# Dietary patterns and colorectal cancer risk in the United Kingdom Women's Cohort Study

Petra Jones

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# INTELLECTUAL PROPERTY AND PUBLICATION STATEMENTS

The candidate confirms that the work submitted is her own, except where work which has formed part of jointly-authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.



The studies presented in chapters 4 and 5 are largely based on the jointly authored publications listed below.

**Chapter 4**

**The Mediterranean diet and risk of colorectal cancer in the UK Women's Cohort Study.**

P. Jones, J.E. Cade, C.E.L. Evans, N. Hancock, D.C. Greenwood

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**Chapter 5**

**Does adherence to the WCRF/AICR cancer prevention guidelines reduce risk of colorectal cancer in the UK Women's Cohort Study?**

P. Jones, J.E. Cade, C.E.L. Evans, N. Hancock, D.C. Greenwood

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Petra Jones was jointly responsible for the concept and design of the analysis, along with Janet Cade and Charlotte Evans. She conducted the analysis, interpreted the findings, wrote the first version and was responsible for submitting the manuscript and incorporating comments from co-authors for all other versions. Darren Greenwood provided statistical advice. Janet Cade and Charlotte Evans supervised the research and were involved in the interpretation of findings. All authors contributed to the review of the final manuscript.

**Other publication arising from this research**

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**Conferences where parts of the research in this dissertation were presented**

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# ABSTRACT

***Background:*** Some dietary patterns have been associated with colorectal cancer (CRC) in observational studies but the findings are inconclusive. The aim of this study is to explore associations between two dietary patterns, derived using different dietary assessment methods, and risk of CRC.

***Methods:*** CRC event data for the UK Women's Cohort Study were obtained from NHS Digital. Adherence scores to the Mediterranean dietary pattern and to the 2007 World Cancer Research Fund / American Institute of Cancer Research (WCRF/AICR) cancer prevention recommendations respectively were generated. Cox regression was used to estimate hazard ratios (HRs) for CRC risk, for each score separately, using a cohort approach for food frequency data and a case-cohort design for analyses with food diary data. Agreement between scores derived by the two different assessment methods was assessed by weighted Kappa statistics and the Bland-Altman method.

**Results:** After 17 years, 527 CRC cases were observed. The Mediterranean dietary pattern, assessed using the food frequency questionnaire (FFQ), was associated with a decreased risk of CRC. For a 2-point increment in the Mediterranean diet (MD) score, HR 0.88, 95% CI: 0.78, 0.99; $P_{trend}$ = 0.03. No evidence of an association was observed when data from food diaries was used for deriving the dietary pattern: for a 1-unit increment in the MD score, HR 0.94; 95% CI: 0.83 to 1.06; $P_{trend}$ 0.32. Similarly, no significant associations were observed between higher adherence to the WCRF/AICR guidelines and risk of CRC. For a 1-unit increment in the WCRF/AICR score, HR 0.92, 95% CI: 0.82, 1.03; $P_{trend}$ 0.169 for FFQ data whilst HR 1.01; 95% CI: 0.83, 1.24; $P_{trend}$ 0.87 for food diary data. The Bland-Altman method showed higher energy intake by the FFQ in comparison to the food diary and agreement between the two methods was slight for the MD score (K=0.15; 95% CI: 0.14, 0.16) and fair for the WCRF/AICR score (K=0.38; 95% CI: 0.37, 0.39).

***Conclusion:*** The Mediterranean dietary pattern is inversely associated with CRC risk whilst a higher adherence to the WCRF/AICR cancer prevention guidelines did not significantly decrease CRC risk in this cohort of British women.

# LIST OF ABBREVIATIONS

| | |
|---|---|
| ACS | American Cancer Society |
| aMed | Alternate Mediterranean diet |
| APC | Adenomatous polyposis coli |
| ASR | Age-standardised incidence rates |
| BF | Breastfeeding |
| BMI | Body mass index |
| CAC | Colitis-associated cancer |
| CI | Confidence interval |
| COX-2 | Cyclooxygenase-2 |
| CRC | Colorectal cancer |
| CUP | Continuous Update Project |
| CVD | Cardiovascular disease |
| DANTE | Diet and Nutrition Tool for Evaluation |
| DASH | Dietary Approaches to Stop Hypertension |
| DGAC | Dietary Guidelines Advisory Committee |
| DPMP | Dietary Patterns Methods Project |
| DQI | Diet Quality Index |
| ED | Energy density |
| EPIC | European Prospective Investigation into Cancer and Nutrition |
| FAP | Familial adenomatous polyposis |
| FD | Food diaries |
| FFQ | Food frequency questionnaire |
| FSA | Food Standards Agency |
| F&V | Fruit and vegetables |
| GI | Gastrointestinal |
| HCA | Heterocyclic amines |
| HDI | Human Development Index |
| HEI | Healthy Eating Index |
| HMPS | Hereditary mixed polyposis syndrome |

| | |
|---|---|
| HNPCC | Hereditary non polyposis colorectal cancer |
| HR | Hazard ratios |
| HSCIC | Health and Social Care Information Centre |
| IARC | International Agency for Research on Cancer |
| IBD | Inflammatory Bowel Disease |
| ICD | International Statistical Classification of Diseases |
| IGF-1 | Insulin-Like Growth Factor |
| IQR | Interquartile range |
| Kcal | Kilocalories |
| MD | Mediterranean diet |
| MUFA | Monounsaturated fatty acids |
| NA | Not available / applicable |
| NDNS | National Diet and Nutrition Survey |
| NF-$_K$B | Nuclear factor kappa B |
| NHS | National Health Service |
| NHSCR | National Health Service Central Register |
| NIH-AARP | National Institutes of Health - American Association of Retired Persons |
| NOC | N-nitroso compounds |
| NRES | National Research Ethics Service |
| NSAIDs | Non-steroidal anti-inflammatory drugs |
| PA | Physical activity |
| PAH | Polycyclic Aromatic Hydrocarbons |
| PLCO | Prostate, Lung, Colorectal and Ovarian |
| PLP | Pyridoxal 5-phosphate |
| PM | Processed meat |
| PREDIMED | PREvención con DIeta MEDiterránea |
| PUFA | Polyunsaturated fatty acids |
| RCT | Randomised controlled trials |
| REC | Research Ethics Committee |
| RFS | Recommended Food Score |

| | |
|---|---|
| RPM | Red and processed meat |
| RR | Relative risk |
| SCFA | Short chain fatty acids |
| SFA | Saturated fatty acids |
| SHBG | Sex-hormone binding globulin |
| SLR | Systematic literature review |
| TNFα | Tumour Necrosis Factor-α |
| TNM | Tumour, Node, Metastasis |
| UKWCS | United Kingdom Women's Cohort Study |
| USDA | United States Department of Agriculture |
| VITAL | VITamins And Lifestyle Cohort |
| WC | Waist circumference |
| WCRF/AICR | World Cancer Research Fund / American Institute for Cancer Research |
| WHO | World Health Organisation |

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# CHAPTER 1 INTRODUCTION, AIM & OBJECTIVES

## 1.1 Introduction

Colorectal carcinoma is one of the main cancer sites in the developed world and both environmental and genetic factors are involved in its aetiology (Hamilton, 2000). Initial epidemiological research based on ecological and international correlation studies showed dietary factors were strongly correlated with several types of cancers, specifically dietary fat, meat and animal protein consumption with incident colon and rectal cancer risk and mortality rates (Drasar & Irving, 1973; Armstrong & Doll, 1975). Such analysis is however considered exploratory and thus limited in its usefulness to identify relationships that may require further study.

Diet is considered to be the second biggest modifiable risk factor on cancer outcomes after tobacco in the developed world with diet-related factors thought to account for about 30% and 20% of cancers in developed and developing countries respectively (Key et al., 2002). The geographical variation of colorectal cancer (CRC) incidence is wide and overall conclusions from migrant studies show that subjects moving from low to high CRC incidence areas acquired the incidence of the native population (Haenszel & Kurihara, 1968). Such evidence supports the theory that diet and nutrition may have a role in the aetiology of CRC.

In 1981, in a quantitive estimate of avoidable US cancer, a potential 90% of stomach and large-bowel carcinogenic mortality was attributed to dietary factors (Doll & Peto, 1981). Nevertheless, nutritional epidemiology is challenged by several interactions, namely genetic, epigenetic and environmental risk determinants, by the extended carcinogenic expression and by the heterogeneous aetiology of CRC (Song et al., 2015). More recently, scientists estimated that 45% of bowel cancers in the UK could be prevented through healthy changes in diet, physical activity and weight. This translates into a potential prevention of approximately 19 000 cases per year (WCRF, n.d.).

## 1.2 Rationale for further research

Notwithstanding the wealth of available data on the associations between diet and risk of CRC, research has focussed on specific foods and nutrients and is inconclusive with

bias resulting from dietary assessment, selection and recall bias in cohort and case-control studies contributing towards inconsistencies in findings. Furthermore, given that several dietary components have been associated with risk of CRC, the dietary pattern approach may prove particularly useful in considering the combined effects of the former, providing additional insight.

In 2007, the World Cancer Research Fund / American Institute of Cancer Research (WCRF/AICR) systematically reviewed research on food, nutrition, physical activity in relation to risk of cancer and published a second expert report (WCRF/AICR, 2007). In 2011, as part of the Continuous Update Project (CUP), a report was published with updated evidence for CRC (WCRF/AICR, 2011), and a third report updating the 2011 CUP CRC report was published very recently in September 2017 (WCRF/AICR, 2017). In all three reports, the following scale for classifying the strength of evidence with respect to a particular food / nutrient and other lifestyle factors decreasing or increasing the risk of CRC was used: convincing, probable, limited – suggestive, limited – no conclusion and substantial effect on risk unlikely. Some cohort studies have provided evidence on the association between CRC and some dietary patterns, but the 2017 WCRF/AICR updated report concluded that there was limited evidence and thus no conclusion for an association between dietary patterns and CRC risk (WCRF/AICR, 2017). The Dietary Guidelines Advisory Committee (DGAC, 2015) of the United States Department of Agriculture (USDA), in a systematic review of dietary patterns and CRC concluded that there was moderate evidence for associations between some dietary patterns and CRC. The findings of both reviews will be discussed in chapter 2.

This research will thus focus on the associations between CRC and dietary patterns rather than with individual foods or nutrients. No dietary pattern specifically predicting CRC was found in the literature and thus the WCRF/AICR cancer prevention recommendations and the Mediterranean dietary pattern were chosen for this research. The rationale for using these specific patterns is discussed in chapter 3.

With specific reference to CRC outcome and adherence to a Mediterranean dietary pattern, studies are limited, results unconvincing and may vary depending on the

definition of the diet used to measure the score. This is discussed at length in the next chapter. Few studies have looked at concordance to the cancer prevention recommendations, specifically the WCRF/AICR recommendations in relation to risk of CRC. Further research is thus merited.

## 1.3 Data source

Data from the UK Women's Cohort Study (UKWCS) will be used in all the analyses carried out to reach the objectives of this dissertation. The UKWCS is one of the largest population-based, prospective cohort studies in the UK. Originating though the WCRF, it was established in 1995 primarily to explore associations between diet and chronic disease, particularly cancer. Criteria for participant inclusion in the cohort were made in a way that maximised variation in participants' dietary habits, thus allowing differences in eating patterns to be detected. Large numbers of fish-eaters, meat-eaters and vegetarians were recruited. Dietary assessment was carried out using a 217-item food frequency questionnaire (FFQ) at baseline (35,372 women) and a 4-day food diary (FD) at phase 2 (12, 453 women) (Cade et al., 2015). Chapter 3 gives additional details on the cohort and on the dietary assessment tools used to capture the data used. It describes the general methods, including statistical tests used in the three main results chapters 4, 5 and 6.

The large size of the cohort, the alternative measures of diet and the high analytical power for exploration resulting from the specific study design make this study population ideal for the investigations required for this research. The prospective nature of the cohort allows for minimization of measurement error, partially arising from recall bias and potentially reverse causality which can occur with other epidemiological study designs. Furthermore, several lifestyle factors that may be considered to be confounders have been captured in the questionnaire, allowing for their adjustment in the analyses. In view of the outlined strengths, the UKWCS is used to explore previously unexploited data related to CRC. The women in the cohort are generally health conscious. Recommendations from the findings of this research would thus be primarily pertinent to similar individuals that may be interested in altering their dietary habits and other lifestyle factors to decrease their risk of CRC.

Notwithstanding, the variation in dietary preferences was taken into account in the analyses and probability weighting was used to account for the large proportion of vegetarians and fish eaters in the cohort. In this way, results would be more applicable to the UK general female population. Table 1.1 depicts the relationship between the two available data sources – the baseline FFQ and the phase 2 FD, the number of incident cancer cases resulting from the data respectively, and the objectives of this dissertation, outlined in section 1.4 below.

