Maternal Dietary Patterns During Pregnancy and Their Association with Offspring Growth Outcomes

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Statement of Originality

This is to certify that, to the best of my knowledge, the content of this thesis is my own work. This thesis has not been submitted for any degree or other purposes.

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

Dr Batool Samir Nadim

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ABSTRACT

Background

There is a growing body of evidence indicating that low birth weight is correlated with the onset of metabolic disorders in adulthood, including obesity, diabetes, and cardiovascular diseases. Dietary interventions have been effective in mitigating excessive maternal weight gain and reducing the prevalence of gestational diabetes, both of which are recognised risk factors for metabolic disorders in offspring and are associated with abnormal fetal growth. Consequently, recent research has focused on maternal diet as a modifiable risk factor that can enhance fetal development. Despite the proliferation of studies on this topic, the relationship between low birth weight and maternal dietary intake remains ambiguous due to the influence of various confounding factors that complicate the analysis. Furthermore, shifts in lifestyle, economic circumstances, and the globalisation of food resources have substantially transformed maternal dietary behaviours and food choices, leading to inconsistencies in the interpretation of available data. It is therefore imperative to gain a comprehensive understanding of the prevalent dietary patterns and food preferences among pregnant women to establish a clearer linkage between diet and fetal growth. Such insights could facilitate the formulation of targeted nutritional recommendations aimed at improving the health outcomes of offspring.

Aim of the study

This study seeks to establish a connection between contemporary maternal nutritional intake, dietary habits, and fetal growth. To investigate this association, we conducted an analysis of the macronutrient composition of the diets of a low-risk pregnant population. Our objective was to identify specific nutritional patterns adopted by these pregnant women and to examine their relationship with various fetal growth parameters. The initial analysis indicated a high prevalence of discretionary foods within the maternal diet. Consequently, we aimed to elucidate potential relationships between these food items, their macronutrient components, and fetal growth. Furthermore, we assessed the association between smoking – an established factor associated with compromised fetal development – and maternal dietary macronutrient intake to evaluate its impact on fetal growth outcomes.

Methods

A validated food frequency questionnaire (Victorian Council Food Frequency Questionnaire, V2) was distributed to 1,500 mothers who gave birth at a metropolitan teaching hospital in Western Sydney, New South Wales, Australia, between 2013 and 2018. Responses were obtained from 1,150 mothers (76.6% participation rate). This comprehensive approach ensured a diverse and representative sample. Nutritional data were extracted from the responses and analysed. Maternal and fetal outcomes were extracted from maternal antenatal records. Results were analysed using SPSS software to establish maternal macronutrient intake and dietary patterns, and to explore their association with fetal growth parameters.

Results

The study population's mean age was 29±6 years. The median energy intake was 7542.3 kJ/d (IQR 3853.4). Multiparous mothers had more energy intake than first-time mothers: 7719.4 kJ/d (IQR 3649.3) vs 7292.2 kJ/d (IQR 4011.9), $p<0.05$.

The energy derived from macronutrient intake was found to be different from the recommended intake during pregnancy. A higher percentage of energy was generated from fat intake (39.7%) compared to the recommended 20-30% of total energy intake, while a lower rate was derived from carbohydrate consumption, 43% as compared to the recommended 45-65%. This was more evident in the diets of multiparous mothers (Chapter 5).

Analysis of food items revealed the higher contribution of discretionary food (DF) intake to the maternal diet, leading to increased fat consumption. 84.9% of mothers reported consuming at least one serving of discretionary food in their daily food intake; the most common DF consumed were potato chips (93.7%), ice cream (92%), chocolate (89.7%), and pizza (89%). (Chapter 6).

The main factors affecting fetal growth were smoking, OR 0.35 (95% CI 0.13-0.94), and maternal BMI recorded at booking, OR 1.1 (95% CI 1.0-1.2). Around 11.1% of mothers reported smoking during pregnancy (Chapter 7). Analysis of food intake in this group revealed higher DF and full cream milk intake but lower fruit and fish than mothers who did not smoke. This dietary pattern may explain the observed higher energy contribution from saturated fat intake in the diets of mothers who smoked during pregnancy compared to those who did not smoke (45.1% vs 44.1%). This trend was consistent across all energy intake levels (Chapter 7). We observed that individual macronutrient intake did not impact fetal growth. Instead, the interaction between macronutrients played a significant role, and this interaction was different between mothers who had previous pregnancies and those who were pregnant for the first time. For multiparous

mothers, diets high in protein and fat were associated with increased fetal growth, while for first-time mothers, diets high in protein, fat, and carbohydrates drove fetal growth (Chapter 5).

Chapter 8 reports on a small study exploring maternal food allergen intake. Results indicate that mothers did not avoid or alter taking common food allergens in their diet regardless of whether they had a history of allergic disorders. Mothers 30 years and older consumed more eggs (19.8 vs 17.7 g/day, $p=0.02$), fish (5.6 vs 4.6 g/day, $p= 0.02$), and tree nuts (1.1 vs 0.6 g/day, $p<0.01$), but less yoghurt (45.2±61.6 vs 58.2 ±73.9 g/day, $p<0.01$) than younger mothers.

Conclusion

This thesis provides insight into the dietary patterns and macronutrient intake in a cohort of Australian pregnant women and explores the association with fetal growth parameters. The results show a higher contribution of fat to maternal energy intake at the expense of carbohydrates. The dietary analysis reveals a high prevalence of discretionary food intake in pregnant mothers' diets. Smoking and maternal BMI at booking are the major factors affecting fetal growth, while the association of macronutrient intake with fetal growth is dependent on the proportion of protein, carbohydrates, and fat in the maternal diet. These findings will need further confirmation with larger studies.

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LIST OF CONTRIBUTIONS

Batool Samir Nadim

Contributed 100% to:

- Patient recruitment
- Formulating the study design,
- Writing and editing all thesis chapters
- Statistical analysis and interpretation of results for all thesis chapters
- Writing discussion and conclusions.

Dr Rosaliene Roberio

Contributed 100% to Geometric Framework nutritional analysis and generated the relevant tables and figures (Chapter 3)

Gary Low

Contributed 10 % to the review of the statistical analysis for all the thesis results

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LIST OF ABBREVIATIONS

BMI:	Body Mass Index
CHO:	carbohydrates
DF:	discretionary food
DQES	The Victorian Council Food Frequency Questionnaire V2
EGWG:	excessive maternal weight gain
FFQ	Food Frequency Questionnaire
GDM:	Gestational Diabetes
GFN:	Geometric Framework Nutritional Analysis
GWG:	gestational maternal weight gain
IDA:	iron deficiency anaemia
IUGR:	intrauterine growth restriction
IQR:	inter quartile range
kJ:	kilojoule
LBW:	low birth weight
MJ:	megajoule
MP:	multiparous mother
MMS:	multiple micronutrient supplement
MD:	Mediterranean Diet
Mon fat	Monounsaturated Fat
DASH	The Dietary Approach to Stop Hypertension
NCDs	Non-communicable Chronic Diseases
PUFA:	Poly Unsaturated Fatty Acids
Poly Fat	Polyunsaturated Fat
PG:	Primigravida mother
PCA:	Principal Component Analysis
SD	Standard Deviation

CHAPTER 1: Introduction

1.1 Nutrition and Pregnancy

Nutrition plays a crucial role in fostering health and supporting development. Enhanced nutrition is closely linked to improved well-being for individuals, contributing to strengthened immune systems, safer pregnancies, reduced risks of non-communicable diseases like diabetes and cardiovascular conditions, and increased longevity. (1, 2).

Over the past few decades, the world has witnessed significant lifestyle changes such as globalisation, demographic shifts, income and economic growth, and urbanisation, which have exerted considerable influence on nutritional status. (3-5). This has led to a substantial worldwide transformation in the quality and quantity of human diets and notable changes in nutrition-related epidemiology. This evolution in the global nutritional landscape has given rise to the phenomenon known as the 'double burden of malnutrition' (DBM) (4, 5). The DBM refers to the simultaneous presence of diverse forms of malnutrition within individuals, households, and communities throughout the various stages of life. Malnutrition encompasses deficiencies, excesses, or imbalances in an individual's energy and/or nutrient intake. In all its forms, malnutrition poses significant threats to human health. This challenge is particularly prevalent in low- and middle-income countries, although developed countries also grapple with various forms of malnutrition (6, 7). The various forms of malnutrition include:

1. Undernutrition encompasses wasting (inadequate weight-for-height), stunting (inadequate height-for-age), and underweight (insufficient weight-for-age).

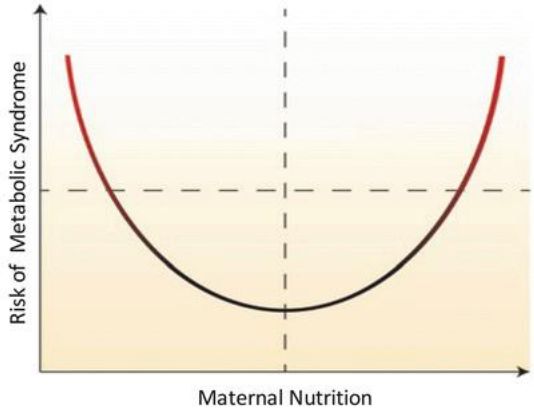
2. Micronutrient-related malnutrition involves either micronutrient deficiencies (inadequate levels of essential vitamins and minerals) or excesses of certain micronutrients.
3. Overweight, obesity, and diet-related noncommunicable diseases, such as heart disease, stroke, diabetes, and specific cancers.

Every country worldwide contends with one or more forms of malnutrition, making the battle against malnutrition a significant global health challenge. Vulnerability to malnutrition is notably observed among women, infants, children, and adolescents. Optimising nutrition during the early stages of life, particularly within the crucial 1000-day window from conception to a child's second birthday, establishes the foundation for a healthier and more promising start in life, with enduring benefits (4, 8, 9).

1.2 Malnutrition and Pregnancy

Inadequate nutrition in pregnancy is linked to various adverse pregnancy outcomes. Both under and over-nutrition are associated with abnormal fetal growth and various metabolic complications in adult life (10) (Figure 1.1). Therefore, it is important to evaluate, monitor, and, when appropriate, make changes to improve maternal nutrition both before and during pregnancy.

Figure 1.1: A U-shaped function describes the relationship between maternal nutrition and various offspring outcomes, such as the development of metabolic syndrome



Adapted from Korgan AC, Perrot TS. 2017. The effects of parental diet on fetal programming of stress-related brain regions and behaviours: implications for development of neuropsychiatric disorders. In Rajendram R, Preedy V, Patel V., editors. Diet, Nutrition, and Fetal Programming. Nutrition and Health. Humana Press, Cham. p.15-28. (28)

The association between maternal undernutrition and low birth weight is very well documented in developing countries (11); however, there is considerable uncertainty about its role in well-developed industrialised countries, where profound malnutrition is uncommon (12, 13). Nevertheless, maternal undernutrition does exist and can be caused by several factors, such as the limited supply of food or persistent severe nausea and vomiting throughout the pregnancy. Furthermore, certain population groups have a high risk of developing undernutrition, such as adolescents (14), twins and high-order multiple pregnancies (15), and women living in rural areas, and refugee and immigrant societies (6, 16). More recently, the wide prevalence of weight reduction surgeries have resulted in an increased number of women undergoing gastric bypass surgeries, leading to malabsorption and subsequent undernutrition (17,18).

Animal studies and data derived from human epidemiological studies have shown that maternal undernutrition impairs placenta development, resulting in a smaller placenta, altered morphology, and diminished blood supply, all contributing to diminished fetal nutrient supply (19,20). The most noticeable consequence of maternal undernutrition is low birth weight and

intrauterine growth restriction (IUGR), with its associated risks of metabolic disorders in adult life. Additionally, undernutrition is associated with preterm birth and maternal complications like postpartum haemorrhage (13).

Maternal overnutrition, manifested as obesity and excessive weight gain during pregnancy, represents another nutritional challenge. Worldwide, there is an upward trend in obesity rates, with more women in the reproductive age group being obese. It is estimated around 20-38% of women entering pregnancy are obese (21,22). Maternal obesity is a risk factor for numerous pregnancy complications, including miscarriage, preeclampsia, and gestational diabetes mellitus (GDM). Obesity is also a significant risk factor for the leading causes of maternal death: cardiovascular disease (CVD) and pulmonary embolism (23-25). Children born to obese mothers have greater birth weight, have a higher risk of growing up obese and are more predisposed to metabolic disorders like diabetes, cardiovascular disease, and cancer (26,27).

Maternal nutrition's importance extends beyond the prenatal period, shaping the long-term health of the offspring. Emerging research underscores the concept of 'fetal programming', suggesting that the maternal diet can imprint lasting effects on the child's health, potentially predisposing them to chronic conditions like obesity, diabetes, and cardiovascular disease in adulthood. Thus, maternal nutrition serves as the foundation for the lifelong health and well-being of the next generation.

1.3 Nutrition and Fetal Growth

Low birth weight (LBW) is a birth weight of less than 2500 g at term (29). LBW not only has a higher risk of neonatal mortality and morbidity in the short term (30, 31), but it also exposes those neonates to long-term consequences of growth stunting (32), low IQ (33), and adult-onset chronic diseases like obesity and diabetes (34, 35). Low birth weight is a global health indicator, with an estimate of 1:7 babies born with low birth weight (7). Due to its significant impact on health, the World Health Organization (WHO) has set a target of reducing LBW by 30% between

2012 and 2030 (36). Although the incidence of LBW is relatively low in developed nations, the progress towards achieving WHO targets has been sluggish (7, 37). Australia, while recognised as a leading developed country with substantial advancements in healthcare, has observed minimal changes in the incidence of low birth weight over the past decade. Data from the Australian Bureau of Statistics (ABS) report in 2023 indicate that 2.3% of babies born full-term had low birth weight (38). Effective strategies to improve birth weight not only yield healthier individuals but also alleviate the socioeconomic burden associated with chronic diseases that manifest in adulthood.

One potential strategy involves modifying the maternal diet. Promoting healthy dietary patterns during pregnancy has the potential to positively influence fetal growth and reduce the risk of LBW. The primary challenge is to identify the optimal nutrient composition of a diet during pregnancy that maximises both short- and long-term health outcomes for mothers and their children.

Research indicates that the maternal macronutrient profile may play a role in fetal development throughout different stages of pregnancy. Inadequate energy intake, insufficient protein consumption, and imbalances in carbohydrate and fat intake have been correlated with an elevated risk of LBW. Nonetheless, the evidence remains inconclusive, necessitating further research to establish a definitive association between macronutrient composition and LBW risk.

Recently, increased emphasis has been placed on the overall dietary patterns of pregnant women as determinants of LBW risk rather than on isolated macronutrients. Diets characterised by high consumption of fruits, vegetables, whole grains, and lean proteins have been linked to a decreased risk of LBW. In contrast, diets abundant in processed foods, refined carbohydrates, and unhealthy fats have been associated with an increased risk of LBW infants.

1.4 The current research study

There is a paucity of data analysing pregnant Australian women's macronutrient intake and dietary habits, with most existing studies originating from ongoing longitudinal epidemiological surveys. This research aims to provide insights into the common dietary patterns and nutrient intakes of pregnant women in Australia and serve as a foundation for subsequent studies aimed at exploring dietary interventions to enhance perinatal outcomes.

Therefore, our investigation's primary objective was to examine the dietary patterns and macronutrient intake of low-risk pregnant women. We aimed to identify specific nutritional patterns adopted by pregnant women and to explore the varying food items contributing to such diets, particularly the influence of discretionary food (DF) intake on maternal dietary patterns. Furthermore, we intended to elucidate the potential relationships between macronutrient components of maternal diets and fetal growth.

The thesis questions were:

1. What is the macronutrient composition of the maternal diet in the Australian population? Does it comply with the recommendations of the dietary guidelines? (Chapter 5)

2. Is there an association between the macronutrient composition of the maternal diet and fetal growth in utero? If so, what is the optimal composition to achieve healthy fetal growth? (Chapter 5)

3. What is the prevalence of discretionary food (DF) intake in Maternal diet? Does DF intake contribute significantly to the energy and macronutrient intake? (Chapter 6)

4. Is there a particular dietary pattern in pregnancy? What is the common dietary pattern of pregnant women? (Chapter 6)

5. Smoking is a significant risk factor impacting fetal growth in utero; we aimed to explore if maternal macronutrient intake differs between mothers who smoke during pregnancy and those who do not. If there is such a difference, does it contribute to the observed effect of smoking on fetal growth? (Chapter 7)

6. What is the pattern of common food allergens intake during pregnancy? Does a mother avoid food allergens as primary prevention to protect their unborn babies? (Chapter 8)

Chapter 2 will provide background information on the mechanisms and various factors that influence the provision of nutrients to the growing fetus. The information included will give a comprehensive review of the factors impacting nutrient transfer from mother to fetus and the physiological changes of pregnancy that may impact maternal dietary choices and the adequacy of nutrient transfer.

Chapter 3 will provide additional background information and a literature review on the association between nutrition and pregnancy outcomes (mainly LBW). It also presents a comprehensive review of difficulties encountered in assessing nutrition in research studies concerning both methods of assessment and the definition of LBW as an outcome.

Chapter 4 details the study recruitment process, the dietary assessment method utilised in this thesis, and the various statistical analyses used to achieve the results.

Chapter 5 will analyse the macronutrient intake of pregnant women and examine its association with fetal growth. In this chapter, we have utilised unique analytical method (e.g geometric frame work analysis) to consolidate our research findings.

Chapter 6 will elaborate on discretionary food intake, analysing various food items that constitute different DF groups and their contribution to the total energy intake of pregnant women. It further explores different dietary patterns in this cohort and their association with fetal growth.

Chapter 7 examines the potential association between smoking and macronutrient intake and explores its impact on fetal growth.

Chapter 8 describes a small study presenting common food allergen intake in this cohort of pregnant women. It will explore the incidence and frequency of intake compared with published data of the non-pregnant population.

Chapter 9 concludes the thesis by summarising the main findings, presenting its limitations, and suggesting possible areas of future research.

CHAPTER 2: A review of the mechanisms and factors that influence nutrition provision to the fetus

2.1. Introduction

This chapter examines the critical role of nutrition during pregnancy and the various factors that influence the maternal nutritional supply to the developing fetus. It also addresses how nutritional requirements evolve throughout gestation. It underscores the importance of a balanced diet, as it plays a vital role in accommodating the physiological changes experienced by expectant women and in supporting optimal fetal development.

It further explores several factors that affect the provision of adequate nutrition to the fetus, with the placenta identified as the primary organ responsible for nutrient transfer. It also elaborates on maternal dietary choices significantly influencing nutritional outcomes during this essential period.

A thorough understanding of these factors is imperative for accurately interpreting the complexities of nutrition during pregnancy and recognising various confounding elements that may complicate its assessment. The information presented highlights the necessity of adequate nutrition in the maternal diet to achieve optimal health outcomes. Nonetheless, the characterisation of such a diet remains incomplete, necessitating ongoing research to accurately define it within the context of the continually evolving landscape of dietary practices.

2.2 Molecular mechanism of nutritional effects on pregnancy

Nutritional programming

The term nutritional programming describes the process through which exposure to early-life nutritional stimuli brings about morphological changes or functional adaption of the offspring (39, 40).

Epidemiological and experimental studies have shown that food substrates supplied to the fetus during pregnancy and to the newborn immediately after birth can have long-term health effects on the development of non-communicable diseases (NCDs), including metabolic diseases, such as cardiovascular diseases, type 2 diabetes, hypertension, and obesity, and the development of allergic diseases, kidney disease, neurocognitive impairments, and non-alcoholic fatty liver disease (NAFLD) (41, 42). NCDs constitute the main cause of death all over the world (43). The long-term consequences of nutritional insults are variable and depend on several factors such as the type of nutrient, exposure duration and intensity, species, sex, and the critical time windows of development during which the insult has occurred(21, 25). Despite the cost to health outcomes, nutritional programming is beneficial for the species. Developmental plasticity offers a survival advantage to the offspring during altered nutritional supply and helps the future generation to adapt to new environmental conditions (44). For example, in response to maternal malnutrition, a fetus may prioritise brain development over other organs, potentially leading to long-term consequences for cognitive function (45).

Numerous research studies exploring strategies to prevent NCDs have focused on early-life nutritional interventions. Although promising results have been obtained from animal studies (46), there are still many challenges in translating these results to humans (39) due to the presence of multiple interactions between different nutrients, the interaction of nutrients with the environment, and the uncertainties about 'critical windows of susceptibility' (39, 47).

Investigations into the mechanisms underlying nutritional programming have revealed several possible mechanisms. These include epigenetic regulation, nutrient-sensing signals, oxidative stress, and tissue remodelling (39).

Epigenetic regulation

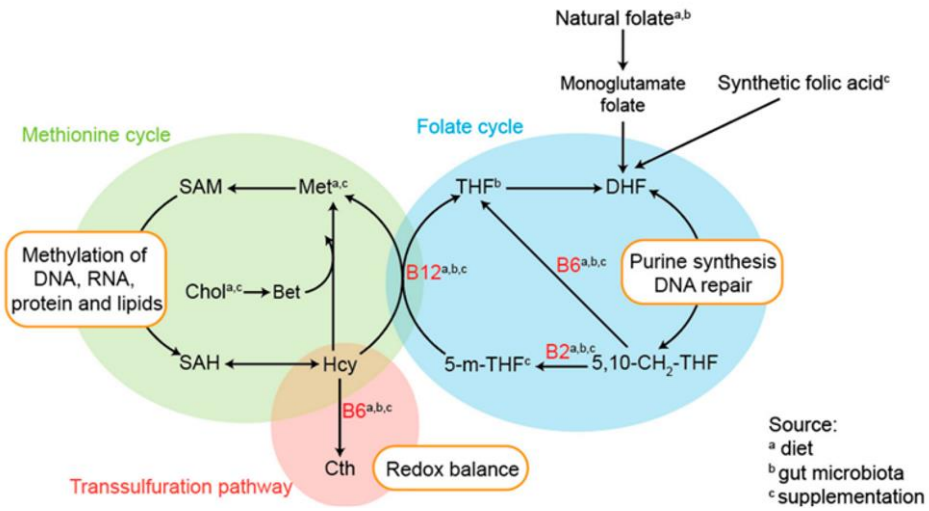
Epigenetic alterations, which encompass DNA methylation, histone modifications, and the regulation of non-coding RNA, are central to the machinery of nutritional programming. These mechanisms can instigate epigenetic modifications that govern gene expression, engraving specific molecular signatures that persist into adulthood.

Nutritional programming can perturb histone acetylation and methylation patterns, altering chromatin accessibility and gene expression. These epigenetic alterations impact genes pivotal for energy homeostasis, inflammation, and cellular growth pathways (48).

Altered DNA methylation patterns induced by nutritional programming can silence or activate genes involved in metabolic processes (49). These modifications are influenced by factors such as maternal diet (50), micronutrient availability (51), exposure to environmental toxins such as smoking (52) and alcohol consumption (53), diabetes (54), and assisted reproductive technologies (55).

Substrates for epigenetic processes are supplied, in part, by one-carbon metabolism (56, 57). One-carbon metabolism is composed of the folate, methionine, and glutathione cycles and trans-sulphuration pathway, which provides one-carbon moieties indispensable for nucleotide and protein synthesis and methylation of DNA and histones (Figure 2.1). The most important nutrients that participate in one-carbon metabolism include choline (and betaine), methionine, vitamin B6, B9/11 (folate), and B12, all of which are supplied by the diet (57) or use of supplementation (58) and are additionally synthesised by the gut microbiota (59).

Figure 2.1: One carbon metabolism depicting the three core pathways and main metabolic/molecular output



One carbon metabolism depicting the three core pathways and main metabolic/molecular output.

Adapted from: Rubini E, Baijens IMM, Horánszky A, Schoenmakers S, Sinclair KD, Zana M, et al. Maternal one-carbon metabolism during the periconceptional period and human fetal brain growth: A systematic review. Genes. 2021;12(10):1634. (56)

Nutrient sensing pathways

At the cellular level, energy and metabolism homeostasis is mediated via nutrition-sensing pathways regulated by nutrient-sensing signals. The sensory pathway signals respond to fluctuations in nutrient concentration, allowing cells to adapt to various environmental changes and increase or decrease nutrient availability (60, 61). Of the well-known nutrient-sensing signals are sirtuin 1 (SIRT1), cyclic adenosine monophosphate (AMP)-activated protein kinase (AMPK), mammalian target of rapamycin (mTOR), and peroxisome proliferator-activated receptors (PPARs) (39, 60). Dysregulation of these signals results in several metabolic diseases (61). Maternal nutrient insult results in the dysregulation of PPARs and their target genes via AMPK and SIRT1 interplay, thus generating programming for adult disease (62, 63).

Oxidative stress

Oxidative stress is associated with the generation of oxygen free radicals (OFRRs) that have a physiological and pathological effect on the fetus and placenta. The embryo develops in a low-oxygen environment and has a very low antioxidant capacity, thus, it is very sensitive to OFRs (64, 65).

Oxidative stress has been associated with various unwanted pregnancy outcomes like preeclampsia (66), GDM (67), small for gestational age, fetal growth retardation (68-70), and preterm birth (71). It is also linked to the occurrence of long-term unwanted outcomes like infant adiposity (72) and risk of asthma and allergic disease (73, 74).

Various nutritional insults are linked to oxidative stress, such as low calorie and protein intake, high-fat diet, high-fructose diet, and iron and zinc deficiency; however, the underlying mechanism of this association is yet to be determined (64). The major antioxidant nutrients in our body are copper, zinc, manganese, selenium, vitamins E, C, and A, and the glutathione system (75).

Metabolic imprinting

Nutritional programming has the potential to imprint metabolic phenotypes (76), influencing energy metabolism, insulin sensitivity, lipid metabolism, and adipose tissue distribution (77-79).

In summary, nutritional programming elucidates the potential for transgenerational effects, where epigenetic modifications induced by maternal nutrition impact the health of subsequent generations. This underscores the importance of maternal nutrition as a modifiable determinant of the developmental origins of health and disease. Understanding nutritional programming holds potential for preventive strategies targeting early-life nutrition to mitigate the risk of non-communicable diseases. Strategies focusing on maternal nutrition,

breastfeeding promotion, and early childhood dietary interventions can offer avenues for disease prevention.

2.3 Maternal Nutrient Requirements During Pregnancy

Pregnancy represents a unique period of human development characterised by rapid fetal growth and organogenesis. The pregnant woman's body undergoes physiological changes to adapt to fetal growth requirements, including increased basal metabolic rate (secondary to increased oxygen consumption), increased heart rate, expanding blood volume, and maternal weight gain (80-82).

Maternal weight gain is not only the result of the growing fetus, placenta, and amniotic fluid but is also the result of maternal organ expansion (uterus and breast) and fat deposition in preparation for lactation. To achieve a healthy pregnancy outcome, energy intake should be balanced between energy expenditure (i.e. supporting maternal weight gain and fetal growth) and energy storage (supporting lactation) (83).

The average maternal weight gain in healthy human pregnancies is 12.5 kg (28 lbs) throughout gestation. In a well-nourished pregnancy, fetal weight accounts for 25% of total weight gain, while in malnourished pregnancies, it may be up to 60% (81, 84).

The energy requirement is defined as the dietary intake that is essential for an individual to sustain optimal health outcomes (85). For non-pregnant individuals, the goal is to maintain weight, while in pregnancy, the goal is adequate weight gain without exceeding the caloric need (85).

Energy (caloric) intake is made available through increased maternal food intake, along with an increased capacity for maternal nutrient absorption (86), but this will vary depending on maternal pre-pregnancy size, age, and level of physical activity, plus the physiological demand of pregnancy in each trimester (86, 87). Studies have demonstrated considerable variability in

total energy expenditure (the sum of BMR, physical activity, and thermal effect of food) across the course of pregnancy (83, 88). Women with a normal BMI displayed a 28% increase in basal metabolic rate (BMR, kcal/day) and a 13% increase from pre-pregnancy to 36 weeks gestation (89).

Calculations of the human energy budget during pregnancy suggest there are three ways in which energy is used: 1) energy deposited as new tissue (conceptus, amniotic fluid, uterus, breast tissue, increased blood volume) (~ 20 Mega Joule (MJ); 2) energy deposited as maternal and fetal fat (~ 150 MJ), 3); and the energy required to maintain the new tissue (~ 150 MJ) (88, 89). Typical caloric needs during pregnancy range from 2,200 to 2,900 kcal/day (9,204.8 to 12,133.6 kJ/d), mostly in the second or third trimester – this is for women with pre-pregnancy BMIs in the normal range (18-25 kg/m^2). It represents an increase of 340 kcal/d (1400kJ/d) in the second trimester and an increase of 450 kcal/d (1900kJ/d) in the third trimester, while during the first trimester, the energy requirement is not different from non-pregnant status. (90, 91). For women with overweight BMI (25-29.9kg/m^2), a lesser increase of 260 to 360 kcal/day (1087-1506 KJ/d) is suggested (85, 86). On the other hand, obese women (BMI >30 kg/m^2) may not need additional calories but rather, they need to mobilise fat stores to promote fetal growth (91).

2.3.1 The role of macronutrients during pregnancy

This section provides a detailed account of the macronutrient requirements and recommendations for intake during pregnancy, while the following section will review the micronutrient and hydration requirements. These are summarised in Appendix 1, Table 2.1.

Proteins:

Proteins are the building blocks of life, and their importance escalates significantly during pregnancy. They are essential for the development of fetal tissues, including the brain, muscles, and organs. Moreover, proteins play a crucial role in supporting maternal tissue growth, expanding blood volume, and producing amniotic fluid.

Pregnant women should increase their protein intake to about 71 grams per day (1.1g/kg/d), compared to the recommended 46 grams for non-pregnant women (0.8g/kg/d) (85, 92). This increase in protein consumption should be proportional to the total caloric intake, as the percentage of calories from protein is recommended to remain at 10-35% of total energy intake for both pregnant and nonpregnant individuals, with some experts recommending 25% (93, 94). A systematic review of pregnant women in developed countries reported an average of 14.1%-16.7% of protein intake as a proportion of total daily energy (95). It was found that while balanced protein and energy in diet are encouraged, high protein intake or protein supplementation in well-nourished pregnant populations did not improve pregnancy outcomes (86, 92). Rather, it was found to be associated with an increased risk of preterm labour (96).

Carbohydrates:

Carbohydrates serve as the primary energy source for both the mother and the fetus. A substantial portion of caloric intake should come from carbohydrates, with an emphasis on complex carbohydrates, such as whole grains, fruits, and vegetables, which provide essential fibre and micronutrients.

Carbohydrate requirements increase to 175 g/day in pregnancy, compared to 130 g/day for nonpregnant females. The dietary guidelines recommend 45-65% of energy intake from carbohydrates for both pregnant and nonpregnant individuals. This increase should be proportional to the increase in pregnancy caloric requirements (85, 97). The relationship between carbohydrates and pregnancy outcomes varies depending on the type of carbohydrates. Carbohydrates with high glycemic index such as rice, white bread, and potatoes have been found to be associated with an increased risk of maternal weight gain and diabetes, while those with low GI (fruit, vegetables, and legumes) are associated with reduced occurrence of large for gestational age infants and reduced insulin requirements in diabetic

mothers (98, 99). On the other hand, it was found to be associated with low birth weight in non-diabetic mothers (100).

Fibre:

Dietary fibre is a type of carbohydrate sourced from plants. It is resistant to digestion by gastrointestinal enzymes. It can be categorised into three types: soluble fiber (which is found in fruits, vegetables, and legumes), insoluble fiber (which is present in nuts and whole grain flour), and starches (which are derived from rice and potatoes) (101). Fibre intake of 28 to 36 g/day is recommended in pregnancy, which, along with adequate fluid intake, may help prevent or reduce constipation (85). In an observational study, high fibre consumption prior to conception was found to be associated with a decreased risk of preeclampsia and dyslipidaemia (101). A large cohort study from Japan involving 76,000 mother-infant pairs showed an association between low fibre in maternal diet and impaired neurodevelopment in infants (102).

Fat:

The daily nutritional goals for pregnant individuals are to have 20-35% of total energy intake from fats and less than 10% of total energy from saturated fat (85, 97). The daily goals for essential fatty acids are 13 g/day of linoleic acid (18:2) and 1.4 g/day of linolenic acid (18:3) (85). These fatty acids, as well as their long-chain derivatives – arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) – are key structural components of cell membranes and are vital for tissue formation (90). DHA can influence the development of the brain and retina in the fetus (103), while EPA may reduce the synthesis of thromboxane A2 from AA, thereby potentially reducing the risk of preeclampsia and preterm labour (104-106). Dietary sources include oil-rich fish such as mackerel or salmon, as well as fish oil supplements (mainly omega-3) (104).

The maternal concentration of essential fatty acid is noted to be reduced by 40% at the time of birth, with a decrease of 52% in DHA and 23% in AA (107). Approximately 75% of pregnant

people exceed the recommended limit for saturated fat (from animal products such as meat and dairy, and coconut, palm, and palm kernel oil), which may have negative metabolic consequences such as diabetes (108) and low birth weight (109).

2.3.2 The role of micronutrients

Micronutrients refer to vitamins and minerals that are present in small quantities in the body but have a significant impact on the health of pregnant women and developing fetuses. Their deficiency can lead to growth and cognitive impairment, developmental problems, and immunodeficiencies. As an excess of micronutrients can also harm our health, it is crucial to establish an appropriate dosage for each specific situation. (110). The recommended daily intake in pregnancy is difficult to estimate; moreover, most reference values are taken from non-pregnant populations. (111).

Iron:

Iron is an essential trace element. It is necessary to produce haemoglobin and oxygen transport and supports the expansion of red blood cell mass during pregnancy. The iron requirement in pregnancy increases with pregnancy progress; therefore, there is an increase in global intestinal absorption of iron from 10% to 40% (112). The recommended daily intake for iron increases from 18 mg to 22-27 mg during pregnancy (113, 114). Iron-rich foods include lean red meat, poultry, fish, fortified cereals, and dark leafy green vegetables.

Iron deficiency anaemia is very common in pregnancy; 20-25% of pregnant women in developed countries are diagnosed with iron deficiency anaemia (IDA), and this is even higher in low to medium-income countries (114, 115). IDA is associated with adverse pregnancy outcome oth for the mother and fetus. Studies have shown a positive correlation between intrauterine growth retardation, low birth weight, premature labour, and neonatal anaemia (116-119), and this is in addition to maternal adverse outcomes, including preeclampsia and post-natal depression (120, 121). Therefore, one of the WHO's organisational targets for 2025 is to achieve a reduction

of 50% in anaemia frequency among reproductive age group women (8, 122). Iron supplementation is currently indicated as part of antenatal care (123, 124).

Folic acid:

Folic acid is crucial in preventing non-genetic neural tube defects (NTD) in the developing fetus (125). Pregnant women require about 600-800 micrograms of folic acid daily from dietary sources and supplements. Supplementation with 0.4 mg of folic acid per day is associated with a 70% reduction of NTD. A higher folic acid supplementation is indicated for pregnant women with gestational diabetes (126).

Good sources of folic acid include fortified cereals, leafy green vegetables, and legumes. Mandatory folic acid fortification of flour and maze was found to be effective in preventing NTD but only practised in 23% of the population worldwide (127). 36% of pregnant women have inadequate folic acid intake; therefore, routine supplementation with folic acid is recommended (124, 128).

Calcium:

Calcium is vital for fetal skeletal development and maintaining maternal bone health. Pregnant women should aim for 1,000-1,300 milligrams of calcium daily, obtained from dairy products, leafy greens, and fortified foods (113, 128). Low levels of calcium in the diet of pregnant mothers have been linked to hypertensive disorders of pregnancy; nevertheless, supplementation with calcium is only recommended for those women with a low dietary calcium intake of less than 1g/d (129). A recent Cochrane review concluded calcium supplementation may have a role in the prevention of preterm birth before 37 weeks but not before 34 weeks, and it has no role in preventing low birth weight (130).

Vitamin D:

Vitamin D is essential for calcium absorption and bone health. Adequate exposure to sunlight and dietary sources of vitamin D are necessary to meet the increased requirement during pregnancy. The recommended intakes have been set at 10-15 µg/day (400-600 international units (IU)/day) (113, 131). Fatty fish liver is a very rich dietary source of natural vitamin D, with limited other nutritional resources. The primary source of vitamin D is dermal synthesis after sun exposure. While many studies have linked low levels of vitamin D to adverse maternal outcomes, including preeclampsia, preterm birth, and low birth weight (132)Studies on vitamin D supplementation to improve outcomes have shown inconclusive results. (133).

Zinc:

Zinc is essential for enzymatic function, DNA synthesis, and gene expression. (134). A daily allowance for zinc of 11-12 mg/day is recommended during pregnancy. (135-138). Data from the National Health and Nutrition Examination Survey (2011 to 2014) indicate that mean zinc intake among pregnant individuals is 10.3 mg/day from food alone and 18.4 mg/day from food plus supplements (138). However, an estimated 11% of pregnant people consume less than recommended amounts (139, 140). Zinc deficiency is associated with neurological defects, preterm birth, and low birth weight (141).

Multiple micronutrient supplement (MMS):

Although the Cochrane review on MMS in pregnancy (142) and multiple systematic analyses have shown a beneficial effect of MMS on adverse pregnancy outcomes – mainly low birth weight and small for gestational age babies in low and middle-income countries – such an effect was not demonstrated in high-income countries (143).

Most dietary guidelines in developed countries do not recommend the routine use of MMS but only in special groups of pregnant women who are at high risk for nutritional deficiencies such

as twin pregnancy (15), teenagers (144), women with conditions that cause malabsorption, e.g. inflammatory bowel disease (145) or bowel resection (146).

2.3.3 The role of hydration

Water is an essential liquid nutrient. It is a major constituent of human cells, tissues, and organs and is involved in many metabolic processes to ensure a balanced homeostasis. Nevertheless, it is often overlooked in dietary recommendations. (147).

Water constitutes 45-75% of the human body. (148)The percentage varies depending on body weight, age, sex, and adiposity. Water accounts for 75% of body weight in infants and 55% in elderly adults; maintaining this level is essential for cellular homeostasis and life. (147, 148).

During pregnancy, women exhibit physiological changes in fluid composition; there is an increase in sodium and water retention in the kidneys, thus creating a hypervolemic hypo-osmolar status. (81, 82). During pregnancy, there is a 20% increase in total body water. Measurement by the deuterium oxide technique showed an increase of 7-8 litres by 36 to 38-week gestation and an additional 0.5-1.0 litre added by term (40 weeks)with a shift in plasma osmolality levels to approximately 10 mOsm/kg lower than that in non-pregnant women. This hypo-osmolar status induces vasopressin secretion; however, the metabolic clearance rate of vasopressin is four times higher in pregnant women, resulting in the resetting of vasopressin release. (81, 82, 149).

The increase in total body water contributes to pregnancy weight gain (150), helps to maintain adequate amniotic fluid volume (151), and plays a significant part in developing the growing fetus (152). Additionally, a substantial amount of water is needed for the production of breast milk (87% of breast milk is water), with an additional increase of water loss during lactation to an average of 750ml/d at 8 weeks postpartum. (153).

Around 70-80% of dietary sources of water are from the consumption of beverages (drinking water and all other fluid types). 20-30% is derived from food, and the type and quantities of foods eaten will determine this contribution (154).

Many institutions have set adequate intake recommendations to promote adequate water intake during pregnancy and lactation. The Institute of Medicine (IOM) has established total water intake (TWI) at 3L/day for pregnant women and 3.3L/day for breastfeeding women. (155) While the European Food Safety Agency (EFSA) has recommended 2.3L (156). Both propose additional water consumption of 300ml/d during pregnancy and compensate for water consumption during breastfeeding with an extra 700-1100 ml/d.

Despite this widespread advice to increase water intake during pregnancy and breastfeeding, worldwide studies that have investigated water consumption patterns of pregnant and breastfeeding women show reduced intake. (157-159). Dehydration of pregnant women contributes to adverse outcomes such as miscarriage, preterm labour, and preeclampsia (160-164). Furthermore, low water intake or low urine volume is associated with an increased risk of renal tract infection, development of kidney stones, and constipation (165-167). While the effect of maternal hydration on pregnancy outcomes is unclear, evidence suggests that increasing water intake in pregnant women can acutely increase the amniotic fluid index (AFI) (151, 168) and, subsequently, improve fetal well-being (169, 170).

2.3.4 The gut microbiome and maternal nutrition

The gut microbiome has been shown to change throughout pregnancy. The microbial diversity in the gut at the start of pregnancy appears to be similar to that of non-pregnant women (171-173); yet, as the pregnancy advances, the abundance of gut bacteria associated with inflammatory states increases in nearly 70% of women. The most significant change in the gut microbiota occurs in the ratio of certain key bacteria (firmicutes: bacteroidetes), mimicking the higher levels of firmicutes seen in obesity (174). The pregnancy hormone progesterone has been found

to shift the gut microbiome community and increase the relative abundance of bifidobacterium during late pregnancy (175, 176). It has been suggested that these changes may promote energy storage and fetal growth (177). There is emerging evidence on the association of pregnant microbiome imbalance (dysbiosis) with pregnancy complications (178), including preterm labour (179), preeclampsia (180), and the development of gestational diabetes GDM (181-183). Additionally, maternal macronutrient intake is significantly associated with the neonatal gut microbiome (184, 185).

Diet has a significant impact on the composition and function of the gut microbiome. (186, 187). A diet rich in fibre, prebiotics (dietary compounds that promote the growth of beneficial gut bacteria), and probiotics (live microorganisms that can provide health benefits when consumed in adequate amounts) can promote a diverse and healthy gut microbiome. (186-189). During pregnancy, a diet high in fat and low in fibre was found to be associated with an altered gut microbiome, increasing the risk of developing diabetes. (190) and alter the infant gut microbiome (191). Two recent systematic reviews did not support probiotic or prebiotic supplements to reduce adverse pregnancy outcomes (192, 193).

2.4 Factors affecting maternal-fetal nutrient transfer

Maternal-fetal metabolic communication is defined as "the bidirectional communication of nutritional status and metabolic demand by various modes, including circulating metabolites, endocrine molecules, and other secreted factors" (89).

The placenta is the primary communication bridge between the mother and the developing fetus. It is a remarkable organ with multiple functions, including endocrine, immunological, and metabolic roles, in addition to its pivotal function in facilitating the exchange of substances between the mother and fetus. A comprehensive understanding of the placenta's functions and its dynamic interactions is essential for understanding how fetal nutrients are provided and the

factors that affect its efficiency. This knowledge also highlights crucial steps for potential interventions to enhance fetal outcomes.

This section will, therefore, review the placenta's fundamental role in fetal nutrient transfer and the factors impacting this process.

2.4.1 The placental barrier and its function

The placental barrier (PB)

The human placenta is hemochorial in nature, meaning there is direct contact between maternal blood and the fetal chorion (194, 195).

The PB is a multilayered, multicellular interface (Figure 2.2). It is composed of (196):

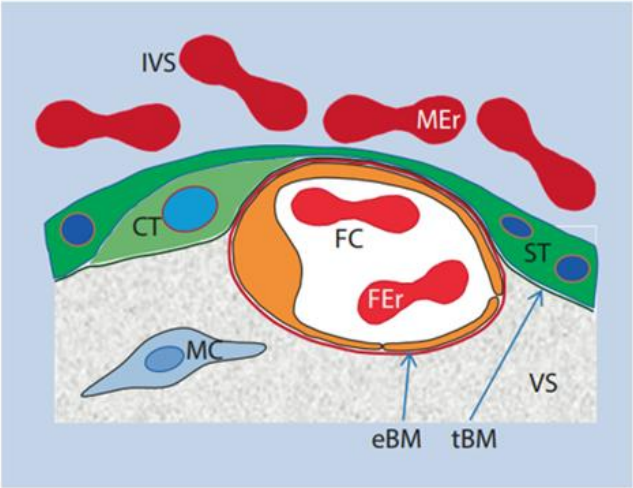
1. *Syncytiotrophoblast:* The syncytiotrophoblast is considered the functional part of the placental barrier. It has multiple functions, including hormone production, protection against infection, and active transport. The syncytiotrophblast is clearly visible in the first trimester, and it comprises a continuous layer of cells without lateral cell borders and a continuous row of nuclei (197). Having no lateral cell boundaries may facilitate the flow of the blood and so help to optimise oxygen supply to the fetus (198). As pregnancy progresses, it shows regional variation where it is very thin and devoted of organelles around areas of vascular syncytiotrophoblast and thicker in non-vascular areas. In the third trimester, the syncytial nuclei are arranged in groups and relocated to specific areas to optimise diffusion from placental vessels (199, 200).

