials Registry: ACTRN12620001151921) of individuals with stable coronary heart disease, who have LAP based on a coronary computed tomography angiography (CCTA). The ILIP group (n = 75) will follow a 5:2 pesco-vegetarian diet, individualised exercise training, and mindfulness-based stress reduction, whereas the SCRP group (n = 75) will follow American Heart Association guidelines for diet and exercise and World Health Organization guidelines for stress reduction. The co-primary endpoints are: 1- LAP volume (mm3), and 2-Adenosine stress myocardial blood flow (stress MBF, mL/min/g). Other key measurements include body weight, liver steatosis, subclinical abnormalities, arterial stiffness, endothelial function, genomic, metabolomic, and gut microbiome-related adaptations to these structural changes. An intention-to-treat principle will be used for all analyses.

Results: To demonstrate the feasibility of our interventions, body weight was used as a secondary compliance indicator of the intervention. Ten participants were recruited by Feb 2023: five randomised to ILIP, three to SCRP, and two awaiting randomisation. Four individuals (three in ILIP, one in SCRP) followed our interventions for more than 6 months, with those following ILIP

Association of a healthy plant-based heart-protective diet with reduced cardiovascular disease incidence and mortality: findings from the UK Biobank Study

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Key Points

Question Do healthy plant-based diets protect individuals against cardiovascular disease (CVD) events and deaths?

Findings In this large prospective cohort study (a median follow-up of 12.3y) of 192,274 participants (mean age: 56.3±7.9y) in the UK Biobank, individuals with the highest adherence to a heart-protective diet score had a lower risk of overall CVD (8% lower), ischemic heart disease (12% lower), and myocardial infarction (18% lower). In addition, those with the highest adherence experienced a 28% lower risk of overall CVD mortality and a 32-35% lower risk of mortality from ischemic heart disease and myocardial infarction.

Meaning These results underscore the pivotal role of overall diet quality in enhancing cardiovascular health and reducing mortality risks.

Abstract

Importance: Previous research examining the effects of omnivorous and plant-based diets on CVD outcomes has produced inconsistent findings, and the importance of diet quality is overlooked.

Objective: To assess the relation between adherence to a healthy plant-based, heart-protective diet and the risk of cardiovascular disease (CVD) events.

Design: Prospective cohort study.

Methods and Results: 192,274 (mean age: 56.3±7.9 years, 43.3% males) participants in UK Biobank without CVD at baseline who completed a 24-hour recall questionnaire. Using data generated by Oxford WebQ, we developed a novel heart-protective diet score (HPDS) based on 22 food groups. Cox proportional hazard models were used to study associations. During a median follow-up of 12.3 years, there were 20,692 CVD events and 1,131 CVD deaths. After adjusting for demographics, Townsend deprivation index, lifestyle factors, and history of chronic diseases, participants in the top quartile of the HPDS were at the lower risk of overall CVD (HR: 0.92, 95% CI: 0.88 to 0.95), ischemic heart disease (HR: 0.88 [95% CI: 0.83 to 0.93]), myocardial infarction (HR: 0.82, 95% CI: 0.74 to 0.90), and heart failure (HR: 0.86, 95% CI: 0.78 to 0.95) than those in the bottom quartile. Participants who adhered closely to a healthy plant-based heart-protective diet had the lowest risk of overall CVD (HR: 0.72, 95% CI: 0.61 to 0.86), ischemic heart disease (HR: 0.68, 95% CI: 0.52 to 0.89), myocardial infarction (HR: 0.65, 95% CI: 0.46 to 0.91), and heart failure (HR: 0.51, 95% CI: 0.30 to 0.85) mortality.

Conclusions and relevance: Adherence to a healthy plant-based heart-protective diet rich in non-starchy vegetables, fruits, whole grains, legumes, and fish, is associated with a reduced cardiovascular disease incidence and mortality. Further research in diverse ethnic populations is necessary to validate our findings and enhance their generalizability.

Funding Sources: The Australian NHMRC Investigator Grant (APP1177797), Australian Youth and Health Foundation and Philip Bushell Foundation.

Keywords: Cardiovascular diseases; Incidence; Mortality; Plant-based diet

Introduction

Despite significant progress in the treatment and management of cardiovascular diseases (CVDs), they remain the leading cause of disease burden, increased healthcare costs, and mortality globally[49]. A key contributing factor to the heightened risk of CVDs is a poor-quality diet. In contrast, adherence to heart-healthy dietary patterns has consistently demonstrated a positive impact on cardiovascular health[50, 51]. These patterns emphasize the consumption of a wide variety of vegetables, fruits, minimally processed whole grains, healthy protein sources (primarily plant-based, fish, seafood, and low-fat dairy products), and liquid plant oils. Additionally, they discourage the intake of red meat, highly processed foods that are rich in empty calories and unhealthy fats, added salt, sugars and sugary beverages, and alcohol[50-52].

Previous research examining the effects of omnivorous and plant-based diets, such as lacto-ovo vegetarian and pesco-vegetarian diets, on CVD outcomes has produced inconsistent findings. Some studies have suggested that incorporating fish into a plant-based diet, as seen in the pesco-vegetarian diet, may provide protection against CVD, ischemic heart disease (IHD), myocardial infarction (MI), stroke, and heart failure (HF)[32, 33]. However, conflicting results have indicated no significant difference or even an elevated risk of CVD and stroke among pesco-vegetarians and lacto-ovo-vegetarians, respectively[34, 35].

Several studies failed to take into account the importance of diet quality, which is a critical factor as various dietary patterns, such as vegetarian and Mediterranean diets, can significantly differ in their nutritional composition. Individuals adhering to "unhealthy" plant-based diets that prioritize refined grains, high-sodium preserved vegetables, deep-fried foods, and sweetened beverages have an elevated CVD risk and mortality[47, 53]. Moreover, certain prospective studies relied on simplistic questionnaires with only four questions to determine participants' vegetarian status and classify them into various diet groups. The quality of diet, which is a critical factor to influence cardiometabolic health, is overlooked by these studies.

In order to overcome some of these limitations, in our study, we developed a novel healthy plant-based heart-protective diet score that considered 22 different food groups. The objective was to evaluate the overall quality

of the diet and explore whether adherence to this plant-based heart-protective diet could potentially lower the risk of cardiovascular events among individuals in the UK Biobank (UKBB) population.

Methods

Study population

The UK Biobank is an extensive prospective cohort study conducted within the general population, which enrolled over 500,000 individuals aged 40-69 years during the period from 2006 to 2010[54].

Dietary information was collected during the recruitment phase using a self-completed touchscreen questionnaire that assessed the frequency of consumption of main food items. A significant subset of participants (n=211,050) completed at least one web-based 24-hour dietary measurement using the Oxford WebQ tool between 2009 and 2012. The results generated from the Oxford WebQ have captured similar food items and nutrient intake estimates in comparison to an interviewer-administrated dietary assessment, with moderate-to-strong correlations for most nutrients (Spearman's correlation coefficients between 0.5 and 0.9) [55]. This indicates a reasonably good agreement between the two methods in capturing dietary information and nutrient intake. A previous study by Bradbury *et al.* evaluated the repeatability of the touchscreen questionnaire in the UK Biobank cohort and found a generally good agreement between reported consumption at baseline and approximately 4 years later [56]. These included fish and meat items (>90% reported the same or adjacent category of intake) and vegetable and fruit (>72% reported the same or adjacent category of intake), with weighted K coefficient showing substantial agreement for oily fish, beef and lamb, poultry, processed meat and fresh fruit. This study also showed good agreement for all foods and food group intake in participants who completed 24-hour recall more than once. In the present study, we calculated the "heart-protective diet score at baseline" and the "averaged heart-protective diet score" based on repeated measurements and examined the association between them and found a moderate correlation (Pearson correlation coefficient=0.53; p-value < 0.001) between these two scores. Sensitivity analyses were further conducted using 24hr recall data from the first three occasions and results were almost identical to the findings generated from the single 24hr recall (Table S1-S3). Therefore, for participants who completed the dietary

measurement multiple times, we used the earliest data to maximize the follow-up duration. A detailed description of the Oxford WebQ[55] can be found in supplementary methods. For our study, we included participants who: (i) had completed at least one 24-hour dietary measurement with the Oxford WebQ between 2009 and 2012, and (ii) had relevant clinical records and death registry data available to measure our specific outcomes of interest (described below). We excluded individuals who had: (i) missing or implausible data regarding total energy intake (men: <800 or >4200 kcal/day; n=2030; women: <600 or >3500 kcal/day; n=2177), and (ii) prevalent cases of CVD at the time of recruitment (n=13,008). Overall, our study included 192,274 participants. Table S4 illustrates the characteristics of all individuals included and excluded from our study.

Measurement of dietary intake and development of the plant-based heart-protective diet scores

Diet quality indices are commonly used by researchers in observational studies to assess the quality of plant-based diets [53, 57]. Marchese et al.[36] recently reviewed 35 plant-based diet quality indices, of which 19, 9 and 5 indices were developed based on FFQ, semi-FFQ and 24hr recall, respectively. Both FFQ and 24hr recall are commonly used dietary assessment approaches in observational studies to reflect participants' dietary patterns. However, as highlighted by Nutritools and Dietary Assessment Guidelines [37], short FFQs are not reliable for evaluating total diet, and FFQ in general is prone to inaccurate or subjective reporting. Thus, to allow a thorough evaluation of diet quality and answer the mixed findings by previous literature, detailed dietary data generated by 24hr recall is needed to reflect individuals' adherence to a plant-based diet.

Table S5 and supplementary methods summarize the current main five plant-based diet quality indices utilizing data from 24hr recall. Only three indices (Comprehensive Diet Quality Index (cDQI) [38], Diet Quality Index Associated to the Digital Food Guide (DQI-DFG) [39], and Global Diet Quality Score (GDQS) [40]) consider healthiness of both animal-based and plant-based foods. Discrepancies in categorization of food groups among these scores are identified in red meats, eggs, processed meats, full-fat dairy products, tubers and roots, refined carbohydrates and sugars and sweets. Yet, none of these scores fully reflect the diet recommended by AHA, HF and ESC/EAS guidelines [28, 29, 41]for the prevention and management of cardiovascular disease.

To address the current research gaps in plant-based diets and cardiovascular events, a new score designed specifically for cardiovascular health incorporating current guidelines recommendations is warranted. We therefore developed a "heart-protective diet score" (HPDS) based on a previously validated plant-based diet index [47, 58], which only evaluates the quality of plant-based food items but assigns all animal food items negative scores. In contrast, our HPDS additionally assesses the healthiness of animal-based foods following the most updated dietary recommendations in the management of cardiovascular health with strong evidence base. These include 2021 American College of Cardiology (ACC)/American Heart Association (AHA), HF, ESC/EAS guidelines and the Global Burden of Disease Nutrition and Chronic Disease Expert Group [59]. This scoring system was developed based on existing evidence[60, 61] regarding the associations between specific foods and nutrients and their impact on cardiometabolic outcomes. The HPDS emphasizes the consumption of a diverse range of vegetables, fruits, whole grains, nuts, healthy protein sources (such as legumes and fish), and non-tropical vegetable oils, while it discourages the consumption of red meats, sweets, sugar-sweetened beverages, added sugars and added salt. Alcoholic beverages are not included in the HPDS given mixed evidence of their associations related to different health outcomes.

To apply the HPDS, we categorized the food and drink items into 22 food groups (Table S6) and ranked consumption into quintiles. The amount of food and drink items consumed was converted in grams or ml based on the Eatwell Guide by the UK National Health Service [62]. Table S7 displays the number of participants with data available for each food item. For food groups associated with positive scores, a score of 5 was assigned to individuals in the highest quintile of consumption, while a score of 1 was given to those in the lowest quintile. Conversely, for food groups linked to negative scores, a score of -1 was assigned to participants in the lowest quintile, and a score of -5 was given to those in the highest quintile. A score of 0 was assigned when a participant reported not consuming a particular food item. The sum of scores for the 22 groups generated the HPDS, reflecting diet quality in terms of cardiovascular health. The validity and reliability of our HPDS were evaluated by these approaches: i). construct validity [36, 63]: the association between HPDS and foods and nutrient intakes, and the difference of HPDS by sociodemographic characteristic; ii). criterion validity[63]: the association of HPDS and

clinical outcomes; iii). reliability [36, 63] was evaluated by Cronbach's Alpha (0.5 or greater is considered to have good internal consistency) method[64] in 5419 participants with all 5 instances of 24-hour recalls, with a result of 0.79 [95%CI: 0.78, 0.81] showing good internal consistency.; and iv). content validity: the draft HPDS were circulated and reviewed by eight subject experts (two professors, six PhD degree holders, two practitioners, two dietitians and three exercise physiologists) of different related disciplines (Nutrition and Food Science, Epidemiology, Cardiology, Life Science, Psychology, and Statistics). We calculated the HPDS at baseline, and for participants with repeated measurements, we calculated the averaged HPDS scores to account for variations over time. For participants with missing baseline data but with subsequent assessments, the earliest assessment served as baseline to maximize sample size and follow-up duration.

Cardiovascular disease incidence and death

The primary outcomes included the CVD incidence and mortality. We defined CVD outcomes based on the earliest diagnosis recorded according to the International Classification of Disease 10th revision (ICD10) for the following conditions: i) IHD (ICD10: I20, I24, I25), ii) MI (ICD10: I21, I22, I23), iii) stroke (ICD10: I61, I62, I63, I64), iv) HF (ICD10: I50), and v) arrhythmia and conduction disorders including atrial fibrillation (ICD10: I48). To ascertain these diagnoses, we obtained data from linked sources including hospital admissions, primary care records, and death registries. In line with prior research findings, we supplemented the diagnoses obtained from medical records with information derived from self-reported codes (Table S8) to ensure a comprehensive assessment of CVD outcomes[65-68]. Furthermore, we incorporated diagnoses for MI, stroke, and IHD obtained from the Electronic Health Records (EHRs) maintained by General Practitioners in primary care[69]. Participants were followed up from the date of their initial assessment (March 2006 to October 2010), until the date of outcome diagnosis, date of death, date of loss to follow-up, or the end of follow-up (31 December 2021), whichever came first. Person-years were calculated accordingly.

Cardiometabolic outcomes

Secondary outcomes included incidence of CVD risk factors: i) overweight/obesity (ICD10: E66); ii) hypertension (ICD10: I10); iii) hyperlipidaemia (ICD10: E785); and iv) hyperglycaemia or type II diabetes mellitus (T2DM) (ICD10: R739, E11). Similar to the primary outcomes, the diagnoses for these conditions were obtained using the same methods as described earlier. Self-reported disease status supplemented hypertension and T2DM (Table S8)[67, 70-73]. Moreover, diagnoses for hypertension and T2DM were also extracted from the EHRs[69]. We excluded participants who had prevalent cases of overweight and obesity (n=3,799), hypertension (n=42,788), hyperglycemia or T2DM (n=3,535), and hyperlipidemia (n=189) at the time of recruitment. We then calculated person-years as previously described for the primary outcomes.

Statistical analysis

Cohorts characteristics within quartiles of HPDS were reported for continuous (mean (standard deviation [SD])) and categorical variables (%). Cox proportional hazard regression models, with age at recruitment as the underlying timescale, were implemented to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between HPDS in quartiles with primary and secondary outcomes. Linear trend was tested keeping HPDS in the model as a continuous variable. To account for confounding, the model was adjusted for variables associated with both diet consumption and CVD risk, including sex, ethnicity, sociodemographic factors (e.g., household income), lifestyle (e.g., physical activity and smoking habits), history of hyperglycaemia/T2DM diagnosis and history of cancer diagnosis. A thorough description of covariates can be found in the Supplementary Methods. Potential multicollinearity of covariates was tested, and the highest correlation is 0.33 between education and income. Therefore, multicollinearity is not a concern. The proportional hazard assumption was checked by tests based on Schoenfeld residuals, and stratification factors were applied to confounders not respecting the assumption, i.e., $p<0.05$. Sensitivity analyses were performed excluding self-reported diagnoses. As secondary analyses, we examined whether sex and Townsend deprivation index (TDI) modified the association between HPDS and primary/secondary outcomes using interaction terms. For significant interactions, subgroup analyses were conducted stratifying by sex and TDI median value. To account for multiple testing, we applied a False Discovery Rate (FDR) of 0.05 with Benjamini-Hochberg adjustment. Missing data for confounding variables were imputed

using multiple imputations with predictive mean matching method on ten datasets. Rubin's rule was used to aggregate the results and obtain HRs with 95%CIs. RStudio 2022.02.2+485 was used for all analyses.

Results

Sociodemographic and dietary characteristics of participants

A total of 192,274 participants (mean age: 56.3±7.9 years, 43.3% males) were included (Table 1; Figure S1). During a median follow-up period of 12.3 years (interquartile range: 11.7, 13.2) with a total of 2,279,893 person-years, we documented 20,692 (10.8%) incident cases of CVD (Figure 1: 11241 IHD, 3452 MI, 3103 stroke, 3189 HF and 8913 AF) with an average age at diagnosis of 67.5±7.4 years. 1131 participants (0.59%) died from CVD (Figure 2: 513 IHD, 292 MI, 351 stroke, 141 HF). Table 1 shows participants' characteristics for quartiles of HPDS. The calculated HPDS had a normal distribution (Figure S2), with a mean value of 2.78±7.60 (ranging from -30.00 to 36.92). Individuals with higher HPDS were older, more likely to be female, non-current smokers, physically active, had a higher likelihood of having a university degree, higher income, and were more likely to take dietary supplements, demonstrating the construct validity of HPDS in differentiating populations by sociodemographic characteristics.

Table 2 shows food groups and nutrient intake by quartiles of HPDS. Compared to Q1, individuals with the highest HPDS (Q4) consumed more non-starchy vegetables (+2.5 servings/d), fruits (+2.5 servings/d), wholegrains (+1.5 servings/d), legumes and beans (+0.5 servings/d), uncoated fish and seafood (+0.5 servings/d), and tea, coffee & other low-calorie drinks (+2 servings/d), resulting in a lower intake of energy (-200kcal/d), total fat (-10g/d), saturated fat (-8g/d) and sodium (-310mg/d, 15% lower), and a higher intake of dietary fibre (+8g/d), vitamin C (+75mg/d), folate (+85 ug/d), beta carotene (+2200 ug/d, 128% higher), potassium (+780 mg/d, 24% higher), magnesium (+80mg/d), iron (+1.8 mg/d), vitamin E (+1.5 mg/d) and vitamin B12 (+1.2 ug/d). These results illustrate the construct validity of HPDS that HPDS is positively correlated with the intake of key health-promoting nutrients and food groups. In contrast, individuals with the lowest HPDS (Q1) consumed more refined grains and cereals (+1.5 servings/d), meat, poultry & processed meat (+1 servings/d), and sweets, desserts, cookies & pastries (+1.5 servings/d) than Q4. The intake of total protein and zinc were similar across groups.

Higher healthy plant-based diet score is associated with lower cardiovascular diseases incidence

The pooled results from the Cox proportional hazard models are presented in Figure 1, Figure 2, Table S9, and Table S10. When comparing individuals with the highest HPDS quartile (Q4) to those in the lowest quartile (Q1), several notable findings emerged. Firstly, individuals in the highest HPDS quartile (Q4) experienced a lower CVD incidence (Figure 1; HR=0.92 [95% CI: 0.88, 0.95]; p-value for linear trend <0.001) and a decreased CVD mortality (Figure 2; HR=0.72 [95% CI: 0.61, 0.86]; p-value for linear trend=0.003). Specifically, compared to Q1, the highest HPDS (Q4) was associated with an 18% decreased risk of MI incidence (HR=0.82 [0.74, 0.90]; p-value for linear trend <0.001), a 14% decreased risk of HF incidence (HR=0.86 [0.78, 0.95]; p-value for linear trend=0.003), and a 12% decreased risk of IHD incidence (HR=0.88 [0.83, 0.93]; p-value for linear trend <0.001). These findings demonstrated the criterion validity of our HPDS.

Higher healthy plant-based diet score is associated with lower CVD mortality

A stronger protective association was observed for individuals in the highest HPDS quartile (Q4) compared to Q1 for CVD mortality outcomes. This included a 49% decreased risk of HF mortality (HR=0.51 [0.30, 0.85]; p-value for linear trend=0.066), a 35% decreased risk of MI mortality (HR=0.65 [0.46, 0.91]; p-value for linear trend=0.070), and a 32% decreased risk of IHD mortality (HR=0.68 [0.52, 0.89]; p-value for linear trend = 0.009).

Higher healthy plant-based diet score is associated with lower incidence of cardiometabolic abnormalities

Comparing individuals in the highest HPDS quartile (Q4) to those in the lowest quartile (Q1), we observed statistically significant protective associations with cardiometabolic health (Figure 3 and Table S11). Specifically, individuals in the highest HPDS quartile (Q4) had a 21% lower risk of being overweight and obese (HR=0.79 [0.75, 0.84]; p-value for linear trend <0.001). They also had a 14% lower risk of developing hyperlipidemia (HR=0.86 [0.77, 0.96]; p-value for linear trend=0.001) as well as hyperglycemia and type 2 diabetes mellitus (HR=0.86 [0.81, 0.92]; p-value for linear trend <0.001). Additionally, there was a 7% lower risk of developing hypertension (HR=0.93 [0.89, 0.97]; p-value for linear trend <0.001). These findings suggest that individuals in the highest HPDS

quartile have a significantly reduced risk of experiencing cardiometabolic abnormalities compared to those in the lowest quartile.

Moderation effects of sex and Townsend deprivation index, and sensitivity analyses

In our analysis, we identified statistically significant statistical interactions ($p<0.05$ after multiple testing correction) between HPDS quartiles and sex, as well as between HPDS quartiles and the Townsend deprivation index, for various cardiometabolic outcomes and the incidence of atrial fibrillation. When stratifying the data by sex (Figure S3; Table S12), we observed a stronger protective association for females with higher HPDS values compared to males across several outcomes. Females had a 27% lower risk of overweight and obesity incidence compared to a 10% lower risk in males. Similarly, females had a 27% lower risk of hyperglycemia and T2DM incidence, while no statistically significant effect was observed in males. These results suggest that a healthy plant-based diet may have a more pronounced beneficial impact on these outcomes for females. We also observed a statistically significant statistical interaction ($p<0.05$, after multiple testing correction) between HPDS quartiles and the Townsend deprivation index (Figure S4; Table S12). When stratifying the analysis by the median value of the Townsend deprivation index (2.6), we found that higher HPDS values had a slightly stronger protective association with overweight/obesity and hypertension diagnoses in the less deprived subgroup. Conversely, higher HPDS values showed a higher protective association with hyperglycemia and T2DM diagnosis in the more deprived subgroup. Furthermore, sensitivity analyses comparing outcomes with and without self-reported diagnoses (Figure S5; Table S13) yielded consistent findings, indicating the robustness of our results.

Discussion

In this large cohort study of middle-aged and older adults, a higher adherence to a healthy plant-based heart-protective diet rich in non-starchy vegetables, fruits, whole grains, legumes, and fish was associated with a reduced risk of cardiovascular disease and lower mortality rates. Those who closely followed this dietary pattern had a remarkable 49% lower risk of mortality from heart failure, along with a 32-35% lower risk of mortality from IHD and MI. Additionally, the healthy plant-based diet score was linked to a lower incidence of overweight,

hyperlipidemia, hypertension, and hyperglycemia. These findings underscore the potential benefits of adopting a healthy plant-based diet rich in relatively unprocessed food and fish in reducing the risk of cardiovascular diseases, mortality, and improving overall cardiometabolic health.

Our study demonstrates that a higher adherence to our healthy plant-based diet score leads to a greater reduction in cardiovascular morbidity and mortality compared to previous studies focusing solely on vegetarian and vegan diets[47, 74-76]. While vegetarian and vegan diets have shown positive associations with cardiovascular health, the comprehensive nature of our HPDS, which includes a diverse range of plant foods with fish and seafood while limiting processed foods, refined carbohydrates, and unhealthy fats, appears to have even more pronounced effects on cardiovascular and metabolic health. By considering the individual components of the diet and integrating them into a simplified scoring system, the combined impact becomes more evident.

Compared to the Mediterranean diet, which typically includes both refined and whole grains, moderate alcohol intake, and discourages dairy products and potatoes[77], our HPDS highlights the significant impact of a healthy plant-based diet that prioritizes minimally processed foods. Notably, a recent UKBB study using the Mediterranean diet score reported only a small 7% reduction in the risk of stroke and no significant effect on myocardial infarction[78]. In that study, both refined and whole grain cereals were included in the Mediterranean dietary score, while discouraging eggs and all dairy products regardless of fat content. Red meats, poultry, organ meats, and processed meats were discouraged but not excluded. In contrast, our HPDS score, aligned with the 2021 AHA/ACC dietary recommendations, emphasizes the consumption of fish and seafood, eggs, low-fat dairy products, and minimally processed plant-based foods including whole grains and legumes, while excluding red meats, poultry, and processed meat.

Our study found that individuals with the highest HPDS, indicating lower intake of saturated and partially hydrogenated fats, had a reduced risk of CVD events, aligning with previous research linking animal and ultra-processed food consumption, as well as saturated and trans-fat intake, to the development of IHD[79, 80]. The highest HPDS, characterized by a rich dietary fiber and sterols content, lower energy density, and favorable nutrient profile, positively impacted serum cholesterol levels, glycemic control, body weight, and other cardiometabolic

markers[81-83]. Increased fish consumption in the highest HPDS provided beneficial long-chain omega-3 fatty acids associated with a reduced risk of IHD[84, 85]. The differences in protein sources between the lowest and highest HPDS further supported these findings, with plant-based proteins associated with a lower risk of obesity and T2DM compared to animal protein rich in branched-chain amino acids[86]. Additionally, the higher intake of potassium, magnesium, folate, beta-carotene, vitamin C, E, and B12, coupled with lower sodium intake without compromising zinc intake, may further promote cardiometabolic health. This underscores the importance of overall diet quality in promoting cardiovascular health, beyond just focusing on fish consumption or excluding meats.

In our study, we did not find a significant effect of a healthy plant-based diet on stroke incidence or mortality, which is consistent with previous findings[32-34, 87]. Tong et al.[32] reported a 43% higher risk of hemorrhagic stroke among vegetarians, even after adjusting for cardiometabolic risk factors. This association could potentially be attributed to the relatively low levels of LDL-cholesterol among the vegetarian participants in Tong's[32] and other prospective studies[84, 88]. It is hypothesized that low LDL-cholesterol concentrations may contribute to the necrosis of smooth muscle cells in the arterial wall's medial layer, resulting in impaired endothelium and increased susceptibility to microaneurysms, ultimately increasing the risk of hemorrhage[84]. Additionally, Tong et al.[32] also reported that being fish-eaters had no significant effect on stroke incidence.

Our study has significant strengths, including the use of the UK Biobank, a large prospective cohort study with extensive data collection and long-term follow-up. We introduced a novel approach, the Heart-Protective Diet Score (HPDS), based on the 2021 ACC/AHA dietary recommendations, which comprehensively evaluates diet quality. The use of detailed and accurate 24-hour dietary recall data minimized misclassification of diet types, setting our study apart from other UK Biobank studies[32-34, 89]. Our outcome assessment methods were robust, including medical record linkage and sensitivity analyses. Notably, the baseline cardiometabolic profiles were comparable across different HPDS quartiles, reducing potential confounding from cardiovascular risk factors. However, there are limitations to consider, such as the predominantly Caucasian study population, which may limit generalizability to other ethnic groups. Also, the use of a single 24-hour recall inevitably results in the measurement error of long-term intake, and we may not capture the usual intakes of participants due to intra-individual variations; thus. However, to address this, we calculated the “heart-protective diet score at baseline” and the “averaged heart-

protective diet score" based on repeated measurements and found a moderate correlation (Pearson correlation coefficient=0.53; p-value < 0.001) between them. We conducted further sensitivity analyses and confirmed the results generated from multiple 24hr recalls were almost identical to findings from the single 24hr recall. This finding is supported by another study [56]demonstrating good agreement for all foods intakes in the UK Biobank cohort who completed 24-hour recall more than once, with a substantial agreement in the touchscreen questionnaire for fish and meat items and vegetable and fruit intakes after 4 years. In addition, as an observational study, we cannot establish causality, and there is a possibility of residual confounding from both dietary and non-dietary factors. Notably, individuals with the highest HPDS exhibited health-conscious behaviors, which may have influenced the observed cardiovascular outcomes.

In summary, findings from this large prospective cohort study revealed a robust link between adherence to a healthy diet score based on the 2021 AHA/ACC guidelines and a substantial decrease in cardiovascular mortality and morbidity, particularly for HF and IHD. These findings emphasize the significance of overall dietary quality in relation to cardiometabolic health, rather than focusing exclusively on specific diet types. Further research in diverse ethnic populations is necessary to validate our findings and enhance their generalizability.

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TW, AN, LB, and LF conceived and designed the study; TW designed and developed the heart-protective score; TW, AN, LB, and LF designed the analysis; TW and AN analysed the data; TW, AN, LF and WW drafted the manuscript; LF, WW, LB, SC, CK, AA and TF supervised the study. All authors contributed to critical revision to the manuscript. TW and AN are the guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest, and none were reported.

Ethical approval: UK Biobank received ethical approval from the research ethics committee (reference 13/NW/0382). This study complies with the Declaration of Helsinki. All individuals had provided written informed consent to participate in the study.

Data availability statement: We have our data ready to be accessed upon reasonable requests and please note the UK Biobank study requires investigators to register in the project to access the data which are not publicly available. The cardiovascular outcomes and dietary UK Biobank data are available on application to the UK Biobank. This research has been conducted using the UK Biobank Resource under Application 62594. R scripts for analyses can be accessed via the online repository (https://github.com/sylviawt/HPDS_UKBB. DOI: 10.5281/zenodo.8115595)

The manuscript's guarantors (TW and AN) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: All authors will work with their home institutions to leverage their unique dissemination platforms including social media communication and organizational websites.

Figure legends

Figure 1. Association between quartiles of heart-protective diet score and risk of incident cardiovascular diseases. Data presented as adjusted hazard ratio [95% confidence interval]. Q1 was used as the reference group. Cox proportional hazard models were adjusted by age (timescale), sex, ethnicity, Townsend deprivation index, average house income, education level, dietary supplement use, history of cancer diagnosis, history of hyperglycemia/type 2 diabetes diagnosis, physical activity level, sitting, sleep quality, smoke habits. CVD, Cardiovascular Disease; IHD, Ischemic Heart Disease; MI, Myocardial Infarction; HF, Heart Failure; AF, Atrial Fibrillation; HR, Hazard Ratio. Adjusted p-values were obtained using Benjamini-Hochberg procedure

Figure 2. Association between quartiles of heart-protective diet score and risk of cardiovascular mortality. Data presented as adjusted hazard ratio [95% confidence interval]. Q1 was used as the reference group. Cox proportional hazard models were adjusted by age (timescale), sex, ethnicity, Townsend deprivation index, average house income, education level, dietary supplement use, history of cancer diagnosis, history of hyperglycemia/type 2 diabetes diagnosis, physical activity level, sitting, sleep quality, smoke habits. CVD, Cardiovascular Disease; IHD, Ischemic Heart Disease; MI, Myocardial Infarction; HF, Heart Failure; HR, Hazard Ratio. Adjusted p-values were obtained using Benjamini-Hochberg procedure.

Figure 3. Association between quartiles of heart-protective diet score and risk of cardiometabolic abnormalities. Data presented as adjusted hazard ratio [95% confidence interval]. Q1 was used as the reference group. Cox proportional hazard models were adjusted by age (timescale), sex, ethnicity, Townsend deprivation index, average house income, education level, dietary supplement use, history of cancer diagnosis, history of hyperglycemia/type 2 diabetes diagnosis, physical activity level, sitting, sleep quality, smoke habits. HR, Hazard Ratio. Adjusted p-values were obtained using Benjamini-Hochberg procedure.

Table 1. Characteristics of participants based on quartile categories of heart-protective diet score.

	Q1 (n=48453)	Q2 (n=47778)	Q3 (n=48012)	Q4 (n=48031)
Heart-protective diet score	-6.8 (3.6)	0.3 (1.5)	5.2 (1.5)	12.5 (3.8)
Age at recruitment, year	55.3 (8.2)	56.1 (8.0)	56.7 (7.8)	57.0 (7.6)
Sex, male	26619 [54.9]	21435 [44.9]	18965 [39.5]	16283 [33.9]
Ethnicity, White	46212 [95.4]	45654 [95.6]	45977 [95.8]	45877 [95.5]
Smoking status				
Never	26818 [55.3]	27386 [57.3]	28022 [58.4]	28192 [58.7]
Former	16313 [33.7]	16460 [34.5]	16710 [34.8]	17000 [35.4]
Current	5195 [10.7]	3806 [8.0]	3176 [6.6]	2724 [5.7]
Missing	127 [0.3]	126 [0.3]	104 [0.2]	115 [0.2]
Townsend deprivation index	-1.5 (3.0)	-1.7 (2.9)	-1.7 (2.8)	-1.6 (2.9)
College or university degree, Y	16714 [34.5]	20026 [41.9]	22205 [46.2]	24424 [50.9]
Average total household income before tax				
< £18000	7119 [14.7]	6302 [13.2]	5923 [12.3]	6017 [12.5]
£18000-30999	10740 [22.2]	10239 [21.4]	10220 [21.3]	10192 [21.2]
£31000- £51999	12937 [26.7]	12195 [25.5]	12374 [25.8]	12173 [25.3]
£52000-100000	10168 [21]	10913 [22.8]	11097 [23.1]	11091 [23.1]
> £100000	2521 [5.2]	3270 [6.8]	3397 [7.1]	3624 [7.5]
Physical activity score				
Low	5965 [12.3]	5437 [11.4]	4660 [9.7]	3910 [8.1]
Moderate	19019 [39.3]	19082 [39.9]	19205 [40.0]	18453 [38.4]
High	14387 [29.7]	14756 [30.9]	15917 [33.2]	18126 [37.7]
Sitting score (hours/day)	5.2 (2.5)	4.8 (2.3)	4.6 (2.2)	4.3 (2.2)
Sleep score [range: 0-5]	3.6 (1.0)	3.7 (1.0)	3.7 (1.0)	3.8 (1.0)
Dietary supplement use, yes	22261 (45.9)	24244 (50.7)	25842 (53.8)	27855 (58.0)
BMI, kg/m^2	27.5 (4.8)	27.0 (4.6)	26.6 (4.4)	26.2 (4.5)
SBP, mmHg	137.1 (17.9)	136.6 (18.3)	136.5 (18.4)	136.1 (18.6)
DBP, mmHg	82.6 (10.0)	82.0 (10.0)	81.6 (10.0)	81.2 (10.0)
TC, mmol/L	5.7 (1.1)	5.8 (1.1)	5.8 (1.1)	5.8 (1.1)
LDL-C, mmol/L	3.6 (0.8)	3.6 (0.8)	3.6 (0.8)	3.6 (0.8)
HDL-C, mmol/L	1.4 (0.4)	1.5 (0.4)	1.5 (0.4)	1.6 (0.4)
Triglycerides, mmol/L	1.8 (1.1)	1.7 (1.0)	1.6 (1.0)	1.6 (0.9)
HbA1c (mmol/mol)	35.6 (6.1)	35.4 (5.9)	35.3 (5.8)	35.3 (5.5)

Data are expressed as mean (SD) for continuous variables, N [%] for categorical variables. BMI, Body Mass Index; DBP, Diastolic Blood Pressure; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, Systolic Blood Pressure; TC, total cholesterol

Table 2. Food groups and nutrient intake based on quartile categories of heart-protective diet scores

Quartiles	Q1 (n=48453)	Q2 (n=47778)	Q3 (n=48012)	Q4 (n=48031)
Heart-protective diet score	-6.8 (3.6)	0.3 (1.5)	5.2 (1.5)	12.5 (3.8)
Food groups intake, servings/d				
Wholegrains (1 serve: 60g)	1.3 (1.7)	1.9 (1.8)	2.4 (1.8)	2.9 (2.0)
Fruits (1 serve: 80g)	0.9 (1.3)	1.5 (1.6)	2.2 (1.8)	3.3 (2.2)
Non-starchy Vegetables (1 serve: 80g)	1.3 (1.7)	2.0 (2.0)	2.6 (2.3)	3.9 (2.9)
Starchy Vegetables (1 serve: 75g)	0.02 (0.12)	0.03 (0.17)	0.06 (0.23)	0.14 (0.37)
Nuts & Seeds (1 serve: 30g)	0.1 (0.3)	0.1 (0.4)	0.2 (0.5)	0.3 (0.7)
Legumes & Beans, Other Vegetarian Protein Alternatives (1 serve: 80g)	0.2 (0.4)	0.3 (0.6)	0.4 (0.6)	0.7 (0.8)
Uncoated Fish & Seafood (1 serve: 140g)	0.1 (0.3)	0.2 (0.5)	0.3 (0.6)	0.5 (0.7)
Eggs (1 serve: 120g)	0.2 (0.5)	0.3 (0.6)	0.3 (0.6)	0.4 (0.7)
(Reduced-fat and/or No Added Sugar) Milk & Dairy Products (1 serve: 250ml)	0.07 (0.31)	0.09 (0.34)	0.13 (0.4)	0.21 (0.51)
Tea, Coffee & Other Low-calorie Drinks (1 serve: 250ml)	1.4 (1.9)	2.0 (2.1)	2.4 (2.1)	3.1 (2.2)
Homemade soup (1 serve: 250ml)	0.03 (0.19)	0.07 (0.27)	0.10 (0.33)	0.19 (0.45)
Refined grains & cereals, including discretionary choices (1 serve: 60g)	1.9 (1.7)	1.0 (1.3)	0.7 (1.0)	0.4 (0.7)
Potatoes (1 serve: 75g)	0.9 (0.9)	0.7 (0.8)	0.7 (0.7)	0.5 (0.6)
Meat, Poultry & Processed Meat (1 serve: 70g)	1.6 (1.3)	1.2 (1.1)	1.0 (1.0)	0.7 (0.9)
Coated Fish & Seafood (1 serve: 140g)	0.08 (0.34)	0.06 (0.27)	0.04 (0.22)	0.02 (0.16)
(Full-fat and/or Added Sugar) Milk & Dairy Products (1 serve: 250ml)	1.3 (1.2)	1.2 (1.2)	1.1 (1.1)	1.1 (1.1)
Processed Soup (1 serve: 250ml)	0.11 (0.33)	0.08 (0.28)	0.07 (0.26)	0.05 (0.21)
Sugar, Sweets & Desserts, Cookies & Pastries (1 serve: 40g)	2.0 (2.0)	1.3 (1.6)	1.0 (1.4)	0.6 (1.1)
Savoury Snacks (1 serve: 30g)	0.07 (0.30)	0.05 (0.23)	0.04 (0.20)	0.03 (0.16)
Sugary Drinks including Juices & Sugar-sweetened Beverages (1 serve: 150ml)	0.14 (0.47)	0.1 (0.38)	0.08 (0.34)	0.06 (0.30)
Artificial sweeteners (1 serve: 4g)	0.4 (0.9)	0.2 (0.7)	0.2 (0.6)	0.1 (0.5)
Unhealthy Fat (with/without Carbohydrates) (1 serve: 10g)	0.6 (1.1)	0.4 (0.9)	0.3 (0.8)	0.2 (0.7)
Daily nutrient intake				
Total energy intake, kcal/d	2187.3 (631.4)	2016.4 (604.0)	1970.7 (580.6)	1991.6 (578.6)
Total protein, g/d	81.6 (28.0)	78.4 (26.3)	78.4 (25.3)	81.9 (26.2)
Total fat, g/d	79.4 (31.0)	71.2 (29.8)	68.5 (29.1)	68.8 (30.2)

Saturated fatty acids, g/d	31.2 (13.8)	27.1 (12.6)	25.0 (12.0)	23.0 (11.6)
Monounsaturated fatty acids, g/d	28.7 (11.8)	25.6 (11.5)	24.7 (11.4)	25.3 (12.3)
n-3 fatty acids, g/d	1.8 (0.9)	1.8 (1.0)	1.9 (1.1)	2.3 (1.4)
n-6 fatty acids, g/d	10.8 (5.3)	10.3 (5.4)	10.5 (5.7)	11.7 (6.5)
Total carbohydrate, g/d	269.7 (85.4)	247.6 (81.9)	244.1 (80.0)	249.3 (80.6)
Total sugar, g/d	125.1 (54.1)	119.4 (50.9)	122.3 (50.2)	132.1 (52.2)
Dietary fibre, g/d	14.6 (5.9)	16.3 (6.3)	18.3 (6.5)	22.3 (7.7)
Alcohol, g/d	18.0 (26.2)	17.7 (24.9)	16.5 (23.1)	14.42 (21.4)
Vitamin C, mg/d	96.8 (71.1)	115.7 (77.9)	134.8 (83.4)	169.8 (97.5)
Vitamin E, mg/d	10.5 (5.0)	10.17 (4.9)	10.65 (4.9)	12.3 (5.2)
Vitamin B12, ug/d	5.7 (3.7)	5.80 (3.7)	6.1 (3.8)	6.9 (4.2)
Folate, ug/d	277.0 (107.3)	292.7 (110.0)	315.5 (110.4)	364.1 (122.7)
Beta carotene, ug/d	1727.4 (2089.6)	2239.4 (2445.7)	2760.2 (2724.9)	3937.7 (3566.4)
Iron, mg/d	11.7 (4.0)	11.8 (4.0)	12.2 (4.0)	13.5 (4.3)
Zinc, mg/d	9.8 (4.0)	9.5 (3.7)	9.5 (3.5)	9.8 (3.5)
Magnesium, mg/d	299.9 (90.3)	313.3 (92.5)	333.8 (93.5)	379.5 (106.4)
Iodine, ug/d	203.8 (109.3)	201.9 (111.5)	207.9 (119.6)	224.2 (135.7)
Sodium, mg/d	2158.5 (912.8)	1895.3 (845.3)	1814.8 (810.0)	1843.1 (820.2)
Potassium, mg/d	3342.3 (1099.5)	3478.5 (1100.8)	3686.0 (1088.8)	4128.9 (1157.0)

Data are expressed as mean (SD).

References

1. Timmis A, Vardas P, Townsend N, Torbica A, Katus H, De Smedt D, Gale CP, Maggioni AP, Petersen SE, Huculeci R, Kazakiewicz D, de Benito Rubio V, Ignatiuk B, Raisi-Estabragh Z, Pawlak A, Karagiannidis E, Treskes R, Gaita D, Beltrame JF, McConnachie A, Bardinet I, Graham I, Flather M, Elliott P, Mossialos EA, Weidinger F, Achenbach S. European Society of Cardiology: cardiovascular disease statistics 2021. Eur Heart J 2022;**43**(8):716-799.
2. Lichtenstein AH, Appel LJ, Vadiveloo M, Hu FB, Kris-Etherton PM, Rebholz CM, Sacks FM, Thorndike AN, Van Horn L, Wylie-Rosett J. 2021 Dietary Guidance to Improve Cardiovascular Health: A Scientific Statement From the American Heart Association. Circulation 2021;**144**(23):e472-e487.
3. Tosti V, Bertozzi B, Fontana L. Health benefits of the mediterranean diet: metabolic and molecular mechanisms. The Journals of Gerontology: Series A 2017;**73**(3):318-326.
4. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, Greenlund K, Daniels S, Nichol G, Tomaselli GF, Arnett DK, Fonarow GC, Ho PM, Lauer MS, Masoudi FA, Robertson RM, Roger V, Schwamm LH, Sorlie P, Yancy CW, Rosamond WD. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. Circulation 2010;**121**(4):586-613.
5. Petermann-Rocha F, Parra-Soto S, Gray S, Anderson J, Welsh P, Gill J, Sattar N, Ho FK, Celis-Morales C, Pell JP. Vegetarians, fish, poultry, and meat-eaters: who has higher risk of cardiovascular disease incidence and mortality? A prospective study from UK Biobank. Eur Heart J 2021;**42**(12):1136-1143.
6. Tong TYN, Appleby PN, Bradbury KE, Perez-Cornago A, Travis RC, Clarke R, Key TJ. Risks of ischaemic heart disease and stroke in meat eaters, fish eaters, and vegetarians over 18 years of follow-up: results from the prospective EPIC-Oxford study. Bmj 2019;**366**:l4897.
7. Appleby PN, Crowe FL, Bradbury KE, Travis RC, Key TJ. Mortality in vegetarians and comparable nonvegetarians in the United Kingdom. Am J Clin Nutr 2016;**103**(1):218-30.
8. Key TJ, Appleby PN, Spencer EA, Travis RC, Roddam AW, Allen NE. Mortality in British vegetarians: results from the European Prospective Investigation into Cancer and Nutrition (EPIC-Oxford). The American Journal of Clinical Nutrition 2009;**89**(5):1613S-1619S.
9. Satija A, Bhupathiraju SN, Spiegelman D, Chiuve SE, Manson JE, Willett W, Rexrode KM, Rimm EB, Hu FB. Healthful and Unhealthful Plant-Based Diets and the Risk of Coronary Heart Disease in U.S. Adults. J Am Coll Cardiol 2017;**70**(4):411-422.
10. Satija A, Bhupathiraju SN, Rimm EB, Spiegelman D, Chiuve SE, Borgi L, Willett WC, Manson JE, Sun Q, Hu FB. Plant-Based Dietary Patterns and Incidence of Type 2 Diabetes in US Men and Women: Results from Three Prospective Cohort Studies. PLoS Med 2016;**13**(6):e1002039.
11. Bycroft C, Freeman C, Petkova D, Band G, Elliott LT, Sharp K, Motyer A, Vukcevic D, Delaneau O, O'Connell J, Cortes A, Welsh S, Young A, Effingham M, McVean G, Leslie S, Allen N, Donnelly P, Marchini J. The UK Biobank resource with deep phenotyping and genomic data. Nature 2018;**562**(7726):203-209.
12. Liu B, Young H, Crowe FL, Benson VS, Spencer EA, Key TJ, Appleby PN, Beral V. Development and evaluation of the Oxford WebQ, a low-cost, web-based method for assessment of previous 24 h dietary intakes in large-scale prospective studies. Public Health Nutr 2011;**14**(11):1998-2005.
13. Bradbury KE, Young HJ, Guo W, Key TJ. Dietary assessment in UK Biobank: an evaluation of the performance of the touchscreen dietary questionnaire. J Nutr Sci 2018;**7**:e6.

14. Martinez-Gonzalez MA, Sanchez-Tainta A, Corella D, Salas-Salvado J, Ros E, Aros F, Gomez-Gracia E, Fiol M, Lamuela-Raventos RM, Schroder H, Lapetra J, Serra-Majem L, Pinto X, Ruiz-Gutierrez V, Estruch R. A provegetarian food pattern and reduction in total mortality in the Prevencion con Dieta Mediterranea (PREDIMED) study. American Journal of Clinical Nutrition 2014;**100**(SUPPL. 1):320S-328S.

15. Marchese LE, McNaughton SA, Hendrie GA, Wingrove K, Dickinson KM, Livingstone KM. A scoping review of approaches used to develop plant-based diet quality indices. Current Developments in Nutrition 2023;**7**(4):100061.

16. Nutritools. *Strengths and Weaknesses of Dietary Assessment Tools (DATs)*. https://www.nutritools.org/strengths-and-weaknesses.

17. Chen F, Ding C, Du M, Keaver L, Liu J, Ruan M, Shan Z, Wang J, Zhang FF. Plant- and animal-based diet quality and mortality among US adults: a cohort study. British Journal of Nutrition 2021;**125**(12):1405-1415.

18. Caivano S, Colugnati FAB, Domene SMÁ. Diet Quality Index associated with Digital Food Guide: update and validation. Cadernos de Saúde Pública 2019;**35**.

19. Bromage S, Batis C, Bhupathiraju SN, Fawzi WW, Fung TT, Li Y, Deitchler M, Angulo E, Birk N, Castellanos-Gutiérrez A, He Y, Fang Y, Matsuzaki M, Zhang Y, Moursi M, Kronsteiner-Gicevic S, Holmes MD, Isanaka S, Kinra S, Sachs SE, Stampfer MJ, Stern D, Willett WC. Development and Validation of a Novel Food-Based Global Diet Quality Score (GDQS). The Journal of Nutrition 2021;**151**:75S-92S.

20. American Heart Association. *The American Heart Associaton Diet and Lifestyle Recommendations*. https://www.heart.org/.

21. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen M-R, Tokgozoglu L, Wiklund O, Group ESD. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). European Heart Journal 2019;**41**(1):111-188.

22. Heart Foundation. *Nutrition Position Statements*. https://www.heartfoundation.org.au/bundles/for-professionals/nutrition-position-statements.

23. Satija A, Bhupathiraju SN, Rimm EB, Spiegelman D, Chiuve SE, Borgi L, Willett WC, Manson JE, Sun Q, Hu FB. Plant-Based Dietary Patterns and Incidence of Type 2 Diabetes in US Men and Women: Results from Three Prospective Cohort Studies. PLoS Medicine / Public Library of Science 2016;**13**(6):e1002039.

24. Micha R, Shulkin ML, Peñalvo JL, Khatibzadeh S, Singh GM, Rao M, Fahimi S, Powles J, Mozaffarian D. Etiologic effects and optimal intakes of foods and nutrients for risk of cardiovascular diseases and diabetes: Systematic reviews and meta-analyses from the Nutrition and Chronic Diseases Expert Group (NutriCoDE). PLoS One 2017;**12**(4):e0175149.

25. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Himmelfarb CD, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA, Williamson JD, Wright JT. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension 2018;**71**(6):e13-e115.

26. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC, Jr., Sperling L, Virani SS, Yeboah J. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;**73**(24):3168-3209.
27. NHS. *The Eatwell Guide*. https://www.nhs.uk/live-well/eat-well/food-guidelines-and-food-labels/the-eatwell-guide/ (29th Nov 2022; date last accessed).
28. Cheung HC, MacLaughlin HL, McAuley E, Ross LJ, Tan MS. Quality and validity of diet quality indices for use in Australian contexts: a systematic review. British Journal of Nutrition 2022;**128**(10):2021-2045.
29. Chamoli R, Jain M, Tyagi G. Reliability and Validity of the Diet Quality Index for 7-9-year-old Indian Children. Pediatr Gastroenterol Hepatol Nutr 2019;**22**(6):554-564.
30. Bolland MJ, Barber A, Doughty RN, Grey A, Gamble G, Reid IR. Differences between self-reported and verified adverse cardiovascular events in a randomised clinical trial. BMJ Open 2013;**3**(3):e002334.
31. Machón M, Arriola L, Larrañaga N, Amiano P, Moreno-Iribas C, Agudo A, Ardanaz E, Barricarte A, Buckland G, Chirlaque MD, Gavrila D, Huerta JM, Martinez C, Molina E, Navarro C, Quiros JR, Rodríguez L, Sanchez MJ, González CA, Dorronsoro M. Validity of self-reported prevalent cases of stroke and acute myocardial infarction in the Spanish cohort of the EPIC study. Journal of Epidemiology and Community Health 2013;**67**(1):71.
32. Okura Y, Urban LH, Mahoney DW, Jacobsen SJ, Rodeheffer RJ. Agreement between self-report questionnaires and medical record data was substantial for diabetes, hypertension, myocardial infarction and stroke but not for heart failure. Journal of Clinical Epidemiology 2004;**57**(10):1096-1103.
33. Eliassen BM, Melhus M, Tell GS, Borch KB, Braaten T, Broderstad AR, Graff-Iversen S. Validity of self-reported myocardial infarction and stroke in regions with Sami and Norwegian populations: the SAMINOR 1 Survey and the CVDNOR project. BMJ Open 2016;**6**(11):e012717.
34. Darke P, Cassidy S, Catt M, Taylor R, Missier P, Bacardit J. Curating a longitudinal research resource using linked primary care EHR data-a UK Biobank case study. J Am Med Inform Assoc 2022;**29**(3):546-552.
35. Pastorino S, Richards M, Hardy R, Abington J, Wills A, Kuh D, Pierce M. Validation of self-reported diagnosis of diabetes in the 1946 British birth cohort. Prim Care Diabetes 2015;**9**(5):397-400.
36. Schneider ALC, Pankow JS, Heiss G, Selvin E. Validity and Reliability of Self-reported Diabetes in the Atherosclerosis Risk in Communities Study. American Journal of Epidemiology 2012;**176**(8):738-743.
37. Jackson JM, DeFor TA, Crain AL, Kerby TJ, Strayer LS, Lewis CE, Whitlock EP, Williams SB, Vitolins MZ, Rodabough RJ, Larson JC, Habermann EB, Margolis KL. Validity of diabetes self-reports in the Women's Health Initiative. Menopause 2014;**21**(8):861-8.
38. Moradpour F, Piri N, Dehghanbanadaki H, Moradi G, Fotouk-Kiai M, Moradi Y. Socio-demographic correlates of diabetes self-reporting validity: a study on the adult Kurdish population. BMC Endocrine Disorders 2022;**22**(1):139.

39. Chen H, Shen J, Xuan J, Zhu A, Ji JS, Liu X, Cao Y, Zong G, Zeng Y, Wang X, Yuan C. Plant-based dietary patterns in relation to mortality among older adults in China. Nature Aging 2022;**2**(3):224-230.
40. Kim J, Kim H, Giovannucci EL. Plant-based diet quality and the risk of total and disease-specific mortality: A population-based prospective study. Clin Nutr 2021;**40**(12):5718-5725.
41. Heianza Y, Zhou T, Sun D, Hu FB, Qi L. Healthful plant-based dietary patterns, genetic risk of obesity, and cardiovascular risk in the UK biobank study. Clinical Nutrition 2021;**40**(7):4694-4701.
42. Martínez-González MA, Gea A, Ruiz-Canela M. The Mediterranean Diet and Cardiovascular Health. Circulation Research 2019;**124**(5):779-798.
43. Livingstone KM, Abbott G, Bowe SJ, Ward J, Milte C, McNaughton SA. Diet quality indices, genetic risk and risk of cardiovascular disease and mortality: a longitudinal analysis of 77 004 UK Biobank participants. BMJ Open 2021;**11**(4):e045362.
44. Sacks FM, Lichtenstein AH, Wu JHY, Appel LJ, Creager MA, Kris-Etherton PM, Miller M, Rimm EB, Rudel LL, Robinson JG, Stone NJ, Van Horn LV. Dietary Fats and Cardiovascular Disease: A Presidential Advisory From the American Heart Association. Circulation 2017;**136**(3):e1-e23.
45. Mensink RP, Zock PL, Kester AD, Katan MB. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. Am J Clin Nutr 2003;**77**(5):1146-55.
46. Abumweis SS, Barake R, Jones PJ. Plant sterols/stanols as cholesterol lowering agents: A meta-analysis of randomized controlled trials. Food Nutr Res 2008;**52**.
47. Theuwissen E, Mensink RP. Water-soluble dietary fibers and cardiovascular disease. Physiol Behav 2008;**94**(2):285-92.
48. Müller M, Canfora EE, Blaak EE. Gastrointestinal Transit Time, Glucose Homeostasis and Metabolic Health: Modulation by Dietary Fibers. Nutrients 2018;**10**(3).
49. Bjerregaard LJ, Joensen AM, Dethlefsen C, Jensen MK, Johnsen SP, Tjønneland A, Rasmussen LH, Overvad K, Schmidt EB. Fish intake and acute coronary syndrome. European Heart Journal 2009;**31**(1):29-34.
50. Strøm M, Halldorsson TI, Mortensen EL, Torp-Pedersen C, Olsen SF. Fish, n-3 fatty acids, and cardiovascular diseases in women of reproductive age: A prospective study in a large national cohort. Hypertension 2012;**59**(1):36-43.
51. Karusheva Y, Koessler T, Strassburger K, Markgraf D, Mastrototaro L, Jelenik T, Simon M-C, Pesta D, Zaharia O-P, Bódis K, Bärenz F, Schmoll D, Wolkersdorfer M, Tura A, Pacini G, Burkart V, Müssig K, Szendroedi J, Roden M. Short-term dietary reduction of branched-chain amino acids reduces meal-induced insulin secretion and modifies microbiome composition in type 2 diabetes: a randomized controlled crossover trial. The American Journal of Clinical Nutrition 2019;**110**(5):1098-1107.
52. Theuwissen E, Mensink RP. Water-soluble dietary fibers and cardiovascular disease. Physiology & Behavior 2008;**94**(2):285-292.
53. Müller M, Canfora EE, Blaak EE. Gastrointestinal Transit Time, Glucose Homeostasis and Metabolic Health: Modulation by Dietary Fibers. Nutrients 2018;**10**(3):275.
54. Matsumoto C, Yoruk A, Wang L, Gaziano JM, Sesso HD. Fish and omega-3 fatty acid consumption and risk of hypertension. Journal of Hypertension 2019;**37**(6).

Figure 1

Outcome	N	Events	HR [95% CI]	Adjusted p-value
CVD Incidence	192274	20692		
Q1 (Ref.)	42731	5722	1.00 (Ref.)	
Q2	42509	5269	0.98 [0.94,1.02]	0.348
Q3	43031	4981	0.94 [0.90,0.98]	0.006
Q4	43311	4720	0.92 [0.88,0.95]	<0.001
IHD Incidence	192274	11241		
Q1 (Ref.)	45180	3273	1.00 (Ref.)	
Q2	44924	2854	0.96 [0.91,1.01]	0.161
Q3	45330	2682	0.93 [0.88,0.98]	0.022
Q4	45599	2432	0.88 [0.83,0.93]	<0.001
MI Incidence	192274	3452		
Q1 (Ref.)	47376	1077	1.00 (Ref.)	
Q2	46900	878	0.94 [0.86,1.02]	0.239
Q3	47193	819	0.93 [0.84,1.01]	0.178
Q4	47353	678	0.82 [0.74,0.90]	<0.001
Stroke Incidence	192274	3103		
Q1 (Ref.)	47605	848	1.00 (Ref.)	
Q2	46994	784	0.97 [0.88,1.07]	0.637
Q3	47296	716	0.89 [0.81,0.99]	0.072
Q4	47276	755	0.96 [0.87,1.07]	0.554
HF Incidence	192274	3189		
Q1 (Ref.)	47525	928	1.00 (Ref.)	
Q2	46958	820	0.95 [0.87,1.05]	0.420
Q3	47271	741	0.88 [0.80,0.97]	0.027
Q4	47331	700	0.86 [0.78,0.95]	0.011
AF Incidence	192274	8913		
Q1 (Ref.)	46141	2312	1.00 (Ref.)	
Q2	45480	2298	1.03 [0.97,1.09]	0.409
Q3	45817	2195	0.99 [0.93,1.05]	0.717
Q4	45923	2108	0.97 [0.92,1.03]	0.469

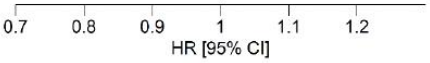


Figure 1. Association between quartiles of heart-protective diet score and risk of incident cardiovascular diseases. Data presented as adjusted hazard ratio [95% confidence interval]. Q1 was used as the reference group. Cox proportional hazard models were adjusted by age (timescale), sex, ethnicity, Townsend deprivation index, average house income, education level, dietary supplement use, history of cancer diagnosis, history of hyperglycemia/type 2 diabetes diagnosis, physical activity level, sitting, sleep quality, smoke habits. CVD, Cardiovascular Disease; IHD, Ischemic Heart Disease; MI, Myocardial Infarction; HF, Heart Failure; AF, Atrial Fibrillation; HR, Hazard Ratio. Adjusted p-values were obtained using Benjamini-Hochberg procedure.

Figure 2

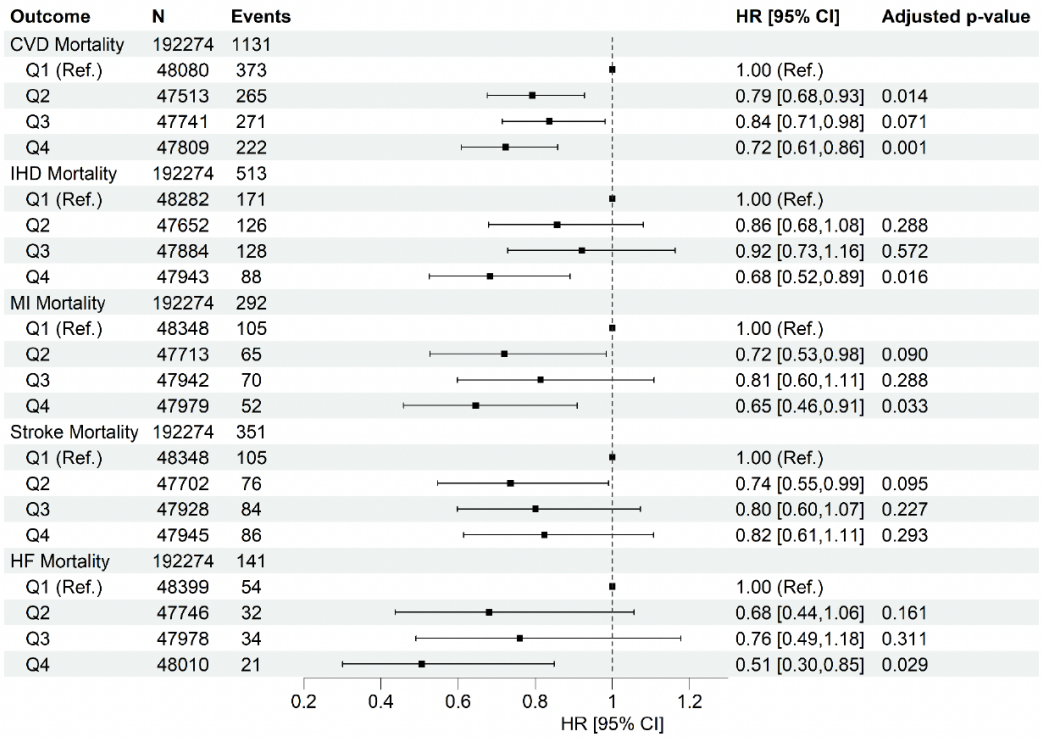


Figure 2. Association between quartiles of heart-protective diet score and risk of cardiovascular mortality. Data presented as adjusted hazard ratio [95% confidence interval]. Q1 was used as the reference group. Cox proportional hazard models were adjusted by age (timescale), sex, ethnicity, Townsend deprivation index, average house income, education level, dietary supplement use, history of cancer diagnosis, history of hyperglycemia/type 2 diabetes diagnosis, physical activity level, sitting, sleep quality, smoke habits. CVD, Cardiovascular Disease; IHD, Ischemic Heart Disease; MI, Myocardial Infarction; HF, Heart Failure; HR, Hazard Ratio. Adjusted p-values were obtained using Benjamini-Hochberg procedure.

Figure 3

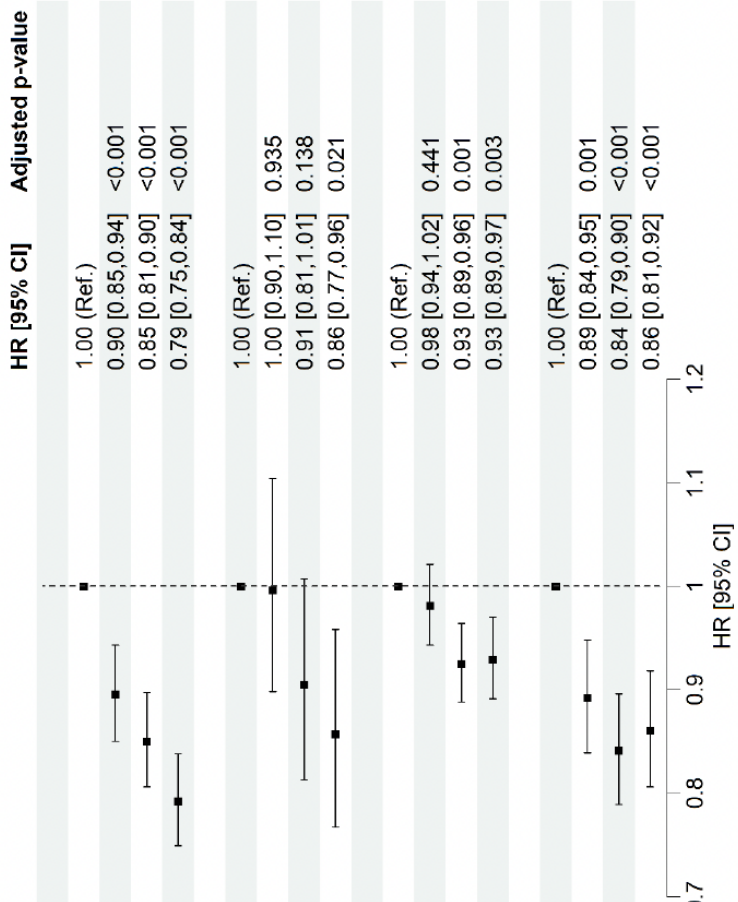


Figure 3. Association between quartiles of heart-protective diet score and risk of cardiometabolic abnormalities. Data presented as adjusted hazard ratio [95% confidence interval]. Q1 was used as the reference group. Cox proportional hazard models were adjusted by age (timescale), sex, ethnicity, Townsend deprivation index, average house income, education level, dietary supplement use, history of cancer diagnosis, history of hyperglycemia/type 2 diabetes diagnosis, physical activity level, sitting, sleep quality, smoke habits. HR, Hazard Ratio. Adjusted p-values were obtained using Benjamini-Hochberg procedure.

CHAPTER 5: Impact of An Intensive Lifestyle Program on Low Attenuation Plaque and Myocardial Perfusion in Coronary Heart Disease: A Randomised Clinical Trial Protocol

Finally, to further address the research gaps identified in CHAPTER 3, we designed and delivered the LIVEPLUS (LIfestyle VulnErable PLaqUe) trial, to test the effect of an intensive lifestyle program (ILP: combining a 5:2 pesco-vegetarian diet, individualized exercise sessions and stress reduction) in patients with stable coronary heart disease (CHD). Nutrition is an integral part of this project, and I am the dietitian (TW) who leads the dietary intervention of this novel and exciting trial. I was responsible for the development of nutritional educational materials and recipes, dietary assessments, delivery of nutritional interventions and performing individualized nutritional counselling with the participants.

The LIVEPLUS trial consists of three chapters of this thesis. This chapter illustrates the design and protocol of the LIVEPLUS trial; CHAPTER 6 describes the demographic, baseline clinical characteristics and dietary habits of participants; and CHAPTER 7 presents preliminary findings from the LIVEPLUS trial. The initial plan was to present data for at least 40 participants, with 20 patients in each arm. However, due to COVID-19 pandemic, the recruitment was delayed for two years. We still feel the data currently collected makes an important contribution to this thesis, but we will not publish results as a manuscript until the sample size is larger.

The paper of this work has been published in the Journal of Nutrition and Healthy Aging:

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Impact of an intensive lifestyle program on low attenuation plaque and myocardial perfusion in coronary heart disease: A randomised clinical trial protocol

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Abstract.
IMPORTANCE: The evidence that maintaining a healthy body weight in conjunction with healthier eating patterns, exercise training, and reduced stress can improve clinical outcomes in patients with atherosclerotic cardiovascular disease is substantial. However, little is known about the magnitude and temporal effects of a comprehensive lifestyle treatment on coronary artery anatomy, myocardial inflammation, and fibrosis in people affected by coronary heart disease.

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OBJECTIVE: To conduct a randomised clinical trial to determine the impact of a 12-month intense lifestyle intervention delivered via an mHealth platform (in the form of a mobile App) versus standard clinical care on low attenuation plaque volume and structure, stress myocardial perfusion, and diastolic function.

DESIGN: A single centre, parallel-group, randomised controlled trial. The co-primary endpoints are: 1-Low Attenuation Plaque (LAP) volume (mm^3) using coronary computed tomography angiography (CCTA) at 12 months, and 2-Adenosine stress myocardial blood flow (stress MBF, mL/min/g) using cardiovascular magnetic resonance imaging (MRI) at 12 months. Other key measurements include liver steatosis by MRI, subclinical abnormalities detected by advanced electrocardiography, arterial stiffness, endothelial function, genomic, metabolomic, and gut microbiome-related adaptations to these structural changes. An intention-to-treat principle will be used for all analyses.

SETTING: Participants will be recruited from a large academic cardiology office practice (Central Sydney Cardiology) and Royal Prince Alfred Hospital (RPAH) Departments of Cardiology and Radiology. All clinical investigations will be undertaken within the Charles Perkins Centre-RPAH clinic.

PARTICIPANTS: Individuals ($n = 150$) with stable coronary heart disease who have low attenuation plaque based on a CCTA within the past 3 months, will be randomised to a lifestyle intervention program comprising a 5:2 pesco-vegetarian diet, exercise training, and mindfulness-based stress reduction ($n = 75$) or usual care ($n = 75$).

DISCUSSION: This trial will represent the single most detailed and integrated analysis of the effects of a comprehensive lifestyle intervention targeting multiple metabolic pathways, delivered via a customized m-Health App on smart devices, on coronary macro- and microcirculation, heart physiology, and cardiometabolic risk. It will provide a new framework for allowing clinicians and individuals to optimise metabolic health for the prevention and management of atherosclerotic cardiovascular diseases that is epidemic in modern society.

Trial registration: Australian New Zealand Clinical Trials Registry (ANZCTR). ACTRN12620001151921. https://www.anzctr.org.au/ACTRN12620001151921.aspx

1. Introduction

Cardiovascular disease (CVD) is becoming the primary cause of morbidity, disability and premature death not only in Western countries but also in the developing world [1]. Lifetime risk of a first CVD event at age 50 is ~65% in men [2], and is increasingly affecting younger women and men, especially in some ethnic groups that for genetic and epigenetic reasons poorly tolerate the caloric surplus and the build-up of excess abdominal fat [3]. Some accumulation of cellular and tissue damage within the cardiovascular system is an inevitable part of advancing age. However, persistent exposure to traditional and emerging risk factors (including insulin resistance, triglyceride-rich lipoproteins, trimethylamine N-oxide, and accelerated clonal haematopoiesis) associated with unhealthy lifestyle behaviours play a substantial role in the initiation and development of CVD [4, 5] (Fig. 1). Approximately 25% of patients who develop a myocardial infarction have extensive coronary atherosclerosis in the absence of any traditional modifiable cardiovascular risk factors [6].

Classical	Novel
Age	Insulin resistance
Gender	Triglyceride-rich lipoproteins
Total cholesterol	Trimethylamine N-oxide
HDL cholesterol	
Diabetes	Clonal hematopoiesis
Smoking	Microbiome
Systolic blood pressure	Inflammation

Fig. 1. Classical and novel modifiable risk factors for cardiovascular disease.

A growing body of data from animal, epidemiological and clinical studies have demonstrated that calorie excess, poor nutrition, physical inactivity, sleep disturbances, smoking, and mental stress by acting on multiple metabolic and molecular pathways play major roles in the pathogenesis of many cardiometabolic diseases [4]. Findings from the CALERIE phase 1 and 2 trials have shown that calorie restriction without malnutrition even in non-obese individuals can reduce inflammation and oxidative stress, and improve left ventricular diastolic function and multiple cardiometabolic risk factors at supra-physiological levels [7, 8]. Fifty-year-old participants of the Framingham Study with cardiovascular risk factors similar to those achieved during CALERIE-2 [8] and in people practicing long-term calorie restriction [9] had a 5% lifetime risk of developing CVD, whereas the risk increased to 69% in those with 2 or more abnormal cardiometabolic risk factors [10].

Data from nutritional secondary prevention trials in patients with hypertension [11], type 2 diabetes [8], diabetic nephropathy [12], fatty liver disease [13], and high cardio-metabolic risk [14] also showed spectacular improvements in metabolic outcomes and a reduction in major cardiovascular events. The Lyon and Indo-Mediterranean Diet Heart trials have demonstrated a striking protective effect of a Mediterranean-style diet against coronary recurrence rate and sudden cardiac death in those who already suffered from a prior myocardial infarction [12, 15]. Modifications of meal timing, diet quality and the gut microbiome [4, 16] together with regular physical activity [17–19], improved sleep patterns [20, 21] and a reduction in mental stress [3, 22, 23] have also been shown to improve cardiovascular outcomes in those at risk.

1.1. Current challenges

Despite substantial evidence supporting lifestyle behaviour change, there are three major challenges to address. Firstly, there is a need for more mechanistic studies to elucidate the impact of lifestyle on macro- and microvascular structure and function, and advancements in imaging techniques will facilitate this. Coronary computed tomography angiography (CCTA) technology has advanced significantly over recent years and can now identify the volume and structure of low attenuation non-calcified plaques (LAP). LAP is characterised by inflammation, microcalcification, a thin fibrous cap and large lipid-rich necrotic core [24], and in a recent study was the strongest predictor of subsequent myocardial infarction compared to classical risk predictors in individuals with stable Coronary heart disease (CHD). Indeed, those with LAP burden >4% were almost 5 times more likely to have subsequent myocardial infarction [25]. Early evidence suggests that lifestyle intervention may yield LAP changes observable as early as 12 months [26], however there is a dearth of evidence in this area.

Quantification of myocardial blood flow during hyperaemic stress is now possible via automated inline perfusion mapping by cardiovascular magnetic resonance imaging (MRI). Non-invasive myocardial and hemodynamic phenotyping by comprehensive and state-of-the-art cardiac stress MRI can provide quantitative characterisation not only of myocardial blood flow measured during adenosine stress, but also of the volumes and function of heart chambers, left ventricular hypertrophy and diastolic dysfunction, focal and global myocardial inflammation, myocardial infarction or non-ischemic scarring, diffuse myocardial fibrosis, coronary microvascular function including coronary spasm measured with the cold pressor test, and pulmonary congestion at rest and at peak supine ergometer exercise stress [27, 28].

Secondly, current lifestyle interventions are limited in their ability to be scaled up and rolled out across the clinical setting in an affordable way. However, over the past decade there has been an exponential rise in smartphone and wearable use [29], and this type of digital platform may address some of these barriers. Thirdly, the greatest limitation to initiating, engaging and sustaining effective lifestyle change, is adherence. Digital health approaches using an ecosystem which uses a smart phone to deliver these programs have been shown to have superior effectiveness. Smartphone delivery of cardiac rehabilitation was delivered much more effectively than traditional face-to-face cardiac rehabilitation, with enhanced engagement (94% vs. 68% $p<0.05$) and program completion (80% vs. 47%, $p<0.05$) being significantly higher with digital health programs delivered by smartphone [30]. Some advantages of smartphone technology are that it can be initiated rapidly, updated easily, and delivered at anytime from anywhere.

1.2. Aims of LIVEPLUS

The primary aim of the LIVEPLUS study is to assess the effectiveness of a 12-month intensive lifestyle intervention which combines a 5:2 pesco-vegetarian diet, physical activity and stress reduction training, on macrovascular coronary disease (CCTA assessed LAP volume) and microvascular disease (MRI measured stress myocardial perfusion). Secondary aims are to identify changes in other cardiovascular and metabolic/molecular adaptations to this lifestyle intervention. At the centre of the LIVEPLUS study program is digital health ecosystem delivered via a smartphone app (Fig. 2) [31]. Such a digital solution, if proven to be effective, is readily scalable and translatable for incorporation into clinical practice across diverse health care systems at a cost these systems can sustain.

2. Methods

2.1. Study design

LIVEPLUS is a parallel-group, randomised controlled trial (RCT) with a total sample of 150

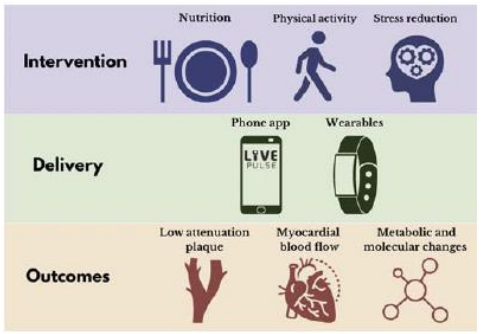


Fig. 2. LIVEPLUS randomised clinical trial.

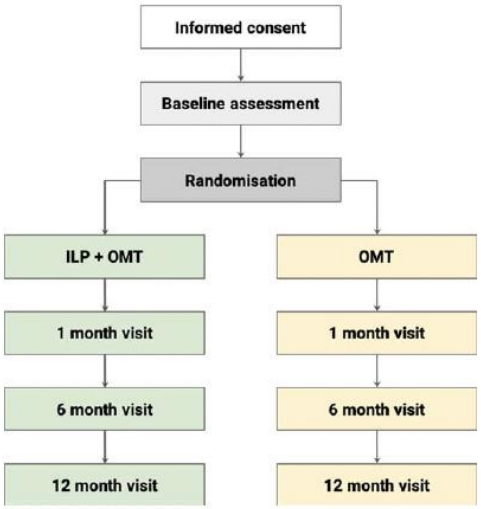


Fig. 3. Study flow. ILP, intensive lifestyle program; OMT, optimal medical therapy.

participants. A 1:1 allocation ratio will be applied to either the intervention group (ILP + OMT) or control group (OMT). Participants in both arms will be followed up over a period of 12 months. A comprehensive set of outcome assessments will be performed prior to initiating the intervention, with follow-up assessments at month 1, 6 and 12 (Fig. 3). This study has been approved by the Sydney Local Health District Ethics committee (2020/ETH01273). Study visits will take place at the Charles Perkins Centre-Royal Prince Alfred Hospital (CPC-RPA) clinic, Royal Prince Alfred Hospital Department of Radiology, and the North Shore Radiology and Nuclear Medicine (NSRNM) facility, Sydney.

2.2. Eligibility criteria

Inclusion criteria are; (1) Presence of LAP on CCTA; (2) 18–80 years of age; (3) BMI >22.0 kg/m^2; (4) Able to provide full informed consent; (5) Considered capable of undergoing all study assessments and adhering to the rigors of the ILP intervention. Exclusion criteria are (1) Non-MRI-compatible implanted devices; (2) Estimated glomerular filtration rate (eGFR) <30 mL/kg/1.73 m^2; (3) Inability to exercise via supine ergometer; (4) Contraindications for adenosine or glyceryl trinitrate; (5) Previous severe allergic reaction to iodinated contrast media; (6) Pregnancy or breastfeeding; and (7) History of any chronic disease process that could interfere with the interpretation of results.