***Table 1.1 CRC cases by diet assessment method and chapter in the dissertation[1]***

| UKWCS dataset | Number of incident cancer cases | | | | | Dietary Pattern | |
|---|---|---|---|---|---|---|---|
| | Colorectal | Colon | Proximal colon | Distal colon | Rectal | Mediterranean | WCRF/AICR Guidelines |
| Baseline FFQ N=35,372 | 527 | 391 | 203 | 130 | 167 | Chapter 4 | Chapter 5 |
| Phase 2 Questionnaire & FD N=12,253 | 173 | / | | | | Chapter 6 | Chapter 6 |

[1]UKWCS; UK Women's Cohort Study; FFQ food frequency questionnaire; FD food diary

Adherence scores to both the Mediterranean dietary pattern and to the WCRF/AICR guidelines for all women in the UKWCS will be derived using data from both data sources. Agreement between the scores will be explored in Chapter 6. The investigation of associations between the dietary patterns chosen for this research and incidence of CRC is carried out using both baseline and phase 2 data. The relatively large number of CRC cases (n=527) identified at baseline allows for associations between dietary patterns and colon, proximal colon, distal colon and rectal cancer to be explored separately. This is novel in comparison to studies with similar objectives whilst the mean follow-up time for cancer incidence of over 17 years allowed for more cases to be identified. Such studies are reviewed in sections 2.7 and 2.8 of chapter 2. Chapter 4 reports findings for the association between the Mediterranean dietary pattern and incidence of CRC using baseline data, whilst chapter 5 is a second results chapter reporting findings on the association between WCRF/AICR guidelines and incident CRC. In exploring links between dietary patterns and CRC incidence using data from FD, a comparatively smaller number of incident CRC cases (n=173) were identified. Thus, only the association between CRC and the respective dietary patterns

was investigated, since there was insufficient power for the separate analyses of different anatomical sub-sites. Nevertheless, FD coding is a laborious process and the cohort studies that have carried out and published work related to data derived from FD are limited. This chapter thus offers a significant contribution to this area of nutritional epidemiology. A summary discussion is given in Chapter 7.

## 1.4 Aim and objectives

The central aim of this research is:

***'To explore the relationship between dietary pattern exposures and CRC incidence as an outcome using data from the UKWCS'.***

To address the overarching aim, the following objectives are being proposed:

- Perform an advanced literature review of associations between CRC risk and dietary patterns (Chapter 2);
- Construct adherence scores for women in the UKWCS, for the culturally defined Mediterranean dietary pattern and for the WCRF/AICR recommendations for cancer prevention using baseline data obtained via FFQ and data from the follow-up phase 2 FD respectively (Chapters 4, 5 & 6);
- Assess adherence to the Mediterranean dietary pattern for UKWCS participants at baseline in relation to incident CRC risk, including different anatomical sub-sites, and explore any associations with dietary habits by linking records available through National Health Service (NHS) Digital (Chapter 4);
- Assess adherence to the WCRF/AICR recommendations for cancer prevention at baseline in relation to incidence of CRC, exploring incidence at sub-sites separately, for women in the UKWCS (Chapter 5);
- Assess the level of agreement between the Mediterranean diet (MD) scores and the WCRF/AICR scores obtained for the women in the UKWCS from the data recorded via FFQ and that recorded via FD (Chapter 6);
- Explore associations between two dietary patterns - the Mediterranean dietary pattern and the WCRF/AICR guidelines respectively and incidence CRC using data from FD derived from phase 2 of the UKWCS (Chapter 6);
- Put forward public health recommendations on dietary patterns to reduce risk of CRC (Chapter 7).

# CHAPTER 2 LITERATURE REVIEW OF ASSOCIATIONS BETWEEN DIET AND COLORECTAL CANCER

## 2.1 Chapter overview

The key purpose of this chapter is to review the research to date on the associations between diet and CRC. A classification of CRC is outlined in section 2.2. An overview of CRC epidemiology is discussed in section 2.3, namely its incidence, mortality and survival rates, its pathogenesis and the major non-dietary risk factors associated with carcinogenesis in this anatomical site.

Observational and interventional studies conducted to determine potential dietary factors associated with CRC risk have given inconsistent results. An advanced review of the literature surrounding diet and CRC will be tackled in section 2.4, where the major food types associated with CRC risk are reviewed. Other lifestyle factors linked to CRC, namely alcohol intake, body mass index (BMI) & obesity, and physical activity levels are discussed in section 2.5. Several of the conclusions drawn in the WCRF/AICR 2007 second expert report, and 2011 and 2017 reports are discussed. Summaries of these conclusions are found in Appendices I, II and III respectively. Results from several recent studies are outlined in this chapter to better summarize the evidence for food and nutrients in relation to cancers of the colon and rectum to date. Reference is made to the associations of diet with the different anatomical sites of the colorectum where relevant. Section 2.6 will consider the range of proposed interacting direct and indirect mechanisms through which some food and nutrients may exert their protective action, thus influencing colorectal carcinogenesis.

Despite the fact that as is common practice, the role of individual foods or nutrients has been explored in relation to risk of CRC in WCRF/AICR report, it is often difficult to separate out the specific effects of single foods and nutrients. Nutrients and foods are likely to interact to influence CRC risk (Song et al., 2015) and this research will thus focus on dietary patterns; a summary of the evidence on the latter from the WCRF/AICR report, from individual studies and from a systematic review published by the USDA in 2015 on dietary patterns and risk of CRC (DGAC, 2015) is indicated in section 2.7.

The Mediterranean dietary pattern and the current cancer prevention recommendations, their definitions, their implications on an individual's general health status and the evidence to date of these dietary patterns in relation to risk of CRC will be discussed in sections 2.8 and 2.9. A summary of the chapter is presented in section 2.10.

## 2.2 Classification of colorectal cancer

### 2.2.1 Histological classification

Tumours of the colon and rectum are histologically classified into epithelial tumours of the colorectal mucosa, non-epithelial tumours, secondary tumours and polyps. The adenoma is the chief precursor lesion which is detected and treated by endoscopic techniques. The carcinoma is an epithelial malignant tumour and one of the chief cancer sites in the developed world. Over 90% of colorectal carcinomas are adenocarcinomas originating from epithelial cells (Bosman et al., 2010). They are characterized by glandular formation, with over 95% of the tumour being gland forming in well differentiated adenocarcinomas and less than 50% gland formation in the mainly solid poorly differentiated adenocarcinomas (Fleming et al., 2012). Other epithelial tumours include the carcinoids, well-differentiated endocrine neoplasms, and mixed carcinoid – adenocarcinomas (Bosman et al., 2010).

Non-epithelial tumours such as lymphomas, mesenchymal and endocrine tumours are less common in the bowel. Polyps that are non-neoplastic are generally not considered precancerous, unless they occur in intestinal polyposis syndromes (Bosman et al., 2010). Such syndromes include the most common familial adenomatous polyposis (FAP), hamartomatous polyposis, and rarer types such as the hereditary-mixed polyposis syndrome (HMPS) (Hsu, 2015). They are characterized by the dominant type of polyp – adenomatous or hamartomatous – and it's location in the gastrointestinal (GI) tract. Such syndromes carry a considerable risk for the development of cancers of the colon, GI tract and of the pancreas, with the two most common heritable syndromes of colon cancer being FAP & hereditary nonpolyposis cancer of the colon (Schreibman et al., 2005).

### 2.1.1 Stages and grades

The anatomic extent of the tumour strongly predicts the treatment; accurate staging is thus of utmost importance. The tumour, node, metastasis (TNM) staging system is used to decide on treatment options. T denotes the depth of tumour invasion (T1 – T3, T4a, T4b) whilst N refers to the extent of nodal metastasis (N0 – N2), both of which are determined via histological examination (Fleming et al., 2012). Metastasis (M) describes whether the cancer has spread to other parts of the body (M1) or not (M0) (Cancer Research UK, 2017).

The grade of the cancer (1 to 3) gives an indication of its rate of growth and likeliness to spread with high grade cancers being faster growing and more likely to spread. Grade 1 (low grade) cancer cells look like normal cells whilst Grade 3 (high grade) cells look very abnormal (Cancer research UK, 2017).

## 2.3 Epidemiology of colorectal cancer

CRC is a major public health concern. It is the third most common cancer in men and the second most commonly diagnosed malignancy in women (Ferlay et al., 2015). In the UK, CRC is the fourth most common cancer in both sexes, and the fourth most common in females, accounting for 12% of all new cases (18, 400 cases) in 2014 (Office for National Statistics, 2016).

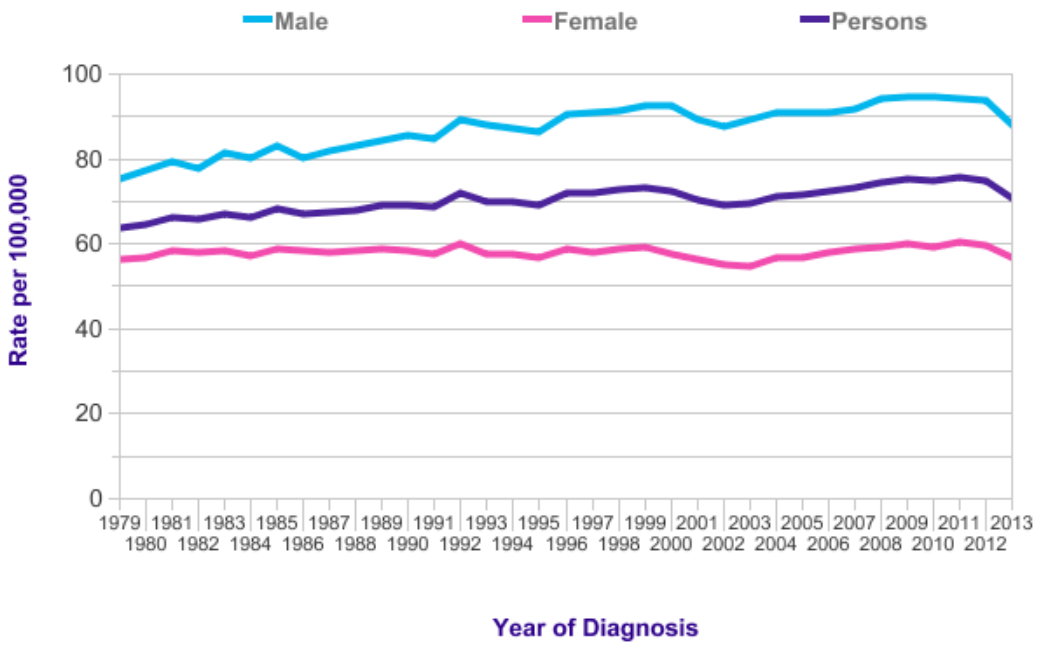
### 2.3.1 Incidence & trends

In 2012, 1.4 million new cases were estimated worldwide, accounting for 9.2% of all female cancer cases. CRC incidence exhibits wide geographical variation and such patterns are similar in both sexes with almost 55% of cases occurring in more developed countries (Ferlay et al., 2015). The variation in incidence and mortality rates varies up to 10-fold worldwide, with distinct gradients across human development levels and increasing burden in countries in transition. Incidence rates in countries with a very high Human Development Index (HDI) were six times greater than countries with a low HDI (Arnold et al., 2016). This may be partly due to better surveillance through screening for CRC in more developed countries, resulting in earlier detection and diagnosis of cases, different prevalence in risk factors and also due to varying data

quality worldwide (Center et al., 2009). The age-standardised incidence rates (ASR) in 2012 for female CRC in Australia/ New Zealand was 32.2 per 100, 000 women compared to the lowest ASR in Western Africa at 3.8 per 100, 000 women (Ferlay et al., 2015).

Figure 2.1 shows that the incidence rates of CRC in the UK have increased by 14% since the 1970s, though this includes a larger increase for males and a smaller 3% increase has been observed for females between 1979-1981 and 2011-2013. Such trends could potentially be the result of a change in risk factor prevalence, with the current incidence trends reflecting past risk factor prevalence, as well as the CRC screening programmes introduced in the mid-2000s (Office for National Statistics, 2016).

***Figure 2.1 European age-standardised colorectal cancer incidence rates, per 100000 population, by sex, for Britain between 1979 and 2013.***



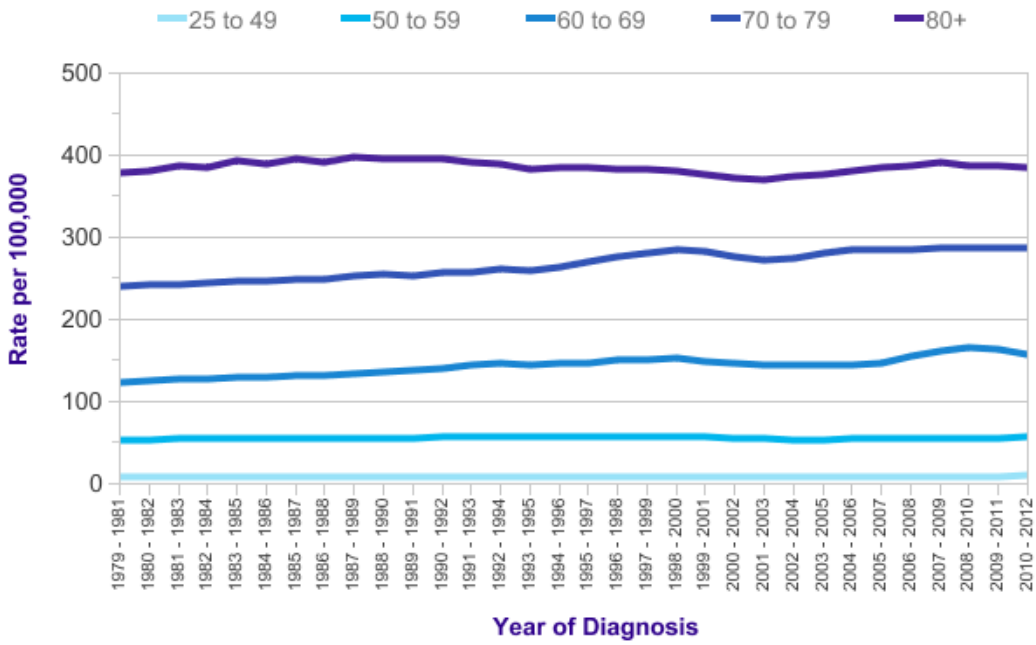

Source: Cancer Research UK (n.d.)

