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A thesis submitted in fulfilment of the requirements for the degree of Master of Philosophy
DECLARATION

This thesis is submitted to The University of Sydney in fulfillment of the requirements for the degree of Master of Philosophy. This thesis comprises, to the best of my knowledge, only my original work except where due acknowledgment had been given in the text. I declare that material in this thesis has not been submitted, either in full or in part, for a degree at this or any other institution.

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Date: June 2017
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Finally, I thank God for this incredible experience.
PRESENTATIONS

This work was presented at 2015 The University of Sydney, School of Public Health Conference "Different perspectives, Working together".
The author, with the advice of her supervisors, was responsible for the development of the methods, the analysis of data and the interpretation of the results as presented in this thesis.

Associate Professor Freddy Sitas, Dr. Visalini Nair-Shalliker, and the CLEAR Study team at Cancer Council NSW have been involved in designing the CLEAR Study and collecting this data.

The statisticians at Cancer Council NSW have given the author expert advice, which allowed her to make the right analytical decisions.
ABSTRACT

Adulthood obesity is a known risk factor for colorectal cancer (CRC), but little is known about the effect of the duration of obesity on CRC risk.

We studied the link between CRC risk and adulthood obesity, using body mass index (BMI) and regional weight gain, as proxies for overall and abdominal obesity, respectively.

We analyzed all CRC cases (483 men and 373 women) and associated cancer-free controls (907 men and 965 women), from the NSW Cancer, Lifestyle and Evaluation of Risk Study. BMI was based on self-reported weight and height (kg/m²), at age 20 and before cancer diagnosis. Regional weight gain during participant's 20s and 30s and after age 50 was self-reported. Those with a BMI <25kg/m² and ≥25kg/m² were grouped as normal (reference) and overweight/obese, respectively. Regional weight gain was grouped as those who reported any weight gain in the abdomen, or in other regions versus no weight gain (reference). BMI at age 20 and before diagnosis were combined to derive the time course of obesity. We conducted a complete case analysis using logistic regression, adjusting for age, socioeconomic factors, alcohol intake, smoking status and physical activity, for the sexes separately.

Although not seen in women, CRC risk was raised in men (odds ratio(OR)=1.48; 95% confidence interval(CI):1.13,1.93) who were overweight/obese before diagnosis compared to men with a normal BMI. Men who also were overweight/obese at age 20 had the highest CRC risk (OR=1.69;95%CI:1.22,2.34), men who had a normal BMI at age 20 had a lower, but still raised, CRC risk (OR=1.39;95%CI:1.04,1.87) compared to men with a normal BMI at both ages. Regional weight gain was not a CRC risk predictor in men or women.

Health professionals should particularly encourage men to maintain a healthy weight, and for men who are overweight/obese at age 20 to monitor their weight during adulthood, and lose weight if they can, as early and prolonged exposure to obesity increases their CRC risk considerably.
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1.1. Colorectal cancer

1.1.1. Pathogenesis and types of colorectal cancer

Colorectal cancer (CRC) covers cancer in the large intestinal tract ranging from the caecum to the rectum (see Figure 1). It is coded as C18-C20 by the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification.

Most CRCs begin as non-malignant adenomas or polyps in the wall of the colon or rectum. If untreated, they can progress over time, to become malignant and eventually metastasize through the wall of the colon or rectum, and to lymph nodes and other areas of the body (1).

There are several types of CRC such as adenocarcinomas, squamous cell cancers, carcinoid tumors, sarcomas and lymphomas (2). More than 95% of all CRCs are classified as adenocarcinomas, which begin in the mucus-secreting glands in the lining of the colon or rectum (3).

Figure 1 The regions of the colon and the rectum.


1.1.2. Global and local trends in colorectal cancer incidence

CRC is the third most common cancer worldwide, and in 2012 almost 1.4 million new cases of CRC were reported worldwide (5). According to the World Cancer Research Fund International, it is predicted that by 2035, worldwide this number of annual CRC cases will increase to 2.4 million (5).

Over 50% of CRC cases were found in more developed countries (5). The perception that CRC is a disease of the high-income countries is supported by the incidence of
CRC doubling, at least, in countries that have recently been classified as high-income countries, such as Japan, Singapore, and Eastern European countries (6). Figure 2 demonstrates that CRC incidence is greater in developed regions, such as North America, Europe, and Australasia, compared to less developed regions, with the highest incidence rate for CRC reported in Australia/New Zealand and the lowest rate reported in Western Africa. In high-income countries with high CRC incidence, the trends in CRC incidence over the last 20 years has varied. This rate stabilized in France and Australia, while it decreased in the USA and this may be explained by the increasing uptake of screening and the removal of precancerous lesions (7). Compared to CRC incidence rate, CRC mortality rate varies to a lesser degree between the regions. Figure 2 also shows that the male to female ratio for both incidence and mortality varied little across geographic regions (8).

**Figure 2** Estimated colorectal cancer incidence and mortality worldwide in 2012

![Graph showing colorectal cancer incidence and mortality worldwide in 2012](image)

Source: IARC Cancer Fact Sheets (8).

In Australia, there were 14,958 new CRC cases diagnosed in 2012 and it is estimated that in 2016, the number of new CRC cases would be 17,520 (9). CRC incidence was higher for males than females. In 2012, the age-standardized incidence rate for males
was 70 cases per 100,000 persons, and for females was 50 cases per 100,000 persons. In 2016, it is estimated that the age-standardized incidence rate will increase to 74 cases for males and 51 cases for females per 100,000 persons (9).

Figure 3 shows that the rate of new CRC cases from 1987 to 2008 in New South Wales (NSW), one of the states of Australia, has fluctuated between 70 to 80 per 100,000 population for males. For females, the rate of new CRC cases was lower as it varied between 45 and 55 per 100,000 population (10).

**Figure 3** Colorectal cancer: new cases and death rated by sex, NSW, 1987 to 2011.

One disability-adjusted life year (DALY) is equivalent to ‘one year of ‘healthy life’ lost due to a disease or injury’ and is used to compare the fatal and non-fatal effects of various medical conditions (11). A 2011 Australian study found that cancer was the leading disease group to cause burden, accounting for 19% of total DALYs lost (11). In particular, CRC was ranked 13 amongst the leading causes of total burden in both sexes, accounting for 53,084 and 39,338 years of ‘healthy life’ lost in males and females, respectively (11).
1.1.3. Risk factors for colorectal cancer

1.1.3.1. Age

In Australia, the age-specific CRC incidence rate increased rapidly from the age of 50 in 2012 (see Figure 4) (12). Similarly, in the UK, the age-specific CRC incidence rate for individuals aged 85-89 years was significantly higher than individuals aged 50-54 years. During 2011-2013, 68% of new CRC cases in the UK were people aged 70 years or older (13). Comparably, the majority (90%) of new CRC cases in the USA were people aged 50 years or older (14).

Figure 4 Age-specific incidence rates for colorectal cancer, 2012

Note: Rates are expressed per 100,000 males/females

1.1.3.2. Country of birth

In countries consisting of many ethnic groups, CRC incidence rate has shown to vary between ethnic groups. In NSW, 23% of its residents were born overseas. The CRC incidence rate for migrants from the most common 25 places of birth was lower or similar to the Australian-born population (15). In the UK, the age-standardized rate is greater for White males (ranging from 54.1 to 55.3 cases per 100,000 people) than Black males (ranging from 29.7 to 43.8 cases per 100,000) and Asian males (ranging from 19.1 to 28.0 cases per 100,000). Similarly, White females experienced the highest age-standardized rate (ranging from 34.0 to 34.8 per 100,000) while Black females (ranging from 20.4 to 31.6 per 100,000) and Asian females (ranging from 11.3 to 17.5 per 100,000) experienced lower rates (13). In North America, CRC incidence rate is greatest for Black males and females and lowest for Asian/Pacific Islander males and females (14). However, studies have shown that the association between racial disparity and CRC risk is modest and it indicates socioeconomic factors may be responsible for the variation seen for CRC risk (16, 17). An Australian study found that Asian and European immigrants were less likely to participate in the cancer screening programs compared to Australian-born individuals, even after adjusting for socioeconomic factors. This finding suggests that the lower
incidence rate in immigrants may be because they are less likely to participate in the screening program. This study concludes that programs promoting cancer screening to target immigrant groups may be necessary (18).

1.1.3.3. Socioeconomic status

In cancer epidemiology, socioeconomic status (SES) measures how accessible basic resources to attain and sustain good health are for an individual. As the International Agency for Research on Cancer (IARC) describes, SES is an abstract concept that is approximated through proxy variables such as income, education, and place of residence. These variables are not the direct cause of cancer but rather indicate exposure to unknown and underlying causes (19).

A 1995 review found that colon cancer risk was lower in individuals with a low SES. However, the review found no consistent trend for the association between rectal cancer risk and SES (20). A 2010 review examined 21 studies on the association between CRC risk and SES, measured by education, occupation, income, poverty or a combination of these proxies. It found that this association varied for different countries. In North America, low SES was associated with higher incidence of colon and rectal cancer compared to high SES. In contrast, in an Australian study and most European studies, low SES was linked with lower CRC incidence. The more recent review explains that this variation in the association between CRC risk and SES between countries may be explained by two factors. Firstly, the link between SES and lifestyle risk factors for cancer, such as physical activity and diet, may vary between countries. Secondly, the CRC screening rate is different between the countries. However, it is suggested that the international variation may change as European countries and Australia roll out CRC screening programs (discussed further in Section 1.1.3.4.). The author expressed hope that if the screening programs encourage the participation of individuals from all SES categories, then the program may narrow the SES gap for CRC detection (21).

Accessibility/Remoteness Index of Australia (ARIA plus)

ARIA plus is an Australian standard measure of remoteness endorsed by the Australian Bureau of Statistics. It is an index that measures the road distance between a populated locality and a health service center. Populated locality is the location from where individuals are traveling from to receive services. ARIA plus has five levels of remoteness: Major City of Australia, Inner Regional Australia, Outer Regional Australia, Remote Australia and Very Remote Australia (22). Figure 5 shows the association between the rate of new CRC cases in NSW by remoteness and sex, with the three categories Outer Regional, Remote and Very Remote Australia combined. In 2008, the rate of new CRC cases was lowest in Major Cities for both males (73.0 per 100,000 population) and females (49.8 per 100,000 population) (23). The highest rate of new CRC cases for males was seen in the combined category, Outer Regional and Remote areas (76.9 per 100,000 population), while the highest CRC cases for females was seen in the Inner Regional area (55.2 per 100,000 population) (23). A Queensland study found that amongst CRC patients, patients living in Inner and Outer Regional areas were more likely to have been diagnosed with advanced CRC compared to patients living in the Major cities (p=0.05) (24).
Figure 5 Colorectal cancer: new cases by remoteness from health service centers and sex, NSW, 2008.

1.1.3.4. Colorectal cancer screening

In Australia, The National Bowel Cancer Screening Program was launched in August 2006 with the aim of reducing illness and death through early detection and prevention. Screening may reduce CRC incidence through the detection of precancerous lesions and their removal (25). In Australia, the current guidelines recommend that every two years individuals aged 50 years and older or those with family history be screened using the fecal occult blood test, a non-invasive test which detects traces of blood in their stool. According to a monitoring report on the screening program, from July 2013 to June 2014, 1.4 million Australians aged 50, 55, 60 or 65 were sent a screening kit. With 36% of kits returned, the 2013-2014 participation rate had increased compared to the 2012-2013 participation rate (33.4%). Of those who returned a valid screening kit, 7.5% had a positive screening result, and 49.5% of these individuals recorded to have received follow-up colonoscopy (18,669 individuals). Of those who underwent colonoscopy, a significant number were diagnosed with confirmed cancer (149 individuals), suspected cancer (599 individuals) and advanced adenoma (1,691 individuals) (26).

In this screening program, males had a lower participation rate (33.6%), compared to females (38.5%), but a higher rate of cancer diagnosed through screening (97 males and 52 females with confirmed cancer). The participation rate was lower for those living in remote (33.0%) and very remote (24.7%) regions, and those in the lowest SES (34.1%). A smaller proportion of Aboriginal and Torres Strait Islanders
participated in the screening program (0.9%) than the compulsory national census, the 2011 Australian Census of Population and Housing (1.5%). Therefore, the indigenous population was less inclined to be screened for CRC than expected. However, rates of positive screening results increased with increasing geographical remoteness, decreasing SES and this rate was higher in indigenous participants compared to non-indigenous participants (26).

1.1.3.5. Family history of colorectal cancer
A 2013 meta-analysis by Johnson et al. pooled results from 16 studies and examined the association between history of CRC in first-degree relatives and CRC risk. Six studies examined this association in females only and found that individuals with positive family history had an increased CRC risk compared with those without family history (Relative Risk (RR):1.60, 95% confidence interval (CI): 1.33–1.92). Whereas, in studies that included both males and females, the relative risk for CRC associated with family history was slightly higher (RR: 1.90, 95% CI: 1.67–2.17). The meta-analysis did not find that this difference between studies with females only and both sexes was statistically significant (27).

1.1.3.6. Smoking
IARC is an interdisciplinary agency with the mission of understanding cancer causes and works with its parent organization, World Health Organization, to reduce the burden of this disease. IARC has confirmed that cigarette smoking is a risk factor for CRC. Most of the studies reviewed by IARC used smoking status as a measure of cigarette smoking and examined its association with CRC risk. Most of the case-control studies reviewed by IARC found a non-significant positive association for CRC risk in current and former smokers, separately (28). However, IARC reported that based on the largest meta-analysis that pooled data from 36 prospective cohort studies, current and former smokers had a significant 15% and 20% increased CRC risk, respectively, compared to never smokers. The meta-analysis did not find evidence of publication bias or heterogeneity (29). Similarly, an Australian case-control study found that current and former smokers had a non-significant 5% and a significant 24% increased CRC risk, respectively, compared to never smokers (30).

1.1.3.7. Alcohol consumption
In a 2007 publication, World Cancer Research Fund International (WCRF) stated that there is convincing evidence that alcohol consumption increases CRC risk in males while in females evidence suggests that this association is probable (6). In their updated 2010 publication, WCRF pooled results from 12 studies and found that one alcoholic drink per day was associated with a non-significant, increased risk of CRC (RR: 1.11; 95% CI: 0.90–1.38), colon cancer (RR: 1.16; 95%CI: 0.97-1.39) and rectal cancer (RR: 1.11; 95%CI: 0.97-1.29). There was heterogeneity between the four CRC studies and five colon cancer studies but not between the three rectal cancer studies. There was no evidence of publication bias (31).