2.3. Recruitment

Participants who have undergone a clinically indicated CCTA within the past 3 months will be recruited if they have quantifiable LAP (plaque within –30 to 150 HU range). At least two experienced CCTA reporters will evaluate the coronary tree for the presence of such plaque. In the general cardiology outpatient population, we expect approximately 20–40% of patients to have LAP. The predominant source of referral for clinically indicated CCTA at RPA for this study will be from a single large academic clinical practice (Central Sydney Cardiology, RPAH Medical Centre) and from patients who have attended the RPA Radiology Department for a clinically indicated CCTA.

2.4. Pre-screening and consent

Following a pre-screening telephone call, an initial video call will take place with eligible, potential participants. During this video call, the research team will deliver a short presentation to the participant to explain the rationale, implications and constraints of the protocol, known side effects and any risks involved in taking part. There will be an opportunity for participants to ask questions and discuss any details of the study. Willing participants will be invited to the CPC-RPA clinic to obtain electronic informed consent through REDCap. Any participant judged by the research team to not possess the capacity for fully informed consent will be excluded from the study, as per the study exclusion criteria.

2.5. Baseline visits

Following consent, participants will be enrolled into the study and undergo a number of clinical baseline assessments. The exact timing of these assessments will be flexible (e.g., due to participant or equipment availability) and can be spread over a number of days, however a potential schedule is shown in Table 1.

2.6. Randomisation and blinding

Enrolled participants will be randomised using random permuted blocks with randomly selected block sizes, via a web-based randomisation system in REDCap, and stratified by age, sex, and BMI. The allocation sequence was generated using blocked size of 2, 4, 6, and 8 from the R package, *blockrand* [32]. An uneven block was included in the middle of the sequence to guard against guessing the group assignment [33]. Investigators and participants will be blinded to the group allocation until all baseline measures have been completed, as the REDCap support statistician is the only individual with access to the upcoming treatment allocations within the randomisation list. After the final baseline measurement, the research co-ordinator will use REDCap to randomise the participant, revealing the group assignment to the study team and participant simultaneously. Due to the nature of the intervention, investigators and participants cannot be blinded during the study, however those performing CCTA, MRI and statistical analysis will be blinded to group allocation.

2.7. Follow-up visits

Table 1 provides an overview of the follow up visits and testing procedures which are planned for months 1, 6, and 12.

2.8. Intervention

The ILP+OMT group will continue to receive standard of care treatment, as well as three main lifestyle intervention components over the 12-month study period. These will target nutrition, physical activity and stress reduction. In the context of each target behaviour, participants will be asked to use the LIVEPULSE app (see section 2.10.1. LIVEPULSE phone app for details) to read 12 education modules (1 per month), and complete multichoice questions at the end of each module to assess learning and provide automatic feedback. The content of the 12 education modules (Table 2) is informed by evidence-based, peer-reviewed research carefully rewritten into lay language, making them accessible and engaging, particularly to those who are new to such lifestyle practices. Participants will also be given online coaching sessions with a dietitian, physical activity coach, and stress reduction coach (Table 3). Each coaching session will be tailored to an individual's progress and needs, using evidence-informed behaviour change techniques [34]. Each coach will receive training in delivery of specific behaviour change techniques to effectively promote change in relation to each target lifestyle behaviour (i.e. nutrition, physical activity and stress reduction). The training will be delivered by a UK-registered practitioner health psychologist with expertise in health behaviour change, and will include use of behaviour change counselling skills as well as behaviour change techniques. Additional online coaching calls may be scheduled to improve adherence to the intervention if considered necessary by the study team.

2.8.1. Nutrition

Several interventional studies have clearly shown that individuals who consume diets rich in fish and nutrient-dense minimally processed plant foods have a lower risk of developing CHD than people who consume energy dense low-fibre Western diets high in saturated and trans fatty acids, animal protein and salt [35–37]. In the LIVEPLUS trial, participants will be asked to follow a 5:2 pesco-vegetarian diet for 12 months. This diet involves a combination of a 5:2 diet and a pesco-vegetarian diet. The aim of a pesco-vegetarian diet will be to substitute meat with fish and processed and refined foods with a range of minimally processed plant-based foods. Red meats, including beef, pork, lamb and other red meat products, and poultry including chicken, duck, goose, and other poultry products are prohibited with this diet. In addition, individual participants will be asked to practice a 5:2 diet, which consists of fasting on 2 non-consecutive days of the week with energy restriction of around 2000 kJ per day for women and around 2500 kJ for men.

During the first 4 weeks of the intervention, participants will receive fresh ingredients and recipes from *Marley Spoon* (a commercial meal delivery service that provides pre-portioned ingredients and recipes to designated addresses for meal preparation), which

Table 1
Schedule of visits and testing procedures at the CPC-RPA clinic. The MRI scan will take place at the North Shore Radiology and Nuclear Medicine facility

	Baseline assessment			1 month	6 month			12 month		
Visit	1	2	3	4	5	6	7	8	9	
Notes	*These visits are flexible and tests can be moved around.*					*These visits are flexible and tests can be moved around but all should be undertaken within 1 week of end-intervention.*				
Informed consent	1									
Full body examination (including BP, weight, waist/hip cm, vital signs)	1			1	1	1			1	
Medical and family history questionnaires	1									
OGTT		1				1				
Psychosocial questionnaires	1					1				
Physical activity assessment (Fitbit & 7-Day PAR)	1					1				
Food diary assessment	1			1	1	1				
Sleep assessment (questionnaires and home sleep study)	1					1				
Urine and Faeces Sample	1			1	1	1				
MRI		1						1		
Randomisation	1									
Fasting blood sample (Biochemistry and Haematology)	1			1	1					
DXA			1						1	
Carotid intima-media thickness			1	1	1				1	
Vascular endothelial function			1	1	1				1	
Autonomic function			1	1	1				1	
Pulse Wave Velocity			1	1	1					
6 minute walk test			1						1	
CCTA							1			

BP, blood pressure; CCTA, coronary computed tomography angiography; DXA, Dual-energy X-ray absorptiometry; OGTT, oral glucose tolerance test; MRI, magnetic resonance imaging; PAR, physical activity recall.

Table 2
Education content for diet, physical activity and stress reduction components for the intervention group

Month	Diet	Physical activity	Stress reduction
1	Introduction of Nutritional Intervention	Importance of physical activity	Introduction
2	Pesco-vegetarian diet	FITT principles and safety	Simple Awareness
3	Intermittent fasting	Physical activity and the heart	Attention and the Brain
4	Healthy eating	Physical activity and the blood vessels	Dealing with Thoughts
5	Dietary measurements	Physical activity and obesity	Biological Basis of Stress: Responding vs. Reacting
6	Fats	Physical activity and mental health	Dealing with Difficult Emotions of Physical Pain
7	Carbohydrates	Physical activity and glucose metabolism	Mindfulness and Communication
8	Protein	Physical activity and fat metabolism	Self-Compassion Cultivation
9	Meal planning	Physical activity and skeletal muscle	Social Connectedness
10	Nutritional labelling	Physical activity and inflammation	A Closer Look at Happiness
11	Dietary patterns and cardiovascular health	Physical activity and brain health	On Relationships
12	Review	Physical activity and cardiorespiratory fitness	Conclusion

FITT: frequency, intensity, time, type.

Table 3
Planned schedule of coaching calls, which can be adapted according to participant preference

	Month 1		Month 2		Month 3		Months 4–12
	Week 1	Week 3	Week 5	Week 7	Week 9	Week 11	Monthly
Dietitian	1 hour	30 min	30 min	30 min	30 min	30 min	30 min
Exercise physiologist	1 hour	30 min	30 min	30 min	30 min	30 min	30 min
Mindfulness coach	1 hour	30 min	30 min	30 min	30 min	30 min	30 min

provides lunch and dinner for 5 days per week to assist with their preparation of a pesco-vegetarian diet. The menu selected by the participants will be sent to the study dietitian and the nutritionist of *Marley Spoon* to ensure it complies with a pesco-vegetarian diet. If participants select meal plans with meat, it will be altered to a pesco-vegetarian diet before delivery. Participants will be required to prepare their breakfasts each day and light meals on fasting days, and the study dietitian will provide the recipes for these meals through the LIVEPULSE mobile app. After the first 4 weeks, they will meet with the study dietitian to design their individualised weekly meal plans and menus to facilitate transition into preparing their own food. The goal is to improve diet quality but also to achieve at least 7-8% weight loss, as we have found this is vital to improve inflammatory, metabolic and cardiac markers [38]. Strategies to implement dietary changes, meal planning, healthy recipes and relevant nutritional information for cardiovascular health will be discussed during dietitian appointments. Along with the education modules, other materials related to the 5:2 pesco-vegetarian diet (e.g. recipes for a pesco-vegetarian diet, recipes for fasting days, food sources that are rich in iron) will also be delivered via the LIVEPULSE mobile app.

2.9. *Physical activity*

There is strong evidence that reducing sedentary behaviour and increasing overall physical activity level is associated with reduced cardiovascular events and mortality [39]. Participants will be given an individualised home-based programme which will be based on the guidelines from the American College of Cardiology Foundation/American Heart Association to manage individuals with stable ischemic heart disease [40]. The principles we will advise include; 1) to perform 30 to 60 minutes of moderate-intensity aerobic physical activity, such as brisk walking, at least 5 days and preferably 7 days per week; 2) increase daily lifestyle physical activity (e.g. walking breaks at work, gardening, household work); and 3) perform resistance training at least 2 days per week. We

do not have one specific training programme for all individuals, but rather these general principles will be individualised based on baseline activity levels and progress throughout the year. To measure baseline activity, participants will wear a *Fitbit* Inspire 2 physical activity tracker for 7 continuous days and will complete a PAR questionnaire. *Fitbit* Inspire 2 is equipped with 3-axis accelerometer and optical heart-rate tracker, however it lacks GPS receiver for accurate distance data. The *Fitbit* device will enable the researchers to access minute by minute step count, heart rate and heart rate variability for all participants, as well as information about duration and timing of sleep, and participants will be asked to wear it for 12 consecutive months. The goal for all participants will be to reach at least 150 minutes of moderate-intensity aerobic physical activity per week within the first 3 months. If participants respond well during the first 3 months of the physical activity intervention, the following 9 months (month 4–12) will aim to vary the prescription in terms of mode, duration, and intensity. Alongside the education modules, the team have also developed a number of exercise circuit videos aimed at a range of intensities to suit a broad range of fitness and confidence levels, which will be available for viewing anytime via the LIVEPULSE app.

2.10. Stress reduction

Chronic stress is an independent risk factor for atherosclerosis [41]. Body-inclusive stress reduction techniques, such as slow breathing [22, 23], gentle yoga [42], and mindfulness [43], have been shown to improve hypertension and autonomic (cardiovagal) function, as well as mental health and quality of life. In the LIVEPLUS trial, the 12-month stress reduction program will draw techniques from Mindfulness Based Stress Reduction (MBSR) and will be supplemented with additional slow and pressurized breathing techniques, gentle yoga, and concepts from positive psychology on evidence-based tips for cultivating happiness and social connectedness. MBSR is a specific mindfulness approach that integrates various mindfulness meditation techniques, as well as gentle hatha yoga, and has been shown clinically and supported by systematic reviews to be beneficial for cardiovascular and mental health [44]. Each month, participants will be introduced to new stress reduction educational content through the app, as well as asked to practice a new breathing (for about 5–10 minutes, 6 days per week) and mindfulness technique (about 20 minutes, once per week). Breathing and yoga videos have been created by our research team to guide participants through their practice. Example breathing and mindfulness practices include slow breathing at six breaths per minute, alternate nostril breathing, sitting meditation, and mindful yoga.

2.10.1. LIVEPULSE mobile app

LivePulse is a health data collection, management and intervention tool consisting of a mobile app for participants and a web dashboard for the research team to use. The app allows participants to create personalised goals, receive reminders, access educational materials, record and share their health data (weight, exercise, diets etc.) with the research team. The app is publicly available both on the Apple App Store and on the Google Play Store in Australia. The underlying technology of the app has been implemented in similar apps created by the developer, Vulsen, for other research studies, some examples include: Success CKD [45], and My Home Hemo [46]. Key features of the app include;

1-Education: Each component of the ILP (nutrition, physical activity and stress reduction) has 12 online modules, and each will be released on a monthly basis for participants to read and interact with. Interactive components include multi-choice questions [26] (Table 2). Video content will be updated throughout the study and will include expert interviews, exercise sessions, breathing techniques and yoga sequences.

2-Monitoring: Participants themselves and members of the research team will be able to monitor progress through a number of app features, including weekly entry of body weight, upload of food images and logging mindfulness practice. The app will also extract data on physical activity and sleep from the *Fitbit* device, and in response to participant progress, the app has a facility for research team members to send short messages and reminders to participants, individually and as a group [47, 48]. The app includes a multi subject weight change simulator to predict whether participants are on track with reaching their dietary goals as evidenced by their weight loss trajectory. The algorithm is modelled from the participant's entry of age, height, gender, and regular updated body weight inputs, as well as our input of their target calorie deficit required to achieve the desired percentage weight loss of 7–8% after 1 year. If a participant falls outside of their error region at any point throughout the study, they will be given the opportunity to receive enhanced support.

3-Goal setting: Participants will be encouraged to set short- and long-term behavioural and outcome goals (e.g., dietary, physical activity and weight), which will be discussed and adapted over the duration of the intervention with the research team coaches [48].

4-Social networks: Participants will be encouraged to connect with other users of the app using the group messaging function to facilitate social support.

5-Just-in-time adaptive intervention (JITAI): Intervention arm participants will receive personalised messages prompting physical activity using JITAI. JITAIs aim is to optimise delivery of intervention components in terms of the right time and location for patients. Micro-randomised trials (MRT) offer a way to optimise such interventions by enabling modelling of causal effects and time-varying effect moderation for individual intervention components within a JITAI [49]. For this reason, we will perform an MRT within the intervention arm.

2.11. Control

OMT group participants will continue to receive standard of care treatment but will also be given a *Fitbit* device, and offered video-call appointments with a study dietitian every 3 months. In addition, they will be instructed to follow the American Heart Association (AHA) Diet and Lifestyle Recommendations to include physical activity [50] and stress reduction. The study dietitian will summarise the content on healthy lifestyles from the AHA website into 8 modules of educational materials. These materials will be delivered to participants each month via email for the first 8 months of the study. The content will cover general healthy eating, healthy meal planning and preparation, and tips to increase vegetable intake. They will also be offered the stress reduction programme at the end of the study.

3. Outcomes

3.1. Primary

3.1.1. Low-attenuation plaque (LAP) volume (mm^3)

LAP volume will be measured at baseline as part of a clinically indicated CCTA and at 12 months for the purpose of this study. CCTA will be performed at Royal Prince Alfred Hospital on a Siemens SOMATOM Force 2 × 192 slice Dual Source scanner and will take approximately 10 minutes, with a total visit duration of approximately 30 minutes. Coronary images will be transferred to a workstation with the use of plaque- analysis software. This software will produce colour-coded maps overlaid with differentiated plaque categories by Hounsfield Unit (HU) values, and those with LAP (–30 to 150 HU) will be invited into the study. LAP volume has been consistently shown to be the best marker of instability and strongest prognostic predictor of a future adverse CV event. CCTA readers will be blinded to group allocation.

3.1.2. Stress myocardial blood flow (MBF, ml/min/g)

Stress MBF will be measured at baseline and at 12 months follow-up during an MRI examination at North Shore Radiology and Nuclear Medicine (NSRNM). The duration of the research MRI examination will be approximately 1.5 hours, with a total visit duration of approximately 2 hours.

The cardiac MRI examination will include the assessment of LV diastolic function at rest and exercise, as well as myocardial perfusion at rest and during different types of stress.

Graded exercise testing will be performed using a supine ergometer while the participant is lying supine in the MRI scanner. The work rate will be increased gradually with a total exercise duration of approximately 8–12 minutes [51]. Assessment of diastolic function at stress will be performed immediately after supine ergometry.

The study utilises the same intravenous gadolinium-based contrast agent that is used clinically to assess myocardial perfusion. The cardiac MRI myocardial perfusion images will be acquired at rest, and during the following stress protocols.

(i) Adenosine stress

Intravenous adenosine infusion will be administered at 140 μg/kg/min via a peripheral intravenous cannula. This is the same protocol as is used at invasive coronary physiological assessment.

(ii) Cold-pressor testing (CPT)

CPT will be carried out, as previously described, by immersing the hands or feet of the participant in ice water measuring at approximately 0–4°C for a duration of 4 minutes. Continuous blood pressure and heart rate will be recorded at one minute intervals

throughout the scan, thus about 10–20 minutes before (depending on how long it takes to finish the initial scans) and during CPT [52].

(iii) Glyceryl Trinitrate (GTN)

Exogenous nitrate is utilised to vasodilate the coronary arteries and assess for endothelial dysfunction. 300 mcg sublingual GTN will be given just prior to acquisition of cardiac MRI images.

3.2. Secondary outcomes

The secondary outcomes to be conducted are listed below. For detailed information on each one, please see the supplement.

- Perivascular Adipose Tissue
- Myocardial inflammation
- Diastolic dysfunction
- Pulmonary congestion during exercise
- Secondary plaque characteristics, including noncalcified plaque volume, dense calcified plaque volume and total atheroma volume (TAV, mm^3)
- Liver fat fraction (%) by MRI
- Flow-mediated dilatation (FMD) (%)
- Carotid intima-media thickness (cIMT) (mm)
- Pulse wave velocity (PWV) (m/s) and Augmentation Index (AI) (%)
- Heart rate variability (HRV) during wakefulness and sleep: Low Frequency (LF) and High Frequency (HF) (ms^2)
- Heart age by resting electrocardiography
- Sleep parameters (total sleep time, Rapid Eye Movement (REM) and Non-REM (NREM) durations, respiratory disturbances, and oxygen saturation)

3.3. Exploratory

There are a number of exploratory outcomes, which are listed below. For detailed information on each one, please see the supplement.

- Body composition
  - Weight (kg)
  - Height (cm)
  - Waist/Hip ratio (cm)
  - Dual-energy X-ray absorptiometry (DEXA) body composition
- Intermediate risk factors that are predictive of developing atherosclerosis
  - Glucose (mmol/L) and Insulin (pmol/L)
  - Blood pressure (mmHg) including both central and peripheral pressures
  - Blood biomarkers
- Urinary levels of F2-isoprostane levels
- Serum hormones, proteomics, lipidomics, metabolomics, genetic and epigenetic profiling of white blood cells
- 6-minute walk test
- Dietary intake (total daily kJ, macronutrient and micronutrient intake (%))
- Time spent in moderate physical activity
- Psychometrics

3.4. Safety reporting

Adverse Events (AE) and Serious Adverse Events (SAE) will be recorded and reported throughout the study to monitor and ensure participant safety. The following information will be reported: description, data of onset and end date, severity, assessment of relatedness to trial intervention or device, and action taken. A team of physicians, including cardiologists, will use their clinical judgement to decide whether an AE is of sufficient severity to remove the participant from the study. SAE will be reported to the primary investigator within 24 hours of the study team becoming aware of the event. The full course of the SAE, including any therapy given, will be reported to the study sponsor. All significant safety issues will be reported to the local Human Research Ethics Committee and Research Governance Officers.

3.5. Sample size calculation

This is a randomised two-arm study design with 2 continuous co-primary endpoints repeatedly measured at baseline and after 12-month follow-up. A total of 150 participants (75 in each arm) will provide 90% power to demonstrate the efficacy of either outcome. The sample size is based on a 2-by-2 repeated measures design using each of the co-primary outcomes (PASS 13 Power Analysis and Sample Size Software (2014)). The conservative Bonferroni correction was applied to control the type I error rate due to multiplicity test. The significance level (alpha) is 0.025 using a two-sided, two-sample *t*-test. The assumptions specific to each co-primary outcome are defined below:

For Low-attenuation plaque volume, an absolute mean difference between groups of $\geq 9.0\,mm^3$ at

12-month is expected to declare the efficacy of the intervention (ILP + OMT) over the control (OMT). The control group mean (standard deviation) is 39.0 (12) mm^3 and 32.3 (15) mm^3 at baseline and after 12-month follow-up respectively [53]. A correlation of between measurement pairs of 0.50 is assumed.

For Myocardial blood flow, an absolute mean difference between groups of $\geq$0.4 ml/min/g at 12-month is expected to declare the efficacy of the intervention (ILP + OMT) over the control (OMT). The control group mean (standard deviation) is 2.71 (0.61) mL/min/g and 2.55 (0.57) mL/min/g at baseline and after 12-month follow-up respectively [54]. A correlation of between measurement pairs of 0.50 is assumed. The overall sample size allows for a 20% attrition rate. Identifying eligible participants, enrolling them into the study, and maintaining their commitment to this intensive intervention over a period of 12 months can be challenging. However, the enrolment of 150 participants over a period of 34–36 months is thought to be feasible with the resources available based on previous research.

3.6. Statistical analysis plan

This is the first detailed investigation of effects of ILP on coronary CT coronary plaque modification and myocardial blood flow over an extended period of time in human participants. Efficacy analyses will be conducted on an 'intention to treat' basis. The primary analysis will be performed using Analysis of Covariance (ANCOVA), adjusted for baseline values [55]. Group comparisons will be two tailed with a nominal 2.5% significance level to adjust for the multiplicity testing using Bonferroni method. Subgroup analyses will be conducted to assess differences in intervention effects across the pre-specified gender and age subgroups. Tests of intervention effect modification will be performed by fitting intervention group and the relevant subgroup main effects and interaction into the models adjusted for baseline scores. Interpretation of evidence of heterogeneity of intervention effects among subgroups will remain exploratory (hypothesis generating) given the study is not powered to test subgroups.

Many of the secondary endpoints are exploratory in nature and will need to be confirmed by follow-up studies. Type-II error, i.e., failing to detect a significant effect when it exists is important to this study for all secondary and exploratory outcomes. Thus, all tests of significance for between-group comparisons will be performed at the $p = 0.05$ level of significance. The primary analysis strategy will utilise Intention-to-Treat principles. LIVEPLUS is also interested in mechanistic questions concerning the effect of ILP, and to address these issues, the Marginal Structural Model (MSM) of Robins and colleagues [56] will be applied. All major secondary outcomes are observed repeatedly at well-defined time points over participant follow-up, so that statistical methods for longitudinal and repeated measures analysis will be applied. Subgroup analyses will be tested by evaluating the treatment by subgroup interaction. Withdrawal from the intervention, drop-out from the study, or death (if any) will be analysed using the standard techniques for survival data.

3.7. Trial status

Recruitment began Feb 2022.

4. Conclusions

LIVEPLUS will help us to identify how a mechanism-based comprehensive lifestyle intervention can affect the major and minor vessels in the heart, perivascular fat, cardiac structure and function, arterial stiffness, endothelial function, and liver steatosis. The sophisticated clinical, metabolic and molecular (multi-omic) phenotyping to nutritional, physical activity and cognitive inputs will provide a unique platform for cybernetic/systems modelling responses in patients affected by coronary heart disease. The data generated will also populate complex systems-based models and provide insights that drive the discovery of new predictive biomarkers of disease. Additionally, the smartphone app is an exciting digital health and educational tool, which can empower individuals to engage with, and sustain, the lifestyle changes they need as individuals to reduce their future risk of adverse cardiovascular outcomes and to track the changes they achieve in a personalised way in near real time. Such a personalised digital health solution, if proven to be effective, is ultimately translational and scalable to use in clinical practice and as an educational tool for health care professionals.

Author contributions

SC drafted the manuscript and integrated additional text by co-authors. CMK managed manuscript

revisions by co-authors. LF conceived the idea for the study and is the senior author of the manuscript. All authors contributed meaningfully to the design of this study, drafted sections of the manuscript based on their respective expertise, provided editorial assistance with early drafts, and approved the final version of the submitted manuscript.

Conflict of Interest

Luigi Fontana is an Editorial Board Member of this journal, but was not involved in the peer-review process nor had access to any information regarding its peer-review.

Protocol version

v4.0.

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The Australian Health and Youth Foundation.

Supplementary data

Supplementary data to this article can be found online at https://dx.doi.org/10.3233/NHA-210146

References

[1] World Health Organization. The top 10 causes of death. 2014. Available at: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death. Accessed: 23rd August 2021

[2] Stenling A, Haggstrom C, Norberg M, Norstrom F. Lifetime risk predictions for cardiovascular diseases: Competing risks analyses on a population-based cohort in Sweden. Atherosclerosis. 2020;312:90-8.

[3] Despres JP, Lemieux I. Abdominal obesity and metabolic syndrome. Nature. 2006;444(7121):881-7.

[4] Fontana L. Interventions to promote cardiometabolic health and slow cardiovascular ageing. Nat Rev Cardiol. 2018;15(9):566-77.

[5] Libby P. The changing landscape of atherosclerosis. Nature. 2021;592(7855):524-33.

[6] Mazhar J, Figtree G, Vernon ST, Galougahi KK, Carlo J, Nissen SE, Nicholls SJ. Progression of coronary atherosclerosis in patients without standard modifiable risk factors. Am J Prev Cardiol. 2020;4:100116.

[7] Most J, Tosti V, Redman LM, Fontana L. Calorie restriction in humans: An update. Ageing Res Rev. 2017;39:36-45.

[8] Lean MEJ, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, Peters C, Zhyzhneuskaya S, Al-Mrabeh A, Hollingsworth KG, Rodrigues AM, Rehackova L, Adamson AJ, Sniehotta FF, Mathers JC, Ross HM, McIlvenna Y, Stefanetti R, Trenell M, Welsh P, Kean S, Ford I, McConnachie A, Sattar N, Taylor R. Primary care-led weight management for remission of type 2 diabetes (DiRECT): An open-label, cluster-randomised trial. The Lancet. 2018;391(10120):541-51.

[9] Fontana L, Meyer TE, Klein S, Holloszy JO. Long-term calorie restriction is highly effective in reducing the risk for atherosclerosis in humans. Proc Natl Acad Sci U S A. 2004;101(17):6659-63.

[10] Lloyd-Jones DM, Leip EP, Larson MG, D'Agostino RB, Beiser A, Wilson PW, Wolf PA, Levy D. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. Circulation. 2006;113(6):791-8.

[11] Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, Obarzanek E, Conlin PR, Miller ER, 3rd, Simons-Morton DG, Karanja N, Lin PH, Group DA-SCR. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. N Engl J Med. 2001;344(1):3-10.

[12] Ruggenenti P, Abbate M, Ruggiero B, Rota S, Trillini M, Aparicio C, Parvanova A, Petrov Iliev I, Pisanu G, Perna A, Russo A, Diadei O, Martinetti D, Cannata A, Carrara F, Ferrari S, Stucchi N, Remuzzi G, Fontana L, Group CRSOS. Renal and systemic effects of calorie restriction in patients with type 2 diabetes with abdominal obesity: A randomized controlled trial. Diabetes. 2017;66(1):75-86.

[13] Franco M, Bilal U, Ordunez P, Benet M, Morejon A, Caballero B, Kennelly JF, Cooper RS. Population-wide weight loss and regain in relation to diabetes burden and cardiovascular mortality in Cuba 1980-2010: Repeated cross sectional surveys and ecological comparison of secular trends. BMJ. 2013;346:f1515.

[14] Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, Gomez-Gracia E, Ruiz-Gutierrez V, Fiol M, Lapetra J, Lamuela-Raventos RM, Serra-Majem L, Pinto X, Basora J, Munoz MA, Sorli JV, Martinez JA, Martinez-Gonzalez MA, Investigators PS. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med. 2013;368(14):1279-90.

[15] Tosti V, Bertozzi B, Fontana L. Health benefits of the mediterranean diet: Metabolic and molecular mechanisms. J Gerontol A Biol Sci Med Sci. 2018;73(3):318-26.

[16] Heianza Y, Ma W, Manson JE, Rexrode KM, Qi L. Gut microbiota metabolites and risk of major adverse cardiovascular disease events and death: A systematic review and meta-analysis of prospective studies. J Am Heart Assoc. 2017;6(7).

[17] Riordan MM, Weiss EP, Meyer TE, Ehsani AA, Racette SB, Villareal DT, Fontana L, Holloszy JO, Kovacs SJ. The effects of caloric restriction- and exercise-induced weight loss on left ventricular diastolic function. Am J Physiol Heart Circ Physiol. 2008;294(3):H1174-82.

[18] Fontana L, Villareal DT, Weiss EP, Racette SB, Steger-May K, Klein S, Holloszy JO, Washington University School of Medicine CG. Calorie restriction or exercise: Effects on coronary heart disease risk factors. A randomized, controlled trial. Am J Physiol Endocrinol Metab. 2007;293(1):E197-202.

[19] Stewart RAH, Held C, Hadziosmanovic N, Armstrong PW, Cannon CP, Granger CB, Hagstrom E, Hochman JS, Koenig W, Lonn E, Nicolau JC, Steg PG, Vedin O, Wallentin L, White HD, Investigators S. Physical activity and mortality in patients with stable coronary heart disease. J Am Coll Cardiol. 2017;70(14):1689-700.

[20] St-Onge MP, Zuraikat FM. Reciprocal roles of sleep and diet in cardiovascular health: A review of recent evidence and a potential mechanism. Curr Atheroscler Rep. 2019;21(3):11.

[21] Khan SU, Duran CA, Rahman H, Lekkala M, Saleem MA, Kaluski E. A meta-analysis of continuous positive airway pressure therapy in prevention of cardiovascular events in patients with obstructive sleep apnoea. Eur Heart J. 2018;39(24):2291-7.

[22] Gerbarg PL, Brown RP, Streeter CC, Katzman M, Vermani M. Breath practices for survivor and caregiver stress, depression, and post-traumatic stress disorder: Connection, Co-regulation, compassion. OBM Integrative and Complementary Medicine. 2019;4(3):1.

[23] Bernardi L, Porta C, Spicuzza L, Bellwon J, Spadacini G, Frey AW, Yeung LY, Sanderson JE, Pedretti R, Tramarin R. Slow breathing increases arterial baroreflex sensitivity in patients with chronic heart failure. Circulation. 2002;105(2):143-5.

[24] Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, Mehran R, McPherson J, Farhat N, Marso SP, Parise H, Templin B, White R, Zhang Z, Serruys PW, Investigators P. A prospective natural-history study of coronary atherosclerosis. N Engl J Med. 2011;364(3):226-35.

[25] Williams MC, Kwiecinski J, Doris M, McElhinney P, D'Souza MS, Cadet S, Adamson PD, Moss AJ, Alam S, Hunter A, Shah ASV, Mills NL, Pawade T, Wang C, Weir McCall J, Bonnici-Mallia M, Murrills C, Roditi G, van Beek EJR, Shaw LJ, Nicol ED, Berman DS, Slomka PJ, Newby DE, Dweck MR, Dey D. Low-attenuation noncalcified plaque on coronary computed tomography angiography predicts myocardial infarction: Results from the multicenter SCOT-HEART Trial (Scottish Computed Tomography of the HEART). Circulation. 2020;141(18):1452-62.

[26] Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, Barengo NC, Beaton AZ, Benjamin EJ, Benziger CP, Bonny A, Brauer M, Brodmann M, Cahill TJ, Carapetis J, Catapano AL, Chugh SS, Cooper LT, Coresh J, Criqui M, DeCleene N, Eagle KA, Emmons-Bell S, Feigin VL, Fernandez-Sola J, Fowkes G, Gakidou E, Grundy SM, He FJ, Howard G, Hu F, Inker L, Karthikeyan G, Kassebaum N, Koroshetz W, Lavie C, Lloyd-Jones D, Lu HS, Mirijello A, Temesgen AM, Mokdad A, Moran AE, Muntner P, Narula J, Neal B, Ntsekhe M, Moraes de Oliveira G, Otto C, Owolabi M, Pratt M, Rajagopalan S, Reitsma M, Ribeiro ALP, Rigotti N, Rodgers A, Sable C, Shakil S, Sliwa-Hahnle K, Stark B, Sundstrom J, Timpel P, Tleyjeh IM, Valgimigli M, Vos T, Whelton PK, Yacoub M, Zuhlke L, Murray C, Fuster V, Group G-N-JGBoCDW. Global burden of cardiovascular diseases and risk factors, 1990-2019: Update from the GBD 2019 study. J Am Coll Cardiol. 2020;76(25):2982-3021.

[27] Messroghli DR, Moon JC, Ferreira VM, Grosse-Wortmann L, He T, Kellman P, Mascherbauer J, Nezafat R, Salerno M, Schelbert EB, Taylor AJ, Thompson R, Ugander M, van Heeswijk RB, Friedrich MG. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: A consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). J Cardiovasc Magn Reson. 2017;19(1):75.

[28] Ramos JG, Fyrdahl A, Wieslander B, Thalen S, Reiter G, Reiter U, Jin N, Maret E, Eriksson M, Caidahl K, Sorensson P, Sigfridsson A, Ugander M. Comprehensive cardiovascular magnetic resonance diastolic dysfunction grading shows very good agreement compared with echocardiography. JACC Cardiovasc Imaging. 2020;13(12):2530-42.

[29] Widmer RJ, Collins NM, Collins CS, West CP, Lerman LO, Lerman A. Digital health interventions for the prevention of cardiovascular disease: A systematic review and meta-analysis. Mayo Clin Proc. 2015;90(4):469-80.

[30] Varnfield M, Karunanithi M, Lee CK, Honeyman E, Arnold D, Ding H, Smith C, Walters DL. Smartphone-based home care model improved use of cardiac rehabilitation in postmyocardial infarction patients: Results from a randomised controlled trial. Heart. 2014;100(22):1770-9.

[31] Cassidy S, Hunyor I, Wilcox I, Fontana L. Changing the conversation from 'chronic disease' to 'chronic health'. Eur Heart J. 2021.

[32] Snow G. blockrand: Randomization for Block Random Clinical Trials. R package version 1.5. https://CRAN.R-project.org/package=blockrand. 2020.

[33] Schulz KF, Grimes DA. Unequal group sizes in randomised trials: Guarding against guessing. The Lancet. 2002;359(9310):966-70.

[34] Michie S, Richardson M, Johnston M, Abraham C, Francis J, Hardeman W, Eccles MP, Cane J, Wood CE. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: Building an international consensus for the reporting of behavior change interventions. Ann Behav Med. 2013;46(1):81-95.

[35] Singh RB, Dubnov G, Niaz MA, Ghosh S, Singh R, Rastogi SS, Manor O, Pella D, Berry EM. Effect of an Indo-Mediterranean diet on progression of coronary artery disease in high risk patients (Indo-Mediterranean Diet Heart Study): A randomised single-blind trial. The Lancet. 2002;360(9344):1455-61.

[36] de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: Final report of the Lyon Diet Heart Study. Circulation. 1999;99(6):779-85.

[37] Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, Gomez-Gracia E, Ruiz-Gutierrez V, Fiol M, Lapetra J, Lamuela-Raventos RM, Serra-Majem L, Pinto X, Basora J, Munoz MA, Sorli JV, Martinez JA, Fito M, Gea A, Hernan MA, Martinez-Gonzalez MA, Investigators PS. Primary prevention of cardiovascular disease with a mediterranean diet supplemented with extra-virgin olive oil or nuts. N Engl J Med. 2018;378(25):e34.

[38] Kraus WE, Bhapkar M, Huffman KM, Pieper CF, Krupa Das S, Redman LM, Villareal DT, Rochon J, Roberts SB, Ravussin E, Holloszy JO, Fontana L. 2 years of calorie restric-

tion and cardiometabolic risk (CALERIE): Exploratory outcomes of a multicentre, phase 2, randomised controlled trial. The Lancet Diabetes & Endocrinology. 2019;7(9):673-83.

[39] Winzer EB, Woitek F, Linke A. Physical activity in the prevention and treatment of coronary artery disease. J Am Heart Assoc. 2018;7(4).

[40] Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, Douglas PS, Foody JM, Gerber TC, Hinderliter AL, King SB, 3rd, Kligfield PD, Krumholz HM, Kwong RY, Lim MJ, Linderbaum JA, Mack MJ, Munger MA, Prager RL, Sabik JF, Shaw LJ, Sikkema JD, Smith CR Jr, Smith SC Jr, Spertus JA, Williams SV, Anderson JL, American College of Cardiology Foundation/American Heart Association Task F. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: A report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation. 2012;126(25):e354-471.

[41] Yao BC, Meng LB, Hao ML, Zhang YM, Gong T, Guo ZG. Chronic stress: A critical risk factor for atherosclerosis. J Int Med Res. 2019;47(4):1429-40.

[42] Bussing A, Michalsen A, Khalsa SB, Telles S, Sherman KJ. Effects of yoga on mental and physical health: A short summary of reviews. Evid Based Complement Alternat Med. 2012;2012:165410.

[43] Reive C. The biological measurements of mindfulness-based stress reduction: A systematic review. Explore (NY). 2019;15(4):295-307.

[44] Praissman S. Mindfulness-based stress reduction: A literature review and clinician's guide. J Am Acad Nurse Pract. 2008;20(4):212-6.

[45] Muscat DM, Lambert K, Shepherd H, McCaffery KJ, Zwi S, Liu N, Sud K, Saunders J, O'Lone E, Kim J, Robbins A, Webster AC. Supporting patients to be involved in decisions about their health and care: Development of a best practice health literacy App for Australian adults living with Chronic Kidney Disease. Health Promot J Austr. 2021;32(Suppl 1):115-27.

[46] Huang R, Liu N, Nicdao MA, Mikaheal M, Baldacchino T, Albeos A, Petoumenos K, Sud K, Kim J. Emotion sharing in remote patient monitoring of patients with chronic kidney disease. J Am Med Inform Assoc. 2020;27(2):185-93.

[47] Shcherbina A, Hershman SG, Lazzeroni L, King AC, O'Sullivan JW, Hekler E, Moayedi Y, Pavlovic A, Waggott D, Sharma A, Yeung A, Christle JW, Wheeler MT, McConnell MV, Harrington RA, Ashley EA. The effect of digital physical activity interventions on daily step count: A randomised controlled crossover substudy of the MyHeart Counts Cardiovascular Health Study. The Lancet Digital Health. 2019;1(7):e344-e52.

[48] Samdal GB, Eide GE, Barth T, Williams G, Meland E. Effective behaviour change techniques for physical activity and healthy eating in overweight and obese adults; systematic review and meta-regression analyses. Int J Behav Nutr Phys Act. 2017;14(1):42.

[49] Klasnja P, Hekler EB, Shiffman S, Boruvka A, Almirall D, Tewari A, Murphy SA. Microrandomized trials: An experimental design for developing just-in-time adaptive interventions. Health Psychol. 2015;34S:1220-8.

[50] The American Heart Associaton Diet and Lifestyle Recommendations. 2021. Available at: https://www.heart.org/en/healthy-living/healthy-eating/eat-smart/nutrition-basics/aha-diet-and-lifestyle-recommendations. Accessed: 1 September 2021.

[51] Mezzani A. Cardiopulmonary exercise testing: Basics of methodology and measurements. Ann Am Thorac Soc. 2017;14(Supplement_1):S3-11.

[52] Hines EA, Brown GE. The cold pressor test for measuring the reactibility of the blood pressure: Data concerning 571 normal and hypertensive subjects. American Heart Journal. 1936;11(1):1-9.

[53] Vaidya K, Arnott C, Martinez GJ, Ng B, McCormack S, Sullivan DR, Celermajer DS, Patel S. Colchicine therapy and plaque stabilization in patients with acute coronary syndrome: A CT coronary angiography study. JACC Cardiovasc Imaging. 2018;11(2 Pt 2):305-16.

[54] Brown LAE, Onciul SC, Broadbent DA, Johnson K, Fent GJ, Foley JRJ, Garg P, Chew PG, Knott K, Dall'Armellina E, Swoboda PP, Xue H, Greenwood JP, Moon JC, Kellman P, Plein S. Fully automated, inline quantification of myocardial blood flow with cardiovascular magnetic resonance: Repeatability of measurements in healthy subjects. J Cardiovasc Magn Reson. 2018;20(1):48.

[55] European Medicines Agency Committee for Medicinal Products for Human Use. Adjustment for baseline covariates in clinical trials | European Medicines Agency. 2015.

[56] Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology. 2000;11(5):550-60.

CHAPTER 6: Dietary Patterns across Cardiometabolic Profiles in Individuals with Coronary Heart Disease: Baseline Cross-sectional Analysis of the LIVEPLUS Trial

Nutrition is an integral part of this project, and I am the dietitian (TW) who leads the dietary intervention of this novel and exciting trial. I was responsible for the development of nutritional educational materials and recipes, dietary assessments, delivery of nutritional interventions and performing individualized nutritional counselling with the participants.

This work has been presented at the American Society for Nutrition (ASN) conference 2023.

The abstract of this work has been published in the Current Developments in Nutrition:

T. Wang, S. Cassidy, C.M. Kroeger, S. Mitra, R. Ribeiro, A. Masedunkas, R. Huang, L. Fontana. P23-080-23. Impact of an Intensive Lifestyle Program on Low Attenuation Plaque and Myocardial Perfusion in Coronary Heart Disease: A Randomised Clinical Trial Protocol. Current Developments in Nutrition. Volume 7, Supplement 1, 2023, 100188, ISSN 2475-2991, https://doi.org/10.1016/j.cdnut.2023.100188

6.1 Abstract

Objective: To analyze the baseline data of nine individuals (mean age: 61.0 ± 10.7 years, 66.7% male) with coronary heart disease participating in the LIVEPLUS (LIfestyle VulnErable PLaqUe Study) trial, and investigate the associations of their dietary patterns with cardiometabolic profiles.

Design: A cross-sectional observational study.

Results: All participants have suboptimal cardiometabolic profiles at baseline. The most common condition is hyperlipidemia (n=9), followed by overweight (n=7), hypertension (n=5) and hyperglycemia (n=1). Their baseline diet is characterized by an excessive intake of saturated fats (12.7%E) and sodium (2227.4mg/d), with insufficient intake of vegetables (4.1 serves/d), fruits (1.2 serves/d) and dietary fibre (24.1g/d).

Conclusions: A possible association is found between a low-quality diet and suboptimal cardiometabolic profiles. Our findings are consistent with the current literature and highlight the need for dietary intervention in these individuals.

6.2 Introduction

Cardiovascular disease (CVD) has become the major cause of disease burden, premature death and escalating healthcare costs globally [90]. Researchers have demonstrated a strong association between suboptimal cardiometabolic profiles at baseline and cardiovascular risk and outcomes. The risk of developing CVD is doubled in people with type 2 diabetes (T2DM) [9], and most individuals in the US who experienced a

myocardial infarction had at least one CVD risk factor before the event [8]. An unhealthy diet, enriched with energy-dense nutrient-poor foods, with an excess amount of saturated fats, added sugars and added salt and insufficient dietary fibre, is mechanistically linked to dyslipidemia, glucose intolerance, high blood pressure, and an elevated risk of CVD morbidity and mortality [91]. In contrast, previous nutritional interventions demonstrate a striking protective effect of a healthy diet, enriched with minimally processed plant-based foods and fish and seafood, against the development of coronary heart disease (CHD) [19, 92, 93]. Calorie restriction also shows a pronounced effect in reducing inflammation and oxidative stress, improving cardiometabolic profiles and lowering risk of developing CVD in both clinical trials and observational studies [94, 95]. Intermittent fasting is a popular approach to restricting energy intake, as it is considered less restrictive and more practical compared to traditional calorie restriction [96]. The 5:2 diet, characterized by energy restriction of two non-consecutive days per week, has been shown to improve glycaemic control and body weight in overweight participants with T2DM [97]. Overall, an improvement in the diet quality [7], combined with regular physical activity [98] and a reduction in chronic stress [99] is associated with reducing cardiovascular events and mortality.

Despite the well-established evidence of modifiable lifestyle factors on primary cardiovascular prevention, there is limited data on intensive lifestyle intervention in secondary prevention of CVD. To the best of our knowledge, no study has evaluated the combined effect of a 5:2 pesco-vegetarian diet, individualized physical activity and stress reduction in individuals with CHD. The year-long LIfestyle VulnErable PLaqUe Study (LIVEPLUS) trial aims to address this gap. In this chapter, we performed a cross-sectional study to analyze the baseline data of nine individuals (mean age: 61.0 ± 10.7 years, 67% males) with stable CHD participating in the LIVEPLUS (LIfestyle VulnErable PLaqUe Study) trial and investigate the associations of their dietary patterns with cardiometabolic health.

6.3 Methods

Data Availability

De-identified data are available on request for the purpose of reproducing the results. R scripts used for statistical analysis are available in the supplementary material.

Study design and participants

In this study, we performed a baseline cross-sectional analysis of the LIfestyle VulnErable PLaqUe Study (LIVEPLUS) trial, a randomized clinical trial testing the effect of an intensive lifestyle intervention (a 5:2 pesco-vegetarian diet combined with individualized physical activity prescription and stress reduction) compared to an American Heart Association lifestyle recommendation in individuals with CHD in Australia. The trial was approved by the Sydney Local Health District Ethics committee (2020/ETH01273) and the study was conducted at the Charles Perkins Centre-Royal Prince Alfred Hospital (CPC-RPA) clinic, Royal Prince Alfred Hospital Department of Radiology, and the North Shore Radiology and Nuclear Medicine (NSRNM) facility, Sydney. The trial was registered in 2020 at the Australian New Zealand Clinical Trials Registry (ACTRN12620001151921), supported by grants from Australian Youth and Health Foundation and the Australian NHMRC Investigator Grant (APP1177797).

Electronic informed consents were obtained from participants through Research Electronic Data Capture (REDCap). Participants in the LIVEPLUS trial are adults aged 18-80 years, with a BMI (body mass index) >22.0kg/m^2, and the presence of LAP on CCTA. The recruitment started in Feb 2022. Nine participants were recruited and randomized by June 2023. In this study, we included all nine participants who attended baseline assessment and completed baseline dietary assessment (**Figure 6.1**).

The protocol of the LIVEPULS trial is published and described in CHAPTER 5. A detailed description of randomization and intervention groups is presented in CHAPTER 7. The secondary outcomes in our study were risk factors of cardiovascular diseases.

Outcome measurements

Participants attended baseline clinical measurement after an overnight fast. All measurements were taken by trained staff. Body weight (kg) was measured using a standardized electronic standing scale with shoes and heavy outer clothing removed. Height (cm) was measured at screening using a wall-mounted stadiometer in conjunction with a right-angled headboard, with shoes and head dressing removed. Participant's head was positioned in the Frankfort plane (the orbitale (lower edge of the eye socket) is in the same horizontal plane as the tragion (the top notch of the ear)). Height measurements were repeated to obtain 2 values that are identical or close to one another (within 0.1cm) and the average of the two measurements were used. Body mass index (BMI; kg/m^2) was calculated using body weight and height. Being overweight is defined as BMI ⩾25kg/m^2 based on the WHO criteria [100].

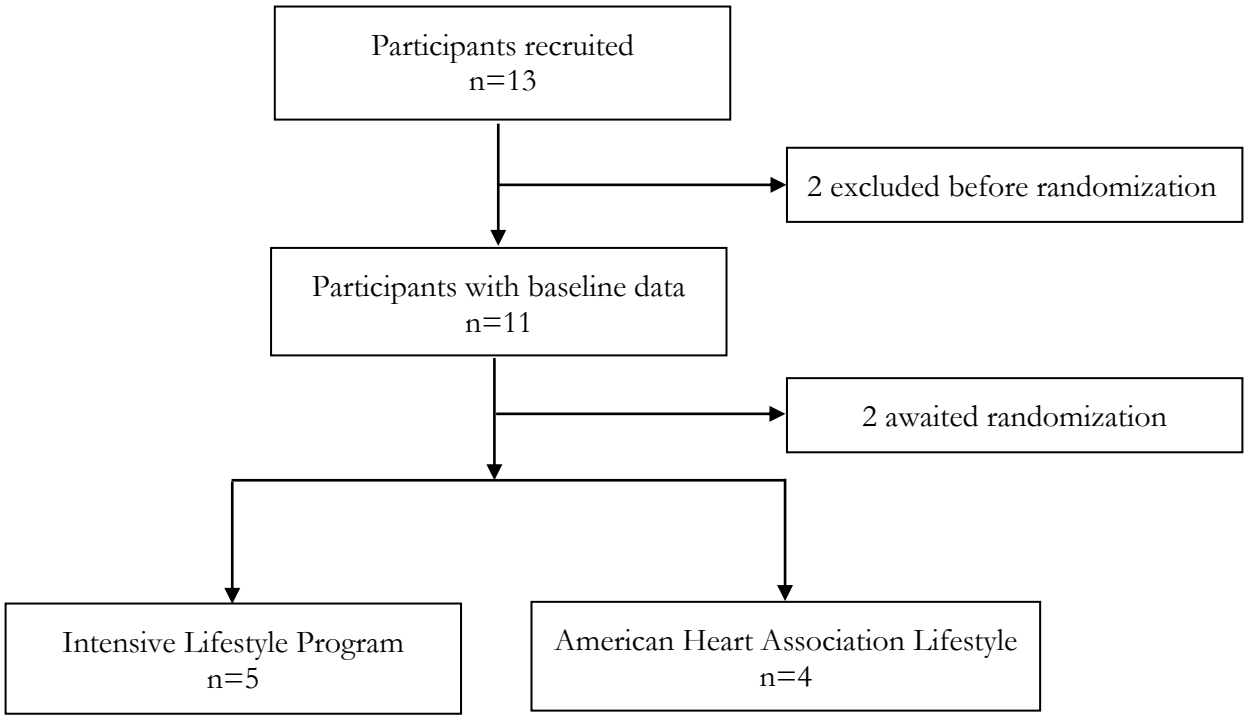


Figure 6.1. Flow diagram of participants in the LIVEPLUS trial

Blood sampling was taken after an overnight fast for blood lipids (triglyceride, total and high-density lipoprotein (HDLc)), glycated haemoglobin (HbA1c; %), and glucose (mmol/L). A cannula was placed in the antecubital vein for blood and blood samples were sent immediately for analysis in an accredited hospital laboratory. Hyperglycaemia is defined as HbA1c ⩾5·7% [101] or on hypoglycemic medication or diagnosis of Type 2 Diabetes Mellitus (T2DM). Hyperlipidaemia [102] is defined as total cholesterol (TC) ⩾200mg/dL (5.2mmol/L); or low-density lipoprotein cholesterol (LDL-C) ⩾ 100mg/Dl (2.6mmol/L); or triglycerides (TG) ⩾150mg/dL (1.7mmol/L); or on lipid-lowering medication.

Blood pressure (mmHg) measurement was performed after the participant had been sat down for 10 minutes, using the SphygmoCor XCEL device (Atcor Medical, Sydney), which also calculates central blood pressure based on the peripheral pulse waveform. At least two readings were taken, with a one-minute interval between them. The average of the measurements was recorded. Additional measurements were performed if the difference between the first two was greater than 5 mmHg. Hypertension is defined as systolic blood pressure (SBP) ⩾ 130mmHg or diastolic blood pressure (DBP) ⩾ 80mmHg based on the ACC/AHA criteria [60] or on antihypertensive medications.

Participants completed weighed food records (WFR) using the 'Research Food Diary' (Xyris Software Australia Pty Ltd) phone app. At the baseline visit, the study dietitian (TW) met with participants individually to provide instructions of dietary measurement. Participants were asked to record food intakes through the 'Research Food Diary' app by scanning barcodes of food products or searching individual food items. To improve the accuracy of self-reported dietary data, the study dietitian provided training of portion size estimation, with weighing scales and household measures (cups, tablespoons, and teaspoons) provided to take home. Participants measured food and drinks consumption for four consecutive days (three weekdays and one weekend day). The study dietitian negotiated the start date of food records with participants to ensure the measurement captured participants' normal eating patterns (for example, if participants were not consuming their usual diets or travelling, the dietary measurements were postponed until they returned to normal eating patterns). After participants entered dietary data into the app, the data was sent to the study dietitian. The study dietitian contacted participants to verify diet diary before generating nutrient analysis (average intake of energy, macronutrient and micronutrient) using FoodWorks 10 Professional (v10.0. Brisbane: Xyris Pty Ltd, 2019), which contains the AUSNUT database [103], the most relevant food database to our study population.

Sociodemographic data including age, sex, and educational level and lifestyle data were collected prior to randomization (see CHAPTER 5 for a detailed description).

Statistical analysis

All data analyses were performed using RStudio 2022.02.2+485 statistical software [104] and jamovi (version 2.3) [105]. Quantitative data was described as means (standard deviations) for outcomes with normal distribution, and as median (interquartile range [IQR]) for outcomes with skewed distribution. Categorial variables were presented as proportions. An independent sample t-test and a Fisher's exact test were used to compare the means and proportions between groups due to a small sample size. Nutrients and foods intakes were compared with the recommendations by the Australian Dietary Guidelines [106] using one sample t-test.

Considering the disease status of LIVEPLUS participants, the suggested dietary targets (SDT) to reduce chronic disease risk were used for dietary fibre, sodium, potassium, Vitamin A, Vitamin C, Vitamin E, selenium, folate, and energy% of macronutrients distribution (carbohydrate, protein, total fat, saturated fat and trans fat). All statistical tests were two-sided, with significance set at $p<0.05$.

6.4 Results

All participants who completed baseline measurements and randomized to dietary interventions by June 2023 were included in the analysis. Baseline characteristics of the LIVEPLUS participants (mean age: 61.0 ± 10.7 years, 66.7% male) are described in **Table 6.1**. No significant differences were detected between randomized groups in terms of baseline characteristics (mean age, gender distribution, ethnicity and education level), and cardiometabolic characteristics (BMI, blood pressure, lipid profiles, HbA1c and past medical history of hypertension, hyperlipidemia and hyperglycemia). All participants have suboptimal cardiometabolic profiles at baseline. The most common condition was hyperlipidemia (n=9), followed by overweight (n=7) and hypertension (n=5).

Table 6.2. and **Table 6.3**. show baseline nutrients and foods intake of LIVEPLUS participants. The intakes of most foods and nutrients were similar between groups. The ILP group had slightly higher intakes of total fat, saturated fat, polyunsaturated fat, sugars and added sugars, total folate and folic acid, calcium, and iodine, as well as fruit, red meats, milk and coffee. In contrast, the AHA group consumed more potatoes and alcohol, and had higher intakes of vitamin C, beta carotene, sodium, and selenium. However, statistical analyses showed no statistically significant difference between groups.

LIVEPLUS participants had significantly higher intake of protein, total fat (>35%E), and saturated fat (>10%E), and a significant lower intake of carbohydrate (%E) and dietary fibre than recommended by the Australian Dietary Guidelines.

LIVEPLUS participants were further grouped by cardiometabolic risk factors at baseline. **Table 6.4** shows dietary characteristics of participants with different risk factors. Overall, food and nutrient intake across individuals with overweight, hypertension and hyperlipidemia at baseline were similar. Their average intakes of vegetables and fruits were 25-40% lower than the minimum recommended daily serves by Australian Dietary Guidelines [106] and they met 63% of the Australian recommended daily intake of dietary fibre for people with chronic disease risk [106]. All three groups exceeded the recommended daily intake of sodium to reduce chronic disease risk [106]. They had moderate alcohol consumption (1-2 standard drinks/day) at baseline. In addition, the average intake of total fat, saturated fat and polyunsaturated fat, as well as oil equivalents were slightly higher in participants with hyperlipidemia. In contrast, there was only one participant with hyperglycemia at baseline. This participant had the highest intake of total fat (energy, %), polyunsaturated fat, monounsaturated fat, dietary fibre, vegetables, nuts and seeds, milk across disease groups, and the lowest intake of grains, refined grains, red meats, alcoholic drinks, saturated fat intake (energy, %), trans fat intake (energy, %), carbohydrate, added sugars and sodium of the whole group. Finally, all participants had relatively low consumption of red meats (<1 serve/day) and poultry (<0.5 serve/day) at baseline. All participants exceeded the upper limit recommended intake of saturated fat by Australian Dietary Guidelines [106].

Table 6.1 Baseline characteristics of LIVEPLUS participants

	ILP group (n=5)	AHA group (n=4)	p-value
Age at recruitment, years	61.4 (10.8)	60.5 (12.1)	0.91
Below 65, n [%]	3 [60]	1 [25]	0.52
65 and over, n [%]	2 [40]	3 [75]	
Sex, male, n [%]	3 [60]	3 [75]	0.64
Ethnicity, n [%]			0.49
Anglo-Celtic (English, Irish, Scottish, Welsh)	3 [60]	2 [50]	
European	1 [20]	2 [50]	
Asian	1 [20]	0 [0]	
Other	0 [0]	0 [0]	
Bachelor degree or higher, n [%]	4 [80]	3 [75]	0.36
Body weight, kg	81.7 (21.5)	90.8 (20.9)	0.54
BMI, kg/m^2	26.8 (4.5)	30.0 (4.6)	0.32
<25 (under and healthy weight), n [%]	2 [40]	0 [0]	0.15
≥25 (overweight), n [%]	3 [60]	4 [100]	
SBP, mmHg	114.5 {28}	121.8 {6}	0.51
DBP, mmHg	77.5 (9.5)	73.9 (6.3)	0.56
TC, mmol/L	3.8 {0.3}	4.9 {1.9}	0.29
LDLc, mmol/L	1.6 {0.5}	2.2 {1.1}	0.41
HDLc, mmol/L	1.4 {0.1}	1.7 {0.4}	0.19
Triglycerides, mmol/L	1.1 (0.4)	1.1 (0.3)	0.95
HbA1c, %	5.5 (0.2)	5.3 (0.3)	0.17
Past medical history			
Hypertension at baseline, n [%]	3 [60]	2 [50]	0.76
Hyperlipidemia at baseline, n [%]	5 [100]	5 [100]	1.0
Diabetes at baseline, n [%]	1 [20]	0 [0]	0.34
On lipid-lowering medication, n [%]	5 [100]	3 [60]	0.24
On blood pressure lowering medication, n [%]	2 [40]	0 [0]	0.15
On oral antidiabetic therapy, n [%]	1 [20]	0 [0]	0.34

AHA, American Heart Association; BMI, Body Mass Index; DBP, Diastolic Blood Pressure; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; ILP, intensive lifestyle program; LDL-C, low-density lipoprotein cholesterol; SBP, Systolic Blood Pressure; TC, total cholesterol

Data are presented as mean (standard deviation), median {interquartile range}, or proportions [%].

Table 6.2 Baseline nutrients intake of LIVEPLUS participants

	ILP group (n=5)	AHA group (n=4)	p-value	NRVs*
Energy, kJ	7836.7 (1781.4)	7877.9 (1700.5)	0.97	9100.0
kcal	1874.8 (426.2)	1884.7 (406.8)	0.97	2177.0
Protein, g	92.7 (22.1)	91.0 (20.8)	0.91	64#
Energy, %	20.1 (1.1)	20.1 (4.9)	0.99	15-25
Total Fat, g	81.1 (14.2)	76.6 (31.5)	0.78	NA
Energy, %	39.3 (7.8)	35.0 (6.8)	0.41	20-35#
Saturated Fat, g	28.0 (7.8)	25.3 (7.0)	0.60	NA
Energy, %	13.5 (4.2)	11.8 (0.8)	0.47	<10#
Trans Fatty Acids, g	1.6 (1.1)	1.2 (0.3)	0.56	NA
Energy, %	0.7 (0.4)	0.6 (0.1)	0.52	<10 with SFA
Polyunsaturated Fat, g	16.2 (10.3)	14.9 (8.5)	0.84	13
Monounsaturated Fat, g	28.4 (7.6)	29.4 (14.5)	0.89	NA
Carbohydrate, g	169.9 (64.8)	172.2 (45.2)	0.95	NA
Energy, %	34.4 (6.4)	36.5 (9.8)	0.71	45-65#
Sugars, g	74.7 (34.7)	63.4 (26.6)	0.61	NA
Dietary Fibre, g	24.2 (5.0)	24.0 (12.6)	0.97	38#
Alcohol, g	7.8 (9.0)	13.7 (10.3)	0.40	NA
Vitamin C, mg	75.5 (112.8)	111.3 (102.9)	0.89	220#
Vitamin E, mg	13.6 (5.5)	14.4 (8.8)	0.88	19
Total Folate, μg	509.1 (140.9)	485.7 (103.5)	0.79	300-600
Total Vit A equivalent, μg	834.8 (573.4)	804.7 (409.2)	0.93	1500#
Sodium, mg	2027.9 (953.9)	2476.8 (501.4)	0.43	2000
Potassium, mg	3431.1 (1155.9)	3330.2 (933.7)	0.89	4700#
Iron, mg	9.8 (2.1)	10.5 (3.3)	0.70	8#
Zinc, mg	11.5 (4.1)	10.7 (3.7)	0.77	14
Iodine, μg	185.5 (93.0)	153.7 (27.2)	0.53	150

NRVs, Nutrient Reference Values; SFA, Saturated Fatty Acids

* Based on the characteristics of included participants: a 60 year-old male with a body weight of 85.8kg and a height of 173.4cm, and a sedentary lifestyle (physical activity level 1.4)

Significant difference ($p < 0.05$) between nutrient intake and NRVs values, analyzed using a one sample t-test

Table 6.3 Baseline food intake of LIVEPLUS participants

	ILP group (n=5)	AHA group (n=4)	p-value	ADGs*
Grains, serve	4.6 (2.7)	4.7 (0.9)	0.93	6
Refined, serve	3.1 (2.4)	2.9 (1.4)	0.88	
Wholegrains, serve	1.5 (1.3)	1.8 (1.3)	0.70	
Fruit, serve	1.5 (1.9)	0.8 (1.2)	0.54	2
Vegetables and legumes, serve	4.3 (2.2)	3.9 (1.6)	0.81	5.5
Starchy vegetables, serve	0.7 (0.9)	0.9 (1.1)	0.73	
Potatoes, serve	0.2 (0.3)	0.9 (1.1)	0.15	
Legumes veg, serve	0.2 (0.4)	0.3 (0.4)	0.78	
Lean meats, poultry, fish, eggs, tofu, nuts and seeds, and legumes, serve	3.1 (0.5)	2.8 (1.6)	0.70	2.5
Red Meats, serve	0.9 (0.8)	0.5 (0.4)	0.48	
Poultry, serve	0.2 (0.2)	0.3 (0.2)	0.62	
Seafood, high long-chain n3	0.2 (0.2)	0.4 (0.5)	0.63	
Seafood, low long-chain n3	0.2 (0.2)	0.3 (0.4)	0.80	
Eggs, serve	0.2 (0.2)	0.1 (0.1)	0.60	
Legumes Protein, serve	0.1 (0.2)	0.2 (0.2)	0.87	
Nuts and Seeds, serve	0.8 (0.9)	0.9 (0.7)	0.88	
Soy Products, serve	0.3 (0.4)	0.1 (0.2)	0.53	
Milk, yoghurt, cheese and/or alternatives, serve	2.2 (1.8)	1.8 (0.3)	0.68	2.5
Milk, serve	1.5 (2.0)	0.9 (0.8)	0.61	
Cheese, serve	0.6 (0.6)	0.5 (0.3)	0.69	
Yoghurt, serve	0.02 (0.06)	0.2 (0.3)	0.38	
Milk Alternatives, serve	0.1 (0.3)	0.3 (0.6)	0.60	
Processed meats, serve	0.2 (0.2)	0.1 (0.1)	0.28	
Alcoholic Drinks, standard drink	0.8 (0.9)	1.4 (1.0)	0.39	<2#
Caffeine, mg	306.5 (149.7)	280.7 (171.0)	0.82	
Oil Equivalents, tsp	9.9 (4.5)	9.5 (5.9)	0.91	
Solid Fat Equivalents, tsp	7.2 (3.8)	6.7 (1.5)	0.82	
Added Sugars, tsp	3.6 (3.2)	2.9 (2.3)	0.93	

ADGs, Australian Dietary Guidelines

* Based on the characteristics of included participants: a 60 year-old male with a body weight of 85.8kg and a height of 173.4cm, and a sedentary lifestyle (physical activity level 1.4)

Table 6.4 Dietary characteristics of participants with cardiometabolic risk factors

Foods and nutrients intake	Overweight (n=7)	Hypertension (n=5)	Hyperglycemia (n=1)	Hyperlipidemia (n=9)
Energy, kJ	8129.4 (1555.3)	7878.0 (1630.8)	8392.7	7855.0 (1634.5)
kcal	1944.8 (372.1)	1884.7 (390.1)	2007.8	1879.2 (391.0)
Protein, g	94.1 (20.4)	93.1 (18.5)	102.2	91.9 (20.2)
Energy, %	19.9 (3.6)	20.4 (3.9)	20.7	20.1 (3.1)
Total Fat, g	77.0 (23.1)	71.0 (15.7)	101.8	79.1 (21.8)
Energy, %	34.7 (5.5)	33.4 (3.8)	44.9	37.4 (7.3)
Saturated Fat, g	26.5 (8.0)	25.6 (8.7)	26.3	26.8 (7.0)
Energy, %	11.9 (1.7)	11.8 (2.0)	11.6	12.7 (3.1)
Trans Fatty Acids, g	1.5 (0.9)	1.6 (1.1)	1.2	1.4 (0.8)
Energy, %	0.7 (0.3)	0.7 (0.4)	0.5	0.7 (0.3)
Polyunsaturated Fat, g	14.5 (7.1)	12.8 (6.0)	32.0	15.6 (9.0)
Monounsaturated Fat, g	29.3 (10.7)	26.6 (6.5)	36.3	28.8 (10.4)
Carbohydrate, g	185.0 (48.3)	180.3 (54.2)	158.6	171.0 (53.6)
Energy, %	37.3 (7.4)	36.8 (3.7)	30.9	35.3 (7.6)
Sugars, g	70.2 (26.5)	72.2 (32.0)	106.8	69.7 (30.0)
Dietary Fibre, g	24.4 (9.4)	23.7 (11.0)	28.3	24.1 (8.5)
Sodium, mg	2492.7 (658.1)	2390.1 (730.9)	1183.0	2227.4 (777.9)
Potassium, mg	3387.5 (704.3)	3416.8 (665.7)	4964.0	3386.2 (998.9)
Grains, serve	5.3 (1.6)	5.5 (1.8)	1.6	4.6 (2.0)
Refined	3.5 (1.8)	4.0 (1.9)	0.2	3.0 (1.9)
Wholegrains	1.8 (1.3)	1.5 (1.4)	1.5	1.6 (1.2)
Fruit, serve	1.4 (1.7)	1.8 (1.9)	1.0	1.2 (1.6)
Vegetables, serve	4.0 (1.6)	3.9 (1.8)	6.9	4.1 (1.8)
Starchy vegetables	0.7 (0.8)	0.4 (0.3)	2.2	0.8 (0.9)
Potatoes	0.6 (0.9)	0.3 (0.3)	0.0	0.5 (0.8)
Legumes veg	0.3 (0.4)	0.3 (0.3)	0.0	0.3 (0.4)
Red Meats, serve	0.8 (0.7)	0.9 (0.9)	0.2	0.7 (0.7)
Poultry, serve	0.2 (0.2)	0.2 (0.2)	0.5	0.2 (0.2)
Seafood, high long-chain n3, serve	0.3 (0.4)	0.2 (0.3)	0.2	0.3 (0.3)
Seafood, low long-chain n3, serve	0.3 (0.3)	0.3 (0.4)	0.2	0.2 (0.3)
Eggs, serve	0.1 (0.1)	0.1 (0.1)	0.1	0.2 (0.1)
Legumes Protein, serve	0.2 (0.2)	0.2 (0.2)	0.0	0.1 (0.2)
Nuts and Seeds, serve	0.7 (0.6)	0.4 (0.4)	2.3	0.9 (0.8)
Processed meats, serve	0.1 (0.2)	0.2 (0.2)	0.1	0.2 (0.2)
Soy Products, serve	0.2 (0.4)	0.2 (0.4)	0.3	0.2 (0.3)
Milk, serve	0.9 (0.8)	0.9 (0.8)	4.7	1.2 (1.5)
Cheese, serve	0.7 (0.4)	0.7 (0.4)	0.04	0.5 (0.5)
Yoghurt, serve	0.1 (0.2)	0.1 (0.3)	0.0	0.1 (0.2)
Milk Alternatives, serve	0.3 (0.5)	0.1 (0.3)	0.0	0.2 (0.4)
Oil Equivalents, tsp	8.9 (4.9)	7.6 (3.7)	15.9	9.7 (4.8)

Solid Fat Equivalents, tsp	7.2 (3.2)	7.2 (3.8)	6.0	6.9 (2.8)
Added Sugars, tsp	3.8 (2.8)	4.2 (3.4)	0.8	3.3 (2.7)
Alcoholic Drinks, standard drink	1.2 (1.0)	1.5 (1.0)	0.0	1.0 (1.0)
Caffeine, mg	294.0 (164.5)	342.3 (174.2)	389.4	295.0 (149.5)

Table 6.5. Food groups and nutrient intake at baseline based on quartile categories of heart-protective diet scores

Quartiles	**Q1**	**Q2**	**Q3**	**Q4**
Heart-protective diet score	-14.0	0.3	11.2	36.0
Food groups intake, servings/d				
Wholegrains	0.3 (0.1)	1.8 (0.9)	2.7 (1.1)	3.3 (1.2)
Fruits	0.1 (0.1)	0.7 (0.3)	1.4 (0.5)	4.8 (1.6)
Vegetables	2.2 (0.2)	4.6 (1.2)	5.3 (1.5)	6.9 (1.8)
Starchy Vegetables	0.3 (0.2)	0.6 (0.2)	0.7 (0.3)	2.5 (0.9)
Nuts & Seeds	0.4 (0.3)	0.7 (0.3)	1.1 (0.4)	2.3 (0.8)
Legumes & Beans, Other Vegetarian Protein Alternatives	0.0 (0.0)	0.0 (0.0)	0.3 (0.1)	1.0 (0.3)
Seafood with high omega-3 fatty acids	0.1 (0.0)	0.2 (0.1)	0.3 (0.1)	1.0 (0.3)
Seafood with low omega-3 fatty acids	0.0 (0.0)	0.2 (0.1)	0.2 (0.1)	0.9 (0.3)
Eggs	0.1 (0.0)	0.1 (0.0)	0.2 (0.1)	0.5 (0.1)
Milk & Dairy Products	1.5 (0.6)	1.9 (0.7)	2.4 (0.8)	4.7 (1.3)
Refined grains & cereals	5.9 (1.9)	5.0 (1.5)	2.5 (0.9)	1.9 (0.9)
Potatoes	2.5 (0.8)	0.5 (0.2)	0.3 (0.1)	0.0 (0.0)
Red Meats	2.0 (0.7)	1.1 (0.4)	0.5 (0.2)	0.2 (0.1)
Poultry	0.5 (0.2)	0.4 (0.2)	0.2 (0.1)	0.0 (0.0)
Processed Meat	0.4 (0.2)	0.2 (0.1)	0.2 (0.1)	0.0 (0.0)
Solid Fat (tsp/d)	11.1 (2.8)	8.7 (2.1)	6.5 (1.9)	6.0 (2.3)
Daily nutrient intake				
Total energy intake, kJ/d	9934.9 (1634.5)	9248.3 (1424.0)	8182.7 (1169.1)	6601.8 (611.9)
Total energy intake, kcal/d	2376.8 (391.0)	2212.5 (340.7)	1957.6 (279.7)	1579.4 (146.4)
Total fat, g/d	120.2 (21.8)	89.3 (13.1)	75.4 (11.1)	67.5 (11.1)
Saturated fatty acids, g/d	34.6 (7.0)	34.3 (6.3)	26.3 (4.4)	23.1 (3.8)
Trans fatty acids, g/d	3.5 (0.8)	1.6 (0.3)	1.2 (0.2)	1.0 (0.2)
Dietary fibre, g/d	19.5 (6.7)	26.8 (7.3)	28.6 (7.6)	36.5 (8.5)
Sodium, mg/d	3267.8 (777.9)	2840.1 (635.7)	2376.5 (477.4)	1433.6 (139.7)

Potassium, mg/d	2543.4 (417.8)	3521.4 (643.7)	4085.1 (820.1)	4964 (998.9)

Data are expressed as mean (SD).

6.5 Discussion

This is a descriptive study to investigate the baseline dietary characteristics of LIVEPLUS participants and their cardiometabolic profiles. Overall, all participants enrolled in the LIVEPLUS trial presented suboptimal cardiometabolic profiles. The most prevalent condition was hyperlipidemia (100%), followed by overweight (77.8%), hypertension (55.6%) and hyperglycemia (11.1%). Their baseline diets were characterized by an excess intake of saturated fat and sodium, and an insufficient intake of dietary fibre.

The baseline characteristics of our study populations are similar to previous studies [2, 107-110]. Individuals enrolled in secondary cardiovascular prevention trials tend to be middle age, overweight, with suboptimal cardiometabolic profiles. However, this population consumed less energy from carbohydrates (%E), and had higher protein intake (%E) at baseline. This might be explained by the increased popularity of a low-carb diet and subsequent demand for 'keto-friendly' products in recent years [111]. Google search trends data of 'low-carbohydrate diet' in Australia increased from a score of 25 in 2007 to a score of 87 in 2021 [112]. Other dietary characteristics are similar to previous studies [109, 110] in people with CVD. This population tends to have a high saturated fat and sodium intake, low dietary fibre intake and insufficient fruit and vegetable intake.

Previous research [79, 80] has demonstrated a strong relationship between saturated fat intake and incident ischemic heart disease. Accumulated evidence demonstrates the association between a low dietary fibre intake with risk factors of CVD [113, 114], including overweight, hyperlipidemia, hypertension and hyperglycemia. Furthermore, it is well-established that excessive sodium intake is linked to elevated blood pressure, CVD and stroke [115]. This may explain the suboptimal cardiometabolic profiles we observed in this cohort.

Strengths and Weaknesses

In this study, we have employed robust outcome assessment methods, for both clinical and dietary data. Our dietary measurement is comprehensive and likely to reflect participants' real dietary patterns. The dietary measurements were performed before the group randomization, minimizing the possible contamination of group allocation. We have used a gold-standard dietary measurement method (weighed food record) to assess dietary intake, with weighing scales and household measures provided to participants. Training was given in portion size estimation (using scales, household measures and other tools) prior to diet assessment and food diaries were verified with participants upon receipt. The duration of the food record included at least one weekend day to account for weekend variation. In addition, all participants enrolled and randomized were included in the analysis. To maximize research rigor, reproducibility, and transparency, we published R script analysis code as supplementary materials and datasets were available upon request for purpose of reproducing the results.

However, this study has several limitations. First, the nature of cross-sectional study design implies that we cannot demonstrate causality from our findings. Second, our study is limited by the small sample size (n=9), therefore may not reflect the eating behaviours of the true population with CVD. In addition, although we have provided everything to improve the accuracy of dietary measurements, this information is self-reported and could be subject to recall bias. However, our findings in dietary outcomes are consistent with previous studies with larger sample sizes.

6.6 Conclusion

In summary, our preliminary findings show that LIVEPLUS participants with CHD have suboptimal cardiometabolic profiles at baseline, with the most common condition of hyperlipidemia. The baseline diet is characterized by insufficient fruits, vegetables and dietary fibre, and excessive intake of saturated fat. Our findings are consistent with the current literature and highlight the need for dietary intervention in these individuals.

6.7 Supplementary material

R scripts and de-identified datasets for statistical analyses can be accessed via the online repository (https://github.com/sylviawt/LIVEPLUS_TW_PhD_Thesis. DOI: 10.5281/zenodo.8371749)

CHAPTER 7: The effect of one month 5:2 pesco-vegetarian diet on cardiometabolic risk factors and dietary intake in individuals with coronary heart disease: a randomised controlled trial

Nutrition is an integral part of this project, and I am the dietitian (TW) who leads the dietary intervention of this novel and exciting trial. I was responsible for the development of nutritional educational materials and recipes, dietary assessments, delivery of nutritional interventions and performing individualized nutritional counselling with the participants.

This work has been presented at the American Society for Nutrition (ASN) conference 2023.

The abstract of this work has been published in the Current Developments in Nutrition:

T. Wang, S. Cassidy, C.M. Kroeger, S. Mitra, R. Ribeiro, A. Masedunkas, R. Huang, L. Fontana. P23-080-23. Impact of an Intensive Lifestyle Program on Low Attenuation Plaque and Myocardial Perfusion in Coronary Heart Disease: A Randomised Clinical Trial Protocol. Current Developments in Nutrition. Volume 7, Supplement 1, 2023, 100188, ISSN 2475-2991, https://doi.org/10.1016/j.cdnut.2023.100188

7.1 Abstract

Background and Objective: The cardioprotective effects of intensive lifestyle programs have been elucidated in primary cardiovascular prevention. However, there is a paucity of data on lifestyle regimens in secondary prevention of cardiovascular disease. The LIVEPLUS (LIfestyle VulnErable PLaqUe Study) trial is an ongoing prospective randomized controlled trial that aims to evaluate the effect of an intensive lifestyle program (ILP), combining a 5:2 pesco-vegetarian diet, individualized physical activity and stress reduction compared to American Heart Association (AHA) diet and lifestyle recommendations in patients with coronary heart disease (CHD). In this chapter, we investigate the effect of a one-month intensive lifestyle intervention on cardiometabolic profiles and dietary intakes in nine individuals (mean age: 61.0 ± 10.7 years, 66.7% male) participating in the LIVEPLUS trial.

Main outcomes: Diet, body weight, body mass index (BMI), low-density lipoprotein cholesterol, haemoglobin A1c, systolic blood pressure

Results: After one month of the intervention, the ILP group significantly reduced body weight by 3.4kg and both groups significantly decreased BMI ($p<0.05$). The ILP group exerted an improvement in blood pressure (systolic blood pressure: -12.1mmHg; diastolic blood pressure: -8.1mmHg) but the time effect was not significant. Both groups significantly decreased energy (-2340kJ/d) and protein (-23g/d) consumption ($p <0.05$). The ILP group had lower consumption of saturated fat (-12.3g/d, -3.7%E) and sugar (-37.3g/d) while the AHA group reduced sodium (-1302.4mg) intake ($p <0.05$).

Conclusions: In patients with CHD, both the ILP and the AHA are effective in improving BMI and diet quality by one month of the intervention. Our findings reinforce the clinical benefits of intensive lifestyle programs in the secondary prevention of cardiovascular disease.