Although globally the burden of CRC is projected to increase by 60% by 2030 (Arnold et al., 2016), the incidence rates in the UK are expected to fall by 11% between 2014 and 2035. This decrease is expected to be larger in males, with a 7% decrease projected for

females, which equates to 63 cases per 100, 000 women in 2035. In 2012, the incidence rate for CRC was 17th highest for females in Europe (Ferlay et al., 2015).

The lifetime risk of diagnosis with CRC in the UK for females is 1 in 19. As indicated in Figure 2.2, CRC increases with age, reflecting cell DNA biological damage and accumulated risk factor exposures over time. Approximately 44% of cases between 2012 and 2014 in the UK were diagnosed in people aged 75 or over and the peak rate of cases was in the 85-89 age group (Office for National Statistics, 2016). A notable increase in incidence is seen in the 60-69 age group in the years following 2006 when the bowel screening programme was started in the UK, where previously undiagnosed cases were identified.

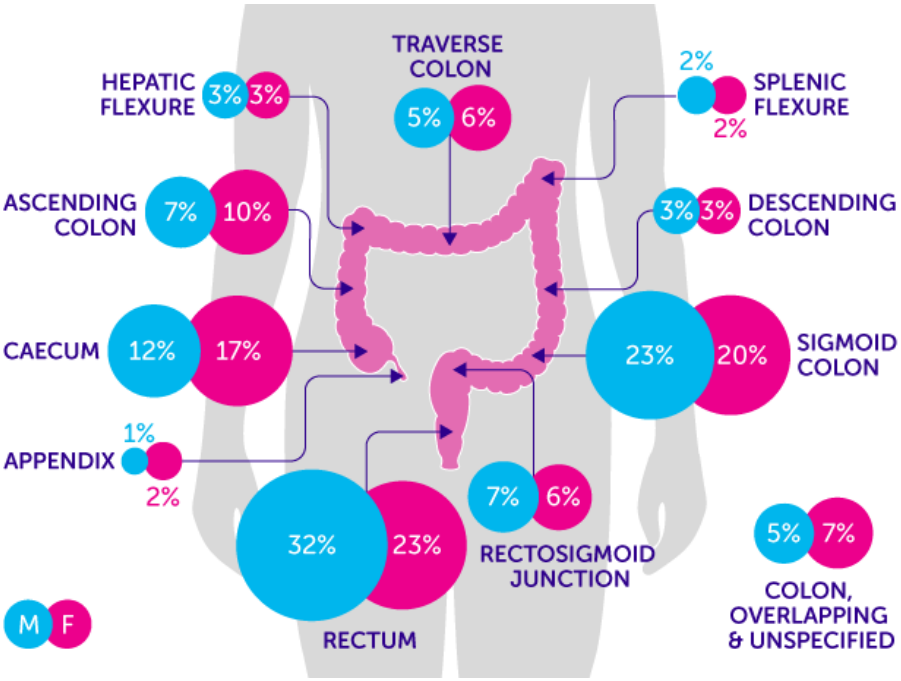
***Figure 2.2 European age-standardised colorectal cancer incidence rates, per 100000 population, by age, for Britain between 1979 and 2012.***




Source: Cancer Research UK (n.d.)

In the UK, the largest proportion of CRC cases in both sexes occurs in the rectum. In females, 23.1% of cases occurred in the rectum, 20.4% in the sigmoid colon, 17.2% in the caecum and 9.8% in the ascending colon. Some cases may be recorded as occurring in the colorectum, with the anatomical site not specified, whilst others may occur in more than one site (Office for National Statistics, 2014).

***Figure 2.3 Distribution of cases diagnosed by anatomical site, UK, between 2010 and 2012***




Source: Cancer Research UK (n.d.)

### 2.3.2 Mortality & survival

Globally, in 2012, an estimated 694 000 deaths were attributed to CRC, accounting for 8.5% of total deaths from cancer, with a four-fold variability in mortality rates in females worldwide (Ferlay et al., 2015). While globally the overall numbers are obviously higher, this is a lower percentage than the 12% of total cancer deaths attributed to CRC in Europe (215, 000 deaths). In Europe, mortality rates are lowest in Albania and highest in Hungary for both sexes, with rates in the UK being the 14$^{th}$ lowest in females. Notwithstanding, CRC is the third most common cause of female cancer deaths in the UK, responsible for 10% of cancer deaths in women in 2014. This translates to a crude mortality rate of 22 CRC deaths for every 100, 000 females (Office for National Statistics, 2016). Variation according to geographical location of CRC mortality rates tend to follow those of incidence, with a greater number of case fatalities in countries with lower levels of HDI indices (Arnold et al., 2016).

The age-standardised net survival for women diagnosed with bowel cancer during 2010-2011 in the UK was 74% for one year or more, and 58% for survival of at least 5 years.

Comparing survival rates across countries is difficult due to the different patient inclusion criteria and methodologies used during analyses (Cancer Research UK, 2014). The EUROCARE study aimed at assessing trends in the 5-year survival rate in 16 European countries, by age, stage and anatomical site (Brenner et al., 2012). The time period covered was from 1988-1990 to 2000-2002. In all regions, an increase in survival was observed, with generally more distinct increases in younger patients, earlier stages of CRC and more for rectal than for colon cancer (Brenner et al., 2012).

### 2.3.3 Major risk factors for colorectal cancer

CRC is a heterogeneous disease of which three major forms have been described, namely hereditary, sporadic and colitis-associated cancer (CAC) (Wang & Dubois, 2010). A number of risk factors are associated with CRC incidence. Age, sex, racial and ethnic background**,** family medical history of adenomatous polyps or of CRC and personal medical conditions such as type 2 diabetes, chronic inflammatory bowel diseases and a history of adenomatous polyps or CRC are established non-modifiable CRC risk factors (American Cancer Society (ACS), 2016; Rasool et al., 2013).

Incidence and mortality rates are higher in men than in women and increase with age with the rate of the former being 15 times higher in adults over 50 years compared with younger adults. Jews of Eastern European descent have one of the highest CRC risks of any ethnic group worldwide (ACS, 2016). With respect to family history, a meta-analysis including 47 studies estimated the relative risk (RR) of developing CRC: the pooled estimate was 2.24 (97% CI 2.06 to 2.43) for individuals with at least one affected first-degree relative and 3.97 with at least two affected relatives (Butterworth et al., 2006). The risk of CRC is around 30% higher in people with type II diabetes, compared with non-diabetics (Larrson et al., 2005). Ulcerative colitis and Crohn's disease are significant aetiological factors in the development of colorectal carcinomas. Clinical studies report up to 20-fold increased incidence in colorectal malignancy in subjects with ulcerative colitis, whilst the incidence increases 3-fold in Crohn's sufferers (Hamilton et al., 2000). Individuals with an adenoma history have an increased risk of developing CRC when compared to individuals with no previous history (de Jong et al., 2005).

Some inherited syndromes have also been linked to CRC, with FAP and hereditary non-polyposis CRC (HNPCC), also known as Lynch syndrome, being the most common syndromes increasing CRC risk. About 5 to 10% of CRC cases stem from a recognized hereditary condition (Haggar & Boushey, 2009). Mutations in the genes MLH1 and MSH2, involved in the DNA repair pathway have been associated with HNPCC. On the other hand, mutations in the tumour suppressor gene adenomatous polyposis coli (APC) cause FAP. Individuals with FAP generally develop hundreds of adenomas, one of which is transformed into a malignancy, typically by the age of 40 if left untreated (Wang & Dubois, 2010). However, only 1% of CRC cases are due to FAP. On the other hand, people with HNPCC typically only develop a few polyps and this syndrome is responsible for 2 to 6% of incident CRC (Haggar & Boushey, 2009). Patients with HNPCC typically develop CRC at approximately 44 years as compared to 64 years in the general population (Wang & Dubois, 2010). There is evidence to show the clinical effectiveness of non-steroidal anti-inflammatory drugs (NSAIDS), including aspirin and cyclo-oxygenase-2 (COX-2) inhibitors for the prevention of CRC and polyps in populations with different risks for developing CRC. Chemoprevention varies for the general population, for individuals with a personal history of polyps or with a family or personal history of CRC and for individuals with FAP or HNPCC (Cooper et al., 2010). Specific COX-2 inhibitors may reduce intestinal polyp burden in patients with FAP (Gupta & DuBois, 2011) whilst aspirin may reduce incidence of adenoma or recurrence of advanced adenomas in individuals with a history of CRC (Cooper et al., 2010). Notwithstanding, data suggests that for chemoprevention, aspirin would be needed in large doses for a period of approximately 10 years and since it is not risk free, it's potential benefit should be weighed against its harms (Dube' eg al., 2007).

Other factors with a less clear effect on CRC risk include night shift work and previous treatment for testicular and prostate cancer (ACS, 2016). Therapeutic pelvic radiation is a rare, but well recognised aetiological factor (Hamilton et al., 2000).

It is widely believed that lifestyle factors such as diet, physical inactivity, overweight and obesity, smoking and alcohol consumption play an important role in the development of CRC and can thus also contribute to risk (Haggar & Boushey, 2009). It

has been estimated that 54.4% of incident CRC in the UK in 2010 – 56.5% in males and 51.9% in females – may be attributed to lifestyle and environmental factors (Parkin et al., 2011). Evidence for environmental factors characterising risk of CRC comes from geographical factors, including migrant studies and urban residence. Incident rates in migrants from low to high risk countries typically increase to agree with those of the host country. Incidence in urban areas is approximately 30% higher than for those in living in rural areas, and is higher for urban residence when compared to urban birth area (Janout & Kollarova, 2001). Such modifiable risk factors are discussed in detail in sections 2.4 and 2.5.

## 2.4 The major foods and nutrients associated with colorectal cancer

Diet is an important component of cancer risk, and as a result of numerous epidemiological and experimental studies, consumption of several foods and nutrients has been associated with incident CRC in the past decades. This section will review the epidemiological evidence to date surrounding the major dietary factors hypothesized to have a role in CRC risk.

### 2.4.1 Dietary fibre, carbohydrates and whole grains

In 1971, Burkitt proposed that dietary fibre may decrease CRC risk (Burkitt, 1971) and research using retrospective recall methods supported this hypothesis. Many mechanisms of this mitigation have been proposed since then, including bulk of the stool, reduction in transit time, alteration of bile acid metabolism, dilution of the colonic lumen pH, increased production of short chain fatty acids and alteration of gut flora (Chan & Giovanucci, 2011), though findings from published studies remain inconsistent. Following systematic reviews of the available literature, the strength of evidence in favour of food containing dietary fibre decreasing risk of colon and rectal cancers was listed as probable – the second level of grading - in the WCRF/AICR 2007 report and raised to convincing in the 2011 version (WRCF/AICR, 2007; 2011), and back to probable in the 2017 updated version (WCRF/AICR, 2017). Fibre may be derived predominantly from cereal as well as from fruit, vegetables and legumes. Notably, in the latest report of the CUP, for the first time in, the expert panel concluded that the

evidence for whole grains in decreasing CRC risk was strong – probable (WCRF/AICR, 2017).

In the Pooling Project of Prospective Studies of Diet and Cancer (Park et al., 2005), including over 725,000 subjects, dietary fibre intake was inversely associated with risk of CRC in age-adjusted analyses but was not significantly associated with a reduced CRC risk when other dietary factors were accounted for. A range of FFQs were used to assess diet in this pooled analyses of primary data, potentially resulting in dietary fibre misclassification arising from measurement error. Conversely, findings from the European Prospective Investigation into Cancer and Nutrition (EPIC) study showed a significant inverse association of dietary fibre with CRC, with fibre from cereal offering a greater risk reduction than fruit, vegetable and legume fibre (Bingham et al., 2005; Bradbury et al., 2014). A meta-analysis including 25 prospective studies found that the summary RR for developing CRC with each increment of 10g daily dietary fibre consumption was as follows: 0.90 (95% Confidence Interval (CI) = 0.86, 0.94) for total dietary fibre, 0.93 (95% CI = 0.82, 1.05) for fruit fibre, 0.98 (95% CI = 0.83, 0.97) for vegetable fibre, 0.62 (95% CI = 0.27, 1.42) for legume fibre and 0.90 (95% CI = 0.83, 0.97) for cereal fibre; and 0.83 (95% CI = 0.78, 0.89) for an increment of 3 servings of wholegrain per day (Aune et al., 2011b).

Little is yet known on the effect of different fibre types on this health outcome and variation in the predominant source of fibre could potentially explain the inconsistency of results from the different studies outlined above. In two recent reviews of the literature surrounding dietary fibre and CRC, it was concluded that recommending the consumption of a high-fibre diet is reasonable as it has been associated with other health outcomes, but increasing fibre intake is unlikely to largely decrease risk of CRC (Chan & Giovanucci, 2010; Song et al., 2015).

The evidence for an association between diets high in highly refined carbohydrates and thus with a high glycaemic index or load and CRC is inconsistent. It is postulated that the surges of insulin secretion resulting from refined carbohydrates may stimulate carcinogenesis of the colorectum. However, a systematic review and meta-analysis of

14 cohort studies concluded that an independent association between diets high in carbohydrate, glycaemic index or glycaemic load and CRC incidence was not supported. The RR for high versus low intake was 1.00 (95% CI = 0.87, 1.14) for carbohydrate, 1.07 (95% CI = 0.99, 1.16) for glycaemic index and 1.00 (95% CI = 0.91, 1.10) for glycaemic load (Aune et al., 2012a). The panel of the 2017 CUP report in fact came to no conclusion on the role of glycaemic index and glycaemic load in CRC development due to limited evidence (WCRF/AICR, 2017).