Similar to the WCRF 2010 publication, a 2013 meta-analysis by Johnson et al. pooled results from 22 studies and found that CRC risk and alcoholic consumption of five drinks per week had a positive yet non-significant association (RR: 1.06, 95% CI:
0.91–1.23). This meta-analysis found that the association between alcohol consumption and CRC risk did not vary by gender, cancer site and study design (27). Also, an Australian case-control study collected data on alcohol consumption 10 years ago and found that one to seven alcoholic drinks per week was associated with non-significant, increased CRC risk (RR: 1.09; 95% CI: 0.83-1.43) (30).

1.1.3.8. Physical activity
In a 2007 publication, WCRF determined that there is convincing evidence that physical activity decreases CRC risk (6). In 2010, WCRF conducted a dose-response meta-analysis by pooling results from six studies. It found that total physical activity measured by metabolic equivalent of task (MET) hour per day, a measure of energy consumption, was associated with decreased risk of CRC (RR: 0.97 per 5 MET hours per day, 95% CI: 0.94-0.99) and colon cancer (RR: 0.92 per 5 MET hours per day, 95% CI: 0.86-0.99) but was not associated with rectal cancer risk (RR: 1.02 per 5 MET hours per day, 95% CI: 0.95-1.10). There was no publication bias detected in the three CRC studies or the three rectal cancer studies but publication bias was detected in the five colon cancer studies (31).

Similar to the WCRF findings, Johnson et al. pooled results from 21 studies and found that CRC risk and increased physical activity measured by a standardized physical activity score had an inverse association (p<0.001) (27).

1.1.3.9. Diet
A 2013 meta-analysis by Johnson et al. found that the consumption of red meat, and low consumption of vegetable and fruit were associated with increased CRC risk (27). By pooling results from 14 studies, this meta-analysis found that the consumption of five servings of red meat per week compared to no consumption increased CRC risk (RR:1.13, 95% CI: 1.09-1.16). The study found no evidence of publication bias or small study effect. Johnson et al. examined nine studies and found that the consumption of one, two or three servings of fruit per day compared to little consumption decreased an individual’s risk of developing CRC by 9%, 15% and 16%, respectively (RR:0.91, 95% CI:0.85-0.96 for one serving/day; RR:0.85, 95% CI: 0.78-0.94 for two servings/day; RR:0.84, 95% CI:0.75-0.96 for three servings/day). This study examined the influence on CRC risk of vegetable consumption using results from eight studies. It found that an individual’s CRC risk decreased by 6% when vegetable consumption per day increased by two servings (RR: 0.94, 95% CI: 0.91-0.98). There was some evidence of publication bias or small study effect (27).

1.2. Adult height: a measure of early experiences
From preconception to early adulthood, optimal genetic, environmental, hormonal and nutritional support is necessary for growth and attaining adult height. It is because of all these factors that adult height is often described as a marker of early life experiences. The secular trend for height has been shown to increase over time as
populations settle into a secure environment with good population health and socio-economic conditions. Nutritional support is also necessary, as a child’s diet should include sufficient energy and key nutrients such as amino acids, fatty acids and vitamins. Nutritional shortage has been related to the stunting of growth. Adoption and migrant studies have shown that individuals who move from an environment where nutritional food is scarce to an environment where food supplies are sufficient, the secular trend for height increases. Also, nutritional style has been related to adult attained height. A nutritional style (typically found in tropical Asia) mainly based on rice-derived protein was related to very small adult male height while a nutritional style (typically found in Northern or Central Europe) mainly based on animal protein was related to greater attained male height (32).

1.2.1. Global and local trends for adult height

An early study from 1976 investigated the secular trends for young adult height in several ethnic groups in Asia, Australia, North America and Europe. It utilized data gathered from 1834 to 1970. It found in Australia, Belgium, Japan, Norway and the United States that on average mean height increased by 0.8cm per decade for young female adults aged 17.5 years. From Norway, United States (African American), Japan, Canada, Australia and Belgium, the mean height for males at age 14 years increased by 3.3cm, 2.1cm 2.0cm, 1.8cm, 1.6cm and 1.1 cm, respectively, per decade (33).

A more recent 2007 study investigated the trends for adult height in ten European countries. Participants in this study were born between 1950 and 1980. Like the 1976 study, this study also found that adult height continued to increase in all ten countries. When comparing the growth rate of participants in Northern and Southern Europe, participants who lived in Southern Europe (Greece, Italy, Portugal, and Spain) experienced greater growth compared to those located in Northern Europe (Austria, Belgium, Denmark, Finland, Ireland, and Sweden) (34).

An Australian study, published in 2000, investigated the secular trend for adult height. This study collected data between 1992 and 1993 of school students who were aged 17 years. They compared this data to historical data collected throughout the 20th century. Like other international studies, adult height in Australia continued to increase during the 20th century by 2.1cm per decade and 1.6cm per decade for males and females, respectively. This positive trend for mean adult height was seen consistently in the following states, Victoria, New South Wales and Western Australia. The growth rate of adult height during the first half of the 20th century increased rapidly compared to the last 20 years of the century (35).

1.2.2. Adult height and colorectal cancer incidence

Studies that explored the association between adult height and the risk of developing colon cancer, rectal cancer or CRC were considered (see in detail in Section 5.1.1.).

Most of the studies in our search found that height was associated with increased CRC risk for both sexes (see Table 3 in Section 5.1.1.). Similar findings were reported in the 2010 WCRF systematic literature review of nine cohort studies. In this review, the relative risk of developing CRC was 1.05 (95% CI:1.03-1.08) per 5
cm increase in height. This relationship was consistent for both sexes. When examining site-specific results, height was associated with colon cancer (OR: 1.09; 95% CI: 1.05-1.12) while the association between height and rectal cancer was non-significant (OR: 1.03; 95% CI: 0.99-1.07) (31).

1.3. Body Mass Index: a proxy for general adiposity

Body mass index (BMI) is the most commonly used, crude measurement of general adiposity. BMI can be calculated by weight divided by height squared (kg/m²). The World Health Organization recommended BMI cut-off points give four categories: underweight (less than 18.50 kg/m²), normal (18.50 kg/m² to 24.99 kg/m²), overweight (25.00 kg/m² to 29.99 kg/m²) and obese (greater than or equal to 30.00 kg/m²). BMI is useful in assessing the prevalence of obesity in a population and evaluating interventions and identifying individuals at risk of developing cancer.

1.3.1. Global and local trends for obesity

In 2014, almost two billion adults around the world were overweight or obese (36). This equates to 39% of male adults and 40% of female adults overweight worldwide and 11% of male adults and 15% of female adults obese (37).

Figure 6 displays the prevalence of obesity in countries worldwide. In some countries of North America, North Africa, and West Asia, 30% or more of their adult population were obese (shaded dark green). In the remaining countries of North America, most of South America, Europe, and Central Asia, some of the countries of North and South Africa, and the Oceania region (Australia and New Zealand), 20.0% to 29.9% of their population were obese (shaded vibrant green) (38).

Figure 6 Prevalence of obesity, ages 18+, 2014 (age-standardized estimate) both sexes

In 2011-2012, over 60% of Australians over the age of 18 years were classified as overweight or obese. In 2011-2012, the proportion of Australian males (69.7%) who were overweight or obese was greater than Australian females (55.7%), but the proportion of obese males and females were similar (27.5%).

Data collected for the Australian Bureau of Statistics has also shown that the prevalence of obesity has increased over time (see Figure 7). In 1995, 26.1% of Australians aged 55-64 were obese. The proportion of Australians in this age range who were obese in 2007-2008 was 34.1% and this percentage increased further in 2011-2012 with 36.7% obese (39).

Figure 7 demonstrates that the prevalence of obesity in Australia continued to rise until the age of 64 years, after which it decreased, and this trend is seen at three time points (1995, 2007-2008 and 2011-2012). When comparing the trends for these three time points, the prevalence of obesity in all age groups increased over time (39).

Figure 7: Persons aged 18 years & over – Proportion who were obese, 1995 to 2011-12.

Footnote: Based on Body Mass Index for persons whose height and weight was measured.
Source: Australian Health Survey: Updated Results, 2011-12 (39).

The data collected by the Australian Bureau of Statistics explored the proportion who were overweight or obese during 2011-2012 by remoteness from health service centers and sex (Figure 8). In 2011-2012, the proportion of Australians who were overweight or obese was lowest in the Major Cities for both males (67.7%) and females (52.5%) compared to those who did not reside in the Major Cities (i.e. males (74.4%) and females (63.2%) who resided in regional and remote Australia) (39).
Figure 8 Persons aged 18 years & over – Proportion who were overweight or obese by remoteness by sex, 2011-12.

Footnote: Based on Body Mass Index for persons whose height and weight was measured.
Source: Australian Health Survey: Updated results, 2011-12 (39).

1.3.2. Body Mass Index and colorectal cancer incidence

Studies that explored the association between BMI and the risk of developing colon cancer, rectal cancer or CRC were considered (see in detail in Section 5.1.2.).

The majority of the studies from our search (see Table 4 in Section 5.1.2.) found that BMI was associated with increased CRC risk for both sexes. Similar findings were seen in the 2010 WCRF systematic literature review that identified 24 new studies. In this review, the relative risk of developing CRC increased by 2% per unit increase in BMI (kg/m$^2$). When examining site-specific results, BMI was associated with both colon cancer (3% increased risk per kg/m$^2$) and rectal cancer (1% increased risk per kg/m$^2$). For males (3% increased risk per kg/m$^2$) the risk of developing CRC was greater than females (2% increased risk per kg/m$^2$) (31). In 2010, it was estimated that 3.4% of all cancers were attributed to obesity and this proportion included 1,101 colon cancer cases (40).
1.4. Proxies of obesity: focusing on abdominal obesity

1.4.1. Limitations of Body Mass Index
Although commonly used as a measure of obesity, BMI has limitations. Firstly, individuals with the same BMI do not necessarily have the same body fat and lean body mass composition (41, 42). Secondly, Renehan et al. showed that self-reported weight underestimates true body weight and the extent of this varies with age and gender (43). Although this variation did not alter the risk estimates in the study by Renehan et al., in a study by Park et al., self-reported BMI in females was significantly associated with CRC risk while measured BMI was not (44). Thirdly, those who were heavier were less likely to self-report their height and weight thus these at-risk participants would be under-represented in any analysis that included BMI (44). Finally, BMI has low sensitivity and classifies over half of the individuals as being normal/overweight whom are classified as obese, by another body fat measurement (45).

Besides the apparent limitation of BMI, the actual distribution of body fat needs further investigation. The 2015 meta-analysis by Karahalios identified the need for more studies that elucidate whether the elevated CRC risk is linked with general weight gain or abdominal obesity (46). Visceral adipose tissue, approximated by measures of abdominal obesity, triggers more metabolic dysfunction, which is linked to increased CRC risk compared to subcutaneous adipose tissue (47, 48). In light of the limitations of BMI and the strong association between abdominal obesity and CRC risk, this study created three proxies of obesity that are related to abdominal as well as general obesity, that do not require measurements and can be cheaply and easily adapted in the clinical and research setting.

1.4.2. Waist circumference: an existing measurement of abdominal adiposity

Studies have tried to determine which of the other anthropometric measurements, such as waist circumference, waist to height ratio and waist to hip ratio, is most correlated to abdominal obesity. According to a 1996 editorial, waist circumference to height ratio had the highest correlation to intra-abdominal fat, while another study showed that waist circumference is a better measure (49, 50). More recent studies show that waist circumference and waist to hip ratio have performed well in predicting colon cancer risk (51, 52). In fact, in Australia, measuring waist circumference has become a recommended practice in primary healthcare along with measuring weight and height (53). However, waist circumference is limited because it can be measured in eight locations according to a 2008 literature review, which may lead to inconsistencies in measurement and thus with associated CRC risk (54). The iliac crest is a bony structure and because it is minimally affected by body changes it is useful when measuring waist circumference. However, waist circumference measured at the iliac crest is done with low precision, as it requires training, again adding to possible inconsistencies (55). As shown in a study by Park et al., self-reported waist circumference was the same as measured waist circumference for only 56% of males and females (44). Although accepted as a
measure of abdominal adiposity, waist circumference cannot distinguish between visceral adipose tissue and subcutaneous adipose tissue, which are separated by the muscular wall of the abdomen. Methods that involve an MRI or a CT can accurately distinguish between visceral adipose tissue and subcutaneous adipose tissue, however, this approach cannot be readily used because of its high cost, low availability, trained skill required, significant time required for scanning and incompatibility for those who are severely obese (56). Therefore, this study created proxies that measure abdominal obesity, weight gain in the waist (WGW) and weight gain in the apple region (WGA), due to the absence of economical and effective measures of abdominal obesity.

1.5. The time course of obesity and weight gain

1.5.1. Trends and the significance of considering the time course of obesity

The previous anthropometric measures explored in Sections 1.2-1.4 are all static measures. Recently there has been increasing interest in the effect of weight change on CRC risk. BMI is a static measure approximating excess general adiposity at one point in time. However, weight gain is a dynamic experience and eventuates over time rather than overnight. To date, four meta-analyses found a positive association between weight gain and CRC risk (46, 57-59). The continuous and cumulative effect of excess adiposity on CRC risk is of growing interest for three reasons.

Measuring adulthood weight gain is important as it is experienced by individuals from most BMI categories. Malhotra et al. followed 10,038 young adults aged between 14 and 22 years for 18 years to understand their weight gain trajectory. Over this period, from early to mid-adulthood, weight gain trajectory for males and females in most of the BMI categories was positive and on average individuals experienced a weight gain of 0.5kg per year. A large proportion of males (52.3%) and females (34.9%) were one BMI category higher than their starting category, while a small proportion of males (0.5%) and females (1.9%) experienced weight loss and were one BMI category lower than 18 years ago (60).

The advantage of using adulthood weight gain is that it is highly correlated with the gain of adiposity and not lean body mass. Whereas, BMI measures adiposity and lean body mass (6). Furthermore, weight gain during adulthood has been associated with weight gain in the abdominal regions, so that adult’s body shape leans towards an apple shape. Lara-Castro et al. followed premenopausal females with a BMI in the normal range for up to four years. During this time, females who experienced a significant weight gain, 6kg in a two-year period, experienced higher visceral adipose tissue accumulation relative to total body fat (61).