7.2 Introduction

Cardiovascular disease (CVD) remains the leading cause of premature death and mortality in both Western countries and the developing world [2], imposing a substantial economic burden on the healthcare system [116]. Much of this is attributable to the failure in addressing modifiable lifestyle risk factors in people at risk [7]. Past research demonstrates the strong association between poor diet, sedentary lifestyles and mental stress with increased risk of developing CVD [7, 117]. For instance, a healthy diet rich in nutrient-dense foods including minimally processed plant-based foods, fish and seafood, and minimizing energy-dense nutrient-poor foods, which are rich in saturated fats, added sugars and added salt, has been demonstrated to exert a strong protective effect against cardiovascular risk [19, 92, 93]. Together with intermittent fasting, which restricts energy intake over a certain period of time, this type of dietary pattern might introduce further benefits to heart health, given calorie restriction is associated with reducing inflammation and oxidative stress, and improving glycaemic control and body weight in populations at risk [94, 95, 97]. Furthermore, reducing sedentary behaviours, increasing physical activity, and managing mental stress have all been shown to lower cardiovascular risk and mortality [98, 99].

Despite the accumulated evidence demonstrating the importance of the above individual element in modifying cardiovascular risk, a study that combines these three components (diet, physical activity and stress reduction) may provide a more powerful tool to evaluate the synergistic and cumulative effects of healthy lifestyles on cardiovascular health. To the best of our knowledge, there is a lack of evidence in the secondary lifestyle prevention of cardiovascular disease. No study has tested the effect of a 5:2 pesco-vegetarian diet in individuals with CVD, and the current evidence of plant-based diet is based on Mediterranean, vegan, lacto-ovo or lacto-vegetarian diets [2, 107]. The LIVEPLUS trial aims to evaluate the effect of such an intensive lifestyle intervention, combining a 5:2 pesco-vegetarian diet, individualized physical activity and stress reduction in patients with coronary heart disease (CHD). In this chapter, we investigate the effect of a one-month intensive lifestyle intervention on cardiometabolic profiles and dietary intakes in nine individuals (mean age: 61.0 ± 10.7 years, 66.7% male) participating in the LIVEPLUS trial.

7.3 Methods

7.3.1 Randomisation

The LIVEPLUS trial is a parallel-group, randomised controlled trial (RCT). The protocol of LIVEPLUS has been published and is described in CHAPTER 5. Enrolled participants were randomised to either the intensive lifestyle program (ILP) group or American Heart Association (AHA) lifestyle intervention group using random permuted blocks with randomly selected block sizes, via a web-based randomisation system in REDCap, and stratified by age, sex, and BMI. The allocation sequence was generated using the blocked size of 2, 4, 6, and 8 from the R package, 'blockrand' [118]. An uneven block was included in the middle of the sequence to guard against guessing the group assignment [119]. Investigators and participants were blinded to the group allocation until all baseline measurements have been completed, as the REDCap support statistician

is the only individual with access to the upcoming treatment allocations within the randomisation list. After the final baseline measurement, the research coordinator used REDCap to randomise the participant, revealing the group assignment to the study team and participant simultaneously.

7.3.2 Intervention of the Intensive Lifestyle Program Group

The ILP group received standard-of-care treatment, as well as three main lifestyle intervention components (nutrition, physical activity and stress reduction) over the 12-month study period. Prior to the start of the trial, each coach (Accredited Practising Dietitian (I), Exercise Physiologist (SC, Ph.D.) and stress reduction coach (CK, Ph.D., certified yoga instructor)) received training by a UK-registered practitioner health psychologist with expertise in health behaviour change. The training included the use of behaviour change counselling skills as well as the delivery of behaviour change techniques, to effectively promote change in relation to each target lifestyle behaviours (i.e. nutrition, physical activity and stress reduction).

At the first three months of the intervention, participants received fortnightly online coaching sessions with a dietitian, a physical activity coach, and a stress reduction coach, and monthly sessions were provided from month 4 to month 12 to further support participants in lifestyle change and improve adherence. Each coaching session was tailored to individual progress and needs, using evidence-informed behaviour change techniques [120]. Additional online coaching calls were scheduled if considered necessary by the study team or when requested by participants.

Table 7.1. Education content for diet, physical activity and stress reduction components for the ILP group.

Month	Diet	Physical activity	Stress reduction
1	Introduction of nutritional intervention	Importance of PA	Introduction
2	Pesco-vegetarian diet	FITT principles and safety	Simple awareness
3	Intermittent fasting	PA and the heart	Attention and the brain
4	Healthy eating	PA and the blood vessels	Dealing with thoughts
5	Dietary measurements	PA and obesity	Biological basis of stress: Responding vs. Reacting
6	Fats	PA and mental health	Dealing with difficult emotions of physical pain
7	Carbohydrates	PA and glucose metabolism	Mindfulness and communication
8	Protein	PA and fat metabolism	Self-compassion cultivation
9	Meal planning	PA and skeletal muscle	Social connectedness
10	Nutritional labelling	PA and inflammation	A closer look at happiness on relationships
11	Dietary patterns and cardiovascular health	PA and brain health	
12	Review	PA and cardiorespiratory fitness	Conclusion

FITT, frequency, intensity, time, type; PA, physical activity

In addition to the online coaching, participants also received education modules (content described in **Table 7.1**) for three main lifestyle intervention components (nutrition, physical activity and stress reduction) over the 12-month study period. Prior to the start of the trial, the Dietitian, the Exercise Coach and the Mindfulness Coach designed and developed these modules and presented them in several formats (full education module, short-version module, and videos with PowerPoint Slides), with multiple-choice questions at the end of each module to assess learning and provide feedback. These modules are informed by evidence-based, peer-reviewed research, and carefully rewritten into lay language, making them accessible, easy to understand and engaging, particularly to those who are new to such lifestyle practices. Participants used the LivePulse app (described below in detail) to access and read these education modules.

Nutrition, Physical Activity and Stress Reduction

For the purpose of this thesis, this CHAPTER will focus on the nutritional component after 1-month on cardiometabolic profiles and dietary outcomes of participants. Please refer to CHAPTER 5 for detailed descriptions of physical activity and stress reduction interventions. The 'Fitbit Inspire 2' physical activity trackers were given to participants, and participants were asked to wear them for 12 consecutive months.

Participants randomized to the ILP group were asked to follow a 5:2 pesco-vegetarian diet for 12 months. This diet involves a combination of a 5:2 diet and a pesco-vegetarian diet. The aim of a pesco-vegetarian diet is to substitute meat with fish, and processed and refined foods with a range of minimally processed plant-based foods. Red meats, including beef, pork, lamb and other red meat products, and poultry including chicken, duck, goose, and other poultry products were excluded from participants' diet. In addition, participants were asked to practice fasting on 2 non-consecutive days a week with an energy restriction of around 500kcal per day for women and 600kcal for men.

To assist in the transition into a pesco-vegetarian diet, participants were provided fresh ingredients and recipes from Marley Spoon (a commercial meal delivery service that provides pre-portioned ingredients and recipes to designated addresses for meal preparation) to prepare their lunch and dinner for 5 days per week, for the first 4 weeks of the intervention. The study dietitian provided instruction on Marley Spoon ordering in the first session of the nutrition intervention with participants. After participants placed the food order, the study dietitian reviewed the meals selected by participants to ensure it complied with a pesco-vegetarian diet (i.e., if participants selected meal plans with meat, it would be altered to a pesco-vegetarian diet before delivery). Participants prepared their breakfasts each day and light meals on fasting days. The study dietitian (TW) designed and developed recipes for these meals and participants accessed recipes through the LivePulse mobile app. After the first 4 weeks, participants met with the study dietitian to design their individualised weekly meal plans and menus to facilitate transition into preparing their own food. The goal was to improve diet quality but also to achieve at least 7-8% weight loss in individuals with overweight over the 1-year intervention, as this is vital to improve metabolic, inflammatory, and cardiac markers [95].

Participants met with a study dietitian on a regular basis (described above) to discuss strategies to implement dietary changes, meal planning, recipes and relevant nutritional information for cardiovascular health. Along

with the education modules, other nutritional materials related to the 5:2 pesco-vegetarian diet (e.g. recipes for a pesco-vegetarian diet, recipes for fasting days, food sources that are rich in iron) were delivered via the LivePulse mobile app.

LivePulse mobile app

LivePulse is a health data collection and intervention tool consisting of a mobile app for participants and a web dashboard for the research team. The app allows participants to create individual goals, receive reminders, access education materials, record and share their health data (e.g. weight, exercise, diets) with the research team. The app is publicly available on both the Apple App Store and on the Google Play Store in Australia. The underlying technology of the app has been implemented in similar apps created by the developer, Vulsen, for other research studies [121, 122].

Key features of the app include:

1-Education: Each component of the ILP (nutrition, physical activity and stress reduction) has 12 online modules with written materials, summarized videos and multiple-choice questions at the end. Each module was released on a monthly basis for participants to read and interact with.

2-Monitoring: Participants and the research team monitored intervention progress through a number of app features (e.g. entry of body weight, logging mindfulness practice). The app extracted data on physical activity and sleep from the Fitbit device. The app includes a multi-subject weight change simulator to predict whether participants are on track with nutrition and physical activity interventions as evidenced by their weight loss trajectory. The algorithm is modelled from the participant's entry of age, height, gender, and regularly updated body weight inputs, as well as the desired percentage weight loss of 7–8% after 1 year. If a participant falls outside of their error region at any point throughout the study, the research team reached out to them to provide additional support.

3-Goal setting: Participants were encouraged to set short- and long-term behavioural and outcome goals (e.g., nutrition, physical activity and weight), which were discussed and adapted over the duration of the intervention with the research team coaches.

7.3.3 Intervention of the American Heart Association Diet Group

The AHA group participants received standard-of-care treatment, and were instructed to follow the AHA Diet and Lifestyle Recommendations [41] to improve heart health. The AHA has developed evidence-based guidance [123] on dietary patterns and lifestyle behaviours which protect individuals against cardiovascular disease. The recommendations by AHA are aligned with the Australian Heart Foundation, however the AHA is more detailed [28]. Participants were given instructions on navigating both the AHA and Heart Foundation websites for searching educational materials (e.g. heart-protective recipes) to improve heart health.

After the initial instruction session with the study dietitian, participants met with the dietitian at month 1, followed by appointments at month 3, month 6, month 9 and month 12. The study dietitian scheduled

additional appointments with participants when necessary to improve compliance with the AHA diet. In addition, the study dietitian summarised the content on healthy lifestyles and nutrition from the AHA website into eight modules of educational materials. These materials were delivered to participants each month via email for the first 8 months of the study. The topics (**Table 7.2**) include general healthy eating, healthy meal planning and preparation, and tips to increase vegetable intake.

Table 7.2. Education content for diet for the AHA group.

Month	Topics
1	Eat Smart
2	Add Colours
3	Practical Tips to Eat Healthier
4	Healthy Cooking At Home
5	Preparing Your Healthy Meals
6	Healthy Essentials for Meal Prep
7	Planning Ahead to Eat Healthy
8	Eat Healthy on a Budged

Participants were given a Fitbit device and met with a stress reduction coach monthly to go through the stress reduction guidelines by the World Health Organization [124].

7.3.4 Outcome Measurements

Outcome measurements have been described in detail in CHAPTER 5 and CHAPTER 6, and the measurements were repeated at month 1.

7.3.5 Statistical Analysis

Analysis was conducted followed the 'intention-to-treat' principle. All statistical analyses were performed using RStudio 2022.02.2+485 statistical software [104] and jamovi (version 2.3) [105]. Quantitative data was described as means (standard deviations) for measured variables with normal distribution, and as median (interquartile range (IQR)) for outcomes with skewed distribution. Categorial variables were presented as proportions. Paired and unpaired t test were used to assess within- and between group changes, respectively. All statistical tests were two-sided, with a significance set at p-value <0.05.

De-identified data are available on request for the purpose of reproducing the results. R scripts used for statistical analysis are available in the supplementary material.

7.4 Results

Table 7.3 Changes in cardiometabolic outcomes of LIVEPLUS participants after 1 month of intervention

	ILP group (n=5)	AHA group (n=4)	p-value*
Body weight, kg	-3.4 (2.4)#	-2.6 (2.4)	0.63
BMI, kg/m^2	-1.1 (0.7)#	-0.8 (0.6)#	0.52
SBP, mmHg	-12.1 (19.2)	3.8 (8.3)	0.17
DBP, mmHg	-8.1 (12.0)	1.8 (5.7)	0.18
TC, mmol/L	0.2 (1.0)	-0.4 (0.3)	0.26
LDLc, mmol/L	0.2 (0.9)	-0.2 (0.3)	0.37
HDLc, mmol/L	0.08 (0.2)	-0.2 (0.2)	0.12
Triglycerides, mmol/L	-0.2 (0.2)	-0.2 (0.4)	0.77
HbA1c, %	0.1 (0.1)#	0.03 (0.1)	0.16

* Significant difference ($p < 0.05$) between the ILP and the AHA groups, analyzed using an independent sample t-test

Significant difference ($p < 0.05$) between baseline and after 1 month of intervention in each variable of each group, analyzed using a paired sample t-test

7.4.1 Changes in Cardiometabolic Outcomes

The baseline clinical and metabolic characteristics of participants have been described in **6.4 Results** and **Table 6.1.** Briefly, five participants (mean age: 61.4±10.8 years) were randomized to the ILP group and four (mean age: 60.5±12.1 years) were randomized to the AHA group. All participants have baseline suboptimal cardiometabolic profiles. The most common condition is hyperlipidemia (n=9), followed by overweight (n=7), hypertension (n=5) and hyperglycemia (n=1).

Table 7.3 demonstrates the changes in cardiometabolic profiles of LIVEPLUS participants after one month of intervention. The ILP group has significantly decreased ($p<0.05$) body weight (-3.4kg) and BMI (-1.1kg/m^2). In addition, the ILP group showed an improvement in both systolic (-12.1mmHg) and diastolic (-9.1mmHg) blood pressure but the time effect was not significant. No difference was detected in changes between groups in all cardiometabolic outcomes.

7.4.2 Changes in Dietary Intake and Dietary Adherence

Baseline nutrients and foods intake of LIVEPLUS participants are shown in **Table 6.2** and **Table 6.3** and described in Chapter 6. The habitual diets of the study patients were characterized by insufficient fruit (1.2 serves/d) and vegetable (4.1 serves/d) and dietary fibre intake (24.1g/d), high protein (20.1%E) and total fat (37.4%E) consumption, and excessive saturated fat intake (12.7%E).

After one month of intervention, both groups significantly decreased their intakes of energy (-2354.5kJ/d) and protein (-25.4g/d), reflecting a high adherence to the prescribed diets and fasting protocol. The ILP group had a significant reduction in intakes of saturated fat (-12.3g/d, -3.7%E), carbohydrate (-60.7g/d) and sugar

(-37.3g/d), aligned with a significant decrease in red meats (-0.9 serve/d), processed meats (-0.2 serve/d), solid fat (-4.3 tsp/d) and refined grains (-2.5 serves/d) consumption ($p<0.05$). The AHA group significantly decreased sodium (-1302.4mg/d) consumption ($p<0.05$). Both groups decreased red meats and poultry intakes, and the ILP group has a slight increase in seafood and nuts and seeds intake, following the prescription of a pesco-vegetarian diet. Moreover, the ILP group significantly reduced their intakes of vegetables (-1.5 serves/d) and dietary fiber (-7g/d). However, the ILP group has reduced intakes of most food groups (**Table 7.5**) and it might be a reflection of incorporating the 5:2 fasting diet in the intervention. Overall, there is no significant difference in changes of nutrient and food intakes between groups.

Table 7.4 Changes in nutrients intake of LIVEPLUS participants after 1 month of intervention

	ILP group (n=5)	AHA group (n=4)	p-value*
Energy, kJ	-2349.2 (1588.9)#	-2361.1 (1632.5)#	0.99
kcal	-562.0 (380.1)#	-564.9 (390.5)#	0.99
Protein, g	-27.3 (14.8)#	-23.1 (23.1)#	0.75
Energy, %	2.4 (5.2)	1.3 (4.7)	0.75
Total Fat, g	9.6 (54.3)	-22.9 (27.6)	0.32
Energy, %	6.0 (9.2)	0.4 (8.0)	0.37
Saturated Fat, g	-12.3 (9.0)#	-9.3 (9.2)	0.63
Energy, %	-3.7 (2.5)#	-1.0 (3.0)	0.19
Trans Fatty Acids, g	-0.9 (1.1)	-0.6 (0.5)	0.60
Energy, %	-0.2 (0.3)	-0.1 (0.2)	0.62
Polyunsaturated Fat, g	-5.1 (5.4)	-3.5 (6.0)	0.70
Monounsaturated Fat, g	-2.4 (19.8)	-7.9 (10.9)	0.63
Carbohydrate, g	-60.7 (48.4)#	-50.0 (62.6)	0.78
Energy, %	-8.1 (6.1)	0.2 (12.3)	0.22
Sugars, g	-37.3 (31.2)#	-7.6 (24.1)	0.16
Dietary Fibre, g	-7.0 (5.1)#	-2.5 (7.8)	0.33
Vitamin C, mg	-66.9 (91.6)	-18.3 (72.4)	0.42
Vitamin E, mg	-2.2 (6.5)	-3.7 (7.8)	0.77
Total Folate, μg	-138.2 (184.1)	-18.3 (231.2)	0.41
Total Vit A equivalent, μg	-375.3 (242.1)	-129.3 (501.8)	0.36
Sodium, mg	-590.2 (829.0)	-1302.4 (769.2)#	0.23
Potassium, mg	-1193.7 (755.0)#	-474.6 (1101.0)	0.28
Iron, mg	-4.6 (2.9)#	-0.4 (4.5)	0.13
Zinc, mg	-6.0 (3.3)#	-3.4 (1.6)#	0.20
Iodine, μg	-56.7 (94.5)	-1.6 (62.9)	0.35

* Significant difference ($p < 0.05$) between the ILP and the AHA groups, analyzed using an independent sample t-test

Significant difference ($p < 0.05$) between baseline and after 1 month of intervention in each variable of each group, analyzed using a paired sample t-test

Table 7.5 Changes in foods intake of LIVEPLUS participants after 1 month of intervention

	ILP group (n=5)	AHA group (n=4)	p-value*
Grains, serve	-2.3 (1.8)#	-1.9 (2.0)	0.79
Refined, serve	-2.5 (2.2)#	-1.5 (1.1)	0.43
Wholegrains, serve	0.2 (1.1)	-0.5 (1.7)	0.49
Fruit, serve	-0.9 (1.2)	0.3 (1.0)	0.14
Vegetables and legumes, serve	-1.5 (0.7)#	-1.2 (1.8)	0.73
Starchy vegetables, serve	-0.3 (0.9)	-0.6 (1.3)	0.66
Potatoes, serve	0.1 (0.8)	-0.6 (1.3)	0.29
Legumes veg, serve	-0.2 (0.4)	-0.02 (0.8)	0.62
Lean meats, poultry, fish, eggs, tofu, nuts and seeds, and legumes, serve	-1.1 (1.7)	-0.8 (1.2)	0.77
Red Meats, serve	-0.9 (0.8)#	-0.3 (0.3)	0.22
Poultry, serve	-0.2 (0.2)	-0.1 (0.5)	0.68
Seafood, high long-chain n3	0.2 (0.7)	-0.04 (0.7)	0.67
Seafood, low long-chain n3	0.04 (0.3)	-0.04 (0.1)	0.64
Eggs, serve	0.1 (0.3)	0.1 (0.3)	0.93
Legumes Protein, serve	-0.1 (0.2)	0.0 (0.4)	0.55
Nuts and Seeds, serve	0.3 (1.3)	-0.4 (0.5)	0.41
Soy Products, serve	-0.2 (0.4)	-0.04 (0.2)	0.39
Milk, yoghurt, cheese and/or alternatives, serve	-0.8 (1.9)	-0.4 (0.8)	0.66
Milk, serve	-0.7 (1.7)	0.09 (0.6)	0.40
Cheese, serve	-0.1 (0.4)	-0.2 (0.4)	0.65
Yoghurt, serve	0.03 (0.07)	0.07 (0.3)	0.80
Milk Alternatives, serve	-0.01 (0.4)	-0.3 (0.5)	0.43
Processed meats, serve	-0.2 (0.2)#	-0.05 (0.07)	0.14
Alcoholic Drinks, standard drink	-0.3 (1.3)	-0.7 (1.0)	0.64
Caffeine, mg	-70.1 (113.3)	-52.8 (214.9)	0.88
Oil Equivalents, tsp	6.6 (8.6)	-2.1 (2.9)	0.10
Solid Fat Equivalents, tsp	-4.3 (2.7)#	-2.9 (3.5)	0.51
Added Sugars, tsp	-2.0 (3.5)	-2.0 (2.8)	0.99

* Significant difference ($p < 0.05$) between the ILP and the AHA groups, analyzed using an independent sample t-test

Significant difference ($p < 0.05$) between baseline and after 1 month of intervention in each variable of each group, analyzed using a paired sample t-test

Table 7.6 A comparison of food and nutrients intake of LIVEPLUS participants with Australian Dietary Guidelines after 1 month of intervention

	ILP group (n=5)	AHA group (n=4)	ADG*
Nutrients			
Energy, kJ	5487.5 (1596.9)	5516.8 (1481.2)	9100.0#
kcal	1312.8 (382.0)	1319.8 (354.3)	2177.0#
Protein, g	65.4 (20.0)	67.9 (19.7)	64
Energy, %	21.3 (4.3)	21.4 (5.3)	15-25
Total Fat, g	90.8 (52.1)	53.8 (20.0)	NA
Energy, %	47.0 (10.4)	35.4 (5.0)	20-35#
Saturated Fat, g	15.7 (5.7)	16.0 (5.5)	NA
Energy, %	10.6 (2.2)	10.8 (2.8)	<10
Trans Fatty Acids, g	0.7 (0.5)	0.6 (0.3)	NA
Energy, %	0.5 (0.2)	0.5 (0.3)	<10 with SFA
Polyunsaturated Fat, g	11.1 (8.3)	11.3 (6.8)	13
Monounsaturated Fat, g	26.0 (24.8)	21.4 (9.0)	NA
Carbohydrate, g	109.3 (40.2)	122.2 (35.5)	NA
Energy, %	27.0 (6.6)	36.7 (8.3)	45-65#
Sugars, g	37.4 (18.1)	55.8 (14.4)	NA
Dietary Fibre, g	17.2 (8.2)	21.5 (8.9)	38#
Alcohol, g	4.9 (6.5)	7.0 (8.2)	NA
Vitamin C, mg	45.9 (38.3)	84.6 (39.2)	220#
Vitamin E, mg	11.4 (10.3)	10.7 (3.1)	19#
Total Folate, μg	371.0 (178.6)	467.4 (242.8)	300-600
Total Vit A equivalent, μg	459.4 (387.6)	675.4 (384.6)	1500#
Sodium, mg	1437.8 (791.5)	1174.4 (468.8)	2000#
Potassium, mg	2237.3 (730.9)	2855.6 (772.8)	4700#
Iron, mg	5.2 (2.8)	10.2 (6.3)	8
Zinc, mg	5.6 (2.4)	7.4 (3.0)	14#
Iodine, μg	128.8 (69.7)	152.2 (56.3)	150
Food groups			
Grains, serve	2.3 (1.2)	2.8 (1.1)	6#
Refined, serve	0.6 (0.5)	1.4 (0.6)	
Wholegrains, serve	1.7 (1.2)	1.3 (0.9)	
Fruit, serve	0.6 (0.8)	1.1 (0.8)	2#
Vegetables, serve	2.7 (2.2)	2.7 (0.9)	5.5#
Starchy vegetables, serve	0.4 (0.6)	0.3 (0.4)	
Potatoes, serve	0.3 (0.6)	0.3 (0.4)	
Legumes veg, serve	0.0 (0.0)	0.3 (0.5)	
Lean meats, poultry, fish, eggs, tofu, nuts and seeds, and legumes, serve	2.1 (2.2)	2.1 (1.2)	2.5
Red Meats, serve	0.0 (0.0)	0.3 (0.2)	

Poultry, serve	0.0 (0.0)	0.2 (0.3)	
Seafood with High Long-chain n3, serve	0.4 (0.5)	0.3 (0.4)	
Seafood with Low Long-chain n3, serve	0.3 (0.4)	0.2 (0.3)	
Eggs, serve	0.3 (0.3)	0.2 (0.3)	
Legumes Protein, serve	0.0 (0.0)	0.2 (0.3)	
Nuts and Seeds, serve	1.1 (2.1)	0.5 (0.8)	
Soy Products, serve	0.02 (0.05)	0.06 (0.08)	
Milk, yoghurt, cheese and/or alternatives, serve	1.4 (0.5)	1.5 (0.6)	2.5#
Milk, serve	0.7 (0.4)	1.0 (0.4)	
Cheese, serve	0.5 (0.4)	0.2 (0.2)	
Yoghurt, serve	0.06 (0.08)	0.2 (0.2)	
Milk Alternatives, serve	0.1 (0.3)	0.04 (0.08)	
Processed meats, serve	0.0 (0.0)	0.04 (0.08)	
Alcoholic Drinks, standard drink	0.5 (0.7)	0.7 (0.8)	<2#
Caffeine, mg	236.4 (95.9)	227.8 (58.1)	
Oil Equivalents, tsp	16.5 (11.6)	7.4 (3.5)	
Solid Fat Equivalents, tsp	2.9 (2.4)	3.8 (3.3)	
Added Sugars, tsp	1.6 (2.2)	0.9 (0.7)	

Table 7.7. Food groups and nutrient intake at one month based on quartile categories of heart-protective diet scores

Quartiles	**Q1**	**Q2**	**Q3**	**Q4**
Heart-protective diet score	-7.5	4.8	14.5	35.8
Food groups intake, servings/d				
Wholegrains	0.7 (0.3)	1.6 (0.6)	1.9 (0.7)	3.4 (1.0)
Fruits	0.2 (0.1)	0.7 (0.3)	1.5 (0.6)	2.1 (0.8)
Vegetables	1.9 (0.7)	2.5 (0.8)	3.5 (1.0)	6.1 (1.7)
Starchy Vegetables	0.0 (0.0)	0.0 (0.0)	0.6 (0.2)	1.4 (0.5)
Nuts & Seeds	0.0 (0.0)	0.1 (0.0)	0.5 (0.2)	4.9 (1.6)
Legumes & Beans, Other Vegetarian Protein Alternatives	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	1.0 (0.3)
Seafood with high omega-3 fatty acids	0.0 (0.0)	0.2 (0.1)	0.7 (0.2)	1.1 (0.4)
Seafood with low omega-3 fatty acids	0.0 (0.0)	0.1 (0.0)	0.3 (0.1)	1.0 (0.4)
Eggs	0.0 (0.0)	0.2 (0.1)	0.5 (0.2)	0.7 (0.3)
Milk & Dairy Products	1.1 (0.2)	1.4 (0.2)	1.5 (0.2)	2.3 (0.5)
Refined grains & cereals	2.2 (0.7)	1.2 (0.4)	1.0 (0.4)	0.5 (0.3)
Potatoes	1.4 (0.5)	0.3 (0.1)	0.0 (0.0)	0.0 (0.0)
Red Meats	0.5 (0.2)	0.2 (0.1)	0.0 (0.0)	0.0 (0.0)
Poultry	0.6 (0.2)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Processed Meat	0.2 (0.1)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Solid Fat (tsp/d)	8.1 (2.7)	4.6 (1.4)	1.8 (0.5)	1.6 (0.5)
Daily nutrient intake				
Total energy intake, kJ/d	7488.8 (1448.4)	6636.5 (1067.2)	5348.8 (690.4)	4381.6 (400.2)
Total energy intake, kcal/d	1791.6 (346.5)	1587.7 (255.3)	1279.6 (165.2)	1048.2 (95.7)
Total fat, g/d	170.6 (43.4)	77.9 (17.8)	64.1 (11.5)	42.8 (3.9)
Saturated fatty acids, g/d	25.4 (5.3)	17.0 (2.7)	14.9 (2.2)	11.9 (1.2)
Trans fatty acids, g/d	1.5 (0.4)	0.8 (0.2)	0.6 (0.2)	0.4 (0.1)
Dietary fibre, g/d	32.0 (8.3)	25.6 (5.5)	15.5 (2.6)	13.0 (1.6)
Potassium, mg/d	1949.1 (243.8)	2322.8 (326.3)	3126.3 (601.0)	3687.5 (772.8)

Data are expressed as mean (SD).

7.5 Discussion

This analysis explores the effect of a one month lifestyle intervention on dietary intakes and cardiometabolic profiles in LIVEPLUS participants with CHD. In this secondary cardiovascular prevention clinical trial, we found a significant improvement in body weight and BMI after one month of intervention. The ILP group also exerted a reduction in both systolic and diastolic blood pressure, but the time effect is not significant. Both groups decreased energy and protein intakes and improved diet quality in terms of heart health but by different means. The ILP group decreased saturated fats and refined carbohydrate intake while the AHA group reduced sodium consumption. This reflects the different emphasizes of the two diets: the ILP group is to replace red meat and poultry with fish and seafood while the AHA group focuses on general healthy eating patterns with low salt content.

To the best of our knowledge, there is no clinical trial delivering a 5:2 pesco-vegetarian diet to individuals with CHD [2]. Our findings are aligned with previous clinical trials delivering vegetarian diets to patients with CVD [2, 108-110]. For example, Aldana et al. [108] found a significant reduction in body weight, BMI and systolic blood pressure after 6 months of the Ornish diet (a very low-fat lacto-ovo vegetarian diet), but no significant effect on lipid profiles. Shah et al. [125] investigated the effect of both an 8-week vegan and AHA diet in patients with CHD. Both groups improved BMI, but no significant difference was detected between groups, and the changes in cardiometabolic profiles (markers of glycemic control and lipid profiles) were not significant.

Although we did not find a significant improvement in cardiometabolic profiles after one month of the intervention, it should be noted that the baseline cardiometabolic markers (**Table 6.1**) of LIVEPLUS participants were within the normal range and eight out of nine participants were on medications to manage their suboptimal cardiometabolic conditions. The use of lipid, glucose and blood pressure-lowering medications might obscure the favourable effects of our interventions on cardiometabolic outcomes. This is supported by the findings of Wang et al. [2] that RCTs delivering vegetarian diets to individuals who were not on medications to manage cardiometabolic conditions showed significant improvements in LDL-C and systolic blood pressure.

The LIVEPLUS trial aims to deliver a comprehensive lifestyle program to improve blood lipids, glucose tolerance and blood pressure with a goal of 7% body weight loss (in patients with overweight) over one year of the intervention. In our cohort, 78% of the participants with CHD were overweight. Being overweight and obese is a well-established risk factor for suboptimal cardiometabolic profiles (hypertension, type 2 diabetes and dyslipidemia) and cardiovascular disease incidence and mortality [13]. A meta-analysis of 57 observational studies including 900,000 adults found that in individuals with overweight (BMI above 25kg/m^2), there is an approximate 8% increase in ischaemic heart disease mortality (hazard ratio per 1kg/m^2: 1.08 [95%CI: 1.06, 1.09]) and stroke mortality (hazard ratio per 1kg/m^2: 1.08 [95%CI: 1.06, 1.10]) with each 1kg/m^2 increase in BMI. Accumulated evidence shows that lifestyle modification and subsequent weight loss improve metabolic syndrome and endothelial dysfunction [13], which is fundamental to the progression of atherosclerosis, a leading cause of cardiovascular disease and is associated with an increased risk of heart attack and stroke. Our

preliminary findings show a significant reduction in body weight and BMI. Furthermore, the reduction in energy, saturated fat and sugar intake and the increase in fish and nut and seed consumption of the ILP group might introduce additional benefits in lowering plasma cholesterol levels and the risk of CHD [48].

Strengths and limitations

The strengths of the current study include: a). the use of a randomized controlled trial study design thus the only differences between two groups are the intervention they receive, evidenced by no significant difference detected at baseline; b). both groups receive personalised counselling from a dietitian, an exercise physiologist and a mindfulness coach during the first month of the intervention c). we have employed robust outcome assessment methods, for both clinical and dietary data, as described in CHAPTER 5 and CHAPTER 6; d). all participants enrolled and randomized were included in the analysis; e). finally, to maximize research rigor, reproducibility, and transparency, we have published R script analysis code as supplementary materials and datasets are available upon request for the purpose of reproducing the results.

However, these limitations should be noted. First, our cohort consists of highly educated individuals (>75% completed tertiary education) and most of them had a sound understanding of a healthy diet for cardiovascular health before the start of the intervention. Participants in the AHA diet group consumed relatively low amounts of red meats and poultry products at baseline and one month (**Table 6.3** and **Table 7.6**). They are considered to adhere to the AHA diet and such a participant would favour the null hypothesis. Thus, it limits the generalizability of our findings to patients with CHD in general and the actual effect of such an intensive lifestyle intervention might be underestimated. Second, the small sample size (n=9) might further undermine the internal and external validity of our study. It is likely that our study is underpowered, due to the small sample size, and thus possible that a true effect has gone undetected (type II error). Third, this study only looks at the very short-term effect (1 month) of such an intensive lifestyle intervention on individuals with CHD. It takes time and effort for participants to learn and adopt strategies to improve lifestyles and the results at one month might not reflect the true benefits of the LIVEPLUS trial. In fact, several participants randomized to the ILP group lost greater than 10% of initial body weight and improved lipid profiles at month 6 of the intervention (results not shown). Fourth, we did not correct for multiple comparisons in outcome analyses, which might increase the likelihood of type I errors. However, we did not detect any significant difference between groups in our outcomes, thus it will not impact the conclusions of this study. Future work with a complete dataset when recruitment finishes should consider correcting for multiple comparisons to avoid (non-transparently) inflating the probability of false positive findings. Finally, although this CHAPTER focuses on the diet component of the lifestyle interventions in both groups, we could not isolate the effects of exercise and stress reduction. However, the improvements in diet quality are evidenced by changes in food groups and nutrient intakes.

7.6 Conclusion

In conclusion, both the intensive lifestyle program and the American Heart Association lifestyle recommendations were effective in decreasing body weight and BMI and improving diet quality after one month of intervention. This analysis should be repeated when the trial is complete to assess the long-term effect of such an intensive lifestyle intervention in individuals with CHD.

7.7 Supplementary material

R scripts and de-identified datasets for statistical analyses can be accessed via the online repository (https://github.com/sylviawt/LIVEPLUS_TW_PhD_Thesis. DOI: 10.5281/zenodo.8371749)

CHAPTER 8: Discussion and Future Directions

Importance of this Thesis and Research Gap

Cardiovascular diseases (CVDs) remain the leading cause of disease burden and premature death worldwide [2]. This is largely attributable to the failure in addressing modifiable risk factors in individuals at risk [7]. People with suboptimal cardiometabolic profiles, including conditions like hypertension, dyslipidemia, and diabetes, face a markedly elevated risk—between two to seven times—of both developing and succumbing to CVD [126, 127]. Diet plays a vital role in managing cardiometabolic conditions and subsequent CVD event risk. Although poor diet is mechanically linked to an elevated risk of CVD morbidity and mortality, adherence to a high-quality heart-healthy diet is associated with optimal cardiometabolic profiles and cardiovascular health [27]. The protective effects of plant-based diets on primary cardiovascular prevention in the general population are well documented [128]. For example, Huang et al. [128] combined data from twelve randomized controlled trials and found that individuals who followed vegetarian diets over a median duration of 18 weeks significantly lowered their body weight. Another meta-analysis [46] included seven studies with more than 120,000 participants from the UK, Germany, US, Netherlands and Japan, and demonstrated that vegetarians experienced a 29% lower risk of ischemic heart disease mortality (relative risk: 0.71, 95%CI: [0.56, 0.87]). However, there is a paucity of data of plant-based diets on the secondary prevention of cardiovascular diseases (CVDs), and past research did not control for key confounders such as physical activity and medication changes [2]. The aim of this thesis was to investigate the associations between plant-based diets and cardiovascular health.

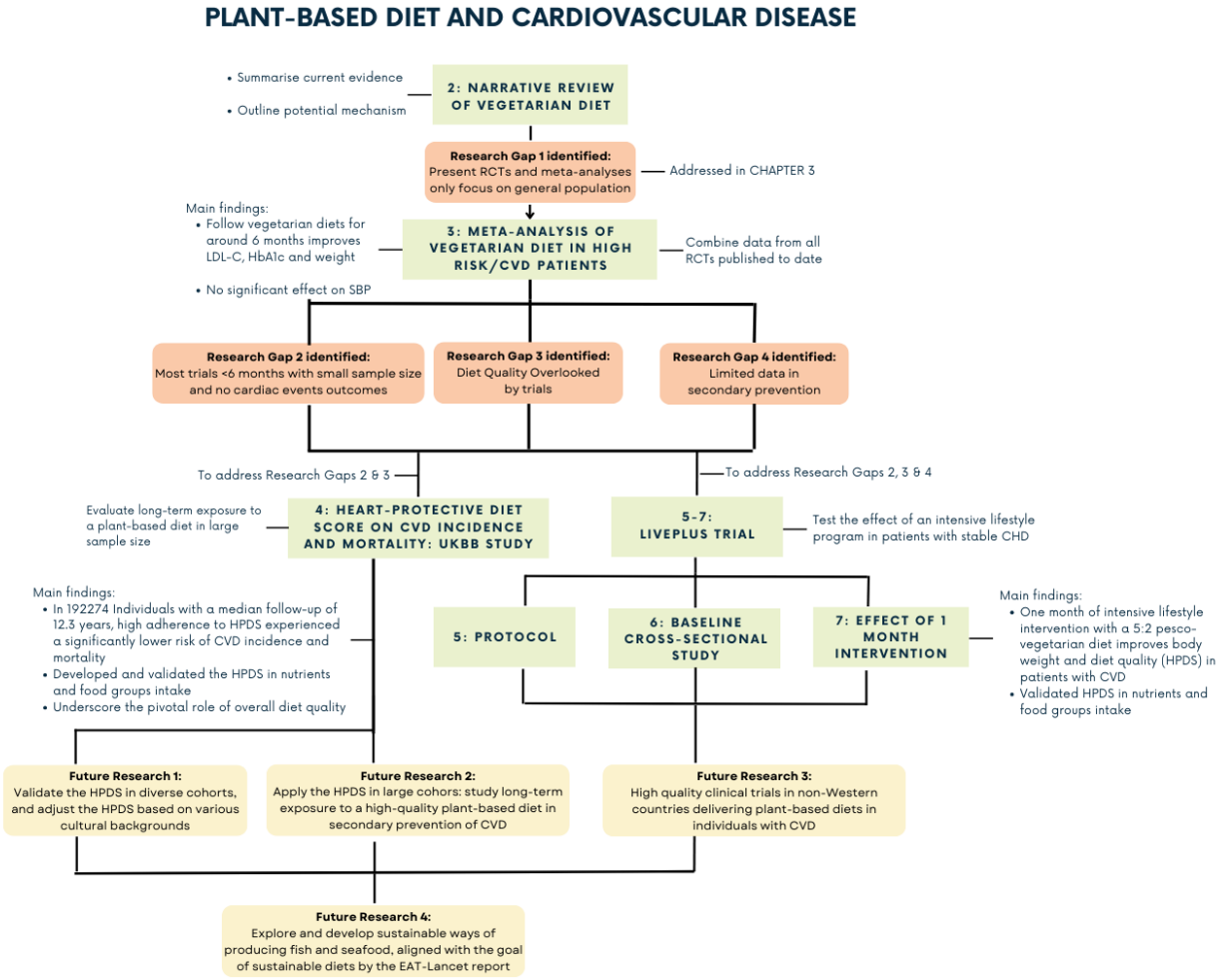


Figure 8.1. Main findings of the thesis and future research directions

Main Findings of the Thesis and Contribution to the Field

In **CHAPTER 2**, we reviewed the current evidence of vegetarian diets on cardiovascular health from clinical trials and large prospective studies, and discussed the potential mechanisms mediating the protective effects of vegetarian diets [2]. Through this narrative review, we determined that most present RCTs and meta-analyses focus on general population. There is currently no study that integrates the evidence concerning the influence of vegetarian diets on cardiometabolic profiles in populations at high risk of CVDs, and investigates the potential establishment of a causal relationship by combining data from randomized controlled trials (RCTs). Therefore, we conducted a meta-analysis to address this question (**CHAPTER 3**), and found that following vegetarian diets for an average of six months is effective in improving low-density-lipoprotein cholesterol (LDL-C), glycated haemoglobin (HbA1c) and body weight [2] in individuals with elevated risk of CVDs. However, we did not observe a significant effect on systolic blood pressure. Among the clinical trials we included, it was notable that the majority did not record comprehensive dietary information for participants; therefore, we were unable to assess the quality of vegetarian diets. Moreover, we were not able to evaluate the long-term effect of following a vegetarian diet on the risk of cardiovascular events, as a significant portion of

the trials we included had a follow-up durations of less than six months. Consequently, we designed and developed our own heart-protective diet score (HPDS), which encompasses an assessment of diet quality and integrates the consumption of fish and seafood, aligning with the dietary guidelines advocated by the American Heart Association (AHA), Australian Heart Foundation and the 2019 European Society of Cardiology (ESC)/ European Atherosclerosis Society (EAS) guidelines [28, 29, 41]. In order to maximize the duration of follow-up and implement our diet score in a large sample size, we tested our developed score in the UK Biobank cohort, as detailed in **CHAPTER 4**. This evaluation specifically focused on individuals who were free of Type 2 Diabetes and cardiovascular diseases at baseline. We demonstrated that individuals who adopted a high-quality plant-based heart-protective diet, rich in whole grains, non-starchy vegetables, fruits, legumes and beans, and inclusive of fish and seafood, experienced a significantly lower risk of CVD incidence and mortality. These findings underscored the pivotal role of overall diet quality in promoting cardiometabolic health, as opposed to exclusively emphasizing specific diet types (e.g. vegetarian diet, Mediterranean diet). In order to provide additional validation for the protective effect of high-quality plant-based diets supplemented with fish and seafood on cardiometabolic health, and to address the existing research gap in secondary prevention of CVD (identified in **CHAPTER 3**), the LIVEPLUS trial was designed. In this clinical trial, individuals diagnosed with low attenuation coronary plaques were randomly assigned to either an intensive lifestyle program (combining a 5:2 pesco-vegetarian diet, individualized exercise session and stress reduction) or to follow the lifestyle recommendations outlined by the AHA. We have applied our new developed HPDS in the LIVEAPLUS trial to validate this new tool and demonstrate the importance of considering diet quality in cardiovascular disease management. The preliminary findings of the LIVEPLUS trial (**CHAPTER 5-7**) indicate that implementing a 5:2 pesco-vegetarian diet for a duration of one month led to positive outcomes, notably in terms of enhanced body weight and diet quality, with an increase of HPDS in all participants, characterizing by an emphasis in consumption of healthy proteins including fish and seafood and eggs, and a large decrease in refined carbohydrates, potatoes, red meats and unhealthy fats. We have used the term 'lifestyle' and 'lifestyle behaviours' throughout the thesis. We are aware of the implied personal responsibility with 'lifestyle behaviours', and we would like to acknowledge the importance of social and environmental determinants of health. Overall, the conclusions drawn from this thesis serve to bridge a critical research gap in the secondary prevention of CVD. It underscores that adopting a high-quality plant-based diet supplemented with fish and seafood, but not purely plant-based diets, holds promise in improving suboptimal cardiometabolic profiles (including overweight, dyslipidemia and hyperglycemia), and potentially reducing the risk of subsequent CVD-related morbidity and mortality in individuals at high risk.

Potential mechanism

The observed protective effects of vegetarian diets might be explained by potential metabolic and molecular mechanisms. As demonstrated by our meta-analysis, individuals following vegetarian diets experienced a significant reduction in LDL-C. Eliminating meats and poultry from the diet results in a reduction in saturated fat and cholesterol intake, both of which are strongly associated with CHD risk [79]. Past clinical trials have shown that replacing saturated fats with vegetable polyunsaturated fats can lower CHD risk by approximately 30% [129-131], a level of effectiveness comparable to that achieved through statin therapy [132]. Moreover, consuming a diet rich in animal protein and branched-chain amino acids (i.e., leucine, isoleucine and valine) has been linked to elevated platelet activation and risk of arterial thrombosis. This diet also promotes atherosclerosis [133], and has been shown to reduce insulin sensitivity in randomized clinical trials [134, 135]. Furthermore, omnivorous dietary patterns, particularly those rich in red meats, egg yolk and full-fat dairy

products that are rich in choline and L-carnitine, increase the production of trimethylamine N-oxide (TMAO) through bacterial metabolism [136]. Individuals with elevated circulating TMAO face an increased risk of cardiovascular events, including heart attack and stroke, that is 20% higher compared to those with lower levels. This increased risk has been attributed to TMAO-induced vascular inflammation and platelet activation [137]. In contrast, high-quality plant-based diets, rich in wholegrains, fruits and vegetables, beans and legumes, and nuts and seeds, are notably high in dietary fibers and phytosterols. These components are known to lower blood cholesterol levels by reducing the reabsorption of cholesterol and bile acids in the small intestine [138, 139]. Data from a randomized clinical trial conducted in individuals with hyperlipidemia demonstrated a 13% reduction in low-density lipoprotein cholesterol (LDL-C) after consuming a diet rich in viscous fibres, nuts and seeds and plant sterol ester-enriched margarine for six months [140]. This is aligned with our findings. In addition, plant-based whole foods, rich in dietary fibre and low in glycemic index, reduce insulin secretion and improve the production of short-chain fatty acids in the gut by fibre fermentation, which are both linked to a decrease in cholesterol synthesis [87]. The high fibre content of plant-based diets additionally promotes satiety, while preventing large fluctuations in postprandial blood glucose levels by inducing gastric distention and delaying gastric emptying [88]. These effects have been clearly demonstrated in randomized clinical trials and our meta-analysis [2], resulting in marked reductions in body weight and blood glucose levels [141, 142]. However, unhealthy plant-based diets, rich in ultra-processed foods, may negatively affect the intestinal epithelial barrier, leading to increased permeability of bacterial endotoxins and food-derived antigens [143]. These substances activate the immune system and generate systematic low-grade inflammation by increasing the circulated levels of interleukin-6 and hs-CRP [144]. The systemic chronic inflammation is an independent risk factors of CVDs, demonstrated by past clinical studies [145].

Impact of Our Findings on Cardiovascular Prevention

Overall, our findings support the nutrition position statements by the Australian Heart Foundation (HF) [28] and the recommendations of the sustainable diets by the EAT-Lancet Commission [107] in relation to the encouragement of plant-based whole foods (including vegetables, fruits, wholegrains) and healthy protein (especially fish and seafood, beans and legumes and nuts and seeds) consumption. Our results provide additional evidence in promoting plant-based dietary patterns with uptake of fish and seafood for cardiovascular health. The most recent dietary patterns recommendations [146], embedded in the HF nutrition position statements, have been informed by an extensive analysis of 33 systematic reviews, encompassing both RCTs and observational studies [147]. These reviews comprehensively cover evidence from seven distinct dietary patterns, including the Prudent Diet, Mediterranean Diet, Vegetarian Diet, DASH Diet, Nordic Diet, Tibetan Diet and the Portfolio Diet. Notably, only one recommendation put forth pertains to the efficacy of a vegetarian diet in lowering blood pressure (Grade B, representing good body of evidence). The most recent dietary patterns recommendations by the Australian Heart Foundation [146], embedded in the HF nutrition position statements, have been informed by an extensive analysis of 33 systematic reviews, encompassing both RCTs and observational studies [147]. These reviews comprehensively cover evidence from seven distrinctdistinct dietary patterns, including the Prudent Diet, Mediterranean Diet, Vegetarian Diet, DASH Diet, Nordic Diet, Tibetan Diet and the Portfolio Diet. Notably, only one recommendation put forth pertains to the efficacy of a vegetarian diet in lowering blood pressure (Grade B, representing good body of evidence). Specifically, this endorsement is based on a solitary systematic review [148], which aggregates findings from six RCTs, one single-arm clinical trial and 32 cross-sectional studies focusing on vegetarian diets in individuals with either normal or elevated blood pressure. However, no further recommendations were provided

concerning other cardiometabolic outcomes and/or the reduction of CVD events and mortality associated with the vegetarian diet.

Hence, the findings presented in this thesis could greatly contribute to the development of Australian Heart Foundation dietary and clinical guidelines for primary and secondary prevention of CVD, and support the sustainable diets incorporating fish and seafoods consumption promoted by the EAT-Lancet Commission [107]: a) **CHAPTER 3** is a meta-analysis of RCTs, in which we utilized the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) tool [149] to evaluate the strength of evidence for all primary outcomes.[149] to evaluate the strength of evidence for all primary outcomes. The GRADE tool is, in fact, the most widely adopted tool to summarize evidence. It provides a systematic approach for making clinical recommendations. Thus, the high-quality results generated from our study provide solid evidence of the protective effects of vegetarian diets on cardiometabolic outcomes (including body weight, LDL-C and HbA1c) in individuals with or at high risk of CVD. Our findings could contribute directly to the development of the HF clinical and dietary recommendations in CVD prevention and management; b) the evidence generated from **CHAPTER 4** underscores the benefits of sustained adherence to a high-quality plant-based diet with adequate fish and seafoods on CVD events and mortality; c) **CHAPTER 5-7** bridge a key research gap by focusing on secondary prevention of CVD, an area lacking substantial evidence in the current dietary recommendations. In line with the recommendations of the EAT-Lancet Commission [150], our results may lead to greater promotion of plant-based diets with fish and seafoods in individuals at high risk of CVD. This is not only due to their health benefits but also to their positive environmental impact. The promising results highlighted in **CHAPTER 4** suggest that following a high-quality heart-protective diet could potentially decrease the total burden of CVD and its related healthcare costs in treating CVDs.

Strengths, Limitations and Future Directions

This thesis has several strengths, including:

(1) the research employs a range of study designs, encompassing a narrative review, a cross-sectional study, a large prospective cohort study, a randomized controlled trial and a meta-analysis of RCTs, all focused on the same research question. The consistent findings across these diverse approaches underscore the robustness of our results;

(2) the development of a novel tool, the Heart-Protective Diet Score (HPDS), offers a new approach to assess diet quality with a focus on cardiovascular health. This novel scoring system can be readily applied by forthcoming studies across various research contexts and settings;

(3) the publication of all R script analysis codes as supplementary materials, to ensure research rigour, reproducibility, and transparency of our findings. In addition the dataset for CHAPTER 3 [2] is available online, while the datasets for CHATPER 4-7 are available upon request for the purpose of replicating the results.

However, it is important to acknowledge several limitations in the investigations presented in this thesis:

(1) the research participants are predominantly of Caucasian ethnicity, which may limit the generalizability of our findings to other ethnic groups;

(2) drawing definitive conclusions from the LIVEPLUS trial is challenging due to the current small sample size (n=9), and preliminary findings at one month might not fully capture the true protective effects of such an intensive lifestyle intervention on secondary prevention of CVD. In fact, several participants lost more than 10% of their initial body weight and improved lipid profiles at month 6 of the intervention (results not shown);

(3) in the UKBB study, we did not isolate the effects of individual nutrients or food groups. Thus, it is difficult for us to discern if specific nutrients or food groups provide more protective effects. However, prior research has already delved into the impact of specific nutrients and food groups on CVD health [32, 151]. Moreover, evaluating the whole dietary pattern might be more predictive of CVD disease risks, as individuals habitually consume a varied diet rather than single nutrients or foods.

Based on our findings, future researchers should focus on:

(1) validating the HPDS in diverse cohorts from various cultural backgrounds, and potentially adjusting HPDS based on their habitual diets (e.g. Asian cuisine);

(2) applying the HPDS in large cohorts of individuals with cardiovascular diseases to investigate the effect of long-term exposure to a high-quality pesco-vegetarian diet in the secondary prevention of CVD;

(3) designing high-quality clinical trials delivering plant-based diets intervention among individuals with CVDs in non-Western countries, with comprehensive dietary data documented and long follow-up period;

(4) exploring and developing sustainable ways of producing fish and seafood, and working closely with policy makers to avoid overfishing and ecosystem damage.

In summary, the findings of this thesis demonstrate the protective effects of adopting a high-quality plant-based diet with fish and seafood on cardiovascular health. It also highlights the need for further research of this dietary approach in the context of secondary prevention of CVD. High-quality nutrition clinical trials, characterized by comprehensive dietary data and extended follow-up periods, are warranted to confirm the effectiveness of such diets in individuals with established CVDs.

Appendix

9.1 Supplementary Materials for Chapter 3

Supplemental Online Content

Wang T, Kroeger CM, Cassidy S, et al. Vegetarian dietary patterns and cardiometabolic risk in people with or at high risk of cardiovascular disease: a systematic review and meta-analysis. *JAMA Netw Open.* 2023;6(7):e2325658. doi:10.1001/jamanetworkopen.2023.25658

eMethods.

eTable 1. Description of PICOS Criteria

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eTable 4. Study Characteristics of Ongoing Clinical Trials That Meet Our Eligibility Criteria

eTable 5. Participant Characteristics and Description of Included Studies

eTable 6. Dietary Data of Included Studies

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eFigure 4. The Forest Plot for Changes in LDL-C, Grouped by Energy Restriction

eFigure 5. The Forest Plot for Changes in LDL-C, Grouped by Physical Activity

eFigure 6. The Forest Plot for Changes in LDL-C, Grouped by Medication Use

eFigure 7. The Forest Plot for Changes in LDL-C, Grouped by Analysis Method

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eFigure 8. The Forest Plot for Changes in LDL-C, Grouped by Disease Status Excluding Imputed Data

eFigure 9. The Forest Plot for Changes in LDL-C, Grouped by Vegetarian Diets Excluding Imputed Data

eFigure 10. The Forest Plot for Changes in LDL-C, Grouped by Control Diets Excluding Imputed Data

eFigure 11. The Forest Plot for Changes in LDL-C, Grouped by Energy Restriction Excluding Imputed Data

eFigure 12. The Forest Plot for Changes in LDL-C, Grouped by Physical Activity Excluding Imputed Data

eFigure 13. The Forest Plot for Changes in LDL-C, Grouped by Medication Use Excluding Imputed Data

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eFigure 23. The Forest Plot for Changes in HbA1c, Grouped by Disease Status Excluding Imputed Data

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eFigure 26. The Forest Plot for Changes in HbA1c, Grouped by Energy Restriction Excluding Imputed Data

eFigure 27. The Forest Plot for Changes in HbA1c, Grouped by Physical Activity Excluding Imputed Data

eFigure 28. The Forest Plot for Changes in HbA1c, Grouped by Medication Use Excluding Imputed Data

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eFigure 29. The Forest Plot for Changes in HbA1c, Grouped by Analysis Method Excluding Imputed Data

eFigure 30. Treatment Effect of HbA1c Across Baseline HbA1c

eFigure 31. Funnel Plot of HbA1c

eFigure 32. The Forest Plot for Changes in SBP, Grouped by Vegetarian Diets

eFigure 33. The Forest Plot for Changes in SBP, Grouped by Control Diets

eFigure 34. The Forest Plot for Changes in SBP, Grouped by Energy Restriction

eFigure 35. The Forest Plot for Changes in SBP, Grouped by Physical Activity

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eFigure 37. The Forest Plot for Changes in SBP, Grouped by Analysis Method

eFigure 38. The Forest Plot for Changes in SBP, Grouped by Disease Status Excluding Imputed Data

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eFigure 50. The Forest Plot for Changes in Body Weight, Grouped by Disease Status Excluding Imputed Data

eFigure 51. The Forest Plot for Changes in Weight, Grouped by Energy Restriction Excluding Imputed Data

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eFigure 53. Treatment Effect of Body Weight Across Baseline Body Weight

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eFigure 55. The Forest Plot for Changes in Energy Intake in Studies Without Energy Restriction, Grouped by Control Diets

eFigure 56. The Forest Plot for Changes in Energy Intake in Studies Without Energy Restriction, Grouped by Control Diets Excluding Imputed Data

eFigure 57. Funnel Plot of Energy Intake in Studies Without Energy Restriction

eFigure 58. Risk of Bias Assessment of Included Randomized Controlled Trials

This supplemental material has been provided by the authors to give readers additional information about their work.

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Methods

Search strategy and selection criteria

This systematic review and meta-analysis has been registered with PROSPERO (CRD 42021218348). We followed the PRISMA guidelines[1] and the AMSTAR-2 checklist[2] for this study.

The PICOS criteria is described in eTable 1, and studies needed to be published in English or Chinese to be included. We searched EMBASE, MEDLINE, CINAHL and CENTRAL (Cochrane Central Register of Controlled Trials), from inception until 31st July 2021 (eTable 2 shows full search strategies). Hand searches of reference lists of reviews, protocols, abstracts, and grey literature (e.g., websites mentioning relevant studies) were performed to supplement searches. The authors of the ongoing trials and abstracts were contacted at least three times to retrieve preliminary findings and full manuscripts.

Retrieved articles were uploaded to the Covidence review platform, and duplicates were removed. The screening process was standardized, and training was provided to all reviewers by the principal investigator (TW). All titles, abstracts, full-texts, and data extraction were independently screened or extracted by the principal investigator (TW) and one other investigator (SC, CK, SM, RR). Discrepancies were resolved by a third investigator.

We followed the Cochrane Handbook[3] and extracted these data: study identifiers, participants' characteristics, inclusion and exclusion criteria, dietary intervention, exercise and medication instructions, primary and secondary outcomes, funding sources and conflict of interest statement, and pre-, post-intervention values and changes in weight, body mass index (BMI), SBP, LDL-C, HbA1c, dietary intake and medication use. If this information could not be found from the published sources, the corresponding author was contacted with at least three attempts, with a waiting period of one month to extract data and clarify information as needed.

Data analysis

The primary outcomes are the mean differences between groups in changes (pre vs post intervention) in LDL-C, HbA1c and SBP. Following the recommendations of the Cochrane Handbook [3], we selected a maximum of three primary outcomes; these biomarkers are primary pharmacological targets for the prevention and treatment of CVD[4,5]. The secondary outcomes are changes in body weight, and energy intake.

To examine the effect of interventions on primary outcomes, we obtained the mean and standard deviation (SD) of changes (post minus pre) in intervention and comparison groups. For studies reporting the median (interquartile range), we converted results into the mean (SD) following the method proposed by Wan *et al.*[6] when values could not be obtained from authors. The Cochrane guidelines[3] were used for SDs of change imputation using data available from similar studies (e.g. studies focused on the same population, i.e. people with CVD or T2DM or at high risk of CVD) when they could not be obtained from authors. The Cochrane guideline[3] were also followed for data extraction from cross-over design studies and only data from the first period was extracted if the carry-over effect was considered significant.

The units of LDL-C, HbA1c, and energy were standardized to mg/dL[7] (from mmol/L to mg/dL, multiplied by 38.67), % (requested from authors), and kcal (from kJ to kcal, divided by 4.18), respectively. We considered results to be clinically significant if LDL-C, HbA1c, and SBP changed by 10mg/dL, 0·5%, and 5mmHg, respectively[8]. The "meta" package of R (version 1.4.1717)[9] was used to perform meta-analysis and meta-regression. The R script and dataset are available in the appendix. A random-effects model was employed, implemented using the 'metacont' function for mean differences. We estimated the overall pooled effect size based on inverse-variance weighting using a restricted maximum likelihood estimator (REML) for the among-study heterogeneity [10]. Confidence intervals (CIs) are at the 95% level and estimated based on a standard-normal distribution (i.e., default method in the meta package). The total heterogeneity was quantified as τ^2 (i.e., variance among effect sizes not attributable to sampling). The statistical significance for heterogeneity was assessed by a modified Q test, which used the Farebrother method to obtain the distribution of Q values, as recommended for mean differences by Kulinskaya *et al.*[11]. Studies were grouped according to patients' conditions (CVD, T2DM or people with ≥2 CVD risk factors) and type of vegetarian diets in the meta-analysis. Exploratory sub-group analyses assessed the effect of: a) different control diets; b) energy restriction; c) physical activity; d) intervention with and without medication changes; e) analyses performed following intention-to-treat versus completers approaches. We performed additional exploratory meta-analysis to examine the impact of interventions on weight with and without energy restriction. In studies that did not prescribe an energy-restricted vegetarian diet, we evaluated their effects on energy intake compared to different control diets. We carried out mixed-effects meta-regression ('metareg' function) with bubble plots to explore if baseline LDL-C, HbA1c, SBP, and body weight could explain heterogeneity between studies.

Publication bias was evaluated by visual inspection of the asymmetry of funnel plots. Results were considered statistically significant if the resulting p-values were <0·05. We used the Cochrane Risk of Bias Assessment Tool 2.0[12] and

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the GRADE[13] (Grading of Recommendations, Assessment, Development, and Evaluation) tool to assess the risk of bias and evaluate the overall quality of evidence for primary outcomes and body weight, respectively. Two independent reviewers appraised each study (TW and either SC, CK, SM, RR or AM), and a third investigator was involved in resolving discrepancies. We constructed summary tables using GRADEpro[14] and assessed these domains following the GRADE guidelines[13,15]: risk of bias, inconsistency between studies, indirectness and imprecision of the outcomes, and potential publication bias. We built four tables for the GRADE assessment: overall quality, people with high risk of CVDs, people with T2DM, and people with CVDs. We did not perform the GRADE assessment if there were less than three studies for that outcome.

Ethical review of study and informed consent of study participants

Given the nature of secondary data extraction and analysis, ethical review and informed consent of participants are not required in this study.

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eTable 1. Description of PICOS criteria

PICOS criteria	Description

Population	Adults living in the community setting aged ≥18 years with: a). CVDs; or b). T2DM; or c) at least two risk factors* of CVDs
	Risk factors are defined as [16-19]:
	• Overweight: BMI ⩾ 25
	• High blood pressure (systolic ⩾130mmHg; diastolic ⩾ 80mmHg) [20]
	• Blood lipid [21]: TC ⩾ 200mg/dL; or LDL ⩾ 100mg/dL; or TG ⩾ 150mg/dL
	• HbA1c ⩾ 5·7% [22]
	• Metabolic syndrome (if ⩾ 3 met) [23]:
	  • Waist circumference: > 40 inches (men) or > 35 inches (women)
	  • Blood pressure over 130/85 mmHg
	  • TG ⩾ 150 mg/dL
	  • Fasting HDL < 40 mg/dL (men) or 50 mg/dL (women)
	  • Fasting blood sugar ⩾ 100 mg/dL

Intervention	The vegetarian diet, in which animal products are not allowed except for fish and seafood (the pesco-vegetarian diet), eggs (the ovo-vegetarian diet or the lacto-ovo vegetarian diet), and dairy products (the lacto-vegetarian diet or the lacto-ovo vegetarian diet)
Comparator	The non-vegetarian diet
Outcome	Changes in SBP, LDL or HbA1c and dietary intake, from pre- to post-intervention
Study design	Randomised controlled trials ≥ 8 weeks, given its power to assess the effect of a vegetarian diet

BMI, body mass index; CVD, cardiovascular disease; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglyceride

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eTable 2. Complete search strategies for different databases

Databases	MEDLINE	EMBASE	CINAHL	Cochrane Central Register of Controlled Trials (CENTRAL)
#	Searches (Results)	Searches (Results)	Searches (Results)	Searches (Results)
1	coronary disease/ or coronary artery disease/ (191771)	exp vegetarian diet/ (4472)	(MH "CoronaryDisease+") OR (MH"CardiovascularDiseases+") OR (MH"Vascular Diseases+")OR (MH "MyocardialInfarction+") (629531)	exp Coronary Disease/ (13685)
2	coronary heart disease*.mp. (51418)	plant based diet*.mp. (1124)	(MH "Heart Diseases+") (295938)	exp Coronary Artery Disease/ (6496)
3	cardiovascular diseases/ or cardiovascular abnormalities/ or heart diseases/ or vascular diseases/ (260016)	exp vegan diet/ or exp vegetarian/ or exp vegan/ (3251)	"coronary heart disease*" (33834)	coronary heart disease*.mp. (7755)
4	heart disease*.mp. (244319)	vegan*.mp. (2091)	(MH "CardiovascularAbnormalities+") (34518)	exp cardiovascular diseases/ or exp cardiovascular abnormalities/ or exp heart diseases/ or exp vascular diseases/ (107566)
5	exp Stroke/ (138850)	vegetarian*.mp. (7788)		heart disease*.mp. (23472)
6	cerebrovascular accident.mp. (4668)	semi-vegetarian*.mp. (106)	(MH "VascularDiseases+") (427307)	exp Stroke/ (9836)
7	exp Myocardial Infarction/ (177456)	pesco-vegetarian*.mp. (58)	(MH "Stroke+") (74183)	cerebrovascular accident.mp. (14685)
8	heart attack*.mp. (5714)	lacto-vegetarian*.mp. (167)	"cerebrovascularaccident" (61456)	exp Myocardial Infarction/ (10847)
9	exp Death, Sudden, Cardiac/ (15787)	vegan diet*.mp. (984)	"heart disease*" (93957)	heart attack*.mp. (1233)
10	exp Triglycerides/ (77510)	vegetarian diet*.mp. (4791)	"heart attack*" (46219)	exp Death, Sudden, Cardiac/ (635)
11	exp Cholesterol/ (161388)	ovo-vegetarian*.mp. (316)	(MH "Death, Sudden,Cardiac") (6885)	exp Triglycerides/ (6344)
12	exp Blood Pressure/ (292805)	lacto-ovo vegetarian*.mp. (308)	(MH "Triglycerides") (15038) (MH "Cholesterol+") OR(MH "Lipoproteins, LDL Cholesterol") OR (MH"Lipoproteins, HDLCholesterol") (29137)	exp Cholesterol, LDL/ or exp Cholesterol, VLDL/ or exp Cholesterol/ or exp Cholesterol, HDL/ (10207)
13	exp Blood Glucose/ (166220)	PBD.tw. (2656)		exp Blood Pressure/ (27585)
14	fasting glucose.mp. (17602)	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (11879)		exp Blood Glucose/ or fasting glucose.mp. (19820)
15	exp Glycated Hemoglobin A/ (35762)	coronary disease.mp. or exp coronary artery disease/ (347474)	(MH "Blood Pressure+") (53929) (MH "Blood Glucose") (39949)	HbA1c.mp. (18010)
16	HbA1c.mp. (35606)	coronary heart disease*.mp. (73390)		exp Hyperlipidemias/ (6430)

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17	stroke.mp. (303219)	exp cardiovascular disease/ (4365472)	"fasting glucose" OR (MH"Blood Glucose") (43025)	hyperlipid?emia.mp. (5089)
18	CVD.tw. (37308)	cardiovascular disease*.mp. (416927)	(MH "Hemoglobin A,Glycosylated") OR"HbA1c" (24897)	high blood pressure.mp. or exp Hypertension/ (19890)
19	heart failure*.mp. (213594)	exp heart disease/ (1963261)	(MH "Hyperlipidemia+") (21760)	exp non insulin dependent diabetes mellitus/ (17877)
20	myocardial infarction.mp. (249631)	heart disease*.mp. (429147)		T2DM.tw. (6609)
21	(cardiovascular disease* or cardiovascular abnormalit* or heart disease* or vascular disease*).mp. (566674)	exp vascular disease/ (2637814)	(MH "Hypertension+") (85038)	NIDDM.tw. (1085)
22	Atrial Fibrillation/ (57164)	vascular disease*.mp. (126351)	(MH "Diabetes Mellitus,Type 2") (65156) "T2DM" (6845)	Non insulin dependent diabetes mellitus.tw. (1421)
23	atrial fibrillation*.mp. (85972)	exp cerebrovascular accident/ (222808)	"NIDDM" (51369)	(Type 2 diabet$ or Type ii diabet$).tw. (37838)
24	Diabetes Mellitus, Type 2/ (136259)	cerebrovascular accident*.mp. (221804)		exp Diabetes Mellitus, Type 2/ (17877)
25	type 2 diabete*.mp. (132954)	exp heart infarction/ (398603)	"non insulin dependent diabetes mellitus" (51319)	stroke.mp. (58522)
26	Cholesterol, HDL/ (28623)	heart attack*.mp. (8473)	"(type 2 or type II) diabet*" (0)	CVD.tw. (5744)
27	Cholesterol TC.mp. (9438)	exp sudden cardiac death/ (16758)	"CVD" (56108)	heart failure*.mp. (31334)
28	cholesterol TG.mp. (465)	exp triacylglycerol/ (208112)		myocardial infarction.mp. (31898)
29	Cholesterol, LDL/ (27953)	exp cholesterol/ (328489)	(MH "Heart Failure+") OR "heart failure*" (70016) (MH "Atrial Fibrillation")OR "Atrial Fibrillation" (37543) "high blood pressure" (122803) (MH "Obesity+") OR"overweight" (117298)	(cardiovascular disease* or cardiovascular abnormalit* or heart disease* or vascular disease*).mp. (56473)
30	cholesterol*.mp. (294142)	exp blood pressure/ (607283)	S1 OR S2 OR S3 OR S4OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 ORS11 OR S12 OR S13 ORS14 OR S15 OR S16 ORS17 OR S18 OR S19 ORS20 OR S21 OR S22 ORS23 OR S24 OR S25 ORS26 OR S27 OR S28 (168)	Atrial Fibrillation/ (4721)
31	Hypertension/ (237017)	exp glucose blood level/ (268775)		atrial fibrillation*.mp. (13745)
32	high blood pressure*.mp. (15590)	fasting glucose.mp. (30688)		Cholesterol TC.mp. (2055)
33	hypertension*.mp. (499685)	exp hemoglobin A1c/ (111523)		cholesterol TG.mp. (136)
34	exp Overweight/ or exp Obesity/ (227431)	exp hyperlipidemia/ (164725)		cholesterol*.mp. (38668)
35	overweight*.mp. (77136)	hyperlipid?emia.mp. (88786)	"PBD" (214) "veganism" (94)	high blood pressure*.mp. (2418)
36	obesity*.mp. (335888)	high blood pressure.mp. or exp hypertension/ (778660)	"lacto-ovo vegetarian*" (3503) "ovo-vegetarian*" (97)	hypertension*.mp. (64404)
37	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or	exp non insulin dependent diabetes mellitus/ (265260)	"vegetarian diet*" (3826) "vegan diet*" (413)	exp Overweight/ (15844)

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	28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 (2560350)		"lacto-vegetarian*" (3487)	
38	exp Vegans/ (92)	T2DM.tw. (39431)	"pesco-vegetarian*" (30)	exp Obesity/ (14018)
39	exp Vegetarians/ (241)	NIDDM.tw. (8060)		overweight*.mp. (17852)
40	exp Diet, Vegetarian/ (3360)	Non insulin dependent diabetes mellitus.tw. (7808)		obesity*.mp. (39590)
41	exp Diet, Vegan/ (190)	(Type 2 diabet$ or Type ii diabet$).tw. (226030)		1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
			"semi-vegetarian*" (50)	or 14 or 15 or 16 or 17 or 18 or
			"vegetarian*" (8282)	19 or 20 or 21 or 22 or 23 or
			"vegan*" (2060)	24 or 25 or 26 or 27 or 28 or
				29 or 30 or 31 or 32 or 33 or
			"plant-based diet*" (995)	34 or 35 or 36 or 37 or 38 or 39 or 40 (344595)
42	semi-vegetarian*.mp. (72)	stroke.mp. (464494)		exp diet, vegetarian/ (198)
43	pesco-vegetarian*.mp. (38)	CVD.tw. (59012)		plant based diet*.mp. (136)
44	lacto-vegetarian*.mp. (122)	sudden cardiac*.mp. (36202)		plant-based diet*.mp. (136)
			"plant based diet*" (995)	
45	veganism.tw. (75)	heart failure*.mp. (421492)	(MH "Plant-Based Diet")OR (MH	vegan*.mp. (237)
46	vegetarianism.tw. (430)	myocardial infarction.mp. (302811)	"Vegetarianism") (7533)	vegetarian*.mp. (632)
47	plant based diet*.mp. (923)	(cardiovascular disease* or cardiovascular abnormalit* or heart disease* or vascular disease*).mp. (897555)	S30 OR S31 OR S32 ORS33 OR S34 OR S35 ORS36 OR S37 OR S38 ORS39 OR S40 OR S41 ORS42 OR S43 (8908)	semi-vegetarian*.mp. (10)
48	vegan*.mp. (1371)	Atrial Fibrillation/ (65837)	S29 AND S44 (1062)	pesco-vegetarian*.mp. (10)
49	vegetarian*.mp. (5362)	atrial fibrillation*.mp. (151907)		lacto-vegetarian*.mp. (20)
50	vegan diet*.mp. (538)	Diabetes Mellitus, Type 2/ (63061)		vegan diet*.mp. (138)
51	vegetarian diet*.mp. (1661)	type 2 diabete*.mp. (205635)		vegetarian diet*.mp. (314)
52	PBD.tw. (1846)	Cholesterol, HDL/ (94811)		lacto-ovo vegetarian*.mp. (46)
53	ovo-vegetarian*.mp. (235)	Cholesterol TC.mp. (14442)		ovo-vegetarian*.mp. (46)
54	lacto-ovo vegetarian*.mp. (232)	cholesterol TG.mp. (753)		veganism.tw. (1)
55	38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 (8201)	Cholesterol, LDL/ (92627)		vegetarianism.tw. (24)
56	37 and 55 (2096)	cholesterol*.mp. (455321)		PBD.tw. (138)
57		hypertension*.mp. (938542)		42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 (978)
58		exp obesity/ (542882)		41 and 57 (488)
59		overweight*.mp. (111538)		
60		obesity*.mp. (570942)		

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61	15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 (5750388)
62	14 and 61 (4119)

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eTable 3. Inclusion and exclusion criteria of included studies

Author, year	Inclusion criteria	Exclusion criteria
Aldana *et al.*, 2006 [24]	Participants were included if they had ≥ 2 of the following criteria: chest pain lasting ≥ 30 mins continuously; electrocardiogram changes typical of an evolving MI (ST segment elevation or depression, evolving Q waves, or symmetric inversion of T waves); elevated levels of cardiac enzymes. Patients were also accepted if they demonstrated any of the following: MI within the past 12 months; coronary artery bypass graft surgery; stent placement; rotoblator within the prior 12 months; stable angina; or pacemakers associated with ≥ 1 of the above diagnoses.	Exclusion criteria included history of substance abuse disorder without documentation of at least 1 year of abstinence; history of psychiatric disorder without documentation of at least 1 year of stability; impaired cognitive function such as dementia or delirium; participation in other lipid-lowering or lifestyle modification trials; and others which were previously documented.
Barnard *et al.*, 2006 [25-28]	Individuals with T2DM, defined by a fasting plasma glucose concentration > 6·9 mmol/l on two occasions or a prior diagnosis of T2DM with the use of hypoglycemic medications for ≥ 6 months.	HbA1c < 6·5 or > 10·5%; use of insulin for > 5 years; current smoking, alcohol or drug abuse; pregnancy; unstable medical status; current use of a LF vegetarian diet.
Barnard *et al.*, 2018 [29]	(1) A diagnosis of T2DM, defined by a fasting plasma glucose concentration ≥ 126 mg/dL on two occasions or a prior physician's diagnosis of T2DM with the use of hypoglycemic medications for ≥ 6 months; (2) HbA1c: 6·5-10·5%; (3) ≥ 18 years; (4) ability and willingness to be assigned to either a LF, vegan, or portion-controlled eating plan and participate in all components of the study; and (5) diabetes medications unchanged for 1 month before volunteering for the study.	(1) BMI > 45 kg/m^2; (2) alcohol consumption of > 2 drinks/d or the equivalent, episodic increased drinking (e.g., > 2 drinks/d on weekends), or a history of alcohol abuse or dependency followed by any current use; (3) use of recreational drugs in the past 6 months; (4) pregnancy; (5) signs or symptoms of acute uncontrolled diabetes, including but not limited to polyuria, polydipsia, blurred vision, or uncontrolled weight loss; (6) unstable medical status; (7) already following a LF, vegetarian eating pattern; and (8) lack of English fluency.
Barnard *et al.*, 2021 [30]	Adults with a BMI between 28 and 40 kg/m^2.	Type 1 diabetes; smoking, alcohol or drug abuse; pregnancy or lactation, and current use of a vegan or Mediterranean diet.
Bunner *et al.*, 2015 [31]	Age 18–65 years, diagnosis of T2DM, and diagnosis or symptoms of painful diabetic neuropathy for ≥ 6 months.	Vitamin B12 deficiency, alcohol consumption of > 2 drinks/d, use of recreational drugs in the past 6 months, pregnancy, unstable medical or psychiatric illness, current adherence to a vegan diet and inability or unwillingness to participate in all components of the study.
Burke *et al.*, 2006 [32-34]	Individuals were eligible if they were 18-55 years of age, had a BMI 27-43 kg/m^2, were willing to be randomized to one of the two treatment preference groups and one of the two dietary groups, and successfully completed a 5-day food diary.	Individuals who had a serious illness or unstable condition for which physician supervision of diet and exercise prescription was needed; had a cardiovascular or orthopedic condition that would require physician clearance before participation; had limitations precluding ability to exercise; were pregnant or intended to become pregnant in the next 18 months; were being treated for a psychological disorder; reported alcohol intake of ≥ 4 drinks/d; were participating or had recently participated in a weight loss treatment program or used weight loss medication; reported no regular intake of meat, fish, and fowl; had a serious binge eating problem; and did not at least moderately prefer one of the dietary treatments (SBT or SBT+LOV) over the other.