2. *Cytotrophoblast:* This is a complete layer of cells that lies directly below the syncytiotrophoblast and is separated from the villous stroma by a basement membrane (200). As pregnancy progresses beyond the first trimester, cytotrophoblast is separated from the villous stroma. They are rarely found in areas where the placenta villous is in

close proximity to the villous trophoblast, resulting in reduced diffusion distance (201, 202).

3. *Basement membrane of the villous trophoblast*.
4. *Placental mesenchyme/connective tissue of the villi*: The connective tissue of the villi is reduced in the third trimester to reduce diffusion distance.
5. *Basement membrane of the placental endothelium*: This membrane develops after the first trimester of pregnancy.
6. *Endothelial cells of the placental vessels*.

Figure 2.2: Schematic representation of the placental barrier



Abbreviations: CT Cytotrophoblast, eBM Endothelial basement membrane; FC Fetal capillary, FEn Fetal endothelium, FEr Fetal erythrocytes, IVS Intervillous space, MEr Maternal erythrocytes, MC Mesenchymal cell, ST Syncytiotrophoblast, tBM Trophoblastic basement membrane, VS Villous stroma.

Adapted from Huppertz B, Schleussner E. The placenta: basics and clinical significance. 1st ed. 2023. ed. Berlin, Germany: Springer; 2023 (199).

Functions of the placenta

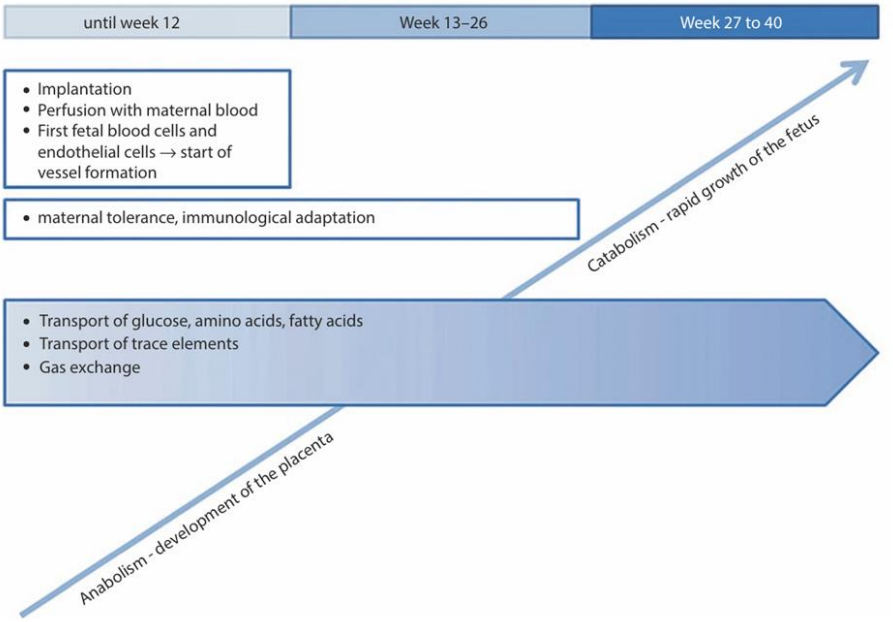
The most important function of the placenta is nutrient transfer to the fetus and gas exchange between maternal and fetal blood; however, the placenta also exhibits endocrine, metabolic,

and immunological function (203). Just as the placenta develops and grows during pregnancy, its functions also change during gestation (Figure 2.3).

Earlier in pregnancy, the immunological interaction of early placenta and maternal decidua is vital in implantation and maternal tolerance to the growing fetus. (199). As pregnancy progresses, the placenta-maternal interaction evolves to include various other functions accompanied by changes in maternal metabolism.

In the first half of pregnancy, maternal metabolism is an anabolic status; that is, the energy from food is used to support the growth of the placenta and fetus and to build up energy reserve (glycogen stores in the liver and fat deposition). In the second half of pregnancy (after 20 weeks), the fetus undergoes accelerated growth; at this stage, most nutrients must be directed towards supporting the child. This involves both an increase in food intake and a transition in maternal metabolism towards a catabolic state (204).

Figure 2.3: Functions of the placenta



Adapted from Gruber M, Hirschmugl B, Schliefsteiner C, Wadsack C. Placental function—nutrient transport—gas exchange. In: Huppertz B., Schleußner E. editors. The Placenta. Springer, Berlin, Heidelberg. (204).

1. The endocrine function

The placenta is the dominant endocrine organ during pregnancy; it plays a pivotal role in regulating the entire hormonal system. Since the placenta lacks innervation, it communicates with both the mother and the fetus through hormonal signals. These signals, released into the maternal and fetal bloodstream, not only serve as a means of communication but also play a crucial role in the local regulation of placental function through paracrine and autocrine mechanisms (205).

Placental hormones influence all maternal endocrine functional circuits and regulatory axes. Even the embryo that has not yet been implanted shortly after fertilisation sends hormonal signals, particularly human chorionic gonadotropin (hCG). These signals lead to the maintenance of the progesterone-producing corpus luteum in the ovary and its transformation into the corpus luteum gravidarum over the first ten weeks of pregnancy. At the same time, successful implantation into the uterine wall and early placentation are mediated through these signals and paracrine signals (199).

The placenta produces two main types of hormones: steroid hormones and peptide-like hormones. These hormones are synthesised mainly in the syncytiotrophoblast and the villous cytotrophoblast of the placental villi, but they can also be generated in the extra villous trophoblast (199, 205).

A. Steroid hormones

The placenta produces large amounts of steroid hormones, mainly estrogen and progesterone.

Estrogen:

Studies have demonstrated that the placenta lacks the P450c- 17 enzyme necessary for the production of estrogen from cholesterol, acetate and conversion of progesterone, and

pregnenolone to C19 steroid; it also lacks enzymes P450 17α AND P450-21, so is unable to synthesise cortisol or DEHA. Therefore, placenta estrogen synthesis depends on a source of androgen precursors – the DHEA-sulphate (DHEA-SO4) – produced by the maternal adrenal gland and by the fetal adrenal gland, both of which act as the androgen precursor for placenta estrogen synthesis. The sulphate form of DHEA is produced in the fetal adrenal and metabolised by the fetal liver to 16-α-hydroxy DHEA. Both forms perfuse to syncytiotrophoblast, then get hydrolysed to androgen, which is subsequently aromatised by syncytiotrophoblast P450 aromatase to estrogen and released to maternal circulation in the form of estriol (199).

Thus, the fetal adrenal glands play a pivotal role through steroidogenesis in regulating intrauterine homeostasis, fetal development, and maturation. (200, 205).

In the human placenta, the 11b-HSD2 enzyme is thought to protect the fetus from the harmful effects of glucocorticoids by inactivating cortisol to cortisone. The gene expression of 11b-HSD-2 increases by more than 50-fold during pregnancy and peaks at term. It appears to be regulated by oxygen tension. Low levels of this enzyme and null gene mutation result in intrauterine growth retardation. (206).

Progesterone:

Progesterone production at term is 10 times the amount secreted by corpus luteum midcycle around 300mg/d. In the fetus, progesterone is converted into fetal adrenal steroids, cortisol and dehydroepiandrosterone (DHEA). Progesterone synthesis involves the activity of P450scc and 3b HSD. There are no known cases of human P450scc deficiency. Progesterone is necessary to maintain a relaxed uterus during pregnancy, as it decreases uterine smooth muscle contractility. Progesterone is an anti-inflammatory and immunosuppressive agent and thereby protects the conceptus from immunological rejection by the mother. In addition, progesterone is also known to inhibit lactation during pregnancy (205).

B. Peptide like hormones

Human chorionic gonadotrophin HCG:

HCG is a glycoprotein-like hormone detected in maternal blood soon after conception (9±10 days after ovulation). HCG enhances the process of differentiation of cytotrophoblast to syncytiotrophoblast and acts like an angiogenic factor involved in the implantation and development of placenta (197, 198).

Human placental lactogen (HPL):

HPL is a glycoprotein produced by the placenta throughout pregnancy. Its production increases towards term, reaching a maximum of 5-7 mg/L. It plays an essential role in the lipid and carbohydrate metabolism of the mother and influences fetal growth.

HPL induces maternal insulin resistance, reducing maternal glucose utilisation and increasing glucose availability to the growing fetus. It also induces lipolysis in the mother, resulting in free fatty acid available to use as fuel with more glucose available to the fetus (207).

Placenta growth factor:

Placenta growth factor is part of the endothelial growth factor family (VEGF), stimulating blood vessel growth. The placenta is the most important site of insulin growth factors IGF-I (produced from syncytiotrophoblast) and IGF-II (produced from fibroblast). IGF-II stimulates the proliferation and differentiation of cytotrophoblast. It plays a vital role in the invasion of trophoblast in the first trimester and stimulates prolactin synthesis and steroidogenesis. (204, 205).

Activin and inhibin:

These work through a paracrine mechanism; inhibin inhibits the release of placenta GnRH and HCG while activin stimulates it (204, 205).

Placenta-associated plasma protein -A:

This protein is secreted in the first 32-33 days after ovulation and used as a marker for Down Syndrome screening in the first trimester. It has an immunosuppressive role in pregnancy. Low levels are associated with early pregnancy failure. (205).

Pregnancy specific glycoprotein:

This protein is detected from 18-23 days after conception and has an immunosuppressive effect on T lymphocyte (205).

C. Hypothalamic-pituitary like hormones

Syncytiotrophoblast produces placenta growth hormone (PGL) – which differs from pituitary growth hormone by 13 amino acids – has one glycosylation site (200). It is secreted from 12 weeks gestation and gradually replaces pituitary growth hormone. It facilitates maternal metabolic adaptation to pregnancy and plays a major role in regulating glucose levels and providing adequate nutrition to the fetus. Lower levels of PGL have been found in pregnancies with intrauterine growth retardation (205).

Gonadotrophin-releasing hormone (GnRH) and corticotropin-releasing hormones (CRH) are both produced by the placenta in response to glucocorticoids and largely replace maternal pituitary hormones to maintain placental control closer to the fetus. CRH level is increased in response to fetal stress, and higher levels are seen in pregnancies with fetal growth restriction (208, 209).

In addition, immune histochemistry studies of trophoblasts have demonstrated that the placenta secretes other hypothalamic-pituitary-like hormones in small amounts, including prolactin, relaxin, human chorionic adrenocorticotropin (hACTH) (believed to have a function similar to ACTH), human chorionic thyrotropin (hCT) (believed to function like thyroid-stimulating hormone), and placental alkaline phosphatase (PLAP) (200).

2. Immunological function

The fetus is considered a foreign tissue to the maternal system since half of its genetic material is of paternal origin. The maternal immune system must not develop a rejection reaction towards the embryo (210). The extravillous trophoblast cells actively contribute to immune regulation through various mechanisms. These cells express nonpolymorphic MHC class I molecules of the type of HLA-G, HLA-E and HLA-F, which are not recognised as foreign by cytotoxic T cells and reduce the cytotoxicity of NK cells. Classical MHC class I molecules such as HLA-A or HLA-B are not expressed on trophoblast cells (211).

Placenta produces anti-inflammatory and immunoregulatory factors including IL-10, prostaglandin E2 (PGE2), and transforming growth factor β (TGFβ). Decidua-derived PGE2 has been shown to block the activation of maternal T cells and NK cells (212).

Indoleamine 2,3-dioxygenase (IDO) is an important enzyme for local immunosuppression in the placenta. It is secreted by the syncytiotrophoblast, uterine glands and antigen-presenting cells. There is a concentration gradient between the fetal and maternal side (213). It is mainly induced by IFN-γ. IDO suppress T-cell activity through its action on tryptophan degradation, resulting in tryptophan defence. It also induces the formation of Tregs cells that suppress T cell inflammatory response locally (212).

Various hormones produced by the placenta, such as estrogen, progesterone, and glucocorticoid play a regulatory role in the immune response. (212). Progesterone has an anti-inflammatory effect mediated by PBIF protein (progesterone induced blocking factor) (214).

Human chorionic gonadotropin plays a role in immune response through stimulating progesterone production in the corpus luteum, activation of regulatory cells, promoting trophoblast differentiation and migration, increasing angiogenesis through VEGF expression,

and increased release of pregnancy-promoting cytokines and growth factors such as M-CSF and LIF (215).

3. Metabolic function

The placenta is capable of synthesising glycogen, protein, cholesterol, and fatty acids. These can be used as sources of energy and nutrients for the fetus. Glycogen synthesis is mediated via a series of enzymatic reactions and regulators. The most important one is the glycogenin enzyme which is co-expressed with high affinity to GLUT-3 transporters (216, 217). The placenta can store large amounts of glycogen that can be mobilised to provide glucose to the developing fetus at times when fetal metabolic demand exceeds maternal supply (218).

Cholesterol in the placenta is synthesised from fatty acid (FA) stores established from maternal fat accumulation in early pregnancy (200). In late gestation, the fetus depends on placenta FA stores for its cholesterol synthesis, while in early pregnancy, maternal cholesterol is the main supply for the fetal cholesterol demands (219, 220).

The placental protein metabolism is largely governed by the demands of fetal growth throughout gestation. At 10 weeks of gestation, placental protein production is approximately 1.5g/day, but by term rises to 7.5g daily (221).

The placenta has its own metabolic demand. The main source of placenta energy is aerobic metabolism, the rate of oxygen consumption per kilogram in the placenta is 3-4 x higher than the fetus as a whole and equals the fetal brain. (216). It has been estimated that the placenta uses 40% of the oxygen supplied to the fetoplacental unit, with roughly one-third devoted to protein synthesis and another third to glycogen synthesis (222, 223). The oxygen consumption increases by 20-25% from mid-gestation to late gestation (216).

Lactate, a waste product of metabolism, is produced in large quantities by the placenta and, therefore, needs to be efficiently removed. L-lactate transporters are active on both the microvillus and basal membranes of the syncytiotrophoblast (224).

Nutrient transport from mother to fetus

Transport across the placenta is based on substrate exchange and net flux from mother to fetus or vice versa. It can be a result of a concentration difference or of unidirectional carrier-mediated transport (204).

Mechanism of transfer

The exchange of nutrients between the placenta and fetus involves three major mechanisms (200):

1. direct placental transfer of nutrients from the maternal to the fetal plasma
2. placental metabolism and consumption of nutrients
3. placental metabolism of nutrient substrates to alternate substrate forms

Blood flow regulates delivery to and removal from the area of placental exchange. Rapidly crossing compounds are dependent on blood flow for their speed of transportation.

The classic membranous transport mechanisms involved in placental exchange are passive transport, active transport, and vesicular transport (225, 226).

- **Passive transport** (without energy consumption) occurs by simple diffusion, osmosis, or simplified transport.
    - In simple diffusion, the non-polar molecules and fat-dissolvable substances follow concentration gradients. They diffuse from the side with the higher concentration to the side with the lower concentration, until a balanced condition is achieved, whereby no energy is used up in this process. The transfer

of oxygen, carbon dioxide, fats, and alcohol across the placenta occurs by simple diffusion.

  - In osmosis, the diffusion of soluble substances occurs through a membrane with selective permeability (e.g. the cellular membrane). Water – a strongly polarised molecule – cannot penetrate this double lipid layer of the cellular membrane, but it crosses the placenta through specialised pores, the aquaporins or water channels, comprised of proteins localised within the plasma membrane.

  - Simplified transport, also known as facilitated diffusion, involves a transition from the side with a higher concentration to the one with a lower concentration with the help of transport molecules (e.g. glucose).

- In **active transport**, the transfer occurs through the cellular membrane against a concentration gradient using the energy transport ATPases system. These include the Na+: K+pump (Na+K+ATPase), which is concentrated in the microvillous and basal membrane (227, 228) and the high-affinity Ca2+ATPase located on the basal membrane (228).

- In **vesicular transport** (endocytosis / exocytosis), macromolecules, such as immunoglobulins, are captured by microvilli and absorbed in the cells or expelled. During endocytosis, the material is engulfed in a sample of extracellular fluid to form a fluid-filled vesicle following the invagination of the cell surface. Exocytosis is the reverse of this process, where vesicles fuse with the cell membrane to release their contents (223, 226). This process can be receptor-mediated and triggered by a specific interaction between the solute and a receptor on the cell membrane e.g. drug transfer (226).

Specific substrate transfer

Gas exchange

The respiratory gas exchange of the placenta is a major determinant of fetal well-being. Oxygen and carbon dioxide are lipophilic and cross the placenta by simple diffusion (204). This exchange is determined by partial pressure and the difference in maternal and fetal haemoglobin affinity to oxygen. The blood flow is the rate-limiting factor of gas exchange through the placenta (229).

Glucose transfer

Glucose is an essential substrate for oxidative metabolism. There is minimum fetal glucose production; therefore, the fetus depends on maternal glucose levels for its supply. Glucose flows from a higher maternal concentration to a lower concentration in the fetus. Fetal glucose levels have a linear relationship with maternal levels (204).

Glucose is transported through the placenta by facilitated diffusion. It does not involve energy consumption and is mediated through sodium-independent transporters named GLUT located in the microvillous and basement membranes. The most important of these are : GLUT1 is the primary transporter in the human placenta and is found in all types of placenta cells, GLUT3 is found in basement and endothelial cells, and GLUT 4 is predominantly in stromal cells (230). The transport of glucose across the placenta is not a regulated process and is unlimited. It remains unchanged, even in pregnancies complicated by gestational diabetes and growth restriction (231). Studies show that not all glucose is transported; around half of it is used for placenta metabolism and stored as glycogen and lactate. (217, 223).

Protein and amino acids transfer

Amino acids are the building blocks of fetal protein and an important source of energy for the growing fetus. Amino acid transfer via the placenta is an active transport process that involves energy expenditure and occurs through transport channels. This process requires three steps:

1. Uptake of amino acids into the trophoblast via transporters at the membrane
2. Transport/turnover in the cytosol
3. Release of amino acids at the basal membrane of the trophoblast and diffusion into the fetal circulation

In the human placenta, there are two types of amino acid transporters (232):

1. *Accumulative transporters*, which transport amino acids into the cell and increase the amino acid concentration in the cell
2. *Exchange transporters*, which transport a particular amino acid only in exchange for another amino acid, thus keeping the amino acid concentration in the cell the same but changing the amino acid composition in the cell. This is essential, e.g. for the uptake of essential amino acids into the cell

At the microvillous membrane, accumulative transporters actively transport amino acids against a concentration gradient into the trophoblast; these transporters include several families: family A, which transports small neutral amino acids, and the Y-AG family, which transports glutamate and aspartic acid. These amino acids can then be further transported by amino acid exchangers in return for other amino acids. (204, 232).

The transport is influenced by hormones, mainly growth hormone and TSH, against a concentration gradient (fetal concentration of amino acid is 2-3 times higher than the mother's) (200). Impaired transfer of amino acid can result in fetal growth restriction. (221, 233).

Lipid transfer

Fatty acids are essential building blocks for the development of fetal lipid reserve both as an energy source and as a precursor of important bioactive compounds such as prostaglandin and thromboxane.

Maternal fatty acids circulate in plasma in two forms: the non-esterified form (the free fatty acids), which account for 1% of total fatty acids, while 99% are bound to lipoprotein in the form of cholesterol ester, triglyceride, and phospholipids (234). The free fatty acids can diffuse through the placenta membrane against a concentration gradient, but the lipoprotein cannot cross the placenta directly. They undergo two important processes: the first is the uptake of lipoprotein by specific protein receptors in the syncytiotrophoblast membrane and hydrolysis by intracellular lips, and the second is the release of fatty acids by extracellular lipases at the microvillous membrane. (219).

Micronutrient transfer

The transport capacity for minerals and trace elements increases with the progression of pregnancy (204).

Iron:

A continuous increase in iron transfer across the placenta is essential for fetal development and probably reaches a transfer rate of up to 7 mg per day in late pregnancy. (112). The placenta uptake iron from maternal ferritin in the form of F+3, then it reduces it to F+2(235). It is transported through the placenta via transport protein DTM1 or zinc transport protein, then to fetal circulation via ferroportin and ferritin. (112).

Zinc:

Zinc transport across the placenta is regulated by potassium-zinc transporter found at the syncytiotrophoblast membrane. Expression of mRNA for the following SLC30 family transporters has been demonstrated for the human placenta: ZnT1, 2, 4. As with iron transport, the involvement of ZIP proteins in zinc transport is inferred from strong expression (236). However, the regulation and fetal release of zinc are the subject of current research and are not yet fully understood. (204).

Magnesium:

While there is little evidence in the literature on the mechanism of magnesium transfer, a calcium-independent energy-consuming mechanism has been suggested. In mice, the protein TRPM6 is linked to magnesium transport and in humans, a link between the TRPM6 protein and hypomagnesemia has been shown (237). Overexpression of the SLC41A1 gene in preeclamptic placentas has been described and may suggest a key function of this magnesium transport protein in magnesium homeostasis (238).

Phosphorus:

In vitro studies have shown phosphorus placental transport is via two sodium-dependent transporters and relies on oxygen and PH levels (239). These transporters mRNA, named Slc20a1 and Slc20a2, have been detected in the human placenta (240).

Calcium transfer:

Calcium is important for skeletal mineralisation. It is transported across the placenta by active transport via sodium-calcium pumps. (241) and calcium ATPases located in the apical syncytiotrophoblast membrane (242). Calcium transport capacity increases with advanced gestation, reaching 140 mg/kg body weight per day at 35 w gestation. This results in approximately 30g being transported across the placenta by the end of pregnancy (243). Maintenance of fetal calcium homeostasis largely depends upon parathyroid hormone-related peptide (PTHrP), which regulates active placental calcium transfer (244).

Vitamin D:

The fetus depends on the transfer of maternal 25-hydroxyvitamin D across the placenta; and fetal cord blood 25-hydroxyvitamin D concentrations are comparable to, or slightly lower than, maternal 25-hydroxyvitamin D concentrations (245). Although maternal 1,25-dihydroxyvitamin D levels rise during pregnancy, the fetal level remains low (246). It appears that 1,25-dihydroxyvitamin D is prevented from crossing the placenta by the action of a placental 24

hydroxylase, which converts 1,25-dihydroxyvitamin D to 24,25-dihydroxyvitamin D3, a less active metabolite of vitamin D than its precursor. (247, 248).

Immunoglobulin:

The maternal proteins do not traverse the placental barrier, except for immunoglobulin (IgG), and transferrin. The transfer of IgG occurs by the process of receptor-mediated endocytosis in syncytiotrophoblast cells. This transfer of IgG occurs mainly towards the end of pregnancy and provides a passive immunity to the fetus (249). IgG is transported across the syncytiotrophoblast via the Fc receptor FcRn (249). The other immunoglobulins, mainly IgM proteins, do not pass through the placental barrier (200).

2.4.2 Factors influencing nutrient transfer efficiency

Placental nutrient transfer is an intricate process orchestrated by a dynamic interplay of physiological adaptations, cellular transport mechanisms, and molecular signalling pathways. There is substantial evidence from studies in animals that the placenta regulates its nutrient transfer efficiency by morphological and functional adaptations, which result in optimal fetal growth (208, 250, 251).

1. Placenta morphology

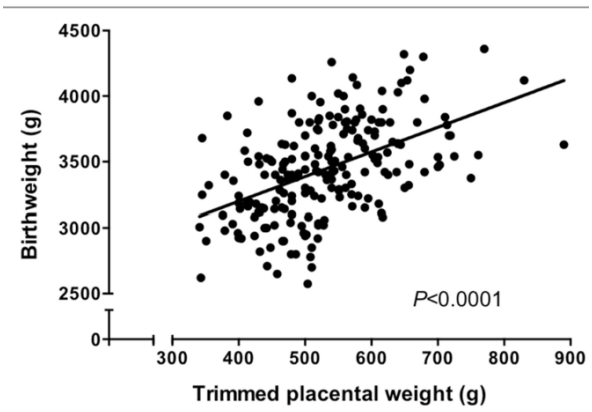
Placenta development and maturation undergo massive changes during pregnancy. Numerous studies in humans and rodents have demonstrated that the placenta changes its size and morphology and alters its gene expression in response to a variety of maternal environmental signals such as malnutrition, smoking, alcohol and drug intake, infections, and stress. These factors influence placental physiology and thus impact its capacity for nutrient transfer (250, 252, 253).

A. The placenta surface area

The total surface area of syncytiotrophoblast (transporting epithelium) available for exchange and the abundance and activity of nutrient transporters can influence the placenta capacity of nutrient transfer. (254, 255). Alterations of exchange surface area, barrier thickness, and cell composition of the different gestational ages of the placenta may all affect placental transport capacity. (231, 256, 257).

Placental weight is a measure utilised to reflect placenta growth and function, and the surface area of the villous tissue – a primary determinant of the capacity to transport nutrients – is linearly related to placental weight (258-260). The relationship between placenta size and nutritional status was demonstrated in the Dutch famine (261). A similar effect has been noted in pregnant women practising fasting during Ramadan in the last two trimesters of pregnancy (262, 263). The placenta weight tends to rise with fetal weight (256, 264) (Figure 2.4). The placenta weight to birth weight ratio (the grams of the fetus per gram placenta) is utilised as a proxy for placental efficiency (265). In rats and mice, the FW/PW is associated with changes in nutrient transfer capacity (250, 266).

Figure 2.4: Trimmed placenta weight versus birth weight in appropriate for gestational age population



Adapted from Hayward CE, Lean S, Sibley CP, Jones RL, Wareing M, Greenwood SL, et al. Placental adaptation: What can we learn from birthweight: weight ratio? Frontiers in Physiology. 2016;7 (254).

B. Perfusion defects

Deficient perfusion of the placenta may result in local or generalised ischemia with resultant infarction. Global ischemia is more severe. The fetal consequences of these maternal vascular pathologies depend on the placental and fetal reserve and can range from intrauterine growth restriction to fetal death.

Certain maternal conditions may affect the uterine arteries, such as hypertension or preeclampsia, where there is reduced perfusion and increased resistance to flow (267). Other maternal vascular pathologies that affect placental perfusion are inherited or acquired thrombophilia. Inherited conditions (protein C or protein S deficiency, factor V Leiden, sickle cell disease or acquired maternal thrombophilia, such as antiphospholipid antibody syndrome) can lead to markedly increased fibrin/fibrinoid deposition in the maternal or intervillous space (268).

Fetal perfusion diseases

In fetal perfusion defect, the villi lack functioning vessels and empty of fetal blood , while the intervillous space (the maternal leaks) are filled with maternal blood ; this may be due to thromboembolism of the fetal vessel or due to toxic, infectious or hypoxemic damage to fetal vessels (200, 269)**.**

C. Transport expression

Evidence suggests that placenta can enhance the expression of nutrient transport per unit surface area; the activity of the placental transport system of glucose and amino acids is influenced by an array of environmental factors such as stress, hypoxia, heat, or maternal under or overnutrition, in addition to the changes in hormonal levels (231, 256, 259, 270). Studies in mice found that the undernourished placentae appear less mature with aberrant transport (251, 271), whereas high fat-fed mice placentae adapt to excessive nutrient supply by reduced placental transports (271-273).

D. Fetal oxygen

The placenta is a highly metabolically active organ; it consumes a large quantity of the oxygen taken up from maternal circulation, some 80% in mid-gestation and 40%-60% in late gestation. (203). Nevertheless, despite decreases in maternal oxygenation and uterine blood flow, the PO2 gradient across the placenta remains constant to sustain fetal oxygen delivery at a normal rate. (231, 274).

2. Abnormal placentation and placenta diseases

Abnormal implantation

Placenta accreta spectrum:

In this condition, the anchoring villi are in direct contact with myometrium. The depth of invasion varies from only myometrium (placenta accreta) to serosa (placenta percreta) (275, 276). The exact pathophysiology is unknown. Several factors are involved in its pathology, including lack of decidua, uterine scarring (from previous surgery), or over-invasiveness of the trophoblast; whether this involves any of these factors alone or in combination is controversial (275).

Placenta previa:

Abnormal placentation in the lower uterine segment with an overall incidence of 4/1000 births (276). The association of placenta previa and growth restriction also remains controversial. A systematic review that included a retrospective analysis of 10,757 cases of placenta previa revealed a mild increase in the risk of IUGR and SGA (277).

Abnormal placenta anatomy:

Several anatomical variations of placenta, like bilobed placenta (placenta with two completely separated lobes), succenturiate placenta (placenta with an additional/accessory lobe or lobes of placental tissue located a few centimetres away) and circumvallate placenta (placenta with an unusually small chorionic plate, but with the growth of extra-chorial placental tissue) were

found to be associated with increased risk of antepartum haemorrhage, preterm labour, and fetal growth restriction (278-280).

Vascular epithelial disease:

Preeclampsia

Studies on placenta from pregnancies complicated with preeclampsia demonstrated a defect of endovascular extravillous trophoblast invasion (EVT), resulting in superficial or lack of invasion in some of the spiral arteries. This impairs the physiological adaptation of these vessels to pregnancy (281), subsequently leading to reduced blood flow into intervillous spaces, affecting nutrient and oxygen supply to the fetus (282, 283). The mechanism for defective invasion may involve defects in protein expression (284, 285), and an increase in EVT apoptosis, with an associated increase in macrophage invasion in spiral arteries (286).

3. Maternal diseases affecting the placenta

Diabetes:

In diabetes, the metabolic disturbance results in increased generation of oxygen free radicals (OFRs) that damage villous tissue. It is believed that oxidative stress associated with diabetes can impair early placenta development resulting in miscarriage, vasculopathy, and fetal structural defect (65, 200, 287).

Infection:

The placenta acts as a mechanical barrier to prevent infection; nevertheless, certain organisms, mainly viruses, can transfer passively through the placenta. The common organisms are cytomegalovirus, parvovirus, hepatitis B and C, and treponema pallidum causing various congenital defects. These infections result in inflammation of the villous stroma, vascular compression resulting in ischemia and necrosis of the villi (288-290).

Placenta villitis and necrosis of unknown aetiology (other than infection) have also been described (291), and found to be associated with fetal growth restriction, neonatal encephalopathy, and cerebral palsy (292).

2.5. Maternal dietary habits and food choices

Being pregnant can be assumed to lead to different food choices. Expecting mothers tend to manipulate their food to avoid harm to their unborn babies. To gain insight into the most effective way to induce dietary changes, it is important to analyse whether pregnant women have different beliefs, behaviours, and dietary patterns than non-pregnant women. The question arises whether these differences result in a healthier diet and whether this diet is more in line with food recommendations.

This section reviews physiological changes in pregnancy that may impact maternal dietary habits and factors influencing maternal food choices.

2.5.1 Changes in maternal appetite and dietary behaviour in pregnancy

Appetite in pregnancy

Anecdotally, changes in appetite, smell, and taste sensation are one of the first indications of women being pregnant. Pregnancy triggers modifications in appetite regulation mechanisms, leading to alterations in hunger and satiety cues (293). Pregnancy induces significant physiological changes, such as increased metabolic rate, altered gastrointestinal motility, and changes in taste and smell perception (80, 81). These adaptations impact maternal food intake behaviour by influencing energy expenditure, digestion, absorption, and food preferences. Understanding these physiological alterations is essential to develop targeted strategies for managing any potential adverse effects on maternal nutrition (87).

Appetite is regulated via a complex interaction between control regions in the central nervous system, mainly the hypothalamus, and peripheral metabolic and nutrient cues.

Central mechanisms of appetite regulation

The control of appetite regulation in the brain involves a complex interaction between different brain regions and neuronal networks that include both stimulatory (orexigenic) and inhibitory (anorectic) factors (294).

The hypothalamus plays a major role in regulating food intake. Various hypothalamic nuclei respond to peripheral satiety signals such as the hormone leptin (derived from adipose tissues), insulin (secreted by the pancreas), and ghrelin (secreted by the stomach) (87, 294).

The key regulator of appetite is the hypothalamic arcuate nucleus (ARC) located in the medial basal hypothalamus. It contains two neuronal populations whose role in energy homeostasis is well characterised: the proopiomelanocortin (POMC)/cocaine and the amphetamine regulated transcript (CART) (295). The POMC has anorectic action; it expresses the POMC receptor polypeptide. The activation of this system yields alpha-melanocyte-stimulating hormone (α-MSH). This is the peptide predominantly responsible for the effects on appetite; it stimulates anorexia melanocortin 4 receptors (MC4R) in the hypothalamic paraventricular nucleus (PVN) (296).

The GABAergic neurones (amphetamine-regulated transcript, the orexigenic neuropeptide Y (NPY) and agouti-related peptide (AgRP) project to different brain regions and release gamma-aminobutyric acid (GABA), which is critical to promote food intake (296).

The NPY acts through its own cognate receptors – Y1, Y2, and Y5 – within the hypothalamus (297) whereas AgRP is an endogenous antagonist to the MC4R and inhibits the anorectic actions of the melanocortin system, particularly in the PVN (296).

Peripheral mechanism of appetite control

Located in the stomach and duodenum wall are sensitive receptors that respond to changes in gut wall stretch distension and changes in food particle size and tactile stimuli; these receptors

generate vasovagal reflex (VA) that regulate gastric emptying and creates a sensation of satiety and fullness, resulting in meal termination (81). Additionally, along the whole length of the small intestine lies enteroendocrine cells that detect macronutrient degradation products like amino acids, monosaccharides, and fatty acids. These nutrient receptors, when activated, generate an intracellular signalling cascade that culminates in the release of peptides/hormones, such as cholecystokinin (CCK) or glucagon-like peptide 1 (GLP-1), which can enter the circulation to access the brain and activate their cognate receptors CCK-A and GLP-1R in the hypothalamus (81, 87).

2.5.2 Physiological adaptation of pregnancy

1. Hormonal regulation of appetite in pregnancy

Hormonal changes, such as increased levels of leptin, ghrelin, and insulin, contribute to shifts in appetite regulation, resulting in variations in energy intake and food preferences (80, 82). Additionally, psychological factors, including mood swings, food cravings, and aversions, exert a significant influence on maternal food intake behaviour (87). Satiety is also influenced by the type of macronutrient intake. For example, carbohydrates are known to be less satiating and produce a less thermogenic effect than protein; thus, a diet characterised by high carbohydrates and low protein may induce excessive energy intake (298, 299).

The most important hormones involved in appetite regulation are:

Leptin:

Leptin is a key regulator of appetite control. It works by modulating the activity of the central melanocortin system. Leptin works by stimulating POMC neurons and by inhibiting AgRP, thus inhibiting food intake. Leptin is primarily known as an adipocyte-derived hormone, but it is also produced by the placenta (300, 301). During pregnancy, there is an increase in leptin concentration both from an increase in adipose tissue mass and placenta production; around 14% will enter fetal circulation to help in fetal growth (302). Despite hyperleptinemia, during

pregnancy, appetite and food intake often paradoxically increases (303-308), reflecting a state of leptin resistance that has likely evolved to support the metabolic demands of fetal growth (87, 303, 304).

Insulin:

During pregnancy, there is a state of insulin resistance and increased production to maintain glucose haemostasis, and the pancreatic β cells become less sensitive to the effect of glucose (305). Both insulin and leptin have suppressive effects on the orexigenic peptides (NPY and AgRP) mRNA expression, resulting in attenuated sensitivity of the brain to anorexic factors, which may facilitate increased food intake during pregnancy. Additionally, both hormones influence food intake by downstream pathways that engage the melanocortin system (305), leading to absent satiety response to α- MSH (87).

Estrogen and progesterone:

Animal studies have demonstrated the suppression effect of estrogen on food intake. Oophorectomy in rats resulted in hyperphagia and weight gain, which was reversed by estrogen implant in satiety control areas (306).

During pregnancy, there is a huge amount of estrogen with a loss of oestradiol cycling (307); there is also an increase in estrogen receptor expression both centrally and in the gut wall (308). Estrogen seems to potentiate the satiating effect of CCK (309) and enhance intestine VA response to stretch (310). Studies have shown progesterone alone has no effect on food intake unless administered in pharmacological doses; however, co-administration with estrogen results in increased food intake by blocking the estrogen effect (309). Progesterone can indirectly alter gut satiety hormones like GLP-1 (308).

Prolactin:

Prolactin receptors are expressed on oxytocin neurones in the PVN. Injecting prolactin into this nucleus increases appetite and food intake .(311, 312). It is speculated that elevated prolactin

during pregnancy might act to functionally antagonise α-MSH action in the PVN, resulting in secondary leptin resistance (312). There is no evidence that prolactin acts peripherally, but some studies in male rats suggest that prolactin interacts with CCK to influence gut motility and gastric emptying, although these responses have not yet been determined in the female population. (313).

Growth hormone:

GH levels increase throughout pregnancy. In humans, pituitary-derived GH is predominant in early pregnancy, whereas the placental GH variant predominates from mid to late pregnancy (314). Rats and mice lack placental GH and their levels of pituitary GH continue to increase in response to placental signals (315). There is strong evidence of the association between GH and food regulation in pregnancy (87). GH acts centrally and peripherally to enhance the insulin-resistant status of pregnancy and increase food intake and adiposity (316).

Studies in mice show intracerebroventricular administration of GH or selective cerebral overexpression of GH, leading to increased food intake (317) and inactivation of whole-brain-specific GH receptors, improved insulin sensitivity, decreased food intake, and body adiposity in pregnant mice (316). These actions are perceived to be mediated via GH effect on AgRP neurons in the leptin-expressed cells, leading to increased sensitivity to leptin in the VMN (316, 317). The placenta GH has an affinity to prolactin receptors and potentiates its effect on increasing food intake (207, 260). The administration of human placental GH to mice was found to be associated with reduced insulin sensitivity in dose-dependent manner (314). Active ghrelin stimulates the release of GH from the pituitary by binding to GHSR1a (growth hormone-releasing hormone cells) in the ARC, suggesting that GH actions are regulated through appetite stimulation (318). Peripherally, in-vitro studies suggest that GH enhance VA intestinal response to stretch (310).

Ghrelin:

Ghrelin is mainly produced by the stomach; it has orexigenic action via increased expression of hypothalamic NYP/AgRP neurons and suppressing CART/POMC neurons. It promotes fatty acid metabolism and CTP1 (carnitine palmitoyl transferase) activation. Free radicals produced by fatty acid metabolism activate mitochondrial Ucp2 (uncoupling protein 2), which is followed by increased dietary intake (319). The effect of ghrelin on food intake in pregnancy is unknown (87). Some studies have shown increased levels of plasma acyl-ghrelin (the active form of ghrelin) concentrations during pregnancy (320-322), while others have suggested a decrease (323) or no change (324). More investigations are required to determine the precise effects of ghrelin on food intake during pregnancy.

2. Peripheral adaptation to food intake in pregnancy

Several changes in gastric VA signalling have been suggested during pregnancy. In general, there is an attenuation of mechanosensitive VA signalling, allowing for larger meals to be consumed prior to signalling for emptying (87). It is likely that nutrient sensors in the small intestine also adapt to pregnancy, contributing to the regulation of food intake (87). Studies in rats and mice have shown a reduction in the rate of gastric emptying with pregnancy (325-327), although in humans, the evidence is equivocal (87, 328-330). The level of intestinal hormones, CCK and GPL-1, has been noted to increase during pregnancy and is thought to be responsible for maternal hyperglycaemia and insulin resistance (324).

3. Changes in gustatory and olfactory sensation in pregnancy

Most pregnant mothers report changes in taste and smell sensation (331), which are anecdotally considered to be the first signs of pregnancy before the introduction of pregnancy tests and ultrasounds. These changes in sensation may interfere with women's dietary choices. While changes in taste sensation during pregnancy have been the subject of many studies, the inconsistent results are due to a variety of methods used for testing, the timing of testing, and

confounding factors related to the population studied, genetics, and physiological changes of pregnancy. Choo et al. reviewed these studies in detail (332) and reported a change of taste across pregnancy in all the studies. The most consistent result was reduced salt sensation in the second and third trimesters, reduced sweet and sour taste in the first trimester, and increased bitter taste in the first trimester. These changes in taste sensation are thought to be protective against toxins and foodborne illnesses (309, 333).

Changes in olfactory sensation have been systematically reviewed in a recent study (334), although the authors did not find any significant differences between pregnant and non-pregnant women in odour discrimination, thresholds, or hedonics. However, the study did show pregnant women had worse odour identification compared to the control (334).

4. Food craving and aversion

Food cravings and aversion during pregnancy are common (335, 336). Both craving and aversion can be a motivation to decrease or increase intake of certain food (337).

Food aversion is different from food avoidance. Whereas food avoidance occurs when certain foods are avoided, limited, or restricted due to social, cultural, and religious beliefs or out of fear of contamination and toxins, food aversion is characterised by the sudden onset of food repulsion, dislike, or disgust of certain food items (338).

Food aversion is associated with nausea and vomiting in pregnancy (NVP) (335). It is hypothesised to be an evolved mechanism that protects women and fetuses, which is commonly referred to as 'the maternal-fetal protection' hypothesis. This hypothesis states that "food aversions protect mothers from ingesting substances that could pose a threat to themselves and the developing fetus and focuses on immunological changes women experience during pregnancy" (339). As most animal products are susceptible to pathogens, the most common food aversion was found to be towards meat, fish, eggs (339), and non-alcoholic caffeinated beverages (335, 339). On the other hand, studies in low-income countries with

limited food resources have proposed that food aversion is an adaptive strategy due to resource scarcity and cultural factors (340-342).

Craving can be defined as the compulsory desire to ingest certain food (338) and women are known to crave high-energy-dense food like sweets and fruit (343). In a study that involved 635 pregnant women, 39% of participants reported craving fruit, sweet, and dairy products; while those women with high cravings had higher energy intake compared to those who did not report craving, there was no difference in glycaemic control or fetal anthropometric measures (337). Craving for non-food items (called 'pica'), such as clay, soil, laundry, or cornstarch, has also been reported in pregnancy (344-346). Pica is more prevalent in pregnant women with iron deficiency anaemia, women undergoing psychological stress, and women with low educational levels (345).

2.5.3 Maternal dietary behaviour

Pregnant women do change dietary behaviours during pregnancy (347). Often, pregnant women choose to improve their food intake as they consider the impact of dietary intake on their health and the health of their babies. This change in dietary behaviour is largely influenced by social pressure from media, family members, and health professionals (348, 349). Furthermore, socioeconomic diversity, individual characteristics, and personal circumstances can impact dietary choices and behaviour (349, 350). Other conditions that commonly occur in pregnancy, such as food craving or aversion, nausea and vomiting, constipation, and heartburn may pose challenges to maternal eating behaviour (351).