Thirdly, carcinogenesis is a long process, and so it is important that measurements for adiposity do account for change over this extended period. So, being an anthropometric measure which incorporates time is a strength.
1.5.2. Adulthood weight gain and colorectal cancer incidence

Almost all of the studies in the meta-analysis by Keum et al. and Chen et al. have been included in the larger two meta-analyses by Karahalios et al. and Schlesinger et al. (57, 59). The meta-analyses by Karahalios et al. and Schlesinger et al. investigated 13 and 12 studies, respectively, on the association between weight gain and CRC risk. All of the meta-analyses found that weight gain was associated with CRC or colon cancer risk. Karahalios et al. found that a 5kg increase of body weight was associated with 3% increased CRC risk (46). Schlesinger et al. found that 5kg weight gain was associated with 4% increased CRC risk and this risk remained after adjusting for weight at a young age. These studies found that some heterogeneity was explained by sex. Schlesinger found that colon cancer risk was higher in males, but rectal cancer risk did not differ between the sexes (58).

1.6. Biological mechanism

The biological mechanisms that explain the association between height, adiposity and CRC risk have been described comprehensively in recent articles (62-64). There are five systems involved in this association; growth hormones, insulin and insulin-like growth factors, sex hormones, adipocyte-derived hormones and low-grade inflammation. These five systems do not act alone but rather in an interrelated and complex manner. It is important to note that although adult attained height is related to increase CRC risk, it is not the adult height that directly influences CRC risk but rather the genetic, environmental, hormonal and nutritional factors that affect linear growth and also influence CRC risk (6).

1.6.1. Growth hormone, insulin and insulin-like growth factor

The growth hormone and insulin growth hormone system involves growth hormone (GH), growth hormone receptor (GHR), growth factors (IGF-1 and IGF-2), cell surface receptors (IGF-1 receptor and IGF-2 receptor), binding proteins (IGF-BPs) and proteases.

GH is secreted from the pituitary gland, and its production is regulated by two hypothalamic peptides called GH-releasing hormone, which induces GH production, and somatostatin, which inhibits GH production. GH secretion is also induced by a stomach peptide called ghrelin. GH can stimulate IGF-1 production, mainly from the liver. IGF-1, in turn, provides negative feedback by inducing the release of somatostatin from the hypothalamus.

In the plasma, IGF is mostly present as a high molecular weight complex that includes IGF and a binding protein. There are six binding proteins (IGFBP 1-6) that bind to IGFs with high affinity. A very small proportion (less than 1%) of total IGF-1 are in a free state in plasma. Insulin is a hormone secreted by the pancreas that regulates the blood glucose level. IGF-1, IGF-2, and insulin can bind with low affinity to each other's receptors. The exception is that free IGF-1 has high affinity for its receptor and the insulin receptor. The binding of insulin and free IGF-1 to a
receptor lead to activities that favor tumorigenesis. Free IGF-1 level have shown to be higher in males and this may explain the sex difference seen in the association between obesity and CRC risk (62).

The extracellular domain of the IGF-2 receptor can break away from the cell membrane and circulate in the blood. As well as binding proteins, IGF-2 receptors are involved in reducing the bioactivity of IGF-2 to bind to the IGF-1 receptor, which would result in downstream carcinogenic activity.

Obesity has been linked to insulin resistance, which is a state where the body does not respond to insulin. Subsequently, the body responds by secreting more insulin and this leads to hyperinsulinemia, where there is a high level of circulating insulin in the plasma. Hyperinsulinemia is linked to decreased insulin binding protein 1 and 2 production in the liver. A low level of insulin binding protein 1 and 2 results in an increased level of free IGF-1. Studies have supported these mechanisms by showing that increased CRC risk is associated with high levels of serum insulin, high levels of IGF receptors and a low level of serum IGF binding proteins 1 and 2 (65-68).

### 1.6.2. Sex hormones

Obesity is linked with increased bioavailability of endogenous sex hormones (such as estrogen, progesterone, and androgen) through several mechanisms. Firstly, estrogen synthesis takes place in adipose tissue in males and postmenopausal females. Adipocytes produce sex hormone metabolizing enzymes such as aromatase that are involved in the formation of estrogen from its precursor. Secondly, (obesity associated) insulin and IGF-1 activity reduce the production of sex hormone binding globulin (SHBG) from the liver. SHBG is the main protein that binds to sex hormones such as testosterone and estradiol and carries it in the plasma. With reduced levels of SHBG, the level of bioavailable sex hormones increases.

In relation to CRC risk, the use of exogenous hormones in postmenopausal females has been shown to lower the level of insulin and subsequently lower CRC risk (69). However, testosterone has an opposite effect. A study found that a low level of testosterone was associated with high CRC risk (68). This association may be mediated by the insulin pathway as a study found that androgen deprivation treatment is related to increased adiposity and decreased insulin sensitivity (70).

### 1.6.3. Adipocyte-derived hormones

Adipokines are hormones produced by adipocytes, and some examples include adiponectin, leptin, interleukin-6 and TNF-α. Adiponectin is mainly produced by mature adipocytes commonly found in visceral adipose tissue. Unlike other adipokines, adiponectin has an inverse association with obesity and is linked to insulin sensitivity and has an anti-inflammatory role and thus is involved in anti-tumorigenic activity. Adiponectin levels have shown to be higher in females and this may explain why the association between BMI and CRC risk is different for the sexes (62). Leptin is produced by adipocytes and is a hormone associated with bioactivities such as mitosis, antiapoptosis and angiogenesis and thus contributes to tumorigenesis. An increased level of leptin has been associated with increased BMI and CRC risk (71).
Studies have demonstrated that adipokine is linked with CRC risk \((65-68)\). A 2014 study by Aleksandrova et al. examined several biomarkers that may explain the link between adiposity and colon cancer risk. Of the eleven biomarkers studied, two biomarkers that explained the association between adiposity and colon cancer risk the most were non-high-molecular-weight (non-HMW) adiponectin and soluble leptin receptor (sOB-R) \((72)\). sOB-R is a biomarker of the impaired activity of leptin, and this study demonstrated that it has an inverse association with colon cancer risk. Adiponectin is present in the plasma in different forms, including the HMW and the non-HMW form. This study found that non-HMW adiponectin was inversely associated with colon cancer risk.

1.6.4. Low-grade inflammation
In obesity, macrophage recruitment is increased in adipose tissue. This marks a proinflammatory state, and there is an increased influx of proinflammatory cytokines in adipose tissue. This can then lead to chronic inflammation which disrupts normal metabolic functions such as insulin resistance. HDL-C is a regulator of cellular apoptosis and proliferation, and a low level signals the presence of chronic inflammation and insulin resistance. Aleksandrova et al. found that low level of HDL-C was associated with increased colon cancer risk \((72)\).

1.7. The New South Wales Cancer, Lifestyle & Evaluation of Risk study
This study used data from the NSW Cancer, Lifestyle & Evaluation of Risk (CLEAR) Study, which is funded by Cancer Council NSW. An overview of the CLEAR study is provided in this section, and details relevant to this current study are presented in the Methods chapter.

Study population
The CLEAR Study is a case-control study that began in 2006. All participants were NSW residents aged 18 years or older at the time of recruitment. Cases were recruited if they had been diagnosed with their first incident cancer (no history of cancer except non-melanocytic skin cancer) within 18 months before enrolment. Surviving spouses of cases who were free of cancer (except non-melanocytic skin cancer) were recruited as controls.

The CLEAR Study has recruited 10,816 participants and data for 8529 participants is complete and ready for analysis (3,015 male cases, 3,611 female cases, 881 male controls and 1022 female controls). The median age of all cases and controls is 61.6 years and 61.3 years respectively. The five cancer types with the largest number of cases are female breast \((n=1691)\), prostate \((n=1102)\), CRC \((n=888)\), melanoma \((n=608)\), and lung \((n=265)\) \((73)\).

1.7.1. Recruitment
A ‘targeted’ and ‘non targeted’ approach was adopted for recruiting cases into the CLEAR Study. In the CLEAR Study, 75% of the cases were recruited through the
‘targeted’ approach. This approach involved identifying potential cases that had been diagnosed with any incident cancer within the last 18 months. The following databases were used to identify potential cases: Sydney South East Clinical Cancer Registry, Sydney South West Clinical Cancer Registry, Melanoma Institute of Australia and Hospitals Contribution Fund. The remaining participants were recruited through the ‘non-targeted’ approach, which involved recruitment through community events and personal invitations by medical practitioners at select oncology clinic rooms. Potential cases were given a study pack that contained invitations for the potential case and their cancer-free spouse to participate in the study, an information sheet on the CLEAR Study, consent forms, and questionnaires. The average response rate for all cases recruited through the ‘targeted’ approach is 25.4% while the response rate for controls is ‘estimated at 48.6%’ (73).

1.7.2. Data collection

After participants had provided consent, all were asked to complete a self-administrated paper-based or online (since 2010) questionnaire. Once the participant's consent and completed questionnaire were received, an initial check for eligibility was conducted, and eligible participants were encouraged to provide a blood sample.

Many of the questions in the CLEAR questionnaire originated from well-known studies and were modified to be suitable for a retrospective case-control, NSW study. In the CLEAR Study, the association between exposures of interest and cancer were investigated by comparing cases to sex-matched controls.

All cases (recruited through the ‘targeted’ and ‘non targeted’ approach) and controls were asked in the CLEAR questionnaire if they had been diagnosed with any incident cancer within the last 18 months or if they were cancer free. Participants who reported having been diagnosed recently were also asked to report the cancer type. Data linkage to a population-based cancer registry, the NSW Central Cancer Registry, was used to verify this information. As of yet, only 20% of the CLEAR participants have had the self-reported information verified as there are delays in the processing of cancer registrations at the cancer registry. All of the self-reported cases in the CLEAR study will be eventually verified. It was confirmed that 96% of the verified cases had correctly reported having cancer within the previous 18 months. For 9 of the 10 most common cancers in the CLEAR Study, over 94% of the verified cases had correctly reported their cancer type (73).

1.7.3. Strengths and Limitations

In the paper by Sitas et al., the strengths and limitations of this study are discussed in greater detail; however, they will be briefly summarized here (73).

Cases and controls, who are spouses of cases, come from the same study base therefore if the controls were to be diagnosed with cancer they would have been recruited as a case into this study. This study design is unique and can be adapted where there is no population registration because the CLEAR Study has used cases through which to recruit controls. The CLEAR Study is resourceful because researchers can investigate participant's medical history because of the data linkage
that the study has with NSW Central Cancer Registry and will have with Medicare. As previously mentioned, participants are given the opportunity to provide a blood sample. The CLEAR Study is unique because it is the first large biobank-based cohort studies in Australia and is a valuable bioresource that allows future studies on the etiology of cancer.

This study is limited by the seemingly low, case response rate. However, this is not surprising as cases were recruited by a once only mail invitation. There is an underrepresentation of the non-English speaking and indigenous population, and individuals diagnosed with cancer types that are rare or have poor survival. As controls were recruited through their partners (cases) there was concern about whether there was evidence for spousal concordance on obesity. Sitas et al. reports that there was some suggestion of spousal concordance of BMI. The sensitivity analysis published by Sitas et al. excluded controls that were partners of CRC cases in the CLEAR Study and the odds of developing CRC with increasing BMI did not change when these controls were excluded. This suggests that any effect of spousal concordance of BMI is small and if it is present, its effect on the estimate of CRC risk would have biased the estimate towards the null (73). Therefore, it was considered appropriate to include all controls whose spouses were CRC cases in this study. There are methodological challenges as this study has a case-control design. However, the CLEAR team have worked to overcome these challenges, and some of these methods will be discussed in Section 4.5.

1.8. Study aims

This thesis aims to examine the influence on colorectal cancer risk of anthropometric measures (height and body mass index) and changes in adiposity (regional weight gain and the time course of obesity and weight gain) in 856 cases and 1876 controls in the CLEAR study. The aims of this thesis were to examine if:

1. Height increases the risk of developing colorectal cancer
2. Body Mass Index increases the risk of developing colorectal cancer
3. General weight gain and regional weight gain in the waist or apple region increases the risk of developing colorectal cancer
4. The time course of obesity and weight gain influences colorectal cancer risk (i.e. longer duration of exposure to obesity or weight gain increases the risk of developing colorectal cancer)
2. METHODS

The data used in this current study comes from the CLEAR Study. An overview of the CLEAR Study is provided in Section 1.7. Information relevant to this current study is presented in this section. The questions and options in the CLEAR study that were used to collect data necessary for this current study are found in Section 5.2.

2.1. Definition of cases and controls

As described in Section 1.7.1., the majority of cases in the CLEAR Study (75%) were identified as recently diagnosed cancer patients through health-related databases and consequently recruited. These participants were classified as cases in the CLEAR study if they reported in the CLEAR questionnaire that they have been diagnosed with cancer in the preceding 18 months. For this study, only those who reported having been diagnosed with CRC were included as cases. Cancer-free spouses of cases were recruited as potential controls, and these participants were classified as controls in this study if they reported in the CLEAR questionnaire that they were cancer-free.

2.2. Selection of study factors

2.2.1. Height

Participant’s self-reported current height was used to predict their CRC risk. We excluded participants with height less than 55 cm or greater than 270 cm as these were considered biologically implausible values. Height was treated as a continuous and a categorical variable. Separate sex-specific tertiles were created for males (less than 173 cm (reference), 173 cm to <179 cm and 179 cm or more) and females (less than 160 cm (reference), 160 cm to <166 cm and 166 cm or more).

2.2.2. Body Mass Index

Participants’ BMI was used to predict CRC risk. Participants reported their weight at age 20 and weight just before their (or their partner’s) cancer diagnosis in kilograms or in stones and pounds (which was converted to kilograms by the CLEAR Study team). Participants reported their current height (as discussed in section 2.2.1.). Participant's weight and height were used to derive BMI (kg/m²) at age 20 (BMI\_{20}) and just before diagnosis (BMI\(_{dx}\)).

We excluded participants with weight less than 30 kg or greater than 240 kg and a BMI less than 10 kg/m² or greater than 70 kg/m², as these were considered biologically implausible values.
In this analysis, we treated BMI as a continuous and a categorical variable. For the latter, the World Health Organization’s classification were used, where BMI<18.5 kg/m\(^2\) was defined as underweight, 18.5 kg/m\(^2\) ≤BMI<25 kg/m\(^2\) was defined as normal (reference), 25 kg/m\(^2\) ≤BMI<30 kg/m\(^2\) was defined as overweight, and BMI≥30 kg/m\(^2\) was defined as obese. For some of the analysis, the overweight and obese categories were combined to create the overweight/obese category. Due to the small sample size in the underweight category (eight males and thirty-seven females underweight just before diagnosis), this category was subsequently combined with the normal BMI category for the main analyses.