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Author, year	Inclusion criteria	Exclusion criteria
Garousi *et al.*, 2021 [35]	Have been diagnosed with NAFLD, to be motivated to participate in the study, aged 20-55 years, overweight (BMI > 25 kg/m^2), and non-consumers of alcohol (< 40 g/week). NAFLD was diagnosed by an ultrasonography scan and associated with a persistently elevated ALT concentration > 19 U/L for women and > 30 U/L for men.	Participants were excluded if they were following a special diet, pregnant, breastfeeding, or suffering from viral hepatitis, diabetes mellitus, untreated hypothyroidism or other causes of chronic liver disease.
Kahleova *et al.*, 2010 [36]	T2DM, age 30–70 years, HbA1c 6-11% (42–97 mmol/mol), BMI 25-53 kg /m^2, and willingness to change dietary habits and follow a prescribed exercise programme.	HbA1c < 6% (< 42 mmol/mol) or > 11% (> 97 mmol/mol), use of insulin, abuse of alcohol or drugs, pregnancy, lactation, or current use of a vegetarian diet.
Kahleova *et al.*, 2020 [37]	Adults aged 25-75 years with a BMI of 28-40 kg/m^2.	Diabetes, smoking, alcohol or drug use, pregnancy or lactation, and current use of a vegan diet. The additional exclusion criteria for the subset of participants undergoing the proton magnetic resonance spectroscopy were the presence of anymetal implant, claustrophobia, BMI > 38 kg/m^2, and waist circumference > 102 cm.
Lee *et al.*, 2016 [38]	Age 30–70 years; use of hypoglycemic medications for ≥ 6 months; and HbA1c level of 6·0–11·0%.	Increased dose of hypoglycemic medication or the addition of a new drug in the regimen during the last 2 months; current vegetarian status; pregnancy; or severe complications such as chronic renal failure.
Liao *et al.*, 2007 [39]	20–60 y of age, have a BMI > 26 kg/m^2, and have no history of chronic disease, including CVD, kidney disease, and diabetes mellitus.	Female subjects could not be pregnant or breastfeeding.
Mahon *et al.*, 2007 [40]	NR. Assume postmenopausal women who do not meet exclusion criteria.	Male, age < 50 y or > 80 y, < 2 y postmenopausal, BMI < 25 and > 34 kg/m^2 at the time of screening, a smoker and clinically abnormal kidney, liver, or heart function. Subjects could not be individuals with diabetes or unstable thyroid disease, in abnormal protein or hematological status, nor receiving insulin replacement therapy or anti-inflammatory steroid medications.
Mishra *et al.*, 2013 [41,42]	>18 years of age with a BMI ≥ 25 kg/m^2 and/or a previous diagnosis of T2DM.	Current alcohol or drug abuse, pregnancy, history of severe mental illness, unstable medical status, current adherence to a LF, vegetarian diet, participation in the previous GEICO two-site study and inability to attend weekly meetings
Nicholson *et al.*, 1999 [43]	T2DM, age > 25 years, willingness to attend all components of the study, and residence within commuting distance of Georgetown University.	Smoking, regular alcohol use, current or past drug abuse, pregnancy, psychiatric illness, and medical instability.
Ornish *et al.*, 1990 [44,45]	Patients with angiographically documented CHD. Age 35-75 years; residence in the greater San Francisco area; no other life-threatening illnesses; no MI during the preceding 6 weeks, and no history of receiving streptokinase or alteplase; not currently receiving lipid-lowering drugs; one, two, or three vessel CHD (defined as any measurable coronary atherosclerosis in a non-dilated or non-bypassed coronary artery); left ventricular ejection fraction > 25%; not scheduled to have coronary artery bypass grafting; and permission granted by patient's cardiologist and primary care physician.	NR. Assume people who do not meet the inclusion criteria.

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Author, year	Inclusion criteria	Exclusion criteria
Shah *et al.*, 2018 [46,47]	Age ≥ 18 years; any patient with angiographically defined CHD (≥50% lesion in an artery with ≥ 2 mm caliber); speak English or Spanish. Participants have to be ≥ 3 months post-myocardial infarction, coronary artery bypass graft surgery, or infection to minimize confounders of the primary endpoint, hs-CRP concentration.	1. History of an eating disorder; 2. On a vegetarian or vegan diet; 3. Use of steroids or non-steroidal anti-inflammatory medications other than aspirin within 5 half-lives of baseline visit and during the study period; 4. History of a MI or coronary artery bypass graft surgery within the preceding 3 months; 5· Presence of infection within the preceding 3 months; 6. Have a planned staged coronary revascularization or other surgical procedure during study period; 7. History of colon cleansing (for stool microbiome analysis); 8. Use of probiotics or over the counter supplements other than standard vitamins (for stool microbiome analysis); 9. Pregnant; 10. Participating in a competing study; 11. Have any condition (e.g., psychiatric illness) or situation that, in the investigator's opinion, may confound the study results, or may interfere significantly with the patient's ability to adhere with study procedures; 12. Score of > 4 to any of the amotivational items or if the relative autonomy index (defined as average of answers for the 6 autonomous items – average of answers for the 6 controlled items) is ≤ 0 on the Treatment Self-Regulation Questionnaire
Sofi *et al.*, 2018 [48,49]	Being overweight (BMI ≥25 kg/m^2) and the simultaneous presence of ≥ 1 of the following criteria defined by the guidelines for CVD prevention of the European Society of Cardiology: TC levels >190 mg/dL, LDL cholesterol levels >115 mg/dL, TG levels >150 mg/dL, and glucose levels >110 but <126 mg/dL.	People taking medications for any reason, had a serious illness or an unstable condition, were pregnant or nursing, were participating or had participated in a weight loss treatment program in the last 6 months, or were following or had followed a food profile that, to a certain extent, excluded meat, poultry, or fish in the last 6 months.
Tang *et al.*, 2013 [50]	(1) Male ≥ 21 years; (2) BMI 25·0-39·9 kg/m^2; (3) weight stable: <4·5 kg weight change within last 6 months; (4) nonsmoking; (5) constant habitual activity patterns within last 3 months; (6) clinically normal blood profiles (specifically, normal liver and kidney functions; fasting blood glucose <110 mg/dL).	(1) Age: < 21 years; (2) BMI: outside of the 25·0-39·9 kg/m^2 range; (3) Gained or lost > 4·5 kg (10 lbs) within the last 6 months; (4) Body fat <25% as assessed by plethysmography; (5) Smoker (currently or within the last 6 months); (6) Intermittently been involved in a diet and/or exercise program within the last 3 months; (7) Clinically abnormal blood profiles; (8) Taking medications (currently or within the last 3 months) known to influence appetite or metabolism; (9) Clinically diagnosed as diabetic; (10) Allergies to eggs; (11) Lactose intolerance; (12) Clinically diagnosed with diverticulosis; (13) Clinically diagnosed with diverticulitis.
Toobert *et al.*, 2000 [51]	Being a postmenopausal female and having documented CHD defined as atherosclerosis, MI, percutaneous transluminal coronary angioplasty, and/or coronary bypass graft surgery.	Having other life-threatening illnesses, infarction during the preceding 6 weeks; receiving streptokinase or alteplase; or being scheduled for bypass surgery.
Wright *et al.*, 2017 [52]	Age 35-70 and overweight (BMI ≥25 kg/m^2), with a diagnosis of: T2DM, CHD, or the CVD risk factors of hypertension or hypercholesterolaemia.	Diagnoses of life-threatening comorbidities; thyroid disease; coronary artery bypass grafting within 6 weeks; MI within 1 month; angioplasty within 6 months; 450% stenosis of the left main coronary artery; unresponsive congestive heart failure; malignant uncontrolled arrhythmias; homozygous hypercholesterolaemia; severe mental health disorders; current alcohol or drug misuse; currently smoking; currently pregnant or breastfeeding women, prior bariatric surgery, other conditions that directly affect weight (e.g. lead toxicity, malignancy).

ALT, aminotransferase; BMI, body mass index; CVD, cardiovascualr disease; CHD, coronary heart disease; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; LF, low-fat; MI, myocardial infarction; NAFLD, non-alcoholic fatty liver disease; NR, not reported; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglyceride

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eTable 4. Study characteristics of ongoing clinical trials that meet our eligibility criteria

Author, year	Country	Trial registration number	Recruitment status	Study arms (target sample size)	Population condition	Diet description		Study design; Intervention duration and follow-up
						Intervention	Comparison	
Fontana *et al.*, 2020 [53]	Australia	ACTRN12620001151921	Not yet recruiting	(1) Intensive lifestyle program (75) (2) AHA diet (75)	CHD	The 5:2 pesco-vegetarian diet: no animal foods other than fish, egg and dairy products; 2 non-consecutive fasting days per week	The AHA diet: general dietary guidelines from the AHA with no energy restriction	1 year, randomized, controlled trial, parallel arm
Kahleova *et al.*, 2019 [54]	USA	NCT04088981	Not yet recruiting	(1) The LF vegan diet (30) (2) The portion-controlled diet (30)	T2DM and BMI 26-40 kg/m^2	The LF, vegan diet: no animal products and added oils; no restriction on energy intake	The portion-controlled diet: participants with an individualized diet plans that reduce daily energy intake by 500 kcal for overweight participants	22 weeks, randomized, controlled trial, crossover design;
Michalsen *et al.*, 2019 [55]	Germany	NCT03901183	Active, not recruiting	(1) The plant-based diet (35) (2) Waiting list (35)	Hypertension and central obesity (WC > 94cm for men and > 80cm for women)	The plant-based diet: detailed diet description not reported	Waiting list: offer equal intervention after the end of study	8 weeks randomized, controlled trial, parallel arm; 8 weeks follow up
Sangeetha *et al.*, 2018	India	CTRI/2018/10/015896	No information	(1) Vegetarian diet (2) Mixed diet	T2DM	Diabetic on Vegetarian diet: T2DM consume the prescribed vegan, pesco-vegetarian and ovo-lacto-vegetarian diet	Diabetics on mixed diet: the prescribed non-vegetarian diet	No information
Turner-Mcgrievy *et al.*, 2017 [56]	USA	NCT03354377	Active, not recruiting	(1) The vegan diet (65) (2) The LF omnivorous diet (65)	BMI 25-49·9 kg/m^2	The vegan diet: a diet consists of whole grains, fruits, vegetables, and legumes; supplemented by the Oldways African Heritage and Health program	The LF omnivorous diet: supplemented by the Oldways African Heritage and Health program, which includes a food pyramid guide	2 years randomized, controlled trial, parallel arm
Wright *et al.*, 2017 [57]	New Zealand	ACTRN12617000541303	Results not published yet	(1) Whole foods plant-based diet (24) (2) Usual care (24)	Obese (BMI ≥ 30 kg/m^2) and T2DM/prediabetes	Whole foods plant-based approach: avoid animal products, including meat, dairy and eggs; no energy restriction; daily 50mcg Vit B12 supplement	Usual care	10 weeks randomized, controlled trial, parallel arm; 42 weeks follow up

AHA, American Heart Associations; BMI, body mass index; CHD, coronary heart disease; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; LF, low-fat; MED, Mediterranean diet; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglyceride; WC, waist circumference.

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eTable 5. Participant characteristics and study description of included studies

Author, year	Race/Ethnicity	Physical activity description	Medication		
			General description	Baseline	EOI
Aldana *et al.*, 2006 [24]	NR	(1) An exercise physiologist prescribed an individualized exercise program. **Stage 1** (intensive 12-week): participants attended two 4-hour sessions/week, including supervised exercise, stress management, a meal, lifestyle-related lecture, and group support. **Stage 2:** one 4-hour session/week with similar content. **Stage 3:** an alumni-based community of previous program participants. (2) The five main components of traditional cardiac rehabilitation: medical evaluation, prescribed exercise, cardiac risk factor modification, education, counselling.	NI	NI	There were no differences in medication use between groups across time.
Barnard *et al.*, 2006 [25-28]	(1) Black, non-Hispanic: 22 White, non-Hispanic: 21 White, Hispanic: 4 Asian, non-Hispanic: 2 (2) Black, non-Hispanic: 22 White, non-Hispanic: 22 White, Hispanic: 2 Asian, non-Hispanic: 4 p-value: 0·71	Participants were asked not to alter their exercise habits during the intervention period.	Continue preexisting medication, except when hypoglycemia*	Insulin: (1) 11 (2) 5 p=0·09 Metformin: (1) 34 (2) 39 p=0·33 Sulfonylurea: (1) 25 (2) 29 p=0·49 Thiazolidinedione: (1) 16 (2) 15 p=0·78 Other diabetes medications: (1) 1 (2) 2 p=0·57 Blood pressure medications: (1) 31 (2) 38 p=0·17 Lipid-lowering medications: (1) 27 (2) 27 p=0·88	↓ diabetes medication, mainly as necessitated by hypoglycemia: (1) 43% (2) 26% ↑ medications without investigators' authorization: (1) 8% (2) 8%
Barnard *et al.*, 2018 [29]	(1) White non-Hispanic: 13 Black non-Hispanic: 7 White, Hispanic: 1 Black, Hispanic: 0 Asian, non-Hispanic: 1 (2) White, non-Hispanic: 7 Black, non-Hispanic: 13 White, Hispanic: 1 Black, Hispanic: 1 Asian, non-Hispanic: 1	All participants were asked not to alter their exercise patterns.	All participants were asked not to change their use of medications or nutritional supplements, except as recommended by their personal physicians.	NR	On glycemic control medication: (1) 4 ↓, 2 mixed (changes in opposite directions) (2) 6 ↓, 3 ↑, 4 mixed On lipid-lowering medications: reported "several participants altered".

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Author, year	Race/Ethnicity	Physical activity description	Medication		
			General description	Baseline	EOI
Barnard *et al.*, 2021 [30]	(1) White: 16 Black: 14 Asian, Pacific Islander: 0 American Indian, Eskimo, Aleut: 0 Did not disclose:0 (2) White: 15 Black: 16 Asian, Pacific Islander: 0 American Indian, Eskimo, Aleut: 1 Did not disclose:0 p-value: 0·90	All study participants were asked not to alter their exercise habits, except as modified by ther personal physicians.	All study participants were asked to continue their preexisting medication regimens for the study duration, except as modified by their personal physicians.	Lipid-lowering therapy: (1) 11 (2) 12 p-value: 0·95 Antihypertensive therapy: (1) 14 (2) 16 p-value: 0·79 Thyroid medications: (1) 1 (2) 3 p-value: 0·61	Lipid-lowering therapy: (1) 7 ↓ or discontinued (2) 2 ↓ or discontinued, 1 ↑ Antihypertensive therapy: (1) 7 ↓ or discontinued, 1 ↑ (2) 6 ↓ or discontinued, 1 ↑
Bunner *et al.*, 2015 [31]	(1) Black: 5 Non-black: 12 (2) Black: 11 Non-black: 6 p-value: 0·09	NI	Participants were asked to keep their diabetes medications constant when possible, but to follow the advice of their personal physicians regarding medication use.	Medications for diabetic neuropathy symptoms: (1) 5 (2) 5 Metformin: (1) 12 (2) 12 p-value: 0·99 Insulin: (1) 6 (2) 9 p-value: 0·30 On other agents: (1) 10 (2) 7 p-value: 0·31	Medications for diabetic neuropathy symptoms: (1) 2 began, 2 eliminated (2) 1 began and then stopped taking pregblin Glucose-lowering medications: (1) 10 ↓, 2 ↑ (2) 1 ↓, 2 ↑ Lipid-lowering medications: (1) 4 ↓, 1 ↑ (2) 0 ↓, 3 ↑ Blood pressure medications: (1) 2 ↓, 4 ↑ (2) 0 ↓, 1 ↑

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Author, year	Race/Ethnicity	Physical activity description	Medication		
			General description	Baseline	EOI
Burke *et al.*, 2006 [32-34]	White: n (%) (1) 59 (70·2) (2) 69 (70·4) p-value: 0·98	Instruct to engage in exercise (walking ≥ 150 min/wk). Walking was recommended as the primary form of structured activity and participants were encouraged to increase daily activities. Four group sessions focused on exercise, e.g., aerobic training, weights. Study personnel monitored and provided feedback to subjects regarding their weekly recorded activity.	NI	Lipid-lowering drugs: (1) SBT-LOV: 8 (2) SBT: 2	3 subjects of the LOV group and 1 of the SBT group no longer on drugs; 1 in each group initiated drugs for hyperlipidemia.
Garousi *et al.*, 2021 [35]	NR	Patients were instructed to follow their routine physical activity regime.	Instruct not to consume supplements and/or medication that affect outcomes of interest.	NI	NI
Kahleova *et al.*, 2010 [36]	Caucasian-White	Participants were asked not to alter their exercise habits during the first 12 weeks. During weeks 13–24, they were prescribed an individualized exercise programme. Participants exercised at 60% of their maximal heart rate twice a week for 1 h under professional supervision, plus once a week at home or at the sports centre with the same intensity; they were given a sport-tester Polar FT4 (Polar, Kempele, Finnland) and a pedometer (Omron HJ-113, Omron, Kyoto, Japan) for individual physical activities and were repeatedly instructed on how to use them.	Ask to continue pre-existing medication regimens, except when hypoglycaemia* occurred repeatedly	Oral hypoglycaemic agents: - Metformin: (1) 29 (2) 28 - Sulphonylurea: (1) 20 (2) 13 - Thiazolidinedione: (1) 7 (2) 5 - Other: (1) 8 (2) 3 Lipid-lowering therapy: (1) 22 (2) 16 Antihypertensive therapy: (1) 25 (2) 22	Diabetes medication: (1) 43% ↓ (2) 5% ↓ p-value < 0·001, difference between groups: 38% (95% CI 17, 58).
Kahleova *et al.*, 2020 [37]	(1) White: 57; Black: 60; Asian, Pacific Islander: 1; American Indian, Eskimo, Aleut: 2; Did not disclose: 2 (2) White: 60; Black: 53; Asian, Pacific Islander: 7; American Indian, Eskimo, Aleut: 0; Did not disclose: 2 p-value: 0·06	All participants were asked to maintain their customary exercise habits and medications unless modified by their personal physicians.	All participants were asked to maintain their customary medications unless modified by their personal physicians.	Lipid-lowering therapy: (1) 22 (2) 21 Antihypertensive therapy: (1) 33 (2) 31 Thyroid medications: (1) 16 (2) 12 p-value: 0·42	Minimal medication changed (reported by corresponding author)

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Author, year	Race/Ethnicity	Physical activity description	Medication		
			General description	Baseline	EOI
Lee *et al.*, 2016 [38]	Korean	The participants were asked to maintain the usual level of physical activity, and to not modify their exercise habits during the intervention period.	Ask to maintain current medication, without any control of the dose or type of medication for 12 weeks; however, dose reduction was permitted when it was necessary according to a physician's judgment.	Oral hypoglycaemic agents: - Insulin: (1) 7 (2) 8 p-value = 0·813 - Metformin: (1) 34 (2) 36 p-value = 0·764 - Sulphonylurea: (1) 17 (2) 21 p-value = 0·449 - Other: (1) 14 (2) 19 p-value = 0·314 Lipid-lowering therapy: (1) 23 (2) 26 p-value = 0·608 Antihypertensive therapy: (1) 18 (2) 22 p-value = 0·455	None of the participants changed their medication dose over the 12 weeks.
Liao *et al.*, 2007 [39]	NR	NI	NI	NI	NI
Mahon *et al.*, 2007 [40]	All caucasian	Subjects were instructed to maintain their habitual activities and to not begin any type of structured exercise program during the study.	Instruct to stop all nutritional supplements (except calcium), nonprescription medication and alcohol from 3 weeks before till the end of study.	NI	NI
Mishra *et al.*, 2013 [41,42]	(1) White: 88; Black: 34; Asian: 10; Other: 10 (2) White: 98; Black: 41; Asian: 5; Other: 6 p-value: 0·3	All participants were asked not to alter their exercise patterns during the study period.	Ask to continue pre-existing medication regimens unless modified by their personal physicians.	NI	NI

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Author, year	Race/Ethnicity	Physical activity description	Medication		
			General description	Baseline	EOI
Nicholson *et al.*, 1999 [43]	NR	No exercise recommendation were made.	Subjects met with the medical director or nurse-project coordinator every 2 weeks. Medication needs were assessed at these visits and as needed between visits, according to an established protocol.	Oral hypoglycaemic agents: (1) 6 (2) 4 Insulin: (1) 2 (2) 0 Antihypertensive therapy: (1) 5 (2) 4 Lipid-lowering medications: (1) 3 (2) 1	Oral hypoglycaemic agents: (1) 1 stopped, 3↓ (2) 4 remain same dosage Insulin: (1) 2 ↓ (2) 0 Antihypertensive therapy: (1) 2 discontinued (2) 1 stopped No changes in lipid-lowering drugs.
Ornish *et al.*, 1990 [44,45]	NR	Individually prescribed exercise (typically walking) according to baseline treadmill test results. Ask to exercise for ≥ 3 h/week and to spend ≥ 30 min/session within target heart rates.	NR	NR	NR
Shah *et al.*, 2018 [46,47]	(1) White: 46 Black: 1 Asian: 3 Other: 0 (2) White: 40 Black: 6 Asian: 3 Other: 1 p-value: 0·17	No instruction was given on exercise.	Participants were randomized at least 7 days after invasive coronary angiography so that medication regimens would be as stable as possible during the study period. All participants are encouraged and expected to continue to take any medication his or her physician has prescribed.	Aspirin: (1) 46 (2) 48 p=0·68 Any P2Y12 inhibitor: (1) 43 (2) 42 p=0·99 Statin: (1) 47 (2) 48 p=0·99 beta-Blocker: (1) 33 (2) 31 p=0·84 Calcium channel blocker: (1) 10 (2) 8 p=0·80 Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker: (1) 28 (2) 26 p=0·84 Long-acting nitrate: (1) 2 (2) 2 p=0·99 Ranolazine: (1) 1 (2) 3 p=0·62	NI

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Author, year	Race/Ethnicity	Physical activity description	Medication		
			General description	Baseline	EOI
Sofi *et al.*, 2018 [48,49]	NR	Participants were instructed not to alter their lifestyle and exercise habits during the study, and no weight loss goal was given.	Participants were excluded if they were taking medications.	NA	NA
Tang *et al.*, 2013 [50]	42 Caucasian (98%) 1 African American (2%)	NI	NI	NI	NI
Toobert *et al.*, 2000 [51]	White, not Latino: (1) 13 (2) 10 Lafino: (1) 0 (2) 1 Native American or Alaskan: (1) 1 (2) 0 p-value: 0·57	Daily group physical activity sessions included warm-up, walking or aerobics, and a cool-down led by an American College of Sports Medicine certified exercise physiologist. Participants were individually prescribed exercise intensity based on their treadmill exercise test performance. Following the retreat, the intervention exercise program required participants to engage in a 1-hour session per day at least 3 days each week.	NR	Lipid-lowering (n) (1) 4 (2) 5 p-value: 0·65 Lipid-lowering (mg) (1) 95 (318) (2) 175 (539) Blood pressure-lowering (n) (1) 10 (2) 9 p-value: 0·73 Antihypertensive (mg) (1) 97 (121) (2) 120 (115) Estrogen replacement therapy (n) (1) 5 (2) 5 p-value: 0·64	Lipid-lowering (mg) (1) 101 (340) (2) 126 (357) p-value group x time: 0·140 Antihypertensive (mg) (1) 92 (207) (2) 262 (354) p-value group x time: 0·083
Wright *et al.*, 2017 [52]	NR	No instruction was given on exercise.	NA	(1) 94 (2) 74	(1) 74, 21% ↓ (2) 80, 8% ↑

*Hypoglycemia: fasting plasma glucose < 4·4 mmol/l or hypoglycemic symptoms accompanied by a capillary glucose reading < 3·5 mmol/l. In such cases, medications were reduced by a study endocrinologist following the medication protocol.
LF, low-fat diet; NA, not applicable; NI, no information; NR, not reported; PN, probably no.

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eTable 6. Dietary data of included studies

Author, year	Dietary assessment method	Energy intake	Saturated fat intake	Trans fatty acid intake	Total cholesterol intake	Dietary fibre intake	Alcohol intake
Aldana *et al.*, 2006 [24]	Self-reported, no detailed information	NR	NR	NR	NR	NR	NR
Barnard *et al.*, 2006 [25-28]	3-d WFR (2 weekdays + 1 weekend day, using a food scale, after participants Had completed a 3-day practice record)	Mean change (kcal): (1) -313.2 ± 411.6 (2) -385.9 ± 498.5 Change between group: 72.8 (95%CI: -109.9, 255.3) p-value: 0·43	Mean change (g): (1) -16.7 ± 10.9 (2) -6.9 ± 10.8 Change between group: -9.8 (95%CI: -14.1, -5.5) p-value < 0.0001	Mean change (g): (1) -2.9 ± 2.9 (2) -1.3 ± 2.5 Change between group: -1.5 (95%CI: -2.6, -0.4) p-value: 0.007	Mean change (mg): (1) -250.3 ± 221.9 (2) -107.6 ± 167.5 Change between group: -142.7 (95%CI: -221.0, -64.4) p-value: 0.001	Mean change (g): (1) 16.4 ± 12.4 (2) -0.4 ± 7.4 Change between group: 16.9 (95%CI: 12.8, 20.9) p-value < 0.0001	NR
Barnard *et al.*, 2018 [29]	3-d food record (instructed portion sizes estimation using food models, along with a sample record)	Mean change (kcal): (1) -204 ± 95 (2) -306 ± 100 p-value between group: 0·4612	Mean change (g): (1) -14 ± 2 (2) -7 ± 2 p-value: 0.0341	NR	Mean change (mg): (1) -169 ± 16 (2) -33 ± 34 p-value: 0.0012	NR	NR
Barnard *et al.*, 2021 [30]	3-d food record, collected and analyzed by an RD or a staff member certified in Nutrition Data System for Research version 2018	Mean change (kcal): (1) -500 ± 327.99 (2) 79 ± 511.92 Change between group: -579 (95%CI: -801, -357) p-value <0.001	Mean change (% of energy): (1) -8 (95%CI: −9, −6) (2) -1 (95%CI: −2, 0) Change between group: -6 (95%CI: -8, -5) p-value < 0.001	NR	Mean change (mg): (1) -273 (95%CI: -317, -230) (2) -25 (95%CI: -93, 43) Change between group: -248 (95%CI: -331, -166) p-value < 0.001	Mean change (g): (1) 10 (95%CI: 8, 13) (2) 5 (95%CI: 2, 7) Change between group: 6 (95%CI: 2, 9) p-value < 0.001	Mean change (g): (1) -2 (95%CI: -4, 0) (2) 0 (95%CI: -3, 3) Change between group: -2 (95%CI: -5, 2) p-value: 0.31
Bunner *et al.*, 2015 [31]	2-d dietary record	NR	NR	NR	NR	NR	NR

(1), vegetarian diet intervention group; (2), non-vegetarian diet comparison group; EOI, end of intervention; LF, low-fat diet; FHQ, Food Habits Questionnaire; NA, not applicable; NI, no information; NR, not reported; PN, probably no; RD, Registered Dietitian; SFA, saturated fatty acid; TC, total cholesterol; TFA, saturated fatty acid; WFR, weighed food records

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eTable 6. Continued

Author, year	Dietary assessment method	Energy intake	Saturated fat intake	Trans fatty acid intake	Total cholesterol intake	Dietary fibre intake	Alcohol intake
Burke *et al.*, 2006 [32-34]	3-d food record (2 work days + one leisure day, reviewed by trained research staff for completeness and clarity)	Mean change (kcal): (1) -535.98 ± 511.81 (2) -519.80 ± 533.15 p-value between group: 0.836	Mean change (% of energy): (1) -3.76 ± 3.75 (2) -3.12 ± 3.86 p-value between group: 0.17	NR	NR	NR	NR
Garousi *et al.*, 2021 [35]	3-d WFR (2 weekdays and 1 weekend day; food models and national food composition tables were used)	EOI Energy intake (kcal): (1) 1911.02 ± 290.04 (2) 2075.54 ± 314.68 p-value between group: 0.061	EOI SFA intake (g): (1) 18.38 ± 3.11 (2) 21.69 ± 4.46 p-value between group: 0.004	NR	EOI TC intake (mg): (1) 298 ± 133 (2) 264 ± 122 p-value between group: 0.397	EOI Dietary fibre intake (g): (1) 42.32 ± 7.02 (2) 27.56 ± 6.31 p-value between group < 0.001	NR
Kahleova *et al.*, 2010 [36]	3-d food record (2 weekdays and 1 weekend day)	Mean change (kcal): (1) -137 ± 477 (2) -128 ± 641	NR	NR	Mean change (mg): (1) -322 ± 224 (2) -55.6 ± 187	Mean change (mg): (1) 6.02 ± 9.58 (2) 1.73 ± 9.89	NR
Kahleova *et al.*, 2020 [37]	3-d food record (collected and analyzed by staff members certified in the Nutrition Data System for Research)	Mean change (kcal): (1) -490.7 ± 646.8 (2) -135.8 ± 603.8 Change between group: -354.9 (95%CI: -519.0, -190.8) p-value <0.001	Mean change (g): (1) -18.6 (95%CI: -20.7, -16.5) (2) -2.4 (95%CI: -4.9, 0.1) Change between group: -16.2 (95%CI: -19.4, -13.0) p-value <0.001	NR	Mean change (mg): (1) -233.1 (95%CI: -259.4, -206.8) (2) -14 (95%CI: -51.7, 23.7) Change between group: -219.1 (95%CI: -264.9, -173.3) p-value <0.001	Mean change (g): (1) 10.6 (95%CI: 7.8, 13.3) (2) -0.56 (95%CI: -2.6, 1.5) Change between group: 11.1 (95%CI: 7.8, 14.5) p-value <0.001	NR
Lee *et al.*, 2016 [38]	A dietitian conducted 24-h recalls (4 times/ month, including 3 weekdays + once on a weekend); baseline not assessed.	EOI Energy intake (kcal): (1) 1496.2 ± 104.8 (2) 1559.7 ± 181.6 p-value between group: 0.042	EOI SFA intake (g): (1) 3.2±1.5 (2) 6.7±2.7 p-value between group <0.001	NR	EOI TC intake (mg): (1) 70.3±57.4 (2) 240.7±74.7 p-value between group <0.001	EOI Dietary fibre intake (g): (1) 33.7 ± 4.8 (2) 24.9 ± 4.5 p-value between group <0.001	NR

(1), vegetarian diet intervention group; (2), non-vegetarian diet comparison group; EOI, end of intervention; LF, low-fat diet; FHQ, Food Habits Questionnaire; NA, not applicable; NI, no information; NR, not reported; PN, probably no; RD, Registered Dietitian; SFA, saturated fatty acid; TC, total cholesterol; TFA, saturated fatty acid; WFR, weighed food records

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eTable 6. Continued

Author, year	Dietary assessment method	Energy intake	Saturated fat intake	Trans fatty acid intake	Total cholesterol intake	Dietary fibre intake	Alcohol intake
Liao *et al.*, 2007 [39]	Daily diet record	EOI Energy intake (kcal): (1) 1156 ± 165 (2) 1229 ± 15	NR	NR	NR	EOI Dietary fibre intake (g): (1) 6.6±0.9 (2) 7.6±1.1	NR
Mahon *et al.*, 2007 [40]	3-d food record	EOI Energy intake (kcal): (1) 1158 ± 341 (2) 1570 ± 633 p-value <0.05	NR	NR	NR	EOI Dietary fibre intake (g): (1) 18 ± 8 (2) 14 ± 8	NR
Mishra *et al.*, 2013 [41,42]	24-h recall over two 24-h periods, using an online program (ASA24: Automated Self-Administered 24-hour Recall)	Mean change (kcal): (1) -264.6 ± 65.6 (2) -36.8 ± 58 Change between group: -130 (95%CI: -281, 20.4) p-value: 0.09	Mean change (% of energy): (1) -2.8 ± 0.4 (2) -0.36 ± 0.45	NR	Mean change (mg): (1) -107.7 ± 21.9 (2) -13.9 ± 19.6 Change between group: -92 (95%CI: -141.5, -42.6) p-value <0.001	Mean change (g): (1) 3.5 ± 1.3 (2) 0.74 ± 0.72	NR
Nicholson *et al.*, 1999 [43]	3-d food record (2 weekdays and 1 weekend day)	Mean change (kcal): (1) -274 ± 464.1 (2) 96 ± 339.4	EOI SFA intake (% of energy): (1) 3 ± 2.0 (2) 8 ± 1.8	NR	EOI TC intake (mg): (1) 4.4 ± 7.4 (2) 122 ± 31	EOI Dietary fibre intake (g): (1) 26±8.2 (2) 20±2.7	NR
Ornish *et al.*, 1990 [44,45]	3-d food record	Energy intake after intervention (MJ): (1) 7.6 ± 2.1 (2) 7.1 ± 1.9 p-value: 0.5082	NR	NR	TC intake after intervention (mg): (1) 12.4 ± 45.8 (2) 190 ± 99 p-value < 0.0001	NR	NR
Shah *et al.*, 2018 [46,47]	4-day WFR (with measuring cups and spoons); RD calls the patient 2/week on random days to obtain 24-h recalls	EOI Energy intake (kcal: Median [IQR]): (1) 1715 [1482–2052] (2) 1531 [1197–1817] p-value: 0.01	EOI SFA intake (g: Median [IQR]): (1) 9 [6–12] (2) 10 [8–15] p-value: 0.03	EOI TFA intake (g: Median [IQR]): (1) 0.06 [0.00–0.74] (2) 0.14 [0.05–0.43] p-value: 0.4	EOI TC intake (mg: Median [IQR]): (1) 0 [0–2] (2) 142 [110–240] p-value < 0.001	EOI Dietary fibre intake (g: Median [IQR]): (1) 36 [30–43] (2) 25 [20–30] p-value < 0.001	NR

(1), vegetarian diet intervention group; (2), non-vegetarian diet comparison group; EOI, end of intervention; LF, low-fat diet; FHQ, Food Habits Questionnaire; NA, not applicable; NI, no information; NR, not reported; PN, probably no; RD, Registered Dietitian; SFA, saturated fatty acid; TC, total cholesterol; TFA, saturated fatty acid; WFR, weighed food records

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eTable 6. Continued

Author, year	Dietary assessment method	Energy intake	Saturated fat intake	Trans fatty acid intake	Total cholesterol intake	Dietary fibre intake	Alcohol intake
Sofi *et al.*, 2018 [48,49]	3-d food record (2 weekdays and 1 weekend day)	Mean change (kcal): (1) -586.3 ± 486.9 (2) 496.7 ± 539.8 p-value between group: 0.18	Mean change (% of energy): (1) -0.31 ± 2.2 (2) -1.0 ± 3.3 p-value between group: 0.41	NR	Mean change (% of energy): (1) -105.6 ± 91.5 (2) -49.7 ± 121.8 p-value between group: 0.001	NR	NR
Tang *et al.*, 2013 [50]	Daily food check-offs noting any foods not consumed and extra foods consumed	EOI Energy intake (kcal): (1) 2273 ± 78 (2) 2254 ± 75	NR	NR	NR	NR	NR
Toobert *et al.*, 2000 [51]	The Kristal FHQ, a 4-d food record, and a paper-and-pencil dietary fat intake screener	EOI Energy intake (kcal): (1) 1349 ± 284 (2) 1394 ± 477 p-value: 0·164	EOI SFA (% of energy): (1) 3.1 ± 2.4 (2) 8.7 ± 3.0 p-value between group < 0.000	NR	NR	NR	NR
Wright *et al.*, 2017 [52]	3-d diet recall to track dietary indiscretions	NR	NR	NR	NR	NR	NR

(1), vegetarian diet intervention group; (2), non-vegetarian diet comparison group; EOI, end of intervention; LF, low-fat diet; FHQ, Food Habits Questionnaire; NA, not applicable; NI, no information; NR, not reported; PN, probably no; RD, Registered Dietitian; SFA, saturated fatty acid; TC, total cholesterol; TFA, saturated fatty acid; WFR, weighed food records

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eTable 7. Detailed risk of bias assessment of included studies

Author, year	Aldana, 2006 [24]	Barnard, 2006 [25]	Barnard, 2018 [29]	Barnard, 2021 [30]	Bunner, 2015 [31]	Burke, 2006 [32]	Garousi, 2021 [35]	Kahleova, 2010 [36]	Kahleova, 2020 [37]	Lee, 2016 [38]	Liao, 2007 [39]	Mahon, 2007 [40]	Mishra, 2013 [41]	Nicholson, 1999 [43]	Ornish, 1990 [44]	Shah, 2018 [46]	Sofi, 2018 [48]	Tang, 2013 [50]	Toobert, 2000 [51]	Wright, 2017 [52]
Domain 1: Bias arising from the randomisation process																				
1.1	NI	Y	Y	Y	Y	PN	PY	Y	Y	Y	NI	Y	Y	Y	NI	Y	Y	NI	NI	Y
1.2	NI	PY	Y	Y	Y	NI	NI	Y	Y	NI	NI	NI	NI	Y	Y	Y	Y	NI	NI	PY
1.3	N	N	N	N	PY	N	Y	PN	PN	N	PN	PN	PN	Y	PY	N	N	N	N	PN
ROB	SC	L	L	L	SC	SC	H	L	L	SC	SC	SC	SC	SC	SC	L	L	SC	SC	L
Domain 2: Bias due to deviations from intended intervention																				
2.1	PY	Y	PY	Y	Y	Y	PY	Y	Y	Y	PY	Y	PY	PY	Y	PY	Y	PY	Y	Y
2.2	PY	Y	PY	Y	Y	PY	PY	PY	Y	PY	PY	PY	PY	PY	PY	PY	Y	PY	PY	PY
2.3	NI	PN	PN	PN	N	NI	NI	NI	N	NI	PN	NI	PN	NI	PN	NI	NI	NI	NI	PN
2.4	NA	NA	NA	PN	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2.5	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2.6	Y	Y	PN	Y	Y	Y	N	Y	Y	Y	Y	PN	Y	Y	Y	Y	Y	PN	Y	PY
2.7	NA	NA	PY	NA	NA	NA	N	NA	NA	NA	NA	PN	NA	NA	NA	NA	NA	PN	NA	NA
ROB	SC	L	H	L	L	SC	SC	SC	L	SC	L	SC	L	SC	L	SC	SC	SC	SC	L
Domain 3: Bias due to missing outcome data																				
3.1	N	Y	N	N	Y	N	Y	N	N	N	Y	PN	Y	N	N	Y	Y	Y	N	Y
3.2	No	NA	N	N	NA	Y	NA	Y	Y	Y	NA	N	NA	N	PN	NA	NA	NA	PN	NA
3.3	Y	NA	PN	PY	NA	NA	NA	NA	NA	NA	NA	Y	NA	PY	PN	NA	NA	NA	PY	NA
3.4	PY	NA	NA	PY	NA	NA	NA	NA	NA	NA	NA	NI	NA	PY	NA	NA	NA	NA	PY	NA
ROB	H	L	L	H	L	L	L	L	L	L	L	H	L	SC	L	L	L	L	H	L

H, high; L, low; N, no; NA, not applicable; NI, no information; PN, probably no; PY, probably yes; Ref, references; ROB, risk of bias; SC, some concerns; Y, yes

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Author, year	Aldana, 2006 [24]	Barnard, 2006 [25]	Barnard, 2018 [29]	Barnard, 2021 [30]	Bunner, 2015 [31]	Burke, 2006 [32]	Garousi, 2021 [35]	Kahleova, 2010 [36]	Kahleova, 2020 [37]	Lee, 2016 [38]	Liao, 2007 [39]	Mahon, 2007 [40]	Mishra, 2013 [41]	Nicholson, 1999 [43]	Ornish, 1990 [44]	Shah, 2018 [46]	Sofi, 2018 [48]	Tang, 2013 [50]	Toobert, 2000 [51]	Wright, 2017 [52]
Domain 4: Bias in measurement of the outcome																				
4.1	NI	N	N	PN	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
4.2	PN	N	N	N	PN	N	PN	N	PN	PN	PN	N	N	PN	N	N	N	N	PN	N
4.3	NI	N	N	NI	NI	NI	NI	N	PN	PN	NI	NI	NI	NI	N	N	N	NI	NI	Y
4.4	PN	NA	NA	PN	PN	PN	PN	NA	NA	NA	PN	PN	PN	PN	NA	NA	NA	PN	PN	PN
4.5	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
ROB	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L
Domain 5: Bias in selection of the reported result																				
5.1	PN	Y	PY	N	NI	PN	PY	PY	PY	PY	PY	PN	PY	PY	PY	Y	Y	NI	PY	PY
5.2	PN	N	N	N	N	Y	PY	N	N	N	PN	N	N	Y	N	Y	N	PN	PN	N
5.3	PY	N	PY	PN	N	N	PN	N	PN	PN	PN	PN	N	PN	N	PN	Y	PN	PN	N
ROB	H	L	H	SC	SC	H	H	L	L	L	L	SC	L	H	L	H	H	SC	L	L
Overall ROB	H	L	H	H	SC	H	H	L	SC	SC	SC	H	SC	H	SC	H	H	H	H	L

H, high; L, low; N, no; NA, not applicable; NI, no information; PN, probably no; PY, probably yes; Ref, references; ROB, risk of bias; SC, some concerns; Y, yes

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eTable 8. GRADE assessment of the certainty of evidence in people with CVD or people at high risk of CVD

Certainty assessment							№ of patients		Effect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vegetarian dietary patterns	Other intervention diets or the usual diet	MD (95% CI)	Certainty	Importance
Low-density lipoprotein cholesterol (follow-up: range 8 weeks to 2 years)											
19	RCTs	not serious[a]	serious[b]	not serious	not serious	none	827	834	**-6·6 mg/dL** (-10·1, -3.1)	⊕⊕⊕◯ Moderate	Important
Hemoglobin A1c (follow-up: range 8 weeks to 6 months)											
10	RCTs	not serious[c]	serious[d]	not serious	not serious	none	393	385	**-0·24 %** (-0·40, -0·07)	⊕⊕⊕◯ Moderate	Important
Systolic blood pressure (follow-up: range 8 weeks to 2 years)											
14	RCTs	not serious[e]	serious[f]	not serious	serious[g]	none	472	483	**-0·1 mmHg** (-2.8, 2·6)	⊕⊕◯◯ Low	Important
Body weight (follow-up: range 8 weeks to 1 years)											
16	RCTs	not serious[h]	very serious[i]	not serious	not serious	none	695	700	**-3·4 kg** (-4·9, -2·0)	⊕⊕◯◯ Low	Important

CI: confidence interval; CVD: cardiovascular disease; MD: mean difference; RCT: randomised controlled trial

a. All included studies lack blinding from patients and probably from caregivers, given it is impossible to blind people from a dietary intervention; nine out of 11 included studies did not provide enough information to judge allocation concealment; four out of 19 included studies did not follow intention-to-treat principle in data analysis; six out of 19 included studies were at risk of selective reporting.
b. I^2=67% and tau-square=37·59 indicate a substantial heterogeneity.
c. All included studies lack blinding from patients and probably from caregivers, given it's impossible to blind people from a dietary intervention; two out of ten included studies did not provide enough information to judge allocation concealment; all studies employed intention-to-treat principle in data analysis; two out of ten included studies were at risk of selective reporting.
d. I^2=88% and tau-square=0·058 indicate a considerable heterogeneity.
e. All included studies lack blinding from patients and probably from caregivers, given it's impossible to blind people from a dietary intervention; seven out of 14 included studies did not provide enough information to judge allocation concealment; three out of 14 included studies did not follow intention-to-treat principle in data analysis; four out of 14 included studies were at risk of selective reporting.
f. I^2=65% and tau-square=14·25 indicate a substantial heterogeneity.
g. The 95% CI of the mean difference includes no effect.
h. All included studies lack blinding from patients and probably from caregivers, given it's impossible to blind people from a dietary intervention; seven out of sixteen included studies did not provide enough information to judge allocation concealment; four out of sixteen included studies did not follow intention-to-treat principle in data analysis; six out of sixteen included studies were at risk of selective reporting.
i. I^2=92% and tau-square=4·73 indicate a considerable heterogeneity.

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eTable 9. GRADE assessment of the certainty of evidence in people at high risk of CVD

Certainty assessment							№ of patients		Effect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vegetarian dietary patterns	Other intervention diets or the usual diet	MD (95% CI)	Certainty	Importance
Low-density lipoprotein cholesterol (follow-up: range 8 to 52 weeks)											
9	RCTs	serious[a]	not serious	not serious	not serious	strong association	391	395	**-9·1 mg/dL** (-12·7, -5·5)	⊕⊕⊕⊕ High	Critical
Hemoglobin A1c (follow-up: range 16 weeks to 6 months)											
3	RCTs	not serious[b]	very serious[c]	not serious	very serious[d]	none	166	158	**-0·19 %** (-0·50, 0·11)	⊕◯◯◯ Very low	Critical
Systolic blood pressure (follow-up: range 8 weeks to 6 months)											
5	RCTs	not serious[e]	serious[f]	not serious	very serious[d]	none	122	127	**-2·5 mmHg** (-7·2, 2·3)	⊕◯◯◯ Very low	Critical
Body Weight (follow-up: range 8 to 52 weeks)											
9	RCTs	serious[a]	very serious[g]	not serious	not serious	none	392	394	**-3·6 kg** (-5·8, -1·4)	⊕◯◯◯ Very low	Important

CI: confidence interval; CVD: cardiovascular disease; MD: mean difference; RCT: randomized controlled trial

a. All included studies lack blinding from patients and probably from caregivers, given it is impossible to blind people from a dietary intervention; five out of nine included studies did not provide enough information to judge allocation concealment; three out of nine included studies did not follow intention-to-treat principle in data analysis; three out of nine included studies were at risk of selective reporting.
b. All included studies lack blinding from patients and probably from caregivers, given it's impossible to blind people from a dietary intervention; all included studies performed allocation concealment properly; all included studies follow intention-to-treat principle in data analysis; one out of three included studies was at risk of selective reporting.
c. I2=97% and tau-square=0·078 indicate a considerable heterogeneity.
d. The sample size is smaller than 400 and 95%CI of the mean difference include 0.
e. All included studies lack blinding from patients and probably from caregivers, given it's impossible to blind people from a dietary intervention; three out of five included studies did not provide enough information to judge allocation concealment; two out of five included studies did not follow intention-to-treat principle in data analysis; one out of five included studies were at risk of selective reporting.
f. I2=66% and tau-square=21·07 indicate substantial heterogeneity.
g. I2=95% and tau-square=8·67 indicate a considerable heterogeneity.

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eTable 10. GRADE assessment of the certainty of evidence in people with T2DM

Certainty assessment							№ of patients		Effect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vegetarian dietary patterns	Other intervention diets or the usual diet	MD (95% CI)	Certainty	Importance
Low-density lipoprotein cholesterol (follow-up: range 12 weeks to 24 weeks)											
6	RCTs	not serious[a]	serious[b]	not serious	serious[c]	none	305	313	**-2·2 mg/dL** (-6.5, 2·1)	⊕⊕◯◯ Low	Important
Hemoglobin A1c (follow-up: range 12 weeks to 24 weeks)											
6	RCTs	not serious[d]	not serious	not serious	serious[e]	none	177	177	**-0·36 %** (-0·53, -0·18)	⊕⊕⊕◯ Moderate	Critical
Systolic blood pressure (follow-up: range 12 weeks to 22 weeks)											
6	RCTs	not serious[f]	not serious	not serious	serious[c]	none	269	280	**2·2 mmHg** (-0·6, 5)	⊕⊕⊕◯ Moderate	Important
Body weight (follow-up: range 12 weeks to 22 weeks)											
5	RCTs	serious[g]	serious[h]	not serious	not serious	none	235	240	**-2·8 kg** (-4·2, -1·4)	⊕⊕◯◯ Low	Important

CI: confidence interval; MD: mean difference; RCT: randomised controlled trial; T2DM: type 2 diabetes mellitus

a. All studies lack blinding from patients and probably from caregivers, given it is impossible to blind people from a dietary intervention; 2 out of 6 studies did not provide enough information to judge allocation concealment; 1 out of 6 studies did not follow intention-to-treat principle in data analysis; 1 out of 6 studies were at high risk of selective reporting and another presented some concerns of selective reporting.
b. I^2=63% and tau-square=17·80 indicate a substantial heterogeneity.
c. The 95% CI of the mean difference includes no effect, therefore rating down for imprecision.
d. All included studies lack blinding from patients and probably from caregivers, given it's impossible to blind people from a dietary intervention; two out of six included studies did not provide enough information to judge allocation concealment; all studies follow intention-to-treat principle in data analysis; two out of six included studies were at risk of selective reporting.
e. The sample size is lower than 400, therefore rating down for imprecision.
f. All included studies lack blinding from patients and probably from caregivers, given it's impossible to blind people from a dietary intervention; two out of six included studies did not provide enough information to judge allocation concealment; one out of six included studies did not follow intention-to-treat principle in data analysis; two out of six included studies were at risk of selective reporting.
g. All included studies lack blinding from patients and probably from caregivers, given it's impossible to blind people from a dietary intervention; one out of five included studies did not provide enough information to judge allocation concealment; one out of five included studies did not follow intention-to-treat principle in data analysis; two out of five included studies were at risk of selective reporting.
h. I^2=67% and tau-square=0·83 indicate a substantial heterogeneity.

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eTable 11. GRADE assessment of the certainty of evidence in people with CVD

Certainty assessment							№ of patients		Effect		
№ of studies	Study design	MD (95% CI)	Inconsistency	Indirectness	Imprecision	Other considerations	Vegetarian dietary patterns	Other intervention diets or the usual diet	Absolute (95% CI)	Certainty	Importance
Low-density lipoprotein cholesterol (follow-up: range 8 weeks to 2 years)											
4	RCTs	not serious[a]	serious[b]	not serious	serious[c]	none	131	126	**-13·2 mg/dL** (-33·0, 6·6)	⊕⊕◯◯ Low	Important
Systolic blood pressure (follow-up: range 1 years to 2 years)											
3	RCTs	not serious[d]	not serious	not serious	very serious[e]	none	81	76	**-0·1 mmHg** (-6·1, 5·9)	⊕⊕◯◯ Low	Important

CI: confidence interval; CVD: cardiovascular disease; MD: mean difference; RCT: randomised controlled trial

a. All included studies lack blinding from patients and probably from caregivers, given it is impossible to blind people from a dietary intervention; two out of four included studies did not provide enough information to judge allocation concealment; all included studies follow intention-to-treat principle in data analysis; two out of four included studies were at risk of selective reporting.
b. I^2=80% and tau-sqaure=194·24 indicate a considerable heteorgeneity.
c. The sample size is lower than 400 and 95%CI of the mean difference includes no effect, therefore rating down for imprecision.
d. All included studies lack blinding from patients and probably from caregivers, given it's impossible to blind people from a dietary intervention; two out of three included studies did not provide enough information to judge allocation concealment; all included studies follow intention-to-treat principle in data analysis; one out of three included studies were at risk of selective reporting.
e. The sample size is lower than 200 and 95%CI include no effect, therefore rating down for imprecision.

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eTable 12. Studies excluded at stage 2 with reasons

Author, year	Journal	Volume (issue):pages	Title	Exclusion reason
Acharya *et al.* 2009 [58]	Patient preference & adherence	3:151-60	Adherence to a behavioral weight loss treatment program enhances weight loss and improvements in biomarkers	No additional data to extract
Acharya *et al.* 2013 [59]	Journal of the American College of Nutrition	32(4):264-71	Weight loss is more important than the diet type in improving adiponectin levels among overweight/obese adults	No additional data to extract
Adebawo *et al.* 2006 [60]	Lipids in Health & Disease	5:14	Fruits and vegetables moderate lipid cardiovascular risk factor in hypertensive patients	Wrong study design
Agarwal *et al.* 2013 [61]	Diabetes	62:A195	A plant-based diet reduces depression and anxiety and improves work productivity: The GEICO multicenter trial	Not a manuscript
Agarwal *et al.* 2015 [62]	American Journal of Health Promotion	29(4):245-54	A multicenter randomized controlled trial of a nutrition intervention program in a multiethnic adult population in the corporate setting reduces depression and anxiety and improves quality of life: the GEICO study	Not relevant outcomes
Agren *et al.* 2001 [63]	British Journal of Nutrition	85(2):137-9	Divergent changes in serum sterols during a strict uncooked vegan diet in patients with rheumatoid arthritis	Wrong patient population
Ahc 2018 [64]	Clinical Cardiology Alert	37(6)	Vegetarian Diet vs. Mediterranean Diet to Reduce Cardiovascular Risk	Not a manuscript
Allen *et al.* 2015 [65]	Cardiology	131:91	The effects of plant-based, mediterranean, paleolithic, and dash diets on cardiovascular disease risk	Not a manuscript
Anderson 1983 [66]	Annals of Internal Medicine	98:842-6	Plant fiber and blood pressure	Wrong study design
Anderson 2018 [67]	Circulation	137(11):1114-1116	Dietary Patterns to Reduce Weight and Optimize Cardiovascular Health: Persuasive Evidence for Promoting Multiple, Healthful Approaches	Not a manuscript
Andrews 2017 [68]	Communicating Food for Health	2017:8	Vegetarian Diets & Heart Disease	Wrong study design
Anonymous 2002 [69]	Pharmaceutical Journal	269(7227):799	Vegetarian diet cuts cholesterol	Not a manuscript
Anonymous 2003 [70]	Pharmaceutical Journal	271(7260):140	Special cholesterol-lowering diet can achieve same effects as statin therapy	Not a manuscript
Arntzenius 1986 [71]	Drugs	31(SUPPL. 1):61-65	Diet, lipoproteins and the progression of coronary atherosclerosis. The Leiden Intervention Trial	Wrong study design
Barnard *et al.* 1992 [72]	Journal of Cardiopulmonary Rehabilitation	12(6):423-431	Adherence and acceptability of a low-fat, vegetarian diet among patients with cardiac disease	No additional data to extract
Barnard *et al.* 2000 [73]	American Journal of Cardiology	85(8):969-72	Effectiveness of a low-fat vegetarian diet in altering serum lipids in healthy premenopausal women	Wrong patient population
Barnard *et al.* 2004 [74]	Journal of Cardiopulmonary Rehabilitation	24(4):229-35	Acceptability of a low-fat vegan diet compares favorably to a step II diet in a randomized, controlled trial	Wrong patient population
Barnard *et al.* 2005 [75]	American Journal of Medicine	118(9):991-7	The effects of a low-fat, plant-based dietary intervention on body weight, metabolism, and insulin sensitivity	Wrong patient population

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Author, year	Journal	Volume (issue):pages	Title	Exclusion reason
Barnard *et al.* 2009 [76]	Nutrition	25(1):58-65	D2 dopamine receptor Taq1A polymorphism, body weight, and dietary intake in type 2 diabetes	Not relevant outcomes
Barnard *et al.* 2020 [77]	Journal of the Academy of Nutrition & Dietetics	10:10	Blood Type Is Not Associated with Changes in Cardiometabolic Outcomes in Response to a Plant-Based Dietary Intervention	Wrong patient population
Beilin 1993 [78]	Annals of the New York Academy of Sciences	676:83-91	Vegetarian diets, alcohol consumption, and hypertension	Wrong study design
Bennett *et al.* 1990 [79]	American Journal of Clinical Nutrition	52(5):808-12	Diet and female sex hormone concentrations: an intervention study for the type of fat consumed	Wrong patient population
Bhardwaj 2017 [80]	Heliyon	3(12):e00472	A randomized controlled trial to evaluate the effects of high Protein Complete (lActo) VEgetaRian (PACER) diet in non-diabetic obese Asian Indians in North India	Wrong comparator
Brestrich 1996 [81]	Zeitschrift fur Kardiologie	85(6):418-427	Lactovegetarian diet: Influence on weight, lipids, fibrinogen and lipoprotein (a) of heart-patients in the course of their clinical rehabilitation. [German]	Other languages
Brom 2009 [82]	South African Family Practice	51(3):196-197	Integrative approach to management of heart disease is heart disease reversible?	Not a manuscript
Bunner 2014 [83]	Diabetes	63:A578	Nutrition intervention for diabetic neuropathy	Not a manuscript
Burke 2007 [84]	American Journal of Clinical Nutrition	86(3):588-96	Effects of a vegetarian diet and treatment preference on biochemical and dietary variables in overweight and obese adults: a randomized clinical trial	Wrong patient population
Campbell 2017 [85]	Journal of Geriatric Cardiology	14(5):321-326	A plant-based diet and stroke	Wrong study design
Campbell 1999 [86]	American Journal of Clinical Nutrition	70(6):1032-1039	Effects of an omnivorous diet compared with a lactoovovegetarian diet on resistance-training-induced changes in body composition and skeletal muscle in older men	Wrong study design
Campbell 2010 [87]	Journals of Gerontology Series A-Biological Sciences & Medical Sciences	65(10):1115-22	Protein intake, weight loss, and bone mineral density in postmenopausal women	Not relevant outcomes
Cesari 2019 [88]	Nutrition Metabolism & Cardiovascular Diseases	29(6):604-610	Mediterranean, but not lacto-ovo-vegetarian, diet positively influence circulating progenitor cells for cardiovascular prevention: The CARDIVEG study	Not relevant outcomes
Chamorro 2020 [89]	Lipids	55(6):639-648	Diet, Plasma, Erythrocytes, and Spermatozoa Fatty Acid Composition Changes in Young Vegan Men	Wrong study design
Crimarco 2020 [90]	American Journal of Clinical Nutrition	112(5):1188-1199	A randomized crossover trial on the effect of plant-based compared with animal-based meat on trimethylamine-N-oxide and cardiovascular disease risk factors in generally healthy adults: Study With Appetizing Plantfood-Meat Eating Alternative Trial (SWAP-MEAT)	Wrong intervention
Dewell 2008 [91]	Journal of the American Dietetic Association	108(2):347-56	A very-low-fat vegan diet increases intake of protective dietary factors and decreases intake of pathogenic dietary factors	Wrong intervention

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Author, year	Journal	Volume (issue):pages	Title	Exclusion reason
Dinu 2020 [92]	International Journal of Food Sciences & Nutrition	71(3):362-369	Effects of a dietary intervention with Mediterranean and vegetarian diets on hormones that influence energy balance: CARDIVEG study	Not relevant outcomes
Dinu 2019 [93]	British Journal of Nutrition	121(7):756-762	Effects of a 3-month dietary intervention with a lacto-ovo-vegetarian diet on vitamin B12 levels in a group of omnivores: results from the CARDIVEG (Cardiovascular Prevention with Vegetarian Diet) study	Not relevant outcomes
Dinu 2019 [94]	Nutrition, Metabolism and Cardiovascular Diseases	29(8):882-883	Effects of a 3-months' dietary intervention with lacto-ovo-vegetarian diet on vitamin B12 levels: results of the CARDIVEG study	Wrong study design
Dinu 2019 [95]	Nutrition, Metabolism and Cardiovascular Diseases	29(8):881	Dietary intervention with vegetarian and mediterranean diets for cardiovascular prevention: Effects on hormones involved in the energy balance	Not relevant outcomes
Dogra 2020 [96]	Circulation	142(SUPPL 3)	Long-term Dietary and Weight Changes Following a Short-term Dietary Intervention Study: 4-year Follow-up of the Evade Cad Trial	Not a manuscript
Elkan 2008 [97]	Arthritis Research & Therapy	10(2):R34	Gluten-free vegan diet induces decreased LDL and oxidized LDL levels and raised atheroprotective natural antibodies against phosphorylcholine in patients with rheumatoid arthritis: a randomized study	Wrong patient population
Elkoustaf 2017 [98]	Journal of the American College of Cardiology	69 (11 Supplement 1):48	Diet and ischemic burden: A comparative analysis of a plant based regimen versus a mediterranean regimen in patients with coronary artery disease	Not a manuscript
Elkoustaf 2019 [99]	The Permanente journal	23:18.196	Lifestyle Interventions and Carotid Plaque Burden: A Comparative Analysis of Two Lifestyle Intervention Programs in Patients with Coronary Artery Disease	Wrong intervention
Fallah Noroozinejad 2015 [100]	Iranian Journal of Endocrinology and Metabolism	16(5)	Effect of legumes intake on the oxidative stress markers in type 2 diabetes patients: A randomized cross-over study. [Persian]	Other languages
Feifer 2003 [101]	Californian Journal of Health Promotion	1(3):7-13	Lifestyle change for weight loss in the inner-city	Wrong study design
Fenton 2019 [102]	Critical Reviews in Food Science & Nutrition	59(7):1044-1045	Plant-based diets do not prevent most chronic diseases	Wrong study design
Ferdowsian 2010 [103]	American Journal of Health Promotion	24(6):384-7	A multicomponent intervention reduces body weight and cardiovascular risk at a GEICO corporate site	Wrong study design
Flynn 2010 [104]	Journal of Women's Health	19(6):1155-1161	Comparing an olive oil-enriched diet to a standard lower-fat diet for weight loss in breast cancer survivors: a pilot study	Wrong intervention
Frassetto 2019 [105]	Journal of Evolution and Health	3	The VA Beach Diet Study: A comparison of the effects of Plant-based, Mediterranean, Paleolithic, and DASH Diets on cardiovascular disease risk	Not a manuscript
Gage 2011 [106]	Topics in Geriatric Rehabilitation	27(2):162-166	Growing old in a circle of friends: Sangha and the lifestyle heart trial	Wrong study design
Gardner 2007 [107]	JAMA	297(9):969-977	Comparison of the Atkins, Zone, Ornish, and LEARN Diets for Change in Weight and Related Risk Factors Among Overweight Premenopausal WomenThe A TO Z Weight Loss Study: A Randomized Trial	Wrong intervention

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Author, year	Journal	Volume (issue):pages	Title	Exclusion reason
Gorder 1986 [108]	Journal of the American Dietetic Association	86(6):744-751	Dietary intake in the Multiple Risk Factor Intervention Trial (MRFIT): Nutrient and food group changes over 6 years	Wrong intervention
Gould 1992 [109]	American Journal of Cardiology	69(9):845-53	Improved stenosis geometry by quantitative coronary arteriography after vigorous risk factor modification	Not relevant outcomes
Gould 1995 [110]	JAMA	274(11):894-901	Changes in myocardial perfusion abnormalities by positron emission tomography after long-term, intense risk factor modification	Not relevant outcomes
Hakala 1989 [111]	European Journal of Clinical Nutrition	43(6):421-30	Weight reduction on lactovegetarian and mixed diets. Changes in weight, nutrient intake, skinfold thicknesses and blood pressure	Wrong patient population
Harsha 1999 [112]	Journal of the American Dietetic Association	99(8 SUPPL.):S35-S39	Dietary Approaches to Stop Hypertension: A summary of study results	Wrong intervention
Harvey 2020 [113]	Heart, Lung & Circulation	29:S375-S375	The Effect of a Plant-Based Diet on Cardiovascular Risk Factors in Patients With Ischaemic Heart Disease	Wrong study design
Haub 2005 [114]	Metabolism: Clinical & Experimental	54(6):769-74	Beef and soy-based food supplements differentially affect serum lipoprotein-lipid profiles because of changes in carbohydrate intake and novel nutrient intake ratios in older men who resistive-train	Wrong patient population
Hosseinpour-Niazi 2015 [115]	European Journal of Clinical Nutrition	69(5):592-597	Substitution of red meat with legumes in the therapeutic lifestyle change diet based on dietary advice improves cardiometabolic risk factors in overweight type 2 diabetes patients: a cross-over randomized clinical trial	Wrong intervention
Hunt 1998 [116]	American Journal of Clinical Nutrition	67(3):421-30	Zinc absorption, mineral balance, and blood lipids in women consuming controlled lactoovovegetarian and omnivorous diets for 8 wk	Wrong patient population
Jenkins 2010 [117]	CMAJ : Canadian Medical Association journal	182(18):1961-1967	Adding monounsaturated fatty acids to a dietary portfolio of cholesterol-lowering foods in hypercholesterolemia	Wrong intervention
Jibani 1991 [118]	Diabetic Medicine	8(10):949-53	Predominantly vegetarian diet in patients with incipient and early clinical diabetic nephropathy: effects on albumin excretion rate and nutritional status	Wrong study design
Kahleova 2018 [119]	Nutrition & Diabetes	8(1):58	A plant-based diet in overweight individuals in a 16-week randomized clinical trial: metabolic benefits of plant protein	No additional data to extract
Kahleova 2014 [120]	Cor et Vasa	56(2):e140-e144	Vegetarian vs. conventional diabetic diet - A 1-year follow-up	Other languages
Kahleova 2017 [121]	Journal of the American College of Nutrition	36(5):364-369	The Effect of a Vegetarian vs Conventional Hypocaloric Diabetic Diet on Thigh Adipose Tissue Distribution in Subjects with Type 2 Diabetes: A Randomized Study	Not relevant outcomes
Kahleova 2017 [122]	Diabetes	66 (Supplement 1):A202	The effect of a vegetarian vs. Conventional hypocaloric diabetic diet on thigh adipose tissue distribution in subjects with type 2 diabetes	Not relevant outcomes
Kahleova 2011 [123]	Diabetes	60:A217	Vegetarian diet increases resting energy expenditure more than conventional diet in subjects with type 2 diabetes after aerobic exercise	Not a manuscript
Kahleova 2011 [124]	Diabetologia	54:S359-S360	The effect of vegetarian diet on fatty acid composition of serum phopholipids and the association with insulin sensitivity and visceral fat in subjects with type 2 diabetes	Not a manuscript

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Author, year	Journal	Volume (issue):pages	Title	Exclusion reason
Kahleova 2010 [125]	Diabetologia	53:S380	Vegetarian diet improves plasma concentrations of adipokines and oxidative stress markers more than conventional diabetic diet in subjects with type 2 diabetes	Not a manuscript
Kahleova 2020 [126]	Diabetologia	63(SUPPL 1):S16-S17	A dietary intervention to alter insulin sensitivity, intramyocellular and hepatocellular lipids, postprandial metabolism, and body weight: A 16-week randomised trial	Not a manuscript
Kahleova 2020 [127]	Nutrients	12(10):24	Effects of a Low-Fat Vegan Diet on Gut Microbiota in Overweight Individuals and Relationships with Body Weight, Body Composition, and Insulin Sensitivity. A Randomized Clinical Trial	Wrong patient population
Kahleova 2021 [128]	Clinical Nutrition ESPEN	41:126-128	Effect of a diet intervention on cardiometabolic outcomes: Does race matter? A randomized clinical trial	Wrong patient population
Kahleova 2016 [129]	Nutrition Metabolism & Cardiovascular Diseases	26(5):430-8	The effect of a vegetarian versus conventional hypocaloric diet on serum concentrations of persistent organic pollutants in patients with type 2 diabetes	No additional data to extract
Kahleova 2018 [130]	Nutrients	10(2):09	A Plant-Based Dietary Intervention Improves Beta-Cell Function and Insulin Resistance in Overweight Adults: A 16-Week Randomized Clinical Trial	No additional data to extract
Kahleova 2018 [131]	Nutrients	10(9):1302	A Plant-Based High-Carbohydrate, Low-Fat Diet in Overweight Individuals in a 16-Week Randomized Clinical Trial: The Role of Carbohydrates	Not relevant outcomes
Kahleova 2019 [132]	Nutrients	11(3):615-615	Fat Quantity and Quality, as Part of a Low-Fat, Vegan Diet, Are Associated with Changes in Body Composition, Insulin Resistance, and Insulin Secretion. A 16-Week Randomized Controlled Trial	No additional data to extract
Kahleova 2021 [133]	Clinical Nutrition ESPEN	NA	A plant-based diet in overweight adults in a 16-week randomized clinical trial: The role of dietary acid load	No additional data to extract
Kalinina 1958 [134]	Terapevticheskii Arkhiv	30(7):72-6	[Changes of arterial pressure, pulse, circulation rate and electrocardiographic indices in hypertension following meat and vegetable diets]	Other languages
Katcher 2010 [135]	Annals of Nutrition & Metabolism	56(4):245-52	A worksite vegan nutrition program is well-accepted and improves health-related quality of life and work productivity	Wrong study design
Kestin 1989 [136]	American Journal of Clinical Nutrition	50(2):280-7	Cardiovascular disease risk factors in free-living men: comparison of two prudent diets, one based on lactoovovegetarianism and the other allowing lean meat	Study duration < 8 weeks
Kjeldsen-Kragh 1991 [137]	The Lancet	338(8772):899-902	Controlled trial of fasting and one-year vegetarian diet in rheumatoid arthritis	Not relevant outcomes
Kochan 2019 [138]	Clinical Nutrition	38 (Supplement 1):S233	N-3 Pufa-Enriched Semi-Vegetarian Diet Lowers Ldl-Cholesterol and Uric Acid Levels in Patients with Familial Hypercholesterolemia	Wrong study design
Koertge 2003 [139]	American Journal of Cardiology	91(11):1316-1322	Improvement in medical risk factors and quality of life in women and men with coronary artery disease in the Multicenter Lifestyle Demonstration Project	Wrong study design
Krishnamoorthy 1999 [140]	Indian Heart Journal	51(3):268-74	Diet and coronary artery disease	Wrong study design

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Author, year	Journal	Volume (issue):pages	Title	Exclusion reason
Lasserre 2017 [141]	Annals of Nutrition & Metabolism	71(895)	Effectiveness of a dietotherapeutic intervention on the lipids profile and the nutritional status in breast cancer women	Not a manuscript
Levin 2010 [142]	Public Health Nutrition	13(10):1629-35	A worksite programme significantly alters nutrient intakes	Wrong study design
Mangels 2019 [143]	Vegetarian Journal	38(2):13-13	People with Type 2 Diabetes Benefit from Vegan and "Plant-Based" Diets	Wrong study design
Marniemi 1990 [144]	International Journal of Obesity	14(2):113-25	Long-term effects on lipid metabolism of weight reduction on lactovegetarian and mixed diet	Wrong patient population
Masarei 1984 [145]	American Journal of Clinical Nutrition	40(3):468-478	Effects of a lacto-ovo vegetarian diet on serum concentrations of cholesterol, triglyceride, HDL-C, HDL2-C, HDL3-C, apoprotein-B, and Lp(a)	Study duration < 8 weeks
Medkova 2000 [146]	Klinicheskaia Meditsina	78(1):21-24	Blood lipids and intensity of free radical oxidant processes in elderly patients with ischemic heart disease on antiatherogenic vegetarian diet. [Russian]	Other languages
Medkova 2006 [147]	Voprosy Pitaniia	75(5):49-52	Clinicohemadynamic and biochemical the effect of patients with coronary heart disease use combinated lactoovovegetarian diets and simvastatin. [Russian]	Other languages
Medkova 2002 [148]	Voprosy Pitaniia	71(4):17-19	Estimation of action of lactoovovegetarian and vegan diets on blood level of atherogenic lipoproteins in healthy people. [Russian]	Other languages
Medkova 1997 [149]	Klinicheskaia Meditsina	75(1):28-31	[Balanced vegetarian diet in combined rehabilitation of patients suffering from ischemic heart disease]	Other languages
Mishra 2012 [150]	Diabetes	61:A192	A plant-based diet reduces body weight and cardiovascular risk: The geico multicenter trial	Not a manuscript
Misquitta 2020 [151]	Journal of Alternative and Complementary Medicine	26(11):A9	Preliminary evaluation of the health achieved through lifestyle transformation (HALT) program, a kaiser permanente lifestyle intervention	Not a manuscript
Monica Dinu 2017 [152]	European Journal of Preventive Cardiology	24 (1 Supplement 1):S136	Comparison between Mediterranean and Vegetarian diets for cardiovascular prevention: The CARDIVEG study	Not a manuscript
Moore 2015 [153]	Eating Behaviors	19:33-8	Dietary adherence and acceptability of five different diets, including vegan and vegetarian diets, for weight loss: The New DIETs study	Wrong patient population
Navas-Carretero 2009 [154]	British Journal of Nutrition	102(4):546-553	An oily fish diet increases insulin sensitivity compared to a red meat diet in young iron-deficient women	Wrong intervention
Nichols 2014 [155]	Clinical Advisor	17(8):24-38	Vegetarianism in the fight against CVD	Wrong study design
Nicholson 1999 [156]	American Journal of Clinical Nutrition	70(35):624S-625S	Effect of a low-fat, unrefined, vegan diet on type 2 diabetes	Not a manuscript
Nomura 1989 [157]	Nippon Rinsho - Japanese Journal of Clinical Medicine	47(9):2074-2078	Non-pharmacological treatment of hypertension. [Japanese]	Other languages
Pagliai 2016 [158]	European Heart Journal	37(340)	Randomized controlled dietary intervention trial comparing mediterranean and vegetarian diets for cardiovascular prevention: preliminary results	Not a manuscript

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Author, year	Journal	Volume (issue):pages	Title	Exclusion reason
Pagliai 2017 [159]	Nutrition, Metabolism and Cardiovascular Diseases	27 (1):e30-e31	Comparison between mediterranean and vegetarian diets for cardiovascular prevention: The cardiveg study	Not a manuscript
Pagliai 2019 [160]	Nutrition, Metabolism and Cardiovascular Diseases	29(8):879	Impact of mediterranean vs vegetarian diets on gut microbiota and short chain fatty acids: the CARDIVEG study	Not a manuscript
Pagliai 2020 [161]	European Journal of Nutrition	59(5):2011-2024	Influence of a 3-month low-calorie Mediterranean diet compared to the vegetarian diet on human gut microbiota and SCFA: the CARDIVEG Study	Not relevant outcomes
Phillips 1999 [162]	Journal of the American Dietetic Association	99(8 SUPPL.):S60-S68	Validation of diet composition for the dietary approaches to stop hypertension trial	Wrong intervention
Prescott 1987 [163]	Clinical & Experimental Pharmacology & Physiology	14(3):159-62	Controlled study of the effects of dietary protein on blood pressure in normotensive humans	Wrong patient population
Prescott 1988 [164]	Clinical Science	74(6):665-72	A randomized controlled trial of the effect on blood pressure of dietary non-meat protein versus meat protein in normotensive omnivores	Wrong patient population
Rajaram 2000 [165]	Nutrition	16(7-8):531-3	Health benefits of a vegetarian diet	Wrong study design
Rodriguez-Rodriguez 2007 [166]	Nutrition Research	27(6):313-320	Restricted-energy diets rich in vegetables or cereals improve cardiovascular risk factors in overweight/obese women	Study duration < 8 weeks
Rouse 1984 [167]	Journal of Hypertension	2(3):231-40	Vegetarian diet and blood pressure	Wrong study design
Rouse 1986 [168]	Journal of Hypertension	4(2):241-50	Nutrient intake, blood pressure, serum and urinary prostaglandins and serum thromboxane B2 in a controlled trial with a lacto-ovo-vegetarian diet	Study duration < 8 weeks
Rugulies 1996 [169]	Zeitschrift fur Gesundheitswissenschaften	4(3):234-247	Comprehensive lifestyle changes among patients with CHD and the integration of inpatient and outpatient cardiac rehabilitation: First results of a secondary prevention intervention trial. [German]	Other languages
Sanchez 2019 [170]	Cogent Medicine	6(1)	Multiple lifestyle interventions reverses hypertension	Wrong study design
Sanders 1977 [171]	Proceedings of the Nutrition Society	36(1):43A	Serum cholesterol and triglycerides concentrations in vegans	Wrong study design
SarveshKumar 2016 [172]	International Journal of Pharmaceutical Sciences Review and Research	39(2):81-84	Effect of aerobics exercise and dietary habits on blood pressure in hypertensives	Wrong study design
Schmidt 1997 [173]	Acta Physiologica Scandinavica	161(640):158-162	Changes in cardiovascular risk factors and hormones during a comprehensive residential three month kriya yoga training and vegetarian nutrition	Wrong study design
Sethna 1960 [174]	Indian Journal of Medical Research	225-230	Cholesterol and phospholipids in aged groups	Wrong study design
Singh 1992 [175]	American Journal of Cardiology	70(9):869-874	Effect of fat-modified and fruit- and vegetable-enriched diets on blood lipids in the Indian Diet Heart Study	Wrong intervention

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Author, year	Journal	Volume (issue):pages	Title	Exclusion reason
Sinha 2012 [176]	Indian Journal of Physiology and Pharmacology	1:122	Study of cardiovascular autonomic function in relation to the duration of menopause and vegetarian diet	No full text
Soare 2014 [177]	Nutrition & Metabolism	11(1):39	The effect of the macrobiotic Ma-Pi 2 diet vs. the recommended diet in the management of type 2 diabetes: the randomized controlled MADIAB trial	Study duration < 8 weeks
Spence 2020 [178]	Neurology	94(11):463-464	Lower risk of stroke with a vegetarian diet	Wrong study design
Talreja 2021 [179]	Catheterization and Cardiovascular Interventions	97(SUPPL 1):S109	An investigation of plant-based, mediterranean, paleolithic, and dash diets study (the Va Beach Diet Study)	Not a manuscript
Talreja 2021 [180]	Journal of the American College of Cardiology	77(18 Supplement 1):1478	THE VA-BEACH DIET STUDY: A COMPARISON OF PLANT-BASED, MEDITERRANEAN, PALEOLITHIC AND DASH DIETS ON LIPID AND BIOMETRIC PARAMETERS	Not a manuscript
Talreja 2020 [181]	Circulation	142(SUPPL 3)	Prospective Comparison of Lipid Responses in Plant-based, Mediterranean, Paleolithic an Dash Diets	Wrong study design
Thedford 2011 [182]	Journal of the American Dietetic Association	111(6):816-8	A vegetarian diet for weight management	Wrong study design
Thomson 2005 [183]	European Journal of Nutrition	44(1):18-25	Longitudinal changes in body weight and body composition among women previously treated for breast cancer consuming a high-vegetable, fruit and fiber, low-fat diet	Wrong intervention
Tjiong 1952 [184]	Nederlands Tijdschrift voor Geneeskunde	96(8):472-474	Influence of diet and of some other factors on the blood cholesterol. [Dutch]	Other languages
Toobert 1998 [185]	Patient Education & Counseling	35(3):177-88	Behavioral and psychosocial effects of intensive lifestyle management for women with coronary heart disease	Not relevant outcomes
Turner-McGrievy 2007 [186]	Obesity	15(9):2276-81	A two-year randomized weight loss trial comparing a vegan diet to a more moderate low-fat diet	Wrong patient population
Turner-McGrievy 2004 [187]	Nutrition	20(9):738-46	Effects of a low-fat vegan diet and a Step II diet on macro- and micronutrient intakes in overweight postmenopausal women	Wrong patient population
Turner-McGrievy 2014 [188]	Nutrition Research	34(6):552-8	Low glycemic index vegan or low-calorie weight loss diets for women with polycystic ovary syndrome: a randomized controlled feasibility study	Not relevant outcomes
Turner-McGrievy 2015 [189]	Nutrition	31(2):350-8	Comparative effectiveness of plant-based diets for weight loss: a randomized controlled trial of five different diets	Wrong patient population
Turner-McGrievy 2016 [190]	Journal of Hunger and Environmental Nutrition	11(3):382-395	Differences in Environmental Impact and Food Expenditures of Four Different Plant-based Diets and an Omnivorous Diet: Results of a Randomized, Controlled Intervention	Wrong patient population
Turner-McGrievy 2015 [191]	Nutrition Research	35(2):97-106	Randomization to plant-based dietary approaches leads to larger short-term improvements in Dietary Inflammatory Index scores and macronutrient intake compared with diets that contain meat	Wrong patient population

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Author, year	Journal	Volume (issue):pages	Title	Exclusion reason
Veleba 2016 [192]	Nutrients	8(11):26	"A Vegetarian vs. Conventional Hypocaloric Diet: The Effect on Physical Fitness in Response to Aerobic Exercise in Patients with Type 2 Diabetes." A Parallel Randomized Study	No additional data to extract
Whitten 1995 [193]	Topics in Clinical Nutrition	10(2):27-33	Vegetarian diets and ischemic heart disease	Wrong study design
Wirths 1988 [194]	Zeitschrift fur Ernahrungswissenschaft	27(2):84-100	[Effect of an egg-milk-vegetarian diet on nutritional and blood status. II. Findings of a study on circulation, blood status; discussion]	Other languages
Yarnell 1992 [195]	Annals of Internal Medicine	117(SUPPL. 3):76	Cardioprotective diet after recent myocardial infarction	Not a manuscript
Zeis 2008 [196]	Schweizerische Zeitschrift fur GanzheitsMedizin	20(3):144-148	Health effect of a fruit and vegetable rich diet. Part 1: Cardiovascular diseases. [German]	Other languages
Zemel 1997 [197]	Nutrition Reviews	55(8):303-305	Dietary pattern and hypertension: The DASH study	Wrong intervention
2006 [198]	Environmental Nutrition	29(10):1-1	Vegan diet helps treat type 2 diabetes	Not a manuscript
2019 [199]	Nephrology News & Issues	33(6):34-34	Plant-based diets can lower CV mortality risk	Wrong study design
2019 [200]	Clinical Nutrition ESPEN	30:42-51	Impact of a 12-month Inflammation Management Intervention on the Dietary Inflammatory Index, inflammation, and lipids	Wrong study design
2018 [201]	Gazzetta Medica Italiana Archivio per le Scienze Mediche	177(9):468-474	Effects of the lifestyle modification program to reduce serum lipoprotein(a) and other cardiovascular risk factors in Korean college women	Study duration < 8 weeks

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eTable 13. Reported Conflicts of Interest (COI) and funding sources of included studies

Author, year	COI statement	Funding (e.g. industry/non-industry)	Funding details	COI exists
Aldana *et al.*, 2006 [24]	NI.	Non-industry.	Supported by the Excellence in Academic Medicine Act of the State of Illinois.	NI.
Barnard *et al.*, 2006 [25-28]	NDB is president of the Physicians Committee for Responsible Medicine and the Cancer Project, organizations that promote the use of low-fat, plant-based diets, and writes books and gives lectures ahout therapeutic diets, including vegan diets. He is the author of Dr. Neal Barnard's Program for Reversing Diabetes and receives royalties from its sales. None of the other authors had any personal or financial conflict of interest.	Non-industry.	The study was supported by grant R01 DK059362-01A2 from the National Institute of Diabetes and Digestive and Kidney Diseases and by the Diabetes Action Research and Education Foundation.	Suspicious.
Barnard *et al.*, 2018 [29]	NDB writes books and articles and gives lectures related to nutrition and health, and has received royalties and honoraria from these sources. NDB, SML, and RF are affiliated with the Physicians Committee for Responsible Medicine, which promotes the use of low-fat, plant-based diets and discourages the use of animal-derived, fatty, and sugary foods. LG practices medical nutrition therapy in her private practice, Nutrition Coaching, LLC, and at several worksite wellness centers.	Non-industry.	The study was supported by the Physicians Committee for Responsible Medicine.	No.
Barnard *et al.*, 2021 [30]	All authors except for AT and RH work for the Physicians Committee for Responsible Medicine in Washington, DC, a nonprofit organization providing educational, research, and medical services related to nutrition. Dr. Barnard is an Adjunct Professor of Medicine at the George Washington University School of Medicine. He serves without compensation as President of the Physicians Committee for Responsible Medicine and the Barnard Medical Center in Washington, DC. He writes books and articles and gives lectures related to nutrition and health and has received royalties and honoraria from these sources.	Non-industry.	Funded by the Physicians Committee for Responsible Medicine.	No.
Bunner *et al.*, 2015 [31]	The authors declare no conflict of interest.	Industry	We gratefully acknowledge Impeto Medical for the Sudoscan device. No other funding support was reported.	Unclear.
Burke *et al.*, 2006 [32-34]	NR.	Non-industry.	Funded by the National Institute of Diabetes and Digestive and Kidney Diseases (Grant RO1-DK58631); the Data Management Core of Center for Research in Chronic Disorders, National Institute of Nursing Research (Grant P30-NR03924); the Obesity and Nutrition Research Center of the National Institute of Diabetes and Digestive and Kidney Diseases (Grant DK-046204); the National Center for Research Resources/General Clinical Research Center (Grant 5MO1-RR00056) at the University of Pittsburgh.	NI.