Nevertheless, consumption of wholegrain, a carbohydrate of high quality with a low glycaemic index has been associated with improved insulin sensitivity and lower fasting insulin levels, potentially mediated by the fibre and magnesium components in wholegrain (McKeown, 2004). Whole grains are rich in other protective nutrients and phytochemicals that have been linked to disease prevention, including antioxidants, phenolic compounds, phytates, phyto-oestrogens, vitamins and minerals (Slavin, 2004). In view of the above, the rationale for recommending an increased wholegrain consumption to decrease colorectal carcinogenesis is sound.

### 2.4.2 Fruit, vegetables and antioxidants

Along with dietary fibre, a growing interest in associations with fruit and vegetable intake and cancer outcome was seen in the 1990s (Willett, 2005). Epidemiological studies carried out before the mid-1990s, using retrospective recall methods correlated fruit and vegetable consumption with protection against cancer of a range of anatomic sites. The chemo-preventative effect provided was often attributed to classes of compounds that can potentially contribute to antioxidant activity. Such compounds include phenolics and glucosinolates in cruciferous vegetables (Antosiewicz et al., 2008) and flavonoids in fruit and vegetables. *In vitro* and *in vivo* studies where flavonoids showed inhibitory effects of various stages in the cancer process suggest tissue protection against free radicals and lipid peroxidation (Wattenberg, 1992; Hollman & Katan, 1999). The WCRF/AICR 1997 report concluded that there was sufficient evidence for a convincing inverse relationship between fruit and vegetable intake and risk of cancer (WCRF/AICR, 1997); this conclusion was however based mostly on case-control studies.

Nevertheless, studies on both the effects of dietary flavonoid consumption and of high fruit and vegetable intakes with risk of several cancers consistently give conflicting findings with risk being significantly reduced in some studies (Knekt et al., 1997; Theodoratou et al., 2007) but not in others (Hertog et al., 1994; Hertog et al., 1995). Based on recommendations of the World Health Organisation (WHO), 2001 saw the launch of the five-a-day fruit and vegetable initiative in the UK. Prospective cohort studies carried out since then have been far less supportive of a benefit for CRC (Boffetta et al., 2010) and in both the 2007 WCRF/AICR report and the 2011 CUP report, the panel concluded that overall evidence towards the protective effect offered by intakes of fruit and non-starchy vegetables against the risk of CRC is limited - suggestive (WCRF/AICR, 2007; 2011). This was further confirmed in a 2011 review which stated that data from epidemiological studies suggested little, if any association between fruit and vegetable consumption and risk of common cancers (Key, 2011). In a meta-analysis of 19 prospective studies, the association between fruit and vegetable intake and CRC risk was reported to be nonlinear, inverse and though weak, statistically significant (Aune et al., 2011a). However, when risk was assessed by colorectal sub site in the EPIC study of 470,000 participants, individuals with the highest fruit and vegetable intake were shown to have a borderline significant 14% and a significant 24% decreased risk of colorectal and colon-only cancer respectively, though findings could potentially depend on smoking status (van Duijnhoven et al., 2009). In view of the inconsistency of observations with respect to colorectal, colon and rectal cancer risk reduction with high fruit and vegetable intake, further studies are warranted investigating associations with each anatomical site separately. Following re-examination of the evidence in 2017, CUP, conclusions with respect to fruits and non-starchy vegetables were on the same level of strength; however the inclusion of the new studies enabled the CUP findings to reach statistical significance, which was not the case in the 2010 systematic literature review (SLR). The panel concluded that there was limited but reasonably consistent – suggestive evidence to show that a low intake (below 100 grams per day) of fruit and non-starch vegetables increased CRC risk (WCRF/AICR, 2017).

Garlic is a vegetable that has attracted particular interest, with the WCRF/AICR 2007 and 2011 reports, together with a 2007 systematic review (Ngo et al., 2007) concluding a probable inverse association between garlic intake and CRC risk. These findings were not however in agreement with a more recent evaluation of garlic and garlic supplement use with CRC in two large cohort studies that did not support this association (Meng et al., 2012), or with an updated meta-analysis of prospective studies that concluded no significant association garlic consumption and CRC risk (Hu et al., 2014). In fact, the 2017 WCRF/AICR CUP reported that the evidence was limited and no conclusion could be made for an association between garlic and CRC risk.

Selenium, beta carotene and vitamins A, C & E are dietary micronutrients believed to have anti-carcinogenic effects due to their anti-oxidant and anti-inflammatory properties, with observational studies showing the strongest associations for selenium (Chan & Giovanucci, 2010). Although early ecologic, case-control and relatively small prospective studies showed an inverse association of antioxidant intake with risk of CRC, this association did not hold when data from several cohort studies testing this hypothesis were pooled or in large randomised controlled trials (RCTs) specifically designed to test the efficacy of antioxidant supplements in tumour prevention (Song et al., 2015). From the evidence to date, it has been concluded that antioxidant supplements are unlikely to prevent CRC (Chan & Giovanucci, 2010; Song et al., 2015).

### 2.4.3 Red & processed meats

The correlation of red and processed meat consumption to increased CRC risk has long been put forward and numerous studies in literature are found on this subject. A meta-analysis of thirteen prospective cohort studies indicated that an increase of 100g of meat on a daily basis significantly increased risk of CRC by 12–17% (Sandhu et al., 2001), whilst in 2007, WCRF/AICR experts concluded that higher intakes of processed and red meat are convincingly positively associated with CRC (WCRF/AICR, 2007). This was confirmed in a review of epidemiologic and experimental evidence in 2008; Santarelli and colleagues stated there was enough evidence to support the hypothesis that high intake of red and processed meat may increase risk of CRC; furthermore that the consumption of 1g of processed meat increased the risk two to ten times more

compared to the same amount of unprocessed meat (Santarelli et al., 2008). A systematic review and meta-analysis of 22 studies (Smolinska & Paluszkiewiczl, 2009) concluded that the frequency of consumption rather than the total amount of consumed red meat is associated with an increased risk of carcinogenesis of both colon (RR of 1.37; 95% CI = 1.09, 1.71) and rectal cancer (RR of 1.43; 95% CI = 1.24, 1.64). Consumption of over 50g of red meat daily was associated with increased risk of colon (RR of 1.21; 95% CI = 1.07, 1.37) but not of rectal cancer (RR of 1.30; 95% CI = 0.90, 1.89). In 2010, a summary of 35 prospective studies concluded that collectively associations were generally weak, were in their majority not statistically significant; and varied by anatomical site and gender thus the available evidence to date does not support an independent positive association between red meat and CRC (Alexander & Cushing, 2010). Alexander and colleagues also arrived to the same conclusion on the association between processed meat and CRC risk following a review of epidemiological studies (Alexander et al., 2010).

Conversely, a 2011 meta-analysis with the aim of updating the evidence from the 2007 WCRF/AICR report with results from 10 additional prospective studies revealed an approximate linear CRC risk increase (Chan et al., 2011). Increasing intake of red and processed meats with RRs for the highest versus the lowest intake and for every 100g /day increase being 1.22 (95% CI = 1.11, 1.34) and 1.14 (95% CI = 1.04, 1.24) respectively, up to around 140g /day and with similar associations for risks of both colon and rectal cancer. Colorectal and colon cancer were also related to intakes of red and processed meat respectively, analysed separately; conversely this association was not observed for rectal cancer. Then again, the WCRF/AICR updated report published in 2011 concluded that the evidence that red and processed meat intake causes CRC is convincing – the strongest level of grading of evidence (WCRF/AICR, 2011).

Nevertheless, Cappellani et al. (2013) argued that because some studies reported no significant association, or an increased risk for only colon but not rectal cancer, and because no significant risk reduction is observed in vegetarian patients, red meat intake does not fully explain the increased CRC risk in developed countries when compared to developing ones. Chan & Giovanucci (2010) suggested that it is

potentially the cooking process that explains the association between red meat and CRC, with consumption of heavily browned meat that has undergone prolonged cooking at high temperatures being associated with increased risk of colon cancer. The potential underlying mechanisms for this association are discussed in section 2.6.

In summary to their reviews, Chan & Giovanucci (2010) and Song et al., (2015) both conclude that based on the evidence to date, limiting red and processed meat and substituting it with poultry or fish is recommended for prevention of CRC. In 2015, on the basis of evidence linked mainly to CRC, the International Agency for Research on Cancer (IARC), classified red meat as 'probably carcinogenic to humans' and processed meat as 'carcinogenic to humans' (IARC, 2015). The recent 2017 CUP reported similar findings with the panel concluding that while consumption of red meat is probably a cause of CRC, processed meat consumption is a convincing cause of CRC. The evidence for the latter was based on a dose-response meta-analysis showing a significant 16% increased CRC risk per 50g of processed meat daily (RR 1.16 (95% CI = 1.08, 1.26) (WCRF/AICR, 2017).

### 2.4.4 Dairy products, calcium and vitamin D

Based on SLRs, experts of the WCRF/AICR 2007 and 2011 reports concluded that the evidence of an inverse association between intake of milk and calcium and CRC risk was strong and graded as probable; whilst only limited evidence that cheese consumption increases CRC risk was available (WRCF/AICR, 2007; 2011). This was previously demonstrated in a pooled analysis of ten cohort studies resulting in over 500,000 subjects, where milk and calcium intake were inversely related to cancer of the distal colon and rectum with a 500 g/day increase in milk intake corresponding to a 12% decrease in risk. Cheese and yoghurt intake were weakly positively and inversely respectively associated with CRC risk, but not statistically significant (Cho et al., 2004). These conclusions were furthermore partly supported by a meta-analysis including 19 cohort studies showing that high intakes of milk and total dairy products as opposed to cheese or other dairy products were significantly associated with reduced risk of colon cancer when compared with a low intake (Aune et al., 2012b). Further studies are needed to identify whether inverse associations are restricted to colon cancer or are

also applicable to rectal cancer and whether the observations made for total dairy products may be explained by the fact that a large proportion of total intake is due to milk consumption.

Song et al. (2015) concluded that in view of the evidence to date, it may be reasonable to encourage milk, and possibly yoghurt consumption, but not cheese for prevention of CRC. This is partly in line with conclusions made by the 2017 CUP panel who, based on the evidence to date, reported dairy products – including total dairy, milk, cheese and dietary calcium as offering probable protection against CRC. Notwithstanding, the panel added that while dose-response meta-analysis were statistically significant for dairy products, milk and dietary calcium, whilst the evidence for cheese was less strong (WCRF/AICR, 2017).

The protective effect of dairy may be related to it being one of the main sources of calcium, for which several mechanisms have been proposed (Larsson et al., 2006); these will however be discussed in section 2.6.6. In summary, data suggest a significant, modest ability of calcium intake to decrease CRC incidence (Chan & Giovanucci, 2010) and individuals should be encouraged to increase their calcium intake to a level above 700-1000 mg/day (Song et al., 2015). There is also some evidence from randomised controlled trials (RCT) suggesting a modest, beneficial effect of supplementation with calcium, on recurrent adenomas. In the large clinical controlled trial of 930 subjects, the Calcium Polyp Prevention Study, calcium carbonate supplementation was associated with a significant, though moderate, decrease in the risk of recurrent colorectal adenomas (Baron et al., 1999). Conversely, in the placebo-controlled European Cancer Prevention Intervention Trial of 665 patients, whilst calcium supplementation was associated with a modest risk reduction of adenoma recurrence, this was non-significant (Bonithon-Kopp et al., 2000). In a third randomized, double-blind, placebo-controlled trial involving over 36000 postmenopausal women from Women's Health Initiative centres, daily supplementation of calcium with vitamin D for seven years had no effect on the incidence of CRC (Wactawski-Wende et al., 2006). The 2017 CUP report concluded that there was strong evidence to show that calcium supplements, at a dose of between

200 – 1000 mg daily, probably decreased the risk of CRC, although no conclusion could be reached on the effect of non-dairy sources of calcium due to limited evidence (WCRF/AICR, 2017).

Dairy products are also commonly fortified with vitamin D. The 2011 WCRF/AICR report concluded that there was limited, suggestive evidence to show that foods containing this vitamin decreased CRC (WCRF/AICR, 2011). Notwithstanding, according to Klampfer (2014), the most active form of vitamin D, calcitriol, 1α, 25-dihydroxyvitamin $D_3$ (1,25 $(OH)_2D_3$), is able to interfere with Wnt signalling and to inhibit inflammation that promotes tumour formation. This enables the regulation of the intestinal lumen, preventing the development of colon cancer (Klampfer, 2014). Furthermore, vitamin D has been implicated in antiproliferation, induction of differentiation and apoptosis, anti-inflammation, inhibition of invasion and metastasis, and suppression of angiogenesis (Feldman et al., 2014). To conclude, the association and exact mechanism by which vitamin D decreases CRC risk is yet unclear and this area thus merits further exploration. The 2017 CUP Panel, after considering the evidence for foods containing vitamin D, plasma vitamin D and vitamin D supplements concluded that there was limited evidence to suggest that vitamin D decreased CRC risk (WCRF/AICR, 2017).