2.2.3. Time course of obesity

The purpose of this study factor was to examine how long participants had been affected by obesity during their adulthood and its influence on CRC risk. Responses to BMI at age 20 and just before diagnosis were further combined to derive the following groups as proxy measures for the time course of obesity in adulthood (BMI\(_{\text{adult}}\)).

Categories for BMI\(_{\text{adult}}\) were based on participants who reported:
- Having a normal BMI at age 20 and just before diagnosis (reference)
- Being overweight/obese at age 20 and having a normal BMI just before diagnosis
- Having a normal BMI at age 20 and being overweight/obese just before diagnosis
- Being overweight/obese at age 20 and just before diagnosis
- Did not respond or provided a missing/invalid response

2.2.4. Proxies of obesity and the time course of weight gain

Proxies of obesity and the time course of weight gain were created based on participants’ responses to the following questions on weight gain, “In your 20’s and 30’s, if you gained weight, where did you mostly put it on?” and “After age 50, if you gained weight, where did you mostly tend to put it on?”. The purpose of these study factors, the proxies of obesity and the time course of weight gain, was to examine the participants' experience of weight gain during early (during the 20’s and 30’s) and late (after the age of 50) adulthood and its influence on CRC risk.

The following three sections outline how the three proxies of obesity (weight gain, weight gain in the waist and weight gain in the apple region) were created (Sections 2.2.4.1. - 2.2.4.3.).
2.2.4.1. Weight gain
We derived three categories for weight gain (WG) which were based on participants who reported:

- No weight gain (reference)
- Weight gain in any region(s) of their body
- Did not respond or provided a missing/invalid response

We created $\text{WG}_{20}$ and $\text{WG}_{50}$ using participants’ reported experience of weight gain in their 20’s and 30’s and after the age of 50, respectively.

2.2.4.2. Weight gain in the waist
We created four categories for regional weight gain in the waist (WGW) which were based on participants who reported:

- No weight gain (reference)
- Weight gain in region(s) of their body including the waist or abdomen
- Weight gain in region(s) of their body other than the waist or abdomen
- Did not respond or provided a missing/invalid response

We created $\text{WGW}_{20}$ and $\text{WGW}_{50}$ using participants’ reported experience of regional weight gain in their 20’s and 30’s and after the age of 50, respectively.

2.2.4.3. Weight gain in the apple region
Regional weight gain was also categorized according to the American Cancer Society Cancer Prevention Study which defined those carrying the most weight in the waist and/or their upper body as apple shaped (74).

We created four categories for weight gain in the apple region (WGA) which were based on participants who reported:

- No weight gain (reference)
- Weight gain in the apple region (i.e. weight gain in the neck, arms, chest, waist and or abdomen exclusively)
- Weight gain in the non-apple region (i.e. weight gain in any region(s) of their body but not in the neck, arms, chest, waist and or abdomen exclusively)
- Did not respond or provided a missing/invalid response

$\text{WGA}_{20}$ and $\text{WGA}_{50}$ were created using participants’ reported experience of regional weight gain in their 20’s and 30’s and after the age of 50, respectively.
2.2.4.4. Time course of weight gain

Responses to weight gain during participants' 20’s and 30’s (WG\textsubscript{20}) and after the age of 50 (WG\textsubscript{50}) were combined to derive the following groups as proxy measures for the time course of weight gain (WG\textsubscript{adult}).

Categories for WG\textsubscript{adult} were based on participants who reported:

- No weight gain during their 20’s and 30’s and after the age of 50 (reference)
- Weight gain in any region(s) of their body during their 20’s and 30’s and no weight gain after the age of 50.
- No weight gain during their 20’s and 30’s and weight gain in any region(s) of their body after the age of 50.
- Weight gain in any region(s) of their body during their 20’s and 30’s and after the age of 50.
- Did not respond or provided a missing/invalid response

2.3. Covariates

Various sociodemographic, behavioral and lifestyle covariates were examined. All of these covariates were treated as categorical variables.

2.3.1. Sociodemographic covariates

The sociodemographic covariates examined were age at diagnosis, ARIA plus, education and household income.

\textit{Age}

Age at the time of the participant's (or their partner's) diagnosis was divided into quartiles (18-49, 50-59, 60-69 and 70 or more). All participants were 18 years old and above.

\textit{ARIA plus}

As mentioned earlier, ARIA plus has five levels of remoteness: Major City of Australia, Inner Regional Australia, Outer Regional Australia, Remote Australia, and Very Remote Australia. The sample sizes of the latter three categories were small and so they were combined.

\textit{Education}

Information on education was based on each participant’s highest qualification and was divided into six groups (no school certificate or other qualifications, school or intermediate certificate, Higher School or leaving certificate, trade/apprenticeship, certificate/diploma, university degree or higher).
Household income
Information on household income was based on each participant’s usual yearly household income before tax, just before their (or their partner's) illness. In the CLEAR Study, this information is provided as eight levels of yearly household income (Less than $10,000, $10,000 to $24,999, $25,000 to $49,999, $50,000 to $74,999, $75,000 to $99,999, $100,000 to $125,000, More than $125,000 and Prefer not to answer). However, due to small sample sizes, the first two categories were combined. Similarly, the two categories ‘$100,000 to $125,000 per year’ and ‘More than $125,000 per year’ were combined.

Country of birth
Country of birth comprised two categories (Born in Australia and Not born in Australia).

Family history of colorectal cancer
Family history of CRC comprised two categories (Participant’s father and or mother have ever been diagnosed with CRC and Participant’s father and mother have never been diagnosed with CRC).

2.3.2. Behavioral and lifestyle covariates
The behavioral and lifestyle covariates examined were alcohol consumption, smoking status and physical activity.

Alcohol consumption
Weekly alcohol consumption just before the participant (or participant’s partner) became ill was divided into three categories (did not consume alcoholic drinks, consumed one to seven alcoholic drinks per week and consumed eight or more alcoholic drinks per week). The median number of alcoholic drinks consumed amongst participants who consumed alcoholic drinks was used as the cut-off value when creating the groups for analysis.

Smoking status
Smoking status comprised three categories (never, former smoker and current smoker). Participants in the former smoker category reported having been a regular smoker and ceased smoking more than five years prior to cancer diagnosis. Participants in the current smoker category included those who reported as still a regular smoker or having been a regular smoker and ceased smoking within five years of cancer diagnosis. This was based on the study by Stein and co-worker (75).

Physical activity
Categories for physical activity were developed as previously described in the 45 and Up Study (76). The intensity of the workout was considered when calculating the total number of physical activity sessions the participants engaged in, during a normal week. Vigorous exercise was given twice the weight of less vigorous exercise. Physical activity comprised three categories (0 to less than three, three to less than eight, and eight or more sessions per week).
Colorectal cancer screening history

CRC screening history comprised two categories (Have ever screened for CRC and Never screened for CRC).

2.4. Statistical analysis

All analyses were performed using SAS statistical software version 9.3. A p-value $\leq 0.05$ was considered statistically significant. A correlation coefficient of 0.6 was used as the cut-off value for moderate correlation. Descriptive statistics were presented for sociodemographic, behavioral and lifestyle characteristics of CRC cases and cancer-free controls. We used unconditional logistic regression to calculate ORs and the 95% CI for CRC risk for each of the sociodemographic, behavioral and lifestyle characteristics, separately for males and females.

The following covariates were selected a priori: age at diagnosis, ARIA plus, household income, education, country of birth, family history of CRC, alcohol consumption, smoking status, physical activity and CRC screening history. All the exposure variables and covariates were treated as categorical variables. Unlike the other covariates, the country of birth, family history of CRC and CRC screening history were not included in the final model, because they did not improve the model’s ability to predict CRC risk as the parameter estimate did not change by 10% or more.

We used unconditional logistic regression to calculate the ORs and the 95% CI for CRC for each of the exposures, BMI, the proxies of obesity (WG, WGW, and WGA) and the time course of obesity and weight gain, separately for males and females, controlling for the covariates as described above. For the exposure, BMI at age 20, we controlled for BMI just before diagnosis in addition to the covariates described above. A sensitivity analysis was carried out, where those who were underweight were excluded. We examined the correlation between categorical variables using polychoric correlation.

Missing data for the covariates and some of the exposure variables (height, $\text{BMI}_{20}$ and $\text{BMI}_{dx}$) were excluded from the analysis while missing data for the proxies of obesity were placed in a separate category for analysis.
3. RESULTS

3.1. Description of the study population

3.1.1. Characteristics of the study population

Table 1 shows the crude odds ratios (ORs) for CRC risk in relation to the covariates, separately for males and females. There were 2,728 participants in this study (483 male CRC cases, 373 female CRC cases, 907 male controls and 965 female controls). In both sexes, CRC risk appeared to be directly related to age, and be inversely related to ARIA plus, education and household income. CRC risk was directly related to smoking status in both males and females, and it was inversely related to alcohol consumption and physical activity in females, but not related in males.

3.1.2. Missing data

Those with missing information at baseline for ARIA plus (n=16), education (n=54), household income (n=78), alcohol consumption (n=35), smoking status (n=59) or physical activity (n=17) were excluded. Participants with an extreme or missing BMI at age 20 (male: n=141; female: n=150) or just before diagnosis (male: n=80; female: n=118) were excluded. Subjects with missing responses for WG_{50} (male: n=42; female: n=37) or WG_{50} (male: n=290; female: n=248) were placed in separate categories.

Male cases with a missing response for WG_{50} correlated with being normal or overweight just before diagnosis (p=0.03, data shown in Section 5.3.3.). Male controls with a missing response for WG_{50} correlated with being overweight or obese at the age of 20 (p=0.007, data shown in Section 5.3.3.). Female cases with a missing response for WG_{50} correlated with being obese at the age of 20 (p=0.04, data shown in Section 5.3.3.). Female controls with a missing response for WG_{50} correlated with having a normal BMI just before diagnosis (p=0.0003, data shown in Section 5.3.3.).
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Male Cases, n</th>
<th>Male Controls, n</th>
<th>Crude OR (95%CI)</th>
<th>Female Cases, n</th>
<th>Female Controls, n</th>
<th>Crude OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age (years)</strong></td>
<td></td>
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<td>18 to 49</td>
<td>64, 56-71</td>
<td>59, 51-67</td>
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<td>63, 53-71</td>
<td>61, 53-67</td>
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<td>50 to 59</td>
<td>114, 23.6</td>
<td>257, 28.3</td>
<td>1.75 (1.20-2.55)</td>
<td>83, 22.3</td>
<td>258, 26.7</td>
<td>0.82 (0.56-1.19)</td>
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<td>60 to 69</td>
<td>179, 37.1</td>
<td>282, 31.1</td>
<td>2.50 (1.75-3.59)</td>
<td>114, 30.6</td>
<td>387, 40.1</td>
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<td>70 and older</td>
<td>139, 28.8</td>
<td>167, 18.4</td>
<td>3.28 (2.24-4.80)</td>
<td>111, 29.8</td>
<td>155, 16.1</td>
<td>1.82 (1.25-2.65)</td>
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<td>Major Cities of Australia</td>
<td>307, 63.6</td>
<td>517, 57.0</td>
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<td>240, 64.3</td>
<td>528, 54.7</td>
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<td>92, 24.7</td>
<td>268, 27.8</td>
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<td>Rural Australia*</td>
<td>52, 10.8</td>
<td>110, 12.1</td>
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<td>41, 11.0</td>
<td>169, 17.5</td>
<td>0.53 (0.37-0.78)</td>
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<td><strong>Education categories</strong></td>
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<tr>
<td>No school certificate or other qualifications</td>
<td>57, 11.8</td>
<td>71, 7.8</td>
<td>1.00</td>
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<td>77, 8.0</td>
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<td>School or intermediate certificate</td>
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<td>273, 28.3</td>
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<td>42, 4.4</td>
<td>0.83 (0.43-1.60)</td>
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<td>Certificate/diploma</td>
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<td>182, 20.1</td>
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<td>University degree or higher</td>
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<td>324, 35.7</td>
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<td>Less than $25,000</td>
<td>121, 25.1</td>
<td>115, 12.7</td>
<td>1.00</td>
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<td>1.00</td>
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<td>$25,000 to $49,999</td>
<td>99, 20.5</td>
<td>180, 19.8</td>
<td>0.52 (0.37-0.75)</td>
<td>69, 18.5</td>
<td>208, 21.6</td>
<td>0.57 (0.39-0.81)</td>
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<td>$50,000 to $74,999</td>
<td>66, 13.7</td>
<td>135, 14.9</td>
<td>0.47 (0.32-0.69)</td>
<td>47, 12.6</td>
<td>140, 14.5</td>
<td>0.57 (0.38-0.86)</td>
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<td>$75,000 to $100,000</td>
<td>48, 9.9</td>
<td>115, 12.7</td>
<td>0.40 (0.26-0.61)</td>
<td>32, 8.6</td>
<td>108, 11.2</td>
<td>0.51 (0.32-0.80)</td>
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<td>More than $100,000</td>
<td>94, 19.5</td>
<td>269, 29.7</td>
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<td>54, 14.5</td>
<td>183, 19.0</td>
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<td>93, 10.3</td>
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<td>142, 14.7</td>
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<td>Characteristics</td>
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<td>Female</td>
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<td>Crude OR (95%CI)</td>
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<tr>
<td></td>
<td>Cases, n %</td>
<td>Controls, n %</td>
<td>Crude OR (95%CI)</td>
<td>Cases, n %</td>
<td>Controls, n %</td>
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<td>Alcohol consumption categories (drinks per week)</td>
<td>N=483 100.0</td>
<td>104 21.5 182 20.1 1.00</td>
<td>N=373 100.0</td>
<td>165 44.2 352 36.5 1.00</td>
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<tr>
<td>0</td>
<td>104 21.5 182 20.1 1.00</td>
<td>N=907 100.0</td>
<td>0.79 (0.58-1.08)</td>
<td>119 31.9 378 39.2 0.67 (0.51-0.89)</td>
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<tr>
<td>1 to 7</td>
<td>143 29.6 317 35.0 0.79 (0.58-1.08)</td>
<td>N=965 100.0</td>
<td>0.79 (0.58-1.08)</td>
<td>119 31.9 378 39.2 0.67 (0.51-0.89)</td>
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<td></td>
</tr>
<tr>
<td>8 or more</td>
<td>236 48.9 408 45.0 1.01 (0.76-1.35)</td>
<td>N=965 100.0</td>
<td>0.79 (0.58-1.08)</td>
<td>119 31.9 378 39.2 0.67 (0.51-0.89)</td>
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<tr>
<td>p-value</td>
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<td>0.1</td>
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<tr>
<td>Smoking status categories</td>
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<td>1.00</td>
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<td>Never</td>
<td>204 42.2 494 54.5 1.00</td>
<td>N=965 100.0</td>
<td>0.79 (0.58-1.08)</td>
<td>119 31.9 378 39.2 0.67 (0.51-0.89)</td>
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<tr>
<td>Former</td>
<td>194 40.2 303 33.4 1.55 (1.22-1.98)</td>
<td>N=965 100.0</td>
<td>0.79 (0.58-1.08)</td>
<td>119 31.9 378 39.2 0.67 (0.51-0.89)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>85 17.6 110 12.1 1.87 (1.35-2.60)</td>
<td>N=965 100.0</td>
<td>0.79 (0.58-1.08)</td>
<td>119 31.9 378 39.2 0.67 (0.51-0.89)</td>
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<td>p-value</td>
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<td>&lt;0.0001</td>
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<td>0.0004</td>
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<tr>
<td>Physical activity categories (sessions per week)</td>
<td>0 to &lt;3 109 22.6 188 20.7 1.00</td>
<td>N=965 100.0</td>
<td>0.79 (0.58-1.08)</td>
<td>119 31.9 378 39.2 0.67 (0.51-0.89)</td>
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<td></td>
</tr>
<tr>
<td>3 to &lt;8</td>
<td>181 37.5 370 40.8 0.84 (0.63-1.13)</td>
<td>N=965 100.0</td>
<td>0.79 (0.58-1.08)</td>
<td>119 31.9 378 39.2 0.67 (0.51-0.89)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 or more</td>
<td>193 40.0 349 38.5 0.95 (0.71-1.28)</td>
<td>N=965 100.0</td>
<td>0.79 (0.58-1.08)</td>
<td>119 31.9 378 39.2 0.67 (0.51-0.89)</td>
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<tr>
<td>p-value</td>
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</tbody>
</table>