During pregnancy, maternal physiological changes concomitant with increased metabolic demands lead to an increase in food intake from early gestation and progressively throughout the rest of the pregnancy (87). Studies on humans have shown an almost 10% increase in food intake in the third trimester (87, 304), and there was a 20-30% increase in food intake observed prior to delivery in mice and rats (352) (Figure 2.5). Meal intake patterns have also been

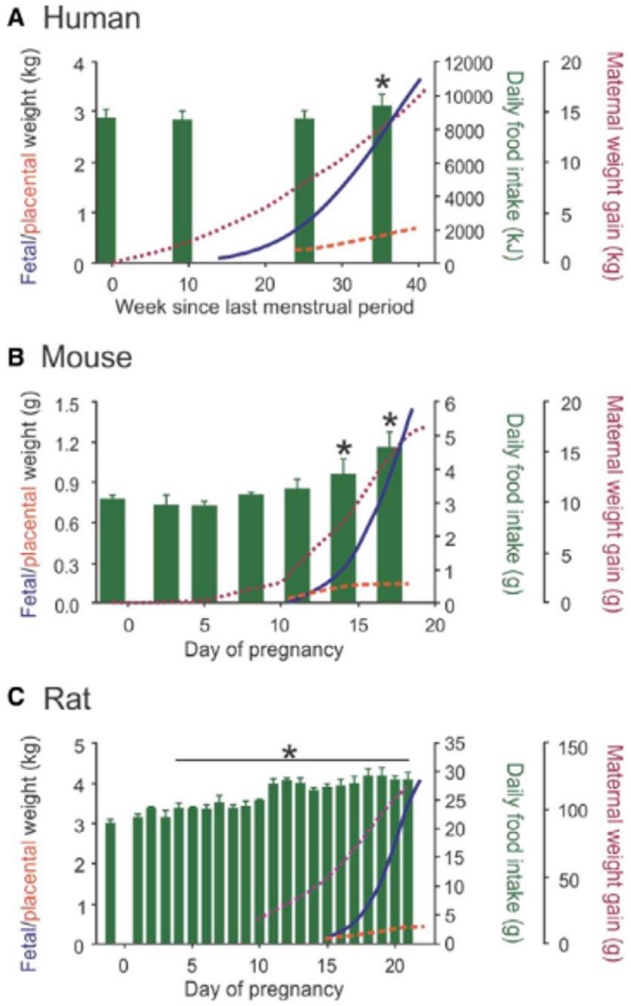
observed to change in pregnant women, with some reporting increased snacking over regular meals (i.e. three main meals per day), particularly in the second and third trimester of pregnancy (349, 353, 354).

The increase in caloric requirements during pregnancy ideally should be met with a balanced diet to ensure adequate maternal health and normal fetal growth. While most women entering pregnancy are aware of healthy eating, the majority lack knowledge and understanding of specific dietary recommendations (355, 356); thus many women do not meet the nutritional recommendations (95, 357-360), with resultant nutritional inadequacies and suboptimal dietary patterns (361-364).

Most women's dietary modifications upon becoming pregnant are limited to avoiding alcohol, caffeine, and foods with safety concerns rather than improving their overall diet (365). On the other hand, for some women, pregnancy is perceived as a period during which to increase caloric intake and to 'eat for two' (366, 367). Such a belief has led many mothers to gain excessive weight beyond the recommendations (356, 368), which increases the risk of adverse pregnancy outcomes.

Dietary behaviour has been the target of interventional studies as a method to control weight gain (356, 369, 370), with pregnancy considered to be a teachable moment for lifestyle behaviour change (365). The increased frequency of antenatal visits and the mother's motivation for a healthy pregnancy outcome has been seen as an opportunity for education and empowerment with respect to women's healthy choices. Numerous studies have been published examining methods of dietary education utilising digital media, group sessions, or phone consultation although these have yielded variable results (369, 371), which indicates the need for further studies in this field.

Figure 2.5: Maternal weight gain, fetal/placenta weight and food intake across pregnancy



Maternal weight (red dotted line) and food intake (green bars) increase in the third trimester in women, and late pregnancy in mice and rats during rapid fetal (orange dash line) and placental growth (purple solid line).

Adapted from Clarke GS, Gatford KL, Young RL, Grattan DR, Ladyman SR, Page AJ. Maternal adaptations to food intake across pregnancy: central and peripheral mechanisms. Obesity (Silver Spring, Md). 2021;29(11):1813-24. (87).

2.5.4 Maternal food choices

The changing faces of the modern diet

The evolution of human dietary patterns over the past century has been nothing short of revolutionary. There has been a transition away from traditional diets – i.e. primarily based on

locally sourced, unprocessed foods – towards modern diets characterised by convenience, globalisation, and an abundance of highly processed options (372-374).

Marketing strategies employed by the food industry have played a crucial role in shaping modern dietary habits. Eye-catching advertisements, appealing packaging, and clever branding often promote discretionary foods, and processed and ultra-processed foods. These items are often high in added sugars, unhealthy fats, and artificial additives, making them attractive choices for consumers. This trend, coupled with busy lifestyles and a lack of nutritional education, has contributed to the prevalence of these foods in daily diets (375). Advances in transportation and communication have also led to increased access to a wide variety of foods from around the world. Globalisation has had both positive and negative effects on dietary choices. While it has allowed for greater diversity in diets, it has also led to the displacement of traditional, locally sourced foods.

Factors influencing food choices

Several factors play a pivotal role in shaping modern dietary choices:

1. *Taste and palatability:* Human preferences for sweet, salty, and fatty flavours, which were once adaptive for survival, are now exploited by the food industry to create addictive, less nutritious products (376).
2. *Convenience:* Modern life's hectic pace has led many individuals to prioritise convenience over nutritional value, opting for fast food or pre-packaged meals.
3. *Socioeconomic status:* Income and socioeconomic status can significantly impact dietary choices. Individuals with limited financial resources may find it more challenging to access and afford healthier options (377).
4. *Cultural and social Influences:* Cultural traditions and social norms substantially shape dietary choices. Peer pressure, family customs, and cultural celebrations can influence the foods people consume (374).

5. *Advertising and marketing:* The food industry invests heavily in advertising, influencing consumer choices through enticing packaging and persuasive marketing campaigns (378).

Food insecurity (FI)

Food insecurity refers to the inability of individuals or households to obtain enough healthy, affordable, and culturally appropriate food. (379), and this issue affects both developed and underdeveloped countries (380-382). It has four dimensions: food access, availability, utilisation, and stability over time. (381, 383). The determinants of food insecurity are complex and multifactorial, occurring at various levels, including individual, social, and environmental. Determinants include poverty, social and economic disadvantage, personal characteristics, and political and social factors. (383).

2.5.5 Maternal Dietary Guidelines

Although indisputably central to early life, maternal nutrition has only recently begun to be highlighted in government or agency policies and activities (122). Led by WHO and the Food and Agriculture Organization of the United Nations (FAO), every country has developed its own guidelines based on population and socioeconomic characteristics. However, they all agree on the same principles:

1. Avoidance of alcohol

2. Encourage healthy weight gain

3. Encourage drinking an adequate amount of water and having a variety of healthy foods, including fruit, vegetables, grain, and unprocessed protein

4. Limit intake of food containing saturated fat, high salt, and added sugars

5. Safe handling of food and avoidance of foodborne diseases.

Examples of guidelines include:

- WHO: Essential nutrition actions – Mainstreaming nutrition through the life course (2019)
- Australian dietary guidelines (2013) /Australian healthy eating in pregnancy
- NICE: Public health guideline on maternal and child nutrition (2008, updated 2014).
- Society of Obstetricians and Gynaecologists of Canada (SOGC): Clinical practice guideline for Canadian consensus on female nutrition – Adolescence, reproduction, menopause, and beyond (2016)
- The Dietary Guidelines Advisory Committee of the United States Department of Health and Human Services and the United States Department of Agriculture (USDA) (2020)

It should be noted that most of the current recommendations on nutritional intake during pregnancy are based on observational studies and expert opinions; therefore, there is an ongoing need to conduct more rigorous studies in large cohorts, taking into consideration the constantly changing maternal nutritional needs and dietary choices, with proper and improved assessment techniques.

2.6 Conclusion

This chapter has provided background information on nutrient requirements during pregnancy, factors influencing nutrient transfer (including the physiological changes of pregnancy), and maternal dietary choices. The next chapter will present a comprehensive literature review on the association of nutrition with pregnancy outcomes.

CHAPTER 3: A review of Maternal Nutrition Intake and its association with Pregnancy Outcomes, Methods of Maternal Nutrition Assessment and the Evaluation of Fetal Growth

3.1 Introduction

This chapter investigates the influence of maternal diet on pregnancy outcomes with particular emphasis on its relationship with fetal growth, which is the central focus of this study. Additionally, it will review the various methodologies employed in dietary studies to analyse nutritional intake, highlighting the difficulties in achieving a universal assessment method and the various confounding factors impacting results interpretation.

A thorough understanding of fetal growth during pregnancy and a precise definition of low birth weight are imperative for the accurate interpretation and comparison of findings across diverse studies. This understanding is also crucial for the formulation of effective intervention strategies. Accordingly, this chapter offers an in-depth review of the factors impacting fetal growth, the approaches used for growth assessment, and the ongoing debates concerning the definitions of low birth weight and intrauterine growth restriction. (section3.4).

3.1.1 Maternal nutrition and fetal outcomes

1. Nutrition, fetal growth, and birth weight

Research conducted on animal subjects has established a clear correlation between dietary habits and fetal weight. In contrast, evidence from human studies has been less consistent. (384,385). Animal studies, being experimental and carried out in controlled environments, provide more definitive results. Most human data, however, are derived from observational studies and epidemiological research involving large cohorts, as well as a limited number of

randomised controlled trials (RCTs). This variability in results can be attributed to several confounding factors, including the populations examined, study designs, methods of dietary assessment (as discussed in section 3.3), and the ethical complexities associated with conducting RCTs involving human participants. Furthermore, while human studies have demonstrated clear associations between antenatal diet and birth weight in malnourished women, the findings among well-nourished women remain ambiguous and less conclusive. (386).

This section will provide a literature review examining the association between macronutrients, micronutrient intake and dietary patterns with pregnancy outcomes.

Macronutrient intake and fetal growth

Many human observational studies have examined the influence of individual nutrients on fetal growth; however, the results of these studies have been largely conflicting. For example, low maternal intake of protein was found to be associated with low birth weight. (12, 387-390) while other studies did not show the same effect.(391-394).

A higher maternal carbohydrate intake has been linked to reduced birth weight (395); however, a recent systematic review that included 86,841 women from 17 studies (with four from developing countries) showed no relationship between carbohydrate intake and neonatal birth weight in 64.7% of the included studies (396). The authors concluded that the results may have been affected by type of carbohydrates, study design, and timing of the study.

A maternal diet high in fat has been associated with maternal obesity and increased maternal weight gain (397), both of which are linked to fetal macrosomia (398, 399). Fetal macrosomia is associated with both short-term risks (shoulder dystocia and fracture) (400) and long-term risks, e.g. childhood obesity and cardiometabolic diseases (401).

The type of fat consumed is an important factor to consider. While increased intake of saturated fatty acids (SFA) is associated with harmful effects on mothers and offspring, polyunsaturated fatty acids (PUFA) – mainly omega 3 and docosahexaenoic acid (DHA) intake – have been proven to be associated with beneficial effects on low birth weight (402, 403) and this may provide some protection against allergic disease in childhood (404).

The observed variations in the effects of macronutrients on birth weight may be attributed to the different stages of pregnancy where the significant impacts have been examined. It should be emphasised that the precise gestational age at which the fetus is most susceptible to dietary changes remains inadequately understood (405). For example ,studies that analysed nutrient intake in early pregnancy show that low protein and high carbohydrate intake in early pregnancy resulted in reduced birth weight (13, 389, 390) while in late pregnancy (after 28 w), a high protein intake was found to be associated with thinner infants (406).

In a recent RCT involving 208 women, an increase in fat and protein at the expense of carbohydrates in late – but not early pregnancy – was found to be associated with lower fat mass in offspring up to 5 years of age (405).

Pre-conception maternal macronutrient intake in a well-nourished population showed that within a group of women with a lower preconception BMI, higher macronutrient intake (except for plant protein) was associated with increased birth weight, independent of energy intake and maternal characteristics. However, at term, the interaction between BMI quintiles and macronutrient intake was not significant (407).

Maternal micronutrient intake and fetal growth

Deficiency of micronutrient intake has been demonstrated in the diet of pregnant women regardless of nutritional status (111, 358, 408, 409).

Iron deficiency is the most common micronutrient deficiency; it has been reported that around 38% of pregnant women have iron deficiency (410). Low iron in the diet has been associated with low birth weight (410, 411, 412); therefore, iron supplementation is recommended (413). Nevertheless, a meta-analysis concluded that iron supplementation was found to increase birth weight but not the incidence of small for gestational age babies (SGA) (142).

Folic acid deficiency is also linked to low birth weight (111, 414), and folic acid supplementation has been found to increase fetal growth and birth weight (415, 416).

A positive correlation between maternal serum 25-hydroxyvitamin D level, antenatal calcium supplementation, and newborns' birthweight has been demonstrated in some observational studies (417-420); however, a systematic review failed to confirm the role of supplementation of vitamin D during pregnancy to improve fetal outcomes (420). A Cochrane review found calcium supplementation during pregnancy to be associated with slightly heavier infants compared to non-supplemented women (421).

A systematic review showed that a low maternal intake of zinc to >17% of predicted values with low serum/plasma levels was associated with low birth weight (141). However, the review authors noted the heterogeneity of the methods used to measure zinc levels and the difference in ethnicity of the population studied.

In a recent large cohort study from Norway, a diet rich in selenium intake was found to be associated with increased birth weight z score and lower risk of SGA (422).

2. Nutrition and preterm labour

Preterm labour is defined as delivery before 37 weeks gestation. Preterm infants face many immediate and long-term health problems (423).

Two recent systematic reviews and meta-analyses concluded that a lower risk of preterm labour was associated with high adherence to dietary patterns characterised by fruits, vegetables,

whole grains, fish, and dairy products (384, 424). Additionally, a prospective cohort study of 1,794 women who had spontaneous preterm delivery found that those adherent to the Mediterranean diet (AMED) and the Dietary Approach to Stop Hypertension diet (DASH) had a lower risk of preterm birth (425). Another systematic review examined folic acid supplementation to prevent preterm labour but found no association (426).

3. Nutrition and congenital anomalies

The association of folic acid deficiency and the occurrence of neural tube defect is well-documented (127, 427); therefore, the recommendation of pre-pregnancy folate supplement with food fortification is widely practised (124, 126, 427).

In a recent systematic review, inadequate niacin intake was associated with an increased risk of congenital anomalies (428). Another study found zinc deficiency to be associated with increased risk (429). A population-based cohort study from the USA found an association of low vitamin D with selected birth defects (anencephaly, hypospadias, gastroschisis, diaphragmatic hernia, and septal defect) (430). On the other hand, a systematic review of observational studies assessing 8 maternal micronutrients: vitamin D, vitamin B12, folate, vitamin A, zinc, copper, selenium, and ferritin concluded that there was not enough evidence to show any association between these micronutrients deficiencies and congenital heart disease (431). In the national US birth defect prevention study, neural tube defects and some of the congenital heart defects were associated with Western and Mexican dietary patterns, after adjusting for folic acid intake (432).

4. Nutrition and cognitive development

The human brain is vulnerable to nutritional insults during periods of rapid growth, particularly during the third trimester of pregnancy and the first two years of infant life (433). This is a critical period for nutrient-gene interactions to affect the expression of multiple genes involved in cell development, signalling, and function in the brain. Although nutrient-gene interactions continue

to occur across the lifespan, the potential for nutrition to influence brain function is much greater during early life than in adulthood (9, 434). A recent systematic review concluded that better maternal diet quality is associated with improved children's neurodevelopment and cognitive function (435).

3.1.2 Nutrition and maternal outcomes

Numerous studies have investigated the relationship between maternal nutrition and adverse maternal outcomes, including gestational weight gain, diabetes, and hypertension. This section offers a brief review of the literature on these associations. It underscores the significance of balanced maternal nutrition and dietary intervention programs designed to mitigate the incidence of such complications.

1. Maternal gestational weight gain (GWG)

Excessive maternal gestational weight gain (EGWG) during pregnancy can lead to adverse pregnancy outcomes (84, 436), and the relationship between maternal nutrition and excessive weight gain has been extensively studied. It is well documented that a high-calorie diet is associated with EGWG (437-439), and an unhealthy dietary pattern characterised by high fat and processed food is highly associated with EGWG (440, 441). Additionally, a high intake of added sugar during pregnancy was found to be associated with a higher rate of weight gain (442). An inverse relationship was found between fruit and vegetables and EGWG in some (443-445) but not all of the studies (446, 447).

The association between diet quality and GWG has been examined in a limited number of studies, although no association has been found between the USA Healthy Eating Index (USA HEI-2005) and EGWG (444). Two other studies, one from Malaysia – which used the Malaysian Healthy Eating Index in the second and third trimesters (448) – and another study from Sweden – which used the National Agency index (449) – both found an association with GWG.

2. Diabetes

Gestational diabetes mellitus (GDM) is a glucose intolerance with the first onset or diagnosis during pregnancy (450, 451). The global prevalence of the condition is rising, with an estimated 13% of pregnancies being affected (452). GDM carries increased perinatal mortality and morbidity (451, 453).

GDM also carries future risks to maternal health, and the development of type 2 diabetes and cardiovascular disease (454, 455). Additionally, children born to diabetic mothers have a higher risk of developing metabolic disorders later in life (456).

Evidence has suggested that dietary intake before and during pregnancy is associated with the risk of GDM. High consumption of red meat, processed meat, egg and animal protein, heme iron, fat, and cholesterol can increase the GDM risk. On the other hand, increased intakes of fibre, nuts, and vegetable-derived protein may lower the risk of GDM (457-461).

3. Preeclampsia

Preeclampsia is one of the leading causes of maternal morbidity. It is estimated to affect 3-7% of pregnant women and is responsible for 14% of maternal deaths (462). Preeclampsia is characterised by the development of maternal hypertension after 20-week gestation accompanied by multi-organ failure, including placental abruption, acute renal failure, cerebrovascular and cardiovascular complications, and disseminated intravascular coagulation (463) as well as fetal/neonatal morbidity and mortality caused by intrauterine growth restriction, abruption, and prematurity.

Oxidative stress and inflammation are well-known pathogenic factors for preeclampsia (464)). A diet associated with reduced inflammation levels and rich in antioxidants has been heavily investigated regarding its ability to reduce the occurrence of preeclampsia. Although studies have shown lower risks of preeclampsia with diets rich in micronutrients like vitamin D and

calcium (465, 466), they do not support routine supplementation with magnesium (467), poly - unsaturated omega 3 (104), or antioxidant vitamins C and E (468). Administration of calcium and aspirin may have a role in certain subpopulations, although optimal treatment regimen will require further research (469).

Studies that have analysed the association of certain dietary patterns with preeclampsia have shown that diets high in calories, sucrose, and poly-unsaturated acids (470, 471) are associated with a higher risk of preeclampsia. On the other hand, studies on adherence to healthy dietary patterns characterised by a high intake of vegetables, fruit, legumes, and whole grains, and diets that are high in fibre and potassium have been found to be associated with reduced risks of preeclampsia (101, 472-475). However, the dietary patterns obtained in these studies were only appropriate for local residents, and the results were not comparable (476). More recently, in a cross-sectional study involving 449 pregnant women, the DASH diet (detailed in next section 3.1.3) was found to be associated with reduced risk of PET, although larger RCTs were recommended to confirm these results (476). Research continues regarding possible nutritional intervention for preeclampsia, with larger studies needed.

3.1.3 Common dietary patterns and pregnancy outcomes

Identifying the best diet or diets to prevent pregnancy complications is important for public health. In the past, nutrition research has mainly focused on individual nutrients or specific foods. However, people do not consume nutrients or foods in isolation, and recent nutritional epidemiological studies have shifted their focus to analysing dietary patterns (477). Such studies describe the overall diet, including the foods, food groups, and nutrients consumed, their combination, the variety, and the frequency and quantity with which they are habitually consumed. Pregnant women recognise and choose a particular dietary pattern based on a combination of individual preferences, cultural influences, health considerations, lifestyle factors, and nutritional awareness (477, 478).

In general, dietary patterns characterised by food with an excellent supply of vegetables, fruits, whole grains, dairy products, and protein may contribute to reducing the risk of LBW (385, 424), whereas dietary patterns characterised by foods high in saturated trans fats, processed meat, sodium, and added sugar but low in vegetables, fruits, and fibre are negatively associated with birthweight (479, 480). Nonetheless, two studies found no particular dietary pattern significantly associated with birth weight (384, 481, 482). Nevertheless, it should be noted that these studies did not differentiate between observed results that were due to an increased intake of a specific nutrient contributing to an increase in total energy intake (non-isocaloric conditions) or results that could be attributed to the relative effects of one nutrient to another (while keeping total energy constant, i.e. isocaloric conditions). This limitation was addressed in a recent study from Japan where the diet of 82,404 women during pregnancy was analysed. The result showed birth weight was highest when the percentage energy from protein was 12%, regardless of whether the isoenergetic replacement was with fat or carbohydrates. It also found that when protein intake was constant, birth weight decreased if <29% of the energy intake was derived from fat or more than 59% was derived from carbohydrates (483).

Worldwide, several common dietary patterns have been investigated in research studies (484): the modern Western Pattern diet (WPD), the Mediterranean diet (MD), the Vegan and Vegetarian diets (VD), the Dietary Approach to Stop Hypertension diet (DASH), and the Palaeolithic diet (Paleo diet).

1. The modern Western Pattern diet (WPD)

The Western diet is marked by red and processed meats, full-fat dairy products, refined grains, high-sodium foods, and sugar, as well as low amounts of fibre, whole grains, legumes, and fruits and vegetables.

A large volume of studies has confirmed the association between this diet and adverse pregnancy outcomes, including excessive GWG or GDM (459, 485), preeclampsia (473,474), fetal growth restrictions, and low birth weight (473, 480).

2. The Mediterranean diet (MD)

The Mediterranean diet (MD) was globally introduced in the 1960s; it represents the diet of the southern European countries of Greece and southern Italy. Since its introduction, there have been multiple variations (486).

The traditional Mediterranean diet is characterised by a high intake of fruits, vegetables, whole grains, beans, nuts, and seeds. Olive oil is heavily consumed in the MD diet and is the main fat source, supplying monounsaturated fat. MD allows low to moderate wine consumption. It generally also includes low to moderate amounts of fish, poultry, and dairy products, and it includes little red meat.

The benefit of MD for general health has been well documented; it has been found to reduce the risk of cardiovascular disease, ischemic stroke, and all-cause mortality from the disease (487). It has also been found to be beneficial in reducing the risk of diabetes (488) and to improve cognitive function (486). Nevertheless, it remains unclear if the observed benefits are the result of a single component of MD or from an aggregation of effects. For instance, the effect of fruit and vegetables was more evident for cognitive function, while the effect of olive oil and nuts was stronger for cardiovascular risk (486).

During pregnancy, adherence to MD has been found to be associated with reduced risk of SGA (489), GDM (490, 491), and preterm birth (492, 493). High adherence to MD in pregnancy has also been shown to reduce the risk of cardiovascular disease in pregnant women (494). It also reduces oxidative stress (74) and adiponectin levels (495), both of which are associated with adverse pregnancy outcomes.

A recent systematic review included 14 cohort and case-control studies, which showed an overall beneficial effect of MD in all pregnancy outcomes, including GDM, obesity, urinary tract infection, low birth weight and prematurity, and improved sleep quality (496).

3. The Vegan and Vegetarian diets (VD)

Vegetarian diets (VD) are typically made up of plant foods such as grains, legumes, nuts, seeds, vegetables, and fruit. They exclude all kinds of animal food, including meat, meat products, fish, molluscs, and crustaceans. Unlike vegan diets, which exclude all animal-based food, vegetarian diets usually include dairy products like eggs and honey (497).

The last decades have witnessed an increase in the popularity of the vegetarian diet, mostly due to increased evidence of its link to good health. Studies have shown a reduced risk of coronary heart disease, lower blood pressure and a better lipid profile (498), reduced risk of cancer (499), and lower incidence of type 2 diabetes (500). However, despite their potential benefits, plant-based diets carry the risk of essential micronutrient deficiencies as they have low content of iron, zinc, vitamin D, and unsaturated fatty acids (501). The Vegetarian diet without supplementation has an increased risk of osteoporosis (502). It is also associated with increased plasma homocysteine levels, a rising risk factor for cardiovascular disease (503).

Systematic reviews and meta-analyses of studies on the effects of a vegetarian-vegan diet on pregnancy outcomes have revealed inconsistent results due to the lack of randomised control trails and the presence of many confounding factors that impact interpretation (504, 505). However, it is generally concluded that vegetarian-vegan diets may be considered safe in pregnancy, provided that attention is paid to vitamin and trace element requirements. (497, 504).

4. The Dietary Approach to Stop Hypertension (DASH diet)

The Dietary Approach to Stop Hypertension (The DASH diet) was first introduced in 1997 and comprises four to five servings of fruit, four to five servings of vegetables, and two to three servings of low-fat dairy per day, with <25 per cent of daily caloric intake from fat (506).

Since its introduction, the DASH diet has been studied in both normotensive and hypertensive populations and has been found to lower systolic and diastolic pressure more than a diet rich in fruits and vegetables alone (507, 508). The DASH diet has also been associated with a lower risk of colorectal cancer, cardiovascular disease, and premature mortality (509, 510).

Adherence to DASH during pregnancy has been shown to reduce the incidence of preeclampsia, large for gestational-age baby, macrosomia and fasting blood glucose (476, 511). It has also been found to reduce the rate of caesarean section and the need for insulin in women diagnosed with GDM during pregnancy (512).

5. The Palaeolithic diet (Paleo diet)

The Palaeolithic diet (Paleo diet) has gained popularity in recent years. It refers to a diet composed of animal and uncultivated plants, which is thought to have been consumed by humans in the Palaeolithic era before the establishment of agriculture and the domestication of animals (513). It consists of lean meat, fish, vegetables, fruits, roots, eggs, and nuts. The diet excludes grains, wheat, legumes, dairy products, refined sugar, and processed oils (514, 515). Several studies have shown improved metabolism and glycaemic control in patients with type 2 diabetes adherent to the Paleo diet (514, 515). Nevertheless, the Paleo diet has faced some criticism as compliance with the diet has proven to be expensive and found to be associated with side effects like diarrhoea (515).

The effect of the Paleo diet in pregnancy was examined in a study of a small group of pregnant women, which reported a positive impact on improving glucose tolerance and maternal

haemoglobin level although there was no difference in fetal weight or other obstetric outcomes (516).

Diet quality

Diet quality is assessed by certain dietary scores and indices; it reflects the adherence of study participants to certain dietary patterns. Findings from studies on the relationship between diet quality and fetal birth weight are heterogeneous. While some studies have suggested that high diet quality is related to a reduction in the risk of low birth weight (517-521), others did not show an association between adherence to the MD or the Alternative Healthy Eating Index for Pregnancy and fetal growth outcomes (446, 522). On the other hand, poor diet quality during pregnancy was found to be associated with higher birthweight and increased risk of LGA independent of maternal obesity and other covariates (523, 524).

3.2. Methods of dietary assessment and analysis

The challenges of dietary assessment

Assessing dietary intake is a crucial component in understanding an individual's nutritional status and overall health although there are several challenges that can impact the accuracy and reliability of the assessment. Most dietary assessment tools rely on self-reporting of food intake over a period of time, making it subject to random and systemic bias (525). An accurate assessment of dietary intake includes assessing dietary patterns and quantity of food, drinks, and supplement consumption. These data are then analysed to measure nutrient intake using an established food composition database, which needs to be accurate and current at the time of analysis (525).

The assessment of dietary intake during pregnancy poses unique challenges due to the physiological changes of pregnancy, the variation in energy requirement in each trimester, and pregnancy-related conditions such as excessive vomiting (526, 527). These changes can

significantly reduce the reliability of dietary assessment in pregnancy and can increase the risk of bias in the studies' findings (528).

This section will review traditional dietary assessment tools and methods of food data analysis.

Common dietary assessment tools

Several widely recognised dietary assessment tools are frequently employed in research studies. Selecting an appropriate dietary assessment tool is of paramount importance to achieving accurate results. The selection of a specific tool necessitates alignment with research objectives, study design, target population, available resources, and the desired level of analytical detail (525). It is important to acknowledge that each dietary assessment tool possesses inherent strengths and limitations. To enhance accuracy and reliability, researchers often adopt a combination of methods (529). Consulting with experts in nutrition and dietary assessment can help researchers identify the most appropriate tool for their specific research study.

The commonly used methods are: dietary history questionnaire, diet records or food diaries, 24-hour dietary recall, food frequency questionnaire (FFQ), and biomarkers.

1. Dietary history questionnaire

This tool encompasses an assessment of long-term dietary patterns (usually 6 months to one year), encompassing data on frequency, portion sizes, and dietary trends. It offers insights into dietary changes over time and captures habitual dietary practices. It includes a structured, detailed interview (which takes 90 minutes to complete) and is conducted by a highly trained professional. It is more suitable for clinical practice than epidemiology and research studies (530).

The original diet history questionnaire was established by Burke in 1947, and has three features: a comprehensive interview about the usual pattern of consumption (usually over a 24 h time

period), a food list probing for quantity and usual frequency of consumption, and a three-day dietary record that is used later as a cross-check of the history (531). There are many variations of this method to determine eating patterns, which include type, frequency, and amount of foods consumed over an extended period of time; many include a cross-check feature (532).

2. Diet records or food diaries

Participants maintain records of their dietary intake in real-time, typically over consecutive days (4-7 days). The amount of food consumed may be measured using a scale (weighted food record), or household measurements, e.g. cup or spoon (estimated food records), or it could be photographed. Leftover food is also recorded (530).

While this method provides comprehensive and granular data, it puts the burden on the respondents as they need to record the type of food, home-made recipes, cooking method, and portion size. It needs a high level of motivation from respondents, or alternatively people who will complete the record for them (parents or caregivers). Moreover, as food diaries often provide unstructured recordings, additional information may need to be gathered, such as location and mood at the time of consumption. On the other hand, the awareness that the type and amount of food must be recorded at the point of consumption may influence both the food selected and the amounts consumed (533, 534) as well as other information related to the research question. Food diaries may be less beneficial in assessing dietary habits as variation in day-to-day intake means many days are needed to establish habitual intake with potential underreporting or modification of dietary habits.

3. 24-hour dietary recall

This methodology involves a well-trained interviewer, usually a nutritionist who contacts participants (face to face or by phone) to recall all food and beverage consumption over a 24-hour period. Multiple calls are commonly utilised to account for variations in intake (530).

This is a retrospective method, often using a structured interview, that relies on respondents' memory, their ability not to over or under-report, and their ability to evaluate portion size. The interviewer usually prompts the respondent to remember what they ate and the portion sizes. One study showed that with interviewer probing respondents reported 25% higher dietary intakes than without interviewer probing (535).

It has been noted that interviewers should use standardised and neutral probing questions to avoid leading the respondent to specific answers when they really do not know or remember. 24-hour recalls have been found to be particularly challenging for young children (536) and the elderly (537). Therefore, while the 24-hour recall can yield detailed information, it may be prone to recall bias.

An additional benefit of this method is that it does not depend on the literacy level of the respondent. Further, as the burden on the respondent is minimal, the 24-hour recall method is useful across a wide range of populations. The 24-hour recall is frequently used in national surveys (538), randomised clinical trials (539), and cohort studies (540). In contrast to the food record method, dietary recalls occur after the food has been consumed, so there is likely to be less impact on dietary habits (541). Finally, 24-hour studies can be conducted by telephone or a web-based automated self-administered method (541), with minimal differences between these and interviewer-administered recalls (542).

Potential limitations of the 24-hour recall method include inaccuracies in the assessment of portion size and individual food intake for a wide range of reasons relating to knowledge, memory, and the interview conditions (530).

In addition, as a single observation provides a poor measure of individual intake, multiple days of recalls may be needed. Although a single 24-hour recall can be used to describe the average dietary intake of a population, multiple recalls can improve precision (543). However, multiple days of recall inevitably increase cost and the burden on the respondent (544).

4. Food frequency questionnaire (FFQ)

The FFQ captures information pertaining to the frequency and portion sizes of diverse food items and beverages consumed over a designated period, typically spanning a year. However, this is subject to study design; the questions might be asked for the last week only or over the past months (545). This tool is favoured due to its relatively low burden on participants and cost-effectiveness.

The FFQ is designed to examine habitual intake; it is useful for collecting data from larger populations (100 or more) and is normally self-conducted (545). It takes only 30-60 minutes to complete. The FFQ contains a food list; the size of the list depends on the nutrients under consideration and may include up to 150 items or more. The challenge with this method is to include a precise food list that reflects the nutrition intake of the nutrients being studied (546). Moreover, the methods of cooking and food combinations cannot be assessed in a predetermined list, which is one of the FFQ's limitations. To improve the validity of the FFQ, researchers have added portion size to the questionnaire; however, the impact of this addition is debatable (547).

Currently, there are two types of FFQ:

1. *Block questionnaire 1986* (546): The Block FFQ is eight pages long and queries 106 foods. It asks for the usual portion size as 'small', 'medium' or 'large', and provides a reference for medium portion sizes. In addition, it includes 13 dietary supplement questions, six questions on restaurant eating, five summary questions, eight questions on fat use or low-fat foods, and seven demographic/health-related questions.

2. *Willet 1998* (548): The four-page Willett FFQ queries 126 foods. It does not include separate portion size questions but asks respondents to report the frequency of a given reference portion size. It includes ten dietary supplement questions and ten questions primarily regarding fat intake. No information has been published about how the nutrient

database for the Willett instrument was constructed. The original FFQ, developed by Willet for the Nurse's Health Study, included only 61 items and accounted for between 60 and 80% of intakes for most nutrients, compared with those estimated by four 1-week diet records. Both types of FFQ have been validated in different epidemiological studies (549-552).

5. Biomarkers

In certain cases, biomarkers, such as blood or urine samples, are employed to objectively assess specific nutrient or food intake. Biomarkers offer increased accuracy but may be limited in terms of cost and availability (553).

Biomarkers could be assessed as:

- *Recovery biomarkers*: the metabolic balance between a chemical compound intake and excretion, mostly urine, in a given period of time (554).
- *Concentration markers*: concentration of specific compounds in biological fluids, for example, serum, blood, urine, in specific tissues or cells, in cellular membranes, and in DNA (554, 555). These markers are correlated with the intake but do not represent the absolute level of intake and do not have the same quantitative relationship with dietary intake levels for every individual in a study population. Most dietary biomarkers are concentration biomarkers, for example, the concentration of vitamin E in lipoproteins, specific carotenoids, and the relative fatty acid composition of circulating phospholipids (556).
- *Prediction biomarkers*: these fall in between the other two types of biomarkers and have the advantage of being less affected by bioavailability and metabolism than concentration biomarkers, but are less quantitatively recovered to the same extent as recovery biomarkers (553, 557).

More recently, the use of doubly labelled water (DLW) as a biochemical marker for the measurement of energy intake has been widely adopted by researchers (558). The literature demonstrates the correlation between energy intake by self-reporting and DLW is very low, with an average sharing of less than 20% in their variance, suggesting underestimated energy intake with self-reporting (559). This was particularly evident in people with high BMI > 30kg/m^2 (560).

Limitations of common dietary assessment tools

All methods of dietary assessment have benefits and limitations. Traditional methods have variable accuracy, and there is no gold standard method to compare with. The common problems associated with dietary assessment are (530):

1. *Self-reporting bias*: People often tend to underreport or overreport their food intake.
2. *Social desirability bias*: Respondents may modify their reports based on social expectations, giving what they perceive as more 'desirable' responses.
3. *Memory and recall*: It can be problematic to ask individuals to remember and accurately report everything they ate in the past. Memory decay, particularly for items consumed a long time ago, can lead to inaccuracies in dietary recall.
4. *Cultural and language barriers*: In multicultural societies, language and cultural barriers can impact the accuracy of dietary assessment. Food items, recipes, and portion sizes may not translate easily.
5. *Special populations:* Dietary assessment in specific populations, such as children, the elderly, or individuals with certain medical conditions, can be especially challenging due to unique dietary needs and difficulties in self-reporting.
6. *Variability in diet*: Dietary habits can vary from day to day, and assessing intake on a single day might not accurately reflect an individual's usual diet.

7. *Seasonal and cultural variation*: Dietary patterns often vary with the season and culture. Dietary assessment tools must account for these variations, which can be challenging.
8. *Portion size estimation*: Estimating portion sizes can be challenging as individuals may not have a good grasp of standard serving sizes. This can result in overestimating or underestimating calorie and nutrient intake.
9. *Complexity of meals*: Many meals are composed of numerous ingredients and dishes, making it challenging for individuals to provide a complete and accurate account of their dietary intake.
10. *Dietary supplements*: Individuals may take dietary supplements that provide nutrients not accounted for in traditional dietary assessments. These supplements can impact nutritional status and need to be considered in assessments.
11. *Lack of standardisation*: There is a lack of standardisation in dietary assessment tools and methods. Different studies and researchers use various tools, questionnaires, and methods, making it difficult to compare data across studies.
12. *Validation and calibration*: Dietary assessment methods require validation against objective measures – like biomarkers or observed intake – to ensure their accuracy. The process of validation can be complex and expensive.
13. *Resource intensive*: Many dietary assessment methods, such as food frequency questionnaires, 24-hour recalls, or food records, can be time-consuming and resource-intensive for both researchers and participants.
14. *Bias in dietary guidelines*: Dietary guidelines and recommendations can be subject to bias, influenced by economic interests, cultural factors, and politics, and may not always reflect the most up-to-date scientific knowledge.

15. *Technology and automation:* While technology offers opportunities for more accurate dietary assessment through apps and electronic records, it also poses challenges, such as the need for accurate databases, accessibility, cost and user compliance (561).

The use of smartphones for dietary data collection has gained popularity in recent years and has been found to be easy to use, reduce participant and interviewer burden, and improve participation rates (562-564); however, smartphone use has yet to be fully exploited within large-scale population surveys (561).

Methods of dietary intake analysis in research studies

Food composition tables and databases provide the foundation on which food and nutrition research, policy, and practice are based (565, 566); therefore, data in these tools must be accurate and representative of foods consumed (567). Many countries have food databases representing foods consumed in their country; the Food and Agriculture Organization (FAO) of the United Nations maintains a list of these food tables on their website (http://www.fao.org/infoods/infoods/tables-and-databases/en/).

Food composition databases should be updated regularly to keep up with new foods, imports, reformulations, and changing demographics and food habits (568).

Assessment of dietary patterns in research studies

As individual foods or nutrients are consumed in various characteristic combinations, nutritional epidemiologists have recommended using overall dietary patterns to find links between diet and diseases (47). Dietary patterns can be defined as the quantities, proportions, variety, or combination of different foods and drinks in diets, and the frequency with which they are habitually consumed (569). The assessment of dietary patterns in observational studies is done through two methods (570):

1. *Index-based*: assessed a priori with the use of dietary indices to measure adherence to a predefined dietary pattern. The foods or nutrients consumed by a person are scored based on some quality score (e.g. the Healthy Eating Index (HEI)), and the results are summarised to produce dietary quality scores (571). Dietary quality scores measure the extent to which individuals adhere to dietary guidelines and recommendations to assess the population's overall dietary quality and predict diseases (572).
2. *Data-driven*: assessed a posteriori where dietary patterns are statistically-derived based on dietary intake reported by a population to obtain a dietary pattern instead of defined dietary guidelines (569, 570). The statistical methods include the cluster method (573), principal component analysis (PCA) (574), and reduced rank regression (575).

Health diet index

A diet quality index (DQI) provides a summary measure of overall diet quality. It represents a collection of scores applied to selected dietary components deemed to be representative of a healthy diet. Internationally, measures of overall diet quality have been associated with chronic disease risk and health outcomes.

Diet quality scores

The diet quality score is used to evaluate dietary pattern association with health outcomes and the effectiveness of dietary intervention. It measures four dimensions (576):

- *Adequacy*: the sufficiency of intake to meet specific requirements and recommendations
- *Balance*: the proportion of energy-yielding macronutrients and fatty acid composition in the overall diet to maintain health
- *Moderation*: the restriction of food portions that pose an increased risk of health outcome

- *Variety of food*: both across and within food groups.

Geometric framework in nutrition analysis

In nutritional ecology, understanding the ways that food components interact to determine the properties of diet that affect behaviour and health is important (577). The geometric framework for nutrition (GFN) serves as a standardised approach to investigating such properties (578).

The foundational principle of GFN is that the:

> nutritional requirement of an organism can be represented geographically either as a point integrated over a period of time or as a moving trajectory within an n-dimensional space, where each dimension is a nutrient (macro- or micro-) or other dietary constituents (fibre, toxin, secondary metabolite, etc.). Such 'intake targets' can be reached if the animal has appropriate foods available (579).

This framework enables researchers to disentangle the effects of different food components – e.g. macronutrients, notably protein and carbohydrates – and effectively captures the intricate nature of its nutritional influences on various levels of individual responses, e.g. growth, life span, energy intake, and performance (577).

Initially, GFN was developed and utilised in animal experimental studies to evaluate the relationship between diet and outcomes such as lifespan across a broad landscape of macronutrient and energy intakes (580, 581). These studies were conducted in a highly controlled laboratory environment and involved randomising animals to various ad libitum-fed diets with different compositions of energy, protein, carbohydrates, and fat; outcomes such as life span, mortality rate, and reproductive measures were plotted against arrays of various measured nutrients intake. Subsequently, GFN proved to be equally effective in field studies (577).

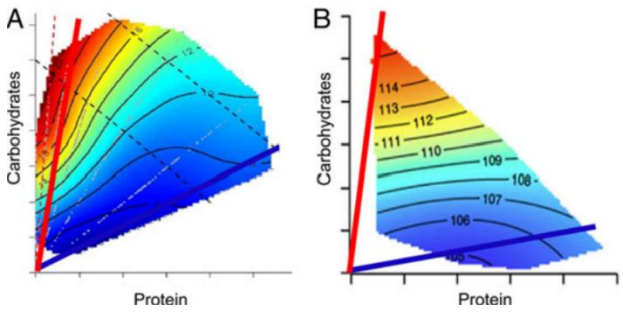
GFN has been utilised to analyse food intake in a variety of species, including birds, insects, fish, rats, mice (582-585), and humans (586-588).

In the GFN, a model is created by plotting responses (called 'response surface') across multidimensional nutrient spaces, i.e. a geometric space built from two or more axes where each axis represents a food component that is suspected to impact the individual response (582).

The response surfaces are derived from individual data points that describe phenotypic traits such as metabolic health, lifespan, and reproductive function, or mechanistic parameters like gene or protein expression, mitochondrial function, and telomere length. By plotting these outcomes against food consumption, the framework accounts for nutrient regulation and compensatory feeding mechanisms (579).

For example, macronutrient components such as protein, carbohydrates, and fat are plotted on a separate axis and presented in slices against a response, e.g. energy intake. A thin-plate spline-fitted response surface is obtained, which resembles a heat map where regions with the highest elevation show the highest value for a given response are coloured in red, and the lowest in blue (577, 587, 590) (Figure 3.1).

Figure 3.1: Geometric framework analysis of dietary protein and carbohydrate



Geometric framework analysis of dietary protein and carbohydrates in (A) fruit flies and (B) mice. The longest life span is shown in red on the heat map and the ratio of dietary protein to carbohydrates associated with the longest lifespan are shown in the red line. In both fruit flies and mice, the longest life span (red) occurred with low-protein, high-carbohydrates diets while the shortest lifespan (blue) was associated with high-protein, low-carbohydrate diets.

Adopted from Le Couteur DG, Solon-Biet S, Wahl D, Cogger VC, Willcox BJ, Willcox DC, et al. New horizons: Dietary protein, ageing and the Okinawan ratio. Age and Ageing. 2016;45(4):443-7 (587).

3.3 Evaluation of fetal growth

Significance of fetal growth for offspring health

The growth of a fetus in the uterus is a complex and carefully controlled process. It involves various factors such as genetics, epigenetics, and the environment, It unfolds in different phases. The process begins with organ development and goes beyond anatomical growth. A well-nourished and growing fetus leads to a healthy birth weight.

3.3.1 Prenatal factors influencing fetal growth

Initially, embryogenesis lays the groundwork for the fetal form as germ layers sequentially differentiate and organise into distinct tissue lineages. Following this embryonic phase, fetal growth enters a period of rapid cellular proliferation and differentiation, characterised by exponential increases in cell numbers and tissue mass (591). The formation of organ primordia and the refinement of their intricate structures and functions are orchestrated by genetic programs and are responsive to diverse signalling cues from maternal and placental sources.