### 2.4.5 B vitamins

In view of the fact that vitamin B6, pyridoxine and vitamin B9, folate, together with other B vitamins are fundamental nutrients in the processes of DNA synthesis, repair, methylation and stability, they have been implicated in cancer prevention. Folate has been investigated widely in relation to CRC risk. Whilst observational studies examining the risk of CRC with folate intake generally show that increased folate intake results in reduced risk, experimental studies do not tend to support this benefit (Chan & Giovanucci, 2010). The folate-CRC relationship is thus complex; whilst folate stimulates antineoplastic activity in normal, healthy tissues, it may stimulate growth by enhancing DNA synthesis in cancerous cells that are rapidly replicating (Song et al., 2015). In a systematic review and meta-analysis investigating the relationship between level of folate intake and incidence of CRC, the summary risk estimate for high vs. low total

folate intake was 0.85 (95% CI = 0.74, 0.99) for case-control studies and 0.92 (95% CI = 0.81, 1.05) for cohort studies, with no significant heterogeneity in both (Kennedy et al., 2011). It has also been hypothesized that the effect of folate is dependent on the individual's baseline level with experimental studies finding that the supplementation of folate decreased the recurrence of adenomas only in individuals with low CRC levels (Wu et al., 2009). A meta-analyses of data on approximately 50 000 individuals looking at the effect of folic acid supplementation on cancer incidence found no significant short-term effect of folic acid allocation on CRC incidence when compared with the placebo (Vollset et al., 2013). Notwithstanding the fact that the evidence is inconsistent, it is currently recommended that individuals should receive 400µg of folate, and populations that are folate deficient may benefit from folate supplementation to reduce CRC risk, particularly if they are do not have a history of cancer (Chan & Giovanucci, 2010).

A focus on the association between vitamin B6 and CRC is only recent. Given the involvement of this coenzyme in several cellular functions, its potential role in cancer prevention is hypothesized to go further than that in one-carbon metabolism (Chan & Giovanucci, 2010). A meta-analysis of nine prospective studies assessing the association of Vitamin B6 intake and blood levels of the active form of vitamin B6 (pyridoxal 5-phosphate - PLP) with risk of CRC reported an inverse association for blood PLP levels but not for Vitamin B6 intake (Larsson et al., 2010). Large-scale intervention trials are thus necessary before any recommendations can be made with respect to vitamin B6 intake and the risk of CRC. In view of the limited evidence, the 2017 CUP Panel have arrived to no conclusion on the role on folate and vitamin B6 on CRC prevention and causation (WCRF/AICR, 2017). Data regarding vitamin B2 and vitamin B12 is scant and inconclusive (Song et al., 2015).

## 2.5 Lifestyle factors associated with colorectal cancer

### 2.5.1 Alcohol

The WCRF/AICR 2011 report concluded that there was convincing evidence that alcoholic drinks increased the risk of CRC in men and probable evidence of the same association in women (WCRF/AICR, 2011); this was confirmed in the latest CUP report where it was concluded that consumption of over 30 grams of alcohol per day was a convincing cause of CRC (WCRF/AICR, 2017). In a meta-analysis of sixteen prospective cohort studies on the relationship between alcohol intake and CRC cancer, including over 6300 patients with CRC, a weekly intake of 100g alcohol was associated with a 15% increased risk, with no significant differences for colon and rectal cancer (Moskal et al., 2007). In another pooled analysis of primary data from 8 cohort studies in 5 countries from North America and Europe, alcohol intake of approximately 490 000 participants was assessed at baseline using a FFQ and followed up a minimum of 6 and maximum of 16 years. An increased risk of both colon and rectal cancer was associated only with consumption of over 2 drinks/day (Cho et al., 2004). This was confirmed by results of a dose-response meta-analysis published in 2011, summarising the evidence from 27 cohort and 34 case-control studies that provided strong evidence for an association between drinking over 1 alcoholic drink / day and CRC risk, with stronger RRs reported for men and in Asian populations when compared to non-/occasional drinkers (Fedirko et al., 2011). In 2010, 11.6% of all CRC cases in the UK were attributed to alcohol consumption: 15.5% of all male cases and 6.9% of all female cases (Parkin et al., 2011). Thus, notwithstanding the fact that epidemiological evidence supports positive associations between alcohol consumption and CRC risk, findings with respect to sex, the dose-response association and geographical region warrant further investigation. Nevertheless, from the evidence to date, it is sensible to recommend that people decrease their alcohol intake, especially if their current level is high, to prevent CRC.

### 2.5.2 BMI and abdominal fatness

Overweight and obesity are risk factors for CRC; the WCRF/AICR classified body fatness, as marked by BMI, waist circumference and waist: hip ratio as being convincing causes of colon and rectal cancer (WCRF/AICR, 2017). In a 2013 systematic

review of prospective studies including over 9 million people, the RR of CRC incidence for obese individuals vs. those in the normal category of BMI was 1.33 (95% CI = 1.25, 1.42), whilst the RR for individuals in the highest vs. the lowest category for waist circumference (WC) was 1.46 (95% CI = 1.33, 1.60) (Ma et al., 2013). Thus both general and central obesity were positively associated with risk of CRC. When the studies were stratified by anatomical site, it was evident that a higher BMI and a higher WC increased the risk of both proximal and distal colon cancer, as well as of rectal cancer (Ma et al., 2013). The association for BMI was stronger for men than for women, with a 47% increased risk in obese vs. normal men, to a 15% increased risk in obese vs. normal women (Ma et al., 2013).

Notwithstanding, Robsahm and colleagues reported a more pronounced association for the distal colon with BMI, with a RR of 1.59 (95% CI = 1.34, 1.89) when compared to the proximal colon and rectum, with a RR of 1.24 (95% CI = 1.08, 1.42) and 1.23 (95% CI = 1.02, 1.48) respectively (Robsahm et al., 2013). They however reported such differences as being minor and added that it is unlikely that the biological mechanisms in place vary in their impact on the different colorectal sites.

A quantitative analysis from 56 observational studies including almost 94 000 cases showed the association of BMI with CRC is stronger in premenopausal women when compared to postmenopausal women. Even women with a BMI in the 'normal' range of 23.0 to 24.9 kg $m^{-2}$ had an increased risk of CRC compared to women with a BMI of < 23.0 kg $m^{-2}$ (Ning et al., 2010). In a systematic review and meta-analysis of observational studies looking at adult weight gain and occurrence and recurrence of colorectal adenomas, even a small amount of weight gain was associated with a higher adenoma occurrence (Schlesinger et al., 2017). The authors argued that in view of the fact that adenomas are precursors of most carcinomas, weight control in adulthood may have a role in the early CRC prevention. Although based on the above studies, obesity, in particular visceral adiposity appears to play a role in CRC, the mechanisms by which obesity increases risk of CRC are still not well understood. The several possibilities that have been hypothesised are discussed in section 2.6.

### 2.5.3 Physical activity

In the WCRF/AICR 2011 report, the evidence for physical activity reducing the risk of CRC was listed as convincing (WCRF/AICR, 2011). Following the report, two meta-analyses were published supporting the role of physical activity in decreasing both proximal and distal colon cancer (Boyle et al., 2012; Robsahm et al., 2013), but not in decreasing rectal cancer (Robsahm et al., 2013). An approximate 33% decreased risk of colon cancer was reported by Robsahm and colleagues for those with the highest level of physical activity when compared to the least physically active. The magnitude of the inverse association was the same for both distal and proximal colon cancer with physical activity (Robsahm et al., 2013). This difference in association by anatomical site could be indicative of different mechanisms in the development of colon and rectal cancer. The 2017 CUP confirmed the findings of the previous 2011 CUP stating there was convincing evidence to show that physical activity reduced the risk of colon cancer, but no conclusion could be drawn on rectal cancer (WCRF/AICR, 2017).

The risk reduction in CRC as a result of physical activity could be due to several mechanisms. Firstly, there is evidence to show that the risk of adenomas decreases with physical activity, with an approximate 16% decrease risk (RR=0.84, 95% CI = 0.77, 0.92) reported, and a similar inverse association in both sexes (Wolin et al., 2011). Adenomas could progress into cancerous tumours, as outlined in section 2.2.1. Physical activity leads to more regular bowel movements, thus decreasing transit time and the contact time of harmful substances in undigested food with the intestinal lumen. Furthermore, it also reduces the levels of insulin, hormones and other growth factors that could stimulate tumour growth, and potentially alters the level of prostaglandins thus reducing inflammation l

## 2.6 Potential mechanisms for diet and colorectal cancer

The literature outlined in sections 2.4 and 2.5 support associations of some dietary components, obesity and physical activity with CRC, and thus they have a potential role in its prevention. It is likely that diet influences colorectal carcinogenesis through numerous interacting mechanisms, including both the direct effects on responsiveness of the immune system and inflammation, and the indirect effects of other risk factors

for CRC such as over nutrition and obesity (Song et al., 2015). This section will give an overview of the different mechanisms proposed to relate such dietary and lifestyle factors to cancer risk.

### 2.6.1 The inflammation and colorectal cancer connection

Genetic, pharmacological and epidemiological data support the association between inflammation and tumourigenesis, and whilst inflammatory bowel disease (IBD) is an important risk factor in CRC development, inflammation is likely to also be involved in sporadic and heritable colon cancer (Terzic et al., 2010). The association between inflammation and cancer can be said to consist of two pathways – an extrinsic one driven by inflammatory conditions that increase risk, such as IBD and an intrinsic pathway driven by genetic alterations, such as oncogenes (Mantovani et al., 2008). Chronic inflammation is indicated by a sustained active inflammatory response and destruction of tissues (Kraus & Arber, 2009). Colorectal tumours are infiltrated by various immune cells all with either pro- or anti-tumourogenic roles. Pro-inflammatory cytokines, released by such cells, and distinct immune cells have in fact been implicated in all phases of colon tumourigenesis (Terzic et al., 2010).

Chronic inflammation promotes carcinogenesis via the induction of gene mutations, the inhibition of apoptosis, the stimulation of angiogenesis and cell proliferation or the induction of epigenetic alterations. Cyclooxygenase-2 (COX-2) and nuclear factor kappa B (NF-$_K$B) family of transcription genes are the central genes in the inflammatory process, providing mechanistic associations with CRC. They are thus considered targets for chemoprevention (Kraus & Arber, 2009). Compounds such as the carbohydrates inulin and oligofructose and the phytochemicals resveratrol and curcumin have been found to reduce CRC risk (Kim et al., 2007). Butyrate produced by colonic bacteria from the fructose polymers seems to modulate COX-2 signalling, as well as signalling of other genes (Tong et al., 2004) whilst phytochemicals reduce the activation of NF-$_K$B thus affecting inflammation (Jeong et al., 2004).

In conclusion, whilst there is evidence to show that the cumulative effect of chronic inflammation, particularly IBD leads to colorectal carcinogenesis, the precise

mechanism is yet unclear (Kraus & Arber, 2009). Furthermore, numerous unanswered questions as yet remain. For instance, it is still unsure whether inflammation is sufficient for neoplasia development without a carcinogenic agent and whether some aspects of cancer-related inflammation are common, irrespective of tumour diversity (Mantovani et al., 2008).

The evidence on the connection between inflammation and cancer is substantial and different dietary factors are implicated in the aetiology of CRC. Some nutrients implicated in CRC development are proposed to do so via their anti-inflammatory properties, and by decreasing the activity of oncogenic signalling pathways (Terzic et al., 2010) amongst other mechanisms. Apart from the carbohydrates and phytochemicals mentioned above, vitamins A, C, E & D, selenium, methionine and omega-3 polyunsaturated fatty acids have been implicated. Nevertheless whilst the level of evidence for vitamin D is suggestive, there is limited evidence for other nutrients and a conclusion cannot be reached as previously discussed in section 2.4 (Song et al., 2015).

### 2.6.2 Microorganisms in inflammation-induced colorectal cancer

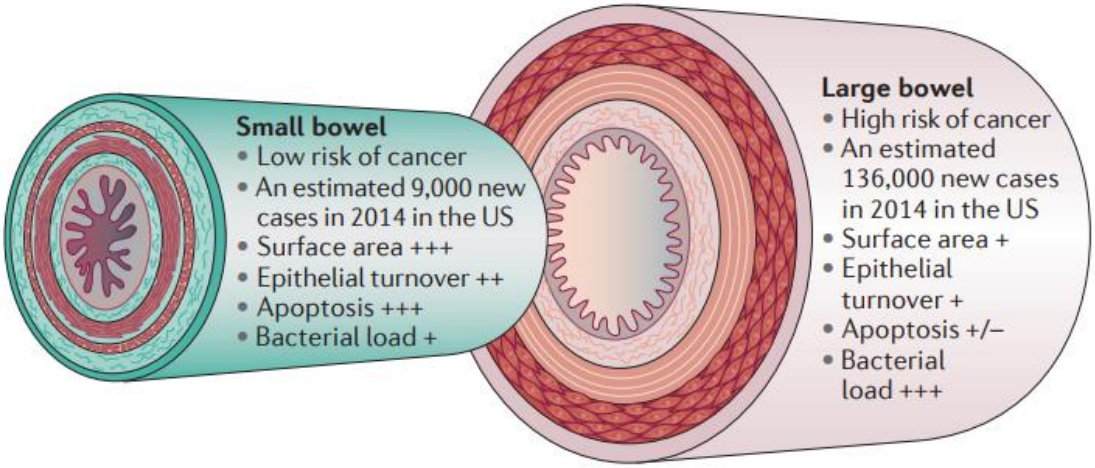
The presence or function of commensal microbial populations is known as the microbiome. The composition or disruption of the microbiota seems to be a predisposing factor to CRC. Diet and nutritional status have an influence on both the composition as well as on the operations of the gut microbiota, and dietary habits influence the structure of the human genome (Kau et al., 2011). In an organ such as the gastrointestinal tract, inflammation drives cancer development and the role of microbial communities in chronic inflammation is pivotal (Elinav et al., 2013). Kau and colleagues report a connection between nutrient metabolism and the immune system and describe how nutrient processing by the microbiota, together with the host's diet shape immune responses – this is described as the diet-microbiota-immune axis (Kau et al., 2011). The microbiome has also been described as interface between food, different fuels absorbed and the human body (Flint, 2012). Short chain fatty acids (SCFAs) are an excellent example – they are end products of macronutrient fermentation by microbes. Their concentration in the lumen varies according to the amount of dietary fibre in the diet

which in turn affects the composition of the microbiota. They act as an energy source for the host and affect the latter's immune responses (Kau et al., 2011).