*a includes participants classified in Outer Regional Australia, Remote Australia, and Very Remote Australia*

*In this percentage column and the other percentage columns that follow, the interquartile ranges for age are provided*

All p-values test for equal proportions in each category of the covariate
3.2. Study factors and Colorectal Cancer

Table 2 shows the adjusted odds ratios for CRC risk in relation to the study factors, separately for males and females.

CRC risk appeared not to be related to height in males and females.

In males, CRC risk was directly related to BMI just before diagnosis but was not related to BMI at age 20. In males, CRC risk was also directly related to BMI at age 20 when BMI just before diagnosis was not adjusted for (data not shown). When BMI just before diagnosis was accounted for, CRC risk was not related to BMI at age 20 in males. In females, CRC risk was not related to BMI at age 20 and just before diagnosis. CRC risk did not change when participants classified as underweight were excluded from the analysis (data not shown).

In males, CRC risk appeared to be increased for those who had a normal BMI at age 20 and were overweight just before diagnosis compared to those who had a normal BMI at both time points. CRC risk appeared to be even greater for those who were overweight at both time points. In females, CRC risk appeared not to be related to the time course of obesity.

In both sexes, CRC risk was not related to the proxies of obesity (WG, WGW, and WGA) during participant’s 20’s and 30’s and after the age of 50. In addition, CRC risk was not related to the time course of weight gain.
Table 2 Odds ratios (ORs) for CRC risk in relation to the study factors, separately for males and females

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Male</th>
<th></th>
<th></th>
<th>Female</th>
<th></th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Cases, n</td>
<td>%*</td>
<td>Controls, n</td>
<td>%</td>
<td>Adjusted ORa</td>
<td>(95% CI)</td>
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<tr>
<td><strong>Median height (cm)</strong></td>
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<td><strong>Height categories</strong></td>
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<tr>
<td>Tertile 1 (shortest)</td>
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<td>172-180</td>
<td>178</td>
<td>172-182</td>
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<tr>
<td>Tertile 2</td>
<td>131</td>
<td>27.1</td>
<td>229</td>
<td>25.2</td>
<td>1.14 (0.86-1.50)</td>
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<tr>
<td>Tertile 3 (tallest)</td>
<td>100</td>
<td>20.7</td>
<td>239</td>
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<td>1.00 (0.72-1.41)</td>
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<tr>
<td><strong>BMI at age 20 categories (kg/m²)</strong></td>
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<tr>
<td>10 to &lt;25 (normal)</td>
<td>329</td>
<td>68.1</td>
<td>663</td>
<td>73.1</td>
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<tr>
<td>25 to 70 (overweight/obese)</td>
<td>154</td>
<td>31.9</td>
<td>244</td>
<td>26.9</td>
<td>1.06 (0.79-1.42)</td>
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<tr>
<td>25 to &lt;30 (overweight)</td>
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<td>26.3</td>
<td>207</td>
<td>22.8</td>
<td>1.05 (0.78-1.42)</td>
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<tr>
<td>30 to 70 (obese)</td>
<td>27</td>
<td>5.6</td>
<td>37</td>
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<td><strong>Median BMI just before diagnosis (kg/m²)</strong></td>
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<tr>
<td><strong>BMI just before diagnosis categories (kg/m²)</strong></td>
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</tr>
<tr>
<td>10 to &lt;25 (normal)</td>
<td>116</td>
<td>24.0</td>
<td>282</td>
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<tr>
<td>25 to 70 (overweight/obese)</td>
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<td>76.0</td>
<td>625</td>
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<td>1.48 (1.13-1.93)</td>
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<td>25 to &lt;30 (overweight)</td>
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<td>44.9</td>
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<td>30 to 70 (obese)</td>
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<td>195</td>
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<td>2.01 (1.44-2.80)</td>
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<td><strong>Time course of obesity</strong></td>
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<td>BMI at 20</td>
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<td>BMI just before diagnosis</td>
<td>Normal</td>
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<td>1.7</td>
<td>11</td>
<td>1.2</td>
<td>1.27 (0.47-3.42)</td>
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<td>Normal</td>
<td>Overweight</td>
<td>221</td>
<td>45.8</td>
<td>392</td>
<td>43.2</td>
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<td>Overweight</td>
<td>Overweight</td>
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<td>25.7</td>
<td>1.69 (1.22-2.34)</td>
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Table 2 (continued)

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<th>Female</th>
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<tbody>
<tr>
<td></td>
<td>Cases, n</td>
<td>%</td>
</tr>
<tr>
<td>Weight gain during 20's and 30's</td>
<td>N=483</td>
<td>100.0</td>
</tr>
<tr>
<td>No weight gain</td>
<td>89</td>
<td>18.4</td>
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<tr>
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p-value: 0.2
Table 2 (continued)

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* In this percentage column and the other percentage columns that follow, the interquartile ranges for each value of height and BMI (at age 20 and just before diagnosis) are provided.

a adjusted for Age, ARIA plus, Household income, Education, Smoking status, Alcohol consumption and Physical activity (BMI just before diagnosis was further adjusted for BMI at age 20)
b When height was treated as a continuous variable, height was unrelated to CRC risk (OR:1.00, 95% CI:0.98-1.01 for males and OR:1.00, 95% CI:0.98-1.02 for females)
c When BMI at age 20 was treated as a continuous variable, BMI at age 20 was unrelated to CRC risk (OR:1.00, 95% CI:0.96-1.04 for males and OR:0.99, 95% CI:0.95-1.03 for females)
d The overweight and obese categories were combined to create one category (overweight/obese)
e P-value tests for equal proportions in the overweight/obese and the normal (reference) categories
f When BMI just before diagnosis was treated as a continuous variable, BMI just before diagnosis was directly related to CRC risk in males but not in females (OR:1.05, 95% CI:1.03-1.08 for males and OR:1.01, 95% CI:0.99-1.03 for females)

Height tertiles were sex-specific: males (Less than 173 cm, 173 cm to <181 cm, 181 cm or more) and females (Less than <160 cm, 160 cm to <168 cm, 168 cm or more)
P-values test for equal proportions in each category of a covariate
4. DISCUSSION

This study found that, in males but not in females, being overweight or obese just before diagnosis was directly related to CRC risk and being overweight or obese at the age of 20 and just before diagnosis was directly related to an even greater CRC risk. However, the proxies of obesity (WG, WGW, and WGA) did not predict participant’s CRC risk. In males, WGW was not a discriminative anthropometric measure during their 20’s and 30’s or after the age of 50 because most males (cases and controls) gained weight in the waist rather than elsewhere.

4.1. Height and colorectal cancer

A 2007 publication by WCRF concluded that there is convincing evidence that adult attained height is associated with increased risk of CRC and the CLEAR Study was used to validate this statement. In this study, CRC risk appeared to be unrelated to adult attained height. Many cohort and nested case-control studies found that height was directly related to an increased CRC risk of between 6% to 38% (77-83). However, like our study, other cohort and co-twin control studies found that height appeared unrelated to CRC risk (84-87). Studies have suggested that the association between height and CRC risk may be different for specific sites of the colon and rectum. A cohort study by Shin et al. found that height was associated with rectal cancer and distal colon cancer but not with proximal colon cancer (88). However, a cohort study by Pischon et al. found that height was associated with colon cancer risk but not with rectal cancer risk (52). These inconsistencies suggest that the association between height and CRC risk and in particular the site-specific associations need further investigation and may explain our null findings.

4.2. Body Mass Index and colorectal cancer

WCRF stated that there is convincing evidence that greater body fatness is a cause of CRC and the CLEAR Study was again used to validate this statement. In this study, BMI just before diagnosis appeared to be directly related to CRC risk in males but not in females. Similarly, other cohort studies found that the association between BMI and CRC risk was only observed in males (89, 90) and the Million Women Study found that CRC risk was not related to BMI in females (91). Also, meta-analyses have found that the associations between BMI and CRC risk or colon cancer risk was stronger in males compared to females or was only seen in males (43, 48, 92). However, the cohort study by Odegaard et al. found that CRC risk was directly related to BMI in both males and females (93). An explanation for the disagreement between our finding and the findings of Odegaard et al. may be that they did not use the World Health Organization’s BMI categories because all of their participants were from Japan and they wanted to examine CRC risk for the underweight category. Also, two cohort studies (by Poynter et al. and Kabat et al.) found that BMI was associated with CRC risk in females (94, 95). All participants in these two studies were postmenopausal women, and this may explain the lack of an association.
between CRC risk and BMI seen in our female participants (some of whom were not postmenopausal).

In this study, BMI at age 20 appeared not to be related to CRC risk. Similarly, the cohort studies by Han et al. and Li et al. (considered in Section 5.1.2.) did not find an association between BMI during early adulthood and CRC risk (89, 96). However, the remaining studies in Section 5.1.2. found an association. An explanation for this disagreement may be that most of the studies did not explore the association between BMI during early adulthood and CRC risk, independent of BMI during late adulthood, by adjusting for the latter BMI. Of all the studies in Section 5.1.2., only two cohort studies (by Zhang et al. and Han et al.) explored the independent risk of BMI during early adulthood (96, 97). In this study, 43.8% of the participants had a normal BMI at age 20 and were overweight or obese just before diagnosis. Therefore, as described in the methods chapter, it seemed appropriate to adjust for BMI just before diagnosis when determining the association between BMI at age 20 and CRC risk. This is because some of the participants in the reference category, those with a normal BMI at age 20, may have become overweight or obese just before diagnosis and have become exposed to obesity later in their adulthood.

4.3. The time course of obesity and colorectal cancer

In males but not females, having a normal BMI at age 20 and being overweight or obese just before diagnosis was linked to a 39% increased CRC risk, compared to participants who had a normal BMI at both time points. The CRC risk increased further (69%) for males who were overweight or obese at both time points.

Although studies have investigated the cumulative effect of weight gain on cancer risk, studies on the cumulative effect of being overweight during life and cancer risk are scarce. A 2016 cohort study by Arnold et al. was the first study to investigate the effect of overweight duration and cancer risk in an older population (98). Like our study, this study found that indeed longer overweight duration was significantly associated with increased CRC risk and this risk was higher for males compared to females. A 2011 case-control study by Lu et al. used a similar approach to investigate the cumulative effect of obesity as our study (99). Long-term obesity was defined as being overweight during participant’s 20’s and 30’s and being overweight thereafter. In females, they found long-term obesity was associated with greater risk of endometrial cancer compared to females who had a normal BMI throughout adulthood.

4.4. Proxies of obesity and colorectal cancer

Although we hypothesized that the experience of weight gain, weight gain in the waist and weight gain in the apple region would be positively associated with CRC risk, this study demonstrated that they did not predict CRC in either sex.

Most of our participants experienced weight gain during their 20’s and 30’s and after the age of 50. This is noteworthy for two reasons. Firstly, several studies also found
that most of their participants experienced weight gain or found that their BMI increased from early adulthood (99-101). Secondly, this finding may explain the high prevalence of obesity in Australian adults (as discussed in Section 1.3.1).

A cohort study by Renehan et al. found that weight gain from the age of 18 years to 35 years was associated with colon and rectal cancer risk in males and the association was stronger compared to females (102). Similarly, in our study, in males but not in females, weight gain during their 20’s and 30’s was associated with an increased CRC risk compared to those who did not experience weight gain, although the relevant confidence interval crossed one and so the significance of the result is not clear. This finding may be important because a large proportion of males experienced weight gain during their 20’s and 30’s. Together our findings and the findings of Renehan et al. suggest that weight gain during early adulthood should be avoided as it is positively associated with CRC risk.

Finally, in males but not in females, weight gain in the waist during their 20’s and 30’s had an increased (but not statistically significant) CRC risk compared to those who did not experience weight gain. Like the finding discussed above, this result is potentially important because a large proportion of males experienced weight gain in the waist during their 20’s and 30’s. Similar to our finding, a cohort study by Song et al. found that males who experienced an increase of ten centimeters or more in their waist circumference had a 59% increased CRC risk compared to males who maintained their waist circumference during a nine-year period. This association was maintained even after adjusting for weight change. When these findings are considered together, it suggests that the redistribution of fat centrally during adulthood may be linked with increased risk of CRC in males only (103).