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Author, year	COI statement	Funding (e.g. industry/non-industry)	Funding details	COI exists
Garousi *et al.*, 2021 [35]	The authors declare no conflict of interest.	NA	Received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.	No.
Kahleova *et al.*, 2010 [36]	Nothing to declare.	Non-industry	Supported by grant IGA MZCR NS / 10534-3 from Ministry of Health, Prague, Czech Republic.	No.
Kahleova *et al.*, 2020 [37]	Dr Kahleova reported being director of clinical research at the Physicians Committee, a nonprofit organization that provides nutrition education and research. Dr Rembert reported compensation from the Physicians Committee for Responsible Medicine outside the submitted work. Dr Holubkov reported receiving personal fees from the Physicians Committee for Responsible Medicine during the conduct of the study. Dr Barnard reported to serving as president of the Physicians Committee for Responsible Medicine and Barnard Medical Center; receiving royalties from Hachette Book Group, Penguin Random House, Rodale, and Da Capo publishers; and receiving honoraria from Yale, Rush, GeorgeWashington, Loma Linda, Rockford Universities, Montefiore Medical Center, the Mayo Clinic, Northwell Health, Christiana Care, Oticon, and the National Organization of Professional Athletes. No other disclosures were reported.	Non-industry.	Funded by the Physicians Committee for Responsible Medicine and grants P30 DK-045735 and R01 DK-113984 from the Yale Diabetes Center (Drs Shulman and Petersen). The Yale Diabetes Center had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.	No.
Lee *et al.*, 2016 [38]	The authors have declared that no competing interests exist.	Industry and non-industry	This research was supported by the Korea Health Industry Development Institute, funded by the Ministry of Health & Welfare (A111716-1202-0000100), as well as the Korean Health Technology R&D Project, funded by the Ministry of Health and Welfare, Republic of Korea (HI13C0715 and HI11C1300).	No.
Liao *et al.*, 2007 [39]	NR	Industry	The American Soy Association provided funding for this project.	Probably yes.
Mahon *et al.*, 2007 [40]	NI	Industry and non-industry.	Cattlemen's Beef Board and the National Cattlemen's Beef Association (Centennial, CO), Agriculture Research Program & Lynn Fellowships at Purdue University, and NIH R29 AG13409	Suspicious
Mishra *et al.*, 2013 [41,42]	Dr Neal Barnard gives lectures and writes books on the subject of plant-based diets and receives occasional honoraria and royalties therefrom. The remaining authors declare no conflict of interest.	Non-industry.	This research is supported by Physicians Committee for Responsible Medicine.	No.
Nicholson *et al.*, 1999 [43]	Reported by corresponding author: Two of the investigators were employees of the Physicians Committee for Responsible Medicine, a nonprofit organization providing educational and research services related to nutrition. In addition, Dr. Barnard writes books and gives lectures on health and nutrition and receives royalties and honoraria from these sources.	Non-industry	Supported by a grant from the Diabetes Action Research and Education Foundation, with additional funding from the Physicians Committee for Responsible Medicine.	PN.

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Author, year	COI statement	Funding (e.g. industry/non-industry)	Funding details	COI exists
Ornish *et al.*, 1990 [44,45]	NR	Industry and non-industry.	This study was supported by grants from the National Heart, Lung, and Blood Institute of the National Institutes of Health (ROI HL42554), the Department of Health Services of the State of California (no 1256SC-01), Gerald D. Hines Interests, Houston Endowment Inc, the Henry J. Kaiser Family Foundation. the John E. Fetzer Institute, Continental Airlines, the Enron Foundation, the Nathan Cummings Foundation, the Pritzker Foundation, the First Boston Corporation, Quaker Oats Co., Texas Commerce Bank, Corrine and David Gould, Pacific Presbyterian Medical Center Foundation, General Growth Companies, Arthur Andersen and Co., and others.	NI
Shah *et al.*, 2018 [46,47]	None.	Probably industry_Private charitable trust	The Purjes Foundation (Salt Lake City, UT) was the primary sponsor of the trial and did not contribute to the study design or data analysis.	PN.
Sofi *et al.*, 2018 [48,49]	None.	None.	NA	No.
Tang *et al.*, 2013 [50]	The authors have no conflict of interest.	Industry and non-industry.	National Pork Board; American Egg Board-Egg Nutrition Center; Purdue Ingestive Behavior Research Center.	PN.
Toobert *et al.*, 2000 [51]	NI.	Non-industry	Study was supported in part by grant R29 HL50181 from the National Heart, Lung, and Blood Institute.	NI.
Wright *et al.*, 2017 [52]	NW is employed by the Royal NZ college of GPs, which is a position funded by Health Workforce New Zealand. MS and NW report being directors/shareholders in Plant Based Lifestyles Ltd, which was initiated after the completion of the BROAD study. BD, NW, MS and PMH report being trustees of the Plant Based New Zealand Health Charitable Trust. PMH reports he is a trustee on the Tairāwhiti Traditional and Complementary Therapies Research Charitable Trust. LW reports being director/shareholder in Two Zesty Bananas Ltd, which was initiated after the intervention.	Industry.	Tairāwhiti Traditional and Complementary Therapies Research Trust, the Tairāwhiti Community Services Trust and the J N Williams Memorial Trust. One researcher and author (PMH) is a trustee on TTCTRT, otherwise the funders had no role in study design and conduct; data collection and analysis; decision to publish; or preparation, review and approval of the manuscript.	No.

NA, not applicable; NI, no information; NR, not reported; PN, probably no.

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eTable 14. Primary and secondary outcomes of included studies

Author, year	Primary outcomes	Secondary outcomes
Aldana *et al.*, 2006 [24]	Carotid Ultrasound Measures: Intimamedia thickness measures	Weight, BMI, blood lipids, blood glucose, CRP, ferritin, fibrinogen, medications, diet composition, program adherence, quality of life, and angina
Barnard *et al.*, 2006 [25-28]	HbA1c	Body weight, waist and hip circumference, plasma glucose, plasma cholesterol and triglyceride concentrations, HDL, LDL, urinary albumin, blood pressure, physical activity, dietary intake, dietary acceptability
Barnard *et al.*, 2018 [29]	Body weight, HbA1c, plasma glucose, plasma lipids, urinary albumin, and blood pressure, indices of renal function (serum creatinine, microalbumin)	Dietary intake, physical activity, medication use
Barnard *et al.*, 2021 [30]	Body weight, plasma lipids, insulin sensitivity, metabolism, blood pressure, and body composition (dual X-ray absorptiometry)	Oral glucose insulin sensitivity, and predicted insulin sensitivity indices, dietary intake
Bunner *et al.*, 2015 [31]	Painful symptoms of diabetic neuropathy: pain and sensory symptoms as measured by visual analog 'worst pain' scale, global impression scale, Short Form McGill Pain Questionnaire, Michigan Neuropathy Screening Instrument questionnaire, Neuropathy Total Symptom Score, a weekly pain diary, and Norfolk Quality of Life Questionnaire; disease activity; HbA1c; mood and depression were measured by the Beck Depression Inventory and the Center for Epidemiological Studies Depression revised scale	Body weight, lipid concentrations (TC, LDL-cholesterol, HDL-cholesterol and TG), blood glucose, blood pressure, dietary changes
Burke *et al.*, 2006 [32-34]	Body weight	Lipid profile (TC, HDL-C, LDL-C, and TG), serum glucose, and insulin measurement. Physical measurements included height, weight, waist circumference, and blood pressure. BMI.
Garousi *et al.*, 2021 [35]	A significant decrease in ALT and AST blood levels	Changes in anthropometric values, insulin metabolic markers, lipid profiles, blood pressure, and NAFLD grade
Kahleova *et al.*, 2010 [36]	Insulin sensitivity measured by hyperinsulinaemic isoglycaemic clamp; volume of visceral and subcutaneous fat measured by magnetic resonance imaging; and oxidative stress measured by thiobarbituric acid reactive substances	Weight, waist circumference, blood pressure and heart rate, plasma glucose, HbA1c, plasma immunoreactive insulin and C-peptide concentrations, plasma lipid, plasma concentrations of total adiponectin and resistin, dietary intake, physical activity, quality of life, magnetic resonance images with the calculation of subcutaneous and visceral abdominal fat volume
Kahleova *et al.*, 2020 [37]	Body weight, insulin resistance, postprandial metabolism, and the concentrations of intramyocellular and hepatocellular lipids	Body composition and visceral fat volume, dietary intake, physical activity, medication use, plasma glucose, immunoreactive insulin, and C-peptide concentrations, HbA1c, lipid concentration
Lee *et al.*, 2016 [38]	Change in HbA1c	Dietary intake, body weight, height, waist circumference, blood pressure, fasting blood glucose, blood lipids
Liao *et al.*, 2007 [39]	Weight, waist circumference, body composition, and blood lipid profiles	Blood pressure, biochemical measurements (serum glucose, triacylglycerols, TC, HDL-C, LDL-C, glutamate oxaloacetate transaminase, and glutamate pyruvate transaminase)
Mahon *et al.*, 2007 [40]	Body mass and body composition	Clinical markers of metabolic and cardiovascular diseases: Serum glucose, total cholesterol, HDL cholesterol and triacylglycerol, CRP, plasma insulin, leptin and adiponectin
Mishra *et al.*, 2013 [41,42]	Anthropometric (body weight) and biochemical measures (blood lipids, HbA1c)	Dietary intake, blood pressure

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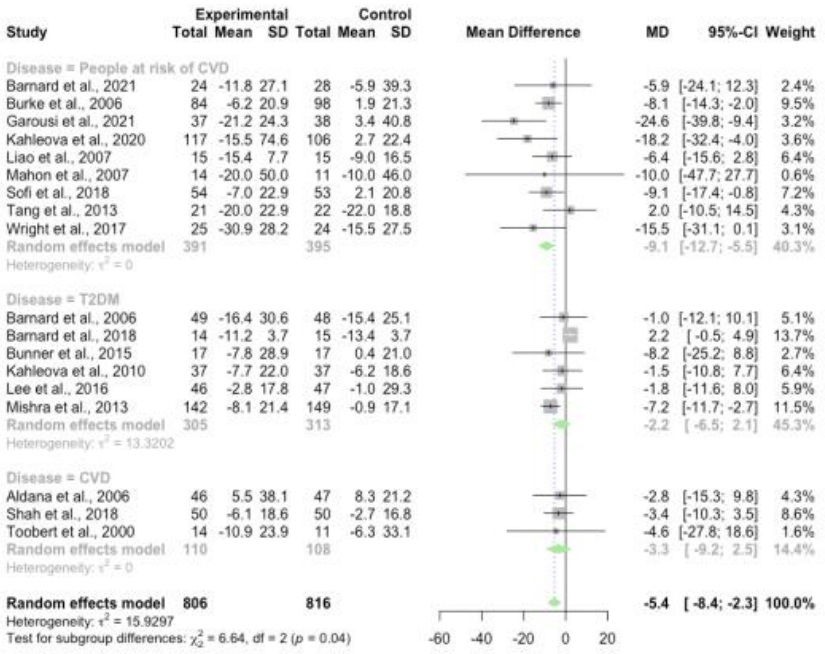
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Author, year	Primary outcomes	Secondary outcomes
Nicholson *et al.*, 1999 [43]	Glycemic (fasting serum glucose, HbA1c) and blood lipid control	Body weight, blood pressure, urinary microalbumin, dietary intake, duration of exercise per week
Ornish *et al.*, 1990 [44,45]	Coronary atherosclerosis: coronary arteriography, selective coronary angiography	Body weight, blood lipid, blood pressure, dietary intake, exercise
Shah *et al.*, 2018 [46,47]	Inflammatory (hs-CRP concentration) and glucometabolic profiles	Anthropometric data, other markers of inflammation, lipid parameters, glycemic markers, endothelial function, dietary intake, quality of life data, and assessment of physical activity. Clinical outcomes: Major adverse cardiovascular events (MACE), Individual components of MACE.
Sofi *et al.*, 2018 [48,49]	Total body weight, BMI, and fat mass.	The circulating cardiovascular risk parameters: lipid profile, glycemic profile, oxidative stress profile, and inflammatory profile
Tang *et al.*, 2013 [50]	Changes in weight, body composition, indices of metabolic syndrome (blood pressure, blood lipid), resting energy expenditure, appetite, selected appetite hormones (insulin, leptin, ghrelin), whole body energy expenditure, and body composition (fat mass and fat-free mass) changes.	Serum insulin concentration, insulin resistance (HOMA-IR), kidney disease risk factor (GFR), total protein intake, dietary intake, the effects of meal frequency on appetite by asking the men to frequently rate their appetite on days that they purposefully eat 3 vs. 6 times/day.
Toobert *et al.*, 2000 [51]	Cardiovascular risk factors: blood lipid, blood pressure	Program adherence (the dietary, stress management, and physical activity changes); changes in body mass, hypolipidemic and anti hypertensive medications; angina symptoms and quality of life
Wright *et al.*, 2017 [52]	BMI and cholesterol	Changes in medication usage, quality of life, cardiovascular risk factors, cardiovascular events, or progression to surgery, and transfer to a higher level of care.

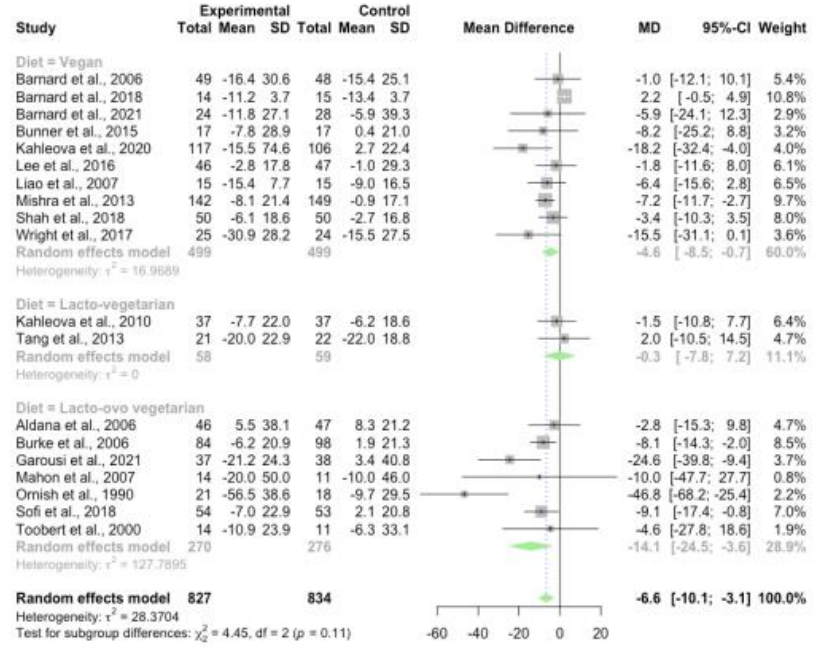
ALT, aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CHD, coronary heart disease; CRP, C-reactive protein; CVD, cardiovascular disease; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; LF, low-fat; MI, myocardial infarction; NAFLD, non-alcoholic fatty liver disease; NR, not reported; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglyceride

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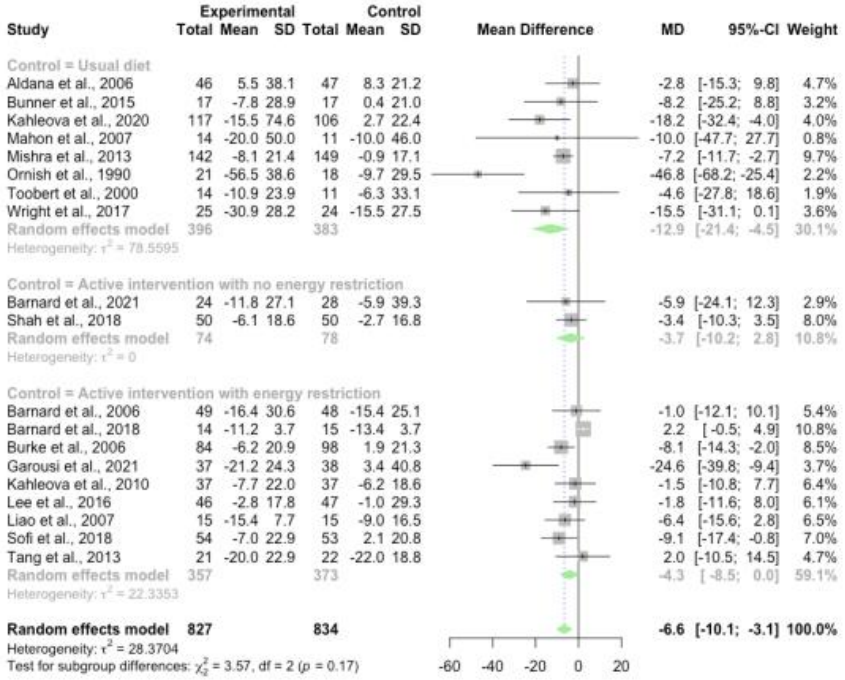


eFigure 1. Random effects model meta-analysis for changes in LDL-cholesterol concentrations comparing vegetarian diets intervention and all comparison diets, grouped by disease status of participants excluding Ornish *et al.*. CI, confidence interval; CVD, cardiovascular disease; MD, mean difference; SD, standard deviation; T2DM, type 2 diabetes mellitus.

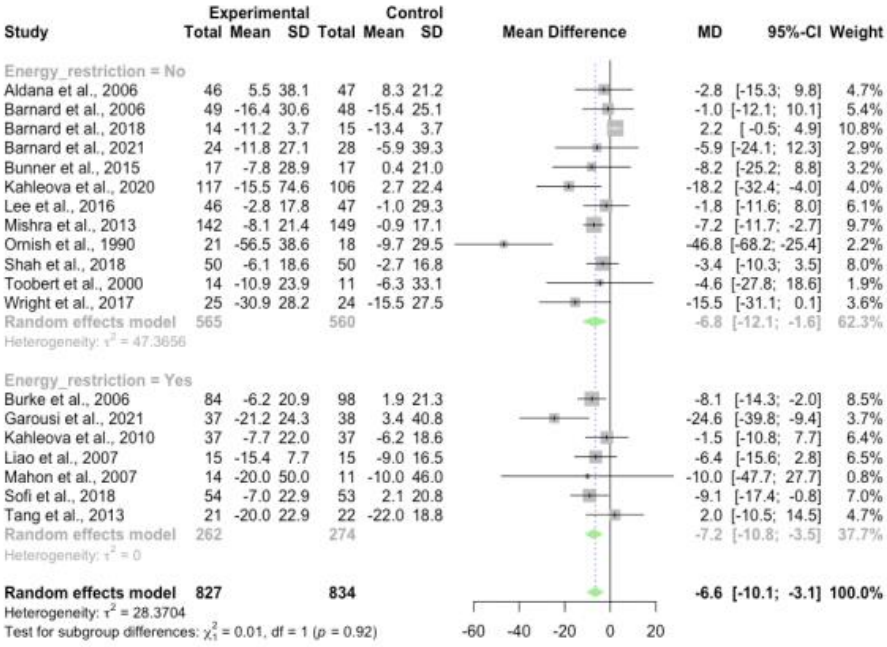


eFigure 2. Random effects model meta-analysis for changes in LDL-cholesterol concentrations comparing vegetarian diets intervention and all comparison diets, grouped by vegetarian diets. CI, confidence interval; MD, mean difference; SD, standard deviation.

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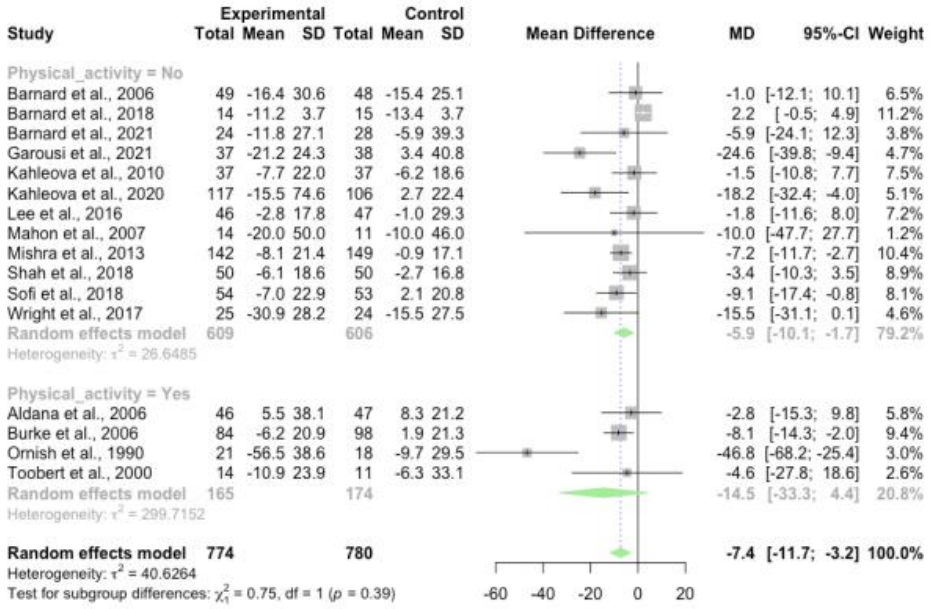


eFigure 3. Random effects model meta-analysis for changes in LDL-cholesterol concentrations comparing vegetarian diets intervention and all comparison diets, grouped by control diets. CI, confidence interval; MD, mean difference; SD, standard deviation.

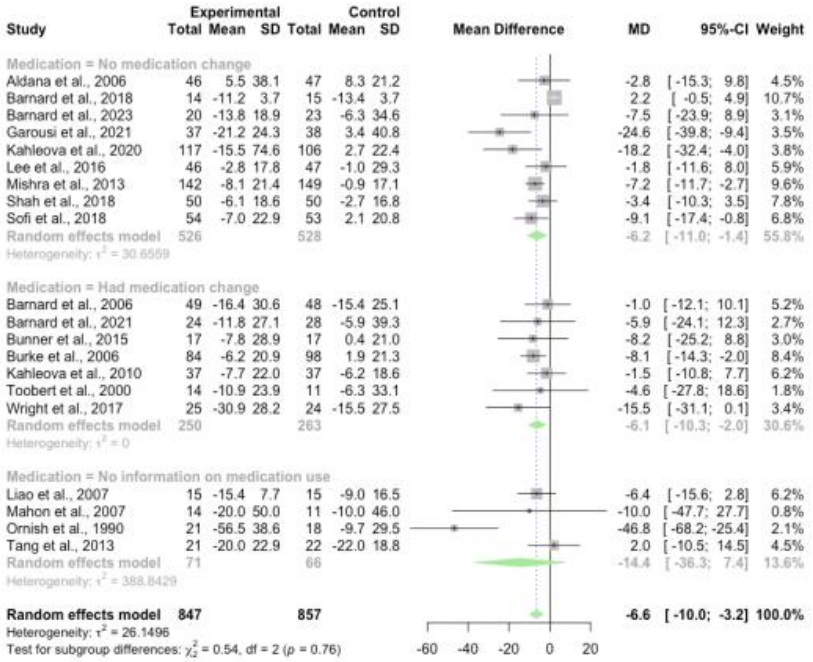


eFigure 4. Random effects model meta-analysis for changes in LDL-cholesterol concentrations comparing vegetarian diets intervention and all comparison diets, grouped by energy restriction. CI, confidence interval; MD, mean difference; SD, standard deviation.

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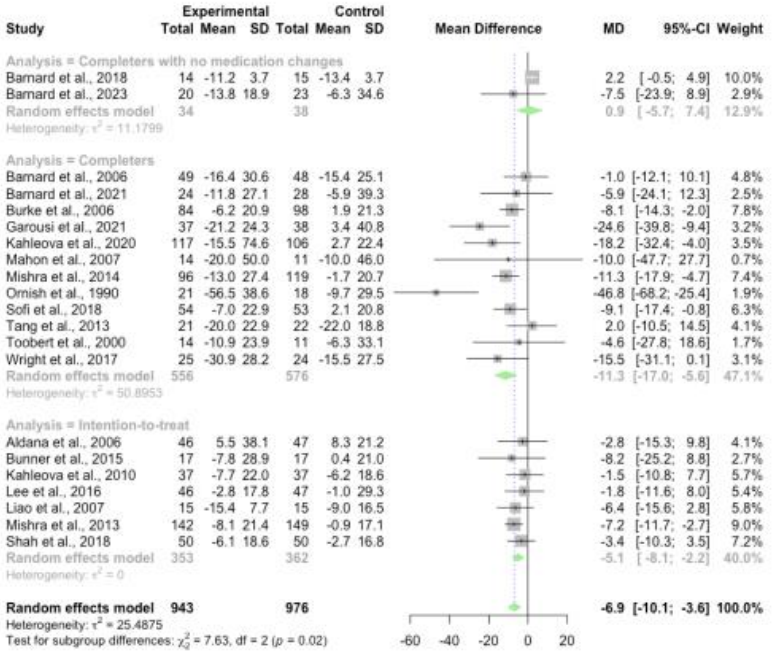


eFigure 5. Random effects model meta-analysis for changes in LDL-cholesterol concentrations comparing vegetarian diets intervention and all comparison diets, grouped by physical activity. CI, confidence interval; MD, mean difference; SD, standard deviation.

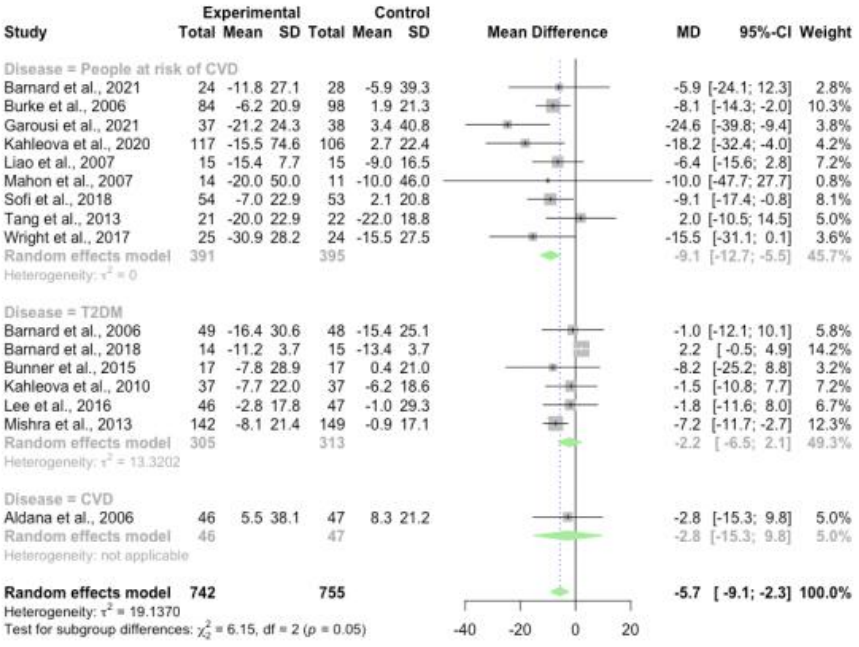


eFigure 6. Random effects model meta-analysis for changes in LDL-cholesterol concentrations comparing vegetarian diets intervention and all comparison diets, grouped by medication use. CI, confidence interval; MD, mean difference; SD, standard deviation.

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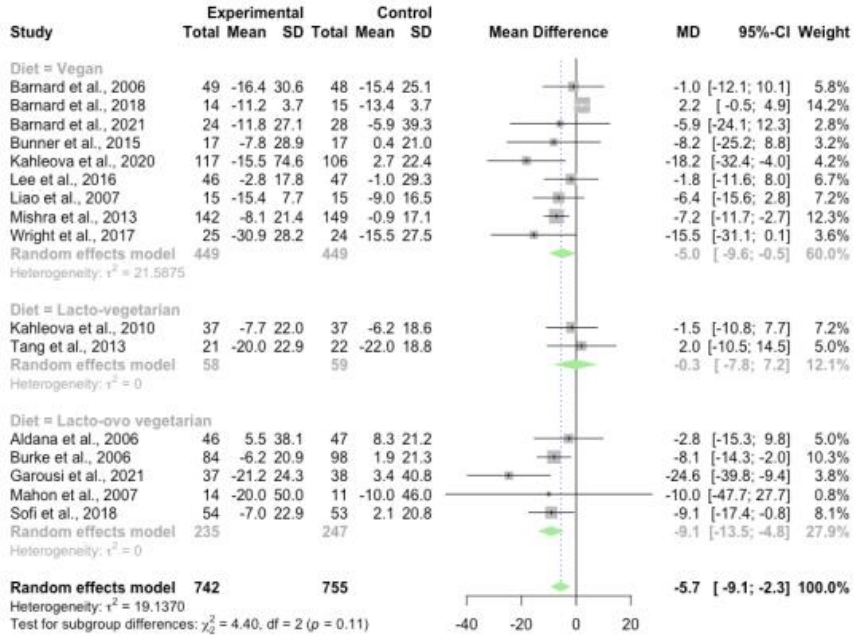


eFigure 7. Random effects model meta-analysis for changes in LDL-cholesterol concentrations comparing vegetarian diets intervention and all comparison diets, grouped by analysis method. CI, confidence interval; MD, mean difference; SD, standard deviation.

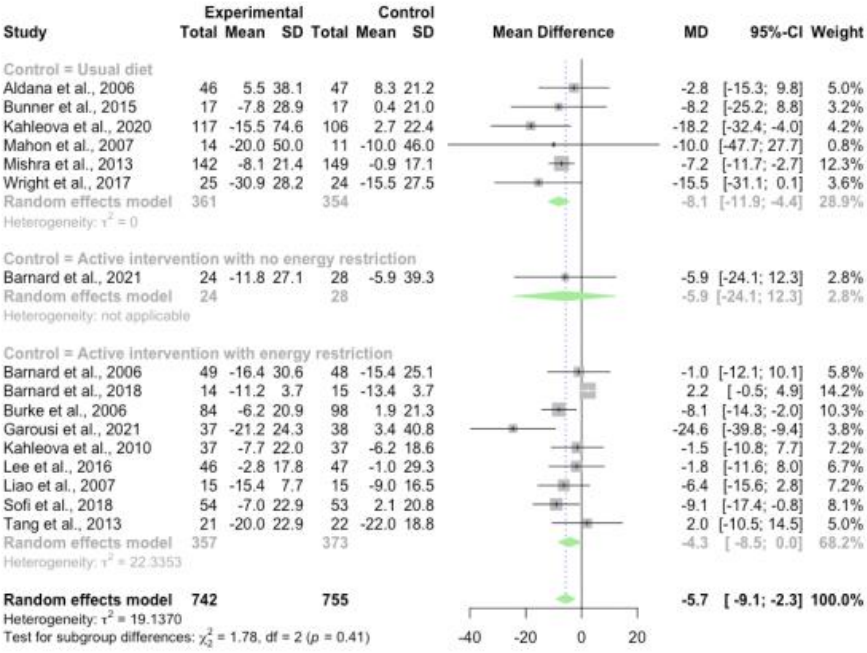


eFigure 8. Random effects model meta-analysis for changes in LDL-cholesterol concentrations comparing vegetarian diets intervention and all comparison diets, grouped by disease status of participants excluding imputed data. CI, confidence interval; CVD, cardiovascular disease; MD, mean difference; SD, standard deviation; T2DM, type 2 diabetes mellitus.

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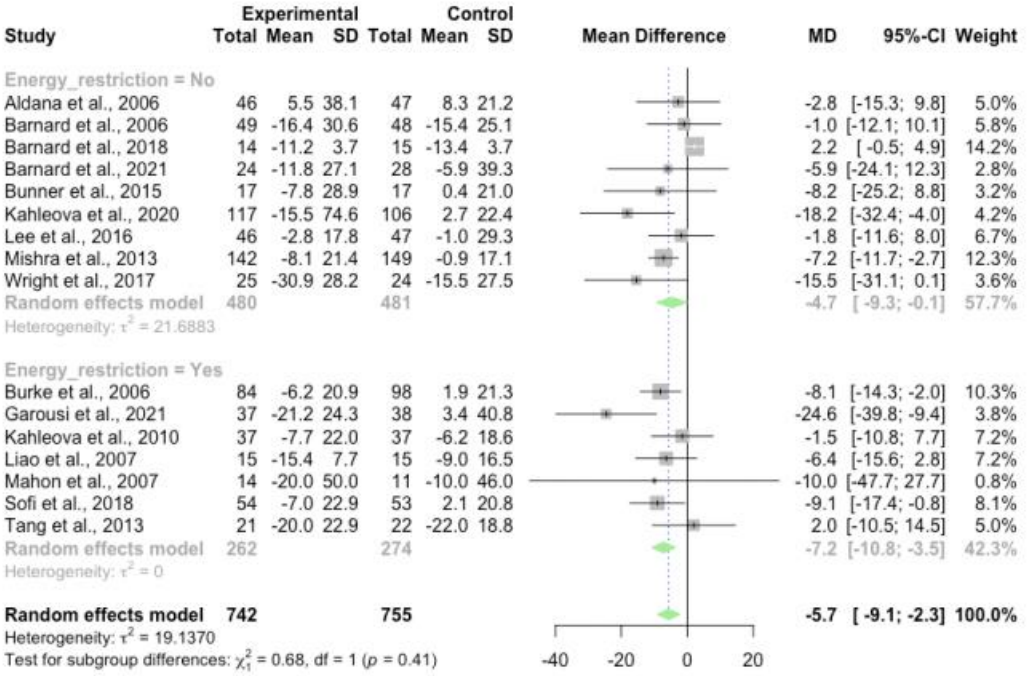


eFigure 9. Random effects model meta-analysis for changes in LDL-cholesterol concentrations comparing vegetarian diets intervention and all comparison diets, grouped by various vegetarian diets excluding imputed data. CI, confidence interval; MD, mean difference; SD, standard deviation.

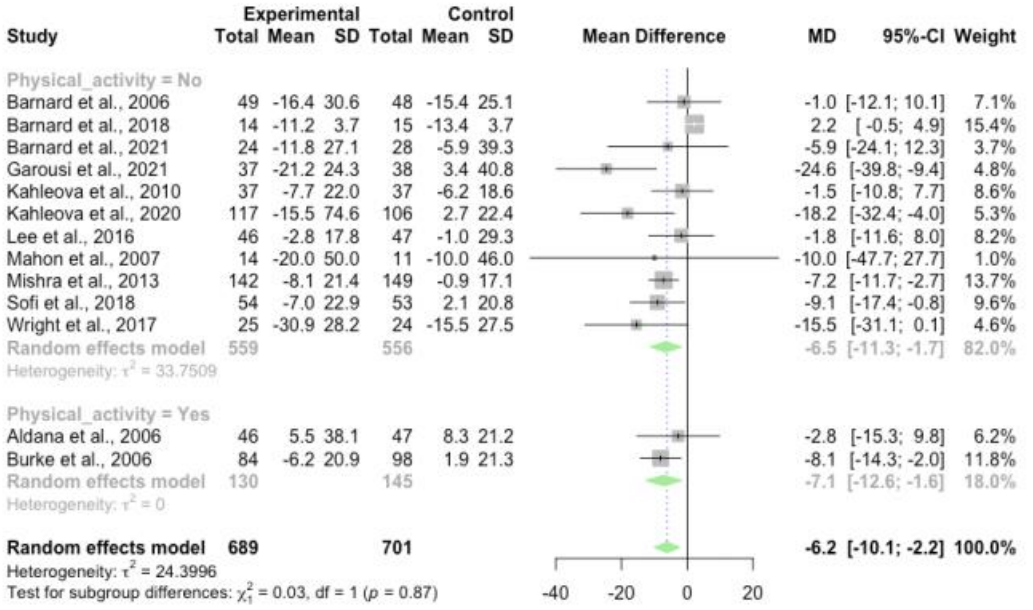


eFigure 10. Random effects model meta-analysis for changes in LDL-cholesterol concentrations comparing vegetarian diets intervention and all comparison diets, grouped by control diets excluding imputed data. CI, confidence interval; MD, mean difference; SD, standard deviation.

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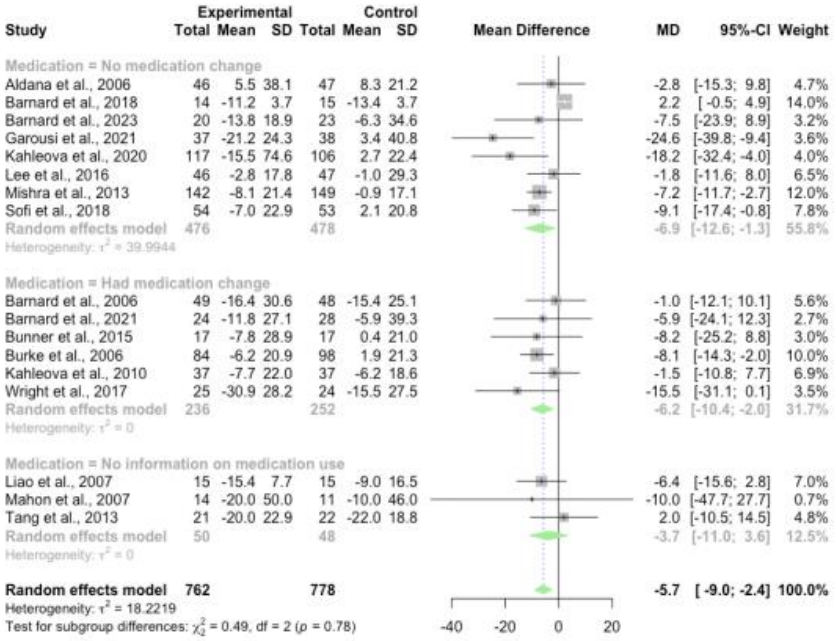


eFigure 11. Random effects model meta-analysis for changes in LDL-cholesterol concentrations comparing vegetarian diets intervention and all comparison diets, grouped by energy restriction excluding imputed data. CI, confidence interval; MD, mean difference; SD, standard deviation.

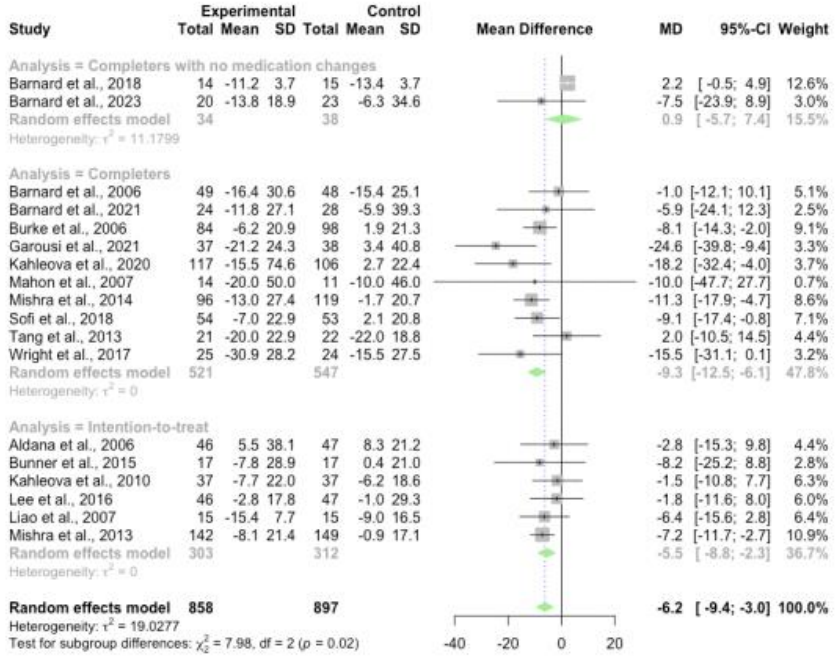


eFigure 12. Random effects model meta-analysis for changes in LDL-cholesterol concentrations comparing vegetarian diets intervention and all comparison diets, grouped by physical activity excluding imputed data. CI, confidence interval; MD, mean difference; SD, standard deviation.

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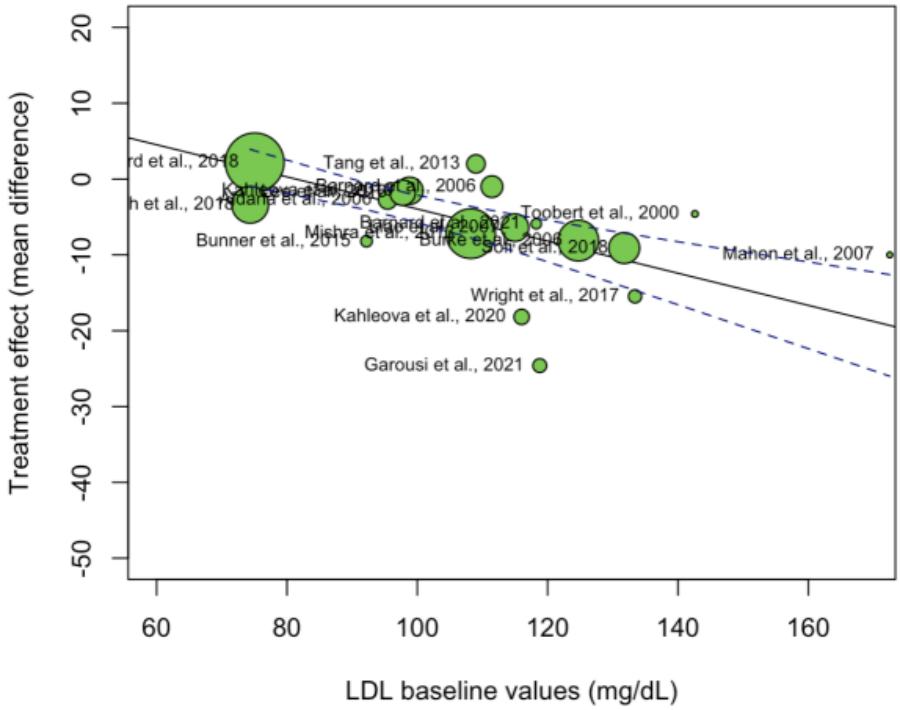


eFigure 13. Random effects model meta-analysis for changes in LDL-cholesterol concentrations comparing vegetarian diets intervention and all comparison diets, grouped by medication use excluding imputed data. CI, confidence interval; MD, mean difference; SD, standard deviation.

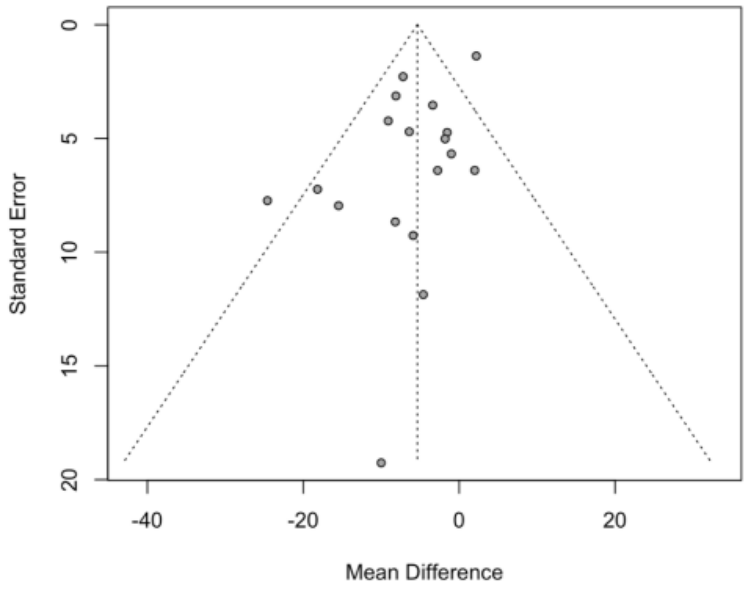


eFigure 14. Random effects model meta-analysis for changes in LDL-cholesterol concentrations comparing vegetarian diets intervention and all comparison diets, grouped by analysis method excluding imputed data. CI, confidence interval; MD, mean difference; SD, standard deviation.

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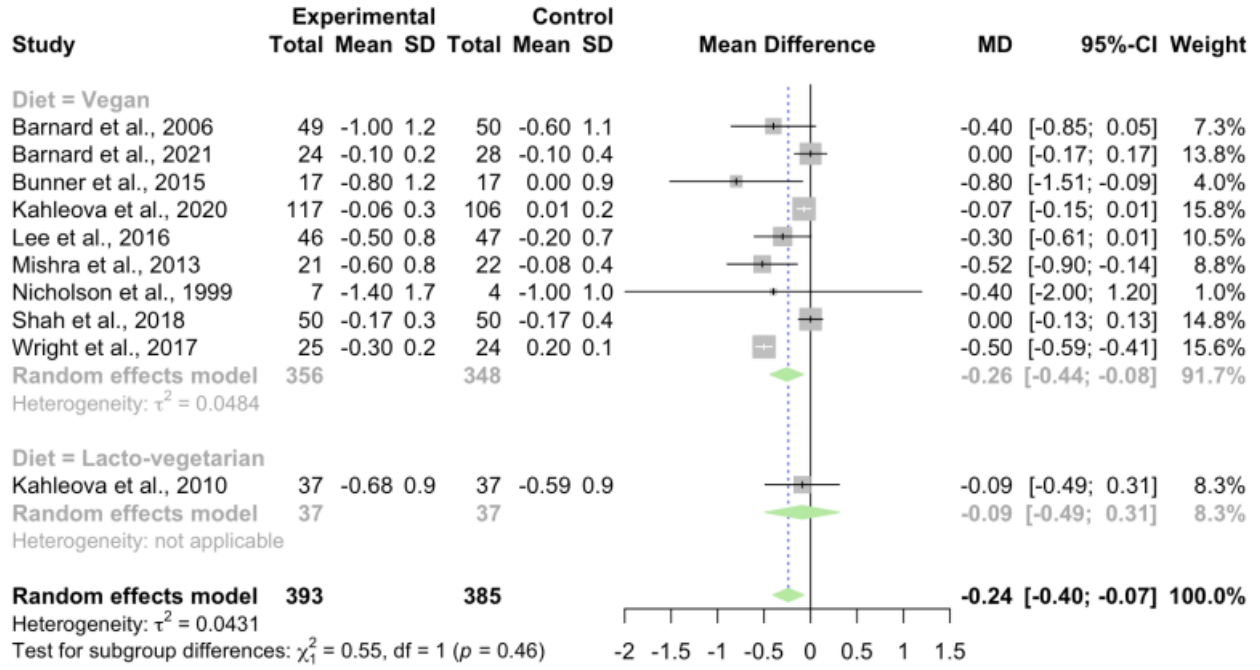


eFigure 15. Treatment effect of LDL-C across increasing levels of baseline LDL-C (mg/dL)

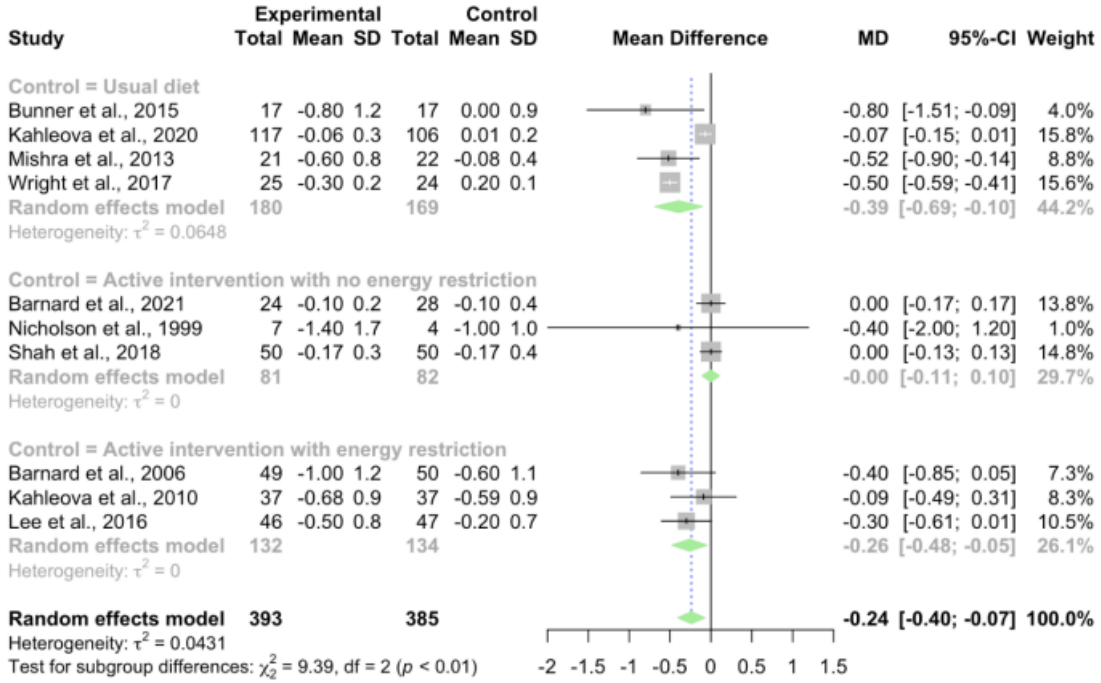


eFigure 16. Funnel plot of LDL-C for risk of publication bias. Mean change in LDL-C plotted against the SE of the mean change. The plot appears fairly symmetrical.

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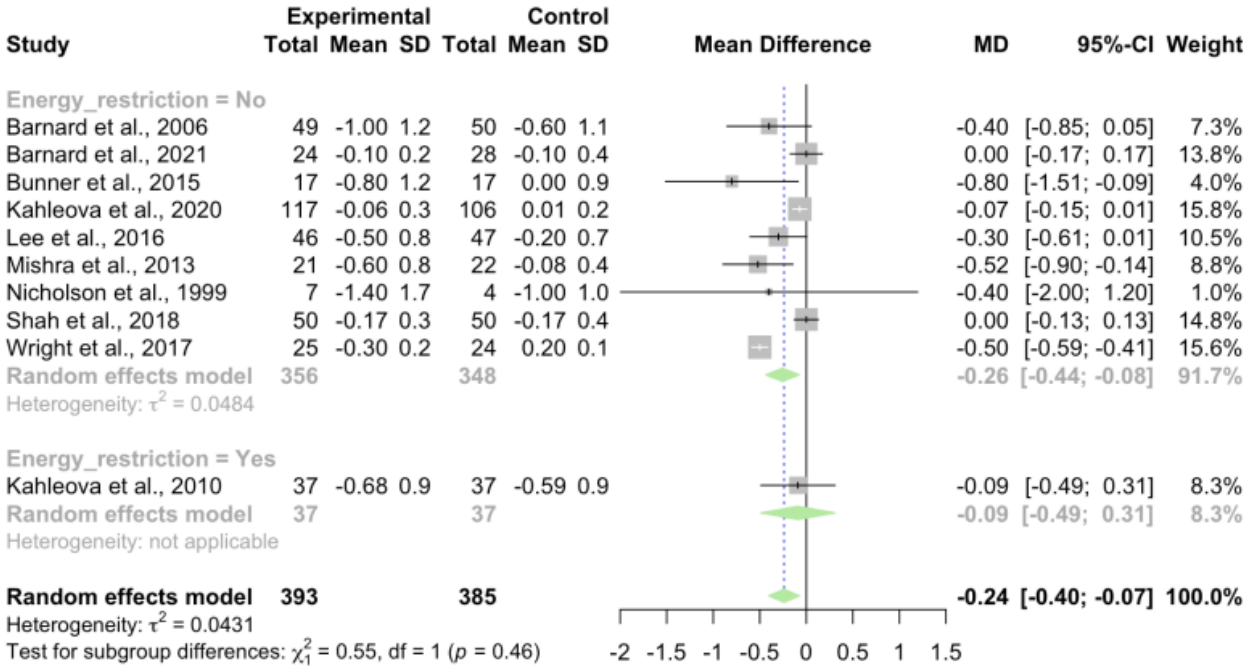


eFigure 17. Random effects model meta-analysis for changes in HbA1c comparing vegetarian diets intervention and all comparison diets, grouped by vegetarian diets. CI, confidence interval; CVD, cardiovascular disease; MD, mean difference; SD, standard deviation; T2DM, type 2 diabetes mellitus.

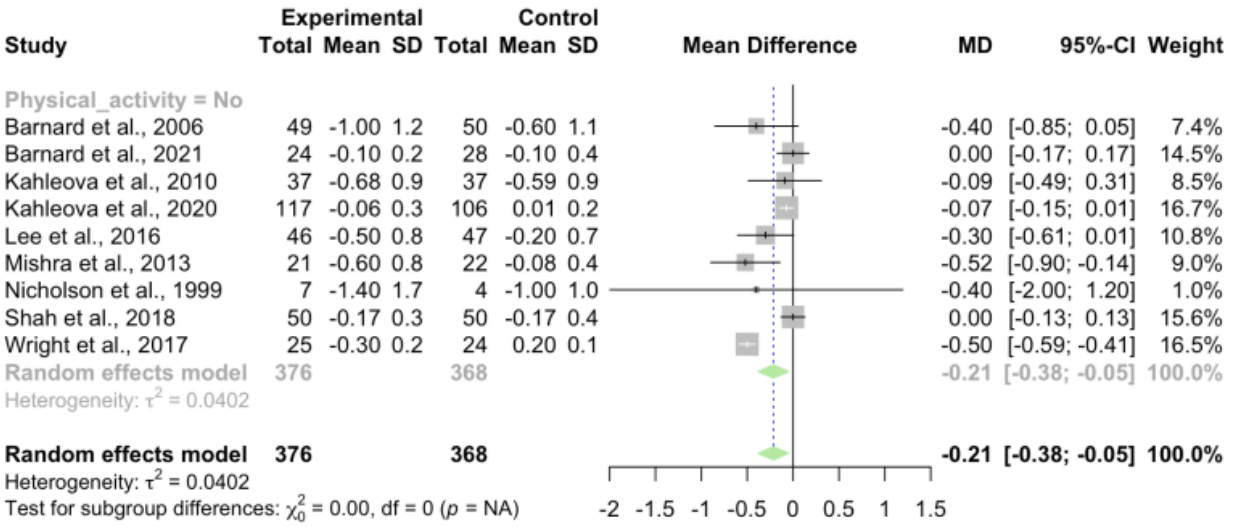


eFigure 18. Random effects model meta-analysis for changes in HbA1c comparing vegetarian diets intervention and all comparison diets, grouped by control diets. CI, confidence interval; MD, mean difference; SD, standard deviation.

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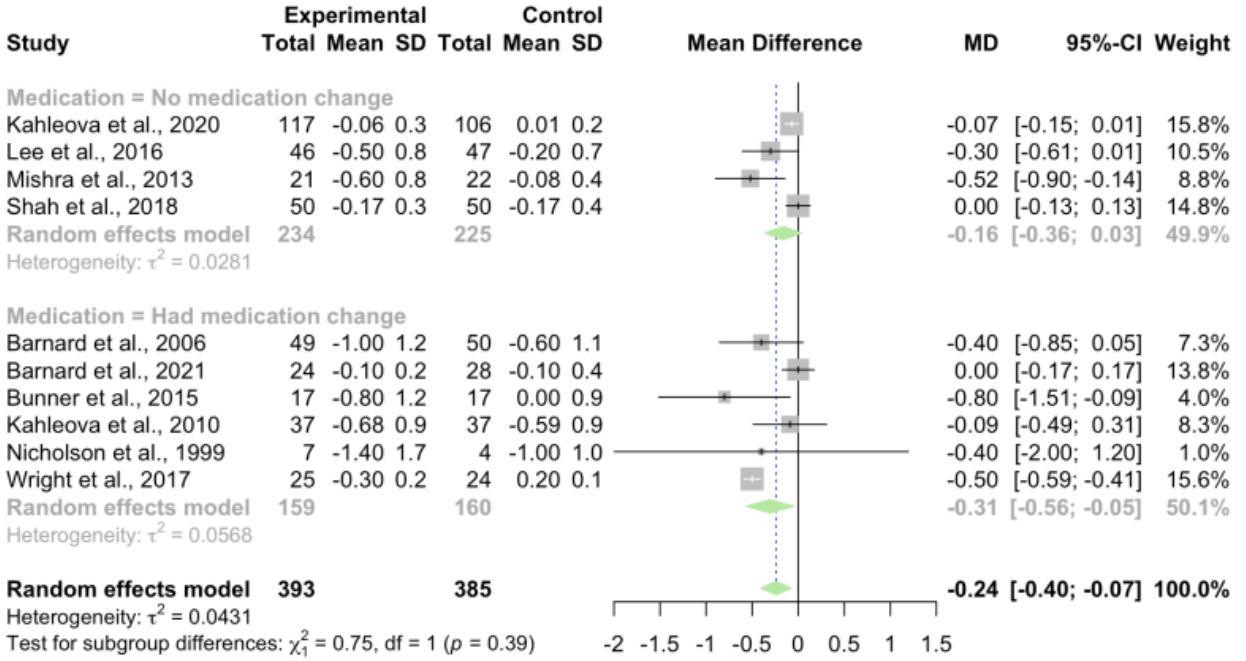


eFigure 19. Random effects model meta-analysis for changes in HbA1c comparing vegetarian diets intervention and all comparison diets, grouped by energy restriction. CI, confidence interval; MD, mean difference; SD, standard deviation.



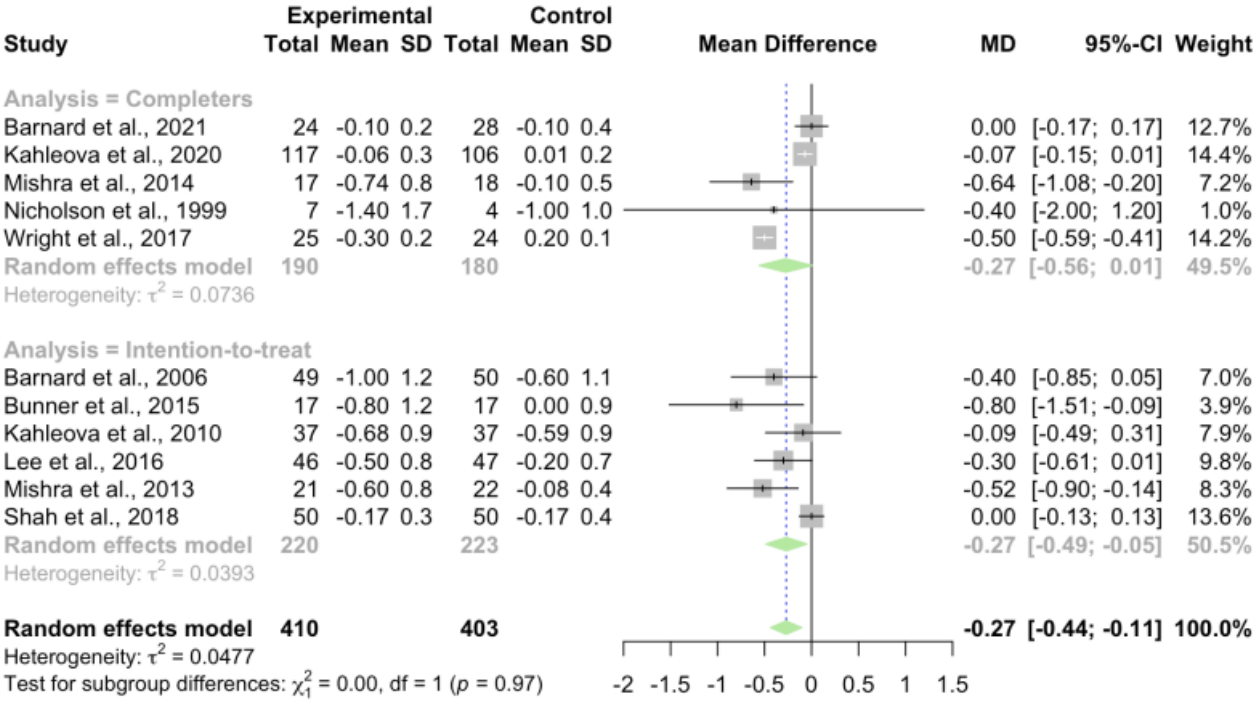
eFigure 20. Random effects model meta-analysis for changes in HbA1c comparing vegetarian diets intervention and all comparison diets, grouped by physical activity. CI, confidence interval; MD, mean difference; SD, standard deviation.

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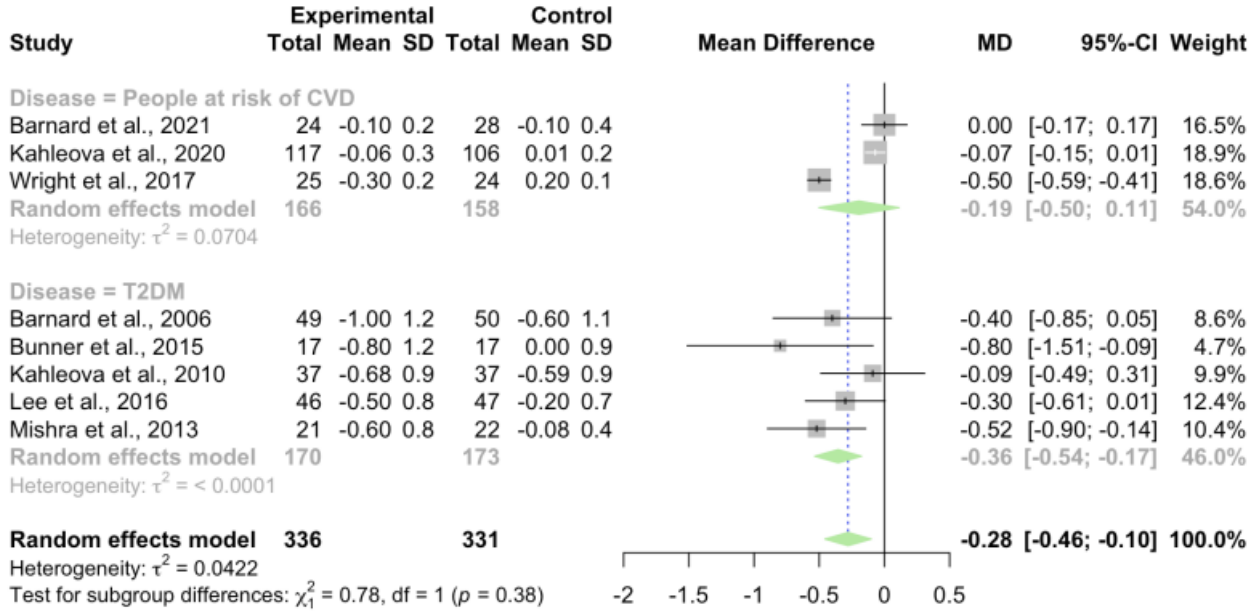


eFigure 21. Random effects model meta-analysis for changes in HbA1c comparing vegetarian diets intervention and all comparison diets, grouped by medication use. CI, confidence interval; MD, mean difference; SD, standard deviation.

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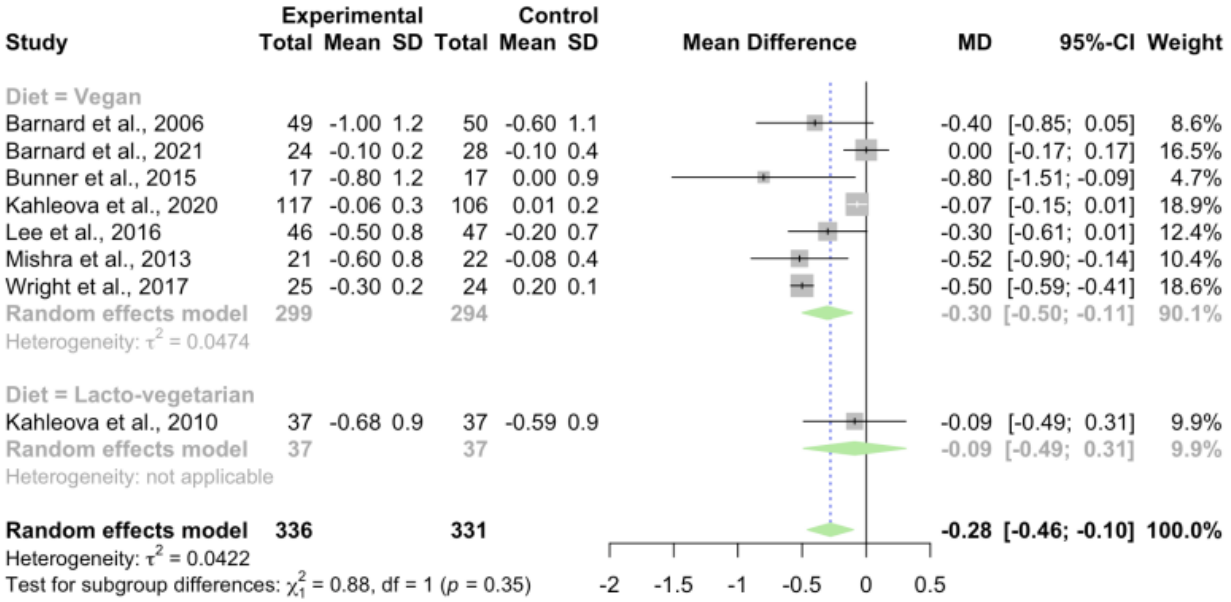


eFigure 22. Random effects model meta-analysis for changes in HbA1c comparing vegetarian diets intervention and all comparison diets, grouped by analysis method. CI, confidence interval; MD, mean difference; SD, standard deviation.

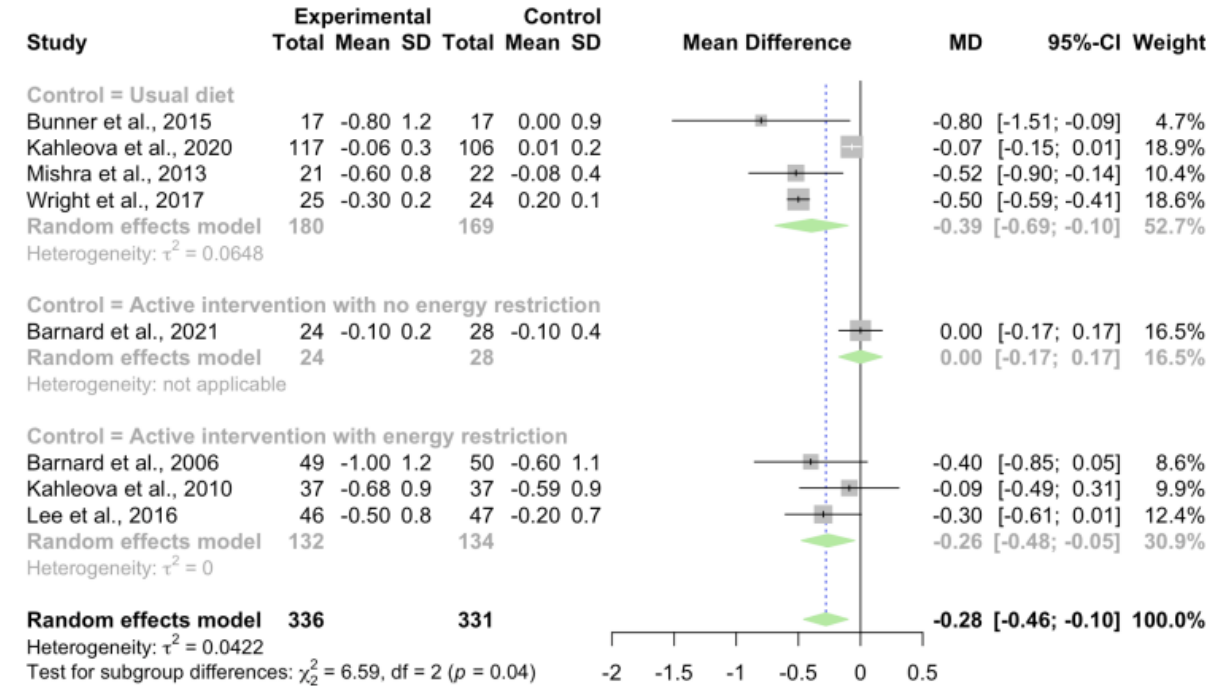


eFigure 23. Random effects model meta-analysis for changes in HbA1c comparing vegetarian diets intervention and all comparison diets, grouped by disease status of participants excluding imputed data. CI, confidence interval; CVD, cardiovascular disease; MD, mean difference; SD, standard deviation; T2DM, type 2 diabetes mellitus.

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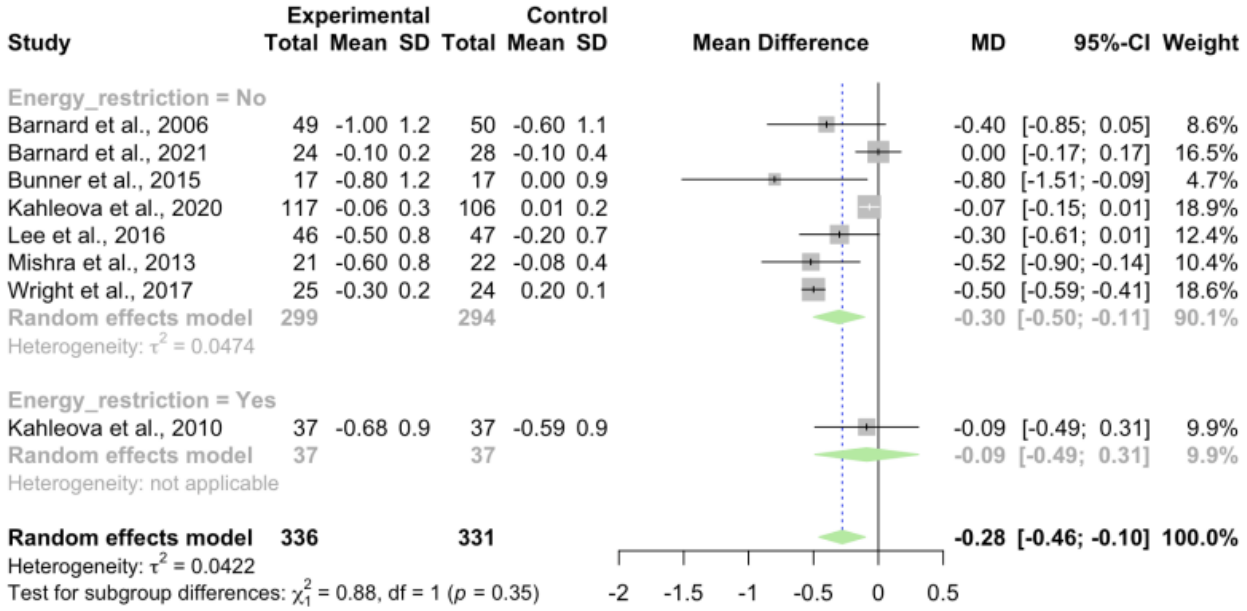


eFigure 24. Random effects model meta-analysis for changes in HbA1c comparing vegetarian diets intervention and all comparison diets, grouped by various vegetarian diets excluding imputed data. CI, confidence interval; MD, mean difference; SD, standard deviation.

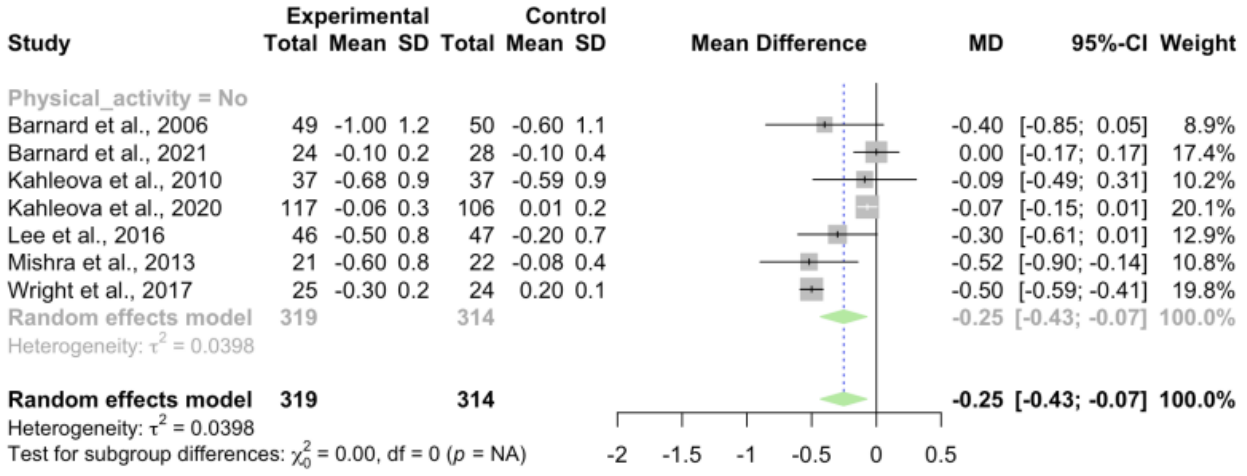


eFigure 25. Random effects model meta-analysis for changes in HbA1c comparing vegetarian diets intervention and all comparison diets, grouped by control diets excluding imputed data. CI, confidence interval; MD, mean difference; SD, standard deviation.