Dietary intake of carbohydrates that are only partially digested, such as resistant starch, prebiotics and non-starch polysaccharides, provide energy for colonic bacteria. The quantity and type of such carbohydrates may influence the species composition the microbial communities in the intestine. Furthermore, gut microbiota respond differently to changes in diet in individuals, thus having varied responses on hosts' metabolism. Manipulation of bacteria through diet could have beneficial health implications (Flint, 2012).

Several potential mechanisms have been implicated that allow microbes to contribute to carcinogenesis. These include metabolite or genotoxin production thus damaging DNA or impeding its repair, penetration of the colonic mucus, induction of epithelial proliferation and mucosal inflammation (Shanahan & O'Toole, 2014). It is plausible that the variation in incident cancer between different anatomical sub sites of the colorectum reflects diversity in microbial niches and their functions. The risk of cancer in the large intestine is much higher than that in the small intestine. The latter boasts a larger surface area and faster epithelial turnover when compared to the larger bowel, but the bacterial load is much lower in the small intestine. Figure 2.4 extracted from Shanahan & O'Toole, 2014, summarises the features of each with regard to the spatial variation in cancer incidence.

***Figure 2.4 Schematic representation of the small bowel and the large bowel***




Source: Shanahan & O'Toole (2014)

### 2.6.3 Mechanisms relating overweight, obesity to colorectal cancer

The mechanisms underlying the association between obesity and cancer are multifaceted, not well recognized and include hormones, growth factors, modulation of energy balance and calorie restriction, multiple signalling pathways and processes related to inflammation (Vucenik & Stains, 2012), as discussed in section 2.6.1. Obesity generates a low grade inflammation state as a result of an increased fat mass, macrophage infiltration of adipose tissue and abnormal production of adipokines and pro-inflammatory cytokines (Vucenik et al., 2016).

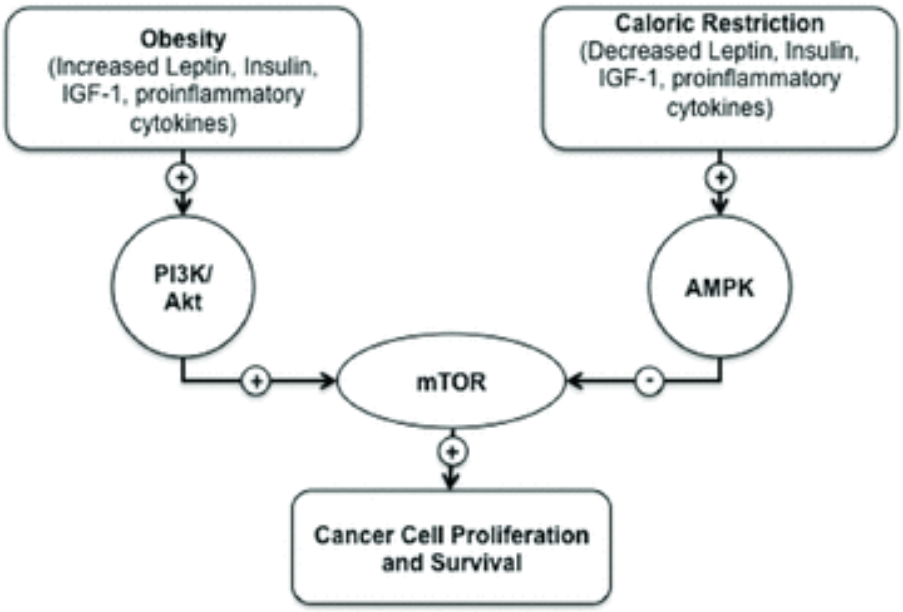
Adipose tissue is an active endocrine organ that releases free fatty acids as fuel in response to signals from other organs and releases peptide hormones such as leptin, adiponectin, resistin and tumour necrosis factor-α (TNFα) (Calle & Kaaks, 2004). Whilst leptin is positively correlated with fat stores and induces cancer progression by activating PI3K, MAPK and STAT3 pathways, adiponectin is inversely associated with adiposity, inflammation and hyperinsulinaemia. Adiponectin exerts its antineoplastic effect by decreasing insulin, insulin-like growth factor (IGF)-1 and mTOR signalling and via its anti-inflammatory inhibition of NF-$_{K}$B (Vucenik & Stains, 2012). Chronic hyperinsulinaemia has been associated with cancer development and the neoplastic effects of insulin could be direct via receptors in target cells, or potentially related to

alterations to endogenous hormone metabolism, such as the promotion of synthesis and activity of IGF-1 (Calle & Kaaks, 2004).

Figure 2.5, extracted from Vucenik & Stains, 2012, portrays obesity as leading to increased signalling via the PI3K/Akt cascade, a promotion of cell proliferation and inhibition of cell apoptosis as a result of increasing levels of circulating leptin, IGF-1 and cytokines. Equally, caloric restriction promotes apoptosis via enhanced signalling through AMPK and suppression of mTOR activity.

Alterations in the metabolism of endogenous sex steroids has also been proposed to potentially explain the association between obesity and CRC, since adiposity influences their synthesis and bioavailability. The increase in circulating levels of insulin and IGF-1 bioactivity via adipose cells, decreases the synthesis of sex-hormone binding globulin (SHBG) in the liver and its concentration in the blood. The decreases in SHBG levels increase the bioavailable oestradiol in both men and women, increase the bioavailable testosterone in men and lead to reduced testosterone production in men (Calle & Kaaks, 2004).

***Figure 2.5 The effect of obesity and caloric restriction on cancer development***




Source: Vucenik & Stains (2012)

Thus, if insulin resistance is a risk factor for CRC, reduced testosterone concentrations as a result of obesity may partly explain sex differences in the strength of association between men and women (Larrson & Wolk, 2007).

It has been previously suggested that insulin resistance and hyperinsulinaemia amongst other factors related to obesity are stronger risk factors for colon than for rectal cancer, with circulating levels of C-peptide, a marker of insulin secretion, and of leptin being more positively associated with incidence of colon cancer than with incidence of overall CRC or rectal cancer (Larsson & Wolk, 2007).

### 2.6.4 Mechanisms relating meat to colorectal cancer

Numerous biological mechanisms have been proposed to explain the association between CRC and red and processed meat and have reviewed by several authors (Ferguson, 2010; Cross et al., 2010; Bastide et al., 2011; Chan et al., 2011). The three most plausible hypotheses underlying this association are discussed below.

- *Mutagenic heterocyclic amines and polycyclic aromatic hydrocarbons*

Cooking meat at high temperatures results in the production of mutagenic heterocyclic amines (HCA). These are however also formed in poultry and consumption of the latter is not associated with increased CRC risk. Furthermore, the amounts resulting in carcinogenesis is animal studies range from 1,000 to 100,000 times higher than the amount consumed by humans. Polycyclic aromatic hydrocarbons (PAHs) result from incomplete combustion of organic compounds and are found in varying amounts in in many common foods, including well cooked meats, but also fish and also poorly washed foods. They are particularly prevalent in processed meats, and are typically transferred into meat during the process of smoking.

- *N-nitroso compounds*

N-nitroso compounds (NOCs) are multisite carcinogens, present in some processed meats, smoked fish and smoked cheeses. They are formed in the GI tract, by N-nitrosation of peptide derived amines or amides, as a result of the nitrates and nitrites added during processing of meats. This reaction is minimized by the addition of Vitamin

C. Nitrite is the primary inhibitor for microorganisms while the latter reduce nitrate to nitrite in raw meat products (Honikel, 2007). Processed meat is typically the main source of human exposure to added nitrite; on the other hand microbes in the oral cavity and in the GI tract may reduce nitrate to nitrite. Nitrite is mixed with food and swallowed; it may form carcinogenic nitrosamines in the acidic environment of the stomach (Honikel, 2007).

- *Heme iron*

It has been suggested by Sesink and colleagues that heme iron, in its ferric form hemin, may explain the association between the consumption of red meat and colon cancer risk (Sesink et al., 1999). Red meat contains 10 times more heme than white meat. Heme iron present in red meat is easily nitrosylated and acts as a nitrosating agent; its presence thus acts as a catalyst increasing the endogenous formation of NOCs from natural precursors.

Additional less likely hypotheses that have been proposed include the high protein, high saturated fat, high cholesterol and high salt content of red meat. For instance, while high fat diets have been hypothesised to promote carcinogenesis, via insulin resistance or faecal bile acids, results from experimental and observational studies have given inconsistent results (Santarelli et al., 2008).

### 2.6.5 Mechanisms relating dietary fibre, whole grains to colorectal cancer

The mechanisms granting dietary fibre a protective effect on CRC incidence are well-established, whilst whole grains are good fibre sources. In the large intestine, fibre increases the weight of stool, dilutes the carcinogenic nature of faeces, reduces transit time and stimulates microbial fermentation. This decreases the contact time between carcinogens and the intestinal mucosa (Lipkin et al., 1999). SCFAs, namely acetate, propionate and butyrate are by-products of fermentation that may act as an energy source for the colonocytes, reduce the pH of the colonic lumen and thus may exert protection against CRC (Slavin, 2003).

Whole grains are also rich in protein and antioxidants, including vitamin E & B complex, trace minerals (iron, magnesium, zinc and selenium) and phytochemicals (Seal et al., 2016). Folate and magnesium have both been associated with a reduced risk of CRC, but in observational studies, results persisted following adjustment for these factors, suggesting an independent association (Aune et al., 2011b). They contain compounds such as phytates, lignin, plant stanols and sterols that may all protect against chronic disease (Slavin, 2003). Furthermore, whole grains mediate insulinaemic and glycaemic responses; whilst this may explain the association between higher intakes offering protection against weight gain and type 2 diabetes (Seal et al., 2016), potentially via reduced insulin resistance, the latter has also been linked to CRC incidence as explained in 2.6.3 above.

### 2.6.6 Mechanisms relating calcium and milk to colorectal cancer

Calcium has been hypothesized to be antineoplastic, by binding to ionized fatty acids and to secondary free bile acids in the lumen of the colon, thus forming insoluble soaps and decreasing the rate of epithelial cell proliferation (Newmark et al., 1984; Van der Meer et al., 1991). Other proposed mechanisms by which calcium may decrease CRC risk is through its influence on multiple intracellular pathways. These include suppression of cell proliferation, promotion of normal cell differentiation and of apoptosis in transformed cells, inhibition of damage from oxidative DNA and modulation of cell-signalling pathways related to CRC (Lapre' et al., 1993; Holt et al., 1998).

Milk, besides being one of the main dietary sources of calcium, could potentially offer protection through other components. The fat content is a source of conjugated linoleic acid and butyric acid, both shown to offer protection in experimental studies. Being a dairy product, it also contains lactoferrin, lactic acid bacteria if fermented and vitamin D if fortified; all three components could be protective (Norat & Riboli, 2003).

## 2.7 Exploring dietary patterns

### 2.7.1 Why explore dietary patterns?

The term diet is broad and encompasses a variety of food consumption aspects. In nutritional epidemiology, diet has been widely studied in relation to CRC risk.

Traditionally, investigations on the role of diet on individual cancer risk focused on varied exposures, including a complex network of individual foods, food groups or nutrients making its role in disease prevention difficult to elucidate (Michels & Schulze, 2005). This approach has been termed 'reductionist' and although it can be instrumental in revealing the role of individual foods, it has its limitations (Willett, 2012), notably also since a change in one component of a diet typically results in substitution by another (Cespedes & Hu, 2015).

A dietary pattern may be defined as 'multiple dietary components operationalised as a single exposure' (Kant, 2004). Dietary pattern analysis is an alternative and complementary approach to such investigations; it represents a more complete picture of food and nutrient intake, takes into account the synergistic effect of food combinations, the variety, frequency and quantity with which they are normally consumed, and may thus be more predictive of disease risk (Hu, 2002). It is likely that it is the interactive effect of several dietary components that predict disease risk. Dietary patterns embody the totality of the diet and allow for several ways to achieve a healthy diet (Cespedes & Hu, 2015).