4.5. Strengths and limitations of the study

This study had a large sample size where measures of obesity were collected at various time points. The measures included BMI, the commonly used measure of adiposity, and more novel approaches to the measurement of weight gain like the time course of obesity and weight gain, and three proxy measures of obesity. The advantage of these proxies of obesity over other measures is that they require no specific measurements. Many studies have investigated the association between weight change and cancer risk, where weight or BMI change are used to measure the cumulative effect of obesity. A 2015 meta-analysis by Karahalios et al., using data from 14 studies published between 1997 to 2014, found that a 5 kilogram weight gain was associated with a 3% increased risk of developing CRC (46). However, to our knowledge, this study is one of the first to combine BMI in early and late adulthood to create a single measure of the cumulative effect of obesity throughout adulthood and investigate its association with CRC risk.

Data used in this current study comes from the CLEAR Study, and there are several advantages of using the CLEAR Study. Firstly, it is an NSW population study, therefore, the conclusions from this study will be relevant locally. Secondly, it is important to use Australian data to answer questions relevant to Australian needs, such as the high prevalence of CRC and obesity, and their association. Finally, being
an in-house dataset meant that this large epidemiology bioresource was easily accessible.

The analysis adjusted for many behavioral and lifestyle factors that have been shown to be associated with CRC, such as smoking, alcohol and physical activity (104). However, other risk factors, such as participants' history of hormone replacement therapy use, were not included (104, 105). Studies have shown that the use of postmenopausal hormone therapy is linked with lowering CRC risk in females (106). Although information on participants' hormone replacement therapy use was collected in the CLEAR Study, appropriately analyzing this information is complex and was considered beyond the scope of this study. The relationship between CRC risk and height or the proxies of obesity were the same for males and females, suggesting (although not guaranteeing) that hormone replacement therapy use may not have altered some of the findings for females. Of course, this information on postmenopausal hormone therapy is not relevant to the analyses for males.

Information on participants’ dietary intake was collected in the CLEAR study and consumption of red meat, and low fruit and vegetable consumption has been shown to be linked with increased CRC risk (see Section 1.1.3.9.). However, this information was also not accounted for as literature suggests that self-reported dietary intake is affected by information bias. Hebert describes that information collected after a diagnosis of a disease of interest in a case-control study can be biased if cases are asked to recall diet-related information from their past, or it may be biased as their diet may have been modified since their diagnosis (107). The association between height or obesity and CRC risk may have altered if dietary intake was accounted for in this study.

There are inherent limitations in using a case-control design, such as selection bias, recall bias, and reverse causation. Although no groups were excluded from recruitment, the participants in the CLEAR Study were found to under-represent some groups, such as people of non-English speaking background, and Aboriginal and Torres Strait Islander people. This may limit the generalizability of the result, and if this study is expanded, targeted recruitment of those underrepresented may be beneficial (73). As mentioned in Section 1.7.1., the CLEAR study used a ‘targeted’ and a ‘non-targeted’ approach to recruit cases. Using two approaches to recruit cases would not have affected the association between height or obesity and CRC risk as height or obesity would not be associated with the recruitment method. It is possible that the ‘targeted’ and the ‘non-targeted’ approaches may have recruited cases with different socioeconomic characteristics. But, as this study adjusted for socioeconomic factors, like education and income, the two different recruitment approaches should not have affected the conclusions of this study. Due to the retrospective nature of this study design, questions shown to be robust in cohort and case-control designs and that require modest recall were included in the CLEAR questionnaire (73). Park et al. found that male and female participants over-reported their height and under-reported weight, waist circumference and hip circumference. This bias affected participants with a higher BMI to a greater extent. Although these anthropometric measures are all affected by recall bias, Park et al. found that BMI may be less affected as weight and height were more accurately reported compared to waist circumference and hip circumference (44). It is possible that BMI just before diagnosis may have been affected by reverse causality as cases may have
experienced weight loss secondary to their CRC diagnosis. If this was the case, the estimate of the effect of obesity on CRC risk would have biased towards the null. The proportion of subjects with missing or invalid information on weight gain after the age of 50 was high (Table 2). So, some of the participants did not report their weight gain experience after the age of 50, which for most requires recollection of a recent experience. The reason for this is unclear, but it may be that as weight gain is a common experience (as discussed in Section 4.4.), participants with missing or invalid information may not have been able to clearly remember the timing of their weight gain (i.e. whether it was just before or after the age of 50).

Male cases who had a missing or invalid response to weight gain after the age of 50 had a lower BMI just before diagnosis, and male controls had a higher BMI at the age of 20, compared to those who responded (Table 9). Since these subjects could not be included in the analysis, this could have resulted in selection bias, as cases and controls were affected differently, and the effect would have been to bias the findings on the association between the proxies of obesity and CRC risk upwards. Female cases who had a missing or invalid response to weight gain after the age of 50 had a higher BMI at the age of 20, and female controls had a lower BMI just before diagnosis, compared to respondents (Table 10). This also could have resulted in selection bias and biased the findings downwards.

There was insufficient sample size to investigate the association between the anthropometric measures and CRC risk for the different anatomical sub-sites of CRC. Studies suggest that the association between height and CRC risk may be different for the subsites (52, 88). Similarly, several studies have shown that BMI was associated with colon cancer risk but could not predict rectal cancer (51, 52, 93, 102, 108). Therefore, this suggests that the association found in this study between BMI and CRC may be attenuated by the inclusion of rectal cancer, since rectal cancer does not appear to be related to BMI.

4.6. Recommendation for future action

In our study, we found using BMI measured at one point in time to determine an individual's CRC risk may provide a limited understanding of the relationship between adiposity and CRC risk. When using BMI at one point in time, male participants who were overweight or obese just before diagnosis had an increased CRC risk (48%) compared to male participants with a normal BMI. However, these participants could have been overweight or obese at the age of 20 as well, and their CRC risk would have been greater (69% increased CRC risk). This finding suggests that monitoring BMI over time provides a better assessment of CRC risk related to adiposity than is obtained when using BMI measured at one point in time.

The sample size for the group of males who were overweight or obese at age 20 and had normal BMI just before diagnosis was very small (1.7% of male cases and 1.2% of males controls). This finding suggests that it is unlikely for male participants who were overweight or obese at age 20 to experience weight loss and have a normal BMI just before diagnosis. However, our findings suggest that prolonged weight gain results in additional CRC risk over and above that arising from being overweight at a single time point. Therefore, male participants who are overweight or obese at age
20 should be strongly advised to maintain a healthy weight throughout adulthood to avoid the associated high risk of developing CRC. Taghizadeh et al. found that chronic obesity was positively linked with cancer mortality in females. The findings from Taghizadeh et al. study and our study serves as a reminder that avoiding chronic obesity may result in lowering CRC risk and cancer mortality (109), in addition to other health gains that may result.

4.7. Synthesis/summary

This study demonstrated that BMI just before diagnosis is a CRC risk predictor in males only. Health professionals should particularly encourage males to maintain a healthy weight, and for those who are overweight or obese at age 20 to monitor their weight throughout adulthood, and lose weight if they can, as early and persistent exposure to obesity places males at considerable risk of developing CRC. The proxies of obesity did not predict CRC risk in this study. In the clinical and research setting, BMI should still be used in relation to CRC risk, despite its flaws, as it appears to be a better CRC predictor than the available proxies of obesity.
5. APPENDIX

5.1. Summary of relevant individual studies

5.1.1. Adult height and colorectal cancer incidence

The individual studies that explored the association between adult height and the risk of developing colon cancer, rectal cancer or CRC were reviewed and summarized in this section.

Pubmed was used to search for studies on the link between height and CRC risk. Search for literature was conducted in 2014 and updated in 2016. It included the following search string: (colon or rectal or colorectal) and cancer and (risk or incidence) and (height or stature). Through Pubmed, 367 papers were found, and 27 papers met the inclusion criteria. The search strategy is detailed in Figure 9. These papers were published between 1988 and 2014.

Table 3 summarizes 15 of the most recent studies on the association between height and CRC incidence. These papers were published between 2005 and 2014 and examined the association in various countries within Europe, North America, and Asia. The sample size of databases that these papers used to examine the association between height and CRC incidence varied from 20,000 to two million.

Figure 9 Flowchart of the search strategy for studies on the association between height and colorectal cancer risk
Table 3 Summary of the individual studies that explored the association between height and colorectal cancer incidence

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<thead>
<tr>
<th>Author, Year</th>
<th>Journal</th>
<th>Country</th>
<th>Database</th>
<th>Study type</th>
<th>Study period (recruitment to follow-up)</th>
<th>Sample size (after exclusions)</th>
<th>Colorectal cancer cases</th>
<th>Exposure/Outcome</th>
<th>Relative risk (95% CI)</th>
<th>Confounders adjusted for</th>
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<td>Wiren et al., 2014 (81)</td>
<td>Cancer Causes and Control</td>
<td>Austria, Norway, Sweden</td>
<td>Metabolic Syndrome and Cancer Project</td>
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<td>1974-2006</td>
<td>585,928</td>
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<td>Cancer Causes and Control</td>
<td>USA</td>
<td>National Institute of Health-AARP Diet and Health Study</td>
<td>Prospective cohort</td>
<td>1995-2006</td>
<td>481,197</td>
<td>6,189</td>
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<td>Colon cancer</td>
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<td>Boursi et al., 2014 (82)</td>
<td>European Journal of Gastroenterology &amp; Hepatology</td>
<td>UK</td>
<td>The Health Improvement Network</td>
<td>Nested case-control</td>
<td>1995-2013</td>
<td>36,825</td>
<td>9,978</td>
<td>Height (per 10cm increase)</td>
<td>Colorectal cancer</td>
<td>1.10 (1.05-1.15)</td>
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<tr>
<td>Kabat et al., 2013 (77)</td>
<td>International Journal of Cancer</td>
<td>Canada</td>
<td>Canadian National Breast Screening Study</td>
<td>Prospective cohort</td>
<td>1980-2000</td>
<td>88,256</td>
<td>1,096</td>
<td>Height (per 10cm increase)</td>
<td>Colon cancer</td>
<td>1.12 (1.01-1.23)</td>
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Table 3 (continued)

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<tr>
<th>Author, Year</th>
<th>Journal</th>
<th>Country</th>
<th>Database</th>
<th>Study type</th>
<th>Study period (recruitment to follow-up)</th>
<th>Sample size (after exclusions)</th>
<th>Colorectal cancer cases</th>
<th>Exposure/Outcome</th>
<th>Relative risk (95% CI)</th>
<th>Confounders adjusted for</th>
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<td>Kabat et al., 2013 (78)</td>
<td>Cancer Epidemiology, Biomarkers &amp; Prevention</td>
<td>USA</td>
<td>Women's Health Initiative</td>
<td>Prospective cohort</td>
<td>1993-2005</td>
<td>144,701</td>
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<td>Park et al., 2012 (44)</td>
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<td>European Prospective Investigation Into Cancer and Nutrition-Norfolk study</td>
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<td>1.42 (1.04-1.93)</td>
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<td>Sweden</td>
<td>Malmo Diet and Cancer Study</td>
<td>Prospective cohort</td>
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<td>28,098</td>
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<td>Age at baseline, smoking habits, alcohol</td>
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<td>1.03 (0.59-1.80)</td>
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<td>Shin et al., 2011 (88)</td>
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<td>Korea</td>
<td>Korean National Health System</td>
<td>Prospective cohort</td>
<td>1996-2003</td>
<td>1,265,226</td>
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<td></td>
<td>distal colon cancer</td>
<td>1.30 (1.10-1.60)</td>
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<td></td>
<td>rectal cancer</td>
<td>1.10 (1.00-1.30)</td>
<td></td>
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<tr>
<td>Author, Year</td>
<td>Journal</td>
<td>Country</td>
<td>Database</td>
<td>Study type</td>
<td>Study period (recruitment to follow-up)</td>
<td>Sample size (after exclusions)</td>
<td>Colorectal cancer cases</td>
<td>Exposure/Outcome</td>
<td>Relative risk (95% CI)</td>
<td>Confounders adjusted for</td>
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<tr>
<td>Green et al., 2011 (79)</td>
<td>Lancet</td>
<td>UK</td>
<td>Million Women Study</td>
<td>Prospective cohort</td>
<td>1996-2008</td>
<td>1,297,124</td>
<td>9,471</td>
<td>Height (10cm increase)</td>
<td>Males 1.25 (1.17-1.32) Females 1.14 (1.05-1.24)</td>
<td>age, region, SES, smoking, alcohol intake, BMI, strenuous exercise, age at menarche, parity, age at first birth</td>
</tr>
<tr>
<td>Oxentenko et al., 2010 (80)</td>
<td>Cancer Prevention Research</td>
<td>USA</td>
<td>Iowa Women's Health Study</td>
<td>Prospective cohort</td>
<td>1986-2005</td>
<td>36,941</td>
<td>1,464</td>
<td>Height (largest quartile vs. smallest quartile) colorectal cancer</td>
<td>Males 1.38 (1.17-1.64)</td>
<td>age at baseline, age at menopause, exogenous estrogen use, oral contraceptive use, smoking status, cigarette pack-years, physical activity level, self-reported diabetes mellitus, and intake of total energy, total fat, red meat, fruits and vegetables, calcium, folate, vitamin E, and alcohol.</td>
</tr>
<tr>
<td>Lundqvist et al., 2007 (84)</td>
<td>International Journal of Cancer</td>
<td>Sweden, Finland</td>
<td>Prospective co-twin control</td>
<td>1961-2004</td>
<td>68,375</td>
<td>837</td>
<td>Males and females combined</td>
<td>Height (per 1 standard deviation increase) colon cancer</td>
<td>Males 1.00 (0.82-1.22) Females 1.04 (0.81-1.34)</td>
<td>smoking, physical activity during leisure time, educational level, diabetes</td>
</tr>
<tr>
<td>Pischon et al., 2006 (52)</td>
<td>Journal of the National Cancer Institute</td>
<td>Europe</td>
<td>European Prospective Investigation Into Cancer and Nutrition</td>
<td>Prospective cohort</td>
<td>1992-2004</td>
<td>368,277</td>
<td>1,570</td>
<td>Height (largest quartile vs. smallest quartile) colorectal cancer</td>
<td>Males 1.40 (0.99-1.98) Females 1.79 (1.30-2.46)</td>
<td>center, age at recruitment, smoking status, education, alcohol intake, physical activity, fiber intake, consumption of red and processed meat, fish and shellfish, fruits and vegetables</td>
</tr>
</tbody>
</table>
Table 3 (continued)

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Journal</th>
<th>Country</th>
<th>Database</th>
<th>Study type</th>
<th>Study period (recruitment to follow-up)</th>
<th>Sample size (after exclusions)</th>
<th>Number of colorectal cancer cases</th>
<th>Exposure/Outcome</th>
<th>Relative risk (95% CI)</th>
<th>Confounders adjusted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bowers et al., 2006 (85)</td>
<td>American Journal of Epidemiology</td>
<td>Finland</td>
<td>Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study</td>
<td>Prospective cohort</td>
<td>1985-2002</td>
<td>29,133</td>
<td>410</td>
<td>Height (largest quintile vs. smallest quintile) colorectal cancer</td>
<td>0.90 (0.64-1.27)</td>
<td>age, number of cigarettes smoked per day, weight</td>
</tr>
<tr>
<td>Otani et al., 2005 (86)</td>
<td>Cancer Causes and Control</td>
<td>Japan</td>
<td>Japan Public Health Centre-based Prospective Study</td>
<td>Prospective cohort</td>
<td>1990-2001</td>
<td>102,949</td>
<td>986</td>
<td>Height (largest quintile vs. smallest quintile) colorectal cancer</td>
<td>1.10 (0.80-1.50)</td>
<td>age, Public Health Center areas, smoking, alcohol consumption, weight</td>
</tr>
<tr>
<td>Engeland et al., 2005 (83)</td>
<td>Cancer Causes and Control</td>
<td>Norway</td>
<td>Prospective cohort</td>
<td>Prospective cohort</td>
<td>1963-2002</td>
<td>2,001,698</td>
<td>47,117</td>
<td>Height (per 10cm increase) colorectal cancer</td>
<td>1.14 (1.11-1.16)</td>
<td>age at measurement, year of birth, BMI</td>
</tr>
</tbody>
</table>
5.1.2. Body Mass Index and colorectal cancer incidence

The individual studies that explored the association between BMI and the risk of developing colon cancer, rectal cancer or CRC were reviewed and summarized in this section.