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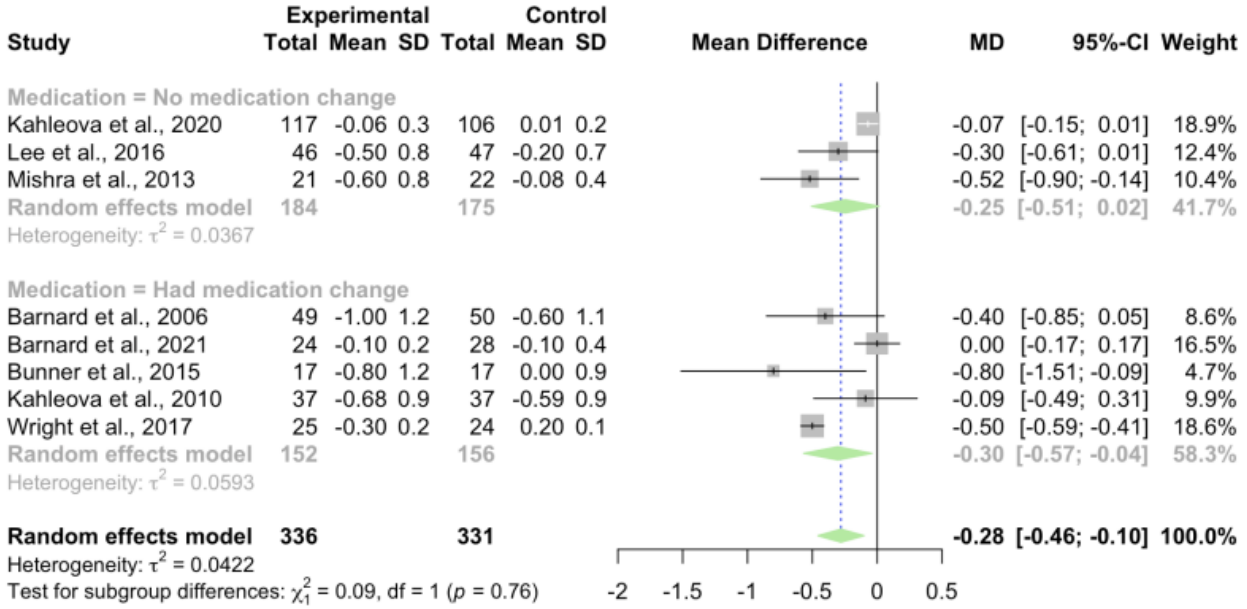


eFigure 26. Random effects model meta-analysis for changes in HbA1c comparing vegetarian diets intervention and all comparison diets, grouped by energy restriction excluding imputed data. CI, confidence interval; MD, mean difference; SD, standard deviation.

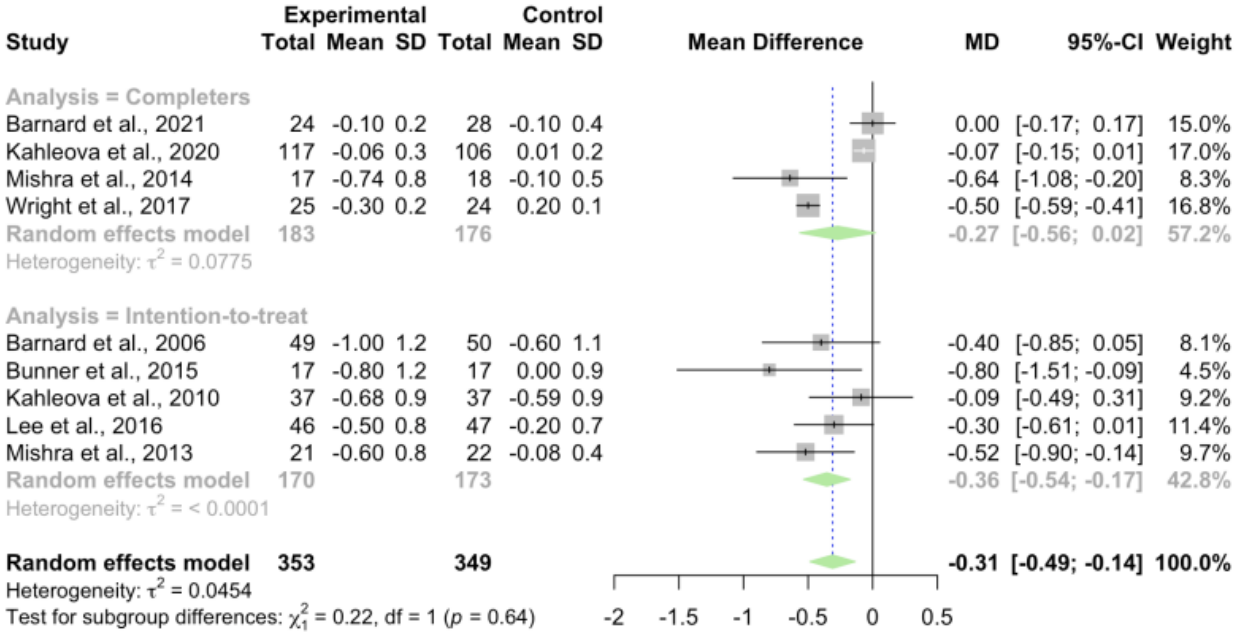


eFigure 27. Random effects model meta-analysis for changes in HbA1c comparing vegetarian diets intervention and all comparison diets, grouped by physical activity excluding imputed data. CI, confidence interval; MD, mean difference; SD, standard deviation.

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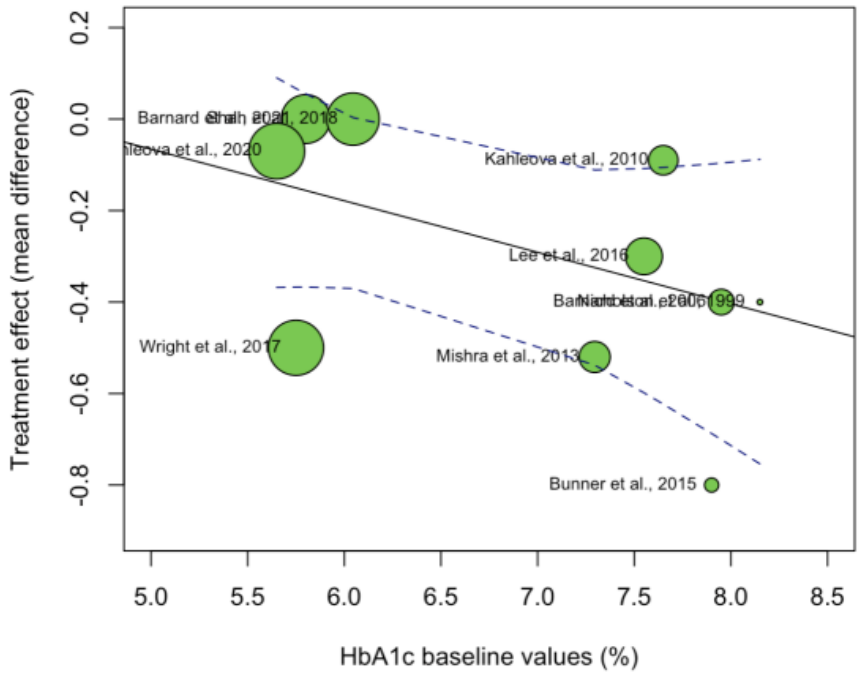


eFigure 28. Random effects model meta-analysis for changes in HbA1c comparing vegetarian diets intervention and all comparison diets, grouped by medication use excluding imputed data. CI, confidence interval; MD, mean difference; SD, standard deviation.

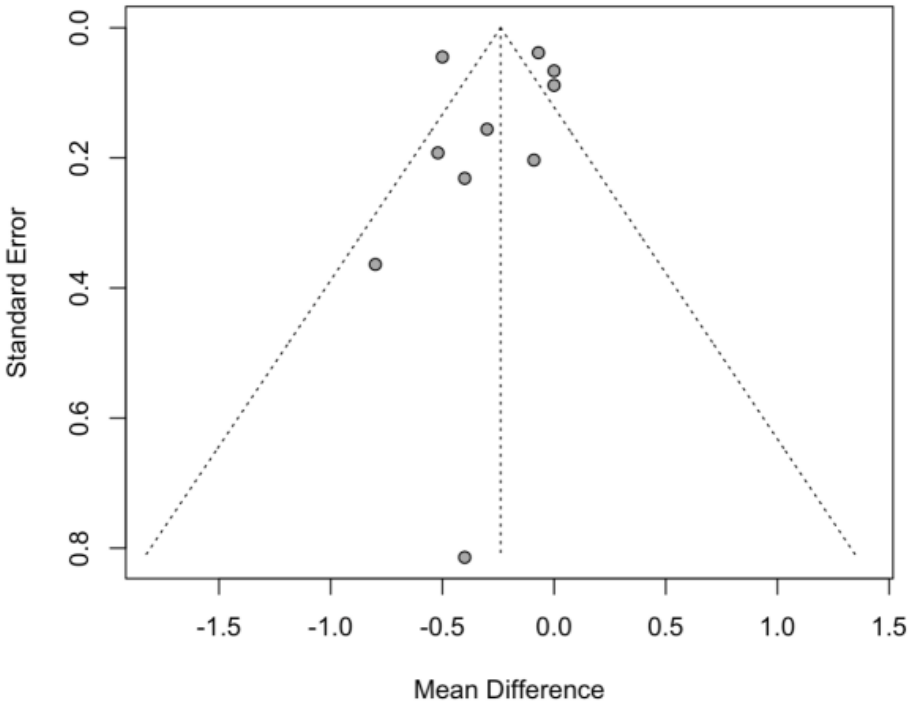


eFigure 29. Random effects model meta-analysis for changes in HbA1c comparing vegetarian diets intervention and all comparison diets, grouped by analysis method excluding imputed data. CI, confidence interval; MD, mean difference; SD, standard deviation.

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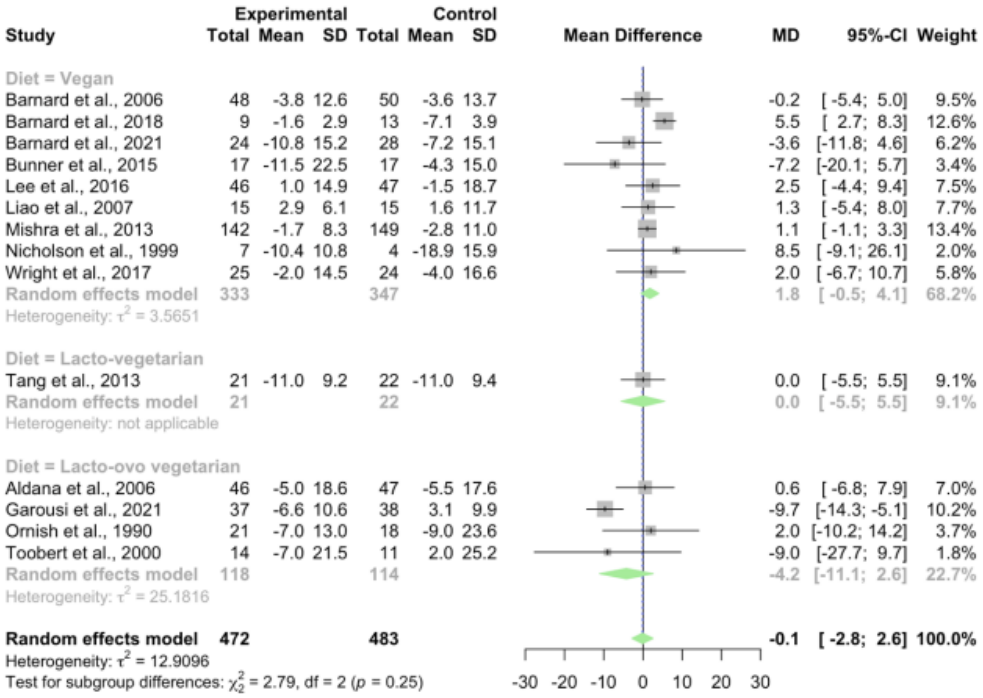


eFigure 30. Treatment effect of HbA1c across increasing levels of baseline HbA1c (%)

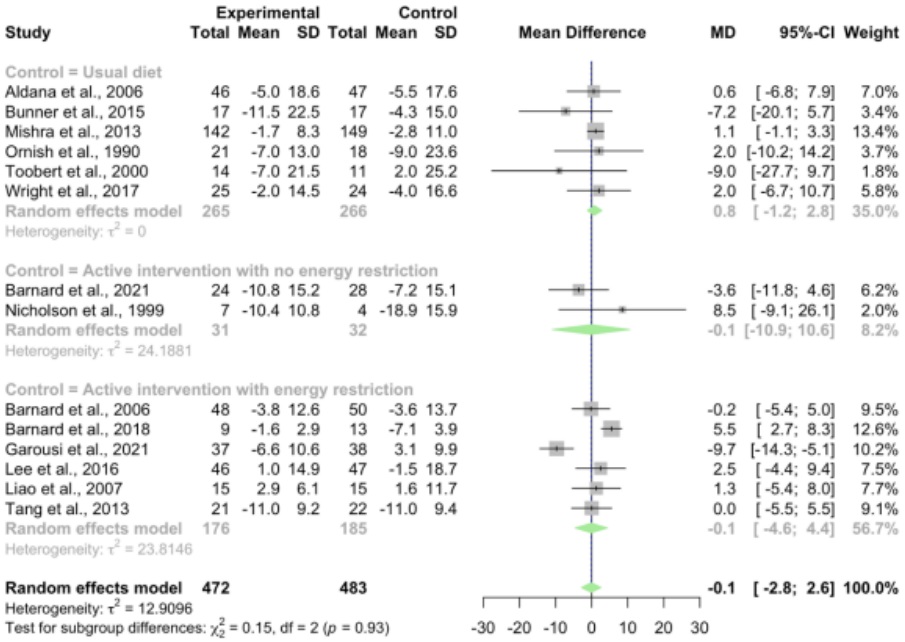


eFigure 31. Funnel plot of HbA1c for risk of publication bias. Mean change in HbA1c plotted against the SE of the mean change. The plot appears fairly symmetrical.

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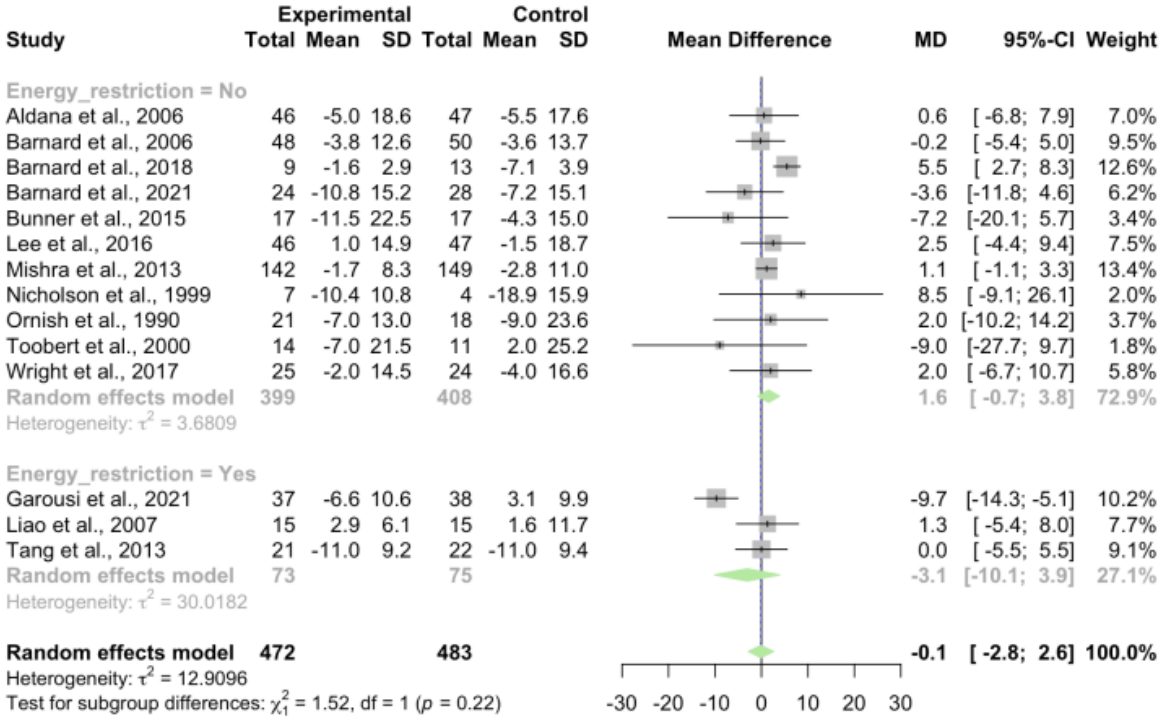


eFigure 32. Random effects model meta-analysis for changes in systolic blood pressure comparing vegetarian diets intervention and all comparison diets, grouped by vegetarian diets. CI, confidence interval; MD, mean difference; SD, standard deviation.

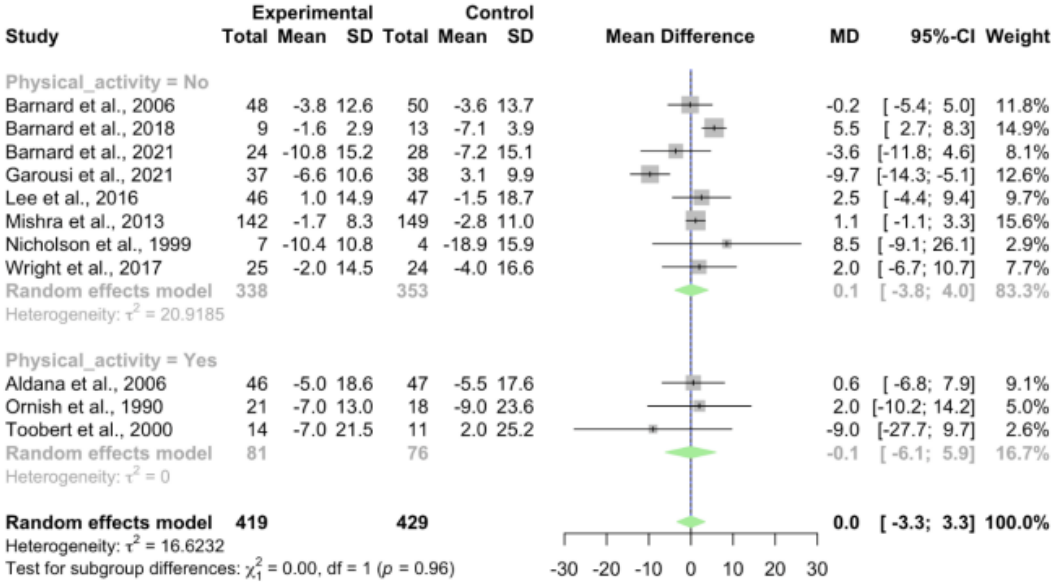


eFigure 33. Random effects model meta-analysis for changes in systolic blood pressure comparing vegetarian diets intervention and all comparison diets, grouped by control diets. CI, confidence interval; MD, mean difference; SD, standard deviation.

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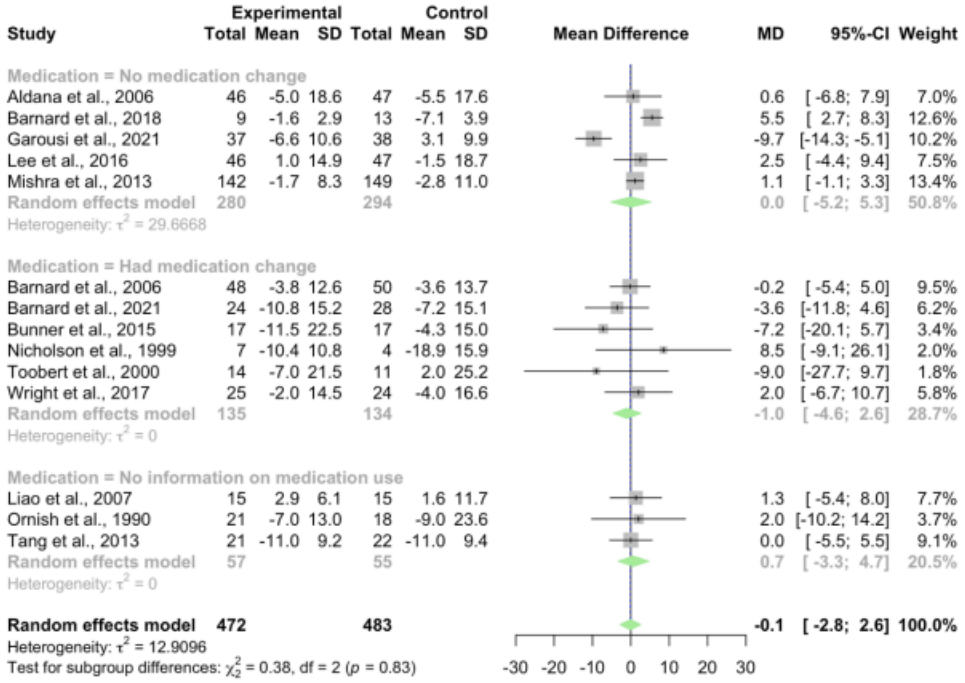


eFigure 34. Random effects model meta-analysis for changes in systolic blood pressure comparing vegetarian diets intervention and all comparison diets, grouped by energy restriction. CI, confidence interval; MD, mean difference; SD, standard deviation.

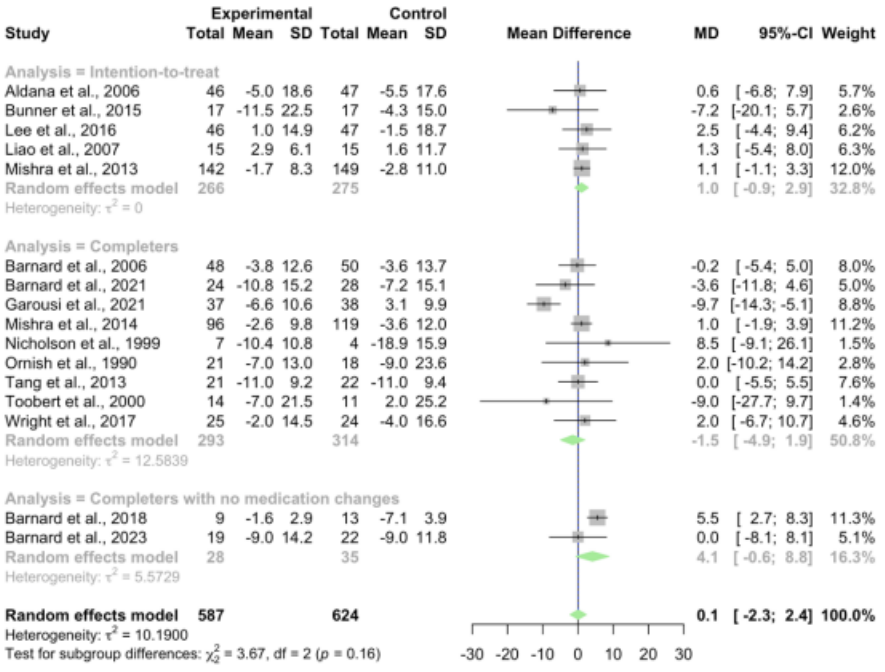


eFigure 35. Random effects model meta-analysis for changes in systolic blood pressure comparing vegetarian diets intervention and all comparison diets, grouped by physical activity. CI, confidence interval; MD, mean difference; SD, standard deviation.

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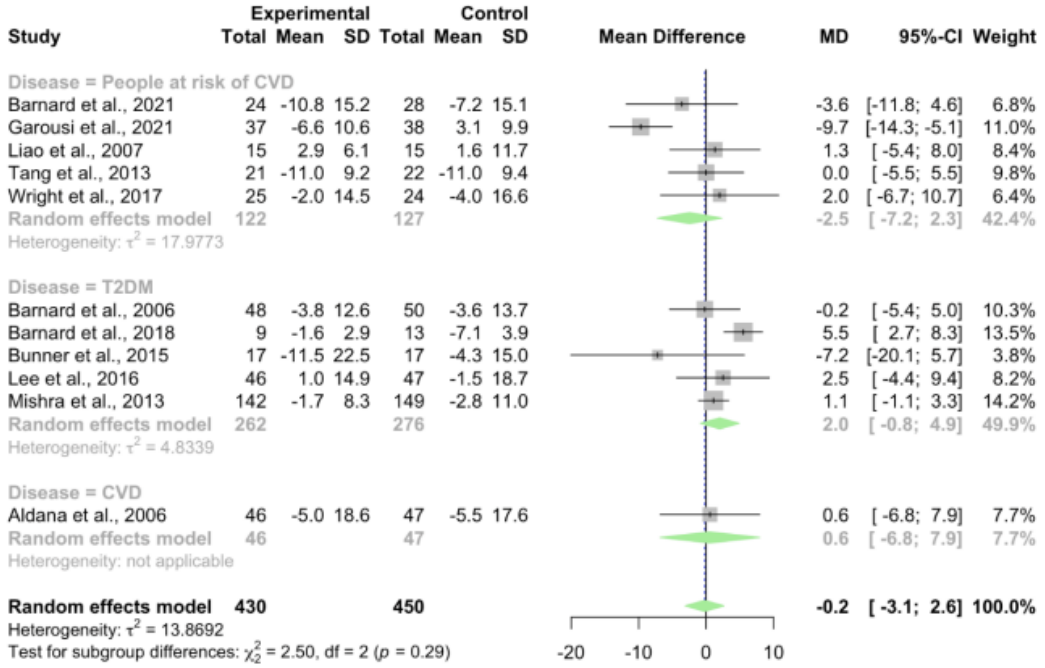


eFigure 36. Random effects model meta-analysis for changes in systolic blood pressure comparing vegetarian diets intervention and all comparison diets, grouped by medication use. CI, confidence interval; MD, mean difference; SD, standard deviation.

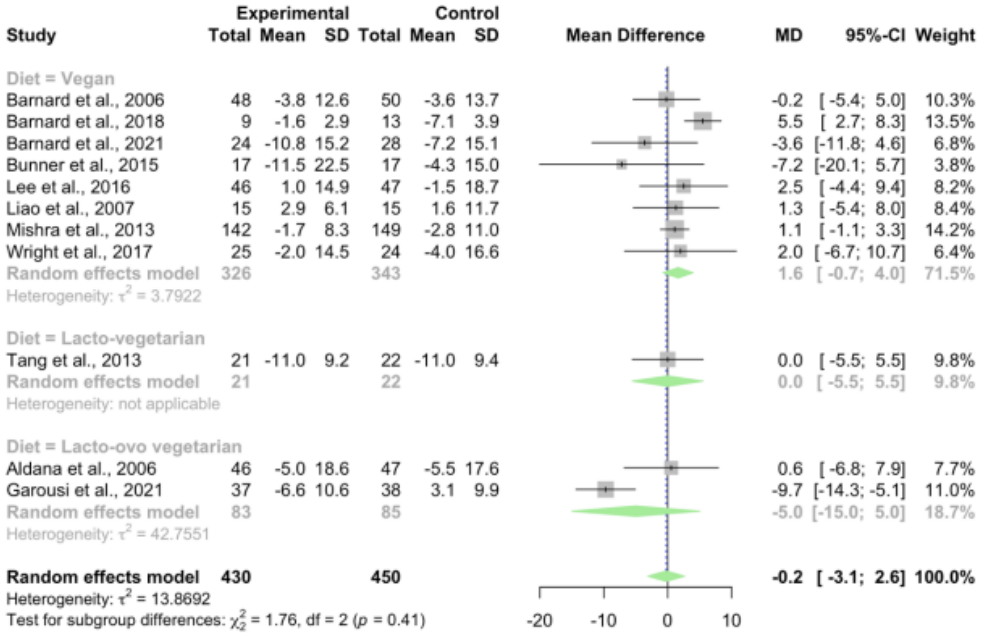


eFigure 37. Random effects model meta-analysis for changes in systolic blood pressure comparing vegetarian diets intervention and all comparison diets, grouped by analysis methods. CI, confidence interval; MD, mean difference; SD, standard deviation.

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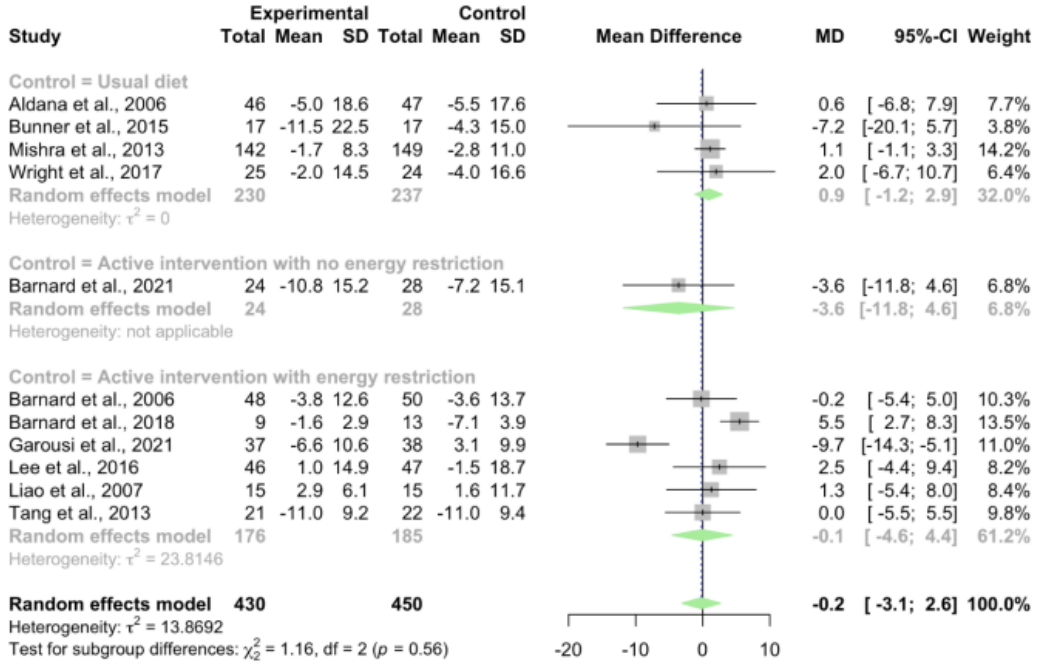


eFigure 38. Random effects model meta-analysis for changes in systolic blood pressure comparing vegetarian diets intervention and all comparison diets, grouped by disease status of participants excluding imputed data. CI, confidence interval; CVD, cardiovascular disease; MD, mean difference; SD, standard deviation; T2DM, type 2 diabetes mellitus.

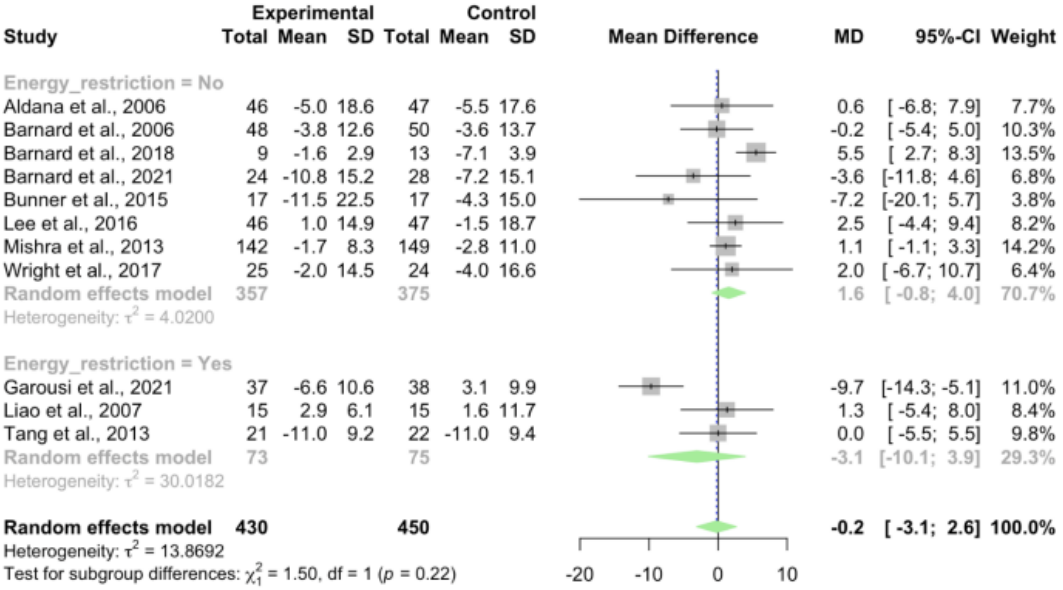


eFigure 39. Random effects model meta-analysis for changes in systolic blood pressure comparing vegetarian diets intervention and all comparison diets, grouped by various vegetarian diets excluding imputed data. CI, confidence interval; MD, mean difference; SD, standard deviation.

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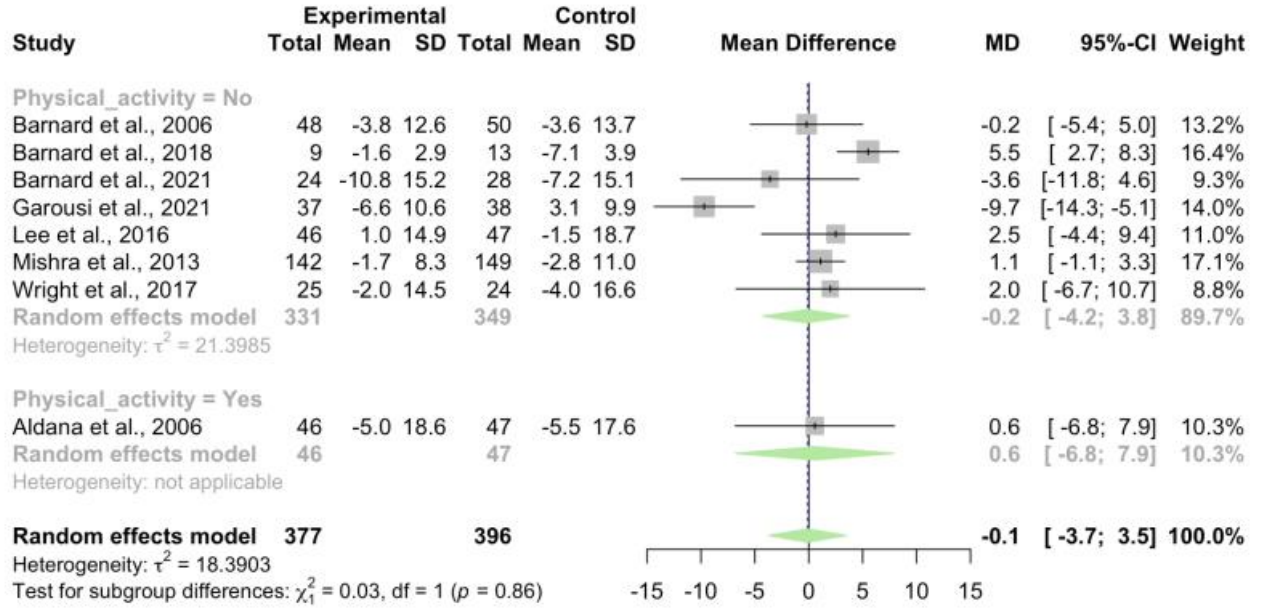


eFigure 40. Random effects model meta-analysis for changes in systolic blood pressure comparing vegetarian diets intervention and all comparison diets, grouped by control diets excluding imputed data. CI, confidence interval; MD, mean difference; SD, standard deviation.

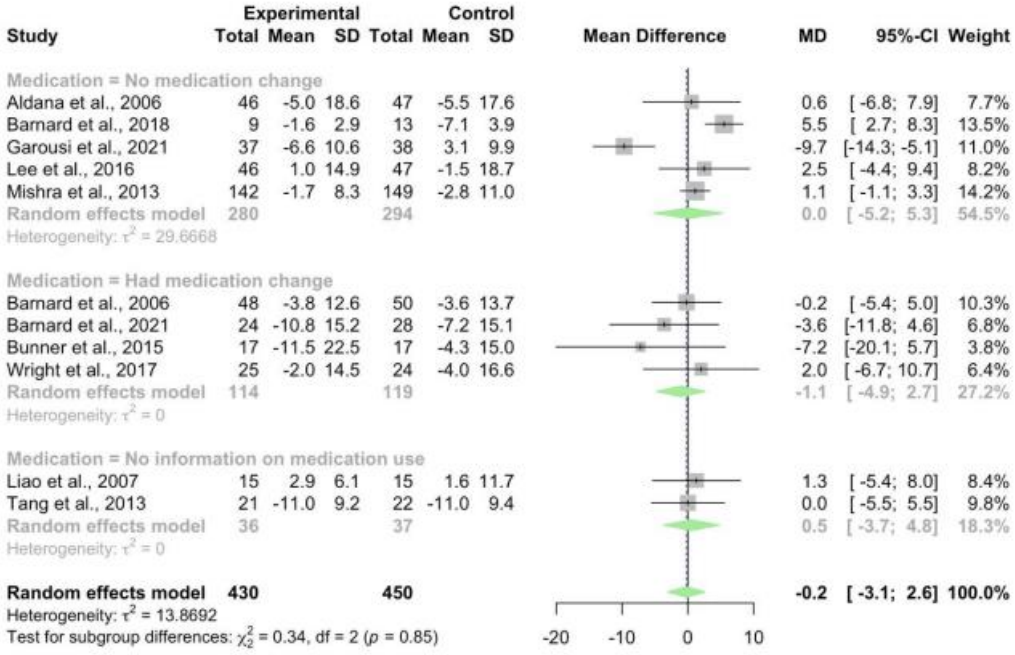


eFigure 41. Random effects model meta-analysis for changes in systolic blood pressure comparing vegetarian diets intervention and all comparison diets, grouped by energy restriction excluding imputed data. CI, confidence interval; MD, mean difference; SD, standard deviation.

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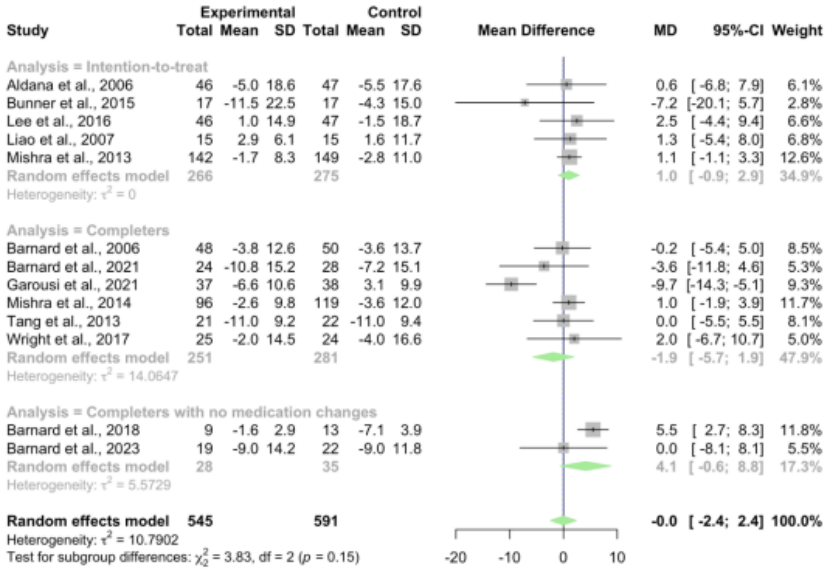


eFigure 42. Random effects model meta-analysis for changes in systolic blood pressure comparing vegetarian diets intervention and all comparison diets, grouped by physical activity excluding imputed data. CI, confidence interval; MD, mean difference; SD, standard deviation.

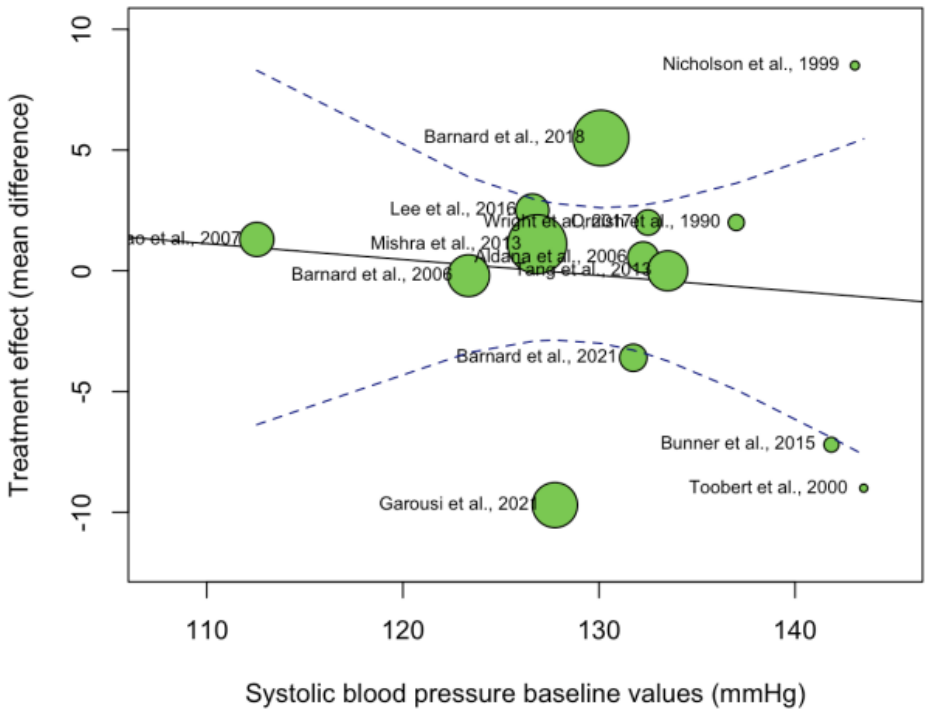


eFigure 43. Random effects model meta-analysis for changes in systolic blood pressure comparing vegetarian diets intervention and all comparison diets, grouped by medication use excluding imputed data. CI, confidence interval; MD, mean difference; SD, standard deviation.

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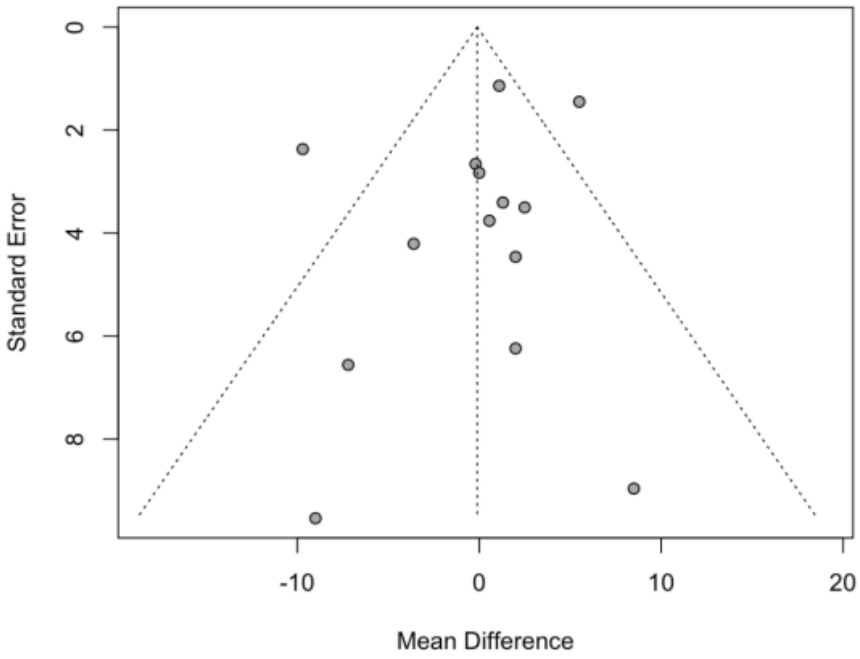


eFigure 44. Random effects model meta-analysis for changes in systolic blood pressure comparing vegetarian diets intervention and all comparison diets, grouped by analysis method excluding imputed data. CI, confidence interval; MD, mean difference; SD, standard deviation.

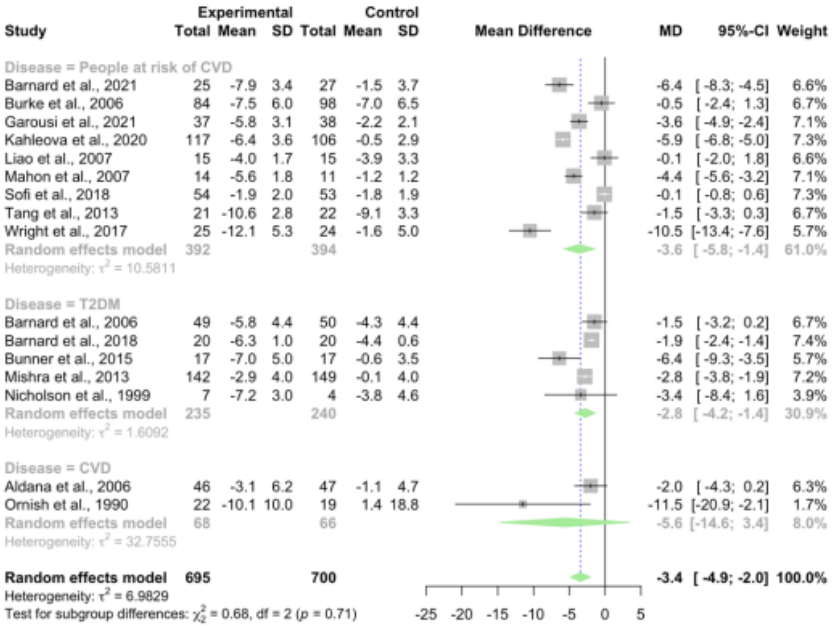


eFigure 45. Treatment effect of systolic blood pressure across increasing levels of baseline systolic blood pressure (mmHg)

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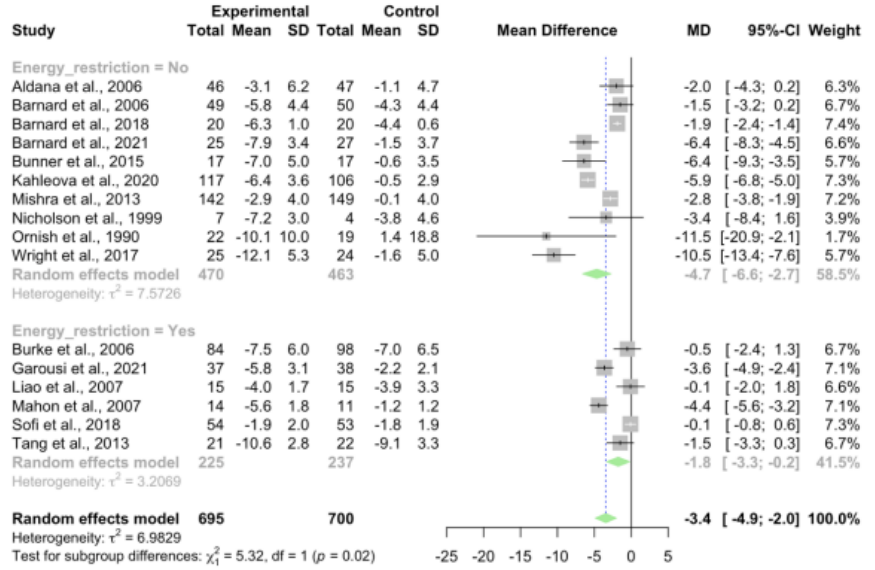


eFigure 46. Funnel plot of systolic blood pressure for risk of publication bias. Mean change in systolic blood pressure plotted against the SE of the mean change. The plot appears fairly symmetrical.

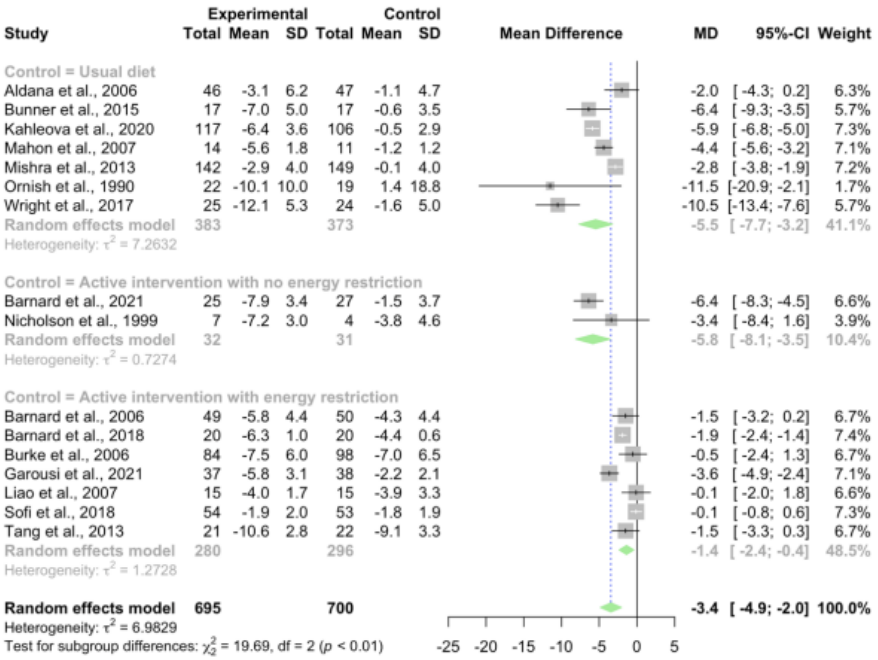


eFigure 47. Random effects model meta-analysis for changes in body weight comparing vegetarian diets intervention and all comparison diets, grouped by disease status of participants. CI, confidence interval; CVDd, cardiovascular disease; MD, mean difference; SD, standard deviation; T2DM, type 2 diabetes mellitus.

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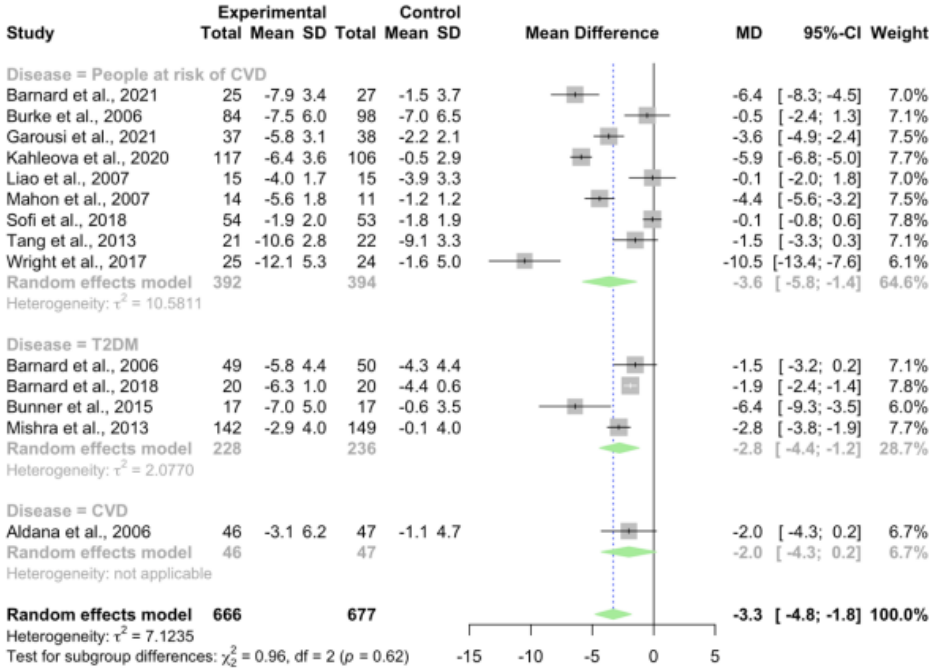


eFigure 48. Random effects model meta-analysis for changes in body weight comparing vegetarian diets intervention and all comparison diets, grouped by energy restriction. CI, confidence interval; MD, mean difference; SD, standard deviation.

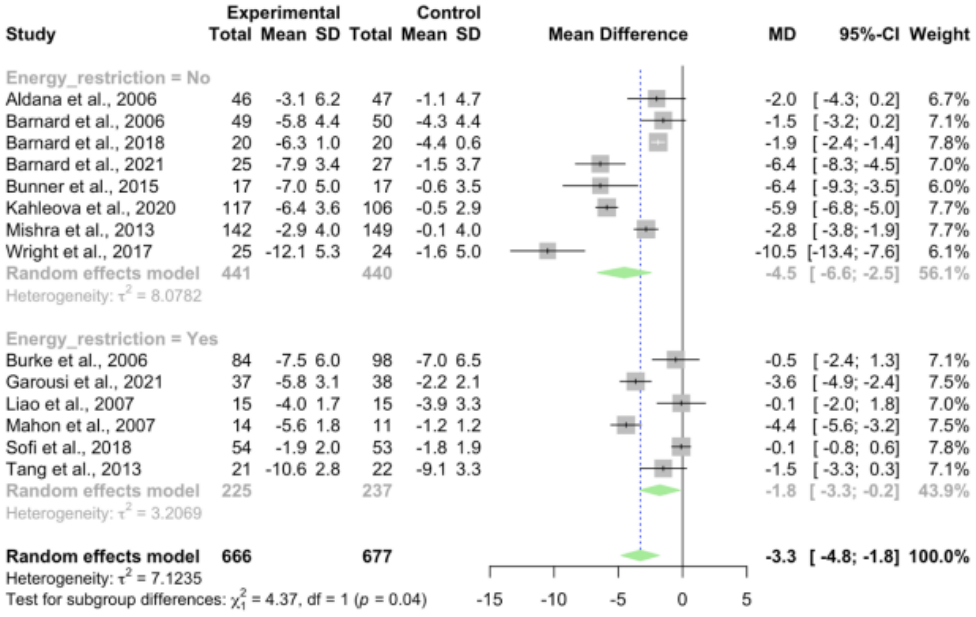


eFigure 49. Random effects model meta-analysis for changes in body weight comparing vegetarian diets intervention and all comparison diets, grouped by comparison diet. CI, confidence interval; MD, mean difference; SD, standard deviation.

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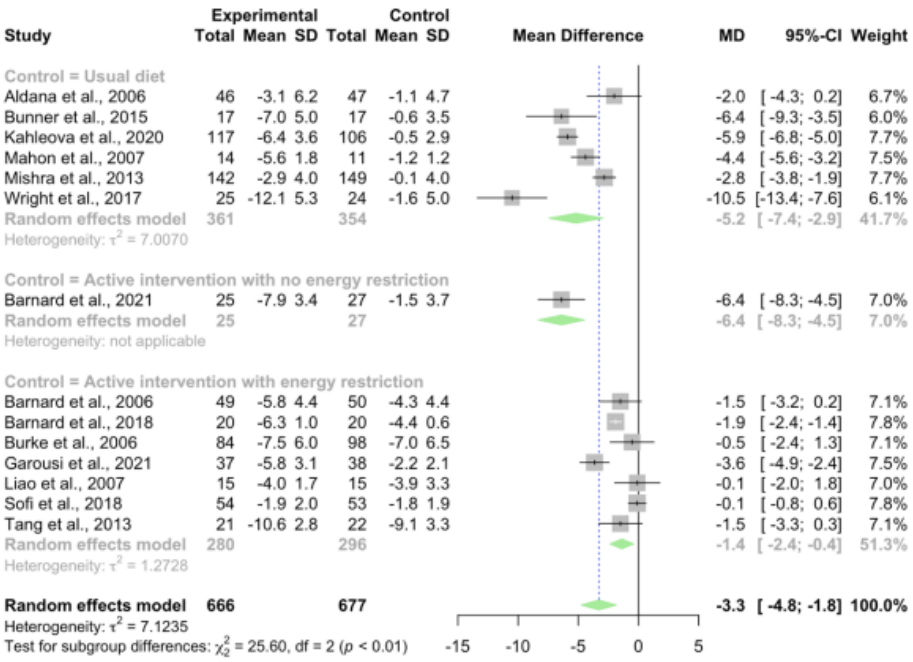


eFigure 50. Random effects model meta-analysis for changes in body weight comparing vegetarian diets intervention and all comparison diets, grouped by disease status of participants excluding imputed data. CI, confidence interval; CVD, cardiovascular disease; MD, mean difference; SD, standard deviation; T2DM, type 2 diabetes mellitus.

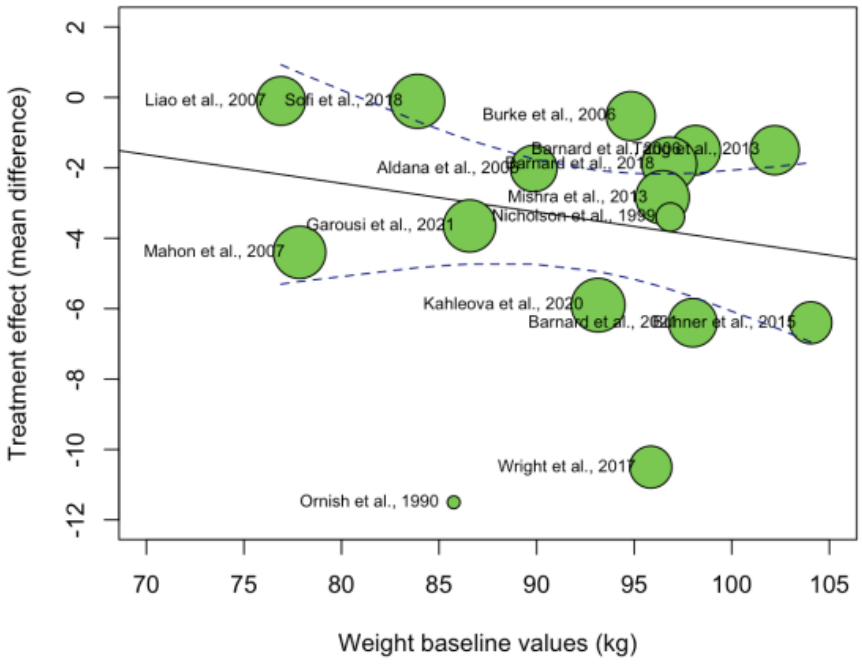


eFigure 51. Random effects model meta-analysis for changes in body weight comparing vegetarian diets intervention and all comparison diets, grouped by energy restriction excluding imputed data. CI, confidence interval; MD, mean difference; SD, standard deviation.

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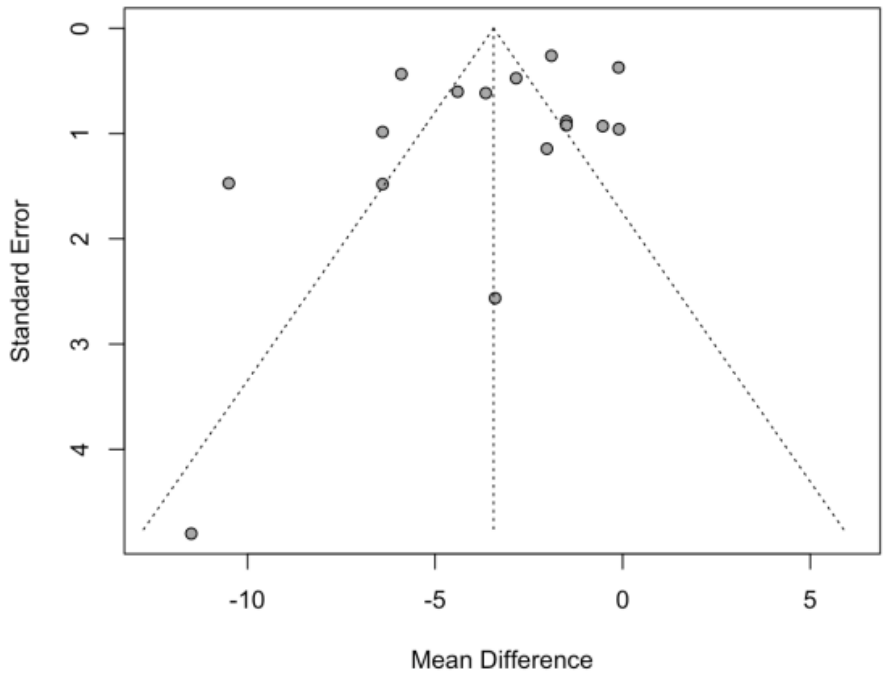


eFigure 52. Random effects model meta-analysis for changes in body weight comparing vegetarian diets intervention and all comparison diets, grouped by control diets excluding imputed data. CI, confidence interval; MD, mean difference; SD, standard deviation.

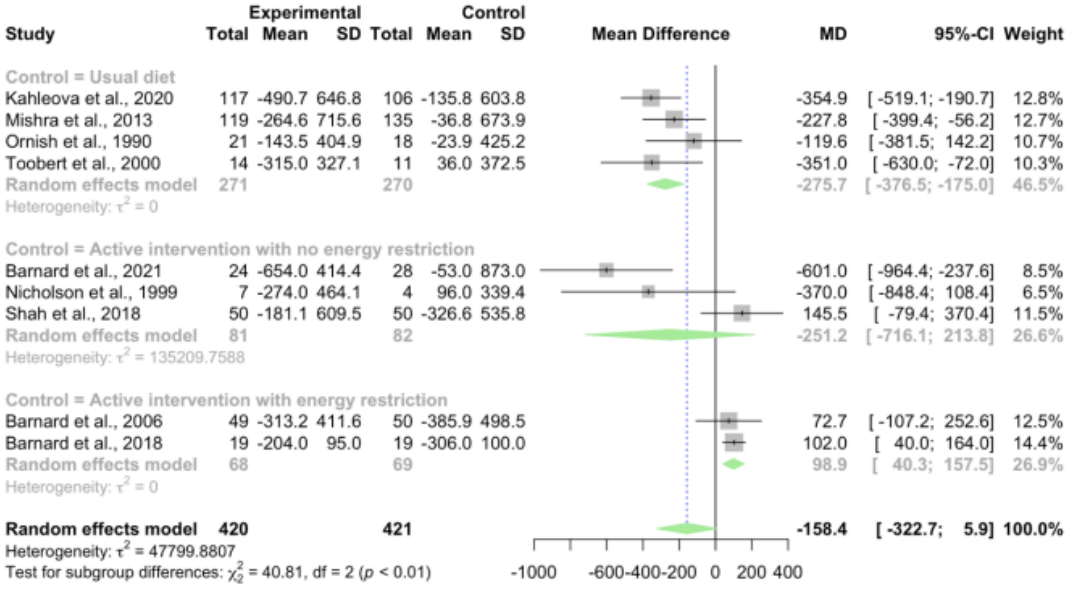


eFigure 53. Treatment effect of body weight across increasing levels of baseline body weight (kg)

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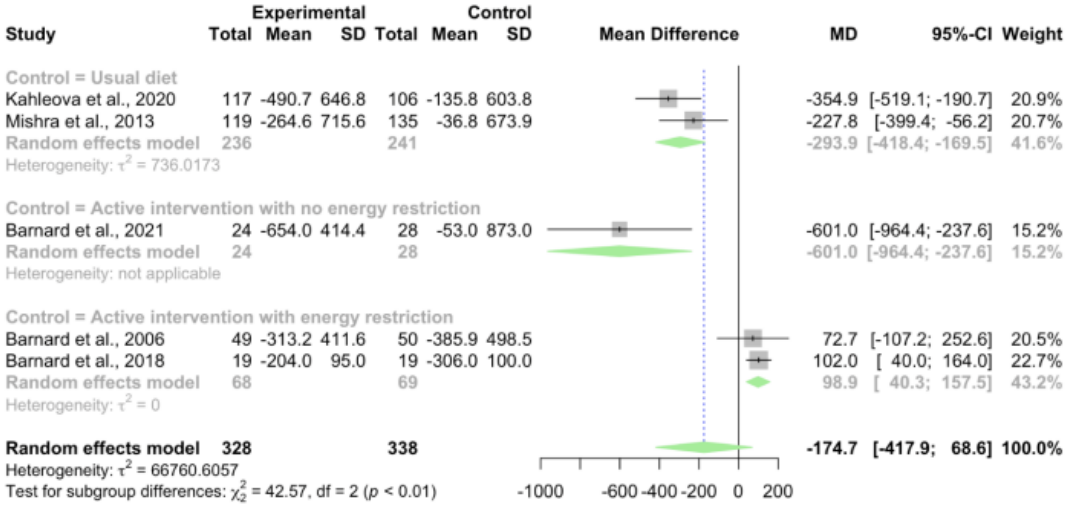


eFigure 54. Funnel plot of body weight for risk of publication bias. Mean change in body weight plotted against the SE of the mean change. The plot appears fairly symmetrical.

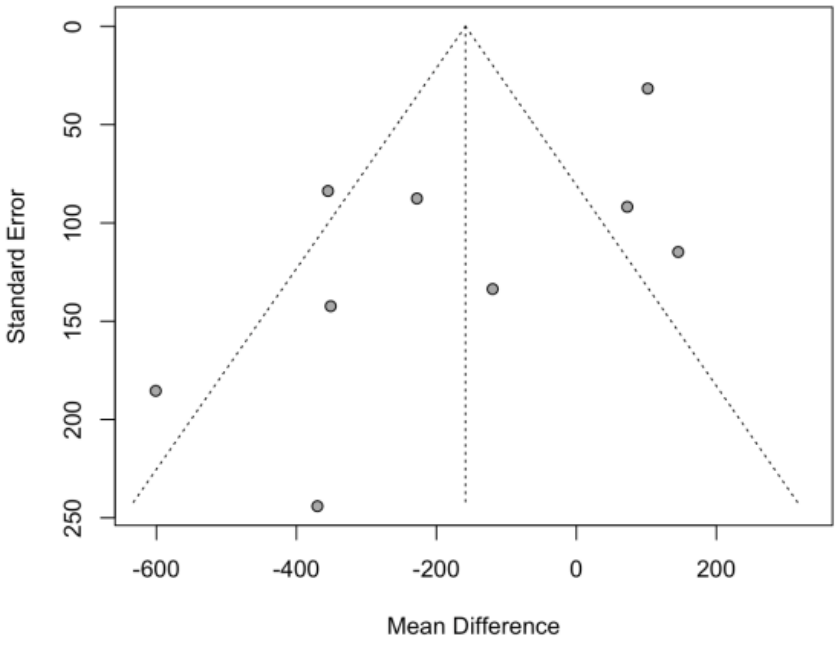


eFigure 55. Random effects model meta-analysis for changes in energy intake comparing vegetarian diets intervention without energy restriction and all comparison diets, grouped by control diets. CI, confidence interval; MD, mean difference; SD, standard deviation.

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eFigure 56. Random effects model meta-analysis for changes in energy intake comparing vegetarian diets intervention without energy restriction and all comparison diets, grouped by control diets excluding imputed data. CI, confidence interval; MD, mean difference; SD, standard deviation.



eFigure 57. Funnel plot of energy intake in studies without energy restriction for risk of publication bias. Mean change in energy intake plotted against the SE of the mean change. The plot appears fairly symmetrical.

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eFigure 58. Risk of Bias assessment of included randomised controlled trials
The green, yellow and red colours indicates low risk, some concerns and high risk of bias, respectively. Twelve out of the 20 included studies were assessed as overall "high risk" of bias. The randomisation process was clear in eight trials. Only eight studies had no deviations from the intended intervention. Outcome data were missing for four trials. All studies measured outcomes appropriately. Seven trials selectively reported outcome data.

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References

1. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;**372**:n71.
2. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ*. 2017;**358**:j4008.
3. Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors),. Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021): Cochrane; 2021. Available from: www.training.cochrane.org/handbook.
4. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;**73**(24):3168-209.
5. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;**71**(6):e13-e115.
6. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Medical Research Methodology*. 2014;**14**(1):135.
7. Nordestgaard BG, Langsted A, Mora S, et al. Fasting is not routinely required for determination of a lipid profile: clinical and laboratory implications including flagging at desirable concentration cut-points-a joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine. *Eur Heart J*. 2016;**37**(25):1944-58.
8. Wing RR, Lang W, Wadden TA, et al. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. *Diabetes Care*. 2011;**34**(7):1481-6.
9. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. *Evid Based Ment Health*. 2019;**22**(4):153-60.
10. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;**7**(3):177-88.
11. Kulinskaya E, Hoaglin DC, Bakbergenuly I, Newman J. A Q statistic with constant weights for assessing heterogeneity in meta-analysis. *Res Synth Methods*. 2021;**12**(6):711-30.
12. Sterne JAC SJ, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng H-Y, Corbett MS, Eldridge SM, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;**366**(l4898).
13. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology*. 2011;**64**(4):383-94.
14. GRADEpro GDT. GRADEpro Guideline Development Tool [Software]: McMaster University and Evidence Prime; 2021 [cited 2021 15th Dec]. Available from: gradepro.org.
15. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *Journal of Clinical Epidemiology*. 2011;**64**(4):395-400.
16. Hajar R. Risk Factors for Coronary Artery Disease: Historical Perspectives. *Heart views : the official journal of the Gulf Heart Association*. 2017;**18**(3):109-14.
17. Nelson RH. Hyperlipidemia as a risk factor for cardiovascular disease. *Primary care*. 2013;**40**(1):195-211.
18. Cavero-Redondo I, Peleteiro B, Álvarez-Bueno C, Rodriguez-Artalejo F, Martínez-Vizcaíno V. Glycated haemoglobin A1c as a risk factor of cardiovascular outcomes and all-cause mortality in diabetic and non-diabetic populations: a systematic review and meta-analysis. *BMJ Open*. 2017;**7**(7):e015949.
19. Tune JD, Goodwill AG, Sassoon DJ, Mather KJ. Cardiovascular consequences of metabolic syndrome. *Translational research : the journal of laboratory and clinical medicine*. 2017;**183**:57-70.

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20. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2018;**71**(19):e127-e248.
21. National Institutes of Health. High Blood Cholesterol. National Cholesterol Education Program [Internet]. 2005. Available from: https://www.nhlbi.nih.gov/files/docs/public/heart/wyntk.pdf.
22. American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*. 2010;**33**(Supplement 1):S62-S9.
23. Huang PL. A comprehensive definition for metabolic syndrome. *Disease models & mechanisms*. 2009;**2**(5-6):231-7.
24. Aldana SG, Greenlaw R, Salberg A, Merrill RM, Hager R, Jorgensen RB. The Effects of an Intensive Lifestyle Modification Program on Carotid Artery Intima-Media Thickness: A Randomized Trial. *American Journal of Health Promotion*. 2007;**21**(6):510-6.
25. Barnard ND, Cohen J, Jenkins DJ, et al. A low-fat vegan diet improves glycemic control and cardiovascular risk factors in a randomized clinical trial in individuals with type 2 diabetes. *Diabetes Care*. 2006;**29**(8):1777-83.
26. Barnard ND, Cohen J, Jenkins DJ, et al. A low-fat vegan diet and a conventional diabetes diet in the treatment of type 2 diabetes: a randomized, controlled, 74-wk clinical trial. *American journal of clinical nutrition*. 2009;**89**(5):1588S-96S.
27. Barnard ND, Gloede L, Cohen J, et al. A low-fat vegan diet elicits greater macronutrient changes, but is comparable in adherence and acceptability, compared with a more conventional diabetes diet among individuals with type 2 diabetes. *Journal of the American Dietetic Association*. 2009;**109**(2):263-72.
28. Turner-McGrievy GM, Barnard ND, Cohen J, Jenkins DJ, Gloede L, Green AA. Changes in nutrient intake and dietary quality among participants with type 2 diabetes following a low-fat vegan diet or a conventional diabetes diet for 22 weeks. *Journal of the American Dietetic Association*. 2008;**108**(10):1636-45.
29. Barnard ND, Levin SM, Gloede L, Flores R. Turning the Waiting Room into a Classroom: Weekly Classes Using a Vegan or a Portion-Controlled Eating Plan Improve Diabetes Control in a Randomized Translational Study. *Journal of the Academy of Nutrition & Dietetics*. 2018;**118**(6):1072-9.
30. Barnard ND, Alwarith J, Rembert E, et al. A Mediterranean Diet and Low-Fat Vegan Diet to Improve Body Weight and Cardiometabolic Risk Factors: A Randomized, Cross-over Trial. *Journal of the American College of Nutrition*. 2021:1-13.
31. Bunner AE, Wells CL, Gonzales J, Agarwal U, Bayat E, Barnard ND. A dietary intervention for chronic diabetic neuropathy pain: a randomized controlled pilot study. *Nutrition & Diabetes*. 2015;**5**:e158.
32. Burke LE, Styn MA, Steenkiste AR, Music E, Warziski M, Choo J. A randomized clinical trial testing treatment preference and two dietary options in behavioral weight management: preliminary results of the impact of diet at 6 months--PREFER study. *Obesity*. 2006;**14**(11):2007-17.
33. Burke LE, Choo J, Music E, et al. PREFER study: A randomized clinical trial testing treatment preference and two dietary options in behavioral weight management - Rationale, design and baseline characteristics. *Contemporary Clinical Trials*. 2006;**27**(1):34-48.
34. Burke LE, Warziski M, Styn MA, Music E, Hudson AG, Sereika SM. A randomized clinical trial of a standard versus vegetarian diet for weight loss: the impact of treatment preference. *International Journal of Obesity*. 2008;**32**(1):166-76.
35. Garousi N, Tamizifar B, Pourmasoumi M, et al. Effects of lacto-ovo-vegetarian diet vs. standard-weight-loss diet on obese and overweight adults with non-alcoholic fatty liver disease: a randomised clinical trial. *Archives of physiology and biochemistry*. 2021:1-9.
36. Kahleova H, Matoulek M, Malinska H, et al. Vegetarian diet improves insulin resistance and oxidative stress markers more than conventional diet in subjects with Type 2 diabetes. *Diabetic Medicine*. 2011;**28**(5):549-59.

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37. Kahleova H, Petersen KF, Shulman GI, et al. Effect of a Low-Fat Vegan Diet on Body Weight, Insulin Sensitivity, Postprandial Metabolism, and Intramyocellular and Hepatocellular Lipid Levels in Overweight Adults: A Randomized Clinical Trial. *JAMA Network Open*. 2020;**3**(11):e2025454.
38. Lee YM, Kim SA, Lee IK, et al. Effect of a Brown Rice Based Vegan Diet and Conventional Diabetic Diet on Glycemic Control of Patients with Type 2 Diabetes: A 12-Week Randomized Clinical Trial. *PLoS ONE [Electronic Resource]*. 2016;**11**(6):e0155918.
39. Liao F-H, Shieh M-J, Yang S-C, Lin S-H, Chien Y-W. Effectiveness of a soy-based compared with a traditional low-calorie diet on weight loss and lipid levels in overweight adults. *Nutrition*. 2007;**23**(7):551-6.
40. Mahon AK, Flynn MG, Stewart LK, et al. Protein intake during energy restriction: effects on body composition and markers of metabolic and cardiovascular health in postmenopausal women. *Journal of the American College of Nutrition*. 2007;**26**(2):182-9.
41. Mishra S, Xu J, Agarwal U, Gonzales J, Levin S, Barnard ND. A multicenter randomized controlled trial of a plant-based nutrition program to reduce body weight and cardiovascular risk in the corporate setting: the GEICO study. *European Journal of Clinical Nutrition*. 2013;**67**(7):718-24.
42. Mishra S BNDGJXJAULS. Nutrient intake in the GEICO multicenter trial: the effects of a multicomponent worksite intervention. *European journal of clinical nutrition*. 2013;**67**(10):1066.
43. Nicholson AS, Sklar M, Barnard ND, Gore S, Sullivan R, Browning S. Toward improved management of NIDDM: A randomized, controlled, pilot intervention using a lowfat, vegetarian diet. *Preventive Medicine*. 1999;**29**(2):87-91.
44. Ornish D, Brown SE, Scherwitz LW, et al. Can lifestyle changes reverse coronary heart disease? The Lifestyle Heart Trial. *Lancet*. 1990;**336**(8708):129-33.
45. Ornish D, Scherwitz LW, Billings JH, et al. Intensive lifestyle changes for reversal of coronary heart disease JAMA 1999 Apr 21;281(15): 1380. *Jama*. 1998;**280**(23):2001-7.
46. Shah B, Ganguzza L, Slater J, et al. The effect of a vegan versus AHA DiEt in coronary artery disease (EVADE CAD) trial: study design and rationale. *Contemporary clinical trials communications*. 2017;**8**:90-8.
47. Shah B, Newman JD, Woolf K, et al. Anti-Inflammatory Effects of a Vegan Diet Versus the American Heart Association-Recommended Diet in Coronary Artery Disease Trial. *Journal of the American Heart Association*. 2018;**7**(23):e011367.
48. Sofi F, Dinu M, Pagliai G, et al. Low-Calorie Vegetarian Versus Mediterranean Diets for Reducing Body Weight and Improving Cardiovascular Risk Profile: CARDIVEG Study (Cardiovascular Prevention With Vegetarian Diet). *Circulation*. 2018;**137**(11):1103-13.
49. Sofi F, Dinu M, Pagliai G, Cesari F, Marcucci R, Casini A. Mediterranean versus vegetarian diet for cardiovascular disease prevention (the CARDIVEG study): study protocol for a randomized controlled trial. *Trials [Electronic Resource]*. 2016;**17**(1):233.
50. Tang M, Armstrong CLH, Leidy HJ, Campbell WW. Normal vs. high-protein weight loss diets in men: Effects on body composition and indices of metabolic syndrome. *Obesity*. 2013;**21**(3):E204-E10.
51. Toobert DJ, Glasgow RE, Radcliffe JL. Physiologic and related behavioral outcomes from the Women's Lifestyle Heart Trial. *Annals of Behavioral Medicine*. 2000;**22**(1):1-9.
52. Wright N, Wilson L, Smith M, Duncan B, McHugh P. The BROAD study: A randomised controlled trial using a whole food plant-based diet in the community for obesity, ischaemic heart disease or diabetes. *Nutrition and Diabetes*. 2017;**7**(3).
53. Cassidy S. A randomised controlled trial to evaluate an intensive lifestyle program for reversal of coronary heart disease 2020 [updated 9th Nov 2020; cited 2021 22nd Sep]. Available from: https://trialsearch.who.int/?TrialID=ACTRN12620001151921.
54. Kahleova H. Effect of a Dietary Intervention on Intracellular Lipid, Insulin Sensitivity, and Glycemic Control in Type 2 Diabetes. *https://clinicaltrialsgov/show/NCT04088981*. 2019.
55. Michalsen A. Plant-based Nutrition for Patients With Cardiovascular Risk Factors (CardioVeg) 2019 [updated 12th Feb, 2021; cited 2021 23rd Sep]. Available from: https://clinicaltrials.gov/ct2/show/NCT03901183.
56. Turner-McGrievy B. Nutritious Eating With Soul (The NEW Soul Study). *https://clinicaltrialsgov/show/NCT03354377*. 2017.