Nutrition, placenta, and hormones

Fetal growth depends on transplacental nutrient and oxygen supply and on its hormonal environment. The carbon and nitrogen in diet are the building blocks for fetal tissues, and hormones regulate their distribution between oxidative metabolism and mass accumulation. Fetal hormones can alter nutrient transfer by changing fetal metabolism and placenta phenotype (209, 592). Placental morphology, vascularisation, and endocrine activity collectively determine the availability of essential substrates required for fetal development (593). Hormonal balance, including factors like insulin-like growth factors (IGFs), leptin, and

cortisol, modulates the intricate dialogue between maternal and fetal compartments, thereby shaping fetal growth trajectories (594).

Genetic factors

Inherited genetic factors can influence fetal growth potential. Parents' height, weight, and health history contribute to genetic predisposition (595, 596).

Epigenetics

The epigenetic landscape exerts significant influence over the dynamics of in-utero fetal growth (252). Epigenetic modifications, including DNA methylation, histone post-translational changes, and non-coding RNA regulation, choreograph gene expression patterns with profound implications for cellular proliferation, differentiation, and organogenesis. These epigenetic marks, often influenced by maternal nutrition and environmental exposures, encapsulate a molecular memory of in-utero experiences, which may resonate into postnatal life (597-602).

Developmental plasticity

Integral to the discussion of in-utero fetal growth is the concept of developmental plasticity, where early-life exposures lead to enduring phenotypic adaptations influencing an individual's susceptibility to diseases in adulthood (44). Disturbances in the in-utero environment, such as maternal undernutrition or gestational stress, can imprint lasting changes in the offspring's metabolic, cardiovascular, and neuroendocrine profiles, setting in motion a cascade of health-related consequences across the lifespan (50).

The DOHaD theory

The DOHaD theory suggests that an individual's health trajectory is shaped by environmental exposures during early development (603). Specifically, prenatal and early postnatal environments determine an individual's susceptibility to chronic diseases (604). The theory highlights the interplay between genetic predisposition and environmental factors, elucidating complex epigenetic mechanisms (605-607). While previous research focused on maternal diet

and risk of cardiometabolic dysfunction, current DOHaD research examines how early developmental environments influence regulatory systems, organs, and tissues that play a crucial role in cardiometabolic functioning (608, 609). Some of these studies include hormone regulatory systems (610-612), cellular mitochondria (613), the structure and function of the pancreas (34), atherogenesis (614), and altered placental function (615, 616).

Fetal growth restriction (FGR) and low birth weight (LBW)

Low birth weight is defined as birth weight below 2500g (5.5 pounds) (29). It is caused by prematurity, fetal growth restriction (FGR), or both.

FGR is a term used to describe fetuses that do not attain their anticipated in-utero growth potential (29). In practice, most FGR cases involve infants identified as small for gestational age (SGA), with birth weights below the 10th percentile for their gestational age (617). Thus, it does not differentiate constitutionally small infants and those who are growth-restricted and small (617). The former exhibit normal birth weights below the 10th percentile due to factors like maternal height, weight, ethnicity, and parity, and they do not face an elevated risk of perinatal mortality or morbidity (618).

Fetal growth restriction occurs when the placenta fails to supply enough nutrients to the developing fetus. This can result in the fetus adopting survival strategies such as reducing overall size, preserving brain growth, accelerating lung maturation, and increasing red blood cell production. Blood flow is redirected from less vital organs to essential ones such as the brain, heart, adrenal glands, and placenta (619). As a result, severe FGR cases can cause a wasted appearance due to reduced total body fat, lean mass, and bone mineral content. Nitrogen and protein content are also lower due to the reduced muscle mass, while glycogen content decreases in skeletal muscle and liver owing to lower fetal plasma glucose and insulin levels. Infants with FGR face an increased risk of mortality and morbidity due to their compromised

growth and reduced energy reserves (620). This makes them more vulnerable during the perinatal period, especially when transitioning from intrauterine to extrauterine life.

Symmetric versus asymmetric fetal growth restriction

Symmetric FGR is a uniform reduction in all organ systems, while asymmetric FGR is a disproportionate growth restriction where the head circumference is preserved, but there is a greater compromise in weight. Symmetric FGR usually starts early in gestation and is caused by intrinsic factors e.g. congenital infection or chromosome defects, while asymmetric FGR occurs later in gestation (late second or third trimester) due to fetal nutrient reduction (29).

3.3.2 Methods of assessment of fetal growth

Identification of FGR during antenatal care is of paramount importance. FGR carries a 4-7-fold increased risk of intrauterine fetal death and a recurrence rate of 40% (617, 621).

Currently, several tools are utilised to assess fetal growth:

1. Fundal height measurements

Measurement of fundal height is an inexpensive and widespread technique performed during antenatal care to detect FGR, as well as other disorders that result in size/date discrepancy.

Measurements of fundal height to symphysis pubis bony landmark are recorded in centimetres and discordant of 3 cm less than the estimated gestational age in weeks is considered abnormal (622). Alternatively, a fundal height measurement below the 3rd or 10th centile can be used (623).

Fundal height measurements have poor sensitivity and have limitations in obese women, women with pelvic masses, and women with twin pregnancies (624, 625). Serial measurements (626) and standardised charts have been proposed to increase their accuracy (624).

2. Ultrasound markers of fetal growth

Ultrasound is the gold standard procedure in assessing fetal growth. Fetal size is computed by standard formulas incorporating accurate measurements of fetal anthropometry: the head circumference (HC), biparietal diameter (BPD), abdominal circumference, and femur length (627, 628).

For appropriate assessment of fetal size and growth, international regulatory bodies have published protocols and guidelines with reference ranges, growth standards, and quality-control processes (627, 629). Nevertheless, there is an ongoing debate regarding the efficacy of customised growth charts (adjusted for maternal height, weight, age, parity, ethnicity, and fetal sex) or population-based non-customised charts (630) for detecting fetal growth abnormalities.

3. Fetal growth velocity

Most screening strategies for fetal growth depend on the cross-sectional estimation of fetal weight or abdominal circumference (AC) at a point in time, which is not truly representative of the dynamic process of fetal growth and may not be enough to detect growth abnormalities. It is reported that around 30% of growth-restricted fetuses are not detected before delivery (631, 632).

Fetal growth velocity is defined by the rate of fetal growth in a given period of time, e.g. g/w. Serial ultrasound scans are used to construct longitudinal growth charts, in which several measurements are taken from the same fetuses at different gestational ages (629, 633, 634). Fetal growth velocity – typically represented as a deviation from growth-velocity charts (change in centiles or Z-score with advancing gestation) (635) – is particularly relevant for assessing fetal growth rather than fetal size (636). There is evidence to suggest that reduced fetal growth velocity in the third trimester is associated with increased risk of adverse outcome (637-639).

4. Birth weight as a marker of fetal growth

Birth weight is used as an indicator of intrauterine growth. Fetuses born with a weight below 10th centile are at high risk of stillbirth and perinatal mortality, and the risk is even higher with birth weight below the 3rd centile; therefore, fetal AC or estimated weight below the 3rd centile on the growth chart can be used as an isolated marker for FGR (640).

The actual pattern of fetal growth in utero can only be determined by serial growth measurement, and far less is known about causes of deviation from normal growth patterns than the causes of abnormal birth weight (259).

The birth weight is highly dependent on gestational length, and the determination of what is an adequate or inadequate birth weight for a given individual is still a matter of debate. The optimal size at birth with the lowest rate of perinatal mortality has been found to be higher than the median birth weight of the normal cohort (641); therefore, to integrate all different perspectives to make use of birth weight as a predictor of health or disease remains a major challenge in current medical practice (642).

Maternal weight gain and fetal growth

Mothers gain little weight in the first trimester: 0.18kg/week, but the weight gain increases to 0.54kg/week in the second trimester (81, 643). Approximately 27% of maternal weight gain is attributed to the fetal weight (84),therefore maternal weight gain during pregnancy has been used as a proxy for fetal growth.

Excessive gestational weight gain has been associated with large for gestational age (LGA), and macrosomia regardless of pre-pregnancy BMI (644). On the other hand, insufficient maternal weight gain was found to be associated with small for gestational age (23, 644) and infant mortality (645).

The Institute of Medicine (IOM) has developed guidelines for maternal weight gain during pregnancy based on BMI (646), which is followed globally; adherence to these guidelines has been shown to reduce the occurrence of low and large birth weights in different ethnic groups (647).

In summary, this section has highlighted that intrauterine fetal growth is a dynamic and complex process involving the interaction between genetics and environmental factors, including nutrition. Hence, the assessment of fetal growth involves multiple measurements and diagnostic tests over the course of pregnancy.

3.4 Limitations and research gap

The field of maternal nutritional research is experiencing significant growth; however, it encounters numerous challenges that affect the generalisation and interpretation of findings. Most of the studies are observational or part of ongoing population-based research, and the limitations of existing dietary assessment tools further complicate the analysis. Additionally, the complex interactions among diverse food items within a typical diet contribute to these difficulties.

There is an imperative need for longitudinal studies involving large cohorts that employ more rigorous and innovative analytical and assessment methods. Such efforts are essential to establish the association between nutrition and various maternal and fetal outcomes and to identify the optimal dietary practices during pregnancy that promote the health of both mothers and their infants.

3.5 Conclusion

This chapter reviewed studies examining the association between maternal nutrition intake and pregnancy outcomes. It highlighted the inconsistencies in the results across various studies, which can be attributed to multiple confounders. Some of these confounders relate to maternal

characteristics, while others stem from different methods of dietary assessment, which are discussed in section 3.2. Another important confounder is the variation in defining outcome measures, specifically fetal growth, as reviewed in section 3.3.

In light of these considerations, we have elected to undertake a study that aims to explore the relationship between macronutrient intake in maternal diets and its association with fetal growth parameters. This investigation will focus on low-risk pregnancies, specifically those involving mothers without pre-existing medical conditions or conditions that may arise during pregnancy, in order to mitigate the potential impact of abnormal placental function on nutrient provision. Moreover, we will concentrate on the proportions of macronutrients in the maternal diet instead of individual amounts based on findings from prior reviews indicating that this approach more accurately reflects maternal nutritional status.

For the assessment of fetal growth outcomes, we have chosen the Intergrowth Z score, which standardises fetal birth measurements according to gestational age and the sex of the infant. Additionally, we will calculate fetal growth on a weekly basis (based on ultrasound measurements)to represent the dynamic process of fetal growth during pregnancy, thereby allowing us to examine its correlation with maternal nutritional intake over time rather than relying on a singular point of measurement (birth)t, which we believe will enhance accuracy.

Our dietary assessment tool will be the Food Frequency Questionnaire, as it is comparatively less burdensome for participants and effectively captures both the frequency of intake and portion sizes.

The subsequent chapter (Chapter 4) will provide a detailed account of the methods and statistical analyses employed in this thesis.

CHAPTER 4: Methods and statistical analysis

4.1 Introduction

This chapter will detail the recruitment process, dietary assessment and the statistical analysis methods used in this thesis.

4.2 Ethics approval

Ethics approval was obtained from the Human Research Ethics Committee of the Nepean Blue Mountain Local Health District /Sydney/Australia (Study 09/7-HERC/09/Nepean 10) (Appendix 2).

4.3 Methods

4.3.1 Study population

The study involved a cohort of women who gave birth at a metropolitan tertiary-level teaching hospital in Western Sydney, New South Wales, Australia. This hospital has 3,000-4,000 births annually and serves both high- and low-risk populations.

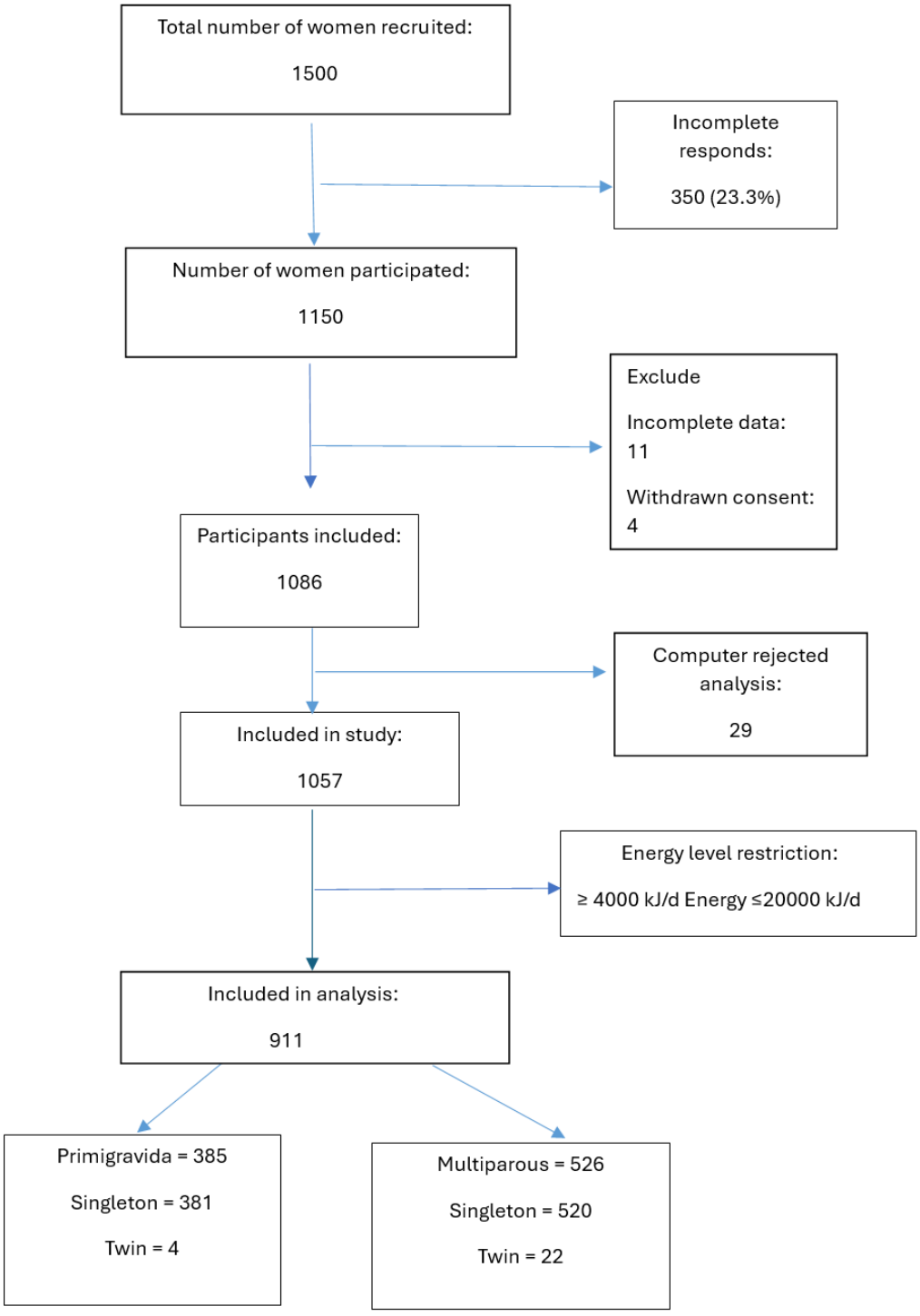
4.3.2 Recruitment process

The recruitment period took place from June 2013 to March 2018. The primary researcher approached all mothers who had given birth within the last 24-48 hours at the postnatal ward to participate in the study. The researcher discussed the research and its objectives with eligible women and provided them with an information sheet, the consent form (Appendices 3 and 4), and a hard copy of the Food Frequency Questionnaire (FFQ) with clear instructions on how to fill it out.

Inclusion criteria included all women regardless of their parity, mode of birth, or gestational age at delivery. The women were hemodynamically stable and free of pain. Exclusion criteria included non-English speaking women or those with high-risk pregnancies (mothers with medical disorders or those who had given birth to babies with congenital abnormalities).

Initially, 1,500 mothers were given the FFQ (Figure 4.1). Of these, 350 women did not return complete forms and were therefore excluded. Eventually, 1,150 mothers entered the study. Despite the meticulous recruitment process, 49 mothers were excluded because their records showed the presence of diabetes. Another 11 mothers were excluded because their antenatal records were missing data, and four mothers withdrew their consent later. The computer analysis rejected a further 29 entries due to unrealistic responses. Ultimately, 1,057 mothers entered the analysis.

Figure 4.1: Flow chart of study participants



4.3.3 Data collection

Details of each pregnancy and the maternal medical history were extracted manually from the e-maternity electronic health record, which is a mandatory, state-wide maternity database system that provides data collection and reporting for inpatient documentation, outpatient electronic medical records, and research (Maternity Information System Advisory Group/Meridian Health Informatics, May 21, 2016). The extracted data included age, parity, height, weight, body mass index BMI (recorded at booking), history of medical disorders, education level, and smoking status.

Maternal BMI was recorded per the WHO classification. (648). Education level was classified according to the Socio-Economic Index for Areas (Australia) (SEIFA). The Index of Education and Occupation (IEO) (649) score was used to capture levels of education in the community based on their area as well as occupation. However, this does not include income variables. A low score on the IEO indicates that many people living in that area are unemployed, have no qualifications, or have low-skilled occupations, and there are fewer people with higher or high-skilled qualifications. The score is based on a weighted combination of selected indicators of advantage and disadvantage, standardised to a mean of 1,000 and a standard deviation of 100.

An area whose indicators are all equal to a national average receives a score of 1,000. In this study, we grouped the index as follows:

Low: 0-950

Medium: 951-1,031

High: 1,032-1,178

Dietary assessment method

Food frequency Questionnaires (FFQs) were chosen as our cohort's dietary assessment tool. The FFQ used in this study is the Victorian Cancer Council Food Frequency Questionnaire Version 2 (DQES V2).

The Victorian Cancer Council Food Frequency Questionnaire

In late 1980 the Cancer Council of Victoria developed an FFQ based on the Willet Questionnaire (650). Initially used to measure the dietary intake of people taking part in the Melbourne Collaborative Cohort Study (MCCS) between 1990-1994, the food list was based on weighted food records from 810 women and men (651).

The DQES v2 was developed from the original FFQ specifically for Australian adults and has been used in the Australian arm of the Breast Cancer CFR, Australian Prostate Cancer Family Study, Australian Longitudinal Study of Women's Health (ALWSH STUDY) and many other smaller epidemiological studies in Australia (652-654). Additionally, The DQES V2 was validated in pregnant women in the Australian population.(528,655-657). Therefore, we have elected to use it in this study. It should be noted that midway through the recruitment process, The Victorian Cancer Council introduced a new version of the questionnaire (2017 DQES V3) to reflect changes in Australian food availability (652). As the recruitment for this project started in 2013, we have elected not to use the new version of the questionnaire to avoid bias in analysis and reporting results.

The DQES V2FFQ is a four-page form and contains short multiple-choice questions in which the participant was asked to highlight the correct answer (Appendix 5). It comprises a food list of 74 items and a section covering the intake of six types of alcohol. This last section was left empty by the participants as the majority of pregnant women refrain from consuming alcohol during pregnancy due to its well-documented adverse effects on their offspring. Furthermore, as women who drink alcohol during pregnancy are typically categorised as having high-risk pregnancies, they were excluded from this study.

The 74 food items are grouped into four food type categories:

1. cereal foods, sweets, and snacks
2. dairy products, meats, and fish

3. fruit
4. vegetables

In brief, the DQES V2 is comprised of the following (Appendix 5):

1. The first page contains questions regarding general fruit and vegetable frequency of intake (Q1-2), types and frequency of milk intake (Q3-4), type and frequency of bread intake (Q5-6), and frequency of egg intake (Q9). It also explores the kinds of spreads used (Q7), sugar intake (Q8), and types of cheese intake (Q10).
2. The second page covers food portions.
3. The third and fourth pages cover the frequency of major food groups and offer ten responses (never, per month, per week, per day).

The output reports from the DQES V2 calculate the average daily intake of common food computed using the NUTTAB 95 database, presented in grams/day (Lewis J, Milligan G, and Hunt A. NUTTAB95 Nutrient Data Table for Use in Australia. 1995, Australian Government Publishing Service: Canberra).

The study participants were given the hard copy DQES V2 FFQ within 24-48 hours after birth; this timing is felt to be more reflective of the mother's food intake in the last nine months (since the beginning of the pregnancy) and while the mother still remembers details of her diet. Furthermore, this timing was influenced by studies that have shown accelerated fetal growth occurs in the last trimester of pregnancy (87). Thus, the nutritional intake in this period may correlate better with fetal growth.

4.4. Statistical analyses

Data were analysed in SPSS V23 software (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp).

Data were checked for normality using graphical and statistical methods (Shapiro-Wilk test). Data with normal distribution were presented as mean ± standard deviation. As data on nutrient intake were found to have a skewed distribution, medians and interquartile ranges were calculated. Between-group comparisons were tested using a 2-sample t-test or one-way ANOVA test, as appropriate, with a significance level of $p<0.05$. An independent 2-group Mann-Whitney U test was performed to compare maternal nutrient and food group intakes. Multi-variate linear regression analyses were performed using the regression function in the base package to investigate the association between maternal food group intakes and offspring outcome variables. The significance was considered when $p<0.05$. A summary of the statistical test used in this thesis is presented in Table 4.1.

4.4.1 Energy calculation

To improve the validity of the dietary analyses, the energy cut-off values recommended by Meltzer et al. (2008) were applied across all pregnancy groups by excluding those who reported daily energy intakes ≥4.000 or ≥20000 kJ/d (527).

Macronutrients, protein, carbohydrates, and fat intake were reported in FFQ output analysis as grams/d. The equivalent energy yield from each nutrient was calculated in kJ as follows:

Protein-energy: g/d x 16.7 kJ

Carbohydrate-energy: g/d x16.7 kJ

Fat-energy: g/d x 37.7 kJ

Discretionary food and energy calculation

The Australian dietary guidelines define discretionary food (DF) as "energy-dense food items that are not necessary to provide the body with nutrition needs." (97) (discussed in Chapter 6). The FFQ v2 included 16 items in this category. However, some of the DF included in the Australian dietary guideline definition, such as energy drinks, sports drinks, sweetened soft drinks, and cordials, are not included in the questionnaire.

The Australian dietary guidelines classify DF (with DF intake reported as gram/day (g/d) for each individual item) as follows:

- ***Higher added sugars group****:* sugar, sweetened drinks (flavoured milk, fruit juice), jam
- ***Higher fat content items****: bacon, ham, salami, sausages, meat pie, pizza, crisps, chips*
- ***Higher fat content and added sugars group****:* biscuits, cakes, ice cream, chocolate

The protein, carbohydrates, and fat content in each food item were calculated based on the serving size for each item, which was extracted from the Australian food database (Appendix 6). The energy yield from each DF item was computed according to its macronutrient content per serve. For each participant, the cumulative intake of DF was calculated and grouped according to the Australian dietary guidelines (97).

Food groups

Food items included in the FFQ v2 were grouped according to similarities in nutritional profile and culinary usage as follows (Chapter 6):

1. **Meat and alternatives group**
    - beef, lamb, pork,
    - fish
    - chicken, eggs
    - seeds (nuts, peanut spread)
    - tofu

2. **Dairy group**

    - milk (full cream, skim milk, reduced-fat milk, soy milk)
    - cheese (hard cheese, firm cheese, soft cheese, cream cheese, low-fat cheese, ricotta)
    - yoghurt

3. **Rice and pasta group**

    - rice
    - noodles
    - pasta

4. **Vegetable group**

    - potatoes, tomatoes, capsicum, lettuce, cucumber, celery, beetroot, carrots, cabbage, cauliflower, broccoli, onion, garlic, mushrooms, zucchini, pumpkin

5. **Fruit group**

    - tinned fruit
    - oranges, apples, pears, bananas, melon, pineapple, strawberries, apricots, peaches, mango, avocado

6. **Legumes group**

    - peas, green beans, beansprouts
    - baked beans
    - other beans (lentils, chickpeas, etc.)

7. **Bread and grains group**

    - bread (white, wholemeal, multigrain)
    - crackers
    - porridge
    - cereals (All Bran, Bran flakes, Weet-Bix, Cornflakes)
    - muesli

8. **Sweet group**

    - biscuits, cake
    - ice- cream
    - sweetened drinks (fruit juice, flavoured milk)
    - jam
    - added sugars

9. **Savory group**

    - meat pies
    - pizza
    - crisps and chips

10. Processed meat group

- sausages
- ham, bacon
- salami

The serve of each group is calculated by dividing the energy yield of each group by 600 kJ as per Australian food recommendation (Appendix 7).

4.5 Conclusion

This chapter has outlined the ethics approval, the methods (study population, recruitment process, data collection, and statistical analysis used in this thesis. Table 4.1 presents a summary of the statistical analyses for each of the chapters that follow.

Table 4.1: Summary of the statistical analysis used in this thesis

	Data source	**Outcome measure**	**Statistical tests**	**Confounders**
Chapter 5				
Participants' demographic characteristics	E maternity records manual extraction	Stratify the study population according to - Age - Parity - BMI - Ethnic group - Socioeconomic status - Smoking status	The mean and standard deviation of the mean were used to compare results. Between-group comparisons were tested using a 2-sample t-test / a Mann-Whitney test or one-way ANOVA test as appropriate with a level of significance of $p<0.05$	N/A
Macronutrient intake	FFQ computer analysis	Establish average intake and compare according to parity	Independent 2-group Mann-Whitney U test was performed to compare maternal nutrient and group intakes with the level of significance $p<0.05$	Stratified according to BMI Gestational age Ethnicity Energy level

Offspring growth parameters Weight at birth Length at birth Fetal weight gain in utero	Data was extracted manually from birth records, e-maternity and ultrasound reports	Compare the study population according to parity and offspring sex	Presented as mean and standard deviation. T-test was used to compare results. The rate of fetal growth per week was calculated using Dr Mongell's formula (Chapter 5)	Birth weight ,length and Z score length was adjusted by using online intergrowth calculators.
Offspring growth parameter and macronutrient intake	N/A	The association of macronutrient intake and offspring growth measures	multivariate linear regression analysis and Geometric Framework Nutrition Analysis (Chapter 5)	Adjusted for Age Maternal BMI Gestational age
Chapter 6				
Discretionary food intake	FFQ responses and computer analysis	Explore the prevalence of intake and compare it between different study demographic groups	Percentage of intake compared using chi square test with a level of significance $p < 0.05$	Stratified according to Age BMI
Discretionary food energy	Derived from FFQ data analysis and calculated values	Explore the contribution of DF-derived energy to total energy intake	Percentage of macronutrient energy intake compared by chi-square	Stratified according to Women's characteristics Different energy levels
Dietary pattern	Derived from FFQ data	Explore common dietary patterns in the study cohort	Principal component analysis (PCA)	N/A
Dietary patterns and offspring growth parameters	N/A	Explore the association of extracted dietary patterns and offspring growth measures	Multi-regression analysis	Adjusted for Age parity BMI Offspring sex

Chapter 7				
Smoking status of the pregnant mother	Participant Self-reporting	Establish nutrient intake for mothers who report smoking during pregnancy and compare it to mothers who did not -smoke	Logistic regression analysis	Adjusted for Age Parity BMI Gestational age Offspring sex
Chapter 8				
Common food allergen intake	Data extracted from FFQ responses	Explore the prevalence of common food allergens in the study cohort	Percentage of intake compared by chi-square test	Stratified according to Age Ethnicity BMI
Allergic status of the pregnant mother	Participants' self-reporting	Explore maternal food avoidance in presence of allergic history	Percentage of intake compared by chi square test	Stratified according to Age Ethnicity BMI

CHAPTER 5: Analysis of maternal macronutrient intake during pregnancy and its association with offspring measurements

5.1 Introduction

Pregnancy represents a unique stage of intense growth and development for both the mother and the fetus. Throughout pregnancy, maternal physiological changes occur, including an increase in blood volume, cardiac output, and basal metabolic rate (81, 82). Additionally, the growth of maternal tissues, such as the breasts and uterus, as well as associated structures, such as the placenta and amniotic fluid, require additional energy for their development and maintenance. This heightened metabolic activity places a greater demand on maternal energy resources. Energy intake is made available through increased maternal food intake, along with an increased capacity for maternal nutrient absorption (87).

Macronutrients – namely protein, fat, and carbohydrates – are essential nutrients that serve as the primary source of energy for the human body. A balanced macronutrient intake in the diet is the key to health and maintenance of adequate body function. Therefore, the contribution of macronutrient intake to maternal health and fetal growth has attracted the interest of numerous researchers. Initially, studies focused on the individual macronutrient association with various pregnancy outcomes, but results were conflicting due to variations in the study methods, type of food analysed, and the inherent difficulties in performing studies on pregnant women (reviewed in Chapter 3 section 3.2). More recently, the focus has shifted to analysing dietary patterns reflecting the interaction of different nutrient intake and its association with pregnancy outcomes (reviewed in Chapter 3 section 3.1.3).

A healthy diet during pregnancy is a common concern, particularly for expecting mothers. Pregnant mothers tend to change their dietary habits and food choices to ensure the well-being

of both themselves and their growing baby. However, it can be challenging to determine what constitutes a healthy diet and how it impacts pregnancy outcomes. Therefore, understanding the interaction between different nutrient intake and its association with pregnancy outcomes is essential to providing optimal dietary advice.

One of the major pregnancy outcomes is fetal weight. Low birth weight is associated with adverse outcomes for neonates both in the short and long term (30, 31). However, studies exploring the relationship between macronutrient intake and low birth weight risk have yielded mixed findings. Inadequate energy intake, insufficient protein consumption, and imbalances in carbohydrate and fat intake have all been implicated in an increased risk of low birth weight (13, 387-395). Yet, the evidence is inconsistent (as reviewed in Chapter 3, section 3.1.1), and further research is needed to establish a clear association between macronutrient composition and low birth weight risk.

This chapter explores maternal macronutrient intake and its association with fetal growth parameters.

5.2 Methods

Chapter 4 of this thesis details the patients' recruitment process and eligibility. After energy intake was adjusted to levels between 4000-20000 kJ/d, 911 mothers were included in the final analysis. Their characteristics are summarised in Table 5.1.

5.2.1 Statistical methods

The data were stratified by parity, primiparous (PG) vs multigravida (MG), and offspring sex (male vs female). An independent 2-group Mann-Whitney U test was performed to compare maternal nutrient and food group intakes. The association between maternal macronutrient intake and an offspring's anthropometric outcomes (weight, length, head circumference (HC), Z score, and average weight gain (g/week) (AWG) was evaluated using multivariate linear regression analysis.

The average weight gain/w was calculated according to the Mongelli et al equation (658):

$$\mathrm{AWG} = \frac{\mathrm{BWT} - 670}{\mathrm{GA} - 24}.$$

This method is based on median ultrasound measurements of fetal weight at 24 weeks gestation to calculate fetal growth velocity expressed as grams per week. The average weight gain per week measures the growth velocity specific to each fetus.

The Z score was calculated as per intergrowth online calculators (623). It is an international multicentre, multiethnic population-based calculator used to standardise assessment of fetal outcome measures.

Geometric Framework for Nutrition (GFN) analysis

To explore the association of macronutrient intake on fetal growth parameters, the Geometric Framework for Nutrition (GFN) analysis was utilised. In this method, the total daily macronutrient food intake (g/d) (protein, carbohydrates and fat) is plotted on a separate axis and presented in slices against an outcome 'response surface'.

The outcome measures were neonate weight at birth (g), neonate length at birth (cm), and in utero-fetal weight gain per week gestation (gram/week)

The outcomes are presented in a three-dimensional space bounded by axes consisting of the intakes of protein, carbohydrates, and fat (these are presented in the figures in a two-dimensional plane at the median of the third axis).

The results are presented as a coloured map, 'response surface', where areas of higher association with a given outcome are coloured in red and the lowest in blue (Figure 5, 6).

5.3 Results

Participants characteristics

Mothers were grouped according to parity (Table 5.1). The average age of mothers was 28.9 years ± 5.7. Multiparous mothers were older than primigravida mothers (30.5 years ± 5.4 vs 26.8 years ± 5.4, $p < 0.05$). The average BMI at booking was 26.9 ± 6.9 kg/cm^2. Multiparous mothers had a higher BMI than primigravida mothers (27.4 ± 7.4 kg/m^2 vs 26.1 ± 6.0 kg/m^2, $p < 0.05$). Around 73% of the study population were of Caucasian origin, while 5.7% were Aboriginal and 6.7% were of Indian ethnicity, representing a similar distribution to the general population (651).

According to the SEIFA education index classification, multiparous mothers had lower education scores than primigravid mothers (59.3% vs 55.1%, $p < 0.05$). 11.4% of mothers reported smoking during pregnancy, with a higher percentage of mothers who smoked in the multiparous group (11.8% vs 10.9%, $p < 0.05$). The majority (56.5%) of the mothers delivered at term (between 37-40 weeks), while more primigravida delivered after 40 weeks (postdates) than multiparous mothers (34.3% vs 29.8%).

Table 5.1: Characteristics of the study cohort of 911 pregnant women from a metropolitan Sydney hospital

	Total 911	**Primigravida N=385**	**Multiparous N=526**
Age (year)*	28.9±5.7	26.8±5.4	**30.5±5.4**
Plurality **Singleton** **Twins**	 865 (95) 46 (5.0)	 361 (93.8) 24 (6.2)	 504 (95.8) 22 (4.2)
BMI (kg/m^2)* **<18.5** **18.5-24.9** **25-29.9** **30-34.9** **35-39.9** **>40**	26.9 ±6.9 39 (4.3) 406 (44.6) 234 (25.7) 116 (12.7) 66 (7.2) 50 (5.5)	26.1±6 13 (3.4) 203 (52.7) 80 (20.8) 51 (13.2) 24 (6.2) 14 (3.6)	27.4±7.4 26 (4.9) 203 (38.9) 154 (29.3) 65 (12.4) 42 (8) **36 (6.8)**

Ethnic group			
Caucasian	663 (72.8)	290 (75.3)	373 (70.9)
Aboriginal	52 (5.7)	22 (5.7)	30 (5.7)
Torres Strait Islander	42 (3.2)	19 (4.9)	23 (3.6)
Asian/Indian	79 (8.7)	29 (7.5)	50 (9.5)
Asian/Chinese	29 (4.6)	10 (2.6)	19 (4.4)
Mediterranean	24 (2.6)	8 (2.1)	16 (3.0)
Others	23 (2.4)	7 (1.8)	15 (2.4)
SIFA ^			
low score	524 (57.8)	212 (55.1)	213 (59.3)
middle score	299 (32.8)	133 (34.5)	136 (31.6)
high score	88 (9.7)	**40 (10.4)**	48 (9.1)
Smoking			
No	806 (88.6)	342 (89.1)	246 (88.2)
Yes	104 (11.4)	42 (10.9)	**62 (11.8)**
Missing	1		
Gestational age			
Less than 37 weeks	107 (11.7)	52 (13.5)	55 (10.5)
Between 37-40 weeks	515 (56.5)	201 (52.2)	314 (59.7)
More than 40 weeks	289 (31.7)	**132 (34.3)**	1579.8)

Bold numbers represent statistically significant results, p<0.05

Data presented as numbers (percentages)

*Normally distributed data presented as mean ± SD

^SEIFA Index of education and occupation :Low: 0-950, Medium: 951-1031, High: 1032-1178

Offspring outcome

The average newborn birth weight was 3336.0±582.1g. The average newborn length was 50.1cm±3.2cm, and the head circumference was 34.3cm±1.7cm (Table 5.2).

Table 5.2: Offspring characteristics

	Total N=911	**Primigravida N=385**	**Multiparous N=526**
		Total	**Total**
Gestational age (w)	38.9±1.8	38.8±2.3	38.9±1.7
Birth weight (g)	3336.0±582.1	3244.2±638.9	**3375.8±569.5**
L (cm)	50.1±3.2	50.0±3.3	50.2±3.1
HC (cm)	34.3±1.7	**34.0±1.9**	**34.4±1.7**

HC/BW	0.0107±0.002	0.0108±0.002	**0.0104±0.001**
HC/L	0.68±0.03	0.68±0.0	0.68±0.0
Z score at birth	-0.8±1.0	-0.21±1.1	**0.01±0.9**
Fetal growth g/w	177.1±37.1	171.9±31.5	**180.9±31.4**

Bold represents a significant result, p <0.05

HC: head circumference. BW: birthweight. L: length at birth. w: week. g: gram

After adjusting for gestational age and excluding twin babies, the rate of SGA (birth weight <2500 g) was 2.6%.

Babies born to multiparous women were heavier and had larger head circumference than first-born babies: 3375.8g±569.5 vs 3244.2g ±638.9 and 34.4cm ±1.7 vs 34.0cm±1.9, respectively.

Babies born to multiparous mothers gained more weekly weight than first-born babies: 180.9g±31.4 vs 171.9g ±31.5. The head circumference to birth weight ratio was 0.017, indicating symmetrical fetal growth in utero.

There was a difference in anthropometry with gender; boys were heavier, longer, and gained more weight per week than girls regardless of parity status (Table 5.3).

Table 5.3: Offspring anthropometry by gender and parity

	Total N=911		**Primigravida N=385**		**Multiparous N=526**	
	Boys 435	**Girls 476**	**Boys 178**	**Girls 207**	**Boys 257**	**Girls 269**
Gestational age (w)	38.9±1.8	38.9±1.8	38.8±2.3	38.8±2.3	38.9±1.6	38.9±1.7
Birth weight (g)	3402.5±573.7	3276.3±583.7	3345.2±641.8	**3157.4±624.9**	3413.8±549.3	3339.5±586.9
L (cm)	50.6±3.1	49.6±3.2	50.5±3.3	**49.6±3.3**	50.7±2.9	49.7±3.1
HC (cm)	34.6±1.7	34.0±1.7	34.4±1.8	**33.7±1.9**	34.7±1.7	34.2±1.6
HC/BW	0.0105±0.002	0.0107±0.002	0.0106±0.001	0.011±0.002	0.0104±0.001	0.0105±0.001
HC/L	0.685±0.04	0.687±0.04	0.68±0.03	0.68±0.03	0.068±0.03	0.68±0.04
Z score	-0.06±0.9	0.156±1.0	-0.04±1.01	-0.36±1.07	0.08±0.94	-0.05±1.01

Fetal growth g/w	182.0±30.3	173.5±31.5	178.3±29.1	**167.2±32.3**	184.6±30.8	177.6±31.8

Bold represents statistically significant result p<0.05
HC: head circumference. BW: birthweight. L: length at birth. w; week. g: gram

Fetal weight gain per week during pregnancy

The average fetal weight gain per week was 177.1g±37.1. Babies born to multiparous women gained more weight than those born to primigravida: 180.9g±31.4 vs 171.9g±31.5 p<0.0.5 (Table 5.3).

Boy offspring gained more weekly weight than girls: 182.0g ±30.3 vs 173.5g±31.5, p<0.05. On the other hand, girls born to primigravida mothers had the least weight gain per week of all groups: 167.2g±32.3) (Table 5.3).

Energy intake

Energy intake was not normally distributed; therefore, the median and interquartile range (IQR) were used.

The median energy intake of the study population was 7542.3kJ/d (IQR 3853.4) (Table 5.4). There was a statistically significant difference in energy intake between primigravida mothers (PG) and multiparous mothers (MP); the MP had more energy intake compared to PG: 7292.2 kJ/d (IQR 4011.9) vs 7719.4 kJ/d (IQR 3649.3), p<0.05. Mothers of Asian ethnic groups had higher energy intake than other groups, regardless of parity.

Table 5.4: Energy intake by maternal characteristics presented as median (IQR)

	Numbers (total = 911)	Energy intake median (IQR)
Age (year)	28.93±5.7	7542.3 (3853.4)
• **Below 30**		7550.1 (3972.4)
• **Above 30**		7525.6 (3527.6)
Parity		
• **Primiparous**	385	7292.2 (4011.9)
• **Multiparous**	526	**7719.4 (3649.3)**
Plurality		
• **Singleton**	883	7539.7 (3786.8)
• **Twin**	28	7667.8 (4406.2)
BMI (kg/m^2)		
• **<18.5**	39	7827.3 (5183.7)
• **18.5-24.9**	406	7635.0 (3782.1)
• **25-29.9**	234	7525.6 (3735.5)
• **30-34.9**	116	7084.8 (3570.9)
• **35-39.9**	66	7571.6 (3859.4)
• **>40**	50	**8360.3 (3965.1)**
Ethnic group		
• **Caucasian**	663	7456.8 (3621.5)
• **Aboriginal**	52	7426.5 (4137.6)
• **Torres Strait Islander**	42	9140.0 (6602.3)
• **Asian/Indian**	79	**7847.1 (3297.7**)
• **Asian/Chinese**	29	7615.3 (3922.6)
• **Mediterranean**	24	7472.2 (4948.8)
• **Others**	22	7473.1 (4157.9)
SIFA classification*		
• **Low**	524	7843.4 (4276.4)
• **Middle**	299	7373.6 (3348.4)
• **High**	88	7204.8 (3195.3)
Smoking		
• **No**	806	7527.0 (3763.7)
• **Yes**	104	7838.9 (4429.2)
• **Missing**	1	
Gestational age		
• **Less than 37 week**s	107	7461.9 (3743.5)
• **Between 37-40 week**s	515	7613.9 (3887.2)
• **More than 40 week**s	289	7525.6 (3580.8)

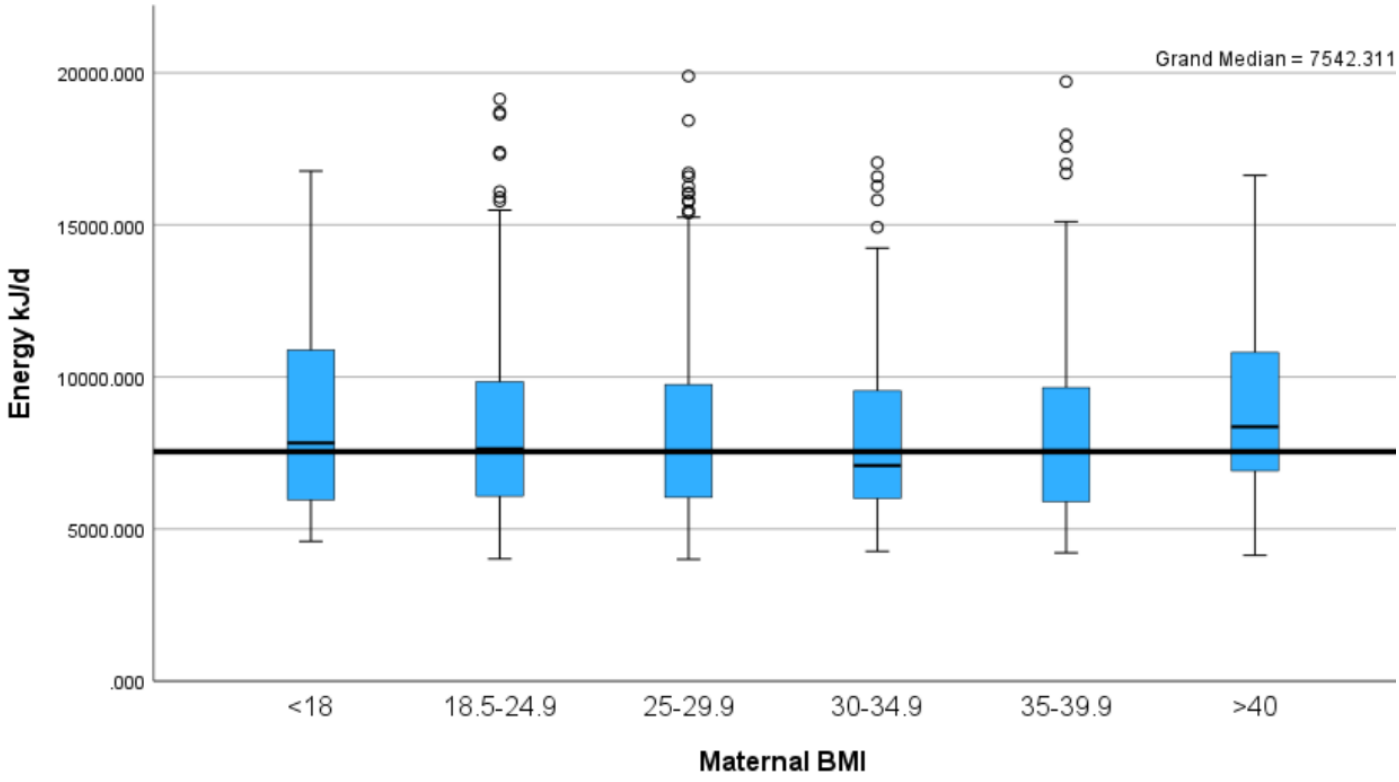
Bold represent statistically significant results<0.05

*SEIFA Index of education and occupation :Low: 0-950, Medium: 951-1031, High: 1032-1178

The relationship between energy intake and BMI shows mothers with high BMI at booking (>40 kg/m^2) had higher energy intake than other BMI categories (Table 4 and Figure 1). The energy intake was slightly higher at the lowest BMI (>18.5 kg/m^2) but did not reach statistical significance, p<0.09.