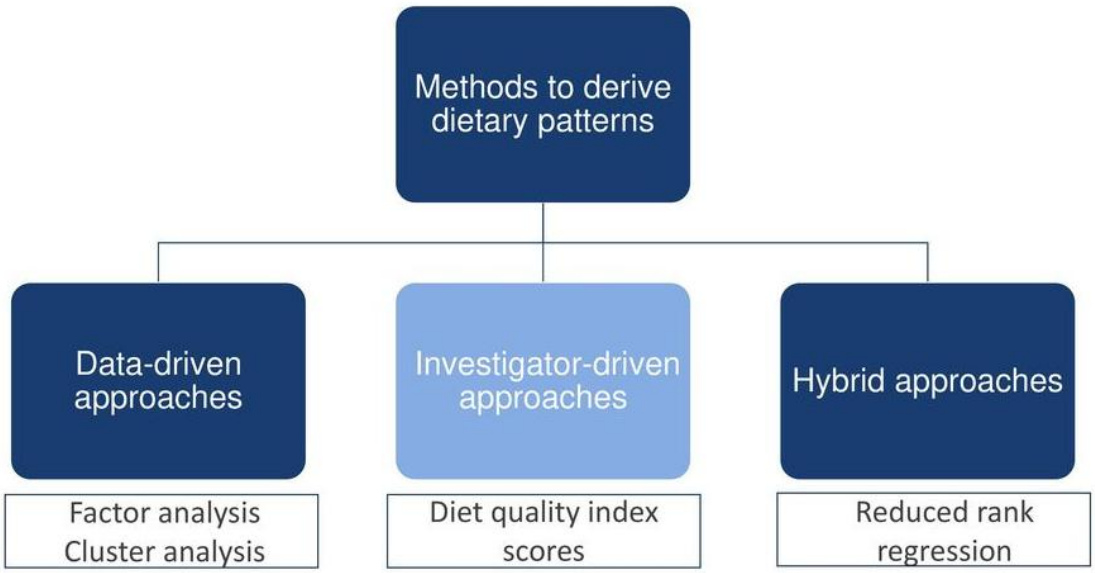
### 2.7.2 Methods used to assess dietary patterns

Statistical methods are used to characterize dietary patterns, using collected dietary information (Hu, 2002). Several methods have been used to relate dietary patterns to disease outcomes, as depicted in Figure 2.6. Each provide information about the diet from a different perspective. These range from data-driven methods that use principal component analysis, factor analysis or cluster analysis to derive dietary patterns, to dietary indices or scores determined and driven by the investigator, and a combination of both methods - reduced rank regression (Michels & Schulze, 2005).

Numerical indices are designed to assess adherence to a specific pattern whilst mathematical approaches derive patterns of food intake common in the study population (USDA, 2014). Dietary patterns that are determined using diet indexes or scores assess compliance with prevailing dietary guidelines / recommendations (Kant, 2004). Such are hypothesis-oriented and are assessed by use of *a priori* scores –

composite numeric scores of foods and / or nutrients assessed as either variables with pre-defined cut-points, or quintiles, or as continuous variables (USDA, 2014). Such indexes are created on the basis of previous knowledge of a 'healthy diet'; the performance of individuals are then compared to these pre-specified standards (Hu, 2002; Michels & Schultze, 2005). It is common that multiple indexes describe variations of the same dietary pattern, such as the MD score or use different scoring and weighting schemes, such as Dietary Approaches to Stop Hypertension (DASH) as opposed to the use of fixed cut offs according to recommended intakes, as in say the Alternate Healthy Eating Index (HEI) (Cespedes & Hu, 2015).

***Figure 2.6 Methods to derive dietary patterns***




Source: Reedy (2016)

Data-driven approaches use factor or cluster analysis to empirically derive dietary patterns, where a large set of dietary variables is aggregated and reduced to form a smaller set of variables. Such analyses are considered *a posteriori* because dietary patterns are determined via statistical modelling of dietary data (Hu, 2002), often assessed using FFQs, 24-hour recalls or diet records (USDA, 2014).

Recently, collaborations were underway to standardize the methodology for dietary patterning across several population based cohorts in view of the fact that the lack of

reliable conclusions has been attributed to inconsistencies in methodologies. In 2012, the Dietary Patterns Methods Project (DPMP) was initiated with the aim of strengthening research evidence on dietary indexes, patterns and health. The collaboration included 4 research groups, 3 large US based cohorts and 4 dietary indexes. Findings suggested that the essential components of a healthy diet were captured by all 4 indexes and reported consistent, strong association for all-cause, cardiovascular disease (CVD) and cancer mortality in all 3 cohorts. This implies that observational research similar to that carried out by the DPMP can be used as a strong basis for making public health recommendations (Liese et al., 2015).

### 2.7.3 Limitations of dietary scores

The approaches to extract dietary patterns listed in section 2.7.2 above both have limitations, and are subject to dietary measurement errors (Kant, 2004). The composition of a diet index, its similarities and differences to other indices, and the choices made in its creation are very important in determining its usefulness as a tool in dietary assessment (Waijers et al., 2007). Randi and colleagues also discuss the reproducibility of dietary patterns as one of the major limitations associated with such research (Randi et al., 2010). They explain that the reproducibility may be threatened by whether the study design is prospective or retrospective, and is dependent on the different study population and geographical region since eating habits including the method of consumption across populations vary (Randi et al., 2010). Dietary pattern analysis is also subject to a low percentage of explained variance of the original food groups; this depends on the number of food items aggregated into food groups; variance increases with the number of items in the same food group. In other words, the broader the classification of foods, the more likely that foods both weakly and strongly associated with a pattern are classified in the same category. Hence, the information captured by a specific pattern increases (McCann et al., 2001).

### 2.7.4 Dietary patterns and colorectal cancer

Notwithstanding the fact that as a result of nutritional epidemiological studies, there is evidence for the role of some dietary factors in CRC development, further experimental studies are required. In spite of its limitations, dietary pattern analysis is

ideal for exploring such a complex association, where several dietary components have been associated with the disease. A dietary pattern specifically predicting risk of CRC has not been established to date but several reviews have looked at diverse dietary patterns in relation to CRC incidence. Findings from these studies are outlined in this section. The specific dietary patterns explored in this research are discussed in sections 2.8 and 2.9, whilst the rationale for the choice of these specific patterns is discussed in chapter 3.

The WCRF/AICR 2011 continuous update report on food, nutrition and physical activity in relation to cancers of the colon and rectum concluded that the evidence for an association with dietary patterns was limited and thus no conclusion could be made (WCRF/AICR, 2011). Several systematic reviews examining studies looking at dietary patterns and CRC risk were published in recent years (Randi et al., 2010; Miller et al., 2010; Magalhaes et al., 2012; Yosof et al., 2012; Fung & Brown, 2013, DGAC, 2015; Tabung eg al., 2017).

A 2010 review by Randi and colleagues investigating 32 articles looking at the association between dietary patterns and risk of CRC, colon and rectal cancer, and adenomas concluded that healthy and prudent dietary patterns, high in fruit and vegetable consumption, proteins such as fish and poultry and whole grains had a favourable effect on risk of CRC. In contrast, traditional and Western dietary patterns rich in refined grains, red and processed meat and potatoes were associated with an increased risk of CRC (Randi et al., 2010). The review of six cohort studies by Yusof and colleagues came to the same conclusion (Yusof et al., 2012). In a third review two dietary patterns were found to modestly influence colorectal adenoma and cancer risk; namely a healthier pattern based on a greater consumption of fruit and vegetables and lower intakes of red and processed meat and a less healthy pattern typified by higher intakes of the meat, potatoes and refined carbohydrates (Miller et al., 2010). A further systematic review of eight cohort and eight case-control studies addressing this same association with *a posteriori* dietary patterns found comparable results for both proximal and distal colon cancer, with an increase for high intake of red and processed meat 'Western' and a decrease for 'healthy' – high fruit and vegetable consumption -

dietary patterns; no significant associations were observed for rectal cancer (Magalhaes et al., 2012). Fung & Brown (2013), concluded that a plant-based diet together with some dairy intake appears to decrease CRC risk, whilst a high intake of meats, refined grains and added sugar in the diet seems to increase risk of CRC, and evidence for alcohol and CRC remains inconsistent.

In 2015, following a systematic review including 21 articles from prospective cohort studies and one article from a RCT, the Scientific Report of the 2015 DGAC of the USDA concluded that the level of evidence for dietary patterns in relation to risk of CRC was moderate (USDA, 2015).

*"Moderate evidence indicates an inverse association between dietary patterns that are higher in vegetables, fruits, legumes, whole grains, lean meats and seafood, low-fat dairy and moderate alcohol; and low in red and processed meats, saturated fat and sodas and sweets relative to other dietary patterns and the risk of colon and rectal cancer. Conversely, diets that are higher in red and processed meats, French fries and potatoes, and sources of sugars (i.e., sodas, sweets and dessert foods) are associated with a greater colon and rectal cancer risk." (DGAC, 2015, Chapter 2, pg. 30).*

More recently, Tabung and colleagues conducted a review synthesizing data from 28 cohort studies and 21 case-control studies related to dietary patterns, covering a 17 year period. Findings were very similar to those reported by the USDA (2015). They showed that a healthy pattern with a high consumption of fruit and vegetable, whole grains, nuts and legumes, fish and other seafood, milk and other dairy products was associated with lower CRC risk, whilst diets with high intakes or red and processed meat, sugary beverages and desserts, refined grains and potatoes were associated with a higher incidence of CRC (Tabung et al., 2017).

## 2.8 The Mediterranean dietary pattern

### 2.8.1 Defining the Mediterranean diet

'Mediterranean diet' refers to the term used to describe the dietary pattern characteristic of Mediterranean Basin countries in the 1960s, associated with greater longevity and reduced mortality and morbidity (Serra-Majem et al., 2004). The

traditional MD is characterised by an abundance of plant foods fruit, vegetables, whole grains, beans, nuts and seeds, a moderate intake of fish, poultry, eggs and dairy and low amounts of red and processed meats. Wine is typically consumed with meals, olive oil is the main fat source and dessert is normally fruit (Willett et al., 1995).

### 2.8.2 The Mediterranean diet and health status

With the available evidence on its associated health benefits (Pauwels, 2011; Kontou et al., 2011), awareness of this eating pattern is widespread. Several of the food components making up the traditional diet, as listed by Willett and colleagues have been consistently associated with increasing or reducing CRC risk, such as red meats and whole grains respectively (Willett et al., 1995), as outlined in section 2.4. Adherence to the MD may thus confer a reduced risk of CRC and several scores have been created to measure this factor. A review of the use of indices in evaluating the adherence to the MD in epidemiological studies has been carried out by Bach et al. (2006). This classification is highlighted further in section 3.8.2.

In meta-analyses reviewing cohort studies exploring adherence to a MD and health status, a significant reduction in overall mortality, mortality from CVD and incidence of or mortality of cancer amongst other diseases was associated with a greater adherence (Sofi et al., 2008; Sofi et al., 2010; Sofi et al., 2014). For a two-point increment of the MD score, an 8% reduction in overall mortality (0.92; 95% CI = 0.91, 0.93), a 10% reduction in CVD risk (0.90; 95% CI = 0.87, 0.92) and a 4% reduction of cancer (0.96; 95% CI = 0.95, 0.97) was observed (Sofi et al., 2014). In a systematic review of observational studies in the elderly, this reduced risk of CVD and some cancer types as a result of a high adherence to a MD is confirmed (Tyrovolas & Panagiotakos, 2009). This is consistent with results from a prospective cohort study on the Greek segment of EPIC where a statistically significant reduction in total mortality (0.86, 95% CI = 0.83, 0.93) was associated with a higher adherence of the Mediterranean eating pattern (Trichopoulou et al., 2009). In a separate investigation also using data from EPIC and looking at the association between concordance to a Mediterranean dietary pattern and overall cancer risk, a lower overall cancer risk

(0.96, 95%CI = 0.95, 0.98 for a two-point increment of the MD score) was found with a greater adherence to the MD (Couto et al., 2011).

Evidence from RCTs in humans are lacking. The only intervention trial investigating adherence to the MD and cancer incidence is the Lyon Heart RCT, which was initially not specifically designed to look at cancer survival. While results suggest that following a Mediterranean-like diet rich in α-linolenic acid is significantly associated with prolonged survival and cancer protection, the number of cases was small (de Lorgeril et al., 1998).

The randomized, primary prevention PREDIMED (PREvención con DIeta MEDiterránea) trial assessed the long term effects of an energy-unrestricted MD on CVD in over 7000 men and women. Results provided convincing evidence that a plant-based MD, rich in unsaturated fats and polyphenols may prevent CVD, especially in those at high risk (Martinez-Gonzalez et al., 2015; Estruch et al., 2013).

### 2.8.3 The Mediterranean diet and colorectal cancer

Studies specifically exploring associations between the MD and risk of CRC are limited and have given inconsistent results, especially in relation to the different anatomical sites of the colorectum and by gender. Fung and colleagues found no association between adherence to the Alternate Mediterranean diet (aMed) and colorectal, colon or rectal cancers in a large cohort of middle-aged men and women (Fung et al., 2010). The aMed was based on the original MD score as defined by Trichopoulou et al. (2003) but modified by excluding potato products from the vegetable group, splitting fruit and nuts into individual groups, eliminating dairy from the score, including only wholegrain products, including only red and processed meats in the meat group and giving a score of 1 for alcohol intake between 5 and 15 g/d (Fung et al., 2006). In a case-control study using data from the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, Dixon and colleagues found a reduced risk of colorectal adenomas in men only (Dixon et al., 2007). This was consistent with findings from a large US cohort study looking at four different index-based dietary patterns that found adherence to the MD reduced risk of distal colon and rectal cancers, but not of proximal cancers, only in

men, whilst no associations were found in women (Reedy et al., 2007). Conversely, in the large European cohort EPIC, there was a reduced risk for colorectal and distal colon cancers, but not for proximal colon or rectal cancers, with associations for CRC more evident among women (Bamia et al., 2013). In the Italian section of EPIC, similar associations were found for all cancer sites, but the risk reduction was observed in both sexes (Agnoli et al., 2013).

Notwithstanding, comparisons between studies should be made with caution in view of the variation in the derivation of the MD scores. Furthermore, the reporting of inconsistency of results by sex and anatomical site across different studies may not be statistically significant, especially in cases where the CI overlap. In such cases, the outcome categories (sex or site) can be said to have been segmented.