Pubmed was used to search for studies on the link between BMI and CRC risk. Search for literature was conducted in 2014 and updated in 2016. It included the following search string: body and mass and index and (colon or rectal or colorectal) and cancer and (risk or incidence). Through Pubmed, 1710 papers were found, and 56 papers met the inclusion criteria. The search strategy is detailed in Figure 10. These papers were published between 1985 and 2016.

Table 4 summarizes 14 of the most recent studies on the association between BMI and CRC incidence. These papers were published between 2011 and 2016 and examined the association in various countries within Europe, Eastern Mediterranean, North America and Asia. The sample size of the databases that these papers used to examine the association between BMI and CRC incidence varied from 11,000 to five million.

**Figure 10** Flowchart of the search strategy for studies on the association between Body Mass Index and colorectal cancer risk
Table 4 Summary of the individual studies that explored the association between Body Mass Index and colorectal cancer incidence

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Journal</th>
<th>Country</th>
<th>Database</th>
<th>Study type</th>
<th>Study period (recruitment to follow-up)</th>
<th>Sample size (after exclusions)</th>
<th>Colorectal cancer cases</th>
<th>Exposure/Outcome</th>
<th>Relative risk (95% CI)</th>
<th>Confounders adjusted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kantor et al., 2016 (111)</td>
<td>British Medical Journal</td>
<td>Sweden</td>
<td></td>
<td>Prospective cohort</td>
<td>1969-2010</td>
<td>239,658</td>
<td>885</td>
<td>BMI at age 16-20 (obese vs. normal)</td>
<td>colorectal cancer 2.38 (1.51-3.76)</td>
<td>age at conscription, erythrocyte sedimentation rate, erythrocyte volume fraction, BMI, household crowding, health status, systolic blood pressure, diastolic blood pressure, muscular strength, physical working capacity, cognitive function</td>
</tr>
<tr>
<td>Zhang et al., 2015 (97)</td>
<td>Cancer, Epidemiology, Biomarkers &amp; Prevention</td>
<td>USA</td>
<td>Nurses' Health Study and Health Professionals Follow-up Study</td>
<td>Prospective cohort</td>
<td>1976-2010</td>
<td>109,771</td>
<td>2,100</td>
<td>BMI at age 21 for males and 18 for females (largest sextile vs. smallest sextile)</td>
<td>colorectal cancer 1.18 (0.84-1.65) 1.44 (1.06-1.95)</td>
<td>age, adult BMI, height, pack-years of smoking before age 30, history of CRC in a parent or sibling, history of sigmoidoscopy/endoscopy, current physical activity, regular aspirin use, multivitamin use, alcohol consumption, current energy-adjusted total intake of calcium, vitamin D, folate, red meat, processed meat, and postmenopausal hormone use (females only)</td>
</tr>
<tr>
<td>Kabat et al., 2015 (95)</td>
<td>Cancer Causes and Control</td>
<td>USA</td>
<td>Women's Health Initiative</td>
<td>Prospective cohort</td>
<td>1993-2013</td>
<td>143,901</td>
<td>1,908</td>
<td>BMI at age (baseline) 50-79 (largest quintile vs. smallest quintile) colorectal cancer</td>
<td>1.44 (1.23-1.68)</td>
<td>age, alcohol, smoking, hormone therapy, MET-hours/week, aspirin intake, diabetes, family history of CRC in a first-degree relative, education, ethnicity, treatment allocation</td>
</tr>
<tr>
<td>Han et al., 2014 (96)</td>
<td>International Journal of Cancer</td>
<td>USA</td>
<td>Atherosclerosis Risk in Communities</td>
<td>Prospective cohort</td>
<td>1987-2009</td>
<td>13,901</td>
<td>198</td>
<td>BMI at age 25 (obese vs. normal) colorectal cancer</td>
<td>1.54 (0.84-2.81) 0.91 (0.37-2.25)</td>
<td>race, center, age and height at baseline, education, cigarette smoking status at age 25, and age at menarche, cigarette smoking, alcohol consumption and physical activity at baseline, menopause status</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Journal</td>
<td>Country</td>
<td>Database</td>
<td>Study type</td>
<td>Study period (recruitment to follow-up)</td>
<td>Sample size (after exclusions)</td>
<td>Colorectal cancer cases</td>
<td>Exposure/ Outcome</td>
<td>Relative risk (95% CI)</td>
<td>Confounders adjusted for</td>
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<tr>
<td>Bhaskaran et al., 2014 (112)</td>
<td>Lancet</td>
<td>UK</td>
<td>Clinical Practice Research Datalink</td>
<td>Prospective cohort</td>
<td>1987-2012</td>
<td>5,243,978</td>
<td>19,588</td>
<td>BMI at (baseline) median age 37.9 (per 5 kg/m²) colon cancer rectal cancer</td>
<td>Males and females combined</td>
<td>1.10 (1.07-1.13) 1.04 (1.00-1.08)</td>
</tr>
<tr>
<td></td>
<td>Cancer, Epidemiology, Biomarkers &amp; Prevention</td>
<td>USA</td>
<td>Iowa Women's Health Study</td>
<td>Prospective cohort</td>
<td>1986-2008</td>
<td>37,459</td>
<td>1,626</td>
<td>BMI at age (baseline) 55-71 (obese vs. normal) colon cancer BMI at age (baseline) 55-71 (obese vs. normal) colon cancer</td>
<td>Younger age band</td>
<td>1.44 (1.16-1.78)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>China</td>
<td>Shanghai Men's Health Study and Shanghai Women's Health Study</td>
<td>Prospective cohort</td>
<td>1997-2009</td>
<td>134,255</td>
<td>935</td>
<td>BMI at age 20 (highest quintile vs. lowest quintile) colorectal cancer colon cancer rectal cancer BMI at age 40 for males and 50 for females (highest quintile vs. lowest quintile) colorectal cancer colon cancer rectal cancer</td>
<td>Older age band</td>
<td>1.38 (1.13-1.69)</td>
</tr>
<tr>
<td>Li et al., 2013 (89)</td>
<td>International Journal of Obesity (London)</td>
<td>China</td>
<td>Shanghai Men's Health Study and Shanghai Women's Health Study</td>
<td>Prospective cohort</td>
<td>1997-2009</td>
<td>134,255</td>
<td>935</td>
<td>BMI at age 20 (highest quintile vs. lowest quintile) colorectal cancer colon cancer rectal cancer BMI at age 40 for males and 50 for females (highest quintile vs. lowest quintile) colorectal cancer colon cancer rectal cancer</td>
<td>Age at baseline, education, income, cigarette use, alcohol consumption, physical activity, family history of CRC, menopausal status and intakes of total energy, red meat, fruits and vegetables</td>
<td>1.61 (1.12-2.31) 2.01 (1.24-3.24) 1.18 (0.67-2.07) 1.19 (0.87-1.63) 1.80 (0.80-1.74) 1.20 (0.72-2.03)</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Journal</td>
<td>Country</td>
<td>Database</td>
<td>Study type</td>
<td>Study period (recruitment to follow-up)</td>
<td>Sample size (after exclusions)</td>
<td>Colorectal cancer cases</td>
<td>Exposure/Outcome</td>
<td>Relative risk (95% CI)</td>
<td>Confounders adjusted for</td>
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<tr>
<td>Kitahara et al., 2013 (90)</td>
<td>Journal of Clinical Oncology</td>
<td>USA</td>
<td>Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial</td>
<td>Prospective cohort</td>
<td>1993-2009</td>
<td>74,474</td>
<td>966</td>
<td>BMI at age (baseline) 50-74 (obese vs. normal) colorectal cancer</td>
<td>1.48 (1.16-1.89) 1.03 (0.80-1.33)</td>
<td>age at baseline, study center; screening adequacy and results before colorectal cancer diagnosis, race/ethnicity, smoking status, and menopausal hormone therapy use</td>
</tr>
<tr>
<td>Kabat et al., 2013 (113)</td>
<td>Cancer Causes and Control</td>
<td>USA</td>
<td>Women's Health Initiative</td>
<td>Prospective cohort</td>
<td>1993-2011</td>
<td>11,124</td>
<td>169</td>
<td>BMI at age (baseline) 50-79 (highest quartile vs. lowest quartile) colorectal cancer</td>
<td>1.07 (0.66-1.75)</td>
<td>age at enrollment, education, ethnicity, family history of CRC, hormone therapy, physical activity, pack-years of smoking, alcohol intake, history of diabetes, intake of energy, randomization status</td>
</tr>
<tr>
<td>Renehan et al., 2012 (102)</td>
<td>American Journal of Epidemiology</td>
<td>USA</td>
<td>National Institutes of Health-AARP Diet and Health Study</td>
<td>Prospective cohort</td>
<td>1995-2006</td>
<td>273,679</td>
<td>4076</td>
<td>BMI at age 18 (per 5 kg/m²) colon cancer rectal cancer BMI at age 50 (per 5 kg/m²) colon cancer rectal cancer</td>
<td>1.10 (1.00-1.20) 1.01 (0.86-1.18) 1.11 (0.96-1.29) 0.89 (0.66-1.21) 1.18 (1.10-1.26) 1.07 (0.96-1.19) 1.13 (1.05-1.23) 1.00 (0.85-1.16)</td>
<td>age, race/ethnicity, educational, physical activity, smoking status, alcohol consumption, menopausal hormone therapy use (females only)</td>
</tr>
<tr>
<td>Park et al., 2012 (44)</td>
<td>International Journal of Obesity</td>
<td>UK</td>
<td>European Prospective Investigation Into Cancer and Nutrition-Norfolk study</td>
<td>Prospective cohort</td>
<td>1993-2006</td>
<td>20,608</td>
<td>357</td>
<td>Measured BMI at age (baseline) 39-79 (per 4 kg/m²) colorectal cancer</td>
<td>0.86 (0.60-1.24) 0.84 (0.58-1.19)</td>
<td>age, sex, smoking, alcohol, education, exercise, family history of CRC, energy intake, folate, fiber, total meat and processed meat, intakes, waist and hip circumference</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Journal</td>
<td>Country</td>
<td>Database</td>
<td>Study type</td>
<td>Study period (recruitment to follow-up)</td>
<td>Sample size (after exclusions)</td>
<td>Colorectal cancer cases</td>
<td>Exposure/Outcome</td>
<td>Relative risk, RR (95% CI)</td>
<td>Confounders adjusted for</td>
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<tr>
<td>Matsuo et al., 2011 (108)</td>
<td>Annals of Oncology</td>
<td>Japan</td>
<td>Japan Public Health Centre-based Prospective Study I and II, Japan Collaborative Cohort Study, Miyagi Cohort Study, Three-Prefecture Cohort Study in Miyagi, Takayama Study, Ohsaki Cohort Study</td>
<td>Population-based cohort</td>
<td>1958-2006</td>
<td>341,384</td>
<td>4,979</td>
<td>BMI at age (baseline) 35-103 (per 1 kg/m²)</td>
<td></td>
<td>Males</td>
</tr>
<tr>
<td>Odegaard et al., 2011 (93)</td>
<td>Cancer, Singapore</td>
<td>The Singapore Chinese Health Study</td>
<td>Prospective cohort</td>
<td>1993-2007</td>
<td>51,251</td>
<td>980</td>
<td>BMI at age (baseline) 45-74 (≥27.5 kg/m² vs 21.5-24.4 kg/m²)</td>
<td></td>
<td>Males and females combined</td>
<td>1.25 (1.01-1.55)</td>
</tr>
<tr>
<td>Levi et al., 2011 (114)</td>
<td>Cancer, Epidemiology, Biomarkers &amp; Prevention</td>
<td>Israel</td>
<td>Prospective cohort</td>
<td>1967-2006</td>
<td>1,109,864</td>
<td>638</td>
<td>BMI at age (baseline) 16-19 (highest quintile vs. lowest quintile)</td>
<td></td>
<td></td>
<td>colon cancer</td>
</tr>
</tbody>
</table>

* Younger age band include female participants who were diagnosed with colorectal cancer, died or were lost to follow-up before the age of 75 years. Otherwise, participants were placed in the older age band.
5.2. Questions and options in the CLEAR Study

The data used in this current study comes from the CLEAR Study. An overview of the CLEAR Study is given in Section 1.7. Information relevant to this current study is given in Section 2. The specific details of the questions and options, as found in the CLEAR Study, that were used in this current study are described in this Section.