Mothers who smoked during pregnancy had higher energy intake than those who did not smoke, 7838.9 kJ/d (4429.2) vs 7527.0 kJ/d (3763.7). However, this was not statistically significant, p=0.6 (Chapter 7 will further analyse the energy and macronutrient intake in mothers who smoked during pregnancy).

Figure 5.1: Energy intake and maternal BMI



Macronutrient intake

Energy intake was divided into three tertiles according to the level of energy intake. The contribution of each macronutrient to energy was analysed (Figure 5.2).

Figure 5.2: Macronutrient intake by energy level

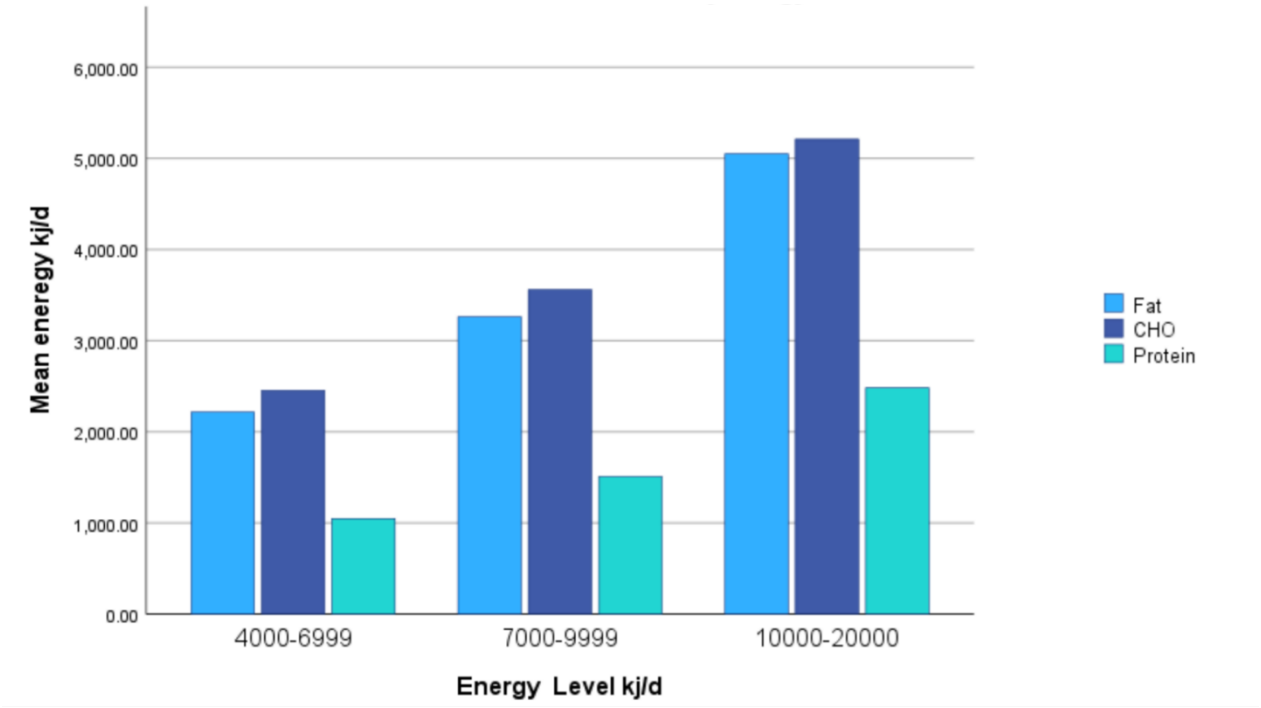


Table 5.5: Macronutrient intake according to energy level

	Total energy	Low energy T1	Medium energy T2	High energy T3
		4000-6999 kJ/d	**7000-9999 kJ/d**	**10000-20000 kJ/d**
Median (IQR)	7542.3 (3853.4)	5767.5 (1334.5)	8222.9 (1501.4)	11891.9 (3230.5)
Protein **Protein E%**	1384.4 (760.7) 18.2 (3.6)	1038.9 (325.6) 18.0 (3.6)	1469.6 (358.8) **17.8 (3.4)**	2363.3 (867.6) **18.9 (4.3)**
Carbohydrates **Carbohydrate E%**	3260.6(1582.2) 42.5 (7)	2455.3 (601.4) 42.7 (6.9)	3555.8 (677.6) 42.7 (6.6)	5084.4 (1368) **41.3 (8.4)**
Fat **Fat E %**	2978.5(1588.4) 39.7 (6.5)	2203.9 (642.1) 39.5 (6.7)	3226.2 (694.9) 39.9 (6.3)	4833.6 (1621.9) 39.9 (6.2)
Protein to non-protein ratio	22.4	22.6	22.2	**24.4**

Bold represents statistically significant results, p<0.05

IQR: Interquartile range ,E% :percentage of total energy

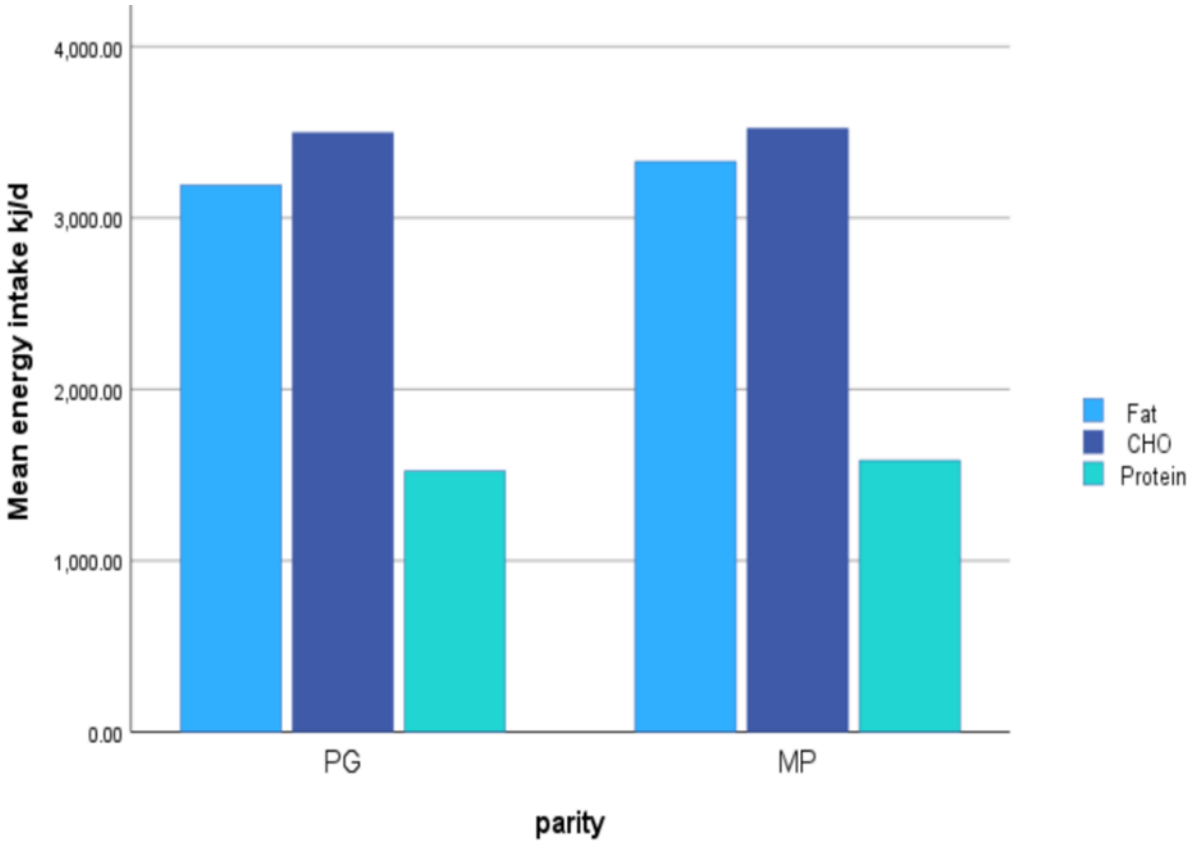
There was a statistically significant difference in maternal intake: primigravida mothers consumed less fat in their diet than multiparous mothers: 74.4g/d (44.4) vs 82.5 g/d (38.8),

p<0.05 (Table5.6), while protein and carbohydrate intake did not show any statistical significance (Table 5.6 and Figure 5.3).

Table 5.6: Macronutrients intake (gram/day) and parity

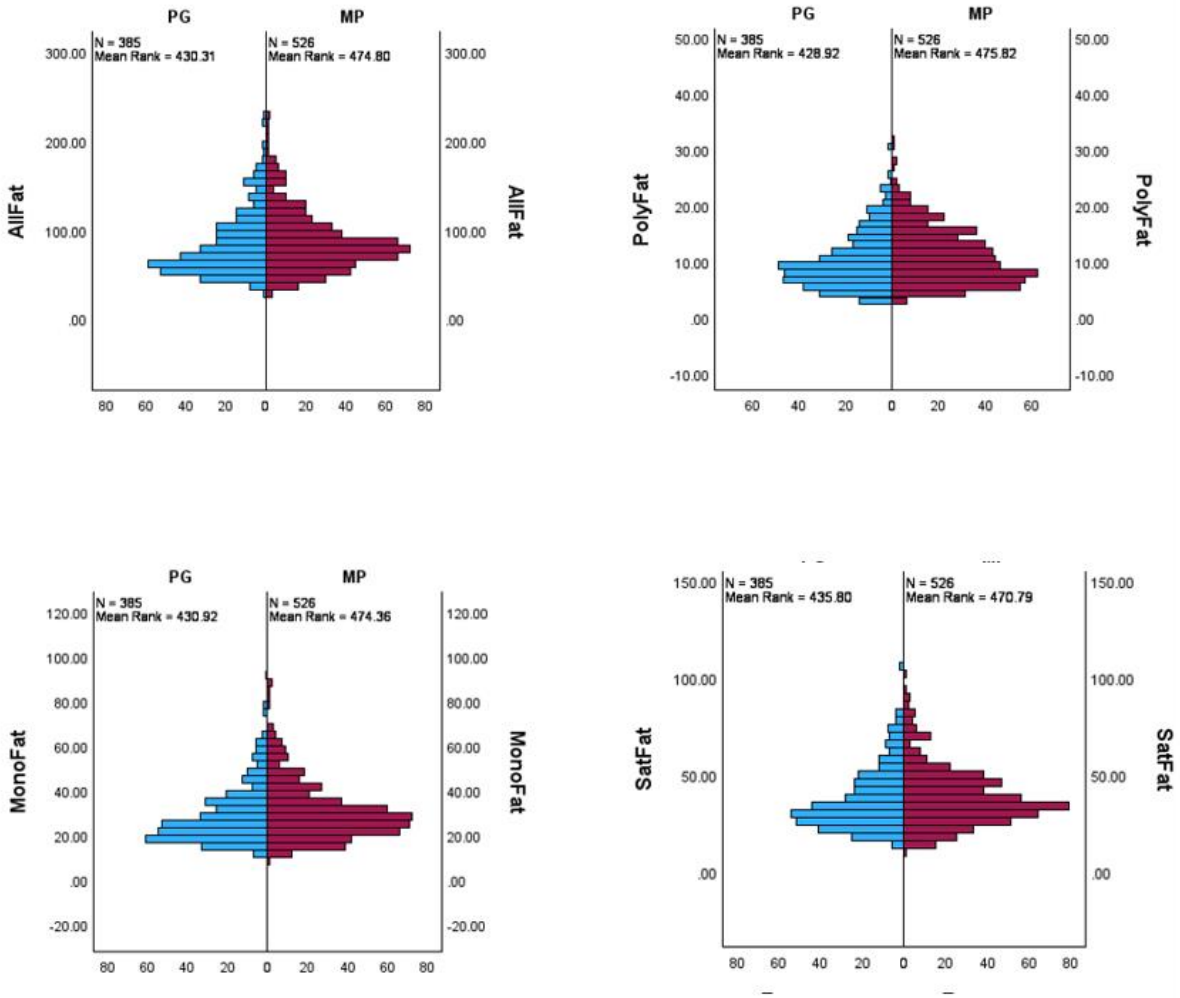
	Primigravida N=385	Multiparous N=526	P value
All fat	74.4 (44.4)	82.5 (38.8)	**0.01**
Polyunsaturated	9.2 (6.4)	10.1 (7.1)	**0.00**
Monounsaturated	25.8 (15.5)	28.2 (13.6)	**0.01**
Saturated fat	32.7 (19.9)	35.9 (17.8)	**0.04**
Protein	81.9 (43.4)	84.1 (43.8)	0.17
Carbohydrates	193.1 (93.9)	195.8 (96.4)	0.15

Figure 5.3: Macronutrient intake by parity



PG: primigrvida.MP: Multiparous ,CHO: Carbohydrates

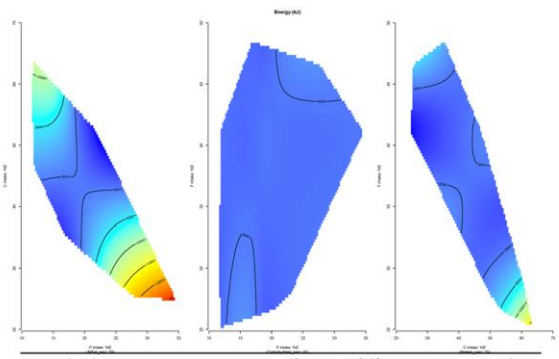
Figure 5.4: Fat consumption by parity



Utilising the geometric framework for nutrition (GFN) analysis, the primigravida mothers were more likely to have a higher energy intake on diets that were high in protein and carbohydrates but low in fat, whereas, for multiparous mothers, it was the ratio of protein to fat that drove high energy levels (Figure 5.5).

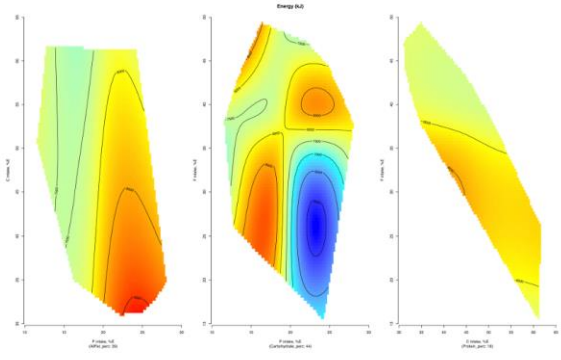
Figure 5.5: Surface plot illustrating the relationship between macronutrient intakes (as a percentage of total energy intakes, %E) and total energy intake according to parity

First-born (n=208)



Energy intake	edf	Ref.df	F	p-value
te(Protein)	0.00	4	0.000	1.00
te(Carbohydrate)	0.00	4	0.000	0.71
te(AllFat)	0.00	4	0.000	0.69
ti(Protein,Carbohydrate)	0.88	16	0.453	<0.001
ti(Protein,AllFat)	0.00	16	0.000	0.50
ti(Carbohydrate,AllFat)	0.00	16	0.000	0.80
ti(Protein,AllFat,Carbohydrate)	3.52	53	0.159	**0.02**

Multi-parous (n=297)



Energy intake	edf	Ref.df	F	p-value
te(Protein)	0.00	4	0.00	0.81
te(Carbohydrate)	0.44	4	0.20	0.16
te(AllFat)	0.00	4	0.00	0.72
ti(Protein,Carbohydrate)	0.33	16	0.03	0.19
ti(Protein,AllFat)	3.45	16	0.62	**0.01**
ti(Carbohydrate,AllFat)	0.37	16	0.03	0.24
ti(Protein,AllFat,Carbohydrate)	0.00	54	0.00	0.96

C, carbohydrate; P, protein; F, total fat; %E, the percentage contribution to energy. All surfaces have been adjusted by mothers' weight and height

Food groups

The food items recorded in the Food Frequency Questionnaire (FFQ) were classified into ten distinct food groups, as outlined in Chapter 4. Preliminary analyses revealed notable differences in dietary intake patterns between primiparous and multiparous women. Specifically, primigravida mothers exhibited a higher consumption of fruits (193.6 vs 176.2 g/d) and dairy products (397.4 vs 387.2 g/d) in comparison to multiparous women, who demonstrated greater intake levels of meat (158.7 vs 147.4 g/d), bread, and grains (200.2 vs 180.6 g/d). However, these observed differences were marginally significant, p= 0.06.

A significant disparity was identified in processed meat consumption, with multiparous women exhibiting a higher intake of compared to primigravid mothers of (18.9 vs 12.5 g/d,$p<0.05$) .The data were further analysed according to energy intake levels to better elucidate these findings.

At the higher energy intake level (T3), multiparous mothers reported greater consumption of meat(292.7 vs 256.1 g/d,p<0.05), bread, and grains (338.1 vs 320.0 g/d ,p<0.05) than their primigravid counterparts, who consumed less fruit (211.9 vs 272.9 g/d, p<0.05). Conversely, at the lower energy intake level (T1), primigravid mothers displayed a lower level of processed meat consumption (9.6 vs 12.7 g/d ,p<0.05)and a higher intake of dairy products relative to multiparous mothers (383.2 vs 335.4 g/d ,p<0.05). Detailed findings are presented in Table 5 7.

Table 5.7: Major food group intake (g/d) according to parity and energy level (median (IQR))

	Total	***LOW (T1) 4000-6999kJ/d***	***MED (T2) 7000-9999kJ/d***	***HIGH (T3) 10000-20000kJ/d***
Vegetables	85.2 (70.2)	76.2 (56.0)	87.8 (74.6)	106 (88.0)
PG	82.1 (64.0)	75 (58.2)	83.7 (65.0)	105.4 (87.9)
MP	87.7 (71.2)	76.5 (53.5)	93.7 (79.6)	107.0 (88.0)
Fruit	184.2 (170.2)	128.7 (139.3)	203.3 (172.3)	245.6 (858.6)
PG	193.6 (187.5)	129.2 (149.6)	220.2 (211.5)	**272.9 (307.1)**
MP	176.2 (158.8)	126.4 (136.5)	202.0 (165.6)	211.9 (182.0)
Meat and alternatives				
PG	154.7 (116.2)	112.7 (65.6)	161.4 (90.2)	274.4 (196.4)
MP	147.4 (113.7)	109.8 (60.2)	160.2 (88.4)	256.1 (199.6)
	158.7 (117.8)	115.0 (72.9)	167.4 (92.1)	**292.7 (197.4)**
Bread and grains	188.1 (167.3)	139.1 (79.6)	212.0 (128.6)	332.1 (200.9)
PG	180.6 (157.4)	132.4 (68.9)	211.4 (119.6)	320.0 (193.3)
MP	200.2 (180.6)	144.6 (96.6)	213.2 (143.7)	**338.1 (208.2)**
Dairy products	390.7 (260.3)	375.0 (195.4)	414.8 (327.1)	417.3 (328)
PG	397.4 (276.9)	**383.2 (212.6)**	438.2 (302.4)	403.2 (234.5)
MP	387.2 (248.5)	335.4 (174.8)	395.4 (249.8)	423.8 (329.5)
Processed meat	15.2 (26.8)	10.4 (14.3)	15.7 (24.8)	35.1 (49.1)
PG	12.5 (23.7)	**9.6 (12.6)**	13.0 (24.5)	34.8 (44.9)
MP	**18.2 (28.2)**	12.7 (18.2)	18.6 (22.6)	36.6 (54.3)
Savoury food	62.4 (63)	46.4 (35.9)	64.7 (55.5)	113.3 (114.9)
PG	61.4 (65.0)	46.8 (36.4)	62.3 (55.9)	133.3 (115.0)
MP	63.2 (60.6)	46.1 (35.7)	65.3 (55.7)	103.9 (107.1)
Sweet food	119.0 (151.4)	75.1 (78.9)	132.3 (135.9)	234.3 (189.3)
PG	123.1 (159.0)	75.1 (89)	140.5 (143.7)	247.5 (197.9)
MP	117.1 (141.2)	75.5 (72.2)	132.0 (131.1)	231.0 (189.6)
Spread	14.7 (14.3)	14.1 (10.9)	15.1 (10.2)	18.4 (14.3)
PG	14.4 (13.5)	14.1 (11.4)	14.5 (7.8)	21.0 (15.0)
MP	14.9 (14.4)	14.1 (12)	15.6 (14)	17.1 (14.0)

Numbers in bold represent statistically significant results, p <0.05

PG = primigravida, MP = multiparous

Energy, macronutrient and fetal anthropometric parameters

For this analysis, only pregnancies with no risk factors for fetal growth were included; twins and preterm deliveries were excluded.

Fetal weight and length at birth

Multivariate regression analysis revealed that maternal BMI and smoking status are major predictors of offspring's birth weight and length (Table 5.8). Maternal BMI was associated with a 14.6 g increase in baby weight for every unit increase in BMI kg/m^2 and an increase in fetal length of 0.62 cm while smoking resulted in a reduction of baby weight of 171.3g and reduced newborn length by 1cm. For every one-week increase in gestational age, baby weight increases by 207.7 g and length increases by 1 cm at birth (Table 5.8). Controlling for the above confounders, energy intake was not associated with fetal growth parameters (Table 5.8).

Table 5.8: Regression analysis of predictors of fetal birth weight and length

	B coefficients	Standard error	Confidence interval	P value
Birth weight (gram)				
Maternal Age/year	-3.172	2.673	-8.4 to -2.074	0.236
Maternal BMI	14.564	2.235	9.5 to 18.2	<0.001
Parity (Multiparous)	111.3	28.0	50.4 to 162.9	<0.001
Smoking status (yes)	-171.268	44.032	-259.3 to -88.5	<0.001
Gestational age / week	207.727	7.548	192.9 to 222.3	<0.001
Energy (kJ/d)	-.004	.005	-.013 to 0.005	0.297
Birth length (cm)				
Maternal age (year)	-.019	.017	-0.052 to 0.015	0.273
Maternal BMI	.062	.014	0.034 to 0.090	<0.001
parity (Multipara)	.206	.193	- 0.172 to 0.584	0.285
Smoking status (yes)	-1.178	.280	-1.728 to -0.628	<0.001
Gestational age (week)	.991	.050	0.893 to 1.089	<0.001
Energy kJ/d	-3.538e-5	.000	0.00 to 0.00	.235

Macronutrient intake and fetal weight and length at birth

To further evaluate the relationship between macronutrient intake and fetal growth parameters, we utilised the GFN analysis. (statistical details in Appendix 8, Supplementary table 1)

GFN analysis showed that primigravid mothers on a high-energy diet (high protein, fat, and carbohydrate) delivered heavier babies, whereas, for multigravidas, it was the ratio of protein to fat (high protein to high fat) and the ratio of carbohydrate to protein (high carbohydrate to high protein) that was associated with delivering heavier offspring (Figure 5.6, A). There were also some differences in the relationship between maternal macronutrient intake and offspring length according to the number of previous pregnancies: primigravidas were more likely to deliver longer babies if their diet was either low or high in protein, fat and carbohydrate (i.e. the source of energy was not as important as the amount of energy itself), which influenced their offspring length. Conversely, for multigravidas it was a diet high in carbohydrate but moderate in fat that resulted in longer offspring (Figure 5.6, B).

Multigravidas' offspring were born heavier if their mothers consumed a diet higher in fresh vegetables, whereas, for primigravidas, diets high in sweet discretionary and unhealthy fats tended to result in heavier babies (Table 5.8). In terms of length at birth, processed meat, wholegrain, tinned fruit, and fruit juice were associated with multigravidas' offspring length, whereas for primigravida's, it was the level of intake of savoury discretionary that was associated with offspring length at birth, after adjusting for maternal weight, height and gestational age (Appendix 8, Supplementary Table 2).

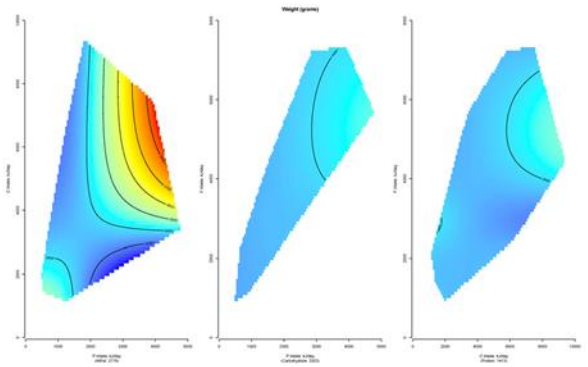
Macronutrient and fetal weight gain per week

GFN analysis revealed that primigravidas' offspring gained more weight on diets that were high in protein and carbohydrates with moderate to high fat. In contrast, multigravida offspring gained more weight on diets that were high in protein and fat (Figure 5.6, C). Multivariate regression analyses reviewed boys who gained more weight if the maternal diet was higher in unprocessed meat; for girls, on the other hand, it was wholegrain cereal intake that appeared to have the strongest association with weight gain (Appendix 8, Supplementary Table 3).

Figure 5.6: Surface plot showing the relationship between parity, macronutrient intake and fetal growth parameters

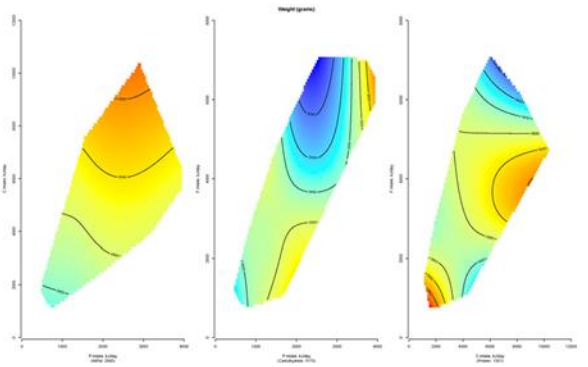
A) Fetal birth weight

First-born (n=208)



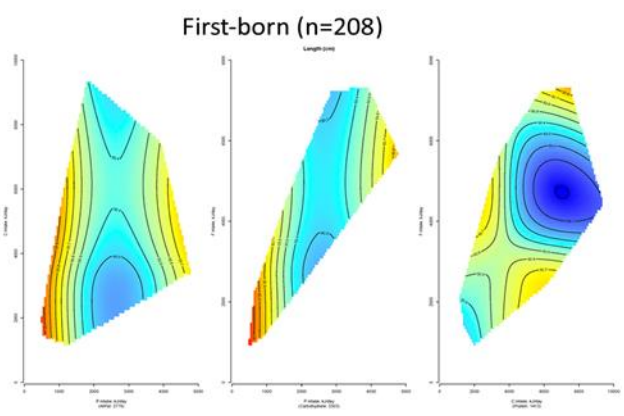
Weight (g)	edf	Ref.df	F	p-value
te(Protein)	0.00	4	0.00	0.82
te(Carbohydrate)	0.00	4	0.00	0.29
te(AllFat)	0.00	4	0.00	1.00
ti(Protein,Carbohydrate)	0.77	16	0.11	0.10
ti(Protein,AllFat)	0.00	16	0.00	0.85
ti(Carbohydrate,AllFat)	0.00	16	0.00	0.55
ti(Protein,AllFat,Carbohydrate)	0.96	50	0.05	**0.05**

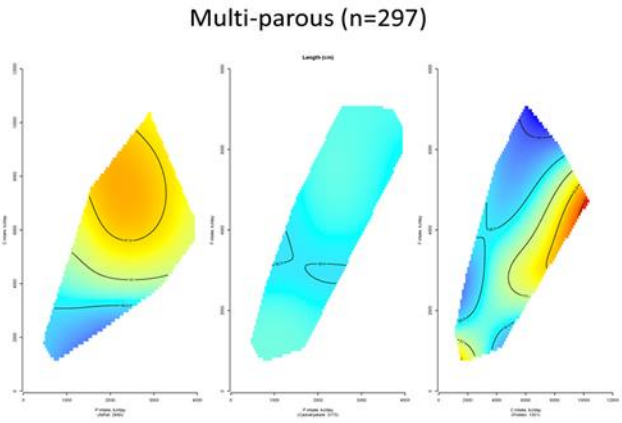
Multi-parous (n=297)



Weight (g)	edf	Ref.df	F	p-value
te(Protein)	**0.97**	4.00	7.59	**<0.001**
te(Carbohydrate)	0.43	4.00	0.19	0.18
te(AllFat)	**2.11**	4.00	20.96	**<0.001**
ti(Protein,Carbohydrate)	0.00	4.00	0.00	0.42
ti(Protein,AllFat)	0.00	4.00	0.00	0.50
ti(Carbohydrate,AllFat)	0.00	4.00	0.00	1.00
ti(Protein,AllFat,Carbohydrate)	0.00	16.00	0.00	0.39

B) Fetal length at birth (cm)

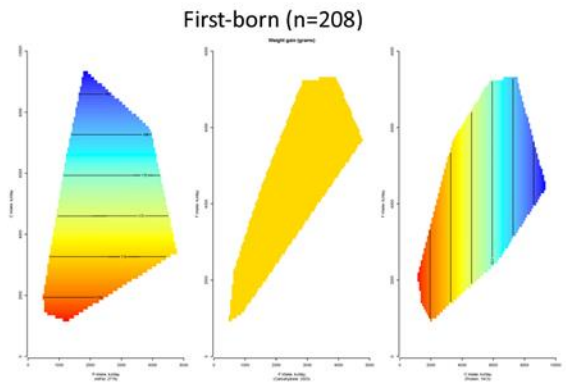


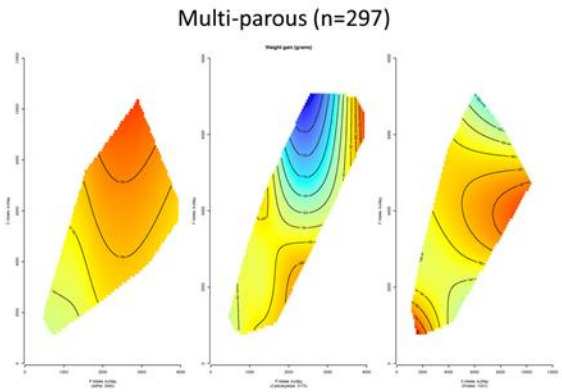


Length (cm)	edf	Ref.df	F	p-value
te(Protein)	0.75	4	0.53	0.07
te(Carbohydrate)	0.00	4	0.00	0.53
te(AllFat)	0.00	4	0.00	0.59
ti(Protein,Carbohydrate)	0.00	16	0.00	0.37
ti(Protein,AllFat)	0.00	16	0.00	0.53
ti(Carbohydrate,AllFat)	1.04	16	0.10	0.16
ti(Protein,AllFat,Carbohydrate)	0.00	50	0.00	0.63

Length (cm)	edf	Ref.df	F	p-value
te(Protein)	0.92	4.00	2.87	**<0.001**
te(Carbohydrate)	0.00	4.00	0.00	0.66
te(AllFat)	0.98	4.00	10.86	**<0.001**
ti(Protein,Carbohydrate)	0.00	4.00	0.00	1.00
ti(Protein,AllFat)	0.42	4.00	0.18	0.12
ti(Carbohydrate,AllFat)	0.00	4.00	0.00	0.94
ti(Protein,AllFat,Carbohydrate)	0.00	16.00	0.00	0.37

C) Fetal weight gain (gram/week





Weight gain (g)	edf	Ref.df	F	p-value
te(Protein)	0.00	4	0.00	1.00
te(Carbohydrate)	0.66	4	0.49	0.09
te(AllFat)	0.00	4	0.00	0.85
ti(Protein,Carbohydrate)	0.00	16	0.00	0.62
ti(Protein,AllFat)	0.00	16	0.00	0.77
ti(Carbohydrate,AllFat)	0.00	16	0.00	0.62
ti(Protein,AllFat,Carbohydrate)	0.00	50	0.00	0.35

Weight gain (g)	edf	Ref.df	F	p-value
te(Protein)	0.97	4.00	6.96	**<0.001**
te(Carbohydrate)	0.48	4.00	0.23	0.16
te(AllFat)	1.32	4.00	1.22	**0.02**
ti(Protein,Carbohydrate)	0.00	4.00	0.00	0.43
ti(Protein,AllFat)	0.00	4.00	0.00	0.47
ti(Carbohydrate,AllFat)	0.00	4.00	0.00	1.00
ti(Protein,AllFat,Carbohydrate)	0.00	16.00	0.00	0.38

5.4 Discussion

This chapter provides insight into maternal consumption of major macronutrients during pregnancy and compares its contribution to different energy levels based on parity status. Results show that high energy intake was associated with a diet high in protein and fat

components. This effect was more observed in the diets of multiparous mothers than primigravida mothers.

Energy intake

In general, the median maternal energy intake was lower than the recommended intake during pregnancy (7542.3 kJ/d vs. 9,204.8 to 12,133.6 kJ/d). This finding is similar to previous reports of intake in other studies (95, 359, 360, 483, 652). It should be noted that this analysis involved healthy women with healthy fetal outcomes. Therefore, we can postulate that despite the lower intake, the reported levels met the individual requirement for healthy outcomes. Furthermore, maternal physical activity was not included in the study; it might be plausible that a lower level of daily activity and a sedentary lifestyle might have contributed to lower energy expenditure, resulting in adequate intake. Additionally, the FFQ tends to underestimate energy intake and is subject to recall bias (659, 660).

The multiparous mothers had higher energy intake than primigravida mothers. The analysis of dietary intake showed that multiparous mothers consumed more meat (both processed and unprocessed) and carbohydrates, but less fruit and dairy products than primigravida mothers. These findings may explain the differences in energy intake – the implication of various food groups and discretionary food to maternal energy intake is further explored in Chapter 6. The difference in maternal food choices could be attributed to prior dietary experience in a previous pregnancy, larger family size, and economic status, all of which might have influenced mothers' choices (374, 375). Further, primigravida mothers tend to be more health conscious in their first pregnancy (349, 350).

Macronutrient intake and energy

The energy derived from protein consumption during pregnancy contributed to 18.4% of total energy intake. This is within the recommended dietary intake (85, 94, 97) and similar to that reported for developed countries (95, 662). Carbohydrate consumption contributed to 43.2% of

total energy intake, which is less than the recommended 45-65% of total energy intake (85,97), although these results are similar to previous published data (358, 661-663). Interestingly, carbohydrate consumption contributed less to the total energy intake at high energy levels than the lower energy level intake (41.3% vs 42.7%) at the expense of higher protein intake in the high energy group (18.9 %vs 18.0%). The average percentage of protein to non-protein nutrients in the maternal diet was 22.4%, with a higher percentage in the higher-energy group (24.4%) (Figure 5.3). This observation reflects the importance of the protein component in achieving high energy intake; however, how to determine the 'optimal' protein intake for pregnant women remains uncertain (483).

The energy derived from fat consumption was similar across all of the three energy levels (39.7%) but was higher than the general Dietary guidelines recommendation of 20-35% total energy intake (85,97). In an analysis of fat intake during pregnancy, Koletzko et al. concluded that there is no need to increase fat composition in pregnant women's diet to meet the energy requirements of pregnancy (363). The extra fat intake is not utilised and may be stored as maternal extra weight gain. It is essential to acknowledge that one limitation of the current study is the absence of recorded weight gain. Nonetheless, the study population comprised low-risk pregnant women in good health, with an average BMI of 26.9 ± 6.9 kg/m^2; moreover, all women exhibited normal neonatal outcomes. Consequently, it is reasonable to infer that this cohort likely experienced typical weight gain during pregnancy.

After adjusting for BMI, the fat intake (both saturated and unsaturated fat) was higher in multiparous than primigravida mothers (Figure 5.4). This finding may be explained by the observed differences in maternal dietary choices (Table 5.7).

In general, these results indicate that pregnant women fail to comply with the recommended dietary macronutrient intake as per published guidelines; on the other hand, the results are in

line with similar studies that reported inadequacy of nutrient intake in the pregnant population. (360, 664, 665).

Macronutrient intake and fetal growth

Studies on the association of macronutrient intake during pregnancy and fetal outcomes have shown conflicting results (reviewed in Chapter 3). The results of this analysis agrees with previous studies which showed no relation between the individual macronutrient intake and fetal growth parameters (391, 394, 518, 664).

Although the individual macronutrient intake failed to show any association with fetal outcome, the GFN analysis showed a diet high in protein and its interaction with fat and carbohydrates was the driver for heavier and longer offspring and improved growth velocity (fetal weight gain g/w). These findings are similar to previously published data (399, 662). The association of protein leverage and fetal growth has been demonstrated in several studies (395, 406, 669). Nevertheless, a U-shaped relationship has been found between maternal protein intake and fetal growth (86, 670). Low protein in the diet has been found to be associated with low birth weight in both animals and humans (671-673) , particularly in the undernourished population (13, 674). On the other hand, protein supplements in more than 20% of diets (in high-income countries) have been shown to have a detrimental effect (389, 675, 676). A Cochrane review recommended a balanced diet with less than 25% protein for optimal fetal growth and no change in maternal weight gain (92).

Morisaki et al. (483) analysed the diet of Japanese pregnant women and concluded that 12% protein in the diet is associated with normal birth weight, while an increase to 14%, regardless of whether the isoenergetic replacement was with fat or carbohydrates, resulted in lower birth weight. Furthermore, when protein density in the maternal diet was held constant, birth weight was highest when 25% of energy intake came from fat and 61% from carbohydrates during early pregnancy. A comparison of these results with our cohort, which comprised a maternal diet

(during pregnancy) consisting of 18.4% protein, 39.5% fat, and 43.2% carbohydrates, could not be conducted with precision due to variations in analytical methodologies. Nevertheless, these findings may serve as a basis for future research endeavours.

5.5 Conclusion

This chapter has provided an analysis of macronutrient intake in maternal diets and its correlation with fetal growth. The findings corroborate earlier studies indicating a prevalence of inadequate macronutrient intake within the pregnant population. Nonetheless, the reported percentages of macronutrient intake among the low-risk pregnant cohort in this study appear adequate for supporting fetal development. Maternal protein intake was identified as a significant contributor to fetal growth in both multiparous and primigravida mothers, while the contribution of fat and carbohydrates to fetal growth differed between multiparous and primigravida mothers. These findings will require further confirmation from more extensive studies. One of the findings of this analysis is the difference in intake of discretionary food (DF), which is further analysed in the next chapter of this thesis.

Acknowledgement

Many thanks to Dr Rosilene Riberio from Charles Perkins Centre/university of Sydney for her contribution to this chapter conducting the geometric framework for nutrition (GFN) statistical analysis.

CHAPTER 6: _Analysis of Discretionary Food intake in pregnant mothers

6.1 Introduction

Discretionary foods (DF) are defined as "energy-dense, nutrient-poor products that contain excess sugar, fat, salt, and alcohol but are low in minerals, vitamins, and fibres. DF is not essential to a healthy diet and does not fall in the five-group system that is identified by dietary guidelines." (97, 677). DF is considered a 'treat food' often consumed at parties and gatherings, adding variety and enjoyment. Items such as sweets, snacks, sugary beverages, and processed foods are part of the DF category. (678). Overconsumption of DF can lead to nutritional imbalances, fostering a cycle of poor dietary choices and potential health risks.

The modern diet has undergone a notable shift over the years, with an increasing reliance on convenient and processed foods (679). DFs are readily available, heavily marketed, and often affordable, making them a convenient food choice for many individuals. The consumption of these foods has risen in tandem with sedentary lifestyles, and is contributing to a rise in health issues such as obesity, diabetes, and cardiovascular diseases (680, 681). The large portion sizes of DF consumed may also be contributing to overconsumption. (682).

Epidemiological studies have demonstrated that 86% of Australians and 90% of Americans exceed the recommended amount of DF in their diets (682, 683). The contribution of DF to total energy intake varies from between 20% and 60% in the different populations studied (684). A survey conducted on Australian adults in 2013 found that DF made up around 35% of respondents' total energy intake, although researchers noted that when being studied, people tend to change their behaviour to under-report – consciously or unconsciously – their true intakes (685).

During pregnancy, women tend to change their eating habits and behaviour to avoid harm to their growing babies. Nevertheless, changes in modern diet and lifestyle have contributed to wider acceptance of DF as a daily food component. (682). While numerous studies have shown that an unhealthy diet characterised by high saturated fat, sodium, and saturated sugar is associated with adverse pregnancy outcomes (e.g. excessive weight gain, gestational diabetes, hypertension, and abnormal fetal weight), the contribution of DF to energy and macronutrient intake was not the focus of these studies (397, 479, 480, 523, 524).

In chapter 5, the study results showed differences in DF intake between primigravida and multiparous mothers and revealed some impact on fetal anthropometric measures. In this chapter, maternal dietary patterns and the contribution of DF to maternal diet is analysed.

6.2 Methods and statistical analysis

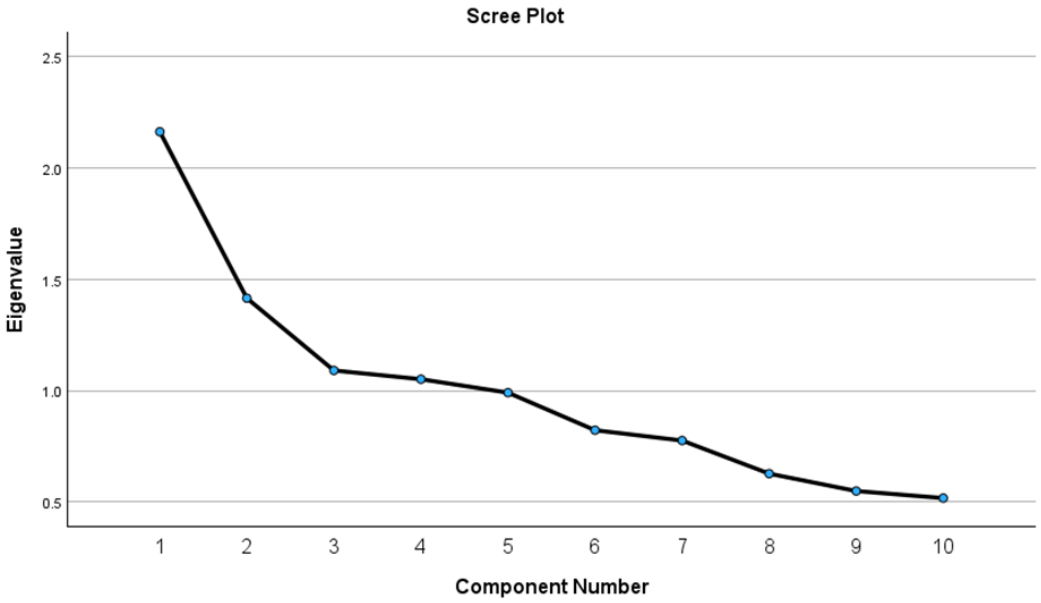
Chapter 4 outlines details on patient recruitment, energy calculation, statistical methods, and the DF classification. Dietary food patterns for this cohort were extracted using the principal component analysis (PCA) statistical method. As described in Chapter 4, food items were grouped into 10 dietary groups for this analysis.

Principal component analysis (PCA)

PCA extracts an a posteriori dietary pattern (571,574, 575). The statistical software SPSS v 29 (IBM Corp. Released 2023. IBM SPSS Statistics for Windows, Version 29.0.2.0 Armonk, NY: IBM Corp) was used for the analysis. For each food group, the energy-adjusted value was entered into the factor analysis, and factors were rotated by orthogonal transformation (varimax rotation). For each dietary pattern, factor scores were calculated as the sum of products between observed energy-adjusted food group intakes and their factor loadings, as described in other papers (575, 686). The number of components that best represented the data was chosen based on the interpretability of the factor loading structure and the scree plot of the proportions of variance explained by each factor. The resultant scree plot displays a bend where the

proportions of variance explained trail off. The factors that best reduce the dimensionality of the data are above the bend (686) (Figure 6.1).