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57. Wright N. The EDGe (End Diabetes Gisborne) trial. Using the whole-foods, plant-based diet in a community programme for people with obesity and diabetes. *http://wwwwhoint/trialsearch/Trial2aspx?TrialID=ACTRN12617000541303*. 2017.
58. Acharya SD, Elci OU, Sereika SM, et al. Adherence to a behavioral weight loss treatment program enhances weight loss and improvements in biomarkers. *Patient preference & adherence*. 2009;**3**:151-60.
59. Acharya SD, Brooks MM, Evans RW, Linkov F, Burke LE. Weight loss is more important than the diet type in improving adiponectin levels among overweight/obese adults. *Journal of the American College of Nutrition*. 2013;**32**(4):264-71.
60. Adebawo O, Salau B, Ezima E, et al. Fruits and vegetables moderate lipid cardiovascular risk factor in hypertensive patients. *Lipids in Health & Disease*. 2006;**5**:14.
61. Agarwal U, Mishra S, Barnard ND, et al. A plant-based diet reduces depression and anxiety and improves work productivity: The GEICO multicenter trial. *Diabetes*. 2013;**62**:A195.
62. Agarwal U, Mishra S, Xu J, Levin S, Gonzales J, Barnard ND. A multicenter randomized controlled trial of a nutrition intervention program in a multiethnic adult population in the corporate setting reduces depression and anxiety and improves quality of life: the GEICO study. *American journal of health promotion*. 2015;**29**(4):245-54.
63. Agren JJ, Tvrzicka E, Nenonen MT, Helve T, Hanninen O. Divergent changes in serum sterols during a strict uncooked vegan diet in patients with rheumatoid arthritis. *British Journal of Nutrition*. 2001;**85**(2):137-9.
64. Ahc M. Vegetarian Diet vs. Mediterranean Diet to Reduce Cardiovascular Risk. *Clinical Cardiology Alert*. 2018;**37**(6):N.PAG-N.PAG.
65. Allen AJ, Talreja DR, Buchanan HA, Wetmore J, Winegar D. The effects of plant-based, mediterranean, paleolithic, and dash diets on cardiovascular disease risk. *Cardiology (Switzerland)*. 2015;**131**:91.
66. Anderson JW. Plant fiber and blood pressure. *Annals of Internal Medicine*. 1983;**98**(5 Pt 2):842-6.
67. Anderson CAM. Dietary Patterns to Reduce Weight and Optimize Cardiovascular Health: Persuasive Evidence for Promoting Multiple, Healthful Approaches. *Circulation*. 2018;**137**(11):1114-6.
68. Andrews L. Vegetarian Diets & Heart Disease. *Communicating Food for Health*. 2017:8-.
69. Anonymous. Vegetarian diet cuts cholesterol. *Pharmaceutical Journal*. 2002;**269**(7227):799.
70. Anonymous. Special cholesterol-lowering diet can achieve same effects as statin therapy. *Pharmaceutical Journal*. 2003;**271**(7260):140.
71. Arntzenius AC. Diet, lipoproteins and the progression of coronary atherosclerosis. The Leiden Intervention Trial. *Drugs*. 1986;**31 Suppl 1**:61-5.
72. Barnard ND, Scherwitz LW, Ornish D. Adherence and acceptability of a low-fat, vegetarian diet among patients with cardiac disease. *Journal of Cardiopulmonary Rehabilitation*. 1992;**12**(6):423-31.
73. Barnard ND, Scialli AR, Bertron P, Hurlock D, Edmonds K, Talev L. Effectiveness of a low-fat vegetarian diet in altering serum lipids in healthy premenopausal women. *American Journal of Cardiology*. 2000;**85**(8):969-72.
74. Barnard ND, Scialli AR, Turner-McGrievy G, Lanou AJ. Acceptability of a low-fat vegan diet compares favorably to a step II diet in a randomized, controlled trial. *Journal of Cardiopulmonary Rehabilitation*. 2004;**24**(4):229-35.
75. Barnard ND, Scialli AR, Turner-McGrievy G, Lanou AJ, Glass J. The effects of a low-fat, plant-based dietary intervention on body weight, metabolism, and insulin sensitivity. *American Journal of Medicine*. 2005;**118**(9):991-7.
76. Barnard ND, Noble EP, Ritchie T, et al. D2 dopamine receptor Taq1A polymorphism, body weight, and dietary intake in type 2 diabetes. *Nutrition*. 2009;**25**(1):58-65.
77. Barnard ND, Rembert E, Freeman A, Bradshaw M, Holubkov R, Kahleova H. Blood Type Is Not Associated with Changes in Cardiometabolic Outcomes in Response to a Plant-Based Dietary Intervention. *Journal of the Academy of Nutrition & Dietetics*. 2020;**10**:10.
78. Beilin LJ. Vegetarian diets, alcohol consumption, and hypertension. *Annals of the New York Academy of Sciences*. 1993;**676**:83-91.
79. Bennett FC, Ingram DM. Diet and female sex hormone concentrations: an intervention study for the type of fat consumed. *American Journal of Clinical Nutrition*. 1990;**52**(5):808-12.

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80. Bhardwaj S, Misra A, Gulati S, Anoop S, Kamal VK, Pandey RM. A randomized controlled trial to evaluate the effects of high Protein Complete (lActo) VEgetaRian (PACER) diet in non-diabetic obese Asian Indians in North India. *Heliyon*. 2017;**3**(12):e00472.
81. Brestrich M, Claus J, Blumchen G. Lactovegetarian diet: Influence on weight, lipids, fibrinogen and lipoprotein (a) of heart-patients in the course of their clinical rehabilitation. [German]. *Zeitschrift fur Kardiologie*. 1996;**85**(6):418-27.
82. Brom B. Integrative approach to management of heart disease is heart disease reversible? *South African Family Practice*. 2009;**51**(3):196-7.
83. Bunner AE, Gonzalez J, Agarwal U, Valente F, Barnard ND. Nutrition intervention for diabetic neuropathy. *Diabetes*. 2014;**63**:A578.
84. Burke LE, Hudson AG, Warziski MT, et al. Effects of a vegetarian diet and treatment preference on biochemical and dietary variables in overweight and obese adults: a randomized clinical trial. *American Journal of Clinical Nutrition*. 2007;**86**(3):588-96.
85. Campbell T. A plant-based diet and stroke. *Journal of Geriatric Cardiology*. 2017;**14**(5):321-6.
86. Campbell WW, Barton Jr ML, Cyr-Campbell D, et al. Effects of an omnivorous diet compared with a lactoovovegetarian diet on resistance-training-induced changes in body composition and skeletal muscle in older men. *American Journal of Clinical Nutrition*. 1999;**70**(6):1032-9.
87. Campbell WW, Tang M. Protein intake, weight loss, and bone mineral density in postmenopausal women. *Journals of Gerontology Series A-Biological Sciences & Medical Sciences*. 2010;**65**(10):1115-22.
88. Cesari F, Dinu M, Pagliai G, et al. Mediterranean, but not lacto-ovo-vegetarian, diet positively influence circulating progenitor cells for cardiovascular prevention: The CARDIVEG study. *Nutrition Metabolism & Cardiovascular Diseases*. 2019;**29**(6):604-10.
89. Chamorro R, Gonzalez MF, Aliaga R, et al. Diet, Plasma, Erythrocytes, and Spermatozoa Fatty Acid Composition Changes in Young Vegan Men. *Lipids*. 2020;**55**(6):639-48.
90. Crimarco A, Springfield S, Petlura C, et al. A randomized crossover trial on the effect of plant-based compared with animal-based meat on trimethylamine-N-oxide and cardiovascular disease risk factors in generally healthy adults: Study With Appetizing Plantfood-Meat Eating Alternative Trial (SWAP-MEAT). *American Journal of Clinical Nutrition*. 2020;**112**(5):1188-99.
91. Dewell A, Weidner G, Sumner MD, Chi CS, Ornish D. A very-low-fat vegan diet increases intake of protective dietary factors and decreases intake of pathogenic dietary factors. *Journal of the American Dietetic Association*. 2008;**108**(2):347-56.
92. Dinu M, Colombini B, Pagliai G, et al. Effects of a dietary intervention with Mediterranean and vegetarian diets on hormones that influence energy balance: results from the CARDIVEG study. *International Journal of Food Sciences & Nutrition*. 2020;**71**(3):362-9.
93. Dinu M, Pagliai G, Cesari F, et al. Effects of a 3-month dietary intervention with a lacto-ovo-vegetarian diet on vitamin B12 levels in a group of omnivores: results from the CARDIVEG (Cardiovascular Prevention with Vegetarian Diet) study. *British Journal of Nutrition*. 2019;**121**(7):756-62.
94. Dinu M, Pagliai G, Cesari F, et al. Effects of a 3-months' dietary intervention with lacto-ovo-vegetarian diet on vitamin B12 levels: Results of the CARDIVEG study. *Nutrition, Metabolism and Cardiovascular Diseases*. 2019;**29 (8)**:882-3.
95. Dinu M, Pagliai G, Colombini B, et al. Dietary intervention with vegetarian and mediterranean diets for cardiovascular prevention: Effects on hormones involved in the energy balance. *Nutrition, Metabolism and Cardiovascular Diseases*. 2019;**29 (8)**:881.
96. Dogra S, Getz A, Woolf K, et al. Long-term Dietary and Weight Changes Following a Short-term Dietary Intervention Study: 4-year Follow-up of the Evade Cad Trial. *Circulation Conference: American Heart Association Scientific Sessions, AHA*. 2020;**142**(SUPPL 3).
97. Elkan A-C, Sjöberg B, Kolsrud B, Ringertz B, Hafström I, Frostegård J. Gluten-free vegan diet induces decreased LDL and oxidized LDL levels and raised atheroprotective natural antibodies against phosphorylcholine in patients with rheumatoid arthritis: a randomized study. *Arthritis research & therapy*. 2008;**10**(2):R34-R.

© 2023 Wang T et al. *JAMA Network Open.*

98. Elkoustaf RA, Ismail M, Batiste C, et al. Diet and ischemic burden: A comparative analysis of a plant based regimen versus a mediterranean regimen in patients with coronary artery disease. *Journal of the American College of Cardiology*. 2017;**69 (11 Supplement 1)**:48.
99. Elkoustaf RA, Aldaas OM, Batiste CD, et al. Lifestyle Interventions and Carotid Plaque Burden: A Comparative Analysis of Two Lifestyle Intervention Programs in Patients with Coronary Artery Disease. *The Permanente journal*. 2019;**23**:18.196.
100. Fallah Noroozinejad E, Hosseinpour-Niazi S, Mirmiran P, Hedayati M, Delshad H. Effect of legumes intake on the oxidative stress markers in type 2 diabetes patients: A randomized cross-over study. [Persian]. *Iranian Journal of Endocrinology and Metabolism*. 2015;**16**(5).
101. Feifer C, Upadhyay P, Potter K. Lifestyle change for weight loss in the inner-city. *Californian Journal of Health Promotion*. 2003;**1**(3):7-13.
102. Fenton T, Gillis C. Plant-based diets do not prevent most chronic diseases. *Critical Reviews in Food Science & Nutrition*. 2019;**59**(7):1044-5.
103. Ferdowsian HR, Barnard ND, Hoover VJ, et al. A multicomponent intervention reduces body weight and cardiovascular risk at a GEICO corporate site. *American Journal of Health Promotion*. 2010;**24**(6):384-7.
104. Flynn MM, Reinert SE. Comparing an olive oil-enriched diet to a standard lower-fat diet for weight loss in breast cancer survivors: a pilot study. *Journal of Women's Health (15409996)*. 2010;**19**(6):1155-61.
105. Frassetto L, Pra M, Thomas B, Talreja D. The VA Beach Diet Study: A comparison of the effects of Plant-based, Mediterranean, Paleolithic, and DASH Diets on cardiovascular disease risk. *Journal of Evolution and Health*. 2019;**3**.
106. Gage A. Growing old in a circle of friends: Sangha and the lifestyle heart trial. *Topics in Geriatric Rehabilitation*. 2011;**27**(2):162-6.
107. Gardner CD, Kiazand A, Alhassan S, et al. Comparison of the Atkins, Zone, Ornish, and LEARN Diets for Change in Weight and Related Risk Factors Among Overweight Premenopausal WomenThe A TO Z Weight Loss Study: A Randomized Trial. *JAMA*. 2007;**297**(9):969-77.
108. Gorder DD, Dolecek TA, Coleman GG. Dietary intake in the Multiple Risk Factor Intervention Trial (MRFIT): Nutrient and food group changes over 6 years. *Journal of the American Dietetic Association*. 1986;**86**(6):744-51.
109. Gould KL, Ornish D, Kirkeeide R, et al. Improved stenosis geometry by quantitative coronary arteriography after vigorous risk factor modification. *American Journal of Cardiology*. 1992;**69**(9):845-53.
110. Gould KL, Ornish D, Scherwitz L, et al. Changes in myocardial perfusion abnormalities by positron emission tomography after long-term, intense risk factor modification. *Jama*. 1995;**274**(11):894-901.
111. Hakala P, Karvetti RL. Weight reduction on lactovegetarian and mixed diets. Changes in weight, nutrient intake, skinfold thicknesses and blood pressure. *European Journal of Clinical Nutrition*. 1989;**43**(6):421-30.
112. Harsha DW, Lin PH, Obarzanek E, Karanja NM, Moore TJ, Caballero B. Dietary Approaches to Stop Hypertension: A summary of study results. *Journal of the American Dietetic Association*. 1999;**99**(8 SUPPL.):S35-S9.
113. Harvey T, Smillie L, Ikin A, Farshid A. 753 The Effect of a Plant-Based Diet on Cardiovascular Risk Factors in Patients With Ischaemic Heart Disease. *Heart Lung and Circulation*. 2020;**29 (Supplement 2)**:S375.
114. Haub MD, Wells AM, Campbell WW. Beef and soy-based food supplements differentially affect serum lipoprotein-lipid profiles because of changes in carbohydrate intake and novel nutrient intake ratios in older men who resistive-train. *Metabolism: Clinical & Experimental*. 2005;**54**(6):769-74.
115. Hosseinpour-Niazi S, Mirmiran P, Hedayati M, Azizi F. Substitution of red meat with legumes in the therapeutic lifestyle change diet based on dietary advice improves cardiometabolic risk factors in overweight type 2 diabetes patients: a cross-over randomized clinical trial. *European Journal of Clinical Nutrition*. 2015;**69**(5):592-7.
116. Hunt JR, Matthys LA, Johnson LK. Zinc absorption, mineral balance, and blood lipids in women consuming controlled lactoovovegetarian and omnivorous diets for 8 wk. *American Journal of Clinical Nutrition*. 1998;**67**(3):421-30.

© 2023 Wang T et al. *JAMA Network Open.*

117. Jenkins DJA, Chiavaroli L, Wong JMW, et al. Adding monounsaturated fatty acids to a dietary portfolio of cholesterol-lowering foods in hypercholesterolemia. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*. 2010;**182**(18):1961-7.
118. Jibani MM, Bloodworth LL, Foden E, Griffiths KD, Galpin OP. Predominantly vegetarian diet in patients with incipient and early clinical diabetic nephropathy: effects on albumin excretion rate and nutritional status. *Diabetic Medicine*. 1991;**8**(10):949-53.
119. Kahleova H, Fleeman R, Hlozkova A, Holubkov R, Barnard ND. A plant-based diet in overweight individuals in a 16-week randomized clinical trial: metabolic benefits of plant protein. *Nutrition & Diabetes*. 2018;**8**(1):58.
120. Kahleova H, Hill M, Pelikanova T. Vegetarian vs. conventional diabetic diet - A 1-year follow-up. *Cor et Vasa*. 2014;**56**(2):e140-e4.
121. Kahleova H, Klementova M, Herynek V, et al. The Effect of a Vegetarian vs Conventional Hypocaloric Diabetic Diet on Thigh Adipose Tissue Distribution in Subjects with Type 2 Diabetes: A Randomized Study. *Journal of the American College of Nutrition*. 2017;**36**(5):364-9.
122. Kahleova H, Klemetova M, Herynek V, et al. The effect of a vegetarian vs. Conventional hypocaloric diabetic diet on thigh adipose tissue distribution in subjects with type 2 diabetes. *Diabetes*. 2017;**66 (Supplement 1)**:A202.
123. Kahleova H, Matoulek M, Hill M, Pelikanova T. Vegetarian diet increases resting energy expenditure more than conventional diet in subjects with type 2 diabetes after aerobic exercise. *Diabetes*. 2011;**60**:A217.
124. Kahleova H, Matoulek M, Kazdova L, Hill M, Pelikanova T. The effect of vegetarian diet on fatty acid composition of serum phopholipids and the association with insulin sensitivity and visceral fat in subjects with type 2 diabetes. *Diabetologia*. 2011;**54**:S359-S60.
125. Kahleova H, Matoulek M, Malinska H, Oliyarnik O, Kazdova L, Pelikanova T. Vegetarian diet improves plasma concentrations of adipokines and oxidative stress markers more than conventional diabetic diet in subjects with type 2 diabetes. *Diabetologia*. 2010;**53**:S380.
126. Kahleova H, Petersen KF, Shulman GI, et al. A dietary intervention to alter insulin sensitivity, intramyocellular and hepatocellular lipids, postprandial metabolism, and body weight: A 16-week randomised trial. *Diabetologia*. 2020;**63 (SUPPL 1)**:S16-S7.
127. Kahleova H, Rembert E, Alwarith J, et al. Effects of a Low-Fat Vegan Diet on Gut Microbiota in Overweight Individuals and Relationships with Body Weight, Body Composition, and Insulin Sensitivity. A Randomized Clinical Trial. *Nutrients*. 2020;**12**(10):24.
128. Kahleova H, Rembert E, Nowak A, Holubkov R, Barnard ND. Effect of a diet intervention on cardiometabolic outcomes: Does race matter? A randomized clinical trial. *Clinical Nutrition ESPEN*. 2021;**41**:126-8.
129. Kahleova H, Tonstad S, Rosmus J, et al. The effect of a vegetarian versus conventional hypocaloric diet on serum concentrations of persistent organic pollutants in patients with type 2 diabetes. *Nutrition Metabolism & Cardiovascular Diseases*. 2016;**26**(5):430-8.
130. Kahleova H, Tura A, Hill M, Holubkov R, Barnard ND. A Plant-Based Dietary Intervention Improves Beta-Cell Function and Insulin Resistance in Overweight Adults: A 16-Week Randomized Clinical Trial. *Nutrients*. 2018;**10**(2):09.
131. Kahleova H, Dort S, Barnard ND, Holubkov R. A Plant-Based High-Carbohydrate, Low-Fat Diet in Overweight Individuals in a 16-Week Randomized Clinical Trial: The Role of Carbohydrates. *Nutrients*. 2018;**10**(9):1302.
132. Kahleova H, Hlozkova A, Fleeman R, Fletcher K, Barnard ND, Holubkov R. Fat Quantity and Quality, as Part of a Low-Fat, Vegan Diet, Are Associated with Changes in Body Composition, Insulin Resistance, and Insulin Secretion. A 16-Week Randomized Controlled Trial. *Nutrients*. 2019;**11**(3):615-.
133. Kahleova H, McCann J, Alwarith J, et al. A plant-based diet in overweight adults in a 16-week randomized clinical trial: The role of dietary acid load. *Clinical Nutrition ESPEN*. 2021.
134. Kalinina OS, Shtraikher AP. [Changes of arterial pressure, pulse, circulation rate and electrocardiographic indices in hypertension following meat and vegetable diets]. *Terapevticheskii Arkhiv*. 1958;**30**(7):72-6.

© 2023 Wang T et al. *JAMA Network Open.*

135. Katcher HI, Ferdowsian HR, Hoover VJ, Cohen JL, Barnard ND. A worksite vegan nutrition program is well-accepted and improves health-related quality of life and work productivity. *Annals of Nutrition & Metabolism*. 2010;**56**(4):245-52.
136. Kestin M, Rouse IL, Correll RA, Nestel PJ. Cardiovascular disease risk factors in free-living men: comparison of two prudent diets, one based on lactoovovegetarianism and the other allowing lean meat. *American Journal of Clinical Nutrition*. 1989;**50**(2):280-7.
137. Kjeldsen-Kragh J, Borchgrevink CF, Laerum E, et al. Controlled trial of fasting and one-year vegetarian diet in rheumatoid arthritis. *The Lancet*. 1991;**338**(8772):899-902.
138. Kochan Z, Mironiuk K, Mickiewicz A, et al. N-3 Pufa-Enriched Semi-Vegetarian Diet Lowers Ldl-Cholesterol and Uric Acid Levels in Patients with Familial Hypercholesterolemia. *Clinical Nutrition*. 2019;**38 (Supplement 1)**:S233.
139. Koertge J, Weidner G, Elliott-Eller M, et al. Improvement in medical risk factors and quality of life in women and men with coronary artery disease in the Multicenter Lifestyle Demonstration Project. *American Journal of Cardiology*. 2003;**91**(11):1316-22.
140. Krishnamoorthy KM. Diet and coronary artery disease. *Indian Heart Journal*. 1999;**51**(3):268-74.
141. Lasserre N. Effectiveness of a dietotherapeutic intervention on the lipids profile and the nutritional status in breast cancer women. *Annals of nutrition & metabolism*. 2017;**71**(895).
142. Levin SM, Ferdowsian HR, Hoover VJ, Green AA, Barnard ND. A worksite programme significantly alters nutrient intakes. *Public Health Nutrition*. 2010;**13**(10):1629-35.
143. Mangels R. People with Type 2 Diabetes Benefit from Vegan and "Plant-Based" Diets. *Vegetarian Journal*. 2019;**38**(2):13-.
144. Marniemi J, Seppanen A, Hakala P. Long-term effects on lipid metabolism of weight reduction on lactovegetarian and mixed diet. *International Journal of Obesity*. 1990;**14**(2):113-25.
145. Masarei JR, Rouse IL, Lynch WJ, Robertson K, Vandongen R, Beilin LJ. Effects of a lacto-ovo vegetarian diet on serum concentrations of cholesterol, triglyceride, HDL-C, HDL2-C, HDL3-C, apoprotein-B, and Lp(a). *American Journal of Clinical Nutrition*. 1984;**40**(3):468-78.
146. Medkova IL, Ivanov AN, Mosiakina LI, Goncharov LF. Blood lipids and intensity of free radical oxidant processes in elderly patients with ischemic heart disease on antiatherogenic vegetarian diet. [Russian]. *Klinicheskaia meditsina*. 2000;**78**(1):21-4.
147. Medkova IL, Ivanov AN, Mosyakina LI, Biryukova LS. Clinicohemadynamic and biochemical the effect of patients with coronary heart disease use combinated lactoovovegetarian diets and simvastatin. [Russian]. *Voprosy Pitaniia*. 2006;**75**(5):49-52.
148. Medkova IL, Mosiakina LI, Biriukova LS. Estimation of action of lactoovovegetarian and vegan diets on blood level of atherogenic lipoproteins in healthy people. [Russian]. *Voprosy pitaniia*. 2002;**71**(4):17-9.
149. Medkova IL, Mosiakina LI, Pavlova VE, Zharkov AP, Bugaev VA, Koryshev VI. [Balanced vegetarian diet in combined rehabilitation of patients suffering from ischemic heart disease]. *Klinicheskaia Meditsina*. 1997;**75**(1):28-31.
150. Mishra S, Barnard ND, Xu J, Trap C. A plant-based diet reduces body weight and cardiovascular risk: The geico multicenter trial. *Diabetes*. 2012;**61**:A192.
151. Misquitta R, Ergas I, Edwards L, Rahbar J, Kushi L. Preliminary evaluation of the health achieved through lifestyle transformation (HALT) program, a kaiser permanente lifestyle intervention. *Journal of Alternative and Complementary Medicine*. 2020;**26 (11)**:A9.
152. Monica Dinu M, Pagliai G, Mangino A, et al. Comparison between Mediterranean and Vegetarian diets for cardiovascular prevention: The CARDIVEG study. *European Journal of Preventive Cardiology*. 2017;**24 (1 Supplement 1)**:S136.
153. Moore WJ, McGrievy ME, Turner-McGrievy GM. Dietary adherence and acceptability of five different diets, including vegan and vegetarian diets, for weight loss: The New DIETs study. *Eating Behaviors*. 2015;**19**:33-8.
154. Navas-Carretero S, Pérez-Granados AM, Schoppen S, Vaquero MP. An oily fish diet increases insulin sensitivity compared to a red meat diet in young iron-deficient women. *British Journal of Nutrition*. 2009;**102**(4):546-53.

© 2023 Wang T et al. *JAMA Network Open.*

155. Nichols A, Grosel J. Vegetarianism in the fight against CVD. *Clinical Advisor*. 2014;**17**(8):24-38.
156. Nicholson AS. Effect of a low-fat, unrefined, vegan diet on type 2 diabetes. *American journal of clinical nutrition*. 1999;**70**(35):624S-5S.
157. Nomura G. Non-pharmacological treatment of hypertension. [Japanese]. *Nippon rinsho*. 1989;**Japanese journal of clinical medicine. 47**(9):2074-8.
158. Pagliai G, Dinu M, Cesari F, et al. Randomized controlled dietary intervention trial comparing mediterranean and vegetarian diets for cardiovascular prevention: preliminary results. *European heart journal*. 2016;**37**(340).
159. Pagliai G, Dinu M, Mangino A, et al. Comparison between mediterranean and vegetarian diets for cardiovascular prevention: The cardiveg study. *Nutrition, Metabolism and Cardiovascular Diseases*. 2017;**27 (1)**:e30-e1.
160. Pagliai G, Russo E, Baldi S, et al. Impact of mediterranean vs vegetarian diets on gut microbiota and short chain fatty acids: The CARDIVEG study. *Nutrition, Metabolism and Cardiovascular Diseases*. 2019;**29 (8)**:879.
161. Pagliai G, Russo E, Niccolai E, et al. Influence of a 3-month low-calorie Mediterranean diet compared to the vegetarian diet on human gut microbiota and SCFA: the CARDIVEG Study. *European Journal of Nutrition*. 2020;**59**(5):2011-24.
162. Phillips KM, Stewart KK, Karanja NM, et al. Validation of diet composition for the dietary approaches to stop hypertension trial. *Journal of the American Dietetic Association*. 1999;**99**(8 SUPPL.):S60-S8.
163. Prescott SL, Jenner DA, Beilin LJ, Margetts BM, Vandongen R. Controlled study of the effects of dietary protein on blood pressure in normotensive humans. *Clinical & Experimental Pharmacology & Physiology*. 1987;**14**(3):159-62.
164. Prescott SL, Jenner DA, Beilin LJ, Margetts BM, Vandongen R. A randomized controlled trial of the effect on blood pressure of dietary non-meat protein versus meat protein in normotensive omnivores. *Clinical Science*. 1988;**74**(6):665-72.
165. Rajaram S, Sabate J. Health benefits of a vegetarian diet. *Nutrition*. 2000;**16**(7-8):531-3.
166. Rodriguez-Rodriguez E, Ortega RM, Lopez-Sobaler AM, et al. Restricted-energy diets rich in vegetables or cereals improve cardiovascular risk factors in overweight/obese women. *Nutrition Research*. 2007;**27**(6):313-20.
167. Rouse IL, Beilin LJ. Vegetarian diet and blood pressure. *Journal of Hypertension*. 1984;**2**(3):231-40.
168. Rouse IL, Beilin LJ, Mahoney DP, et al. Nutrient intake, blood pressure, serum and urinary prostaglandins and serum thromboxane B2 in a controlled trial with a lacto-ovo-vegetarian diet. *Journal of Hypertension*. 1986;**4**(2):241-50.
169. Rugulies R, Jager A, Benesch L, Siegrist J. Comprehensive lifestyle changes among patients with CHD and the integration of inpatient and outpatient cardiac rehabilitation: First results of a secondary prevention intervention trial. [German]. *Zeitschrift fur Gesundheitswissenschaften*. 1996;**4**(3):234-47.
170. Sanchez A, Chung SC, Mejia A, et al. Multiple lifestyle interventions reverses hypertension. *Cogent Medicine*. 2019;**6**(1).
171. Sanders TA, Ellis FR. Serum cholesterol and triglycerides concentrations in vegans. *Proceedings of the Nutrition Society*. 1977;**36**(1):43A.
172. Sarvesh Kumar J, Preetha S. Effect of aerobics exercise and dietary habits on blood pressure in hypertensives. *International Journal of Pharmaceutical Sciences Review and Research*. 2016;**39**(2):81-4.
173. Schmidt T, Wijga A, Von Zur Muhlen A, Brabant G, Wagner TOF. Changes in cardiovascular risk factors and hormones during a comprehensive residential three month kriya yoga training and vegetarian nutrition. *Acta Physiologica Scandinavica, Supplement*. 1997;**161**(640):158-62.
174. Sethna N, Magar NG. Cholesterol and phospholipids in aged groups. *Indian Journal of Medical Research*. 1960:225-30.
175. Singh RB, Rastogi SS, Niaz MA, Ghosh S, Singh R, Gupta S. Effect of fat-modified and fruit- and vegetable-enriched diets on blood lipids in the Indian Diet Heart Study. *American Journal of Cardiology*. 1992;**70**(9):869-74.

© 2023 Wang T et al. *JAMA Network Open.*

176. Sinha SD, Prasad RR, Sharma SN. Study of cardiovascular autonomic function in relation to the duration of menopause and vegetarian diet. *Indian Journal of Physiology and Pharmacology*. 2012;**1)**:122.
177. Soare A, Khazrai YM, Del Toro R, et al. The effect of the macrobiotic Ma-Pi 2 diet vs. the recommended diet in the management of type 2 diabetes: the randomized controlled MADIAB trial. *Nutrition & Metabolism*. 2014;**11**(1):39.
178. Spence JD, Tangney C. Lower risk of stroke with a vegetarian diet. *Neurology*. 2020;**94**(11):463-4.
179. Talreja A, Talreja S, Talreja DR. An investigation of plant-based, mediterranean, paleolithic, and dash diets study (the Va Beach Diet Study). *Catheterization and Cardiovascular Interventions*. 2021;**97**(SUPPL 1):S109.
180. Talreja DR, Talreja S, Talreja A. THE VA-BEACH DIET STUDY: A COMPARISON OF PLANT-BASED, MEDITERRANEAN, PALEOLITHIC AND DASH DIETS ON LIPID AND BIOMETRIC PARAMETERS. *Journal of the American College of Cardiology*. 2021;**77**(18 Supplement 1):1478.
181. Talreja S, Talreja D. Prospective Comparison of Lipid Responses in Plant-based, Mediterranean, Paleolithic an Dash Diets. *Circulation Conference: American Heart Association Scientific Sessions, AHA*. 2020;**142**(SUPPL 3).
182. Thedford K, Raj S. A vegetarian diet for weight management. *Journal of the American Dietetic Association*. 2011;**111**(6):816-8.
183. Thomson CA, Rock CL, Giuliano AR, et al. Longitudinal changes in body weight and body composition among women previously treated for breast cancer consuming a high-vegetable, fruit and fiber, low-fat diet. *European Journal of Nutrition*. 2005;**44**(1):18-25.
184. Tjiong BK, Groen J, Kamminga CE, Willebrands AF. Influence of diet and of some other factors on the blood cholesterol. [Dutch]. *Nederlands Tijdschrift voor Geneeskunde*. 1952;**96**(8):472-4.
185. Toobert DJ, Glasgow RE, Nettekoven LA, Brown JE. Behavioral and psychosocial effects of intensive lifestyle management for women with coronary heart disease. *Patient Education & Counseling*. 1998;**35**(3):177-88.
186. Turner-McGrievy GM, Barnard ND, Scialli AR. A two-year randomized weight loss trial comparing a vegan diet to a more moderate low-fat diet. *Obesity*. 2007;**15**(9):2276-81.
187. Turner-McGrievy GM, Barnard ND, Scialli AR, Lanou AJ. Effects of a low-fat vegan diet and a Step II diet on macro- and micronutrient intakes in overweight postmenopausal women. *Nutrition*. 2004;**20**(9):738-46.
188. Turner-McGrievy GM, Davidson CR, Wingard EE, Billings DL. Low glycemic index vegan or low-calorie weight loss diets for women with polycystic ovary syndrome: a randomized controlled feasibility study. *Nutrition Research*. 2014;**34**(6):552-8.
189. Turner-McGrievy GM, Davidson CR, Wingard EE, Wilcox S, Frongillo EA. Comparative effectiveness of plant-based diets for weight loss: a randomized controlled trial of five different diets. *Nutrition*. 2015;**31**(2):350-8.
190. Turner-McGrievy GM, Leach AM, Wilcox S, Frongillo EA. Differences in Environmental Impact and Food Expenditures of Four Different Plant-based Diets and an Omnivorous Diet: Results of a Randomized, Controlled Intervention. *Journal of Hunger and Environmental Nutrition*. 2016;**11**(3):382-95.
191. Turner-McGrievy GM, Wirth MD, Shivappa N, et al. Randomization to plant-based dietary approaches leads to larger short-term improvements in Dietary Inflammatory Index scores and macronutrient intake compared with diets that contain meat. *Nutrition Research*. 2015;**35**(2):97-106.
192. Veleba J, Matoulek M, Hill M, Pelikanova T, Kahleova H. "A Vegetarian vs. Conventional Hypocaloric Diet: The Effect on Physical Fitness in Response to Aerobic Exercise in Patients with Type 2 Diabetes." A Parallel Randomized Study. *Nutrients*. 2016;**8**(11):26.
193. Whitten C. Vegetarian diets and ischemic heart disease. *Topics in Clinical Nutrition*. 1995;**10**(2):27-33.
194. Wirths W, Rehage-Thones C, Bonnhoff N, Passelewitz U. [Effect of an egg-milk-vegetarian diet on nutritional and blood status. II. Findings of a study on circulation, blood status; discussion]. *Zeitschrift fur Ernahrungswissenschaft*. 1988;**27**(2):84-100.
195. Yarnell SR. Cardioprotective diet after recent myocardial infarction. *Annals of Internal Medicine*. 1992;**117**(SUPPL. 3):76.

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196. Zeis BM, Muller-Nothmann SD. Health effect of a fruit and vegetable rich diet. Part 1: Cardiovascular diseases. [German]. *Schweizerische Zeitschrift fur GanzheitsMedizin*. 2008;**20**(3):144-8.
197. Zemel MB. Dietary pattern and hypertension: The DASH study. *Nutrition Reviews*. 1997;**55**(8):303-5.
198. Vegan diet helps treat type 2 diabetes. *Environmental Nutrition*. 2006;**29**(10):1-.
199. Plant-based diets can lower CV mortality risk. *Nephrology News & Issues*. 2019;**33**(6):34-.
200. Impact of a 12-month Inflammation Management Intervention on the Dietary Inflammatory Index, inflammation, and lipids. *Clinical nutrition ESPEN*. 2019;**30**:42-51.
201. Effects of the lifestyle modification program to reduce serum lipoprotein(a) and other cardiovascular risk factors in Korean college women. *Gazzetta medica italiana archivio per LE scienze mediche*. 2018;**177**(9):468-74.

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9.2 Supplementary Materials for Chapter 4

Association of a healthy plant-based heart-protective diet with reduced cardiovascular disease incidence and mortality: findings from the UK Biobank Study

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Supplementary methods

Description of the UK Biobank

The UK Biobank is an extensive prospective cohort study conducted within the general population, which enrolled over 500,000 individuals aged 40-69 years during the period from 2006 to 2010 [54]. As part of their participation, the UK Biobank participants were required to complete a touch-screen questionnaire that gathered information about their sociodemographic characteristics and lifestyle factors. Additionally, they provided biological samples, including blood samples, and underwent various anthropometric measurements as part of the study protocol [54]. The UK Biobank was approved by the North-West Multi-Centre Research Ethical Committee (REF: 11/NW/03820). This study complies with the Declaration of Helsinki. All individuals had provided written informed consent to participate in the study.

The online 24-hour dietary measurement (the Oxford WebQ)

The Oxford WebQ is an online 24-hour dietary measurement tool, which collected consumption data of 206 types of foods and 32 types of drinks during the previous 24 hours. Standard categories and descriptions (e.g., slices of bread, slices of bacon) were used to assist participants in portion sizes estimation of each item. Example questions of the Oxford WebQ include: "Did you have any of these yesterday?", "How much of the following did you drink yesterday?", or "Would you say that what you ate and drank yesterday was fairly typical for you? (yes/no)". The results generated from the Oxford WebQ has captured similar food items and nutrient intake estimates in comparison to an interviewer-administrated dietary assessment, with moderate-to-strong correlations for most nutrients (Spearman's correlation coefficients between 0.5 and 0.9)[55]. This indicates a reasonably good agreement between the two methods in capturing dietary information and nutrient intake.

A previous study by Bradbury *et al.* evaluated the repeatability of the touchscreen questionnaire in the UK Biobank cohort and found a generally good agreement between reported consumption at baseline and approximately 4 years later[56]. These included fish and meat items (>90% reported the same or adjacent category of intake) and vegetable and fruit (>72% reported the same or adjacent category of intake), with weighted K coefficient showing substantial agreement for oily fish, beef and lamb, poultry, processed meat and fresh fruit. This study also showed good agreement for all foods and food groups intake in participants who completed 24-h recall for more than once. In the present study, we calculated the "heart-protective diet score at baseline" and the "averaged heart-protective diet score" based on repeated measurements and examined the association between them and found a moderate correlation (Pearson correlation coefficient=0.53; p-value < 0.001) between these two scores. Therefore, for participants who completed the dietary measurement multiple times, we used the earliest data to maximize the follow-up duration.

Summary of current main five plant-based diet quality indices using data from 24-hour recall

Table S1 summarize the current main five plant-based diet quality indices utilizing data from 24hr recall. Among them, only three indices (Comprehensive Diet Quality Index (cDQI), Diet Quality Index Associated to the Digital Food Guide (DQI-DFG) [34], and Global Diet Quality Score (GDQS) [35]) consider healthiness of both animal-based and plant-based foods. Discrepancies in categorization of food groups among these scores are identified in red meats, eggs, processed meats, full-fat dairy products, tubers and roots, refined carbohydrates and sugars and sweets. For example, red meats, refined grains and sweets are included as 'moderation components' groups by DQI-DFG, and all dairy products including full-fat dairy and cream are categorized as 'adequacy

components'; cDQI considers 'eggs' as unhealthful animal groups while the other two scores put 'eggs' in healthy food groups.

Covariates

To adjust for confounding, we included covariates in the models for each outcome: age at recruitment (determined from dates of birth and baseline assessment), sex, ethnicity (white, non-white), education (college or university degree, yes), average total household income before tax (< £18000, £18000-30999, £31000- £51999, £52000-100000, or > £100000), Townsend Social Deprivation Index, lifestyle factors (including physical activity, sitting, sleep quality and smoking habits), dietary supplement use (including vitamin, mineral and other dietary supplements), history of hyperglycaemia or T2DM diagnosis (ICD10: R739, E11) and history of cancer diagnosis (excluding malignant neoplasm of skin) (ICD10: CXX [excluding C449], D0X) at baseline. The Townsend Social Deprivation Index[152], created by the UK Biobank group, generates a composite measure of deprivation based on four variables: unemployment, non-car ownership, non-home ownership, and household overcrowding. A negative value of the Townsend Social Deprivation Index corresponds to high socio-economic status. For physical activity, sitting and sleep quality, we created a score as follows:

1. *Physical activity score*

Participants' self-reported answers on International Physical Activity Questionnaire (IPAQ)[153] based questions were used to calculate physical activity score as "Low", "Moderate", or "High". The number of days in a week with walking 10+ mins, moderate activity 10+ mins and vigorous activity 10+ mins, and the duration of that activity in a typical day, were used to derive the metabolic equivalent of task (MET) minutes/week for each activity[154], as well as for outliers for which the total sum duration of walking, moderate and vigorous physical activity was > 960 mins/day. Responses of < 10 mins and their associated days were re-coded to zero (minimum values for duration activities). Walking, moderate, and vigorous physical activity time, when >180 mins, were truncated to be equal to 180 mins. Following IPAQ algorithm: a "High" score was assigned if the vigorous-intensity activity was performed on ≥3 days with total MET-minutes/week ≥1500 OR a combination of walking, moderate- or vigorous- intensity activities was performed 7 days accumulating ≥3000 MET-minutes/week; a "Moderate" score was assigned if vigorous-intensity activity was performed on ≥3 days and ≥ 20mins/day OR a moderate intensity activity was performed ≥5 days and/or walking of ≥30 mins/day OR a combination of walking, moderate- or vigorous- intensity activities was performed ≥5 days achieving ≥600 MET-minutes/week; a "Low" score was assigned in all the other cases (i.e., none or insufficient activity). Physical scores for subjects who answered "Do not know" or "Prefer not to answer" for any question used to build the score were set as missing values.

2. *Sitting score*

Sitting score was calculated based on the total sum of reported answers about time (hours/day) of i) watching TV, ii) using the computer, iii) driving. Sitting scores for subjects who answered "Do not know" or "Prefer not to answer" for any question used to build the score were set as missing values. Finally, we categorized the score in tertiles.

3. *Sleep score*

Sleep score was calculated based on reported answers about sleep duration (hours/day), chronotype (e.g., "morning" or "evening" person), sleeplessness/insomnia (i.e., "never/rarely", "sometimes", "usually"), snoring ("yes", "no"), and daytime dozing/sleeping (narcolepsy) (i.e., "never/ rarely", "sometimes", "often", "all of the time"). This approach was already used in the UKBB[155]. Reporting an early chronotype (i.e., "morning" or

"morning than evening"), ≥7 hours/day of sleep, never or rarely insomnia symptoms, no snoring and no (i.e., never/rarely or sometimes) daytime sleepiness correspond to have low-risk sleep factors. For each factor, participants were scored as 1 if they had it and 0 if they did not have it. All factors were then summed to obtain the overall sleep score. Sleep scores for subjects who answered "Do not know" or "Prefer not to answer" for any question used to build the score were set as missing values.

Table S1. Association between quartiles of heart-protective diet score and risk of incident cardiovascular diseases considering baseline and first two recalls.

Outcome	HR [95% CI]	Unadjusted p-value
CVD Incidence		
Q1 (Ref.)	1.00	
Q2	0.98 [0.94,1.03]	0.417
Q3	0.95 [0.90,0.99]	0.023
Q4	0.92 [0.87,0.96]	<0.001
IHD Incidence		
Q1 (Ref.)	1.00	
Q2	0.96 [0.91,1.01]	0.134
Q3	0.92 [0.87,0.98]	0.006
Q4	0.88 [0.83,0.93]	<0.001
MI Incidence		
Q1 (Ref.)	1.00	
Q2	0.96 [0.87,1.06]	0.424
Q3	0.91 [0.82,1.01]	0.073
Q4	0.80 [0.72,0.89]	<0.001
Stroke Incidence		
Q1 (Ref.)	1.00	
Q2	0.95 [0.88,1.07]	0.323
Q3	0.91 [0.81,0.99]	0.098
Q4	0.97 [0.87,1.07]	0.567
HF Incidence		
Q1 (Ref.)	1.00	
Q2	0.95 [0.86,1.05]	0.317
Q3	0.90 [0.80,1.00]	0.044
Q4	0.83 [0.74,0.93]	0.001
AF Incidence		
Q1 (Ref.)	1.00	
Q2	1.04 [0.97,1.11]	0.242
Q3	1.00 [0.94,1.07]	0.957
Q4	0.98 [0.92,1.05]	0.617

Cox proportional hazard models were adjusted by age (timescale), sex, ethnicity, Townsend deprivation index, average house income, education level, dietary supplement use, history of cancer diagnosis, history of hyperglycemia/type 2 diabetes diagnosis, physical activity level, sitting, sleep quality, smoke habits. AF, Atrial Fibrillation; CVD, Cardiovascular Disease; HF, Heart Failure; HR, Hazard Ratio; IHD, Ischemic Heart Disease; MI, Myocardial Infarction.

Table S2. Association between quartiles of heart-protective diet score and risk of cardiovascular mortality using baseline and first two recalls.

Outcome	HR [95% CI]	Unadjusted p-value
CVD Mortality		
Q1 (Ref.)	1.00	
Q2	0.82 [0.69,0.97]	0.023
Q3	0.87 [0.73,1.03]	0.107
Q4	0.74 [0.61,0.89]	0.001
IHD Mortality		
Q1 (Ref.)	1.00	
Q2	0.86 [0.67,1.11]	0.242
Q3	0.93 [0.72,1.20]	0.559
Q4	0.73 [0.55,0.97]	0.029
MI Mortality		
Q1 (Ref.)	1.00	
Q2	0.71 [0.51,1.01]	0.054
Q3	0.81 [0.58,1.14]	0.225
Q4	0.65 [0.45,0.95]	0.025
Stroke Mortality		
Q1 (Ref.)	1.00	
Q2	0.83 [0.60,1.15]	0.254
Q3	0.91 [0.66,1.26]	0.573
Q4	0.84 [0.60,1.17]	0.304
HF Mortality		
Q1 (Ref.)	1.00	
Q2	0.66 [0.41,1.05]	0.078
Q3	0.69 [0.43,1.12]	0.132
Q4	0.52 [0.31,0.90]	0.018
AF Mortality		
Q1 (Ref.)	1.00	
Q2	NE	NE
Q3	NE	NE
Q4	NE	NE

Cox proportional hazard models were adjusted by age (timescale), sex, ethnicity, Townsend deprivation index, average house income, education level, dietary supplement use, history of cancer diagnosis, history of hyperglycemia/type 2 diabetes diagnosis, physical activity level, sitting, sleep quality, smoke habits. AF, Atrial Fibrillation; CVD, Cardiovascular Disease; HF, Heart Failure; HR, Hazard Ratio; IHD, Ischemic Heart Disease; MI, Myocardial Infarction; NE, Not Estimable.
*Adjusted p-values were obtained using Benjamini-Hochberg procedure.

Table S3. Association between quartiles of heart-protective diet score and risk of cardiometabolic abnormalities using baseline and first two recalls.

Outcome	HR [95% CI]	Unadjusted p-value
Overweight/Obesity		
Q1 (Ref.)	1.00	
Q2	0.89 [0.84,0.94]	<0.001
Q3	0.85 [0.80,0.90]	<0.001
Q4	0.79 [0.74,0.84]	<0.001
Hyperlipidaemia		
Q1 (Ref.)	1.00	
Q2	1.01 [0.90,1.13]	0.826
Q3	0.92 [0.81,1.03]	0.142
Q4	0.85 [0.75,0.97]	0.012
Hypertension		
Q1 (Ref.)	1.00	
Q2	0.98 [0.94,1.03]	0.418
Q3	0.91 [0.87,0.95]	<0.001
Q4	0.92 [0.88,0.96]	<0.001
Hyperglycaemia/Type 2 Diabetes		
Q1 (Ref.)	1.00	
Q2	0.87 [0.81,0.93]	<0.001
Q3	0.83 [0.78,0.89]	<0.001
Q4	0.84 [0.78,0.90]	<0.001

Cox proportional hazard models were adjusted by age (timescale), sex, ethnicity, Townsend deprivation index, average house income, education level, dietary supplement use, history of cancer diagnosis, history of hyperglycemia/type 2 diabetes diagnosis (except when hyperglycemia/type 2 diabetes was the outcome), physical activity level, sitting, sleep quality, smoke habits. HR, Hazard Ratio.

Table S4. Characteristics of participants included (n=192,274) and excluded (n=310,120) in this study.

	Included (n=192274)		Excluded (n=310120)	
	Total		**Total**	
Characteristics	**N**	**Data**	**N**	**Data**
Age, years	192274	56.3 (7.9)	310117	57.5 (8.2)
Sex, male	192274	43.3%	310120	47.0%
Ethnicity, White	189733	95.6%	303866	93.2%
Townsend Deprivation Index	192028	-1.6 (2.9)	309740	-1.1 (3.2)
College or university degree, Y	191371	43.4%	300891	25.1%
Average total household income before tax, < £18000	172512	13.2%	252740	23.2%
Smoking habit, current	191802	7.7%	307642	12.3%
Physical activity score, never	158917	10.4%	227076	10.3%
Sitting score (hours/day)	189448	4.7 (2.3)	293906	4.9 (2.5)
Sleep score	160974	3.7 (1.0)	249634	3.6 (1.0)
Heart-protective diet score	192274	2.9 (7.7)	16941	1.8 (8.2)
BMI, kg/m2	191785	26.8 (4.6)	307502	27.8 (4.9)
SBP, mmHg	185097	136.6 (18.3)	287180	138.6 (18.9)
DBP, mmHg	185100	81.9 (10.0)	287182	82.4 (10.3)
TC, mmol/L	182092	5.8 (1.1)	288648	5.6 (1.2)
LDL-C, mmol/L	181789	3.6 (0.8)	288113	3.53 (0.9)
HDL-C, mmol/L	167016	1.5 (0.4)	265025	1.4 (0.4)
Triglycerides, mmol/L	181967	1.7 (1.0)	288403	1.79 (1.1)
HbA1c (mmol/mol)	180738	35.4 (5.8)	287067	36.6 (7.3)

Data are expressed as mean (SD) or %. HPDS, Heart-protective diet score; BMI, Body Mass Index; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; HbA1c, glycated haemoglobin

Table S5. A summary of the main five plant-based diet quality indices

Index name	Country	Food groups	Calculation
Animal-based diet quality index (aDQI) [38]	U.S.	6 food groups Healthy animal groups: fish/seafood, poultry and dairy products Unhealthful animal groups: red meats, eggs and processed meats	Dietary intake of each food component is adjusted for total energy intake (EI) using density method, divided into sex-specific quintile cut offs, and each quintile scored from 0 to 5. Intake of each food group adjusted for total EI using density method. EI adjusted in analysis models.
Comprehensive Diet Quality Index (cDQI) [38]	U.S.	17 food groups Healthy plant groups: wholegrains, vegetables (excluding white potatoes), whole fruits, nuts/seeds/legumes, vegetable oils, and coffee/tea. Unhealthful plant group: refined grains, fruit juices, white potatoes, sugar-sweetened beverages (SSBs), and sweets/desserts Healthy animal groups: fish/seafood, poultry and dairy products. Unhealthful animal groups: red meats, eggs and processed meats	Same as aDQI. Healthy animal and plant foods positively scored; unhealthy animal and plant foods reverse scored. EI adjusted in analysis models.
Diet Quality Index Associated to the Digital Food Guide (DQI-DFG) [39]	Brazil	11 food groups Moderation components: sugars and sweets; meats: beef, pork and processed meat; refined cereals, and processed fats Adequacy components: poultry, fish and eggs, whole cereals, tubers and roots, fruits, vegetables, legumes and oilseeds, milk and dairy products, and oils and fats	All food groups scored a maximum of 5 or 10, on the basis of portion per 1,000 kcal. Dichotomous scoring for moderation components, where the maximum score is awarded for being within the recommended intake range or scored 0 when this range exceeded. For adequacy components, increasing score for higher intake with the maximum score awarded for being within or above the recommended intake range. For whole cereals, tubers and roots, fruits, and milk and dairy products with intake above the recommendation, decreasing scores were given for intake that is twice the upper limit, and no points for intake above twice the upper limit
Global Diet Quality Score (GDQS) [40]	African countries, China, India, Mexico, US	25 food groups Healthy food groups: citrus fruits, deep orange fruits, other fruits, dark green leafy vegetables, cruciferous vegetables, deep orange vegetables, other vegetables, deep orange tubers, legumes, nuts and seeds, whole grains, liquid oils, fish and shellfish, poultry and game meat, low-fat	All foods ranked into 3 categories of consumed amounts (g/d) (apart from high-fat dairy which has 4 categories). The categories of consumption are specific for each food group and points are assigned on the basis of these categories. Healthy foods have higher scores for higher consumption. Unhealthy when consumed in excess foods are scored in increasing points until specific amounts are

		dairy, and eggs. Unhealthy groups when consumed in excess: high-fat dairy and red meat. Unhealthy food groups: processed meat, refined grains and baked goods, sweets and ice cream, SSBs, juice, white roots and tubers, and purchased deep fried foods	consumed. Unhealthy foods are given more points for lower consumption. All groups scored from 0 to 2 points, apart from: cruciferous vegetables, deep orange vegetables, other vegetables, and deep orange tubers (0–0.5 points); red meat (0–1 point); dark green leafy vegetables, legumes, nuts and seeds (4 points). EI adjusted in some analysis models.
Plant-based Diet Quality Index (pDQI) [47]	U.S.	11 food groups Healthy plant group: whole grains, vegetables (excluding white potatoes), whole fruits, nuts/seeds/legumes, vegetable oils, and coffee/tea Unhealthful plant group: refined grains, fruit juices, white potatoes, SSBs, and sweets/desserts	Dietary intake of each food component was adjusted for total EI using density method, divided into sex-specific quintile cut offs, and each quintile scored from 0 to 5. Healthy plant foods positively scored, and unhealthy plant foods reverse scored. EI adjusted in analysis models.

Table S6. Food items in the 22 food groups

FOOD GROUPS	FOOD ITEMS	SCORING
Wholegrains (14 items)	Porridge, muesli, oat crunch, bran cereal, non-white bread (flour types, brown, wholemeal, other type), seeded or other bread, crispbread, whole-wheat cereal, other cereal, oatcakes, wholemeal pasta, brown rice, couscous, other cooked grains (such as bulgur).	+
Fruits (20 items)	Avocado, mixed fruit, apple, banana, berries, cherries, grapefruit, grapes, mango, melon, orange, orange-like small fruits (such as satsuma), peach/nectarine, pear, pineapple, plum, other fruits, stewed/cooked fruit, prunes, other dried fruit	+
Non-starchy Vegetables (26 items)	Mixed vegetables, vegetable pieces, coleslaw, side salad, beetroot, broccoli, cabbage/kale, carrots, cauliflower, celery, courgette, cucumber, garlic, leeks, lettuce, mushrooms, onion, parsnip, sweet peppers, spinach, sprouts, fresh tomatoes, cooked or tinned tomatoes, turnip/swede, watercress, other vegetable intake	+
Starchy Vegetables (3 items)	Butternut squash, sweetcorn, sweet potato	+
Nuts & Seeds (5 items)	Unsalted peanuts, unsalted nuts, seeds, salted peanuts, salted nuts	+
Legumes & Beans, Other Vegetarian Protein Alternatives (9 items)	Beans (baked beans), other beans or lentils (pulses), broad beans, green beans, peas, vegetarian sausages/burgers, tofu, quorn, other vegetarian alternative	+
Uncoated Fish & Seafood (7 items)	Tinned tuna, oily fish, white fish, prawns, lobster/crab, shellfish, other fish intake	+
Eggs (5 items)	Whole eggs, omelettes or scrambled egg, eggs in sandwiches, scotch egg, other egg dishes	+
(Reduced-fat and/or No Added Sugar) Milk & Dairy Products (4 items)	Milk, low fat hard cheese, low fat cheese spread, cottage cheese	+
Tea, Coffee & Other Low-calorie Drinks (11 items)	Instant coffee, filtered coffee, cappuccino, latte, espresso, other coffee drinks, standard tea, rooibos tea, green tea, herbal tea, other tea	+
Homemade soup (1 item)	Homemade soup	+
Refined grains & cereals, including discretionary choices (12 items)	Sweetened cereal, plain cereal, white sliced bread, white bread, white bap, white bread roll, naan bread, garlic bread, white pasta, white rice, pancake, snackpot	-
Potatoes (4 items)	Fried potatoes, boiled/baked potatoes, mashed potatoes, crisps (e.g., potato chips)	-
Meat, Poultry & Processed Meat (10 items)	Sausage, beef, pork, lamb, crumbed or deep-fried poultry, poultry, bacon, ham, liver, other meat intake	-
Coated Fish & Seafood (2 items)	Breaded fish, battered fish	-

(Full-fat and/or Added Sugar) Milk & Dairy Products (10 items)	Flavored milk, yogurt, hard cheese, soft cheese, blue cheese, cheese spread, feta cheese, mozzarella cheese, goat's cheese, other cheese	-
Processed Soup (2 items)	Powdered/instant soup intake, canned soup intake	-
Sugar, Sweets & Desserts, Cookies & Pastries (23 items)	Intake of sugar added to coffee/tea/cereal, ice-cream, milk-based pudding, other milk-based pudding, soya dessert, fruitcake, cake, doughnuts, sponge pudding, cheesecake, other dessert, chocolate bar, white chocolate, milk chocolate, dark chocolate, chocolate-covered raisin, chocolate sweet, diet sweets, chocolate-covered biscuits, chocolate biscuits, sweet biscuits, cereal bar, other sweets	-
Savoury Snacks (2 items)	Savoury or cheesy biscuits, other savoury snack	-
Sugary Drinks including Juices & Sugar-sweetened Beverages (3 items)	Low-calorie hot chocolate, hot chocolate, other non-alcoholic drink	-
Artificial sweetener (1 item)	Artificial sweetener added to coffee/tea/cereal	-
Unhealthy Fat (with/without Carbohydrates) (2 items)	Butter/margarine on bread/crackers (spreadable, low fat, normal fat, or unknown type), number of bread slices/baps/bread rolls/crackers/crispbreads/oatcakes/other bread types with butter/margarine	-

Table S7. Number of participants with available dietary data for each food item to calculate heart-protective diet score considering baseline and following instances.

Total	Baseline	First instance	Second instance	Third instance	Fourth instance
192274	63408 (33%)	72707 (38%)	25019 (13%)	18316 (9%)	12824 (7%)

Food groups	Baseline N (%)	At least one instance including baseline data N (%)
Wholegrains	69426 (13.8%)	209215 (41.6%)
Fruits	70684 (14.1%)	210954 (42.0%)
Non-starchy Vegetables	70684 (14.1%)	210954 (42.0%)
Starchy Vegetables	70684 (14.1%)	210954 (42.0%)
Nuts & Seeds	70684 (14.1%)	210954 (42.0%)
Legumes & Beans, Other Vegetarian Protein Alternatives	70684 (14.1%)	210954 (42.0%)
Uncoated Fish & Seafood	70684 (14.1%)	210954 (42.0%)
Eggs	70684 (14.1%)	210954 (42.0%)
(Reduced-fat and/or No Added Sugar) Milk & Dairy Products	70684 (14.1%)	210954 (42.0%)
Tea, Coffee & Other Low-calorie Drinks	70684 (14.1%)	210954 (42.0%)
Homemade soup	70684 (14.1%)	210954 (42.0%)
Refined grains & cereals, including discretionary choices	69426 (13.8%)	209215 (41.6%)
Potatoes	70684 (14.1%)	210954 (42.0%)
Meat, Poultry & Processed Meat	70684 (14.1%)	210954 (42.0%)
Coated Fish & Seafood	70684 (14.1%)	210954 (42.0%)
(Full-fat and/or Added Sugar) Milk & Dairy Products	70684 (14.1%)	210954 (42.0%)
Processed Soup	70684 (14.1%)	210954 (42.0%)
Sugar, Sweets & Desserts, Cookies & Pastries	70684 (14.1%)	210954 (42.0%)
Savoury Snacks	70684 (14.1%)	210954 (42.0%)
Sugary Drinks including Juices & Sugar-sweetened Beverages	70684 (14.1%)	210954 (42.0%)
Artificial sweeteners	70684 (14.1%)	210954 (42.0%)
Unhealthy Fat (with/without Carbohydrates)	70684 (14.1%)	210954 (42.0%)

Table S8. Ascertainment of CVD outcomes (ICD and UK Biobank field codes)

Disease	ICD10 codes	UK Biobank Field for diagnosis date	UK Biobank Field for source of diagnosis*	Diagnosis from Electronic Health Records
Cardiovascular diseases (CVDs)				
IHD	I20, I24, I25	131296 Date I20 first reported (angina pectoris)	131297 Source of report of I20 (angina pectoris)	Angina
		131304 Date I24 first reported (other acute IHDs)	131305 Source of report of I24 (other acute IHDs)	
		131306 Date I25 first reported (chronic IHD)	131307 Source of report of I25 (chronic IHD)	
MI	I21, I22, I23	131298 Date I21 first reported (acute MI)	131299 Source of report of I21 (acute MI)	MI
		131300 Date I22 first reported (subsequent MI)	131301 Source of report of I22 (subsequent MI)	
		131302 Date I23 first reported (certain current complications following acute MI)	131303 Source of report of I23 (certain current complications following acute MI)	
Stroke	I61, I62, I63, I64	131364 Date I62 first reported (other nontraumatic intracranial haemorrhage)	131365 Source of report of I62 (other nontraumatic intracranial haemorrhage)	Stroke
		131362 Date I61 first reported (intracerebral haemorrhage)	131363 Source of report of I61 (intracerebral haemorrhage)	
		131366 Date I63 first reported (cerebral infarction)	131367 Source of report of I63 (cerebral infarction)	
		131368 Date I64 first reported (stroke, not specified as haemorrhage or infarction)	131369 Source of report of I64 (stroke, not specified as haemorrhage or infarction)	
HF	I50	131354 Date I50 first reported (HF)	131355 Source of report of I50 (HF)	-
Arrhythmia and conduction disorders including AF	I48	131350 Date I48 first reported (AF and flutter)	131351 Source of report of I48 (AF and flutter)	-
Cardiometabolic diseases				
Overweight and Obesity	E66	130792 Date E66 first reported (obesity)	130793 Source of report of E66 (obesity)	-
Hypertension	I10	131286 Date I10 first reported (essential (primary) hypertension)	131287 Source of report of I10 (essential (primary) hypertension)	Hypertension
Hyperglycaemia/ T2DM	R739, E11	130708 Date E11 first reported (non-insulin-dependent diabetes mellitus)	130709 Source of report of E11 (non-insulin-dependent diabetes mellitus)	Type II diabetes mellitus
		41270 Diagnoses – ICD10 (to identify ICD10 R739 diagnosis)		

* Source includes primary care, death register, hospital admission and self-report.
AF, Atrial Fibrillation; CVD, Cardiovascular Disease; HF, Heart Failure; HR, Hazard Ratio; IHD, Ischemic Heart Disease; MI, Myocardial Infarction; T2DM, Type 2 diabetes mellitus.

Table S9. Association between quartiles of heart-protective diet score and risk of incident cardiovascular diseases.

Outcome	N	Events	HR [95% CI]	Unadjusted p-value	Adjusted p-value*
CVD Incidence	192274	20692			
Q1 (Ref.)	42731	5722	1.00		
Q2	42509	5269	0.98 [0.94,1.02]	0.255	0.348
Q3	43031	4981	0.94 [0.90,0.98]	0.002	0.006
Q4	43311	4720	0.92 [0.88,0.95]	<0.001	<0.001
IHD Incidence	192274	11241			
Q1 (Ref.)	45180	3273	1.00		
Q2	44924	2854	0.96 [0.91,1.01]	0.084	0.161
Q3	45330	2682	0.93 [0.88,0.98]	0.007	0.022
Q4	45599	2432	0.88 [0.83,0.93]	<0.001	<0.001
MI Incidence	192274	3452			
Q1 (Ref.)	47376	1077	1.00		
Q2	46900	878	0.94 [0.86,1.02]	0.150	0.239
Q3	47193	819	0.93 [0.84,1.01]	0.100	0.178
Q4	47353	678	0.82 [0.74,0.90]	<0.001	<0.001
Stroke Incidence	192274	3103			
Q1 (Ref.)	47605	848	1.00		
Q2	46994	784	0.97 [0.88,1.07]	0.569	0.637
Q3	47296	716	0.89 [0.81,0.99]	0.030	0.072
Q4	47276	755	0.96 [0.87,1.07]	0.466	0.554
HF Incidence	192274	3189			
Q1 (Ref.)	47525	928	1.00		
Q2	46958	820	0.95 [0.87,1.05]	0.331	0.420
Q3	47271	741	0.88 [0.80,0.97]	0.009	0.027
Q4	47331	700	0.86 [0.78,0.95]	0.003	0.011
AF Incidence	192274	8913			
Q1 (Ref.)	46141	2312	1.00		
Q2	45480	2298	1.03 [0.97,1.09]	0.317	0.409
Q3	45817	2195	0.99 [0.93,1.05]	0.650	0.717
Q4	45923	2108	0.97 [0.92,1.03]	0.381	0.469

Cox proportional hazard models were adjusted by age (timescale), sex, ethnicity, Townsend deprivation index, average house income, education level, dietary supplement use, history of cancer diagnosis, history of hyperglycemia/type 2 diabetes diagnosis, physical activity level, sitting, sleep quality, smoke habits. AF, Atrial Fibrillation; CVD, Cardiovascular Disease; HF, Heart Failure; HR, Hazard Ratio; IHD, Ischemic Heart Disease; MI, Myocardial Infarction.
*Adjusted p-values were obtained using Benjamini-Hochberg procedure.

Table S10. Association between quartiles of heart-protective diet score and risk of cardiovascular mortality.

Outcome	N	Events	HR [95% CI]	Unadjusted p-value	Adjusted p-value*
CVD Mortality	192274	1131			
Q1 (Ref.)	48080	373	1.00		
Q2	47513	265	0.79 [0.68,0.93]	0.004	0.014
Q3	47741	271	0.84 [0.71,0.98]	0.029	0.071
Q4	47809	222	0.72 [0.61,0.86]	<0.001	0.001
IHD Mortality	192274	513			
Q1 (Ref.)	48282	171	1.00		
Q2	47652	126	0.86 [0.68,1.08]	0.190	0.288
Q3	47884	128	0.92 [0.73,1.16]	0.488	0.572
Q4	47943	88	0.68 [0.52,0.89]	0.005	0.016
MI Mortality	192274	292			
Q1 (Ref.)	48348	105	1.00		
Q2	47713	65	0.72 [0.53,0.98]	0.040	0.090
Q3	47942	70	0.81 [0.60,1.11]	0.191	0.288
Q4	47979	52	0.65 [0.46,0.91]	0.012	0.033
Stroke Mortality	192274	351			
Q1 (Ref.)	48348	105	1.00		
Q2	47702	76	0.74 [0.55,0.99]	0.043	0.095
Q3	47928	84	0.80 [0.60,1.07]	0.136	0.227
Q4	47945	86	0.82 [0.61,1.11]	0.199	0.293
HF Mortality	192274	141			
Q1 (Ref.)	48399	54	1.00		
Q2	47746	32	0.68 [0.44,1.06]	0.086	0.161
Q3	47978	34	0.76 [0.49,1.18]	0.220	0.311
Q4	48010	21	0.51 [0.30,0.85]	0.010	0.029
AF Mortality	192274	35			
Q1 (Ref.)	48437	16	1.00		
Q2	47775	3	NE	NE	NE
Q3	48007	5	NE	NE	NE
Q4	48020	11	NE	NE	NE

Cox proportional hazard models were adjusted by age (timescale), sex, ethnicity, Townsend deprivation index, average house income, education level, dietary supplement use, history of cancer diagnosis, history of hyperglycemia/type 2 diabetes diagnosis, physical activity level, sitting, sleep quality, smoke habits. AF, Atrial Fibrillation; CVD, Cardiovascular Disease; HF, Heart Failure; HR, Hazard Ratio; IHD, Ischemic Heart Disease; MI, Myocardial Infarction; NE, Not Estimable.
*Adjusted p-values were obtained using Benjamini-Hochberg procedure.

Table S11. Association between quartiles of heart-protective diet score and risk of cardiometabolic abnormalities.

Outcome	N	Events	HR [95% CI]	Unadjusted p-value	Adjusted p-value*
Overweight/Obesity	188475	10763			
Q1 (Ref.)	44014	3332	1.00		
Q2	44105	2729	0.90 [0.85,0.94]	<0.001	<0.001
Q3	44668	2474	0.85 [0.81,0.90]	<0.001	<0.001
Q4	44925	2228	0.79 [0.75,0.84]	<0.001	<0.001
Hyperlipidaemia	192085	2681			
Q1 (Ref.)	47636	763	1.00		
Q2	47020	708	1.00 [0.90,1.10]	0.935	0.935
Q3	47340	631	0.91 [0.81,1.01]	0.068	0.138
Q4	47408	579	0.86 [0.77,0.96]	0.007	0.021
Hypertension	149486	20394			
Q1 (Ref.)	31486	5439	1.00		
Q2	31828	5195	0.98 [0.94,1.02]	0.353	0.441
Q3	32656	4911	0.93 [0.89,0.96]	<0.001	0.001
Q4	33122	4849	0.93 [0.89,0.97]	0.001	0.003
Hyperglycaemia/Type 2 Diabetes	188739	8006			
Q1 (Ref.)	44906	2557	1.00		
Q2	44898	2001	0.89 [0.84,0.95]	<0.001	0.001
Q3	45412	1759	0.84 [0.79,0.90]	<0.001	<0.001
Q4	45517	1689	0.86 [0.81,0.92]	<0.001	<0.001

Cox proportional hazard models were adjusted by age (timescale), sex, ethnicity, Townsend deprivation index, average house income, education level, dietary supplement use, history of cancer diagnosis, history of hyperglycemia/type 2 diabetes diagnosis (except when hyperglycemia/type 2 diabetes was the outcome), physical activity level, sitting, sleep quality, smoke habits. HR, Hazard Ratio.
*Adjusted p-values obtained using Benjamini-Hochberg procedure.

Table S12. Stratified analyses for statistically significant interactions between heart-protective diet score and sex or Townsend deprivation index.

Outcomes	Interaction	Interaction adjusted p-value*	Subgroup	N	Events	HR [95% CI]	p-value
AF Incidence	**HPDS*Sex**	0.034	**Females**	108972	3434		
			Q1 (Ref.)	21139	695	1.00	
			Q2	25488	855	0.97 [0.88,1.07]	0.545
			Q3	28146	901	0.89 [0.81,0.99]	0.024
			Q4	30765	983	0.87 [0.79,0.96]	0.006
			Males	83302	5479		
			Q1 (Ref.)	25002	1617	1.00	
			Q2	19992	1443	1.05 [0.98,1.13]	0.176
			Q3	17671	1294	1.04 [0.96,1.12]	0.341
			Q4	15158	1125	1.04 [0.96,1.13]	0.303
Overweight/Obesity	**HPDS*Sex**	<0.001	**Females**	106771	6105		
			Q1 (Ref.)	19640	1638	1.00	
			Q2	24243	1556	0.87 [0.81,0.94]	<0.001
			Q3	27027	1498	0.82 [0.76,0.88]	<0.001
			Q4	29756	1413	0.73 [0.67,0.78]	<0.001
			Males	81704	4658		
			Q1 (Ref.)	24374	1694	1.00	
			Q2	19862	1173	0.91 [0.85,0.99]	0.019
			Q3	17641	976	0.89 [0.82,0.96]	0.003
			Q4	15169	815	0.90 [0.82,0.98]	0.015
	HPDS*Townsend	<0.001	**< -2.6**	86836	4327		
			Q1 (Ref.)	19909	1243		
			Q2	20773	1126	0.92 [0.84,1.00]	0.038
			Q3	21110	1039	0.87 [0.80,0.95]	0.001
			Q4	20717	919	0.82 [0.75,0.90]	<0.001
			>= 2.6	101639	6436		
			Q1 (Ref.)	24105	2089	1.00	
			Q2	23332	1603	0.87 [0.82,0.93]	<0.001

			Q3	23558	1435	0.83 [0.78,0.89]	<0.001
			Q4	24208	1309	0.77 [0.72,0.83]	<0.001
Hypertension	**HPDS*Sex**	<0.001	**Females**	88179	10394		
			Q1 (Ref.)	15127	2203	1.00	
			Q2	18667	2598	0.96 [0.90,1.02]	0.172
			Q3	20956	2665	0.87 [0.82,0.93]	<0.001
			Q4	23035	2928	0.88 [0.83,0.94]	<0.001
			Males	61307	10000		
			Q1 (Ref.)	16359	3236	1.00	
			Q2	13161	2597	0.99 [0.94,1.05]	0.766
			Q3	11700	2246	0.98 [0.92,1.03]	0.397
			Q4	10087	1921	0.97 [0.92,1.04]	0.409
	HPDS*Townsend	<0.001	**< -2.6**	68962	9324		
			Q1 (Ref.)	14285	2403	1.00	
			Q2	14867	2454	1.02 [0.96,1.08]	0.613
			Q3	15369	2248	0.92 [0.87,0.98]	0.010
			Q4	15117	2219	0.95 [0.89,1.01]	0.103
			>= 2.6	80524	11070		
			Q1 (Ref.)	17201	3036		
			Q2	16961	2741	0.94 [0.89,1.00]	0.045
			Q3	17287	2663	0.93 [0.88,0.99]	0.016
			Q4	18005	2630	0.92 [0.87,0.97]	0.005
Hyperglycaemia/Type 2 Diabetes	**HPDS*Sex**	<0.001	**Females**	107570	3437		
			Q1 (Ref.)	20560	934		
			Q2	25164	833	0.80 [0.73,0.88]	<0.001
			Q3	27886	820	0.75 [0.68,0.83]	<0.001
			Q4	30523	850	0.73 [0.66,0.81]	<0.001
			Males	81169	4569		
			Q1 (Ref.)	24346	1623	1.00	
			Q2	19734	1168	0.95 [0.88,1.03]	0.182
			Q3	17526	939	0.90 [0.83,0.97]	0.010
			Q4	14994	839	0.97 [0.89,1.06]	0.547
	HPDS*Townsend	<0.001	**< -2.6**	87041	3154		

			Q1 (Ref.)	20258	980	1.00	
			Q2	21143	805	0.87 [0.79,0.96]	0.005
			Q3	21460	714	0.82 [0.74,0.91]	<0.001
			Q4	21026	655	0.81 [0.73,0.90]	<0.001
			>= **2.6**	101698	4852		
			Q1 (Ref.)	24648	1577	1.00	
			Q2	23755	1196	0.90 [0.83,0.98]	0.011
			Q3	23952	1045	0.86 [0.79,0.93]	<0.001
			Q4	24491	1034	0.90 [0.83,0.98]	0.020

Cox proportional hazard model were adjusted by age (timescale), sex (except when represented the stratification factor), ethnicity, Townsend deprivation index (except when represented the stratification factor), average house income, education level, dietary supplement use, history of cancer diagnosis, history of hyperglycemia/type 2 diabetes diagnosis (except when hyperglycemia/type 2 diabetes was the outcome), physical activity level, sitting, sleep quality, smoke habits. AF, Atrial Fibrillation; HPDS, heart-protective diet score; HR, Hazard Ratio.
*Adjusted p-values were obtained using Benjamini-Hochberg procedure.

Table S13. Sensitivity analyses: association between quartiles of heart-protective diet score and risk of incident cardiovascular diseases and cardiometabolic abnormalities excluding self-reported diagnoses.

Outcomes	N	Events	HR [95% CI]	p-value
CVD incidence	196294	22064		
Q1 (Ref.)	42954	6129	1.00	
Q2	43513	5636	0.97 [0.93,1.00]	0.064
Q3	43703	5303	0.93 [0.90,0.97]	<0.001
Q4	44060	4996	0.91 [0.87,0.94]	<0.001
IHD Incidence	196294	12549		
Q1 (Ref.)	45405	3678	1.00	
Q2	45966	3183	0.94 [0.89,0.98]	0.007
Q3	46013	2993	0.92 [0.88,0.97]	0.001
Q4	46361	2695	0.87 [0.83,0.91]	<0.001
MI incidence	196294	3450		
Q1 (Ref.)	48011	1072	1.00	
Q2	48265	884	0.93 [0.85,1.02]	0.139
Q3	48190	816	0.92 [0.84,1.01]	0.074
Q4	48378	678	0.82 [0.74,0.90]	<0.001
Stroke Incidence	196294	3199		
Q1 (Ref.)	48210	873	1.00	
Q2	48326	823	0.98 [0.89,1.08]	0.724
Q3	48274	732	0.88 [0.80,0.98]	0.016
Q4	48285	771	0.95 [0.85,1.05]	0.278
HF Incidence	196294	3509		
Q1 (Ref.)	48058	1025	1.00	
Q2	48255	894	0.94 [0.86,1.02]	0.153
Q3	48189	817	0.88 [0.80,0.96]	0.006
Q4	48283	773	0.86 [0.78,0.95]	0.003
AF Incidence	196294	9085		
Q1 (Ref.)	46721	2362	1.00	
Q2	46801	2348	1.02 [0.96,1.08]	0.504
Q3	46762	2244	0.99 [0.93,1.05]	0.629
Q4	46925	2131	0.96 [0.91,1.02]	0.216
Hypertension	188623	19149		
Q1 (Ref.)	41933	5111	1.00	
Q2	42250	4929	1.00 [0.95,1.05]	0.925
Q3	42594	4566	0.93 [0.88,0.98]	0.006
Q4	42697	4543	0.94 [0.89,0.98]	0.011
Hyperglycaemia/Type 2 Diabetes	193566	8213		
Q1 (Ref.)	45694	2608	1.00	
Q2	46409	2061	0.87 [0.82,0.93]	<0.001
Q3	46543	1814	0.83 [0.78,0.89]	<0.001
Q4	46707	1730	0.84 [0.78,0.90]	<0.001

Cox proportional hazard model adjusted by age (timescale), sex, ethnicity, Townsend deprivation index, average house income, education level, dietary supplement use, history of cancer diagnosis, history of hyperglycemia/type 2 diabetes diagnosis (except when hyperglycemia/type 2 diabetes was the outcome), physical activity level, sitting, sleep quality, smoke habits. HR, Hazard Ratio.

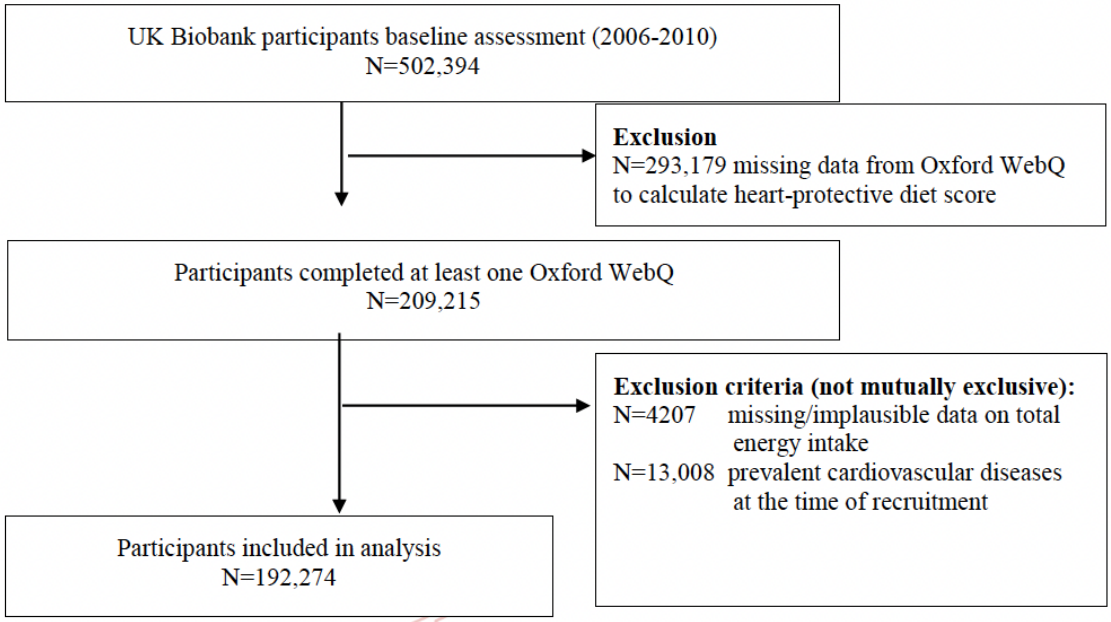


Figure S1. Flow diagram of participants included in the study.