5.2.1. Definition of cases and controls

Participants in the CLEAR Study were asked to select one of two responses:

(A) *I have been diagnosed with cancer in the last 18 months.*

(B) *I have never been diagnosed with cancer.*

5.2.2. Height

Height was based on the following CLEAR Study question:

*How tall are you without shoes? (please give to the nearest cm or inch).*

5.2.3. Body Mass Index

Participants were asked to recall weight from two points in time in the following CLEAR Study questions:

(C) *About how much did you weigh before you, or your partner, became ill?*

(D) *About how much did you weigh when you were 20 years old?*

5.2.4. Proxies of obesity

Information used to create the proxies of obesity was based on responses to the following CLEAR Study questions:

(E) *In your 20’s and 30’s, if you gained weight, where did you mostly put it on?*

(F) *After age 50, if you gained weight, where did you mostly tend to put it on?*

Participants could select one or more of the following options, which were provided for each question:

1. Neck
2. Arms
3. Chest
4. Waist/Abdomen
5. Hips
6. Thighs
7. Buttocks
8. You didn’t gain weight
9. Other, please specify

Participants who chose Other, please specify could specify a region of the body in a comment section.

5.2.5. Education

Education was based on the following CLEAR Study question:

What is the highest qualification you have completed?

Participants could choose one of the six options listed below. Each option defined a category for the covariate, Education.

1. No school certificate or other qualifications
2. School or intermediate certificate (Yr 10 or equivalent)
3. Higher School or leaving certificate (Yr 12 or equivalent)
4. Trade/Apprenticeship (e.g. hairdresser, chef)
5. Certificate/Diploma (e.g. child care, technician)
6. University degree or higher

5.2.6. Household income

Household income was based on the following CLEAR Study question:

Just before you, or your partner, became ill, what was your usual yearly HOUSEHOLD income before tax, from all sources? (please include benefits, pensions, superannuation etc)

Participants could choose one of the eight options listed below.

1. Less than $10,000 per year
2. $10,000-$25,000 per year
3. $25,000-$50,000 per year
4. $50,000-$75,000 per year
5. $75,000-$100,000 per year
6. $100,000-$125,000 per year
7. More than $125,000 per year
8. I would prefer not to answer question 81
5.2.7. Alcohol consumption

Alcohol consumption in the CLEAR Study was based on the answers to the following question:

Just before you, or your partner, became ill, about how many alcoholic drinks did you have each week? (one drink = a glass of wine, middy of beer or nip of spirits)

5.2.8. Smoking status

Smoking status in the CLEAR Study was based on the answers to the following questions:

(G) Have you ever been a regular smoker?
(H) If yes, how old were you when you started smoking regularly?
(I) Just before you, or your partner, became ill, were you a regular smoker?
(J) If yes, are you still a regular smoker?
(K) If no, how old were you when you stopped smoking regularly?

5.2.9. Physical activity

Participants were asked in the CLEAR Study about the number of sessions of vigorous activity undertaken in a week as follows:

Just before you or your partner, became ill, in a NORMAL week, how many times did you engage in VIGOROUS exercise lasting for 20 minutes or more? (exercise which makes you breathe harder or puff and pant, such as netball, squash, jogging, aerobics, vigorous swimming, etc.)

Participants were asked in the CLEAR Study about the number of sessions of less vigorous activity undertaken in a week as follows:

Just before you, or your partner, became ill, in a NORMAL week, how many times did you engage in LESS VIGOROUS exercise lasting 20 minutes or more? (exercise which does not make you breathe harder or puff and pant such as walking, gardening, swimming, lawnbowls, etc.)

(please cross (X) one only)

For each of the two questions, participants could select one of the following responses:

1. Never
2. Once a week
3. Two or three times a week
4. Four, five or six times a week
5. Once every day
6. More than once every day.
5.3. Approach to develop the Proxies of obesity

5.3.1. Correlation between individual body regions

Tables 5 and 6 show the correlation between the individual body regions where participants gained the most weight, separately for their 20's and 30's and after the age of 50. At both time points, if an individual had gained weight in the arms, they were likely to have also gained weight in the neck, as arms and neck were highly correlated. The following regions were also highly correlated at the two-time points, chest and arms, thighs and hips, buttocks and hips, and buttocks and thighs. At both time points, weight gain in the waist was not correlated with any other regions.

Table 5 During the 20’s and 30’s, the polychoric correlation between the individual body regions where participants gained the most weight

<table>
<thead>
<tr>
<th></th>
<th>Neck</th>
<th>Arms</th>
<th>Chest</th>
<th>Waist</th>
<th>Hips</th>
<th>Thighs</th>
<th>Buttocks</th>
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</thead>
<tbody>
<tr>
<td>Neck</td>
<td>1.00</td>
<td></td>
<td>0.63</td>
<td>0.57</td>
<td>0.42</td>
<td>0.23</td>
<td>0.30</td>
</tr>
<tr>
<td>Arms</td>
<td></td>
<td>1.00</td>
<td></td>
<td>0.74</td>
<td>0.13</td>
<td>0.36</td>
<td>0.52</td>
</tr>
<tr>
<td>Chest</td>
<td>1.00</td>
<td></td>
<td></td>
<td>0.28</td>
<td>0.19</td>
<td>0.28</td>
<td>0.17</td>
</tr>
<tr>
<td>Waist</td>
<td>1.00</td>
<td>1.00</td>
<td>0.007</td>
<td></td>
<td>-0.07</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Hips</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.00</td>
<td>0.81</td>
<td>0.75</td>
</tr>
<tr>
<td>Thighs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.00</td>
<td>0.84</td>
</tr>
<tr>
<td>Buttocks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.00</td>
</tr>
</tbody>
</table>

Table 6 After the age of 50, the polychoric correlation between the individual body regions where participants gained the most weight

<table>
<thead>
<tr>
<th></th>
<th>Neck</th>
<th>Arms</th>
<th>Chest</th>
<th>Waist</th>
<th>Hips</th>
<th>Thighs</th>
<th>Buttocks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck</td>
<td>1.00</td>
<td></td>
<td>0.62</td>
<td>0.55</td>
<td>0.44</td>
<td>0.28</td>
<td>0.28</td>
</tr>
<tr>
<td>Arms</td>
<td></td>
<td>1.00</td>
<td></td>
<td>0.66</td>
<td>0.27</td>
<td>0.57</td>
<td>0.59</td>
</tr>
<tr>
<td>Chest</td>
<td>1.00</td>
<td>1.00</td>
<td>0.40</td>
<td>0.35</td>
<td>0.36</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>Waist</td>
<td>1.00</td>
<td>1.00</td>
<td>0.03</td>
<td>0.02</td>
<td></td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>Hips</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.00</td>
<td>0.86</td>
<td>0.79</td>
</tr>
<tr>
<td>Thighs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.00</td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>Buttocks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.00</td>
</tr>
</tbody>
</table>
5.3.2. Association between Body Mass Index and the Proxies of obesity

Within controls, BMI was compared to the three proxies of obesity, separately for the sexes. The aim of this comparison was to examine whether information on participant’s experience of weight gain, measured by the proxies of obesity, was in line with their experience of obesity, measured by BMI.

BMI was compared to the three proxies of obesity measured for their 20’s and 30’s (Table 7). In both sexes, being overweight or obese at the age of 20 or just before diagnosis corresponded to having experienced weight gain or weight gain in the waist during their 20’s and 30’s. In both sexes, having a normal BMI at the age of 20 or just before diagnosis corresponded to having experienced weight gain in the apple region during their 20’s and 30’s.

Again, BMI was compared to the three proxies of obesity measured for after the age of 50 (Table 8). In both sexes, being overweight or obese just before diagnosis corresponded to having experienced weight gain after the age of 50. Male controls who had a normal BMI or female controls who were overweight or obese just before diagnosis were more likely to have experienced weight gain in the waist after the age of 50. In both sexes, having a normal BMI just before diagnosis corresponded to having experienced weight gain in the apple region after the age of 50. However, in both sexes, BMI at the age of 20 was not associated with having experienced weight gain, weight gain in the waist or the apple region after the age of 50.
Table 7 In controls, Body Mass Index compared to the proxies of obesity measured for the 20’s and 30’s (weight gain, $WG_{20}$; weight gain in the waist, $WGW_{20}$; and weight gain in the apple region, $WGA_{20}$)

<table>
<thead>
<tr>
<th>BMI categories at the age of 20 (kg/m$^2$)</th>
<th>Males</th>
<th></th>
<th>Females</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$WG_{20}$</td>
<td>$WGW_{20}$</td>
<td>$WGA_{20}$</td>
<td>$WG_{20}$</td>
</tr>
<tr>
<td>No, %</td>
<td>Yes, %</td>
<td>No, %</td>
<td>Yes, %</td>
<td>No, %</td>
</tr>
<tr>
<td>N=168</td>
<td>N=713</td>
<td>N=48</td>
<td>N=665</td>
<td>N=160</td>
</tr>
<tr>
<td>10 to &lt;25</td>
<td>85.7</td>
<td>69.7</td>
<td>79.2</td>
<td>69.0</td>
</tr>
<tr>
<td>25 to &lt;30</td>
<td>10.7</td>
<td>26.1</td>
<td>18.8</td>
<td>26.6</td>
</tr>
<tr>
<td>30 to 70</td>
<td>3.6</td>
<td>4.2</td>
<td>2.1</td>
<td>4.4</td>
</tr>
<tr>
<td>p-value</td>
<td>$&lt;0.0001$ $^a$</td>
<td>$0.0003$ $^b$</td>
<td>$0.0006$ $^c$</td>
<td>$0.0003$ $^a$</td>
</tr>
<tr>
<td>BMI just before diagnosis categories (kg/m$^2$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 to &lt;25</td>
<td>54.8</td>
<td>25.0</td>
<td>33.3</td>
<td>24.4</td>
</tr>
<tr>
<td>25 to &lt;30</td>
<td>38.7</td>
<td>49.5</td>
<td>52.1</td>
<td>49.3</td>
</tr>
<tr>
<td>30 to 70</td>
<td>6.5</td>
<td>25.5</td>
<td>14.6</td>
<td>26.3</td>
</tr>
<tr>
<td>p-value</td>
<td>$&lt;0.0001$ $^a$</td>
<td>$&lt;0.0001$ $^b$</td>
<td>$&lt;0.0001$ $^c$</td>
<td>$&lt;0.0001$ $^a$</td>
</tr>
</tbody>
</table>

$^a$ p-value for the association between BMI and WG  
$^b$ p-value for the association between BMI and WGW  
$^c$ p-value for the association between BMI and WGA
Table 8 In controls, Body Mass Index compared to the proxies of obesity measured for after age 50 (weight gain, $WG_{50}$; weight gain in the waist, $WGW_{50}$; and weight gain in the apple region, $WGA_{50}$)

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$WG_{50}$</td>
<td>$WGW_{50}$</td>
</tr>
<tr>
<td></td>
<td>No, %</td>
<td>Yes, %</td>
</tr>
<tr>
<td>$N=80$</td>
<td>N=605</td>
<td>N=9</td>
</tr>
<tr>
<td>BMI categories at the age of 20 (kg/m$^2$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 to &lt;25</td>
<td>76.3</td>
<td>75.5</td>
</tr>
<tr>
<td>25 to &lt;30</td>
<td>18.8</td>
<td>21.3</td>
</tr>
<tr>
<td>30 to 70</td>
<td>5.0</td>
<td>3.1</td>
</tr>
<tr>
<td>p-value</td>
<td>0.6</td>
<td>0.1</td>
</tr>
<tr>
<td>BMI just before diagnosis categories (kg/m$^2$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 to &lt;25</td>
<td>63.8</td>
<td>25.6</td>
</tr>
<tr>
<td>25 to &lt;30</td>
<td>31.3</td>
<td>51.6</td>
</tr>
<tr>
<td>30 to 70</td>
<td>5.0</td>
<td>22.8</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

$^a$ p-value for the association between BMI and WG  
$^b$ p-value for the association between BMI and WGW  
$^c$ p-value for the association between BMI and WGA
5.3.3. Missing data for the Proxies of obesity

Table 9 Body Mass Index distributions of males who with missing/invalid information (i.e. Missing) compared to males with information (i.e. Respondents) on weight gain after the age of 50 ($WG_{50}$).

<table>
<thead>
<tr>
<th>BMI categories at the age of 20 (kg/m$^2$)</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Missing, $n$</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td>N=68</td>
<td>100.0</td>
</tr>
<tr>
<td>10 to &lt;25</td>
<td>45</td>
<td>66.2</td>
</tr>
<tr>
<td>25 to &lt;30</td>
<td>19</td>
<td>27.9</td>
</tr>
<tr>
<td>30 to 70</td>
<td>4</td>
<td>5.9</td>
</tr>
<tr>
<td>p-heterogeneity</td>
<td>0.9</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BMI just before diagnosis categories (kg/m$^2$)</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Missing, $n$</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td>N=68</td>
<td>100.0</td>
</tr>
<tr>
<td>10 to &lt;25</td>
<td>21</td>
<td>30.9</td>
</tr>
<tr>
<td>25 to &lt;30</td>
<td>35</td>
<td>51.5</td>
</tr>
<tr>
<td>30 to 70</td>
<td>12</td>
<td>17.6</td>
</tr>
<tr>
<td>p-heterogeneity</td>
<td>0.03</td>
<td></td>
</tr>
</tbody>
</table>
Table 10 Body Mass Index distributions of females who with missing/invalid information (i.e. Missing) compared to females with information (i.e. Respondents) on weight gain after the age of 50 ($WG_{50}$).

<table>
<thead>
<tr>
<th>BMI categories at the age of 20 (kg/m²)</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Missing, $n$</td>
<td>Respondents, $n$</td>
</tr>
<tr>
<td></td>
<td>N=72</td>
<td>100.0</td>
</tr>
<tr>
<td>10 to &lt;25</td>
<td>61</td>
<td>84.7</td>
</tr>
<tr>
<td>25 to &lt;30</td>
<td>7</td>
<td>9.7</td>
</tr>
<tr>
<td>30 to 70</td>
<td>4</td>
<td>5.6</td>
</tr>
<tr>
<td>p-heterogeneity</td>
<td>0.04</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BMI just before diagnosis categories (kg/m²)</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Missing, $n$</td>
<td>Respondents, $n$</td>
</tr>
<tr>
<td></td>
<td>N=72</td>
<td>100.0</td>
</tr>
<tr>
<td>10 to &lt;25</td>
<td>36</td>
<td>50.0</td>
</tr>
<tr>
<td>25 to &lt;30</td>
<td>23</td>
<td>31.9</td>
</tr>
<tr>
<td>30 to 70</td>
<td>13</td>
<td>18.1</td>
</tr>
<tr>
<td>p-heterogeneity</td>
<td>0.4</td>
<td></td>
</tr>
</tbody>
</table>
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