Figure 6.1: Scree plot for dietary patterns



6.3 Results

The association of DF consumption with total energy intake

The median energy intake of the study population was 7542.3kJ/d (IQR 3853). The overall contribution of DF to the daily energy consumption was 2295.6kJ/d (IQR 1752.1), constituting 30.3% of the total energy intake (Table 6.1).

The energy derived from DF consumption showed some differences between study groups. The contribution of DF's derived energy to total energy intake was higher in Aboriginal mothers (36%) and women who smoked during pregnancy (34.5%), while it was lowest in mothers from the Mediterranean ethnic group (15.7%) (Table 6.1). Furthermore, the contribution of DF to total energy was higher in extremes of BMI (the under-nutrition <18kg/m2, obese, and the morbid obese >40kg/m2) (Table 6.1).

Table 6.1: Discretionary Food intake by study population presented as median and interquartile range (IQR)

	All N=911	Energy intake Total kJ/d	DF energy kJ/d	Percentage of DF energy intake to total energy intake
Age(y)	28.93±5.7	7542.3 (3853.4)	2295.6 (1752.1)	30.3
Parity				
Primiparous	385	7292.1 (4011.9)	2178.3 (1735.1)	29.8
Multipara	526	7719.4 (3649.3)	2400.7 (1739.2)	**31.0**
Plurality				
Singleton	883	7539.7 (3786.8)	2306.1 (1699.7)	30.5
Twin	28	7667.8 (4406.2)	2017.6 (2574.7)	26.3
BMI				
<18	40	7827.3 (5183.7)	2665.2 (2071.0)	**34.0**
18.5-24.9	405	7635.0 (3782.1)	2171.3 (1716.4)	28.4
25-25.9	234	7525.6 (3735.5)	2346.1 (1575.4)	31.2
30-34.9	116	7084.8 (3570.9)	2180.6 (1696.3)	30.7
35-39.9	18	7571.6 (3859.4)	2522.9 (2487.6)	**33.3**
>40	98	8360.3 (3965.1)	2848.2 (3139.8)	**34.0**
Ethnic group				
Caucasian	663	7456.9 (3621.5)	2395.1 (1771.3)	**32.1**
Aboriginal	52	7426.5 (4137.6)	2674.1 (2637.2)	**36.0**
Torres Islander	42	9140.1 (6602.4)	2552.1 (3064.5)	27.9
Asian/Indian	79	7847.1 (3297.7)	2098.0 (1100.8)	26.7
Asian/Chinese	29	7615.3 (3922.6)	1915.1 (1405.0)	25.2
Mediterranean	24	7472.2 (4948.8)	1778.6 (1969.8)	15.7
Others	22	7473.1 (4157.9)	1871.4 (1906.6)	25.0
SEIFA*				
Low	524	7843.4 (4276.4)	2479.7 (1932.7)	**31.6**
Middle	299	7373.6 (3348.4)	2098.0 (1620.5)	28.4
High	88	7204.8 (3195.2)	2119.9 (1687.5)	29.4
Smoking				
No	806	7527.0 (3763.7)	2224.1 (1697.7)	29.5
Yes	104	7838.9 (4429.2)	2711.2 (2003.8)	**34.5**
Missing	1			
Gestational age				
Less than 37 w	107	7459.4 (4406.5)	2338.6 (1715.6)	31.3
Between 37-40 w	515	7421.3 (4292.4)	2258.3 (1842.9)	30.4
More than 40 w	289	7425.3 (3945.9)	2335.0 (1638.5)	**31.4**

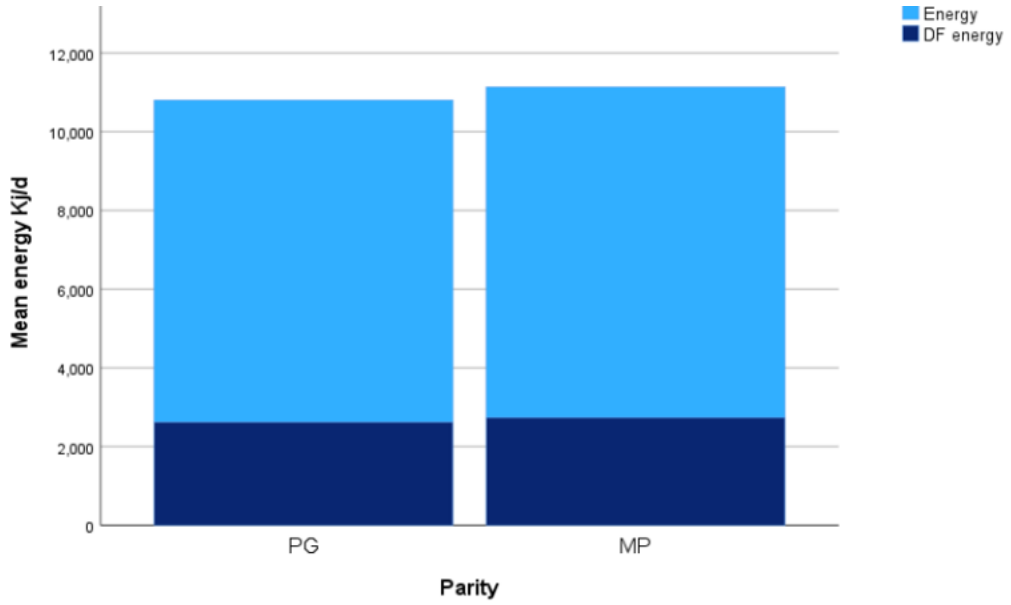
Significant results in bold, p<0.05

SEIFA Index of education and occupation: Low: 0-950, Medium: 951-1031, High: 1032-1178

The multiparous mothers had more energy intake than primigravida mothers (7719.4 kJ/d vs 7292.2 kJ/d), p<0.05. Similarly, the contribution of the DF-derived energy to total intake was

higher in multiparous mothers than primigravida (2400.7kJ/d vs 2178.3kJ/d), representing 31% and 29.8% of total energy intake, respectively (Figure 6.2).

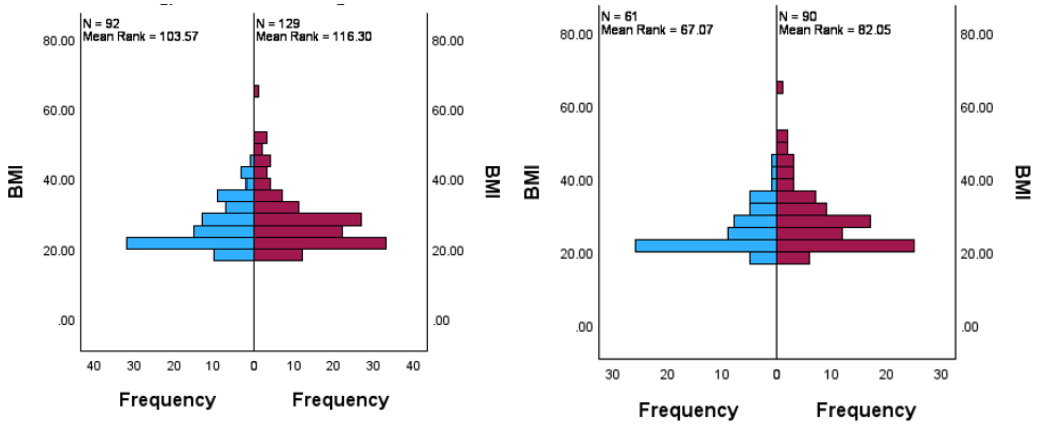
Figure 6.2: Discretionary Food energy intake by parity



PG = primigravida, MP = multiparous

Of the studied cohort, 221 mothers had high energy intake (T3); there were 129 multiparous and 92 primigravida. The correlation between high BMI > 30 kg/m^2 and high energy level was found only in Caucasian mothers (Spearman's correlation rho, 0.169, CI 95% 0.004-0.324, $p < 0.05$). In this subset of women, multiparous mothers (n=90) had a higher BMI than primigravida (n=60), although this difference was marginally significant (p=0.054) (Figure 6.3).

Figure 6.3: High energy tertile and maternal BMI



A: All cohort, n=221

B: Caucasian, n=151

Discretionary food classification

Table 6.2 outlines the various types of DF foods classified according to the Australian dietary guidelines (97). For each food item, the average daily intake is presented in grams per day, and the energy yield is calculated in kilojoules per day(kJ/d) based on the Australian food database (Appendix 6). To assess the contribution of energy derived from DF to total energy intake, the DF foods were categorised into three main groups – savoury, sweet, and processed meat – according to standard culinary definitions (Table 6.3). Within this classification, the processed meat group contributed 3.02% of total energy intake, while the savoury and sweet groups accounted for 14.3% and 14.9% of total energy intake, respectively.

Table 6.2: Average intake of Discretionary Food classified as per Australian dietary guidelines presented as median (IQR)

	Serving value*	Average daily intake g/d	Average daily Energy kJ/day
Higher added sugars			
Sugar	40g	12.5 (0.0)	208.7 (0.0)
Sweetened drinks **Flavoured milk** **Fruit juice**	 250ml =259g 250ml=265g	 1.1 (3.8) 43.6 (115.2)	 4.3 (15.0) 71.1 (187.7)
Jam	60g	1.1 (3.4)	11.5 (35.7)
Higher Fat			
Bacon	50 g	2.5 (4.2)	32.7 (52.5)
Ham	50 g	2.5 (4.9)	11.6 (22.9)
Salami	50 g	0.00 (3.9)	0.0 (55.0)
Sausages	60 g	5.9 (13.7)	58.2 (135.2)
Meat pie	70 g	11.9 (20.3)	112.2 (191.4)
Pizza	60 g	18.9 (27.7)	197.3 (289.2)
Crisps	30 g	3.9 (8.1)	83.5 (173.3)
Chips	60 g	15.3 (21.7)	331.2 (469.8)
Higher fat and added sugar			
Biscuits	28 g	4.4 (10.9)	79.7 (197.5)
Cakes	40g	8.6 (16.5)	127.8 (245.2)
Ice cream	75g	10 (18.8)	78.8 (148.1)
Chocolate	25g	7.2 (16.1)	156.8 (350.6)

*Serving value as per Australian food data base (Appendix 6)
g/d : gram/day .IQR : Interquartile Range

Table 6.3: Discretionary Food classification as per commercial terminology and its contribution to total energy by groups

	Serving value	Median intake g/d (IQR)	Mean Energy kJ /d	Total energy kJ/d/group	Percentage contribution to the total energy kJ/d
Savoury Group					
Pizza	60g	18.9(27.7)	300.9±416.8	1191.6±955.3	14.3%
Meat Pie	70g	11.9(20.3)	211.7±312.7		
Crisp	30g	3.9(8.1)	168.7±230.8		
Chips	60g	15.3(21.7)	510.3±650.3		
Processed Meat Group					
Bacon	50 g	2.5(4.2)	57.6±99.8	251.3±359.2	3.02%
Ham	50 g	2.5(4.9)	24.5±43.7		
Salami	50 g	0.00(3.9)	58.4±153.2		
Sausages	60 g	5.9(13.7)	110.7±185.0		
Sweet Group					
Biscuits	28 g	4.4(10.9)	162.1±243.9	1242.9±936.6	14.9%
Cakes	40g	8.6(16.5)	241.6±334.1		
Ice cream	75g	10(18.8)	152.3±239.2		
Chocolate	25g	7.2(16.1)	290.1±375.1		
Sugar	40g	12.5(0.0)	206.1±176.5		
Sweetened drinks **Flavoured milk** **Fruit juice**	 250ml =259g 250 ml= 265g	 1.1(3.8) 43.6(115.2)	 11.8±17.3 150.7±206.8		
Jam	60g	1.1(3.4)	28.4±46.6		

Serving values as per the Australian food database (Appendix 6)
Median intake is the median (IQR), Mean intake is the mean± SD
The total energy is the Mean ±SD

Table 6.4: Discretionary Food macronutrient contribution to energy at different levels of Energy intake

	Low Energy tertile T1 4000-6999 KJ/d		**Medium energy tertileT2 7000-9999 KJ/d**		**High energy tertile T3 10000-20000 KJ/d**	
	DF	ALL	DF	ALL	DF	ALL
Energy KJ/d **E% of total**	1577.3 (1008.3) 27.3	5767.5(1334.5)	2482.5(1306.3) 30.2	8222.9(1501.4)	4157.3(2536.8) 34.9	11891.9(3230.5)
Protein **E % of DF** **E% of protein**	145.3(93.0) 9.2	1038.9(325.6) 13.9	225.9(139.7) 9	1469.6(358.8) 15.4	397.2(287.0) 9.5	2363.3(867.6) 16.8
Fat **E% of DF** **E% of fat**	628.02(449.3) **39.8**	2203.9(642.1) 28.5	968.0 (604.9) 38.9	3226.2(694.9) 30.0	1681.0 (1211.6) **40.4**	4833.6(1621.) 34.7
CHO **E % of DF** **E% of CHO**	607.5 (448.6) 38.5	2455.3(601.4) 24.7	1010.3(559.4) **40.8**	3555.8(677.6) 28.4	1654.7(1081.9) 39.8	5084.4(1368.0) 33.2
Sugar **E % of DF** **E% of Sugar**	418.1(284.9) 26.5	1106.0(437.0) 37.8	645.2(415.8) 25.9	1567.6(510.0) 41.2	930.4(733.6) 22.3	2050.9(851.8) 45.3
Fibre **E% of DF** **E% of fibre**	15.0(9.9) 0.9	119.7(45.2) 12.5	22.1(14.2) 0.8	165.8(57.6) 13.3	40.5(27.1) 0.9	243.9(89.9) 16.6

Bold represents significant results<0.05

E% percentage of energy

DF: Discretionary Food, All: total energy from food, CHO: Carbohydrates.

Table 6.5: Frequency of Discretionary Food Intake.

	Less than Once per month	1-3 times per month	1-4 times per week	At least Once per day	More than Twice per day
High-added sugars group					
Sugar*					
Sweetened drinks					
Flavoured milk	187(21.3)	89(10.2)	316(36)	143 (16.5)	141(16.0)
Fruit juice	73 (8.7)	83(9.5)	356 (40.6)	162(18.5)	202 (23.0)
Jam	217(2.5)	130 (14.8)	375(42.8)	115 (13.2)	39 (4.5)
High-fat group					
Bacon	211(24)	127(14.5)	480(54.8)	39(4.5)	19 (2.2)
Ham	274)(31.3)	113(12.8)	394(44.9)	78 (8.9)	17 (2.1)
Salami	442(50.4)	130(14.8)	260(29.6)	31(3.1)	13 (1.5)
Meat pie	159(18.2)	132(15)	531(60.6)	40 (4.6)	14 (1.6)
Sausages	240(27.40	166(18.9)	437 (49.8)	28 (3.2)	4 (0.5)
Pizza	64(7.39)	215(24.5)	564 (64.4)	27(3.2)	6 (0.6)
Crisp	89(10.2)	132(15)	495 (56.5)	128(14.6)	32 (3.6)
Chips	28(3.2)	46(5.3)	488(55.7)	236(26.9)	78 (8.9)
Higher fat and added sugar group					
Biscuits	125(14.3)	77(8.8)	408 (46.5)	182 (20.7)	84 (9.6)
Cakes	85(9.7)	119(13.6)	520 (59.3)	108 (12.3)	44 (5.0)
Ice cream	56(6.4)	115 (13.2)	528 (60.3)	120 (13.7)	62 (7.1)
Chocolate	48(5.4)	72 (8.3)	395 (45)	232(26.5)	129 (14.7)

Data presented as number (percentage)

Table 6.6: Pattern of Discretionary Food intake by the number of servings /day

	Missing (not reported)	Reported no intake	Reported intake 1 serves/d	Reported intake 2-2.5 serves/d	Reported intake More than 2.5 serves/d
High-added sugars group					
Sugar N/A					
Sweetened drinks **Flavoured milk** **Fruit juice**	 340 32	 192 (21.1) 78 (8.6)	 289 (31.7) 779 (85.5)	 14(1.5)	 8(0.9)
Jam					
High-fat group					
Bacon	1	223(24.5)	781 (71.9)	1 (0.1)	0
Ham	2	284(31.2)	625(75.4)	2(0.2)	0
Salami	2	462 (50.7)	445 (48.8)	2 (0.2)	0
Meat pie	3	167 (18.3)	730(80.1)	11(1.2)	3 (0.3)
Sausages	0	252(27.7)	654(71.8)	0.3 (3)	2 (0.2)
Pizza	0	69 (7.6)	820(89.1)	1.1 (10)	20 (2.2)
Crisp	0	95(10.4)	809(88.8)	0.7 (6)	1 (0.1)
Chips	14	29(3.2)	854(93.7)	0.8 (70)	7 (0.8)
Higher fat and added sugar group					
Biscuits	0	134 (14.7)	767 (84.2)	3 (0.3)	7 (0.8)
Cakes	0	92 (10.1)	802(88.0)	7 (0.8)	10 (1.1)
Ice cream	0	62(6.8)	838 (92.0)	4 (0.4)	6 (0.7)
Chocolate	3	54 (5.9)	817(89.7)	14 (1.5)	23(2.5)

Data presented as number (percentage)

A Serve is calculated as per the Australian Dietary Food recommendation (Appendix 7)

Dietary patterns

The principal component analysis (PCA) extracted three dietary patterns with eigenvalues >3, explaining 46.7% of the total variance among 10 food groups. PCA components that explained less than 10% of the variance were excluded (Figure 6.1).The first dietary pattern (Diet 1) involves a high intake of meat, processed meat, and savoury foods. The second pattern (Diet 2) involves a high intake of vegetables, legumes, and fruit. The third pattern (Diet 3) involves a high intake of dairy and sweet foods (Table 6.7).

This analysis was repeated using the data from the total cohort of 1,057 women, and the same results were obtained.

Table 6.7: Dietary patterns extracted by PCA

	Diet 1	Diet 2	Diet 3
Savory food Group	.722	-.028	-.168
Process meat Group	.698	-.106	-.164
Meat and Alternative Group	.668	.344	-.003
Rice and Pasta Group	.388	.182	.102
Vegetable Group	.019	.831	-.026
Legumes Group	.052	.739	-.121
Fruit Group	.133	.486	.256
Dairy Group	-.035	.062	.750
Sweet Group	.508	.054	.546
Bread Group	.145	.043	-.331

Fetal growth parameters association with discretionary food-derived macronutrient and dietary patterns

Multiple regression analysis examined the relationship between extracted dietary patterns, macronutrient intake from discretionary foods, and fetal growth parameters. After adjusting for maternal factors such as parity, body mass index (BMI), ethnicity, smoking status, and infant gender, no significant association was found between the extracted dietary patterns and fetal growth parameters (see Table 6.8). Similarly, no association was found between DF macronutrient intake and fetal growth parameters (Table 6.9). However, a sub-analysis of DF intake in the high-energy group (T3) showed a negative association between fat derived from discretionary foods with fetal birth weight (β -6.2, 95% CI -11.3 to -1.04, $p < 0.05$)) and average fetal weight gain per week (β -0.491, 95% CI -0.90 to -0.075, $p < 0.05$) but no association found

with fetal length or head circumference measurements at birth, these findings were not reproducible at lower and middle energy levels. These observations will need further confirmation with the larger cohort.

Table 6.8: Regression analysis of diet type and fetal growth anthropometry

		Significance	**95% confidence interval for B**	
	β	P value	Lower bound	Upper bound
Birth weight (g)				
Diet 1	139.471	.467	-236.705	515.648
Diet 2	-73.937	.476	-277.399	129.524
Diet 3	23.352	.763	-128.869	175.573
Length at birth (cm)				
Diet 1	2.053	.055	-.040	4.146
Diet 2	.010	.986	-1.086	1.105
Diet 3	.061	.884	-.757	.879
Head circumference (cm)				
Diet 1	-.029	.960	-1.160	1.103
Diet 2	.010	.974	-.610	.631
Diet 3	.083	.722	-.375	.541
Average weight gain per week (g/w)				
Diet 1	5.342	.590	-14.089	24.772
Diet 2	-1.158	.829	-11.667	9.352
Diet 3	1.097	.784	-6.766	8.960

Table 6.9: Regression analysis of Discretionary Food and fetal growth anthropometry

		Significance	95% confidence interval for B	
	β	P value	Lower bound	Upper bound
Birth weight (gram)				
DF total fat	-3.052	.139	-7.100	.995
DF total CHO	.439	.544	-.0980	1.858
DF total protein	.317	.901	-4.697	5.330
Length at birth (cm)				
DF total fat	-.021	.108	-.046	.005
DF total CHO	.004	.429	-.005	.012
DF total protein	.004	.777	-.027	.036
Head circumference (cm)				
DF total fat	.002	.756	-.012	.016
DF total CHO	.001	.649	-.004	.006
DF total protein	-.012	.173	-.029	.005
Average weight gain per week (gram /week)				
DF total fat	-.208	.165	-.503	.086
DF total CHO	.036	.490	-.067	.140
DF total protein	-.044	.811	-.409	.320

Macronutrient intake is calculated as gram /day
DF: discretionary Food, CHO: carbohydrates

6.4 Discussion

This chapter has examined the DF intake among pregnant women and its contribution to daily energy intake. To our knowledge, this is the first study to explore discretionary food (DF) intake in Australian pregnant women. The analysis found that 30.3% of energy intake is attributed to DF consumption; there was a higher intake in multiparous mothers, Aboriginal mothers, and mothers who smoke. The most considerable contribution to energy intake was from DF items that contained high fat and sugar.

Around 84.9% of mothers reported consuming at least one item of DF during their pregnancy; this is similar to previous reports in the non-pregnant population (682, 687, 688) and in the pregnant population (397, 680, 689, 700). These results point to the high prevalence of DF intake in modern dietary choices (372, 373, 701).

The percentage of DF energy in this cohort was lower than that reported by the Australian Health Survey for non-pregnant women (685) but similar to results reported by other studies on pregnant women elsewhere. One study reported 32% intake in a sample of Brazilian women (702)Likewise, a rate of 30.6% was reported in another study. (703).

It should be noted that in Australian dietary guidelines, the term 'discretionary food' is different from the term 'ultra-processed' food used in other studies. The new system NOVA, which categorises food according to the degree of processing (704), correlated poorly with the Australian AUSNUT classification of DF (705). Of the 1,616 DF items within AUSNUT, 15% were classified under NOVA as processed, 40% as ultra-processed and 40.5% as mixed dishes containing a large proportion of ultra-/processed food. Data from NNPAS showed DF consumption contributed approximately 33.7% of total energy intake in Australian adults, and less than a quarter of total energy intake was contributed by unprocessed foods (22.3%) (705).

A Brazilian study of 189 pregnant women that considered the consumption of ultra-processed food during gestation found that 43.1% of their daily calories came from this type of food (706). Similarly, 63.2% of the energy consumption of pregnant women in the USA was found to be based on processed and ultra-processed foods (440).

Analysis of the daily served intake of DF showed the intake to be less than 2 serves per day, which is in line with dietary guidelines (97) but in contrast to previously published studies that showed an increased number of serves in the general population (397, 707). This could be explained by the difference in the definition of DF, the population studied, and the study's methodology; on the other hand, it could be related to pregnant women's increased awareness of the potentially harmful effects of DF on their health. Nevertheless, utilising PCA to extract the dietary pattern for this cohort showed the contribution of DF to diet type was noticeable. The savoury and processed meat groups were part of Diet 1, while the sweet DF group was part of

Diet 3. This could reflect the changes in maternal food choices and the reliance on ready-made, easy, fast food.

The three diet types extracted in this study were diverse, and none showed an association with fetal growth parameters, although Diet 2 was more representative of a healthy diet. This finding supports other published studies in which no association between diet type and fetal growth was found (481, 482). This lack of association might be due to the inclusion of DF in the dietary patterns, as well as to the fact that all servings of vegetables, fruit, and meat were below the recommended intake, a finding consistent across many studies exploring maternal dietary patterns (95, 357, 708, 709). On the other hand, the use of PCA as a method for dietary pattern extraction is known to be associated with inconsistencies due to the high intercorrelation between dietary patterns, energy intake, and nutrient components, which may impact the interpretation of results (710). Furthermore, the associations between dietary patterns and various nutrients have been inconsistent across different studies conducted in the general population (71-713) and in pregnant women (714) due to methodological differences.

The regression analysis of discretionary food individual macronutrient intake with fetal growth parameter did not show a statistically significant association; this is in agreement with the results reported by other two studies . (715,716),but in contrast to the results of another study that did show an association (479). However, this study result showed,the fat intake from discretionary food consumption correlated negatively to fetal growth parameters in the high energy intake group; this interesting finding will need further evaluation in future studies. Some studies reported an association between increased fat consumption in the maternal diet and fetal birth weight reduction. (717, 718), Nevertheless, these studies did not specify whether the fat source in the diet was related to DF intake. This may be a focus of future studies.

6.6 Conclusion

This study points out the high prevalence of discretionary food (DF) in the maternal diet and its contribution to daily maternal energy intake. The results may open the door for future studies to further evaluate the impact of DF on pregnancy outcomes. Moreover, it reinforces the need for proper education of pregnant women on healthy dietary choices.

CHAPTER 7: Smoking, maternal macronutrient intake, and its association with fetal growth

7.1 Introduction

Despite global and national campaigns against smoking, women continue to smoke during pregnancy. Globally, rates of smoking have been declining over the last two decades (720), and a similar trend was noted in pregnant mothers (721,722), although rates are still high. It is estimated that the prevalence of smoking during pregnancy is 10-20%; this rate is higher in high-income countries, for women with low education levels, and for young mothers (721).

The harmful effects of smoking on pregnancy are well established, and prenatal exposure to smoking is associated with multiple adverse pregnancy outcomes. (723). Two of the most important outcomes are low birth weight and intrauterine growth restriction. (722, 724, 725), both of which are associated with high rates of perinatal mortality and morbidity (30, 31). Additionally, there is a growing body of evidence supporting the association between maternal smoking, childhood obesity, and the risk of cardiovascular disease later in adult life (726-731).

While the association between maternal smoking and fetal growth has been clearly demonstrated in animal studies (732-734), there remain concerns regarding results from human studies. To date, human studies have been largely observational, and the observed effects of smoking are confounded by the presence of many factors, such as the effect of passive smoking (paternal and neighbourhood smoking), the dose of nicotine, the sex of the offspring, and the diet (735-737). Poor diet quality and malnutrition have been linked to poor fetal growth and low birth weight (reviewed in detail in Chapter 3).

The effect of smoking on fetal growth is presumed to be the result of toxic materials in cigarettes – namely nicotine and carbon monoxide – which leads to vascular constriction and reduced supply to the placenta (738-741); other studies have suggested an altered methylation of genomic DNA as a mechanism (742-746). On the other hand, smoking is known to be associated with poor appetite and reduced weight gain, and many women use smoking as an excuse to maintain a lower weight (747-749). Smokers also often make unhealthy dietary choices, leading to inadequate nutrient intake (523,750). These observations raise the question of whether the link between smoking, poor diet, and low birth weight is a confounding factor or an augmenting influence. Consequently, the objective of the study reported in this chapter was to investigate the dietary intake of mothers who smoke during pregnancy and to analyse its association with fetal growth parameters.

7.2 Methods

Participant recruitment, dietary assessment methods, and the statistical analysis were described in Chapter 4. Out of the 1,057 mothers included in this study, 117 (11.1%) reported smoking during pregnancy. After adjusting for energy levels (4,000 kJ/d - 20000 kJ/d) (527, 652), the final analysis included 911 participants. Of these, 104 women reported smoking during pregnancy, which accounts for 11.4% of the study cohort.

7.3 Results

Smoking and maternal characteristics

Mothers who reported smoking during pregnancy, as compared to mothers who did not smoke, were younger (27.6y vs 29.6y) and had a lower SEIFA education score (75% vs 55%) (Table 7.1). While the total incidence of smoking in the cohort was 11.4%, it differed between different ethnic groups. The incidence of smoking was 12.1% in the Caucasian group, 28.8% in the Aboriginal group, and no smoking was reported in the Asian ethnic groups (Table 7.1).Around

70% of the mothers entered pregnancy with normal BMI (18.5-30kg/m^2); there was no statistical difference in BMI between mothers who smoked during pregnancy and those who did not (27.1kg/m^2 vs 26.9kg/m^2, p=0.38). Nevertheless, 21.1% of mothers with low BMI (<18.5kg/m^2) reported smoking during pregnancy, in contrast to 13.8% of mothers with high BMI >30kg/m^2 (Table 7.1).

Table 7.1: Demographic characteristics of the study population according to smoking status

	Total N= 910	**Mothers who smoked N=104**	**Mothers who did not smoke N=806**
Age*	28.9±5.7	27.6±5.9	**29.1±5.6**
Parity			
• **Primigravida**	385 (42.3)	42 (10.9)	342 (89.1)
• **Multiparous**	526 (57.7)	62 (11.8)	464 (88.2)
Plurality			
• **Singleton**	865 (95)	102 (11.8)	762 (88.2)
• **Twins**	46 (5.0)	2 (4.3)	44 (95.7)
BMI*		27.1±6.5	26.9 ±6.9
• **<18.5**	38 (4.3)	8 (21.1)	30 (78.9)
• **18.5-24.9**	406 (44.6)	37 (9.1)	369 (90.9)
• **25-29.9**	234 (25.7)	27 (11.5)	207 (88.5)
• **30-34.9**	116 (12.7)	21 (18.1)	95 (81.9)
• **35-39.9**	66 (7.2)	8 (12.1)	58 (87.9)
• **>40**	50 (5.5)	3 (6)	47 (94)
Ethnic group			
• **Caucasian**	663 (72.8)	80 (12.1)	582 (78.2)
• **Aboriginal**	52 (5.7)	**15 (28.8)**	37 (71.2)
• **Torres Islander**	42 (3.2)	8 (19)	34 (81)
• **Asian/Indian**	79 (8.7)	0	79
• **Asian/Chinese**	29 (4.6)	0	29
• **Mediterranean**	24 (2.6)	1 (4.2)	23 (95.8)
• **Others**	23 (2.4)	0	22
Level of education			
• **SEIFA Low score**	524 (57.8)	**78 (14.9)**	446 (85.1)
• **SEIFA Middle score**	299 (32.8)		276 (92.6)
• **SEIFA High score**	88 (9.7)	22 (7.4)	84 (95.5)
		4 (4.5)	

Bold lines represent significant results, p<0.05
All results are expressed as numbers (%)
* results are expressed as mean±SD

Smoking and Offspring Anthropometry

There was no difference in gestational age at delivery between mothers who smoked during pregnancy and those who did not Table 7.2). Adjusting for gestational age, there was a significant difference in baby birth weight, length, head circumference and average weight gain per week between the two groups. Babies born to mothers who smoked during pregnancy were lighter at birth (131 g less in birthweight), 1 cm shorter, and gained less weight (g)/week (168.6g ±29.6 vs 178.7g ±31.2) than those born to non-smoking mothers (Table 7.2).

Table 7.2: Offspring anthropometry according to smoking status

	Total N=910	**Mother who smoked N=104**	**Mothers who did not smoke N=806**
GA	38.9±2	38.9±1.6	38.8±2.0
Birth weight (g)	3320.2±603.0	**3220.9±530.8**	3351.3±587.3
Length at birth (cm)	50.1±3.2	**49.2±3.1**	50.2±3.2
HC (cm)	34.3±1.8	**33.9±1.6**	34.4±1.8
HC/W	0.056±0.15	0.053±0.06	0.056±0.16
HC/L	0.022±0.02	0.020±0.002	0.021±0.02
Z score	0.41±1.03	**0.08±1.08**	0.46±1.01
Average weight gain (g/d)	177.1±31.8	**168.6±29.6**	178.7±31.2

Significant results are highlighted in bold, p<0.05
HC: head circumference; HC/W: head circumference to weight ratio;
HC/L: head circumference to fetal length

Energy, macronutrient intake, and smoking

Mothers who engaged in smoking during pregnancy exhibited a higher energy intake compared to their non-smoking counterparts Figur 7.1; however, this difference did not achieve statistical

significance (7838.9 kJ/day vs 7527.0 kJ/day, p=0.6). This observation remained consistent even among individuals with higher body mass index (BMI) levels exceeding 35 kg/m^2: Mothers who smoked reported an average energy intake of 8467.6 kJ/day (n=11), while mothers who did not smoke reported 7886.2 kJ/day (n=104). However, this was not statistically significant, p=0.75.(figure 7.1) Furthermore, the proportion of energy obtained from fat sources was greater in the smoking group than in the non-smoking group (40.5% vs 39.5%), with a notable difference in energy derived from saturated fat (45.1% vs 44.1%) as illustrated in Table 7.3 and Figure 7.2.

Figure 7.1: Energy intake by smoking status

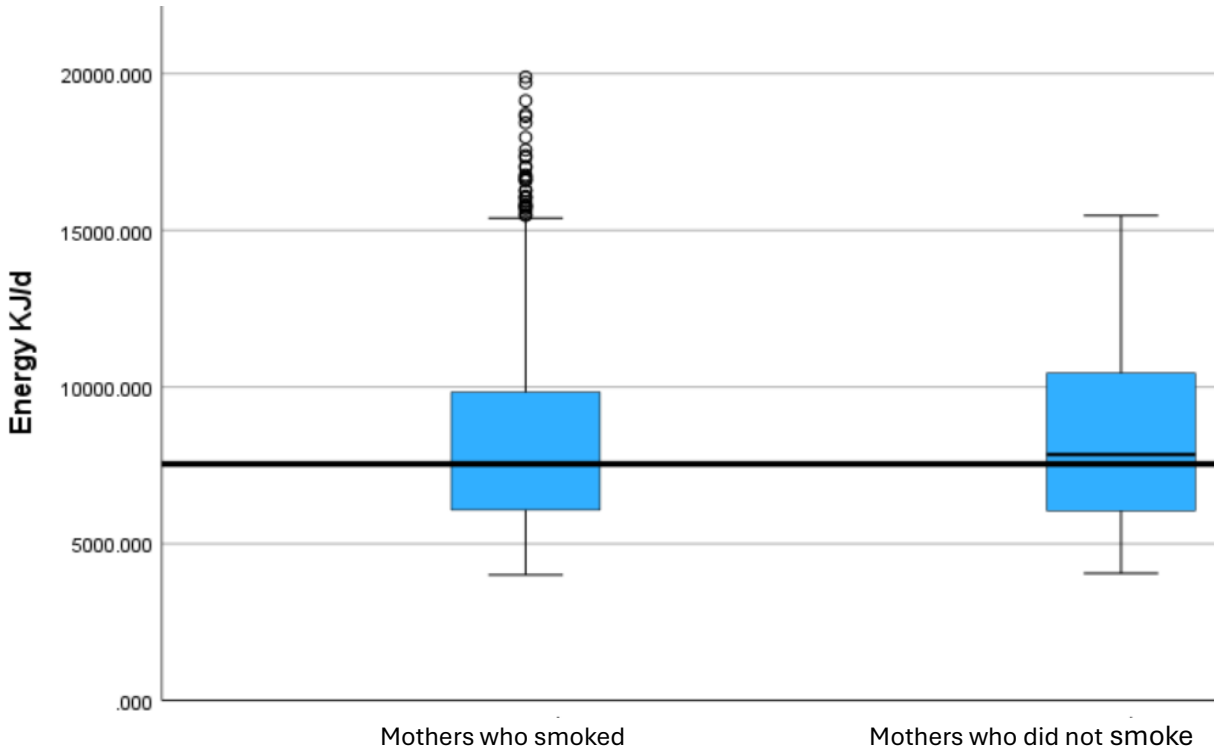
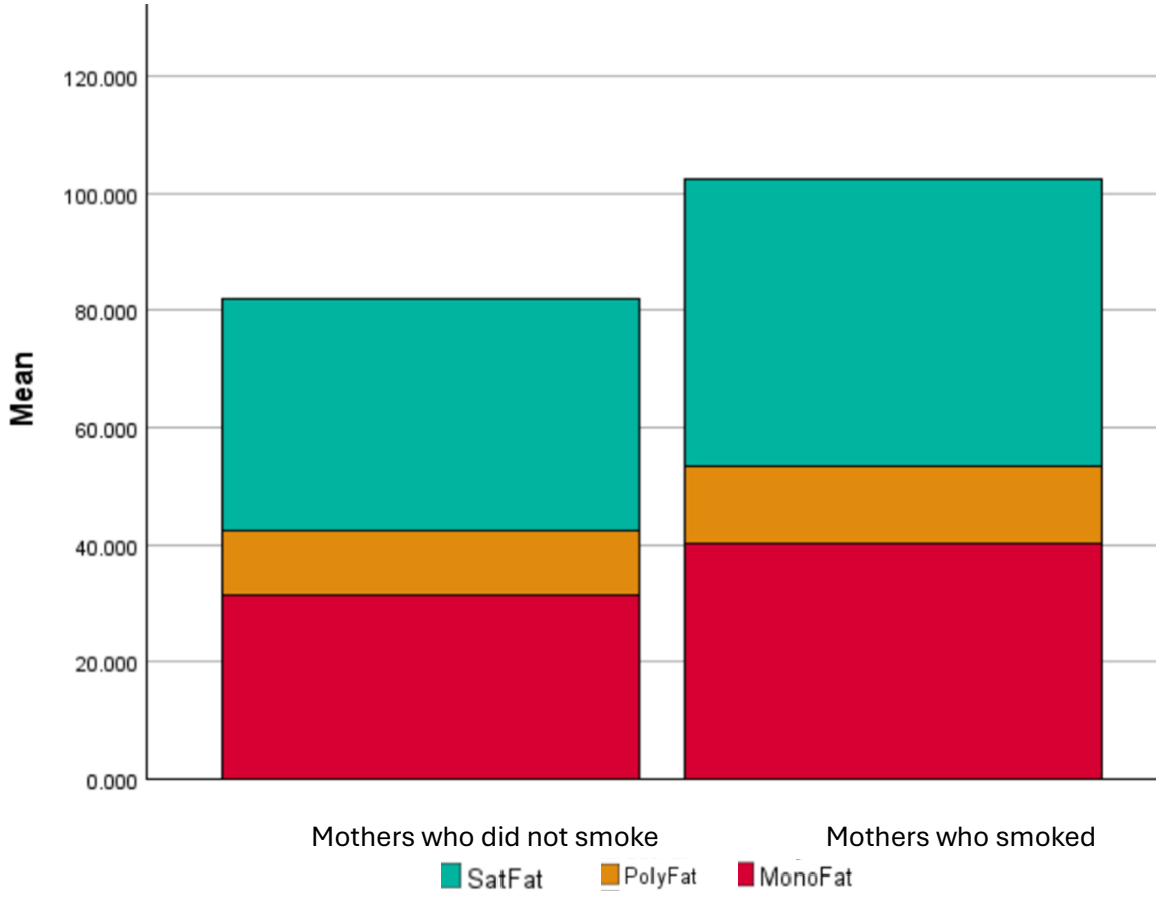


Figure 7.2: Fat intake by smoking status



Sat Fat : Saturated Fat, Mono Fat : Mono un-saturated Fat, Poly Fat : Poly unsaturated Fat

Table 7.3: Macronutrient and energy intake by smoking status

	Total N=910	**Mother who smoked N=104**	**Mothers who did not smoke N=806**
Energy kJ/d	7542.3 (3853.4)	7838.9 (4429.2)	7527.0 (3763.7)
All fat g/d • **E%**	79.2 39.7	82.2 (40.5) **40.5**	78.9 (42.5) **39.5**
• **Sat fat g/d** **E%**	34.7 (18.9) 44.2	37.5 (18.3) **45.1**	34.5 (19.0) **44.1**
• **Poly fat g/d** **E%**	9.6 (7.0) 11.8	9.9 (6.3) 11.6	9.5 (7.1) 11.9
• **Mono fat g/d** **E%**	27.3(14.7) 34.5	28.5 (14.5) 34.8	27.2 (14.3) 34.5
Protein g/d • **E %**	82.9 (42.9) 18.2 (3.6)	83.3 (53.3) **17.8**	82.9 (44.8) **18.3**
Carbohydrates g/d • **E%**	195 (94.7) 42.5	196.3 (110.6) 41.8	195.2 (93.2) 42.5
Protein to non-protein ratio	22.2 (40.5)	**21.6**	**22.3**

E% percentage of total energy /d. Data presented as median (IQR)

Sat fat: Saturated Fat, Poly fat : Poly- unsaturated Fat, Mono fat : Mono-unsaturated Fat

Numbers in bold are significant, p<0.05

This trend was consistent across all three evaluated energy levels, as detailed in Table 7.4.

Table 7.4: Energy derived from saturated fat at different energy levels and smoking status

	Low energy level T1 4000-6999 kJ/d		Medium energy level T2 7000-9999 kJ/d		High energy level T3 10000-20000 kJ/d	
	Mothers who smoke N=43	**Mothers who did not smoke N=326**	**Mothers who smoke N=32**	**Mothers who did not smoke N=288**	**Mothers who smoke N=29**	**Mothers who did not smoke N=192**
All fat kJ/d Median (IQR))	2398.2 (2023.6)	2185.9 (2208.6)	3429.7 (1794.8)	3208.1 (2784.6)	5020.0 (3744.8)	4794.9 (5770.5)
Saturated fat% contribution to fat energy	**44.6**	43.8	**45.7**	44.7	**44.7**	43.3
Protein to non-protein ratio	20.7	22.3	21.3	21.6	23.8	23.2

Bold represents significant results

Food groups and smoking

Various food items were analysed to further examine the differences in fat intake between mothers who smoke and those who do not. The Food Frequency Questionnaire (FFQ) incorporated 74 food items; however, only those demonstrating significant consumption differences are presented here (Table 7.5). Mothers who smoked during pregnancy reported higher intakes of DFs compared to their non-smoking counterparts, e.g. processed meat (19.8 g/d vs 14.8 g/d) and savoury foods (83.5 g/d vs 60.6 g/d). These food items are recognised for their high fat content (reviewed in Chapter 6). Furthermore, there was a higher intake of full cream milk (375 vs 200 g/d) . Conversely, mothers who smoked during pregnancy exhibited lower consumption of fruit (140.1 vs 190.6 g/d), fish (9.8.0 vs 16.6 g/d), and yoghurt (10.2 vs 20.4 g/dthan mothers who did not smoke as illustrated in Table 7.5.

Table 7.5: Food group consumption and smoking status

Food group intake g/d	Mothers who smoke smoking N=104	Mothers who did not smoke N=806
Vegetables	80.9 (88.9)	86.1 (68.1)
Fruit	**141.1 (196.4)**	190.6 (167.2)
Lean meat **Fish**	53.5 (60.3) **9.8 (30)**	51.6 (60.3) 16.6 (33.6)
Bread and cereal	173.7 (140.1)	191.0 (172.3)
Dairy • **Full cream milk** • **Yoghurt** • **cheese**	394.3 (311.9) **375 (875)** **10.2 (347)** 8.0 (12.5)	389.4 (258.3) 200 (875) 20.4 (437) 6.5 (12.4)
Savoury	**83.5 (80.3)**	60.6 (62.1)
Process meat	**19.8 (36.4)**	14.8 (24.8)
Sweet	117.2 (209.3)	118.9 (114.5)

Bold results are significant, p<0.05
Values expressed as median and IQR

Smoking status, macronutrient intake and fetal growth parameters

The interaction of smoking and macronutrient intake on baby weight gain was further evaluated. After adjusting for gestational age, parity, sex of baby, and ethnicity, the multiple regression analysis showed smoking OR 0.35 (95% CI 0.13-0.94)and maternal BMI recorded at booking OR 1.1 (95% CI 1.0-1.2) were associated with low birth weight less than 2500 g at term. while the macronutrient intake did not show any association. as illustrated in appendix 9 Supplementary Table 1

6.4 Discussion

This chapter has examined the effects of smoking on fetal growth and its association with maternal macronutrient intake. The results confirmed the harmful effect of smoking on baby size and growth in utero. The study also found that mothers who smoked during pregnancy

consumed more saturated fat in their diet, although this did not contribute to the effect of smoking on fetal growth.