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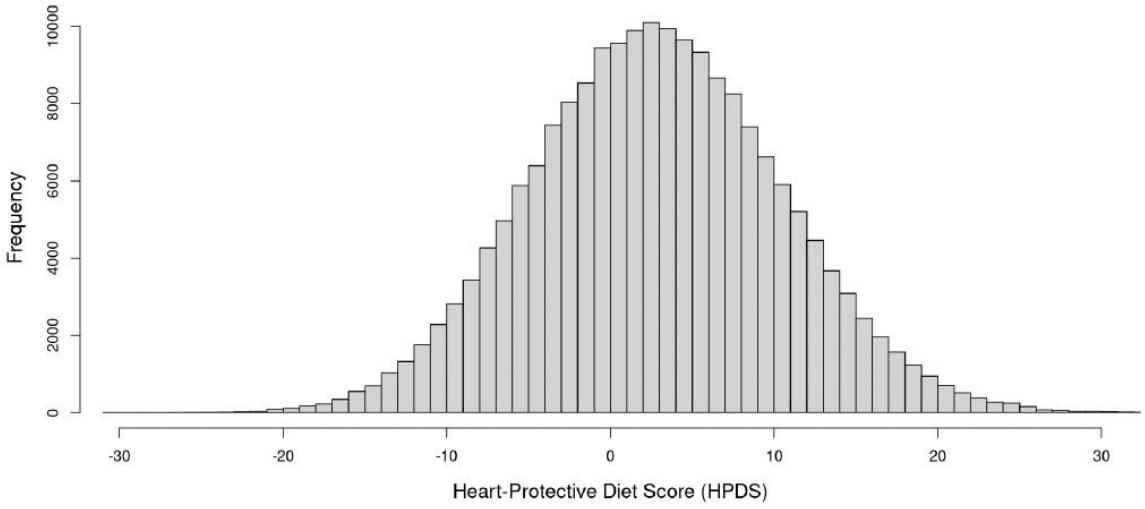


Figure S2. Distribution of the heart-protective diet score

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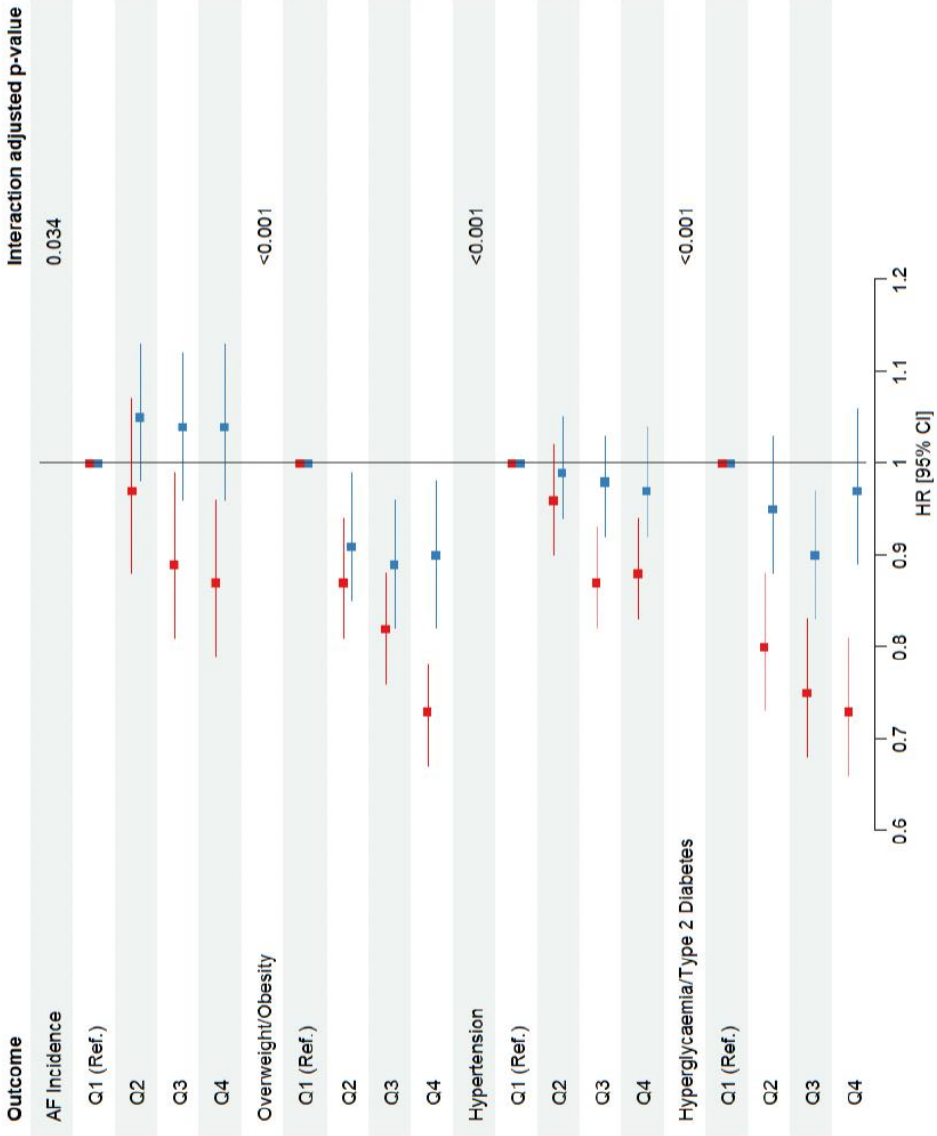


Figure S3. Stratified analyses for statistically significant interactions between heart-protective diet score and sex. Data presented as adjusted hazard ratio [95% confidence interval]. Q1 was used as the reference group. Cox proportional hazard models were adjusted by age (timescale), sex (except when represented the stratification factor), ethnicity, Townsend deprivation index (except when represented the stratification factor), average house income, education level, dietary supplement use, history of cancer diagnosis, history of hyperglycemia/type 2 diabetes diagnosis (except when hyperglycemia/type 2 diabetes was the outcome), physical activity level, sifting, sleep quality, smoke habits. HR, Hazard Ratio. Adjusted p-values were obtained using Benjamini-Hochberg procedure.

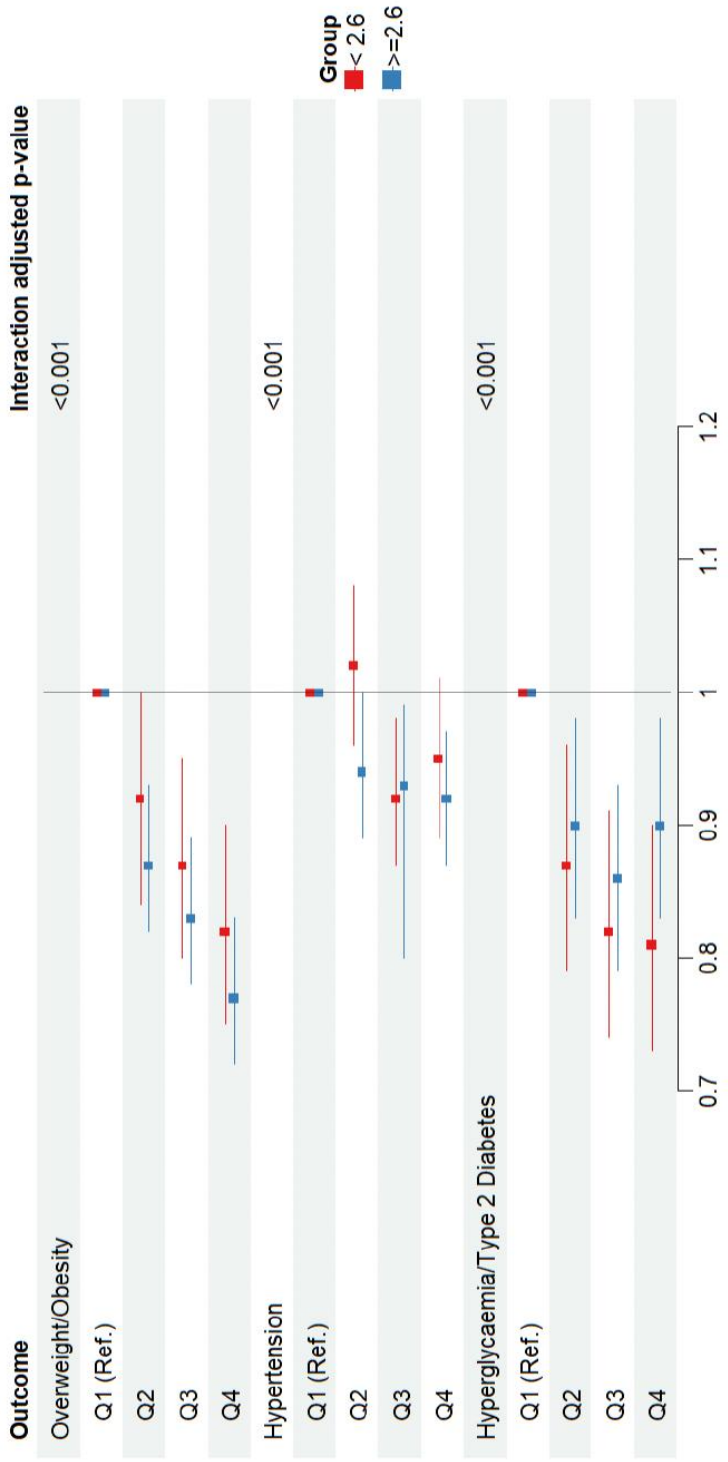


Figure S4. Stratified analyses for statistically significant interactions between heart-protective diet score and Townsend deprivation index. Data presented as adjusted hazard ratio [95% confidence interval]. Q1 was used as the reference group. Cox proportional hazard models were adjusted by age (timescale), sex (except when represented the stratification factor), ethnicity, Townsend deprivation index (except when represented the stratification factor), average house income, education level, dietary supplement use, history of cancer diagnosis, history of hyperglycemia/type 2 diabetes diagnosis (except when hyperglycemia/type 2 diabetes was the outcome), physical activity level, sitting, sleep quality, smoke habits. HR, Hazard Ratio. Adjusted p-values were obtained using Benjamini-Hochberg procedure.

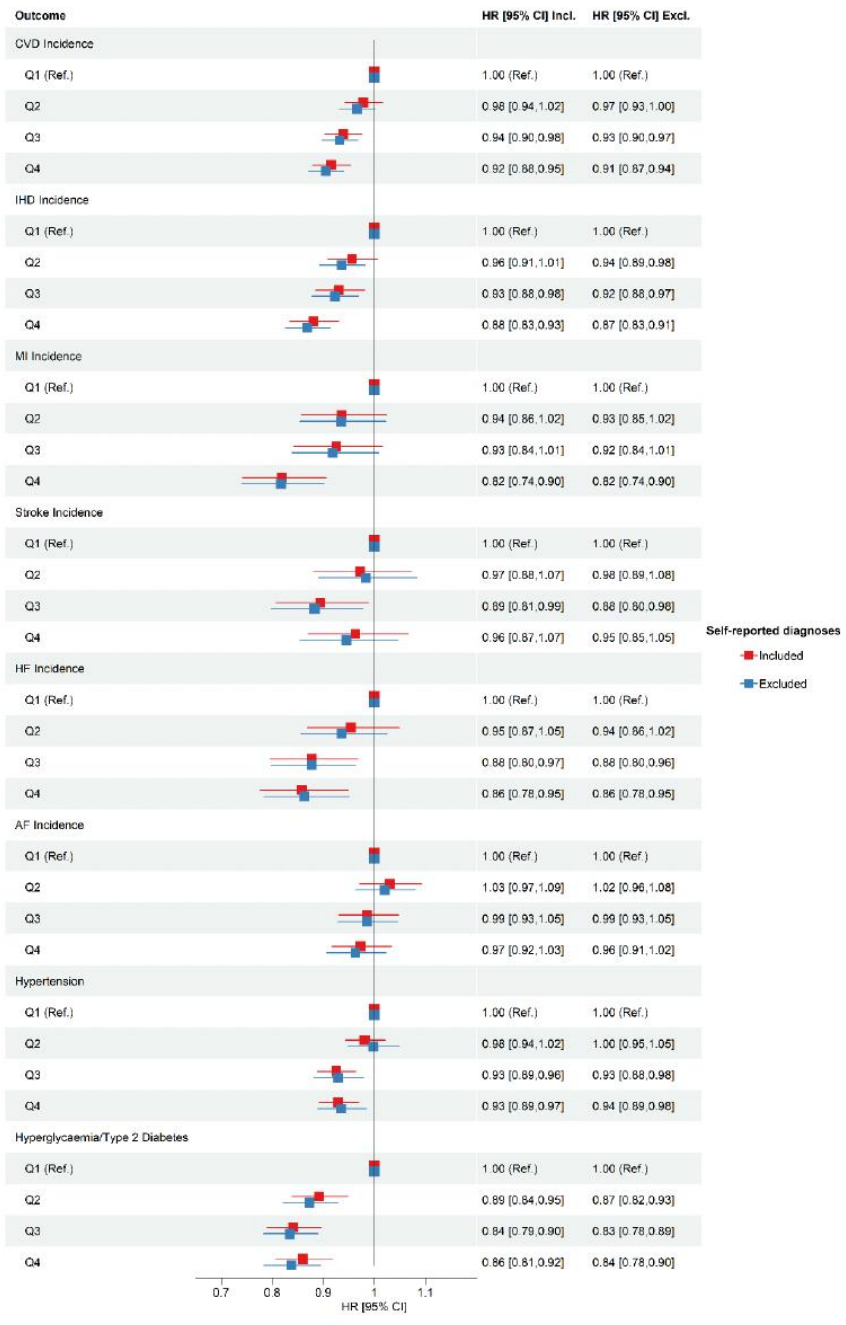


Figure S5. Sensitivity analysis: association between quartiles of heart-protective diet score and risk of incident cardiovascular diseases and cardiometabolic abnormalities including and excluding self-reported diagnoses. Data presented as adjusted hazard ratio [95% confidence interval]. Q1 was used as the reference group. Cox proportional hazard models were adjusted by age (timescale), sex, ethnicity, Townsend deprivation index, average house income, education level,

dietary supplement use, history of cancer diagnosis, history of hyperglycemia/type 2 diabetes diagnosis, physical activity level, sitting, sleep quality, smoke habits. CVD, Cardiovascular Disease; IHD, Ischemic Heart Disease; MI, Myocardial Infarction; HF, Heart Failure; AF, Atrial Fibrillation; HR, Hazard Ratio. Adjusted p-values were obtained using Benjamini-Hochberg procedure.

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References

1. Bycroft C, Freeman C, Petkova D, et al. The UK Biobank resource with deep phenotyping and genomic data. *Nature*. 2018;**562**(7726):203-9.
2. Liu B, Young H, Crowe FL, et al. Development and evaluation of the Oxford WebQ, a low-cost, web-based method for assessment of previous 24 h dietary intakes in large-scale prospective studies. *Public Health Nutr*. 2011;**14**(11):1998-2005.
3. Bradbury KE, Young HJ, Guo W, Key TJ. Dietary assessment in UK Biobank: an evaluation of the performance of the touchscreen dietary questionnaire. *J Nutr Sci*. 2018;**7**:e6.
4. Adams J, Ryan V, White M. How accurate are Townsend Deprivation Scores as predictors of self-reported health? A comparison with individual level data. *J Public Health (Oxf)*. 2005;**27**(1):101-6.
5. Guidelines for data processing and analysis of the International Physical Activity Questionnaire (IPAQ) 2005 [Available from: http://www.IPAQ.ki.se.
6. Craig CL, Marshall AL, Sjöström M, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc*. 2003;**35**(8):1381-95.
7. Fan M, Sun D, Zhou T, et al. Sleep patterns, genetic susceptibility, and incident cardiovascular disease: a prospective study of 385 292 UK biobank participants. *Eur Heart J*. 2020;**41**(11):1182-9.
8. Chen F, Ding C, Du M, et al. Plant- and animal-based diet quality and mortality among US adults: a cohort study. *British Journal of Nutrition*. 2021;**125**(12):1405-15.
9. Caivano S, Colugnati FAB, Domene SMÁ. Diet Quality Index associated with Digital Food Guide: update and validation. *Cadernos de Saúde Pública*. 2019;**35**.
10. Bromage S, Batis C, Bhupathiraju SN, et al. Development and Validation of a Novel Food-Based Global Diet Quality Score (GDQS). *The Journal of Nutrition*. 2021;**151**:75S-92S.
11. Satija A, Bhupathiraju SN, Spiegelman D, et al. Healthful and Unhealthful Plant-Based Diets and the Risk of Coronary Heart Disease in U.S. Adults. *J Am Coll Cardiol*. 2017;**70**(4):411-22.

9.3 Supplementary Materials for Chapter 5

Secondary outcomes

Perivascular Adipose Tissue (PVAT)

Perivascular adipose tissue (PVAT) is a new biomarker of coronary inflammation enhancing cardiac risk prediction [156]. The PVAT will be measured at baseline from the initial clinically indicated CCTA and then at 12 months (End-study CCTA visit).Perivascular adipose tissue (PVAT) is a new biomarker of coronary inflammation enhancing cardiac risk prediction [156]. The PVAT will be measured at baseline from the initial clinically indicated CCTA and then at 12 months (End-study CCTA visit).

Myocardial inflammation and diffuse myocardial fibrosis

Myocardial inflammation and diffuse myocardial fibrosis will be quantified at baseline and 12 months by T1 mapping, T2 mapping, and extracellular volume (ECV) mapping by MRI [157].

Myocardial infarction or non-ischemic scarring

Presence and severity of myocardial infarction or non-ischemic scarring will be measured at baseline and 12 months using MRI late gadolinium enhancement [158, 159].

Coronary spasm

Coronary spasm will be measured at baseline and 12 months using quantitative myocardial perfusion mapping by MRI [160] during cold pressor testing [161].

Diastolic dysfunction

Diastolic dysfunction will be measured at baseline and 12 months using MRI encompassing diastolic blood flow velocities across the mitral valve (E, A), diastolic myocardial tissue velocities (e'), left atrial volume index, mean pulmonary artery pressure [162], and left atrial strain [163].

Pulmonary congestion during exercise

Pulmonary congestion at rest and during exercise will be measured at baseline and 12 months during supine ergometry MRI using lung water density mapping [164].

Secondary plaque characteristics

Components of atheroma will be distinguished based on tissue attenuation ranges in Hounsfield units (HU), at baseline as a clinically indicated CCTA (i.e. not part of this study) and then at 12 months (End-study CCTA visit) for this study. Noncalcified plaque volume (encompassing fibrofatty and low attenuation plaque), dense calcified plaque and total atheroma volume (TAV) will be measured. TAV is calculated as; Total vessel volume – total lumen volume.

Liver fat fraction (%)

The degree of hepatic steatosis will be evaluated using the MR proton density fat fraction (PDFF) technique, at the same time as the participant is undergoing cardiac imaging. MR PDFF generates quantitative volumetric measurements of fat density in the liver, and produces an evaluation report displaying percentage of fat density throughout the liver. MR PDFF has been shown to have a high degree of correlation with liver biopsy [165, 166] and studies have also found

it to have superior accuracy compared with controlled attenuation parameter (*Fibroscan*) for the diagnosis and grading of steatosis in participants with biopsy proven non-alcoholic fatty liver disease [167-169]. The AUROC in a number of studies has been >=0.90 for MR PDFF [168-170]. MR PDFF is currently the most accurate non-invasive method of assessing hepatic steatosis [167-169], and allows assessment of the entire volume of the liver, better accounting for fat heterogeneity.

Flow-mediated dilatation (FMD) (%)

FMD will be measured at baseline, month 1, month 6 and at follow up. Assessment of vascular endothelial function by FMD is performed using high-resolution ultrasound (*Philips EPIQ 7*) with a 10 MHz linear array transducer (or similar) and ECG gating. A non-invasive method is employed which involves a brief (5-minute) cuff-mediated arterial occlusion in the arm followed by non-invasive ultrasound scanning of the artery proximal to the site of occlusion.

Carotid intima-media thickness (cIMT) (mm)

cIMT will be measured at baseline, 1 month, 6 months and 12 months follow up. This involves bilateral ultrasound examination of the right and left distal common carotid arteries using a high-resolution ultrasound (*Philips EPIQ 7*) with a 10 MHz linear array transducer (or similar) and ECG gating. Mean cIMT of the far wall will be measured offline from a section of the vessel at least 5 mm below the end of the common carotid artery, as per Mannheim Carotid Intima-Media Thickness and Plaque Consensus [171], using validated semi-automated edge-detection software.

Pulse wave velocity (PWV) (m/s) and Augmentation Index (AI) (%)

PWV and AI will be measured at baseline, 1 month, 6 months and follow up. The *SphygmoCor XCEL* system enables the non-invasive measurement of PWV of the blood pressure waveform travelling between two arterial sites. Measurements will be performed by recording pressure waveforms concurrently at the carotid artery (using a tonometer pressure sensor) and the femoral artery (using a specialised blood pressure cuff). The *SphygmoCor XCEL* system also enables us to assess peripheral arterial stiffness as an output using the AI. AI = (P2-P1)x100/P1(%), where P1=pulse pressure and P2=pressure corresponding to the inflection point on the pulse wave.

Heart rate variability (HRV): Low Frequency (LF) and High Frequency (HF) (ms^2)

HRV, LF and HF will be measured at baseline, 1 month, 6 months and follow up. Continuous blood pressure waveform and ECG will be recorded for 10 minutes in the supine position, using the Human Non-Invasive Blood Pressure System (NIBP). The Human NIBP system also accurately determines beat-to-beat blood pressure. Together, these enable assessment of autonomic cardiovascular control such as heart rate variability, spontaneous baroreflex function, and blood pressure variability [172]. The human NIBP system operates via a photoplethysmographic cuff (blood pressure cuff with an infrared sensitive photocell), a pressure manometer, an automatic unit for cuff inflation, a 3-lead ECG and a monitor for the digital display of systolic blood pressure, diastolic blood pressure and heart rate. The finger cuff is designed for the adult finger with an automated calibration device attached to the cuff which maintains constant transmural pressure on the finger. Therefore, assessment of autonomic function will be derived from the recorded blood pressure and ECG trace.[172]. The human NIBP system operates via a photoplethysmographic cuff (blood pressure cuff with an infrared sensitive photocell), a pressure manometer, an automatic unit for cuff inflation, a 3-lead ECG and a monitor for the digital display of systolic blood pressure, diastolic blood pressure and heart rate. The finger cuff is designed for the adult finger with an automated calibration device attached to the cuff which maintains constant transmural pressure on the finger. Therefore, assessment of autonomic function will be derived from the recorded blood pressure and ECG trace.

Heart Age by electrocardiography

Electrocardiographic (ECG) Heart Age has been shown to accurately reflect biological age in healthy volunteers, and to increase in relation to chronological age in subjects with cardiovascular risk factors or established heart disease [173]. Anecdotally, ECG Heart Age has been shown to reduce following lifestyle improvements. ECG Heart Age will be measured by resting 12-lead ECG at baseline and 12 months.Electrocardiographic (ECG) Heart Age has been shown to accurately reflect biological age in healthy volunteers, and to increase in relation to chronological age in subjects with cardiovascular risk factors or established heart disease [173]. Anecdotally, ECG Heart Age has been shown to reduce following lifestyle improvements. ECG Heart Age will be measured by resting 12-lead ECG at baseline and 12 months.

Sleep Parameters

All participants will undergo a clinical home sleep test (HST). The home sleep device is TGA approved and is used clinically in Australia. The Nox-T3+ device by NoxMedical (Iceland) is a level 2 device. The variables collected include oximetry, nasal airflow signal via a nasal pressure transducer, as well as respiratory effort and pulse signals, EEG and ECG. Participants will wear the device overnight to assess a number of sleep parameters including total sleep time (mins), sleep latency, sleep efficiency (total sleep time/time in bed*100, %), time in various sleep stages. Sleep disorders such as Obstructive Sleep Apnoea will be quantified according to clinical standards. Participants diagnosed with a clinical sleep disorder will be referred to their GP for consideration of clinical management as required.

The following questionnaires will also be given to participants as a measure of sleep (SAGIC short, Stop Bang, and Epworth sleepiness scale). All questionnaires will be administered to participants during their clinic visits through the secure SLHD REDCap database. Any questionnaires that do not get completed during visit hours will be sent to participants to complete via email.

Explanatory endpoints

Body composition

- Weight (cm): This will be measured at baseline, 1 month, 6 months and 12 months using a standardized electronic standing scale. All measurements will be performed after an overnight fast at approximately the same time and under similar conditions.
- Height (cm): Height will be measured at screening only using a wall-mounted stadiometer in conjunction with a right- angled head board. Shoes and head dressing will be removed and participant's head will be positioned in the Frankfort plane (the orbitale (lower edge of the eye socket) is in the same horizontal plane as the tragion (the top notch of the ear). Height measurements will be repeated to obtain 2 values that are identical or close to one another (within 0.1cm) and the average of the two measurements will be used.
- Waist/Hip ratio (cm): This will be measured at screening, 1 month, 6 months and 12 months. Waist circumference will be measured at the midpoint between the lower margin of the least palpable rib and the top of the iliac crest. Hip circumference will be measured around the widest portion of the buttocks, with the tape parallel to the floor [174]. Hip circumference will be measured around the widest portion of the buttocks, with the tape parallel to the floor [174].
- DEXA body composition: Whole body fat mass (FM (kg)), whole body fat-free mass (FFM (kg)), visceral fat area (cm^2) and bone mineral density (BMD (g/cm^2)) of the hip and anterior posterior lumbar spine (L1-L4) will be measured. Body fat, lean mass, bone mineral density (BMD) bone mineral content (BMC), and bone areas will be measured by DEXA using our Hologic Discovery W Dual Energy X-Ray Absorptiometry Scanner. This will be performed as the baseline visit and the follow up visit. Measurements using DEXA have replaced underwater weighing as the reference standard for body composition studies, reflecting the ease of use, the low radiation dose, and the fact that it provides a 3-compartment model of body density, i.e., lean body mass, bone mass, and fat mass, compared to the 2-compartment model of underwater weighing. Measurements will be made using a standardized protocol for subject positioning, scan mode and analysis. The measurements will take approximately 30 minutes to perform.

Intermediate risk factors that are predictive of developing atherosclerosis

- Glucose (mmol/L) and Insulin (pmol/L): Measured at baseline and at 12 months during an OGTT (oral glucose tolerance test) examination. After an overnight fast a cannula will be placed in the antecubital vein for blood

sampling. A fasting sample will be taken, then participants will consume a 75g glucose load/drink over a 5 min period. Blood samples will be collected at 0 min, 30 min, 60 min, 90 min and 120 min and centrifuged for plasma and serum. These will be stored in -80°C freezer storage until the end of the study when they will be assessed for glucose and insulin.

- Blood pressure (mmHg): Blood pressure will be recorded at baseline, 1 month, 6 months and 12 months. 2 measurements will be recorded after the participant has been sat down for 10 mins. An average of 3 readings will be taken. At least two readings will be taken, with a one-minute interval between them, and the average of the measurements recorded. Additional readings should be taken if the difference between the first two is greater than 5 mm Hg. Blood pressure will be assessed using the SphygmoCor XCEL device (Atcor Medical, Sydney), which also calculates central blood pressure based on the peripheral pulse waveform.
- Blood Biomarkers: At the baseline and 12-month visit, bloods will be taken as standard care for FBC, EUC, LFTs, lipids, HbA1c, and glucose. These bloods will be sent immediately for analysis in an accredited hospital laboratory.

Urinary levels of F2-isoprostane levels

First morning void (12 hour specimen) with a midstream clean catch specimen is collected by the participant for biochemical analysis including markers of oxidative stress, urinary F2-isoprostanes [175].First morning void (12 hour specimen) with a midstream clean catch specimen is collected by the participant for biochemical analysis including markers of oxidative stress, urinary F2-isoprostanes [175].

Serum hormones, proteomics, lipidomics, metabolomics, genetic and epigenetic profiling

Blood samples will be processed and analysed with state-of-the-art ELISA, metabolomics and proteomic techniques. Faeces will be collected for microbiome analysis including 16S rRNA sequencing [176, 177]. Protocol for collection will be mentioned inside the collection kit. Genetic and epigenetic profiling will be undertaken in order to understand individual variation in disease phenotype and how genotype influences response to this lifestyle intervention. For example, we know that people with the PNPLA3 genotype (that causes fatty liver disease) respond better to dietary restriction, while other genes like FGF21 are involved with nutrient intake. This analysis will be based on the latest next generation technologies including genome wide association studies, candidate gene studies, exome sequencing, epigenetic association studies and studies of the circulating proteome and metabolome.

6-minute walk test distance (m)

The 6-minute walk test (6-MWT) is a submaximal exercise test that entails measurement of distance walked over a span of 6 minutes. Participants will be asked to walk as far as they can between 2 cones roughly 30 metres apart, within the 6 minutes. A member of the research team will supervise the test and record distance.

Dietary intake (total daily kJ, macronutrient and micronutrient intake (%))

Dietary intake will be assessed for 4 consecutive days (three weekdays and one weekend day) at baseline visits, 1 month, 3 months, 6 months, 9 months and then again at 12 months. At the baseline visit, the study dietitian will meet with participants individually to instruct them on how to use the *Research Food Diary* (Xyris Software Australia Pty Ltd) phone app. Participants will be asked to record their food intake through this app by scanning a barcode or searching individual food items. To improve the accuracy of self-reported dietary data, the study dietitian will provide training of portion size estimation, and food scales and household measures will be given to participants to assist them in completing food diary. After participants enter food intake data into the *Research Food Diary*, the data will be sent to the study dietitian and research team with generated nutrient analysis (average intake of energy, macronutrient and micronutrient) with FoodWorks 10 software which contains the AUSNUT database.

Time spent in moderate physical activity

A *Fitbit* activity tracker will be worn for 7 consecutive days between two baseline visits, and then at the end of the intervention between the 12-month and Follow-up visits. The tracker will record steps, distance, active minutes, heart rate and calories burned. It will also record workouts like walks, runs, swims and bike rides. Participants will also be asked to complete a 7-Day Physical Activity Recall (PAR). PAR is a semi-structured interview that estimates an individual's time spent in physical activity, strength, and flexibility activities for the previous 7 days. The interviewer guides the participant through the recall process, day-by-day, to determine duration and intensity of the physical activities.

Psychometrics

To better understand individual variability in treatment response, we plan to implement outcomes developed by the Accumulating Data to Optimally Predict obesity Treatment (ADOPT) Core Measures Project [178].To better understand individual variability in treatment response, we plan to implement outcomes developed by the Accumulating Data to Optimally Predict obesity Treatment (ADOPT) Core Measures Project [178]. The ADOPT working group identified a core list of current, best constructs and measures to include in trials with the included goal of losing weight. Using comparable outcomes will help the research community identify predictors of treatment response, as well as advance the design of clinical trials to help tailor behavioural interventions involving weight loss and metabolic disease. In addition to other biological outcomes being measured in this study, ADOPT recommends assessing psychosocial, behavioural, and environmental domains. Affect and stress can impact non-homeostatic eating in a way that promotes increased deposition of visceral fat and metabolic disease [179-181]. Further, it will be meaningful to determine whether these psychometric outcomes change as a result of this intensive lifestyle intervention, which includes mindfulness-based stress reduction. A list of the questionnaires, time burden, constructs measured, and time points obtained are described below. To ensure participant autonomy, we will inform study participants that their participation in these surveys is voluntary, they may stop the process at any time, and questions may be skipped.

Psychosocial, Behavioural and Environmental Predictors of Response			**TIME POINT OBTAINED**	
Questionnaire to be Used	**Time (mm:ss)**	**Construct Measured**	**0**	**12**
Positive and Negative Affect Schedule (PANAS)	01:35	positive and negative affect	x	x
Perceived Stress Scale (PSS)	01:32	perceived stress	x	x
RED (Reward based eating drive)	01:01	reward based eating drive	x	x
Mini-IPIP (International Personality Item Pool)	01:26	personality	x	x
Weight Efficacy Lifestyle-Short Form (WEL-SF)	00:30	diet self-efficacy	x	x
POMS (Profile of Mood States, 40-item)	00:40	mood	x	x
RAND-36	02:30	health-related quality of life	x	x
Australian Quality of Life (AQOL)	02:00	social-related quality of life	x	x

Life Events Questionnaire (LEQ)	02:00	stressful life events (past 12 months)	x	x
Body Perception Questionnaire-Short Form (BPQ)*	1:00	subjective body awareness and autonomic reactivity	x	x
Adverse Childhood Experiences International (ACE-IQ)**	10:00	history of past adverse experiences	x	
Traumatic Antecedents Questionnaire (TAQ)**	10:00	history of past trauma by age	x	
Social Support for Healthy Behaviours	3:30	perceived social support for healthy eating and physical activity	x	x
Mindful, Attention and Awareness Scale (MAAS)	01:27	state of mindfulness	x	x
Self-Compassion Scale (SCS-SF)	01:42	trait levels of self-compassion	x	x
Substance Use Risk Profile Scale (SURPS)	02:27	personality risk profiles associated with addiction	x	x
Estimated Time all Outcome Questionnaires at each Time Point (mm:ss)			42:20	22:20

*The BPQ also will be measured at month 1 and 6, as it pairs well with objective measures of autonomic function: FMD (flow-mediated dilatation) and HRV (heart rate variability)

**Optional

References

1. Oikonomou EK, Marwan M, Desai MY, Mancio J, Alashi A, Hutt Centeno E, Thomas S, Herdman L, Kotanidis CP, Thomas KE, Griffin BP, Flamm SD, Antonopoulos AS, Shirodaria C, Sabharwal N, Deanfield J, Neubauer S, Hopewell JC, Channon KM, Achenbach S, Antoniades C. Non-invasive detection of coronary inflammation using computed tomography and prediction of residual cardiovascular risk (the CRISP CT study): a post-hoc analysis of prospective outcome data. The Lancet. 2018;392(10151):929-39.
2. Messroghli DR, Moon JC, Ferreira VM, Grosse-Wortmann L, He T, Kellman P, Mascherbauer J, Nezafat R, Salerno M, Schelbert EB, Taylor AJ, Thompson R, Ugander M, van Heeswijk RB, Friedrich MG. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: A consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). J Cardiovasc Magn Reson. 2017;19(1):75.
3. Mahrholdt H, Wagner A, Judd RM, Sechtem U, Kim RJ. Delayed enhancement cardiovascular magnetic resonance assessment of non-ischaemic cardiomyopathies. Eur Heart J. 2005;26(15):1461-74.
4. Piehler KM, Wong TC, Puntil KS, Zareba KM, Lin K, Harris DM, Deible CR, Lacomis JM, Czeyda-Pommersheim F, Cook SC, Kellman P, Schelbert EB. Free-breathing, motion-corrected late gadolinium enhancement is robust and extends risk stratification to vulnerable patients. Circ Cardiovasc Imaging. 2013;6(3):423-32.
5. Kellman P, Hansen MS, Nielles-Vallespin S, Nickander J, Themudo R, Ugander M, Xue H. Myocardial perfusion cardiovascular magnetic resonance: optimized dual sequence and reconstruction for quantification. J Cardiovasc Magn Reson. 2017;19(1):43.
6. Fairbairn TA, Motwani M, Mather AN, Biglands JD, Larghat AM, Radjenovic A, Greenwood JP, Plein S. Cardiac MR imaging to measure myocardial blood flow response to the cold pressor test in healthy smokers and nonsmokers. Radiology. 2014;270(1):82-90.
7. Ramos JG, Fyrdahl A, Wieslander B, Thalen S, Reiter G, Reiter U, Jin N, Maret E, Eriksson M, Caidahl K, Sorensson P, Sigfridsson A, Ugander M. Comprehensive Cardiovascular Magnetic Resonance Diastolic Dysfunction Grading Shows Very Good Agreement Compared With Echocardiography. JACC Cardiovasc Imaging. 2020;13(12):2530-42.
8. Backhaus SJ, Lange T, George EF, Hellenkamp K, Gertz RJ, Billing M, Wachter R, Steinmetz M, Kutty S, Raaz U, Lotz J, Friede T, Uecker M, Hasenfuss G, Seidler T, Schuster A. Exercise Stress Real-Time Cardiac Magnetic Resonance Imaging for Noninvasive Characterization of Heart Failure With Preserved Ejection Fraction: The HFpEF-Stress Trial. Circulation. 2021;143(15):1484-98.
9. Thompson RB, Chow K, Pagano JJ, Sekowski V, Michelakis ED, Tymchak W, Haykowsky MJ, Ezekowitz JA, Oudit GY, Dyck JRB, Kaul P, Savu A, Paterson DI. Quantification of lung water in heart failure using cardiovascular magnetic resonance imaging. J Cardiovasc Magn Reson. 2019;21(1):58.
10. Middleton MS, Heba ER, Hooker CA, Bashir MR, Fowler KJ, Sandrasegaran K, Brunt EM, Kleiner DE, Doo E, Van Natta ML, Lavine JE, Neuschwander-Tetri BA, Sanyal A, Loomba R, Sirlin CB, Network NCR. Agreement Between Magnetic Resonance Imaging Proton Density Fat Fraction Measurements and Pathologist-Assigned Steatosis Grades of Liver Biopsies From Adults With Nonalcoholic Steatohepatitis. Gastroenterology. 2017;153(3):753-61.
11. Idilman IS, Aniktar H, Idilman R, Kabacam G, Savas B, Elhan A, Celik A, Bahar K, Karcaaltincaba M. Hepatic steatosis: quantification by proton density fat fraction with MR imaging versus liver biopsy. Radiology. 2013;267(3):767-75.
12. Park CC, Nguyen P, Hernandez C, Bettencourt R, Ramirez K, Fortney L, Hooker J, Sy E, Savides MT, Alquiraish MH, Valasek MA, Rizo E, Richards L, Brenner D, Sirlin CB, Loomba R. Magnetic Resonance

Elastography vs Transient Elastography in Detection of Fibrosis and Noninvasive Measurement of Steatosis in Patients With Biopsy-Proven Nonalcoholic Fatty Liver Disease. Gastroenterology. 2017;152(3):598-607 e2.

13. Paige JS, Bernstein GS, Heba E, Costa EAC, Fereirra M, Wolfson T, Gamst AC, Valasek MA, Lin GY, Han A, Erdman JW, Jr., O'Brien WD, Jr., Andre MP, Loomba R, Sirlin CB. A Pilot Comparative Study of Quantitative Ultrasound, Conventional Ultrasound, and MRI for Predicting Histology-Determined Steatosis Grade in Adult Nonalcoholic Fatty Liver Disease. AJR Am J Roentgenol. 2017;208(5):W168-W77.
14. Imajo K, Kessoku T, Honda Y, Tomeno W, Ogawa Y, Mawatari H, Fujita K, Yoneda M, Taguri M, Hyogo H, Sumida Y, Ono M, Eguchi Y, Inoue T, Yamanaka T, Wada K, Saito S, Nakajima A. Magnetic Resonance Imaging More Accurately Classifies Steatosis and Fibrosis in Patients With Nonalcoholic Fatty Liver Disease Than Transient Elastography. Gastroenterology. 2016;150(3):626-37 e7.
15. Runge JH, Smits LP, Verheij J, Depla A, Kuiken SD, Baak BC, Nederveen AJ, Beuers U, Stoker J. MR Spectroscopy-derived Proton Density Fat Fraction Is Superior to Controlled Attenuation Parameter for Detecting and Grading Hepatic Steatosis. Radiology. 2018;286(2):547-56.
16. Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N, Csiba L, Desvarieux M, Ebrahim S, Hernandez Hernandez R, Jaff M, Kownator S, Naqvi T, Prati P, Rundek T, Sitzer M, Schminke U, Tardif JC, Taylor A, Vicaut E, Woo KS. Mannheim carotid intima-media thickness and plaque consensus (2004-2006-2011). An update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the 13th, 15th and 20th European Stroke Conferences, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011. Cerebrovasc Dis. 2012;34(4):290-6.
17. Maestri R, Pinna GD, Robbi E, Capomolla S, La Rovere MT. Noninvasive measurement of blood pressure variability: accuracy of the Finometer monitor and comparison with the Finapres device. Physiol Meas. 2005;26(6):1125-36.
18. Ball RL, Feiveson AH, Schlegel TT, Starc V, Dabney AR. Predicting "heart age" using electrocardiography. J Pers Med. 2014;4(1):65-78.
19. World Health Organisation (WHO). WHO | Waist Circumference and Waist–Hip Ratio. Report of a WHO Expert Consultation. Geneva, 8-11 December 2008. 2008.
20. Bartsch H, Nair J. New DNA-based biomarkers for oxidative stress and cancer chemoprevention studies. European Journal of Cancer. 2000;36(10):1229-34.
21. de la Cuesta-Zuluaga J, Mueller NT, Alvarez-Quintero R, Velasquez-Mejia EP, Sierra JA, Corrales-Agudelo V, Carmona JA, Abad JM, Escobar JS. Higher Fecal Short-Chain Fatty Acid Levels Are Associated with Gut Microbiome Dysbiosis, Obesity, Hypertension and Cardiometabolic Disease Risk Factors. Nutrients. 2018;11(1).
22. den Besten G, van Eunen K, Groen AK, Venema K, Reijngoud DJ, Bakker BM. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. J Lipid Res. 2013;54(9):2325-40.
23. MacLean PS, Rothman AJ, Nicastro HL, Czajkowski SM, Agurs-Collins T, Rice EL, Courcoulas AP, Ryan DH, Bessesen DH, Loria CM. The Accumulating Data to Optimally Predict Obesity Treatment (ADOPT) Core Measures Project: Rationale and Approach. Obesity (Silver Spring). 2018;26 Suppl 2:S6-S15.
24. Sinha R, Jastreboff AM. Stress as a common risk factor for obesity and addiction. Biol Psychiatry. 2013;73(9):827-35.
25. Sutin AR, Boutelle K, Czajkowski SM, Epel ES, Green PA, Hunter CM, Rice EL, Williams DM, Young-Hyman D, Rothman AJ. Accumulating Data to Optimally Predict Obesity Treatment (ADOPT) Core Measures: Psychosocial Domain. Obesity (Silver Spring). 2018;26 Suppl 2:S45-S54.
26. Mason A, Epel E. Stress and Obesity: Guilford Press; 2017.

References

1. *Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013.* The Lancet, 2015. **385**(9963): p. 117-171.
2. Wang, T., et al., *Vegetarian Dietary Patterns and Cardiometabolic Risk in People With or at High Risk of Cardiovascular Disease: A Systematic Review and Meta-analysis.* JAMA Network Open, 2023. **6**(7): p. e2325658-e2325658.
3. World Health Organization. *Cardiovascular diseases (CVDs)*. 2021 11th June, 2021 [cited 2023 Aug 30th]; Available from: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds).
4. MedlinePlus. *Coronary heart disease*. 2020 2nd Jul 2020 [cited 2020 12th Jul]; Available from: https://medlineplus.gov/ency/article/007115.htm.
5. Welfare., A.I.o.H.a. *Deaths in Australia*. 2019 [cited 2020 12th Jul]; Available from: https://www.aihw.gov.au/reports/life-expectancy-death/deaths-in-australia/contents/leading-causes-of-death.
6. Australian Institute of Health and Welfare. *Heart, stroke and vascular disease: Australian facts*. 2023 [cited 2023 Aug 31st]; Available from: https://www.aihw.gov.au/reports/heart-stroke-vascular-diseases/hsvd-facts/contents/summary-of-coronary-heart-disease-and-stroke/coronary-heart-disease.
7. Timmis, A., et al., *European Society of Cardiology: cardiovascular disease statistics 2021.* European Heart Journal, 2022.
8. Greenland, P., et al., *Major risk factors as antecedents of fatal and nonfatal coronary heart disease events.* Jama, 2003. **290**(7): p. 891-7.
9. Sarwar, N., et al., *Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies.* Lancet, 2010. **375**(9733): p. 2215-22.
10. Grundy, S.M., et al., *2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.* Circulation, 2019. **139**(25): p. e1082-e1143.
11. Mortensen, M.B. and B.G. Nordestgaard, *Elevated LDL cholesterol and increased risk of myocardial infarction and atherosclerotic cardiovascular disease in individuals aged 70–100 years: a contemporary primary prevention cohort.* The Lancet, 2020. **396**(10263): p. 1644-1652.
12. Ettehad, D., et al., *Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis.* The Lancet, 2016. **387**(10022): p. 957-967.
13. Powell-Wiley, T.M., et al., *Obesity and Cardiovascular Disease: A Scientific Statement From the American Heart Association.* Circulation, 2021. **143**(21): p. e984-e1010.
14. Afshin, A., et al., *Health effects of dietary risks in 195 countries, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017.* The Lancet, 2019. **393**(10184): p. 1958-1972.
15. Willett, W., et al., *Food in the Anthropocene: the EAT–Lancet Commission on healthy diets from sustainable food systems.* The Lancet, 2019. **393**(10170): p. 447-492.
16. United Nations. *17 goals to transform our world*. 2023 [cited 2023 28th Nov]; Available from: https://www.un.org/sustainabledevelopment/.
17. World Health Organization, *Sustainable healthy diets–guiding principles*. 2019, Food and Agriculture Organization of the United Nations and the World Health Organization: Rome, Italy.
18. Hargreaves, S.M., et al., *Plant-based and vegetarian diets: an overview and definition of these dietary patterns.* European Journal of Nutrition, 2023. **62**(3): p. 1109-1121.
19. Estruch, R., et al., *Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts.* New England Journal of Medicine, 2018. **378**(25): p. e34.
20. Craig, W.J., A.R. Mangels, and A. American Dietetic, *Position of the American Dietetic Association: vegetarian diets.* Journal of the American Dietetic Association, 2009. **109**(7): p. 1266-82.

21. Dyson, P.A., et al., *Diabetes UK evidence-based nutrition guidelines for the prevention and management of diabetes.* Diabetic medicine, 2018. **35**(5): p. 541-547.
22. Sievenpiper, J.L., et al., *Nutrition Therapy.* Canadian Journal of Diabetes, 2018. **42**: p. S64-S79.
23. Huang, R.-Y., et al., *Vegetarian Diets and Weight Reduction: a Meta-Analysis of Randomized Controlled Trials.* Journal of General Internal Medicine, 2016. **31**(1): p. 109-116.
24. Lee, K.W., et al., *Effects of Vegetarian Diets on Blood Pressure Lowering: A Systematic Review with Meta-Analysis and Trial Sequential Analysis.* Nutrients, 2020. **12**(6): p. 1604.
25. Wang, F., et al., *Effects of Vegetarian Diets on Blood Lipids: A Systematic Review and Meta-Analysis of Randomized Controlled Trials.* J Am Heart Assoc, 2015. **4**(10): p. e002408.
26. Viguiliouk, E., et al., *Effect of vegetarian dietary patterns on cardiometabolic risk factors in diabetes: A systematic review and meta-analysis of randomized controlled trials.* Clinical Nutrition, 2019. **38**(3): p. 1133-1145.
27. Lichtenstein, A.H., et al., *2021 Dietary Guidance to Improve Cardiovascular Health: A Scientific Statement From the American Heart Association.* Circulation, 2021. **144**(23): p. e472-e487.
28. Heart Foundation. *Nutrition Position Statements*. 2023 [cited 2024 Feb 6]; Available from: https://www.heartfoundation.org.au/bundles/for-professionals/nutrition-position-statements.
29. Mach, F., et al., *2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS).* European Heart Journal, 2019. **41**(1): p. 111-188.
30. Glenn, A.J., et al., *Relation of Vegetarian Dietary Patterns With Major Cardiovascular Outcomes: A Systematic Review and Meta-Analysis of Prospective Cohort Studies.* Frontiers in Nutrition, 2019. **6**: p. 80.
31. Benatar, J.R. and R.A.H. Stewart, *Cardiometabolic risk factors in vegans; A meta-analysis of observational studies.* PLoS ONE [Electronic Resource], 2018. **13**(12): p. e0209086.
32. Tong, T.Y.N., et al., *Risks of ischaemic heart disease and stroke in meat eaters, fish eaters, and vegetarians over 18 years of follow-up: results from the prospective EPIC-Oxford study.* Bmj, 2019. **366**: p. l4897.
33. Petermann-Rocha, F., et al., *Vegetarians, fish, poultry, and meat-eaters: who has higher risk of cardiovascular disease incidence and mortality? A prospective study from UK Biobank.* Eur Heart J, 2021. **42**(12): p. 1136-1143.
34. Appleby, P.N., et al., *Mortality in vegetarians and comparable nonvegetarians in the United Kingdom.* Am J Clin Nutr, 2016. **103**(1): p. 218-30.
35. Key, T.J., et al., *Mortality in British vegetarians: results from the European Prospective Investigation into Cancer and Nutrition (EPIC-Oxford).* The American Journal of Clinical Nutrition, 2009. **89**(5): p. 1613S-1619S.
36. Marchese, L.E., et al., *A scoping review of approaches used to develop plant-based diet quality indices.* Current Developments in Nutrition, 2023. **7**(4): p. 100061.
37. Nutritools. *Strengths and Weaknesses of Dietary Assessment Tools (DATs)*. [cited 2023 20th Dec]; Available from: https://www.nutritools.org/strengths-and-weaknesses.
38. Chen, F., et al., *Plant- and animal-based diet quality and mortality among US adults: a cohort study.* British Journal of Nutrition, 2021. **125**(12): p. 1405-1415.
39. Caivano, S., F.A.B. Colugnati, and S.M.Á. Domene, *Diet Quality Index associated with Digital Food Guide: update and validation.* Cadernos de Saúde Pública, 2019. **35**.
40. Bromage, S., et al., *Development and Validation of a Novel Food-Based Global Diet Quality Score (GDQS).* The Journal of Nutrition, 2021. **151**: p. 75S-92S.
41. American Heart Association. *The American Heart Associaton Diet and Lifestyle Recommendations*. 2022 [cited 2022 22nd, June]; Available from: https://www.heart.org/.
42. Kwok, C.S., et al., *Vegetarian diet, Seventh Day Adventists and risk of cardiovascular mortality: a systematic review and meta-analysis.* International Journal of Cardiology, 2014. **176**(3): p. 680-6.

43. Jabri, A., et al., *Meta-analysis of effect of vegetarian diet on ischemic heart disease and all-cause mortality.* Am J Prev Cardiol, 2021. **7**: p. 100182.
44. Huang, T., et al., *Cardiovascular disease mortality and cancer incidence in vegetarians: a meta-analysis and systematic review.* Annals of Nutrition & Metabolism, 2012. **60**(4): p. 233-40.
45. Schwingshackl, L., et al., *Comparative effects of different dietary approaches on blood pressure in hypertensive and pre-hypertensive patients: A systematic review and network meta-analysis.* Critical Reviews in Food Science & Nutrition, 2019. **59**(16): p. 2674-2687.
46. Huang, T., et al., *Cardiovascular Disease Mortality and Cancer Incidence in Vegetarians: A Meta-Analysis and Systematic Review.* Annals of Nutrition & Metabolism, 2012. **60**(4): p. 233-240.
47. Satija, A., et al., *Healthful and Unhealthful Plant-Based Diets and the Risk of Coronary Heart Disease in U.S. Adults.* J Am Coll Cardiol, 2017. **70**(4): p. 411-422.
48. Wang, T., et al., *Vegetarian and vegan diets: benefits and drawbacks.* European Heart Journal, 2023: p. ehad436.
49. Timmis, A., et al., *European Society of Cardiology: cardiovascular disease statistics 2021.* Eur Heart J, 2022. **43**(8): p. 716-799.
50. Lichtenstein, A.H., et al., *2021 Dietary Guidance to Improve Cardiovascular Health: A Scientific Statement From the American Heart Association.* Circulation, 2021. **144**(23): p. e472-e487.
51. Tosti, V., B. Bertozzi, and L. Fontana, *Health benefits of the mediterranean diet: metabolic and molecular mechanisms.* The Journals of Gerontology: Series A, 2017. **73**(3): p. 318-326.
52. Lloyd-Jones, D.M., et al., *Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond.* Circulation, 2010. **121**(4): p. 586-613.
53. Satija, A., et al., *Plant-Based Dietary Patterns and Incidence of Type 2 Diabetes in US Men and Women: Results from Three Prospective Cohort Studies.* PLoS Med, 2016. **13**(6): p. e1002039.
54. Bycroft, C., et al., *The UK Biobank resource with deep phenotyping and genomic data.* Nature, 2018. **562**(7726): p. 203-209.
55. Liu, B., et al., *Development and evaluation of the Oxford WebQ, a low-cost, web-based method for assessment of previous 24 h dietary intakes in large-scale prospective studies.* Public Health Nutr, 2011. **14**(11): p. 1998-2005.
56. Bradbury, K.E., et al., *Dietary assessment in UK Biobank: an evaluation of the performance of the touchscreen dietary questionnaire.* J Nutr Sci, 2018. **7**: p. e6.
57. Martinez-Gonzalez, M.A., et al., *A provegetarian food pattern and reduction in total mortality in the Prevencion con Dieta Mediterranea (PREDIMED) study.* American Journal of Clinical Nutrition, 2014. **100**(SUPPL. 1): p. 320S-328S.
58. Satija, A., et al., *Plant-Based Dietary Patterns and Incidence of Type 2 Diabetes in US Men and Women: Results from Three Prospective Cohort Studies.* PLoS Medicine / Public Library of Science, 2016. **13**(6): p. e1002039.
59. Micha, R., et al., *Etiologic effects and optimal intakes of foods and nutrients for risk of cardiovascular diseases and diabetes: Systematic reviews and meta-analyses from the Nutrition and Chronic Diseases Expert Group (NutriCoDE).* PLoS One, 2017. **12**(4): p. e0175149.
60. Whelton, P.K., et al., *2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.* Hypertension, 2018. **71**(6): p. e13-e115.
61. Grundy, S.M., et al., *2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.* J Am Coll Cardiol, 2019. **73**(24): p. 3168-3209.
62. NHS. *The Eatwell Guide*. 2022 29th Nov 2022 [cited 2024 8th Feb]; Available from: https://www.nhs.uk/live-well/eat-well/food-guidelines-and-food-labels/the-eatwell-guide/.

63. Cheung, H.C., et al., *Quality and validity of diet quality indices for use in Australian contexts: a systematic review.* British Journal of Nutrition, 2022. **128**(10): p. 2021-2045.
64. Chamoli, R., M. Jain, and G. Tyagi, *Reliability and Validity of the Diet Quality Index for 7-9-year-old Indian Children.* Pediatr Gastroenterol Hepatol Nutr, 2019. **22**(6): p. 554-564.
65. Bolland, M.J., et al., *Differences between self-reported and verified adverse cardiovascular events in a randomised clinical trial.* BMJ Open, 2013. **3**(3): p. e002334.
66. Machón, M., et al., *Validity of self-reported prevalent cases of stroke and acute myocardial infarction in the Spanish cohort of the EPIC study.* Journal of Epidemiology and Community Health, 2013. **67**(1): p. 71.
67. Okura, Y., et al., *Agreement between self-report questionnaires and medical record data was substantial for diabetes, hypertension, myocardial infarction and stroke but not for heart failure.* Journal of Clinical Epidemiology, 2004. **57**(10): p. 1096-1103.
68. Eliassen, B.M., et al., *Validity of self-reported myocardial infarction and stroke in regions with Sami and Norwegian populations: the SAMINOR 1 Survey and the CVDNOR project.* BMJ Open, 2016. **6**(11): p. e012717.
69. Darke, P., et al., *Curating a longitudinal research resource using linked primary care EHR data-a UK Biobank case study.* J Am Med Inform Assoc, 2022. **29**(3): p. 546-552.
70. Pastorino, S., et al., *Validation of self-reported diagnosis of diabetes in the 1946 British birth cohort.* Prim Care Diabetes, 2015. **9**(5): p. 397-400.
71. Schneider, A.L.C., et al., *Validity and Reliability of Self-reported Diabetes in the Atherosclerosis Risk in Communities Study.* American Journal of Epidemiology, 2012. **176**(8): p. 738-743.
72. Jackson, J.M., et al., *Validity of diabetes self-reports in the Women's Health Initiative.* Menopause, 2014. **21**(8): p. 861-8.
73. Moradpour, F., et al., *Socio-demographic correlates of diabetes self-reporting validity: a study on the adult Kurdish population.* BMC Endocrine Disorders, 2022. **22**(1): p. 139.
74. Chen, H., et al., *Plant-based dietary patterns in relation to mortality among older adults in China.* Nature Aging, 2022. **2**(3): p. 224-230.
75. Kim, J., H. Kim, and E.L. Giovannucci, *Plant-based diet quality and the risk of total and disease-specific mortality: A population-based prospective study.* Clin Nutr, 2021. **40**(12): p. 5718-5725.
76. Heianza, Y., et al., *Healthful plant-based dietary patterns, genetic risk of obesity, and cardiovascular risk in the UK biobank study.* Clinical Nutrition, 2021. **40**(7): p. 4694-4701.
77. Martínez-González, M.A., A. Gea, and M. Ruiz-Canela, *The Mediterranean Diet and Cardiovascular Health.* Circulation Research, 2019. **124**(5): p. 779-798.
78. Livingstone, K.M., et al., *Diet quality indices, genetic risk and risk of cardiovascular disease and mortality: a longitudinal analysis of 77 004 UK Biobank participants.* BMJ Open, 2021. **11**(4): p. e045362.
79. Sacks, F.M., et al., *Dietary Fats and Cardiovascular Disease: A Presidential Advisory From the American Heart Association.* Circulation, 2017. **136**(3): p. e1-e23.
80. Mensink, R.P., et al., *Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials.* Am J Clin Nutr, 2003. **77**(5): p. 1146-55.
81. Abumweis, S.S., R. Barake, and P.J. Jones, *Plant sterols/stanols as cholesterol lowering agents: A meta-analysis of randomized controlled trials.* Food Nutr Res, 2008. **52**.
82. Theuwissen, E. and R.P. Mensink, *Water-soluble dietary fibers and cardiovascular disease.* Physiol Behav, 2008. **94**(2): p. 285-92.
83. Müller, M., E.E. Canfora, and E.E. Blaak, *Gastrointestinal Transit Time, Glucose Homeostasis and Metabolic Health: Modulation by Dietary Fibers.* Nutrients, 2018. **10**(3).
84. Bjerregaard, L.J., et al., *Fish intake and acute coronary syndrome.* European Heart Journal, 2009. **31**(1): p. 29-34.
85. Strøm, M., et al., *Fish, n-3 fatty acids, and cardiovascular diseases in women of reproductive age: A prospective study in a large national cohort.* Hypertension, 2012. **59**(1): p. 36-43.

86. Karusheva, Y., et al., *Short-term dietary reduction of branched-chain amino acids reduces meal-induced insulin secretion and modifies microbiome composition in type 2 diabetes: a randomized controlled crossover trial.* The American Journal of Clinical Nutrition, 2019. **110**(5): p. 1098-1107.
87. Theuwissen, E. and R.P. Mensink, *Water-soluble dietary fibers and cardiovascular disease.* Physiology & Behavior, 2008. **94**(2): p. 285-292.
88. Müller, M., E.E. Canfora, and E.E. Blaak, *Gastrointestinal Transit Time, Glucose Homeostasis and Metabolic Health: Modulation by Dietary Fibers.* Nutrients, 2018. **10**(3): p. 275.
89. Matsumoto, C., et al., *Fish and omega-3 fatty acid consumption and risk of hypertension.* Journal of Hypertension, 2019. **37**(6).
90. Cassidy, S., et al., *Impact of an intensive lifestyle program on low attenuation plaque and myocardial perfusion in coronary heart disease: A randomised clinical trial protocol.* Nutrition and Healthy Aging, 2022. **7**: p. 9-22.
91. Visseren, F.L.J., et al., *2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies With the special contribution of the European Association of Preventive Cardiology (EAPC).* European Heart Journal, 2021. **42**(34): p. 3227-3337.
92. de Lorgeril, M., et al., *Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study.* Circulation, 1999. **99**(6): p. 779-85.
93. Singh, R.B., et al., *Effect of an Indo-Mediterranean diet on progression of coronary artery disease in high risk patients (Indo-Mediterranean Diet Heart Study): a randomised single-blind trial.* Lancet, 2002. **360**(9344): p. 1455-61.
94. Lean, M.E., et al., *Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial.* Lancet, 2018. **391**(10120): p. 541-551.
95. Kraus, W.E., et al., *2 years of calorie restriction and cardiometabolic risk (CALERIE): exploratory outcomes of a multicentre, phase 2, randomised controlled trial.* Lancet Diabetes Endocrinol, 2019. **7**(9): p. 673-683.
96. Malinowski, B., et al., *Intermittent Fasting in Cardiovascular Disorders-An Overview.* Nutrients, 2019. **11**(3).
97. Carter, S., P.M. Clifton, and J.B. Keogh, *The effects of intermittent compared to continuous energy restriction on glycaemic control in type 2 diabetes; a pragmatic pilot trial.* Diabetes Res Clin Pract, 2016. **122**: p. 106-112.
98. Stewart, R.A.H., et al., *Physical Activity and Mortality in Patients With Stable Coronary Heart Disease.* Journal of the American College of Cardiology, 2017. **70**(14): p. 1689-1700.
99. Bernardi, L., et al., *Slow Breathing Increases Arterial Baroreflex Sensitivity in Patients With Chronic Heart Failure.* Circulation, 2002. **105**(2): p. 143-145.
100. World Health Organization. *A healthy lifestyle - WHO recommendations*. 2010 6th May, 2010 [cited 2022 28th Oct, 2022]; Available from: https://www.who.int/europe/news-room/fact-sheets/item/a-healthy-lifestyle---who-recommendations.
101. American Diabetes Association, *Diagnosis and Classification of Diabetes Mellitus.* Diabetes Care, 2010. **33**(Supplement 1): p. S62-S69.
102. National Institutes of Health *High Blood Cholesterol*. National Cholesterol Education Program, 2005.
103. Food Standards Australia & New Zealand, *AUSNUT 2011-13 food nutrient database* 2013.
104. R language, *R: A Language and environment for statistical computing.* 2021.
105. jamovi., *The jamovi project*. 2022.
106. Australian Government, *Australian Dietary Guidelines*, Health and Ageing, Editor. 2013, National Health and Medical Research Council,.
107. Jimenez-Torres, J., et al., *Mediterranean Diet Reduces Atherosclerosis Progression in Coronary Heart Disease: An Analysis of the CORDIOPREV Randomized Controlled Trial.* Stroke, 2021. **52**(11): p. 3440-3449.

108. Aldana, S.G., et al., *The Effects of an Intensive Lifestyle Modification Program on Carotid Artery Intima-Media Thickness: A Randomized Trial.* American Journal of Health Promotion, 2007. **21**(6): p. 510-516.
109. Shah, B., et al., *Anti-Inflammatory Effects of a Vegan Diet Versus the American Heart Association-Recommended Diet in Coronary Artery Disease Trial.* Journal of the American Heart Association, 2018. **7**(23): p. e011367.
110. Ornish, D., et al., *Can lifestyle changes reverse coronary heart disease? The Lifestyle Heart Trial.* Lancet, 1990. **336**(8708): p. 129-33.
111. Mary Ellen Shoup. *Keto, a long-lasting trend? New keto product launches double in past year*. 2021 [cited 2023 Aug 6]; Available from: https://www.foodnavigator-usa.com/Article/2021/06/28/Keto-a-long-lasting-trend-New-keto-product-launches-double-in-past-year?utm_source=copyright&utm_medium=OnSite&utm_campaign=copyright.
112. Google Trends. *'Low-carbohydrate' topic in Australia*. 2023 6 Aug, 2023 [cited 2023 Aug 6]; Available from: https://trends.google.com/trends/explore?date=2007-07-06%202023-08-06&geo=AU&q=%2Fm%2F02c3sn&hl=en-GB.
113. Chandalia, M., et al., *Beneficial Effects of High Dietary Fiber Intake in Patients with Type 2 Diabetes Mellitus.* New England Journal of Medicine, 2000. **342**(19): p. 1392-1398.
114. Larrosa, S., et al., *Fibre Intake Is Associated with Cardiovascular Health in European Children.* Nutrients, 2020. **13**(1).
115. Whelton, P.K., et al., *2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.* J Am Coll Cardiol, 2018. **71**(19): p. e127-e248.
116. Brown, J.R. and G.T. O'Connor, *Coronary Heart Disease and Prevention in the United States.* New England Journal of Medicine, 2010. **362**(23): p. 2150-2153.
117. Tawakol, A., et al., *Relation between resting amygdalar activity and cardiovascular events: a longitudinal and cohort study.* The Lancet, 2017. **389**(10071): p. 834-845.
118. Snow G., *blockrand: Randomization for Block Random Clinical Trials. R package version 1.5.* 2020.
119. Schulz, K.F. and D.A. Grimes, *Unequal group sizes in randomised trials: guarding against guessing.* Lancet, 2002. **359**(9310): p. 966-70.
120. Michie, S., et al., *The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions.* Ann Behav Med, 2013. **46**(1): p. 81-95.
121. Muscat, D.M., et al., *Supporting patients to be involved in decisions about their health and care: Development of a best practice health literacy App for Australian adults living with Chronic Kidney Disease.* Health Promot J Austr, 2021. **32 Suppl 1**: p. 115-127.
122. Huang, R., et al., *Emotion sharing in remote patient monitoring of patients with chronic kidney disease.* Journal of the American Medical Informatics Association, 2020. **27**(2): p. 185-193.
123. Lichtenstein, A.H., et al., *2021 Dietary Guidance to Improve Cardiovascular Health: A Scientific Statement From the American Heart Association.* Circulation, 2021. **144**(23): p. e472-e487.
124. World Health Organization, *Doing What Matters in Times of Stress*, M.H.a.S. Use, Editor. 2020. p. 132.
125. Shah, B., et al., *Anti-Inflammatory Effects of a Vegan Diet Versus the American Heart Association-Recommended Diet in Coronary Artery Disease Trial.* Journal of the American Heart Association, 2018. **7**(23): p. 1-14.
126. Ormazabal, V., et al., *Association between insulin resistance and the development of cardiovascular disease.* Cardiovascular Diabetology, 2018. **17**(1): p. 122.
127. Sowers, J.R., M. Epstein, and E.D. Frohlich, *Diabetes, Hypertension, and Cardiovascular Disease.* Hypertension, 2001. **37**(4): p. 1053-1059.
128. Huang, R.Y., et al., *Vegetarian Diets and Weight Reduction: a Meta-Analysis of Randomized Controlled Trials.* Journal of General Internal Medicine, 2016. **31**(1): p. 109-116.

129. Dayton, S., et al., *CONTROLLED TRIAL OF A DIET HIGH IN UNSATURATED FAT FOR PREVENTION OF ATHEROSCLEROTIC COMPLICATIONS.* The Lancet, 1968. **292**(7577): p. 1060-1062.
130. Leren, P., *The Oslo Diet-Heart Study.* Circulation, 1970. **42**(5): p. 935-942.
131. Turpeinen, O., *Effect of cholesterol-lowering diet on mortality from coronary heart disease and other causes.* Circulation, 1979. **59**(1): p. 1-7.
132. Cholesterol Treatment Trialists, C., *The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials.* The Lancet, 2012. **380**(9841): p. 581-590.
133. Zhang, X., et al., *High-protein diets increase cardiovascular risk by activating macrophage mTOR to suppress mitophagy.* Nature Metabolism, 2020. **2**(1): p. 110-125.
134. Xu, Y., et al., *Branched-Chain Amino Acid Catabolism Promotes Thrombosis Risk by Enhancing Tropomodulin-3 Propionylation in Platelets.* Circulation, 2020. **142**(1): p. 49-64.
135. Weickert, M.O., et al., *Effects of supplemented isoenergetic diets differing in cereal fiber and protein content on insulin sensitivity in overweight humans123.* The American Journal of Clinical Nutrition, 2011. **94**(2): p. 459-471.
136. Beckman, J.A. and C.A. Shibao, *Trimethylamine-N-Oxide, More Red Meat for the Vascular Scientists.* Hypertension, 2020. **76**(1): p. 40-41.
137. Tang, W.H.W., et al., *Intestinal Microbial Metabolism of Phosphatidylcholine and Cardiovascular Risk.* New England Journal of Medicine, 2013. **368**(17): p. 1575-1584.
138. Kris-Etherton, P.M., et al., *Bioactive compounds in foods: their role in the prevention of cardiovascular disease and cancer.* American Journal of Medicine, 2002. **113 Suppl 9B**: p. 71S-88S.
139. AbuMweis, S.S., R. Barake, and P.J.H. Jones, *Plant sterols/stanols as cholesterol lowering agents: A meta-analysis of randomized controlled trials.* Food & Nutrition Research, 2008. **0**(52).
140. Jenkins, D.J.A., et al., *Effect of a Dietary Portfolio of Cholesterol-Lowering Foods Given at 2 Levels of Intensity of Dietary Advice on Serum Lipids in Hyperlipidemia: A Randomized Controlled Trial.* JAMA, 2011. **306**(8): p. 831-839.
141. Alkhezi, O.S., et al., *Comparative effectiveness of glucagon-like peptide-1 receptor agonists for the management of obesity in adults without diabetes: A network meta-analysis of randomized clinical trials.* Obesity Reviews, 2023. **24**(3): p. e13543.
142. Marx, N., et al., *GLP-1 Receptor Agonists for the Reduction of Atherosclerotic Cardiovascular Risk in Patients With Type 2 Diabetes.* Circulation, 2022. **146**(24): p. 1882-1894.
143. Khan, S., et al., *Dietary simple sugars alter microbial ecology in the gut and promote colitis in mice.* Sci Transl Med, 2020. **12**(567).
144. Chassaing, B., et al., *Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome.* Nature, 2015. **519**(7541): p. 92-6.
145. Tristan Asensi, M., et al., *Low-Grade Inflammation and Ultra-Processed Foods Consumption: A Review.* Nutrients, 2023. **15**(6).
146. Heart Foundation. *Healthy eating to protect your heart*. 2021 [cited 2023 Sep 3]; Available from: https://www.heartfoundation.org.au/Bundles/Healthy-Living-and-Eating/healthy-eating.
147. The Sax Institute for the National Heart Foundation of Australia, *Dietary Patterns and Cardiovascular Disease Outcomes*, N.H.F.o. Australian, Editor. 2017: Australia.
148. Yokoyama, Y., et al., *Vegetarian diets and blood pressure ameta-analysis.* JAMA Internal Medicine, 2014. **174**(4): p. 577-587.
149. R Siemieniuk, G.G. *What is GRADE?* 2023 [cited 2023 27th Sep]; Available from: https://bestpractice.bmj.com/info/toolkit/learn-ebm/what-is-grade/.
150. !!! INVALID CITATION !!! [15].
151. Mohan, D., et al., *Associations of Fish Consumption With Risk of Cardiovascular Disease and Mortality Among Individuals With or Without Vascular Disease From 58 Countries.* JAMA Internal Medicine, 2021. **181**(5): p. 631-649.

152. Adams, J., V. Ryan, and M. White, *How accurate are Townsend Deprivation Scores as predictors of self-reported health? A comparison with individual level data.* J Public Health (Oxf), 2005. **27**(1): p. 101-6.
153. *Guidelines for data processing and analysis of the International Physical Activity Questionnaire (IPAQ)*. 2005; Available from: http://www.IPAQ.ki.se.
154. Craig, C.L., et al., *International physical activity questionnaire: 12-country reliability and validity.* Med Sci Sports Exerc, 2003. **35**(8): p. 1381-95.
155. Fan, M., et al., *Sleep patterns, genetic susceptibility, and incident cardiovascular disease: a prospective study of 385 292 UK biobank participants.* Eur Heart J, 2020. **41**(11): p. 1182-1189.
156. Oikonomou, E.K., et al., *Non-invasive detection of coronary inflammation using computed tomography and prediction of residual cardiovascular risk (the CRISP CT study): a post-hoc analysis of prospective outcome data.* The Lancet, 2018. **392**(10151): p. 929-939.
157. Messroghli, D.R., et al., *Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: A consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI).* J Cardiovasc Magn Reson, 2017. **19**(1): p. 75.
158. Mahrholdt, H., et al., *Delayed enhancement cardiovascular magnetic resonance assessment of non-ischaemic cardiomyopathies.* Eur Heart J, 2005. **26**(15): p. 1461-74.
159. Piehler, K.M., et al., *Free-breathing, motion-corrected late gadolinium enhancement is robust and extends risk stratification to vulnerable patients.* Circ Cardiovasc Imaging, 2013. **6**(3): p. 423-32.
160. Kellman, P., et al., *Myocardial perfusion cardiovascular magnetic resonance: optimized dual sequence and reconstruction for quantification.* J Cardiovasc Magn Reson, 2017. **19**(1): p. 43.
161. Fairbairn, T.A., et al., *Cardiac MR imaging to measure myocardial blood flow response to the cold pressor test in healthy smokers and nonsmokers.* Radiology, 2014. **270**(1): p. 82-90.
162. Ramos, J.G., et al., *Comprehensive Cardiovascular Magnetic Resonance Diastolic Dysfunction Grading Shows Very Good Agreement Compared With Echocardiography.* JACC Cardiovasc Imaging, 2020. **13**(12): p. 2530-2542.
163. Backhaus, S.J., et al., *Exercise Stress Real-Time Cardiac Magnetic Resonance Imaging for Noninvasive Characterization of Heart Failure With Preserved Ejection Fraction: The HFpEF-Stress Trial.* Circulation, 2021. **143**(15): p. 1484-1498.
164. Thompson, R.B., et al., *Quantification of lung water in heart failure using cardiovascular magnetic resonance imaging.* J Cardiovasc Magn Reson, 2019. **21**(1): p. 58.
165. Middleton, M.S., et al., *Agreement Between Magnetic Resonance Imaging Proton Density Fat Fraction Measurements and Pathologist-Assigned Steatosis Grades of Liver Biopsies From Adults With Nonalcoholic Steatohepatitis.* Gastroenterology, 2017. **153**(3): p. 753-761.
166. Idilman, I.S., et al., *Hepatic steatosis: quantification by proton density fat fraction with MR imaging versus liver biopsy.* Radiology, 2013. **267**(3): p. 767-75.
167. Park, C.C., et al., *Magnetic Resonance Elastography vs Transient Elastography in Detection of Fibrosis and Noninvasive Measurement of Steatosis in Patients With Biopsy-Proven Nonalcoholic Fatty Liver Disease.* Gastroenterology, 2017. **152**(3): p. 598-607 e2.
168. Paige, J.S., et al., *A Pilot Comparative Study of Quantitative Ultrasound, Conventional Ultrasound, and MRI for Predicting Histology-Determined Steatosis Grade in Adult Nonalcoholic Fatty Liver Disease.* AJR Am J Roentgenol, 2017. **208**(5): p. W168-W177.
169. Imajo, K., et al., *Magnetic Resonance Imaging More Accurately Classifies Steatosis and Fibrosis in Patients With Nonalcoholic Fatty Liver Disease Than Transient Elastography.* Gastroenterology, 2016. **150**(3): p. 626-637 e7.
170. Runge, J.H., et al., *MR Spectroscopy-derived Proton Density Fat Fraction Is Superior to Controlled Attenuation Parameter for Detecting and Grading Hepatic Steatosis.* Radiology, 2018. **286**(2): p. 547-556.
171. Touboul, P.J., et al., *Mannheim carotid intima-media thickness and plaque consensus (2004-2006-2011). An update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the 13th,*

15th and 20th European Stroke Conferences, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011. Cerebrovasc Dis, 2012. **34**(4): p. 290-6.
172. Maestri, R., et al., *Noninvasive measurement of blood pressure variability: accuracy of the Finometer monitor and comparison with the Finapres device.* Physiol Meas, 2005. **26**(6): p. 1125-36.
173. Ball, R.L., et al., *Predicting "heart age" using electrocardiography.* J Pers Med, 2014. **4**(1): p. 65-78.
174. *World Health Organisation (WHO). WHO | Waist Circumference and Waist–Hip Ratio. Report of a WHO Expert Consultation. Geneva, 8-11 December 2008. 2008.*
175. Bartsch, H. and J. Nair, *New DNA-based biomarkers for oxidative stress and cancer chemoprevention studies.* European Journal of Cancer, 2000. **36**(10): p. 1229-1234.
176. de la Cuesta-Zuluaga, J., et al., *Higher Fecal Short-Chain Fatty Acid Levels Are Associated with Gut Microbiome Dysbiosis, Obesity, Hypertension and Cardiometabolic Disease Risk Factors.* Nutrients, 2018. **11**(1).
177. den Besten, G., et al., *The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism.* J Lipid Res, 2013. **54**(9): p. 2325-40.
178. MacLean, P.S., et al., *The Accumulating Data to Optimally Predict Obesity Treatment (ADOPT) Core Measures Project: Rationale and Approach.* Obesity (Silver Spring), 2018. **26 Suppl 2**: p. S6-S15.
179. Sinha, R. and A.M. Jastreboff, *Stress as a common risk factor for obesity and addiction.* Biol Psychiatry, 2013. **73**(9): p. 827-35.
180. Sutin, A.R., et al., *Accumulating Data to Optimally Predict Obesity Treatment (ADOPT) Core Measures: Psychosocial Domain.* Obesity (Silver Spring), 2018. **26 Suppl 2**: p. S45-S54.
181. Mason, A. and E. Epel, *Stress and Obesity*. Eating Disorders and Obesity: A Comprehensive Handbook. 2017: Guilford Press.