The smoking rates among Australian pregnant women varied between states and territories; they ranged from 1.8 % in North Sydney to 22% in western New South Wales and Northern Territories. (751, 752). The Australian Institute of Health and Welfare (AIHW) reported 14.5 % rate of smoking among pregnant women for the same period of the study (2013-2018)(38).This rate is higher than the rate reported in this cohort (11.1%). This difference might be attributed to mothers under-reporting; studies showed that up to 25% of pregnant smokers do not disclose their smoking status often because of the social stigma. (753, 754). It should be noted that the most recent edition from AIHW in 2024 reported a reduced incidence of mothers who continued to smoke during pregnancy 8.3--11%. (755).

The study results support the association of smoking with low birth weight. Babies born to mothers who smoked during pregnancy were smaller than their non-smoking counterparts regardless of parity, maternal BMI and gestational age. The odds ratio of having a baby smaller than 2500 g at term in this cohort was OR 0.35 (95% CI 0.13-0.94); this ratio is lower than the reported ratio by other studies (757-759). It should be noted that this study cohort is a low-risk pregnancy, with only 3% of babies born after 37 weeks weighing less than 2500 g compared to other studies where the rate ranged between 6.6 % to 11.4% . The effect of smoking on birth weight was independent of maternal energy intake despite a noticeable difference in energy intake between mothers who smoked and those who did not (7838.9 kJ/d vs 7527.0 kJ/d); nevertheless, energy intake was not associated with fetal growth parameters, which is in agreement with data published in other studies (389, 518, 664).On the other hand, the intake of protein and carbohydrates showed no difference between mothers who smoked and those who did not, while the daily saturated fat intake was higher in mothers who smoked. This difference in fat intake contrasts with the findings of another study that analysed the diet of 398 women

(50 of whom reported smoking at the time of the study) and found no difference in fat intake. (759). However, this comparison should be approached with caution due to the differences in the methodologies used (4-day diet history vs FFQ) and the timing of the dietary assessment (early pregnancy vs third trimester). The timing of the FFQ distribution in our study (third trimester) was chosen to reflect the intake during the whole pregnancy period. Additionally, it may better reflect the effect of smoking on fetal growth as per findings from a study that involved a large cohort of women(n= 927,424) and reported that the maximum impact of smoking on fetal growth takes place in the third trimester (758).

The observed difference in fat intake between mothers who smoked and those who did not smoke during pregnancy may be attributed to changes in the behaviour and food choices of mothers who smoke. Some studies have suggested a reduced ability to perceive fat and sweeteners, particularly in women who are obese and smokers (760, 761). A negative correlation between maternal smoking and appetite in the second and third trimesters was also reported (762). Furthermore, many young women use smoking as a weight control strategy and an excuse to either initiate or continue smoking during pregnancy (764-766), an idea that is supported by the increase in weight gain observed after smoking cessation, both in the non-pregnant (768) and the pregnant populations (767). Maternal food choices are another factor that may give other possible explanations for the observed differences in maternal fat intake. The analysis of individual food items intake in this cohort revealed high DF, low fruit, and high full cream dairy intake in the diet of mothers who smoke. These results are similar to those reported in the non-pregnant smoker population (768, 769) and agree with previously published papers that document the association between smoking and an unhealthy diet (523, 770). Interestingly, mothers who smoked during pregnancy had lower fish intake than mothers who did not smoke. Fish is a good source of healthy fat polyunsaturated n-23 fatty acids, and the current dietary guidelines encourage its intake during pregnancy. This finding is consistent with the results from a large observational study conducted in the Netherlands involving 3,380

women (The Generation R study), which reported a 14.7% smoking rate (746). However, only 8-19% of the mothers who smoked also consumed fish (an average of 210g/w) as compared to 65-78% of those mothers who did not smoke during pregnancy. (771). The association between low fish intake in the diet of mothers who smoked and improved fetal outcomes was further reinforced by findings from an analysis of fish intake involving 151,880 mother-child pairs (from 19 European countries). This analysis found a profound association between eating fish >3 times per week and improved birth weight in mothers who smoke during pregnancy (772).

The current study has several limitations. First, the use of the FFQ is subject to recall bias and may not reflect actual intake, a problem frequently encountered in nutritional studies (531). Second, the tobacco smoking dose (number of cigarettes/day) or smoking biomarker (nicotine, CO_2) was not measured, and the effect of passive smoking was not recorded. The inclusion of such information would improve the validity of the results. Third, maternal weight gain during pregnancy was not recorded. Nevertheless, the study participants were all healthy mothers with healthy offspring outcomes and no pregnancy complications, and only 3% of the study population had low birth weight at term. Therefore, it is plausible to assume that weight gain during pregnancy impacted the results. Further studies addressing this limitation and a larger cohort are needed to improve the validity of the results.

6.5 Conclusion

This study has offered insights into the dietary patterns and macronutrient intake of mothers who smoke during pregnancy. The results did not indicate a synergistic effect of maternal diet and smoking on fetal growth parameters. However, it was observed that mothers who smoke had a higher fat intake in their diets. The analysis of these mothers' dietary intake showed a prevalence of high discretionary foods, along with low consumption of fruits and fish. These findings will need further confirmation in a larger cohort.

CHAPTER 8: Maternal consumption of common food allergens during pregnancy

8.1 Introduction

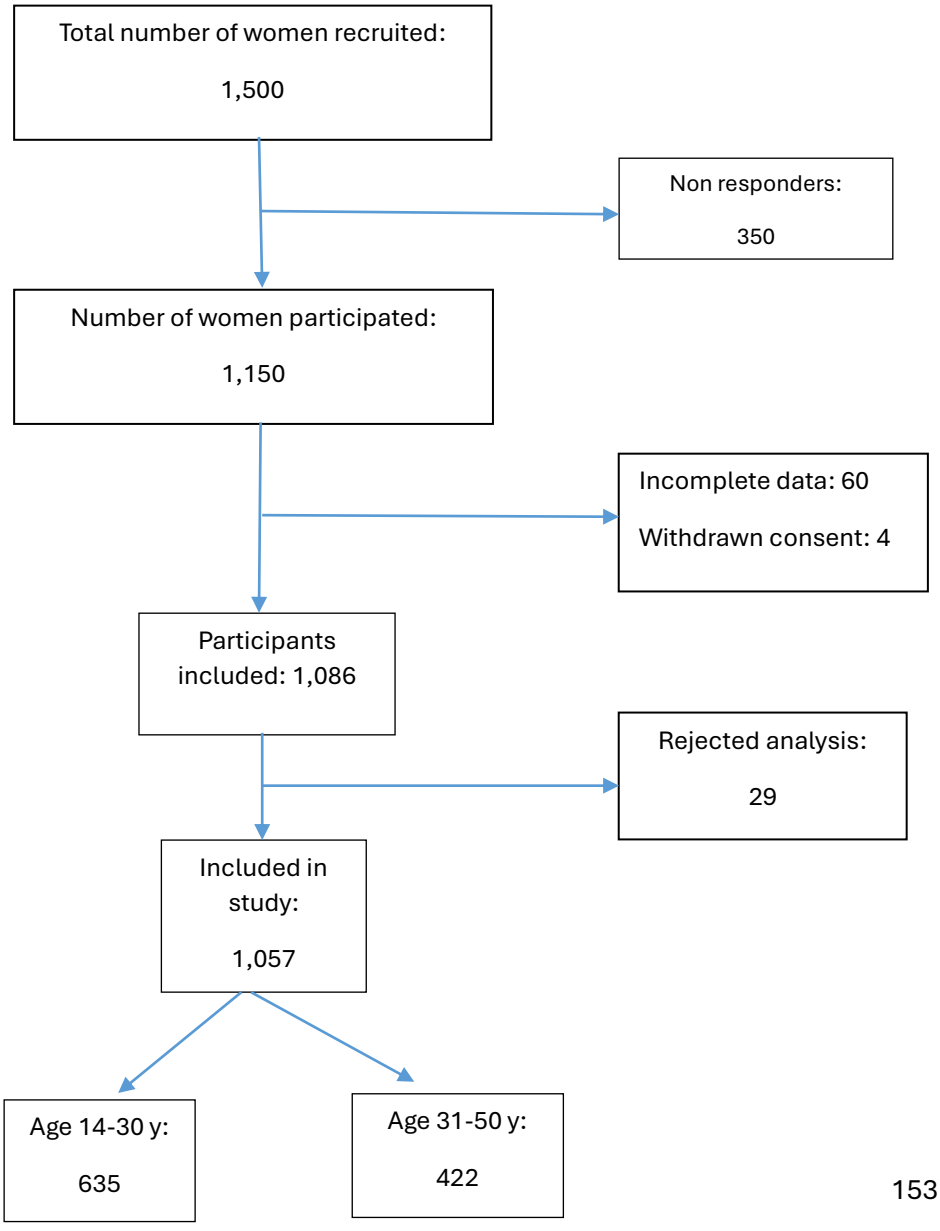
Food allergy is a chronic health problem that impacts family life and health resources (773, 774). The incidence and severity of allergic diseases has increased in the last few decades (775). Food allergies now affect 2% of adults and 4-8% of children under 5 years of age, with the peak prevalence in the first year of life, and it is estimated that around 10% of infants under one year of age will develop food allergies (776). Numerous studies have shown an association between early childhood food allergies and the development of adult respiratory atopic conditions (i.e. allergic rhinitis, asthma) and atopic dermatitis (777-779). Current research is being directed towards primary methods aimed at preventing allergic diseases and their associated major health, psychological, and social impacts. Recently, there has been more emphasis on the possibility that primary prevention strategies can be implemented as early as the intrauterine period (780, 781). Maternal dietary consumption of either food allergens or dietary supplementation of immunomodulatory nutrients during pregnancy and lactation has been the focus of many studies (782-789). A 2014 Cochrane review concluded that avoiding dietary food allergens in pregnancy does not substantially affect a child's risk of atopic disease and may even adversely affect maternal or infant nutrition (790). Some of these studies have been criticised, however, because the population selection included high-risk populations with a family history of atopic disease. There is also a paucity of data regarding what constitutes a normal daily intake of common food allergens during pregnancy in various populations to ascertain the impact on allergic disease outcomes.

In this study, we examined the pattern and average daily intake of common food allergens (hen's egg, cow's milk, tree nuts, peanuts, and fish) to establish baseline data for future intervention studies.

8.2 Methods

The details of the participant recruitment process, dietary assessment methods, and statistical analysis were described in Chapter 4. The study reported in this chapter aims to explore common food allergen intake during pregnancy. As no energy correlation was required, the whole population of 1150 mothers were included in this analysis (Figure 8.1).

Figure 8.1: Flowchart of study participants



Dietary analysis

The dairy food allergen group included yoghurt and milk (full cream, reduced fat, and skimmed milk). The total intake of all milk types per individual was reported in grams/day. Cheese intake included hard, soft, ricotta, cream cheese, and low-fat cheese, and the combined intake per individual was reported as grams/per day. Fish intake included combined intake of grilled, fried, or tinned fish per individual, reported as grams/day. Eggs, tree nut, and peanut (in the form of peanut butter) intakes were reported as grams/day. The frequency of all food allergens' intake was reported as the number of times consumed per day, week, or month; milk was reported as cup/day.

Statistical analysis

SPSS version 24 (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp) was used to analyse the data. Data are presented here as means and standard deviations for normally distributed data (milk, yoghurt, and egg) or median and interquartile ranges for non-parametric data (fish, cheese, tree nut, and peanut butter). Mean and standard error of the mean were used to compare the results with other studies as required. Between-group comparisons were tested using a 2-sample t-test / a Mann-Whitney test, or a one-way ANOVA test, as appropriate, with a level of significance of $p<0.05$.

8.3 Results

Figure 8.1 above illustrates the participant recruitment flow. The 1,057 women were included for the purpose of this analysis as no energy calibration was needed. Table 8.1 demonstrates participant characteristics.

Table 8.1: Participant demographic characteristics

	Total n=1057
Age (average y) *	29.0±5.7
14-30 y	635(61.1%)
31-51 y	422(39.9%)
Maternal BMI (average)^	25.3 (15.8-65.9)
Underweight <18.5	45 (4.3%)
Normal 18.5-24.9	464 (43.9%)
Overweight 25-29.9	263 (24.9%)
Obese 30-34.9	147 (13.9%)
Morbidly obese>35	138 (13.1%)
Education level (n=1053)	
• **Low level**	601 (57%)
• **Intermediate level**	232 (22%)
• **High level**	224 (21%)
Ethnic group	
• **Caucasian**	758 (71.7%)
• **Non-Caucasian**	299 (28.3%)
Parity	
• **Primigravida**	436 (41.2%)
• **Multiparous**	621 (58.8%)
Smoking (n=1056)	
• **No**	939 (88.9%)
• **Yes**	117 (11.1%)

*mean ±SD ,^ BMI kg/m^2 presented as average and range (lower and upper value)

In general, pregnant women consumed an average of 18.6±15.4 g/day of eggs, 350.1±193.9 g/day of cow's milk, 8.0 (1.5-14.4) g/day of cheese, 50.4 ±66.9 g/day of yoghurt, 0.80 (0.0-3.4) g/day of tree nuts, 0.60 (0.0-2.7) g/day of peanuts, and 5.1 (1.3-12.6) g/day of fish (Table 8.2). We compared food allergen consumption in the different maternal age groups per the age distributions of non-pregnant women from the Australian Bureau of Statistics (ABS) (Nutrition

First Result, Food, and Nutrition 2011-2012). Initially, the study population was divided into three groups: 14-18 years, 19-30 years, and 31-51 years; however, as the number of women in the 14-18-year-old group was too small, these women were added to the 19-30 years age group for the statistical analysis. Table 8.2 shows the final two age groups: mothers below 30 years of age and mothers above 30 years of age. Comparing the two groups, mothers >30 years of age consumed more eggs (19.8 vs 17.7 g/day, p=0.02), fish (5.6 vs 4.6 g/day, p= 0.02), and tree nuts (1.1 vs 0.6 g/day, p<0.01), but less yoghurt (45.2±61.6 vs 58.2 ±73.9 g/day, p<0.01) than younger mothers.

Table 8.*2*: Common food allergen intake

	All n=1057	**14-30 (y) n=635**	**31-51 (y) n=422**	**p-value**
Eggs	18.6±15.4	17.7±15.0	19.8±15.8	**0.02**
Dairy products				
• **Milk**	350.1±193.9	351.8±198.7	347.3±186.7	0.71
• **Cheese**	7.7 (12.9)	6.5 (12.9)	8.0 (12.9)	0.46
• **Yoghurt**	50.4±66.9	58.2±73.9	45.2±61.6	**<0.01**
Fish				
• **Total fish intake**	15.3 (34.1)	13.7 (34.8)	17.0 (32.5)	**0.02**
• **Grilled /steamed**	6.5 (16.9)	5.8 (15.9)	7.4 (15.9)	
• **Canned fish**	1.3 (9.3)	0.9 (6.9)	1.9 (9.5)	
• **Fried fish**	2.2 (8.2)	2.2 (9.3)	2.2 (9.3)	
Tree nuts	0.8 (3.2)	0.6 (2.6)	1.1 (4)	**<0.01**
Peanuts	0.6 (2.6)	0.6 (2.5)	0.5 (2.8)	0.72

*Values are g/d, presented as mean ±SD for normally distributed data, and as median (IQR) for non-normally distributed data

Table 8.3 describes the frequency of food allergen intake across all maternal groups. In general, 38% of expecting mothers had 1-2 eggs per week, and only 8.5% of the study population reported no eggs in their diet. For milk (of any type), a daily consumption of 1-2 cups per day was reported in 41% of the study population, while 2.9% did not consume any milk. The

percentage of younger pregnant women (less than 30 years of age) who did not consume any milk and eggs in their diet was higher than in the older mother group: 3.8 vs 1.7%, p<0.05, and 10.1 vs 6.8%, p<0.05, respectively.

Table 8.3: Frequency of common food allergens intake. Presented as number (%)

		AGE		p value
	Total n=1057	14-30 y n=635	31-50 y n=422	
Eggs				
• **Never**	90 (8.5)	64 (10.1)	26 (6.2)	
• **<1 egg/week**	242 (22.9)	150 (23.6)	92 (21.8)	
• **1-2 eggs/week**	399 (37.7)	238 (37.5)	161 (38.2)	0.07
• **>3 eggs/week**	236 (30.8)	183 (28.8)	143 (33.9)	
Milk				
• **Never**	31 (2.9)	24 (3.8)	7 (1.7)	
• **<1cup/day**	414 (39.2)	236 (37.2)	178 (42.4)	
• **1-2 cup/day**	427 (40.4)	265 (41.7)	162 (38.4)	0.10
• **>3cup/day**	185 (17.5)	110 (17.3)	75 (17.8)	
Cheese				
• **Never**	94 (8.9)	62 (9.8)	32 (7.6)	
• **1-3x/month**	177 (16.7)	99 (15.6)	78 (18.5)	
• **3-4x/week**	535 (50.6)	327 (51.5)	208 (49.3)	0.37
• **>5x/week**	25 (23.7)	147 (23.1)	104 (24.6)	
Yoghurt				
• **Never**	180 (17)	112 (17.6)	68 (16.1)	
• **1-3x/month**	252 (23.8)	160 (25.2)	92 (21.8)	
• **3-4x/week**	425 (40.2)	259 (40.8)	166 (40.2)	0.06
• **>5x/week**	200 (18.9)	104 (16.4)	96 (18.9)	
Fish				
• **Never**	197 (18.1)	129 (20.3)	68 (16.1)	
• **1-3x/month**	368 (33.9)	234 (36.9)	134 (31.8)	**0.03**
• **3-4x/week**	430 (39.6)	238 (37.5)	192 (45.5)	
• **>5x/week**	62 (5.7)	34 (5.4)	28 (6.6)	
Tree nuts				
• **Never**	297 (28.1)	209 (32.9)	88 (20.9)	
• **1-3x/month**	368 (34.8)	215 (33.9)	153 (36.3)	
• **3-4x/week**	285 (27)	158 (24.9)	127 (30.1)	**<0.01**
• **>5x/week**	107 (10.1)	53 (8.3)	54 (12.8)	
Peanut				
• **Never**	369 (34.9)	217 (34.2)	152 (36)	
• **1-3x/month**	287 (27.2)	175 (27.6)	112 (26.5)	
• **3-4x/week**	305 (28.9)	188 (29.6)	117 (27.7)	0.8
• **>5x/week**	96 (9.1)	55 (8.7)	41 (9.7)	

Yoghurt was reportedly consumed 3-4 times per week in 40% of pregnant women, while 17% did not report any yoghurt intake. Cheese (of any type) was consumed 3-4 times per week in 51% of the study population, while 17% did not report any intake. Peanut consumption during pregnancy was not reported in 34.9 % of the study population. On the other hand, 28% did not report Tree nut intake; there was a significant difference between age group intake of tree nuts where younger mothers less than 30 years did not include Tree nuts in their diet in comparison to the older age group (32.9% vs 20.9% $p<0.01$)

The reported frequency of fish consumption showed interesting findings. A higher percentage of women older than 30 reported eating fish 3-4 times per week compared to younger pregnant women (45.5 vs. 37.5%, $p<0.05$). In general, 19 % of the Study population did not report any fish intake in their diet. The average daily fish intake was 37.4 g/d with a wide range of intake (0.00 - 2320.8 g/d). After adjusting for energy levels (4000-20000 kJ /d), the average fish intake was 31.6 (0.00-430 g/d).

When comparing primiparous to multiparous mothers and across different maternal BMI, there was no difference in food allergen consumption between the groups, except for tree nut consumption, where mothers with a high BMI reported less tree nut intake than lower BMI women (Table 8.4). In addition, we compared those mothers with a self-reported history of allergic disorders (asthma, eczema, rhinitis, and hay fever) with those who do not have such history, 138 (13%) vs 919 (87%) there was no difference in intake between those two groups of women (Table 8.4).

Table 8.4: Comparison of food allergen intakes (g/day) by parity, body mass index (BMI), and maternal history of allergic disorders

	Number	Egg	Milk	Cheese	Yoghurt	Fish	Tree nut	Peanut
Parity								
• **Primigravida**	436	18.3 ±15.2	363.3± 200.9	8.0 (2.0-14.4)	50.0±61.8	4.7 (1.1-11.7)	0.9 (0.0-3.1)	0.6 (0.0-2.5)
• **Multiparous**	621	18.7±15.5	340.8 ±188.5	8.0 (1.5-14.4)	50.5±70.4	5.5 (1.5-13.4)	0.8 (0.0-3.4)	0.6 (0.0-2.7)
P value		0.58	0.06	0.33	0.90	0.07	0.49	0.38
Body mass index (BMI)*								
• **14-18.5**	45	18.9±14.7	341.6±172.7	5.5 (1.7-14.4)	58.6±88.9	4.2 (1.4-8.6)	1.1 (0.0-3.1)	0.6 (0.0-2.3)
• **18.6-24.9**	464	17.8±15.2	361.6±201.8	8.0 (1.5-14.4)	50.8±60.2	5.4 (1.4-13.1)	1.1 (0.0-4.2)	0.5 (0.0-2.5)
• **25-29.9**	263	20.1±15.6	336.4±186.9	8.0 (1.8-14.4)	47.6±61.9	4.9 (1.2-11.7)	0.9 (0.0-2.9)	0.8 (0.0-2.9)
• **Above 30**	285	18.2±15.5	345.4±190.2	8.0 (1.5-14.4)	50.6±77.5	5.2 (1.5-13.7)	0.4 (0.0-2.1)	0.4 (0.0-2.6)
P value		0.25	0.36	0.86	0.76	0.55	0.04	0.14
History of allergy								
• **Yes**	138	17.2±13.2	351.6±198.9	8.0 (1.5-14.4)	52.2±75.5	4.8 (1.3-14.0)	1.0 (0.0-3.4)	0.7 (0.0-2.7)
• **No**	919	18.7±15.6	349.8±193.3	8.0 (1.5-14.4)	50.1±66.2	5.1 (1.3-12.3)	0.8 (0.0-3.2)	0.6 (0.0-2.5)
P value		0.26	0.91	0.94	0.72	0.85	0.91	0.61

* One-way ANOVA test used to analyse the between-group differences. Data presented as mean± Standard error for comparison

^Data from 43640DO005_20112012 Australian Health Survey: Nutrition First Results – Foods and Nutrients 2011-2012 Australia.

8.4 Discussion

This study is the first in Australia to present data on the ingestion of common food allergens in a large cohort of pregnant women. A total of 1,500 mothers were approached, achieving a participation rate of 77%. The intake of common food allergens during pregnancy varied with maternal age groups; however, there was no difference in intake between mothers with a history of allergic disorders and those without such a history.

The study has its limitations. Firstly, it is widely acknowledged that accurately assessing maternal dietary intakes during pregnancy is challenging due to various confounding factors, including physiological, metabolic, and hormonal changes, as well as pregnancy-related symptoms such as nausea, vomiting, and altered appetite, all of which may influence women's dietary choices (293, 791). Secondly, although the FFQ utilised in this study is a commonly employed tool for dietary assessment and has been validated in the pregnant population. (528, 655-657), Nevertheless, it is susceptible to recall bias (530). Furthermore, the inclusion of selected food items in the questionnaire may have impacted the mothers' responses.

It is essential to recognise that pregnant women's allergic status was self-reported and not verified through immunological testing. Furthermore, information concerning participants avoiding eating nuts due to their mothers' actual nut allergies was not obtained.

The timing of the administration of the FFQ in our study was another limiting factor. The FFQ was given immediately in the postpartum period as it was felt that mothers could still accurately recall their food intake during pregnancy (since conception). We felt that providing the FFQ in the first trimester may not have been appropriate as appetite and food choices in the first trimester are likely to be confounded by cravings and/or aversions to certain foods and hyperemesis gravidarum, whereas this often reduces after the first trimester. In addition, the foods consumed during later pregnancy may have more influence during this most critical

period for immune development. Two previous studies examined maternal dietary intake and its association with childhood allergies; the FFQ used in these studies was given at different times of gestation. The first study (792) used the Victorian Council QQE2 FFQ to analyse pre-conception maternal nutrient intake and the occurrence of childhood allergic disorders. The study involved 309 women, of which 50% had a history of asthma. The FFQ was distributed at 18 weeks gestations; the results of this study showed a protective effect of pre-conception intake of fish on childhood eczema and asthma. The authors acknowledged the limitations of FFQ, and the timing of its administration may have impacted the results (792). The second study. (793) distributed a different type of FFQ (the Commonwealth Scientific and Industrial Research Organization FFQ involving 160 items) immediately after the birth with 80% participation rate; this study investigated peanut ingestion during pregnancy with the development of allergic disorders in Children at 16 y of age, the study found an association between women with family history of asthma (35% of cohort), peanut ingestion, and peanut and rye sensitisation of offspring But no such association was not found with fish and yoghurt ingestion.

In the current study, 13% of pregnant women self-reported allergic disorders, which is a smaller percentage than in the previous two studies; this could be due to selection bias. Asthma and Atopic disease were shown to be associated with maternal and neonatal complications (794-796). Therefore, women with such conditions are considered high-risk pregnancies and cared for by specialised clinics. Mothers recruited in this study were selected to be considered low-risk pregnancies, and those deemed high risk either due to maternal or fetal complications were excluded; therefore, the reported incidence may not reflect the true incidence of such disorders in the Australian pregnant population.

At the time of the study, there were no comparable data in the pregnant Australian population. Therefore, the results were compared with previously published data of age-matched non-pregnant Australian women from the Australian Health Survey (ABS12) (797) (presented in Table

8.4). The comparison showed that Australian pregnant women consume more eggs, milk but less tree nuts than non-pregnant women. It is important to emphasise that this comparison should be taken with caution as the method used for dietary assessment is different; the ABS survey was based on a 24-hour recall, which reflects food intake in a shorter period than the FFQ could be not a true reflection of the whole diet (798).

The average fish intake could not be compared with the ABS-published data due to differences in the types of fish and data reporting. The Australian dietary guidelines encourage pregnant women to increase fish intake due to its high content of protein, omega-3 essential fatty acids and iodine; on the other hand, the guideline advises against the consumption of fish with a high mercury content; additionally, it specify the different types of fish consumed (97). The guideline generally advises intake of 2-3 servings of fish /week (a serving is 100-150mg depending on fish type). The V2 FFQ used in this study does not differentiate between fish types and reports daily rather than weekly intake; therefore, a comparison of the recommended intake cannot be made. Globally systematic reviews reported a lower fish intake in pregnant women compared to the general population (657, 771). A possible explanation for this lower intake could be due to maternal concern about fish contamination with mercury and industrial waste products (799, 800). Similarly, a lower fish intake was reported in Australian pregnant population (657). This study investigated fish intake in young women (25-30y of age, n=606) as part of the Australian longitudinal study on women's health (ALWASH) (801), the average daily fish intake was lower than the intake in non-pregnant women cohort (28.2±37.4 g/d vs 33.5 ±37.4 g/d). Comparing this study result to our cohort same age group (n=368) and after adjusting for the same chosen level of energy (4500-20000kJ/d), our study results showed higher average fish intake (31.3±46.3 vs 28.2±37.4 vs g/d) than the reported study but did not reach statistical significance; nevertheless, it was still lower than the average for non-pregnant women reported in the same study (supplementary table 8.5). Notably, there was a difference in a fried fish category where a higher intake was reported in our cohort (9.2±24.4 g/d vs 6.2±12.5 g/d). This finding could be

related to changing maternal dietary choices over time between the two studies (ALWASH recruitment was in 1996, while the current study was in 2013-2018).

Table 8.5: Main food allergen average daily intake in grams per day (g/d) compared with non-pregnant women of the same age

	Total Study cohort all ages N=929	Selected study cohort age 25-30 y N=368	ALWASH cohort Age 25-30 y N=606	P value
Fish steamed, grilled or baked	14.7±23.4	14.0± 23.0	13.7±19.0	0.8
Fried Fish	9.4±19.9	9.2±24.4	6.2±12.5	**0.01**
Tinned Fish	8.3±19.4	8.0±16.8	8.3± 13.6	0.7
Mean for all types	32.4 ±47.7	31.3±46.3	28.2 ±37.4	0.2

Bold results are significant p<0.05

Results presented as mean ±SD

ALWASH cohort results extracted from: Taylor AL, Collins CE, Patterson AJ. The relationship between potential contaminant exposure from fish and nutrient intakes in Australian women by pregnancy status. Nutrition & Dietetics. 2014;71(4):229-35.(657)

Women tend to change their food behaviour during pregnancy to ensure optimal healthy outcomes for themselves and their growing fetuses (347-349). Koplin et al. showed a family history of any allergy in a family member has a modest increase in food allergy in offspring (OR1.4, 95% CI (1.1-1.7) (802). Similarly, Saito-Abe et al (803) found childhood food allergy was strongly associated with a parental history of food allergy (aOR 2.60; 95%CI 1.58−4.27) when both parents reported food allergy, and the aOR was 1.71 (95%CI 1.54−1.9) when either parent had food allergy. Therefore, it seems prudent for mothers with a history of allergic disorders to avoid food allergens in their diet for the prevention of allergy occurrence in their offspring (804). Numerous studies and systematic reviews proved this concept to be inaccurate (805, 806).

Dietary guidelines do not support food allergen avoidance during pregnancy (807-810). In our study cohort there was no difference in food allergen intake between mothers with history of allergic disorder and those without such history, a trend that agrees with the guidelines.

Nuts are good source of unsaturated fat. It is proved to have beneficial effect on lowering cholesterol levels and has anti -inflammatory properties(811)s. Dietary guidelines encourage the intake of nuts unless the individual has true nut allergy(97). The recommended nut intake is 4g/d. There is no national data on nut consumption during pregnancy, but comparing this study result with ABS data, a reduced intake is noticed within the maternal age group 31-50 years. As the incidence of true nut allergy in this cohort is not known, no conclusions can be made regarding avoiding nut intake .

The objective of this study was to examine common food allergens during pregnancy to establish baseline consumption data. It would be beneficial to gather follow-up data on the incidence of allergic disorders in offspring, extending from infancy into the teenage years, as this would present a valuable avenue for future research.

8.5 Conclusion

This study examines maternal common food allergen ingestion during pregnancy in a cohort of low-risk pregnant populations. The results may inform the design of future intervention studies on maternal dietary intake and offspring atopy.

CHAPTER 9: Discussion and Conclusions

9.1 Introduction: Maternal Macronutrient Intake and its association with fetal growth

This thesis has provided insight into maternal dietary patterns and macronutrient intake during pregnancy in a cohort of healthy pregnant women and explored the relationship between diet, macronutrient intake, and fetal growth parameters.

Assessing maternal diet presents several challenges. The study has underscored the complexities of analysing dietary intake due to multiple confounders, which include the varied types of foods consumed, the interactions between different food items, and the difficulties in quantitatively measuring single food items. Additionally, the accuracy of self-reported dietary data can be influenced by recall and social desirability biases, leading to potential underreporting or overreporting of specific food intakes. The study participants' diverse characteristics further contribute to the variability in dietary patterns, complicating the assessment process. Nonetheless, a strength of the study is the recruitment of 1,500 women, with a commendable participation rate of 77%. Furthermore, it included low-risk pregnant women from various backgrounds, ethnic groups, and socioeconomic statuses, thereby reflecting the current diversity of the Australian population (812). This diversity significantly enhances the credibility and trustworthiness of the findings. To the best of our knowledge, this study represents the first investigation into discretionary food (DF) intake among the Australian pregnant population. It examines the various dietary patterns consumed by pregnant women. Additionally, it analysed macronutrient intake in pregnant women who report smoking during pregnancy, an area which has been not widely investigated. The thesis employed innovative analytical methods to scrutinise dietary intake, such as the geometric framework for nutrition

(GFN) analysis of macronutrient intake (Chapter 6)and principal component analysis (PCA) to uncover common dietary patterns (Chapter 7). This may open the door to broader use of these methods in future studies.

9.2 Key results of the study

Maternal energy and macronutrient intake

The median energy intake of the study population was 7542.3 kJ/d (IQR 3853.4), less than the recommended energy intake of 10100 kJ/d but similar to that reported in previous studies. Notably, there was a statistically significant difference in energy intake between primigravida and multiparous mothers; the multiparous mothers had more energy intake, 7719.4 kJ/d (IQR 3649.3), compared to the primigravida's 7292.2 kJ/d (IQR 4011.9), $p<0.05$. Mothers who smoked during pregnancy had higher energy intake, 7838.9 kJ/d (IQR 4429.2), as compared to non-smokers' 7527.0 kJ/d (IQR 3763.7, regardless of their parity status. Nevertheless, it did not reach statistical significance.

Analysis of individual macronutrient intake revealed that the energy contribution from protein and carbohydrate consumption varied with energy levels but remained within the recommended intake. In contrast, the energy derived from fat intake in the maternal diet was above the general recommendation (39% of energy intake vs the recommended 20-30% of total energy intake). This contribution was more evident at higher energy intake levels (> 10000kJ/d).

Dietary patterns and food items

To our knowledge, there is a paucity of data examining common dietary patterns in Australian pregnant women. We have therefore utilised the principal component analysis (PCA) statistical method to explore this. The study did not show any specific dietary pattern similar to the commonly recognised dietary patterns, which may be attributable to the pregnant population's diverse multiethnic and multicultural backgrounds. Nevertheless, three major dietary patterns

were identified: the first dietary pattern (Diet 1) involves a high intake of meat, processed meat, and savoury foods; the second pattern (Diet 2) involves a high intake of vegetables, legumes, and fruit; the third pattern (Diet 3) involves a high intake of dairy and sweet foods.

DF intake was reported in 84.9% of the study population; the most commonly consumed items were savoury food (pizza and pies), potato chips, and ice cream. These items are known to have high-fat content, which could explain the high fat intake observed in this pregnant population. This finding may aid in giving nutritional advice during pregnancy. Additionally, DF intake was high in the diets of mothers who reported smoking during pregnancy; interestingly, these mothers also had lower fish intake than mothers who did not smoke, and this dietary pattern might have contributed to the noticeable difference in energy and saturated fat intake between mothers who smoked during pregnancy and those who did not.

Furthermore, mothers in this cohort did not avoid including common food allergens in their diets. Pregnant women consumed more eggs, milk, and peanuts than age-matched non-pregnant women.

Macronutrient intake and fetal growth

Fetal growth parameters (birth weight, length, and head circumference) were strongly associated with maternal parity, sex, booking BMI, and smoking status. Despite different levels of energy intake, there was no association between energy level and fetal growth parameters.

This study utilised a unique formula to measure fetal growth in utero (g/w) produced by Mongeli and colleagues [Mongelli, 1999 #6191]. We believe this formula better reflects fetal growth as a dynamic process rather than as situated at a single point in time (birth). The study showed a difference in the rate of fetal weight gain (g/week) between primigravida and multiparous women. The fetal weight gain was greater in babies of multiparous women than in primigravida women (181.7 vs 175.4 g/week).

In general, fetal growth parameters were not associated with individual macronutrient intake; it was the interaction between protein, carbohydrates, and fat influenced these. Diets high in protein to fat resulted in better fetal weight gain per week. Notably, the amount of carbohydrates in the diet of primigravida mothers influenced the growth of their fetuses; this effect was not observed in the diet of multigravida mothers.

In this study population, 11.1% of the women reported smoking while pregnant. Babies born to mothers who smoked were smaller, shorter, and gained less weight than those born to non-smoking mothers, regardless of their energy level and macronutrient intake.

9.3 Study limitations

The study has several limitations. The first is the use of a Food Frequency Questionnaire (FFQ) for dietary data collection. Although the FFQ used is a well validated research tool that has been used in many epidemiological studies, it is subject to memory and recall bias, which may result in under- or over-estimating dietary intake. For this reason, unrealistic results were excluded from the study to reduce the bias.

Although great care was taken when approaching low-risk pregnant women to participate in the study, many still failed to disclose relevant health information, such as a special diet for irritable bowel syndrome or food preferences due to cultural beliefs. These cases were excluded from the analysis, impacting the total number of participants.

Another limitation is the large diversity in food intake observed, this may reflect the diversity of the ethnic and cultural backgrounds of the participants. While this can be seen as a strength of the study, it may also interfere with interpreting the results. Furthermore, availability and access to food items may have impacted maternal food choices. This is a common problem encountered in many dietary studies. However, unfortunately, it cannot be rigorously analysed as it entails including the individual women's income and shopping list details, which was not

part of this current study. The other limitation is the complex nature of diets, encompassing different food items, which makes it difficult to ascertain the relationship between certain food items or a specific macronutrient and the measured outcome.

It is well-established that maternal health and placental diseases confound the correlation between maternal nutrient intake and pregnancy outcome. Therefore, this study has focused on healthy women with no pre-existing or pregnancy-induced diseases to reduce the impact of these confounders. Nonetheless, other confounding factors, such as genetics and the difference in maternal adaptation to physiological changes of pregnancy, could not be excluded.

9.4 Interpretation of results and future directions

The cohort in this study comprised a sample drawn from the pregnant population at a tertiary metropolitan hospital in Sydney, New South Wales, Australia. This study represents the first time an analysis of the dietary intake of this cohort. Although the study's findings have provided valuable insights into maternal dietary patterns and macronutrient intake during pregnancy, the results reflect the dietary choices and patterns of intake for the current cohort, which might not apply to a different population from other countries with different backgrounds and socioeconomic statuses. On the other hand, the extensive database obtained from this study is expected to provide a valuable foundation for future studies as it can be utilised in comparative studies with larger cohorts and different populations elsewhere.

The results underscore the importance of balanced dietary choices, characterised by a variety of food items, to support the health of both mothers and infants. The food items included in the study were constrained by the options presented in the Food Frequency Questionnaire (FFQ). The incorporation of additional food items in the questionnaire would have potentially enhanced the analysis and validity of the results. At the same time, food availability presents an evolving challenge, and it may not be feasible to include all contemporary food items within a

single questionnaire. As noted in Chapter 4, although the new version of the Cancer Council Victoria FFQ (v3) (released in 2017) does include new food items, it was not employed in the current study as it was introduced midway through the recruitment phase, and switching to the new version could have influenced the interpretation of the results. Future studies could utilise the updated version of the questionnaire to make a comparison with the current findings.

Furthermore, this study emphasises the critical importance of abstaining from smoking during pregnancy. While most women cease smoking upon becoming pregnant, there has been a lack of recorded information regarding women who quit smoking in the early weeks of pregnancy. The inclusion of such data may impact the interpretation of results pertaining to the smoking demographic. Future studies that estimate serum nicotine levels would contribute further validity to the findings.

The novel statistical methods implemented in this thesis – specifically geometric framework for nutrition (GFN) analysis and principal component analysis (PCA) – have the potential to encourage further research using similar methodologies. They hold special promise for future broader applications and larger studies aimed at enhancing their validity.

This study provides the first report on the intake of discretionary foods (DF) and common allergens among Australian pregnant women, which may serve as a basis for future comparative studies with other cohorts or the general population.

9.5 Conclusion

Analysing pregnancy nutrition status is a complex task influenced by various factors, such as maternal characteristics, food choices, and the limitations of the currently available statistical methods for assessment of food intake. Determining the ideal diet during pregnancy remains an ongoing challenge due to ever-changing environmental conditions and the health and wealth of individuals and societies, which impacts food availability and choices. It is, therefore, crucial to

understand the relationship between different dietary components to optimise pregnancy outcomes and to enable mothers to make more appropriate dietary choices that suit their lifestyle and budget without compromising their own health or that of their offspring.

The findings of this study provide valuable insights into maternal dietary patterns during pregnancy that can serve as a baseline for future research. They may also assist healthcare professionals and nutritionists offer appropriate dietary advice to pregnant women. The results underscore the significance of balanced nutritional choices (and various food items) to support the health of both mothers and babies and highlight the advice to refrain from smoking during pregnancy.

Finally, The relationship between maternal diet and fetal growth remains a critical area of research. Identifying the optimal dietary regimen during pregnancy presents significant challenges due to various confounding factors, the continually evolving nutritional landscape, and the ethical considerations pertinent to conducting randomised trials among pregnant populations. Future investigations should encompass larger cohorts and utilise more rigorous dietary and statistical analysis methodologies to address this pressing issue effectively.

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Appendices

Appendix 1: Supplementary Table. Energy and Nutrient intake requirements in pregnancy

	source	Requirements in pregnancy *	Guidelines Recommendation*	Current status of intake in the pregnant population	Effects of Imbalance intake
Energy	Balanced nutrition with adequate weight gain and physical activity	Increase in second 1400kJ/d and third trimester1900kJ/d	(9,204.8 to 12,133.6 KJ/d) depending on the maternal BMI, physical activity and gestational age	Lower energy intake reported in several studies	Excessive energy intake leads to excess maternal weight gain
Protein	Meat, poultry Fish, eggs, legumes Tofu, beans, dairy	Increase to 71g/d (1.1g/kg/d Compared to 45g/d for non-pregnant	10-35% of total caloric intake	Lower than recommended Ranging between (14-16%) of total caloric intake	Maternal protein intake has a U-shaped relationship with outcomes. Low protein intake is associated with low birth weight, while high intake is associated with preterm birth.
Fat	Healthy fat Oil, nuts fatty fish, seed unhealthy saturated fat ice cream, fried food	13g/d for linoleic acid 1.4g/d for linolenic acid	20-35% of total energy intake And limit 10% of saturated fat Recommend Fish intake 100-150mg/week	Saturated fat exceeds recommendation in 75% of the population	Healthy fat oils (n-3-LCPUFAS) improve the development of the neurological system of the fetus and may prevent preterm birth Unhealthy fat is associated with gestational diabetes and excessive weight gain
CHO	Healthy low GI; Vegetables, fruit and fibre Unhealthy high GI: white bread, rice, potato	Increase to 175 g/d compared to 130g/d for non-pregnant	45-65% of total caloric intake Recommendation to increase fruit, vegetables and fibre in the diet	The variable depends on the type of CHO studied.	Higher CHO intake is linked to low birth weight, but results are controversial. Healthy CHO is beneficial to pregnancy outcomes.
Fibre	Vegetables, fruit and whole grains	14g per 1000Kcal(4184kJ)	28-36g/d	Low fibre intake	Increased fibre intake is associated with reduced constipation and better blood sugar control. It may also reduce pre-eclampsia dyslipidaemia and improve offspring neurodevelopment.
Water	Beverage (70-80%) Food (20-30%)	Increase 300ml/d over non-pregnant	750-1000 ml/d above basic need (3 L/day)	Reduced intake	Dehydration is linked to pre-eclampsia, miscarriage, preterm labour, urinary tract infection and kidney stones.
Micronutrient					
iron	Red meat Poultry Dark, leafy green vegetables	Increases with pregnancy progress RDI increase from	22-28 mg/d Supplementation is recommended	Low intake in 20-25% of pregnant women in developed	Iron deficiency anaemia is associated with pre-term labour, pre-eclampsia, low birth weight

		18 mg/d to 22-27mg/d		countries	
Folic acid	Fortified flour, cereals, maze Green vegetables, legumes	Supplement of 400 µg/d	600-800 µg /d Supplementation is recommended	36% of the pregnant population has low intake	Deficiency causes neural tube defects
Iodine	Iodised salt Seafood	220 µg	150 µg/d Supplementation is not recommended, but encourages iodised salt intake	Data suggest a low intake	Deficiency causes maternal and fetal hypothyroidism. Excess intake is associated with harmful effects,
Calcium	Diary product Leafy green vegetable	1000-1300 mg/d	1000-1300 mg/d Supplement is indicated only in women with low levels of calcium	Low intake is reported with variable percentages in different populations	Low calcium level is associated with hypertension in pregnancy. Supplementation is only advised in a high-risk population
Vitamin D	Fatty fish liver Dermal synthesis with sun exposure	10-15µg/d(400-600iu/d)	10-15 µg/d Supplementation is recommended for high-risk population	Low levels are associated with ethnic group, ow sun exposure and geographic location	Low levels are linked to adverse outcomes, but the role of supplementation is still controversial
Zinc	Poultry, Meat, Cereals, legumes Seafood (oyster , lobster, crab).	11-12 mg	11-12 mg	11% of pregnant women have low intake	Low zinc is associated with low birth weight, preterm birth and neurological defect

BMI : Body mass Index kg/^{m2} . CHO : Carbohydrates. LCPUAS : Long chain Polyunsaturated Faty Acids

***Sources:**

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Appendix 2: Ethics Approval

Appendix 3: Participant Consent Form

PARTICIPANT INFORMATION SHEET AND CONSENT FORM

Study Title: Nutritional assessment of mothers giving birth to intrauterine growth restricted

Study Title: Nutritional assessment of mothers giving birth to intrauterine growth restricted

CONSENT TO PARTICIPATE IN RESEARCH

Name of Researcher: Dr BATOOL NADIM

1. I understand that the researcher will conduct this study in a manner conforming to ethical and scientific principles set out by the National Health and Medical Research Council of Australia and the Good Clinical Research Practice Guidelines of the Therapeutic Goods Administration.

2. I acknowledge that I have read, or have had read to me the Participant Information Sheet relating to this study. I acknowledge that I understand the Participant Information Sheet. I acknowledge that the general purposes, methods, demands and possible risks and inconveniences which may occur to me during the study have been explained to me by __Dr Batool Nadim__ ("the researcher") and I, being over the age of 16 acknowledge that I understand the general purposes, methods, demands and possible risks and inconveniences which may occur during the study.

3. I acknowledge that I have been given time to consider the information and to seek other advice.

4. I acknowledge that refusal to take part in this study will not affect the usual treatment of my condition.

5. I acknowledge that I am volunteering to take part in this study and I may withdraw at any time.

6. I acknowledge that this research has been approved by the Nepean Blue Mountains Local Health District Human Research Ethics Committee.

7. I acknowledge that I have received a copy of this form and the Participant Information Sheet, which I have signed.

8. I acknowledge that any regulatory authorities may have access to my medical records to monitor the research in which I am agreeing to participate. However, I understand my identity will not be disclosed to anyone else or in publications or presentations.

Before signing, please read 'IMPORTANT NOTE' following.

IMPORTANT NOTE:

This consent should only be signed as follows:

Where a participant is over the age of 16 years , then by the participant personally.

Name of participant _____ Date of Birth _____

Address of participant _____

Signature of participant _____
Date:_____

Signature of researcher _____ Date: _____

Appendix 4: Participant Information Form

PARTICIPANT INFORMATION SHEET

Study Title: Nutritional assessment of mothers giving birth to intrauterine growth restricted infants.

11/06/2013
Chief Investigator: Dr Batool Nadim
Department of Obstetrics and Gynaecology, Sydney Medical School - Nepean, The University of Sydney

Invitation
You are invited to participate in a research study which is being conducted by Dr Anthony Liu and Prof Ralph Nanan from the Department of Paediatrics and by Dr Batool Nadim from department of obstetrics and gynecology . The study is looking into the nutritional assessment of mothers of growth restricted babies compared to mothers of non-growth restricted babies.
Before you decide whether or not you wish to participate in this study, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with others if you wish.

What is the purpose of the study?
The purpose of this study is to investigate whether there are nutritional differences between mothers who give birth to babies with intrauterine growth restriction defined as birth weights less than 10% for gestation compared to mothers who give birth to babies with no growth restriction.

Who will be invited to enter the study?
You are eligible to participate in this study because you have given birth to a baby.

Do you have a choice?
Participation in this study is voluntary. It is completely up to you whether or not you participate. If you decide not to participate, it will not affect the treatment you receive now or in the future. Whatever your decision, it will not affect your relationship with the staff caring for you. If you wish to withdraw from the study once it has started, you can do so at any time without having to give a reason. You can also have your data withdrawn as well if you wish.

What will happen on the study?
If you agree to participate in this study, you will be asked to sign the Participant Consent Form.

If you consent, you will be asked to complete a nutritional questionnaire which will take approximately 10 minutes to complete. The result will be analyzed and compared with

outcome of pregnancy using local database (electronic data records and /or patient file) looking at baby birth weight and gestational age at delivery.

Are there any risks? NO

Are there any benefits?
This study aims to further medical knowledge and may improve future treatment of intrauterine growth restriction however it may directly benefit you if are planning on having more children. This study may establish a link between maternal nutrition and IUGR.

Confidentiality / Privacy
Of the people treating you, only those named above or necessary others eg. all nursing staff involved in your care will know whether or not you are participating in this study. Any identifiable information that is collected about you in connection with this study will remain confidential and will be disclosed only with your permission, or except as required by law. Only the researchers named above will have access to your details and results that will be held securely in the Department of Paediatrics, Nepean Hospital.

Financial Disclosure
This study is not funded by any commercial sponsors.

Will taking part in this study cost me anything, and will I be paid?
Participation in this study will not cost you anything. Unfortunately we have no funding to reimburse for your time.

What happens with the results?
If you give us your permission by signing the consent document, we plan to discuss/publish the results with the HREC for monitoring purposes, peer-reviewed journals, presentations at conferences or other professional forums.
In any publication, information will be provided in such a way that you cannot be identified. Results of the study will be provided to you if you wish.

Complaints

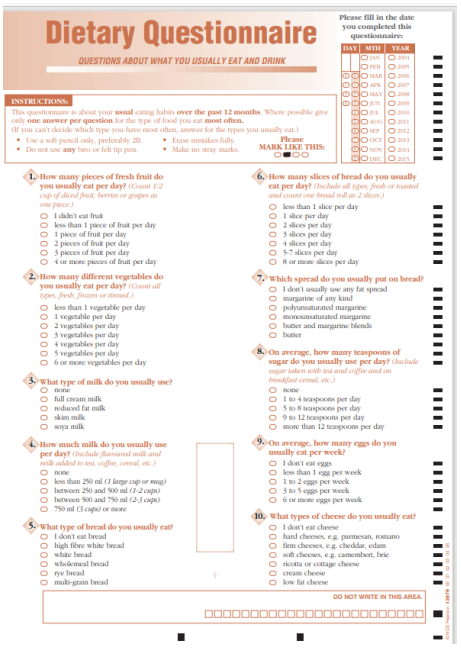
This study has been approved by the Nepean Blue Mountains Local Health District Human Research Ethics Committee. If you have any concerns about the conduct of the study or your rights as a study participant, you may contact Ms Felicity Lindfield, Nepean Hospital Patient Representative (Contact details: 02 47 34 2286 - Email address: Felicity.Lindfield@swahs.health.nsw.gov.au). You should quote HREC number 09/7.

Contact details

When you have read this information, the researcher, Dr Batool Nadim, will discuss it with you and any queries you may have. If you would like to know more at any stage, please do not hesitate to contact her at 47343363. If you have any problems while on the study, please contact

Dr Batool Nadim
Working hours Telephone No – 02 4734 3363
Thank you for taking the time to consider this study.
If you wish to take part in it, please sign the attached consent form.
This information sheet is for you to keep.

Appendix 5: Food Frequency Questionnaire DQES V2 hard copy



Dietary Questionnaire

QUESTIONS ABOUT WHAT YOU USUALLY EAT AND DRINK

Please fill in the date you completed this questionnaire:

DAY MTH YEAR

INSTRUCTIONS:

This questionnaire is about your **usual** eating habits **over the past 12 months**. Where possible give only **one answer per question** for the type of food you eat **most often**.
(If you can't decide which type you have most often, answer for the types you usually eat.)

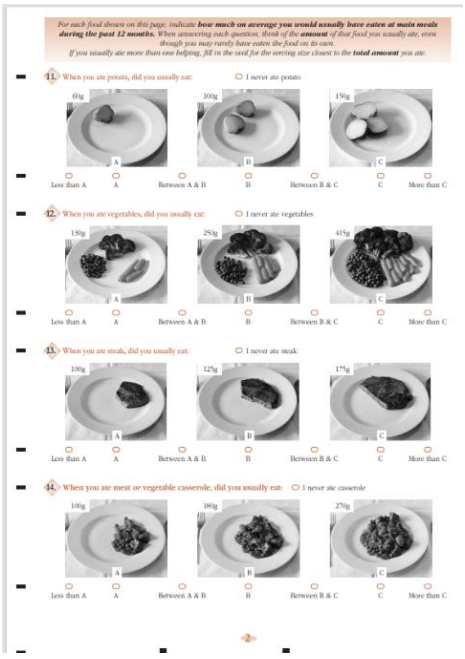
- Use a soft pencil only, preferably 2B.
- Do not use **any** biro or felt tip pen.
- Erase mistakes fully.
- Make no stray marks.

Please MARK LIKE THIS:

1. **How many pieces of fresh fruit do you usually eat per day?** *(Count 1/2 cup of sliced fruit, berries or grapes as one piece.)*
   - I didn't eat fruit
   - less than 1 piece of fruit per day
   - 1 piece of fruit per day
   - 2 pieces of fruit per day
   - 3 pieces of fruit per day
   - 4 or more pieces of fruit per day
2. **How many different vegetables do you usually eat per day?** *(Count all types, fresh, frozen or tinned.)*
   - less than 1 vegetable per day
   - 1 vegetable per day
   - 2 vegetables per day
   - 3 vegetables per day
   - 4 vegetables per day
   - 5 vegetables per day
   - 6 or more vegetables per day
3. **What type of milk do you usually use?**
   - none
   - full cream milk
   - reduced fat milk
   - skim milk
   - soya milk
4. **How much milk do you usually use per day?** *(Include flavoured milk and milk added to tea, coffee, cereal, etc.)*
   - none
   - less than 250 ml *(1 large cup or mug)*
   - between 250 and 500 ml *(1-2 cups)*
   - between 500 and 750 ml *(2-3 cups)*
   - 750 ml *(3 cups)* or more
5. **What type of bread do you usually eat?**
   - I don't eat bread
   - high fibre white bread
   - white bread
   - wholemeal bread
   - rye bread
   - multi-grain bread
6. **How many slices of bread do you usually eat per day?** *(Include all types, fresh or toasted and count one bread roll as 2 slices.)*
   - less than 1 slice per day
   - 1 slice per day
   - 2 slices per day
   - 3 slices per day
   - 4 slices per day
   - 5-7 slices per day
   - 8 or more slices per day
7. **Which spread do you usually put on bread?**
   - I don't usually use any fat spread
   - margarine of any kind
   - polyunsaturated margarine
   - monounsaturated margarine
   - butter and margarine blends
   - butter
8. **On average, how many teaspoons of sugar do you usually use per day?** *(Include sugar taken with tea and coffee and on breakfast cereal, etc.)*
   - none
   - 1 to 4 teaspoons per day
   - 5 to 8 teaspoons per day
   - 9 to 12 teaspoons per day
   - more than 12 teaspoons per day
9. **On average, how many eggs do you usually eat per week?**
   - I don't eat eggs
   - less than 1 egg per week
   - 1 to 2 eggs per week
   - 3 to 5 eggs per week
   - 6 or more eggs per week
10. **What types of cheese do you usually eat?**
    - I don't eat cheese
    - hard cheeses, e.g. parmesan, romano
    - firm cheeses, e.g. cheddar, edam
    - soft cheeses, e.g. camembert, brie
    - ricotta or cottage cheese
    - cream cheese
    - low fat cheese

DO NOT WRITE IN THIS AREA.

Page 1



For each food shown on this page, indicate ***how much on average you would usually have eaten at main meals during the past 12 months.*** *When answering each question, think of the* ***amount*** *of that food you usually ate, even though you may rarely have eaten the food on its own.*

If you usually ate more than one helping, fill in the oval for the serving size closest to the ***total amount*** *you ate.*

11. When you ate potato, did you usually eat: ○ I never ate potato

60g 100g 150g

Less than A | A | Between A & B | B | Between B & C | C | More than C

12. When you ate vegetables, did you usually eat: ○ I never ate vegetables

150g 250g 415g

Less than A | A | Between A & B | B | Between B & C | C | More than C

13. When you ate steak, did you usually eat: ○ I never ate steak

100g 125g 175g

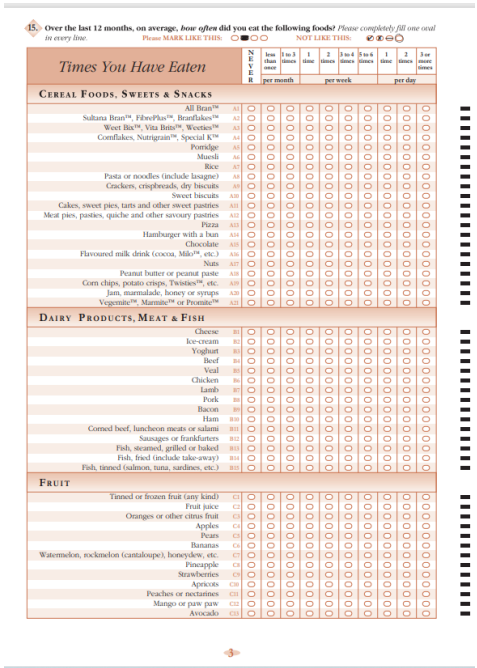
Less than A | A | Between A & B | B | Between B & C | C | More than C

14. When you ate meat *or* vegetable casserole, did you usually eat: ○ I never ate casserole

100g 180g 270g

Less than A | A | Between A & B | B | Between B & C | C | More than C

Page 2



15. **Over the last 12 months, on average,** ***how often*** **did you eat the following foods?** *Please completely fill one oval in every line.* Please MARK LIKE THIS: NOT LIKE THIS:

Times You Have Eaten	NEVER	less than once	1 to 3 times	1 time	2 times	3 to 4 times	5 to 6 times	1 time	2 times	3 or more times
		per month		per week				per day		
CEREAL FOODS, SWEETS & SNACKS										
All Bran™	A1									
Sultana Bran™, FibrePlus™, Branflakes™	A2									
Weet Bix™, Vita Brits™, Weeties™	A3									
Cornflakes, Nutrigrain™, Special K™	A4									
Porridge	A5									
Muesli	A6									
Rice	A7									
Pasta or noodles (include lasagne)	A8									
Crackers, crispbreads, dry biscuits	A9									
Sweet biscuits	A10									
Cakes, sweet pies, tarts and other sweet pastries	A11									
Meat pies, pasties, quiche and other savoury pastries	A12									
Pizza	A13									
Hamburger with a bun	A14									
Chocolate	A15									
Flavoured milk drink (cocoa, Milo™, etc.)	A16									
Nuts	A17									
Peanut butter or peanut paste	A18									
Corn chips, potato crisps, Twisties™, etc.	A19									
Jam, marmalade, honey or syrups	A20									
Vegemite™, Marmite™ or Promite™	A21									
DAIRY PRODUCTS, MEAT & FISH										
Cheese	B1									
Ice-cream	B2									
Yoghurt	B3									
Beef	B4									
Veal	B5									
Chicken	B6									
Lamb	B7									
Pork	B8									
Bacon	B9									
Ham	B10									
Corned beef, luncheon meats or salami	B11									
Sausages or frankfurters	B12									
Fish, steamed, grilled or baked	B13									
Fish, fried (include take-away)	B14									
Fish, tinned (salmon, tuna, sardines, etc.)	B15									
FRUIT										
Tinned or frozen fruit (any kind)	C1									
Fruit juice	C2									
Oranges or other citrus fruit	C3									
Apples	C4									
Pears	C5									
Bananas	C6									
Watermelon, rockmelon (cantaloupe), honeydew, etc.	C7									
Pineapple	C8									
Strawberries	C9									
Apricots	C10									
Peaches or nectarines	C11									
Mango or paw paw	C12									
Avocado	C13									

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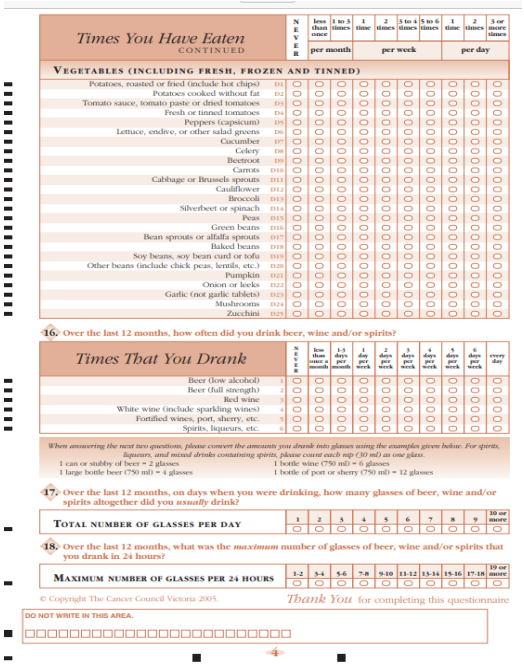

Times You Have Eaten CONTINUED	NEVER	less than once	1 to 3 times	1 time	2 times	3 to 4 times	5 to 6 times	1 time	2 times	3 or more times
		per month		per week				per day		
VEGETABLES (INCLUDING FRESH, FROZEN AND TINNED)										
Potatoes, roasted or fried (include hot chips)	D1									
Potatoes cooked without fat	D2									
Tomato sauce, tomato paste or dried tomatoes	D3									
Fresh or tinned tomatoes	D4									
Peppers (capsicum)	D5									
Lettuce, endive, or other salad greens	D6									
Cucumber	D7									
Celery	D8									
Beetroot	D9									
Carrots	D10									
Cabbage or Brussels sprouts	D11									
Cauliflower	D12									
Broccoli	D13									
Silverbeet or spinach	D14									
Peas	D15									
Green beans	D16									
Bean sprouts or alfalfa sprouts	D17									
Baked beans	D18									
Soy beans, soy bean curd or tofu	D19									
Other beans (include chick peas, lentils, etc.)	D20									
Pumpkin	D21									
Onion or leeks	D22									
Garlic (not garlic tablets)	D23									
Mushrooms	D24									
Zucchini	D25									

16. **Over the last 12 months, how often did you drink beer, wine and/or spirits?**

Times That You Drank	NEVER	less than once a month	1-3 days per month	1 day per week	2 days per week	3 days per week	4 days per week	5 days per week	6 days per week	every day
Beer (low alcohol)	1									
Beer (full strength)	2									
Red wine	3									
White wine (include sparkling wines)	4									
Fortified wines, port, sherry, etc.	5									
Spirits, liqueurs, etc.	6									

When answering the next two questions, please convert the amounts you drank into glasses using the examples given below. For spirits, liqueurs, and mixed drinks containing spirits, please count each nip (30 ml) as one glass.

1 can or stubby of beer = 2 glasses
1 large bottle beer (750 ml) = 4 glasses
1 bottle wine (750 ml) = 6 glasses
1 bottle of port or sherry (750 ml) = 12 glasses

17. **Over the last 12 months, on days when you were drinking, how many glasses of beer, wine and/or spirits altogether did you** ***usually*** **drink?**

TOTAL NUMBER OF GLASSES PER DAY	1	2	3	4	5	6	7	8	9	10 or more
	○	○	○	○	○	○	○	○	○	○

18. **Over the last 12 months, what was the** ***maximum*** **number of glasses of beer, wine and/or spirits that you drank in 24 hours?**

MAXIMUM NUMBER OF GLASSES PER 24 HOURS	1-2	3-4	5-6	7-8	9-10	11-12	13-14	15-16	17-18	19 or more
	○	○	○	○	○	○	○	○	○	○

Thank You for completing this questionnaire

DO NOT WRITE IN THIS AREA.

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Appendix 6: Australian Food Database (attached as a separate Excel file)

Appendix 7: Eat for Health

Australian Government
National Health and Medical Research Council

NHMRC

BUILDING A HEALTHY AUSTRALIA

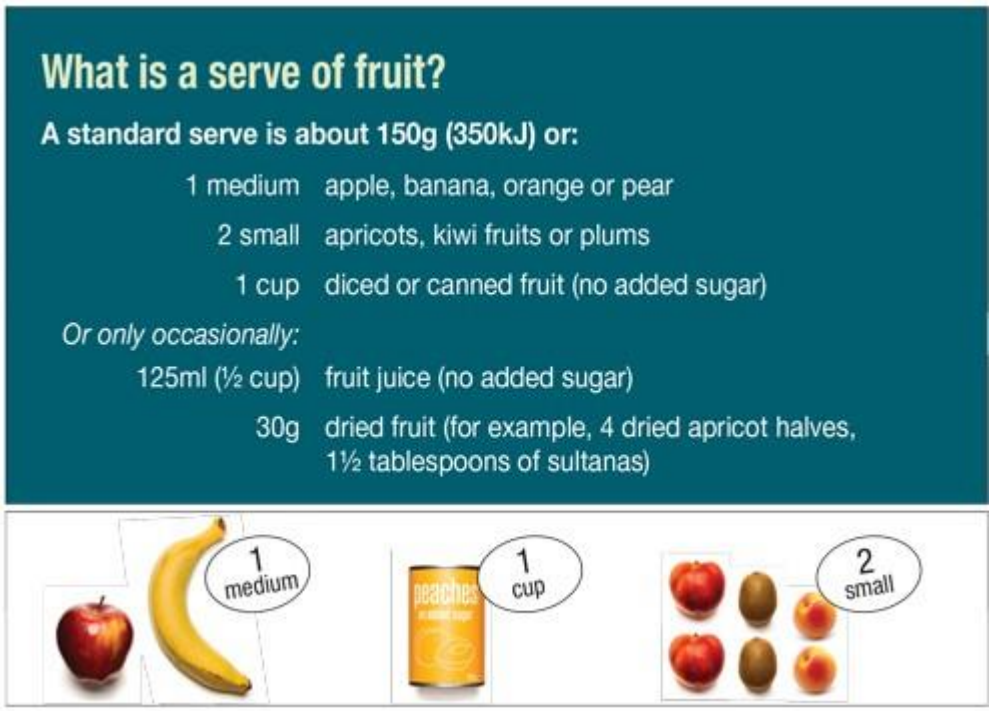
Serve sizes

What is a serve of vegetables?

A standard serve is about 75g (100–350kJ) or:

- ½ cup cooked green or orange vegetables (for example, broccoli, spinach, carrots or pumpkin)
- ½ cup cooked dried or canned beans, peas or lentils (preferably with no added salt) • 1 cup green leafy or raw salad vegetables
- ½ cup sweet corn
- ½ medium potato or other starchy vegetables (sweet potato, taro or cassava) • 1 medium tomato

What is a serve of fruit?



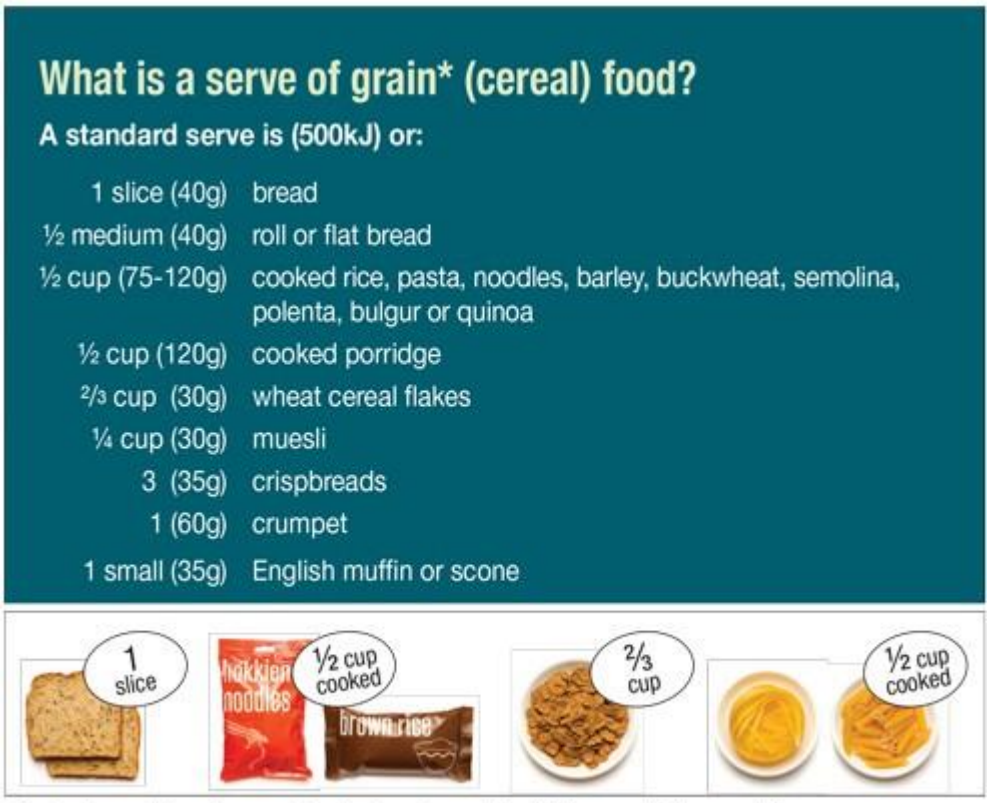
A standard serve is about 150g (350kJ) or:

- 1 medium apple, banana, orange or pear
- 2 small apricots, kiwi fruits or plums
- 1 cup diced or canned fruit (no added sugar)

Or only occasionally:

- 125ml (½ cup) fruit juice (no added sugar)
- 30g dried fruit (for example, 4 dried apricot halves, 1½ tablespoons of sultanas)

What is a serve of grain* (cereal) food?



*Grain (cereal) foods, mostly wholegrain and/or high cereal fibre varieties

A standard serve is (500kJ) or:

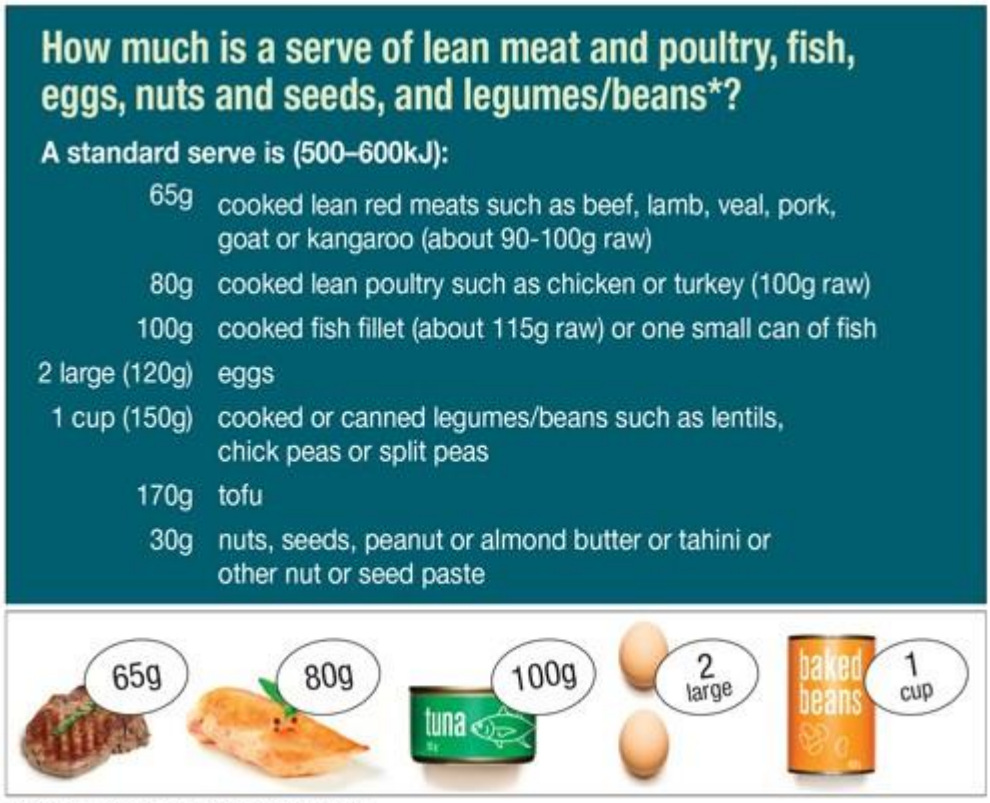
- 1 slice (40g) bread
- ½ medium (40g) roll or flat bread
- ½ cup (75-120g) cooked rice, pasta, noodles, barley, buckwheat, semolina, polenta, bulgur or quinoa
- ½ cup (120g) cooked porridge
- ⅔ cup (30g) wheat cereal flakes •

¼ cup (30g) muesli

- 3 (35g) crispbreads
- 1 (60g) crumpet
- 1 small (35g) English muffin or scone

**Grain (cereal) foods, mostly wholegrain and/or high cereal fibre varieties*

How much is a serving of lean meat and poultry, fish, eggs, nuts and seeds, and legumes/beans?

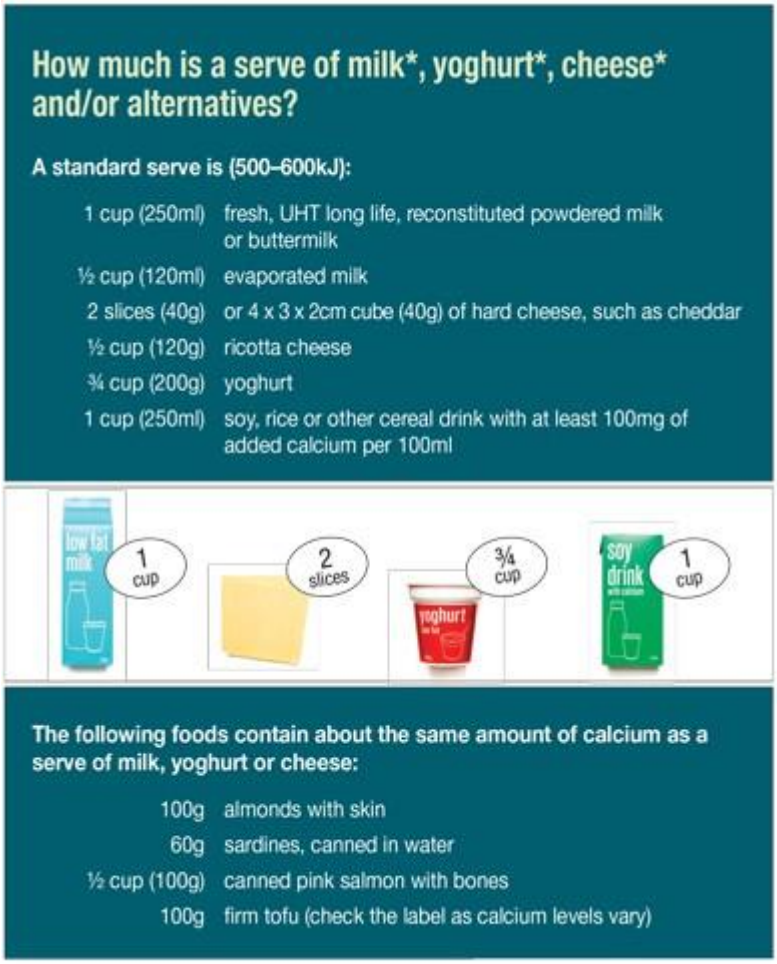


A standard serve is (500–600kJ):

- 65g cooked lean red meats such as beef, lamb, veal, pork, goat or kangaroo (about 90-100g raw)
- 80g cooked lean poultry such as chicken or turkey (100g raw)
- 100g cooked fish fillet (about 115g raw) or one small can of fish
- 2 large (120g) eggs
- 1 cup (150g) cooked or canned legumes/beans such as lentils, chick peas or split peas (preferably with no added salt)
- 170g tofu
- 30g nuts, seeds, peanut or almond butter or tahini or other nut or seed paste (no added salt)*

**Only to be used occasionally as a substitute for other foods in the group (note: this amount for nuts and seeds gives approximately the same amount of energy as the other foods in this group but will provide less protein, iron or zinc).*

How much is a serve of milk*, yoghurt*, cheese* and/or alternatives?



A standard serve is (500–600kJ):

- 1 cup (250ml) fresh, UHT long life, reconstituted powdered milk or buttermilk
- ½ cup (120ml) evaporated milk
- 2 slices (40g) or 4 x 3 x 2cm cube (40g) of hard cheese, such as cheddar
- ½ cup (120g) ricotta cheese
- ¾ cup (200g) yoghurt
- 1 cup (250ml) soy, rice or other cereal drink with at least 100mg of added calcium per 100ml

*Choose mostly reduced fat

If you do not eat any foods from this group, try the following foods, which contain about the same amount of calcium as a serve of milk, yoghurt, cheese or alternatives (note: the kilojoule content of some of these serves (especially nuts) is higher so watch this if trying to lose weight).

- 100g almonds with skin

- 60g sardines, canned in water
- ½ cup (100g) canned pink salmon with bones
- 100g firm tofu (check the label as calcium levels vary)

How many kilojoules are in a serve of each food group?

Not all food groups provide the same number of kilojoules (kJ) per serve.

A serve of the grain (cereals) food group; milks/yoghurt/cheese and/or alternatives group; lean meats, poultry, fish, eggs and/or alternatives group; will provide about 500-600kJ.

About 2 serves of fruit, and from 2 serves (for starchy vegetables) to 5 serves (of green leafy vegetables) of different varieties in the vegetables group will provide about 500-600kJ. This is one reason that it makes good sense to fill up on leafy green and other lower kilojoule vegetables when you are trying to lose weight.

Also, while discretionary food serves can have similar kilojoules (about 600kJ) to a serve of the five food groups, they are usually much smaller and less filling, don't provide you with the fibre and nutrients you need and contain too much saturated fat, added sugars and added salt for good health.

Appendix 8: Supplementary Tables for Chapter 5

Table 1 - Coefficients from GAMs for maternal energy intake and offspring outcomes according to parity

Outcomes	Primigravida				Multigravida			
Energy (kJ)	**edf**	**Ref.df**	**F**	**p-value**	**edf**	**Ref.df**	**F**	**p-value**
te(Protein %)	0.00	4	0.00	1.00	0.00	4	0.00	0.81
te(Carbohydrate %)	0.00	4	0.00	0.71	0.44	4	0.20	0.16
te(AllFat %)	0.00	4	0.00	0.69	0.00	4	0.00	0.72
ti(Protein %,Carbohydrate %)	0.88	16	0.45	0.002	0.33	16	0.03	0.19
ti(Protein %,AllFat %)	0.00	16	0.00	0.50	3.45	16	0.62	0.01
ti(Carbohydrate %,AllFat %)	0.00	16	0.00	0.80	0.37	16	0.03	0.24
ti(Protein %,AllFat %,Carbohydrate %)	3.52	53	0.16	0.02	0.00	54	0.00	0.96
te(Weight)	0.00	4	0.00	0.60	0.00	4	0.00	0.38
te(Height)	0.59	4	0.35	0.12	0.00	4	0.00	0.89
Offspring weigh (g)								
te(Protein)	0.00	4	0.00	1.00	0.00	4	0.00	0.48
te(Carbohydrate)	0.00	4	0.00	0.58	0.00	4	0.00	0.49
te(Total fat)	0.00	4	0.00	1.00	0.00	4	0.00	1.00
ti(Protein, Carbohydrate)	0.00	16	0.00	0.29	0.00	16	0.00	0.37
ti(Protein, Total fat)	0.00	16	0.00	1.00	1.51	16	0.23	0.04
ti(Carbohydrate, Total fat)	0.86	16	0.11	0.11	1.07	16	0.16	0.05
ti(Protein, Total fat, Carbohydrate)	0.75	52	0.06	0.04	0.00	56	0.00	0.39
te(Weight)	0.83	4	1.18	0.02	0.97	4	7.59	0.00
te(Height)	1.74	4	1.62	0.02	0.43	4	0.19	0.18
te(GA)	1.50	4	17.87	0.00	2.11	4	20.96	0.00
Offspring length (cm)								
te(Protein)	0.65	4	0.39	0.11	0.00	4	0.00	1.00
te(Carbohydrate)	0.00	4	0.00	0.65	0.47	4	0.23	0.12
te(Total fat)	0.00	4	0.00	0.49	0.00	4	0.00	1.00
ti(Protein, Carbohydrate)	0.00	16	0.00	0.90	0.00	16	0.00	0.35
ti(Protein, Total fat)	0.31	16	0.03	0.21	0.00	16	0.00	0.31
ti(Carbohydrate, Total fat)	0.00	16	0.00	0.56	2.40	16	0.39	0.02
ti(Protein, Total fat, Carbohydrate)	0.91	37	0.08	0.04	0.64	56	0.01	0.14
te(Weight)	0.00	4	0.00	1.00	0.92	4	2.89	0.00
te(Height)	0.87	4	1.71	0.01	0.00	4	0.00	0.62
te(GA)	0.96	4	6.51	0.00	0.98	4	10.80	0.00
Offspring weight gain (g)								
te(Protein)	0.00	4	0.00	1.00	0.00	4	0.00	0.56
te(Carbohydrate)	0.00	4	0.00	0.54	0.00	4	0.00	0.47
te(Total fat)	0.00	4	0.00	1.00	0.00	4	0.00	1.00
ti(Protein, Carbohydrate)	0.85	16	0.13	0.09	0.00	16	0.00	0.40
ti(Protein, Total fat)	0.00	16	0.00	1.00	1.97	16	0.27	0.04
ti(Carbohydrate, Total fat)	0.00	16	0.00	0.61	0.74	16	0.08	0.11
ti(Protein, Total fat, Carbohydrate)	0.83	52	0.09	0.01	0.00	56	0.00	0.33
te(Weight)	0.86	4	1.50	0.01	0.97	4	6.96	0.00
te(Height)	1.67	4	1.35	0.03	0.48	4	0.23	0.16
te(GA)	0.67	4	0.29	0.17	1.32	4	1.22	0.02

GAMs, generalised additive models; Edf, estimated degrees of freedom for the model terms; Ref. DF, reference degrees of freedom; GA, gestational age.

Appendix 8 : Supplementary tables for Chapter 5

Table 2: The association of various food items with Fetal growth parameters by parity adjusted for BMI

	Primigravida		Multigravidas	
Weight gain (g)/week	**β**	**p-value**	**β**	**p-value**
Processed meat				
Intercept	43.82	0.53	67.24	0.30
High	-2.43	0.50	-3.53	0.28
Unprocessed meat				
Intercept	44.45	0.52	69.96	0.28
High	-1.91	0.60	-0.21	0.95
Fish				
Intercept	42.52	0.54	70.04	0.28
High	-0.20	0.96	-0.01	1.00
Full cream dairy				
Intercept	43.64	0.54	75.10	0.25
High	-0.37	0.92	-5.20	0.11
Wholegrain cereals				
Intercept	43.76	0.53	70.22	0.28
High	3.82	0.29	5.48	0.09
White cereal/potato				
Intercept	60.84	0.39	69.84	0.28
High	-4.76	0.20	-0.95	0.77
Sweet discretionary				
Intercept	44.87	0.52	69.86	0.28
High	-6.24	0.08	-0.19	0.95
Savoury discretionary				
Intercept	50.91	0.47	70.90	0.27
High	-4.71	0.20	0.89	0.78
Fresh fruit				
Intercept	34.22	0.63	68.96	0.29
High	2.57	0.48	1.14	0.72
Tinned fruit/juice				
Intercept	45.28	0.52	66.02	0.31
High	-3.49	0.33	3.21	0.32
Fresh vegetables				
Intercept	39.56	0.57	67.19	0.29

High	-1.73	0.63	-8.30	0.01
Legumes				
Intercept	40.48	0.56	71.87	0.27
High	2.55	0.49	4.56	0.15
Polyunsaturated fats				
Intercept	49.08	0.48	66.32	0.31
High	5.58	0.12	-3.32	0.30
Saturated fats				
Intercept	48.48	0.49	74.23	0.25
High	6.21	0.09	-4.08	0.20
Birth weight (g)				
Processed meat				
Intercept	-5519.42	<0.001	-5331.99	<0.001
High	-29.40	0.60	-47.37	0.33
Unprocessed meat				
Intercept	-5501.85	<0.001	-5296.51	<0.001
High	-33.22	0.56	-7.54	0.88
Fish				
Intercept	-5535.72	<0.001	-5290.49	<0.001
High	-5.22	0.93	-1.59	0.97
Full cream dairy				
Intercept	-5517.46	<0.001	-5225.16	<0.001
High	-5.87	0.92	-71.21	0.14
Wholegrain cereals				
Intercept	-5517.59	<0.001	-5291.69	<0.001
High	54.20	0.33	80.30	0.10
White cereal/potato				
Intercept	-5264.73	<0.001	-5297.13	<0.001
High	-70.21	0.22	-12.80	0.79
Sweet discretionary				
Intercept	-5497.46	<0.001	-5296.95	<0.001
High	-100.45	0.07	-2.77	0.95
Savoury discretionary				
Intercept	-5415.05	<0.001	-5281.78	<0.001
High	-67.51	0.23	13.03	0.79
Fresh fruit				
Intercept	-5653.73	<0.001	-5314.82	<0.001
High	36.75	0.52	21.80	0.65
Tinned fruit/juice				
Intercept	-5490.37	<0.001	-5362.31	<0.001
High	-56.88	0.31	54.40	0.26
Fresh vegetables				
Intercept	-5592.47	<0.001	-5339.49	<0.001
High	-33.44	0.55	-131.72	0.01
Legumes				

Intercept	-5570.13	<0.001	-5265.45	<0.001
High	43.70	0.44	71.86	0.14
Saturated fats				
Intercept	-5436.18	<0.001	-5350.84	<0.001
High	84.29	0.13	-50.41	0.30
Polyunsaturated fats				
Intercept	-5440.16	<0.001	-5229.77	<0.001
High	99.05	0.08	-62.81	0.19
Baby length (cm)				
Processed meat				
Intercept	8.55	0.20	13.19	0.03
High	-0.25	0.48	-0.69	0.02
Unprocessed meat				
Intercept	8.46	0.21	13.71	0.02
High	-0.03	0.94	-0.09	0.77
Fish				
Intercept	8.45	0.21	13.88	0.02
High	0.06	0.86	-0.06	0.85
Full cream dairy				
Intercept	9.51	0.16	14.14	0.02
High	-0.37	0.29	-0.42	0.16
Wholegrain cereals				
Intercept	8.48	0.21	13.77	0.02
High	0.17	0.63	0.93	<0.001
White cereal/potato				
Intercept	8.74	0.20	13.71	0.02
High	-0.08	0.82	-0.12	0.68
Sweet discretionary				
Intercept	8.58	0.20	13.56	0.02
High	-0.44	0.21	-0.22	0.46
Savoury discretionary				
Intercept	9.81	0.14	13.31	0.03
High	-0.75	0.03	-0.42	0.16
Fresh fruit				
Intercept	9.00	0.19	13.26	0.03
High	-0.17	0.62	0.51	0.08
Tinned fruit/juice				
Intercept	8.53	0.21	12.90	0.03
High	-0.12	0.72	0.67	0.02
Fresh vegetables				
Intercept	8.37	0.22	13.70	0.02
High	-0.04	0.91	-0.10	0.74
Legumes				
Intercept	7.96	0.23	13.94	0.02
High	0.60	0.09	0.51	0.09

Saturated fats				
Intercept	7.99	0.23	13.45	0.02
High	-0.40	0.26	-0.25	0.39
Polyunsaturated fats				
Intercept	8.93	0.18	13.64	0.02
High	0.50	0.15	0.09	0.77

Appendix 9: Supplementary Table for Chapter 7

Table: Logistic regression analysis of Smoking, nutrient intake and various confounders.

	β	**P value**	**Exp(B)**	**95% C.I. for EXP(B)**	
Smoking status =yes	-1.061	.037	.346	.128	.938
BMI kg/m²	.125	.009	1.133	1.032	1.244
Energy kJ/d	.005	.682	1.005	.982	1.027
All Fat g/d	-.253	.700	.777	.215	2.802
Sat Fat g/d	.082	.813	1.085	.551	2.136
Poly Fat g/d	.032	.925	1.032	.533	1.999
Mono Fat g/d	.057	.882	1.059	.499	2.249
Protein g/d	-.070	.717	.932	.637	1.364
Carbohydrate g/d	-.075	.695	.928	.639	1.347
Parity =primigravida	.939	.034	2.557	1.076	6.075
Sex of offspring =Female	.843	.070	2.323	.934	5.776
Ethnicity =Caucasian	-.004	.993	.996	.369	2.686

g/d: gram/day, kJ/d =kilojoule/day, Mono fat: mono saturated fat, Poly fat: polys un- saturated fat, Sat Fat: Saturated fat