## 2.9 Cancer prevention recommendations

### 2.9.1 Defining the recommendations

In 2007, the WCRF/AICR issued public health goals and recommendations on diet, physical activity and weight management for cancer prevention, based on judgments made of the available evidence to date. The aim is to reduce cancer incidence and risk of other non-communicable disease throughout the world. The issuing panel proposed that the recommendations should form the basis of public health policies, influence choices on an individual level and direct future scientific research and cancer prevention education programmes. Eight general and two special goals and recommendations are listed, with public health goals and / or personal recommendations following each general recommendation (WCRF/AICR, 2007). The recommendations are listed below whilst the sub-recommendations are found in Appendix IV.

**General recommendations**

1. Body fatness

*Be as lean as possible within the normal range of body weight.*

2. Physical activity

*Be physically active as part of everyday life.*

3. Food and drinks that promote weight gain

*Limit consumption of energy-dense foods and avoid sugary drinks.*

4. Plant foods

*Eat mostly foods of plant origin.*

5. Animal foods

*Limit intake of red meat and avoid processed meat.*

6. Alcoholic drinks

*Limit alcoholic drinks.*

7. Preservation, processing and preparation

*Limit consumption of salt and avoid mouldy cereals (grains) or pulses (legumes).*

8. Dietary supplements

*Aim to meet nutritional needs through diet alone.*

**Special recommendations**

1. Breastfeeding

*Mothers to breastfeed and children to be breastfed.*

2. Cancer survivors

*Follow the recommendations for cancer prevention.*

The ACS also publishes Nutrition and Physical Activity Guidelines based on the current scientific evidence on diet and activity patterns in relation to cancer risk. These guidelines are developed by a panel of experts with the fields of cancer research, epidemiology, public health and policy – the current version was last updated in 2012 (Kushi et al., 2012).

### 2.9.2 Adherence to cancer prevention recommendations and health status

Researchers have turned cancer prevention guidelines into a dietary index, enabling them to assess the extent to which a population adheres to cancer prevention guidelines and the health outcomes associated with doing so. This was first done using the ACS cancer prevention guidelines. In 2012, Romaguera and colleagues were the first research group to publish a study using the WCRF/AICR cancer prevention guidelines as a dietary pattern (Romaguera et al., 2012). More information on the

WCRF/AICR score, and its construction are given in chapters 3 and 5. Since then, a number of studies have tested indexes based on adherence to WCRF/AICR cancer-prevention recommendations in relation to different health outcomes.
In the Cancer Prevention study II Nutrition cohort - investigating the effect of adherence to the ACS cancer prevention guidelines, a lower risk of death from cancer, CVD, and all causes was found only in non-smokers (McCullough et al., 2011). Thomson and colleagues also examined the association between the ACS guidelines and cancer; the highest adherence scores were associated with a 17% reduced risk of any cancer, 27% lower risk of mortality from all causes, and 20% lower risk of cancer-specific mortality in postmenopausal women (Thomson et al., 2014).

In EPIC, a study of approximately 380 000 participants from 9 European countries, concordance with WCRF/AICR recommendations was investigated in relation to cancer risk (Romaguera et al., 2012) and to mortality risk (Vergnaud et al., 2013). Participants with the highest adherence score were found to have a 34% lower death risk (95% CI = 0.59, 0.75) when compared to the lowest scores (Vergnaud et al., 2013), whilst a 5% lower total cancer risk was reported (95% CI = 3%, 7%) for a one-point increment in the WCRF/AICR score (Romaguera et al., 2012). Conversely, in the Framingham Offspring cohort of approximately 3000 participants, the overall score was not associated with obesity-related cancer risk (Makarem et al., 2015); notably the results may be less reliable than for the EPIC study in view of the much smaller sample population. In a follow up of the Iowa Women's Health study among older female cancer survivors, adherence to the WCRF/AICR guidelines was associated with lower all-cause mortality, with the strongest association being that of the physical activity recommendation, implying that older cancer survivors may reduce their death risk by following the recommendations (Inoue-Choi et al., 2013).

### 2.9.3 Adherence to cancer prevention recommendations and colorectal cancer

When investigating associations between adherence to cancer prevention guidelines and incidence of cancers of the colon and rectum, studies have mainly explored adherence to ACS guidelines (Thomson et al., 2014; Kabat et al., 2015), or looked at incidence of total CRC rather than differentiated between the colon and rectal cancer-

sites (Makarem et al., 2015; Romaguera et al., 2012; Hastert & White, 2016 & Nomura et al., 2016). Furthermore, results of the latter studies are conflicting.

In the Women's Health Initiative Observational Study, with approximately 66,000 post-menopausal women, a 52% reduced CRC risk (95% CI = 27%, 68%) was reported for the highest ACS guidelines scores compared with the lowest (Thomson et al., 2014). Romaguera and colleagues reported a 12% decreased CRC incidence (95% CI = 9%, 16%) with a 1-point increase in the WCRF/AICR score in the EPIC population (Romaguera et al., 2012). In the National Institutes of Health - American Association of Retired Persons (NIH-AARP) Diet and Health Study, a cohort study of over 565,000 adults, a high ACS score was association with a significantly reduced risk of both colon (HR=0.65; 95% CI = 0.54, 0.78) and rectal (HR=0.64; 95% CI = 0.49, 0.83) cancer (Kabat et al., 2015). In the VITamins And Lifestyle (VITAL) cohort, meeting 1-3 WCRF/AICR recommendations was associated with 34-45% lower CRC incidence, whilst meeting 4-6 recommendations was associated with 58% reduced CRC risk (Hastert & White, 2016). Conversely, in the Framingham Offspring cohort (Makarem et al., 2015) and in the Black Women's Health Study (Nomura et al., 2016), no significant associations were reported between the overall score and CRC.

In view of the limited evidence and the inconsistency in results, further studies operationalising the WCRF/AICR guidelines in diverse populations and looking at the association between CRC, and exploring the different anatomical sites separately are needed. This will allow an assessment of the validity of cancer prevention recommendations for specific cancers, and in different populations.

## 2.10 Summary

The combined evidence from observational and experimental studies looking at associations between diet and CRC suggests, at the very least, that cancer risk is modifiable. Routine screening assists in the reduction of CRC incidence and mortality, but may be foiled in regions with limited resources. The preventive channel, via lifestyle modifications may contribute in lowering the overall risk and is potentially

more appropriate in reducing the global burden. The several modes of action of different dietary components on CRC risk have been discussed in this chapter.
As methods to assess dietary patterns improve, the level of evidence is strengthened and the advantage of their use in research over individual foods and nutrients becomes more apparent. The way forward is thus their use not only in nutritional epidemiologic analysis but also as an approach for giving public health recommendations (Cespedes & Hu, 2015). This dissertation will explore the association between dietary patterns and risk of CRC in a population of British women, thus contributing to the body of evidence in the area of dietary chemoprevention.

# CHAPTER 3 GENERAL METHODS

## 3.1 Chapter overview

A number of methodological approaches are required in order to satisfy the objectives outlined in chapter 1. These include summarising the evidence to date as well as investigating dietary patterns and relating them to CRC. This chapter gives details to the UKWCS study design, including the sampling methods undertaken in section 3.3. The dietary assessment tools used for data collection are discussed in section 3.4, the assessment of UKWCS participants' health and lifestyle in section 3.5 and the ethical considerations made at the initiation of the study are outlined in section 3.6. The information used to define cases is outlined in section 3.7 whilst a description leading to the choice of the two dietary patterns used is given in section 3.8. Furthermore, details of statistical methods common to the results chapters 4, 5 & 6 are outlined in section 3.9. Section 3.10 depicts the analytical framework of this thesis in a flow chart whilst section 3.11 summarises the chapter.

## 3.2 Gap analysis

There is a body of research associated with diet and cancer as outlined in the previous chapter. For the purpose of this study, studies specifically investigating links between diet and incidence of colorectal, colon and rectal cancer have been considered. Evidence to date concerning this relationship was examined to identify gaps and areas in the literature that have been least explored. An advanced, non-systematic search for existing reviews, using several databases including EMBASE, Ovid MEDLINE, The Cochrane Database of Systematic Reviews and Web of Science amongst others was conducted to gather the relevant literature. Titles and abstracts were screened for relevance. Findings from the 2007 and 2011 WCRF/AICR Systematic Literature Reviews on the associations between food, nutrition and physical activity and CRC incidence were considered in particular. The literature search and reading led to the identification of a gap in the scientific evidence on the associations between some dietary patterns and CRC. The search was eventually expanded to look at recent, original studies, focusing mainly on cohort studies.

## 3.3 Study design & population

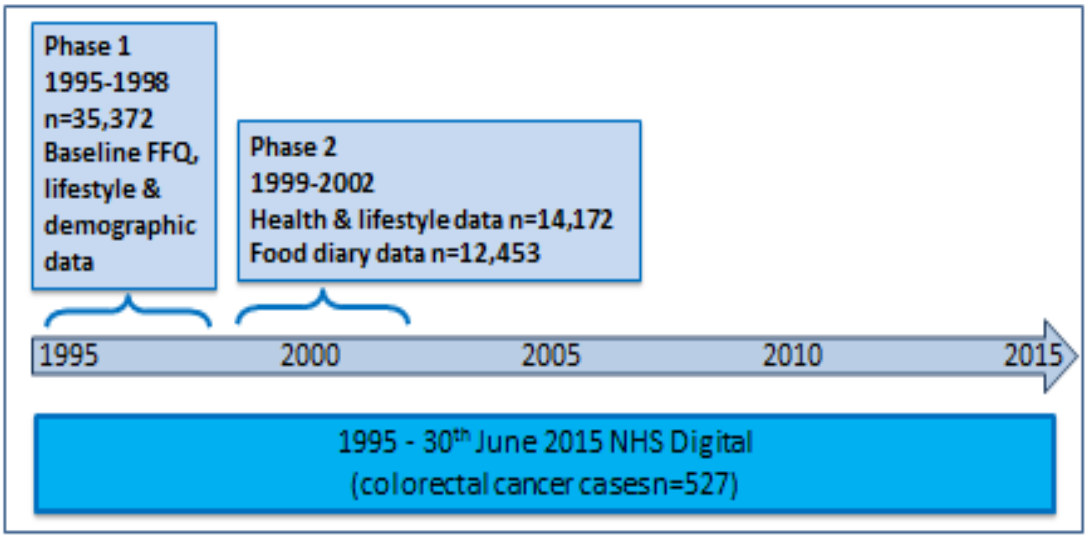
The analyses in this study will use existing, pre-gathered data from one of the largest population-based prospective studies in the UK that was primarily designed to investigate links between diet and chronic diseases – the UKWCS. Two phases for the cohort were planned at the start, baseline data collection and phase 2 follow-up data collection 4 years later. Nevertheless, subsamples of the cohort were contacted several times since then, and numerous investigations have been carried out since then, as detailed in the cohort profile (Cade et al., 2015). For the first time this dataset will be used to assess CRC risk in relation to the dietary patterns derived from the MD and the WCRF/AICR cancer prevention guidelines.

The UKWCS of 35 372 middle-aged women was in its majority formed from participants of a WCRF 1995 direct mail survey, targeted towards women. 75% of those who initially responded were willing to participate in further studies. In view of the fact that the dataset was initially designed to compare disease incidence in vegetarians, fish-eaters and red meat eaters, all eligible 35-69 year old women stating they were vegetarian or non-red meat eaters were asked to participate (approximately 16,000) whilst only a percentage of meat eaters were included in the study. Further recruits were identified by respondents of the baseline questionnaire themselves. 58% of the 61,000 women invited to participate completed a self-administered FFQ between 1995 and 1998, providing data for the baseline dataset. Information on diet, lifestyle and health was also provided. Approximately four years after initial recruitment, between 1999 and 2002 participants were re-contacted and asked to complete a follow-up health and lifestyle questionnaire as well as a four day FD and exercise diary for one day. 14 172 (40%) and 12 453 (35%) completed the questionnaires and diary respectively.

This information resulted in a second, smaller, follow-up dataset. Participant details – including the NHS number, name and date of birth were submitted to the Office of National Statistics for flagging on NHS Digital (at the time called the NHS Central Register – NHSCR). In this way, health outcome episodes and registration of participant deaths would be recorded. This was successful for over 98% of the full cohort

participants. For the purpose of this study, the main health outcome of interest is incidence of CRC. The censor date used was 1st April 2014, and 527 incident cases of CRC were documented with NHS Digital. Figure 3.1 depicts the timeline for women completing different phases of the UKWCS.

***Figure 3.1 Timeline depicting phase 1 & phase 2 of the UKWCS***




The cohort participants are mainly white, middle-class and well-educated with 27% having a degree and 86% are married and have children. In view of the recruitment process partly via the WCRF, (women ready to fill in relatively long questionnaires) together with the fact that over a quarter claimed to be vegetarian, the women may be said to be generally health conscious – only a small percentage are smokers whilst more than half report taking dietary supplements. The women's baseline characteristics are tabulated in chapters 4, 5 & 6, in tables 4.2, 5.2 and 6.1 respectively. This implies that the cohort is not representative of the UK population and thus limits the generalizability of results. Notwithstanding, it was never intended to be and subjects were selected in a way that ensured representation of a range of dietary patterns. Such a selection ensured that the exposure to the dietary factors of interest was optimised, increasing the power for potential associations between diet and cancer (Cade et al., 2004a).

## 3.4 Dietary assessment tools

### 3.4.1 Food frequency questionnaire

The questionnaire sent to participants at baseline was developed from one used by the Oxford arm of the EPIC (Riboli & Kaaks, 1997), with the addition of vegetable-based composite dishes to accommodate the high proportion of vegetarians in the UKWCS. This modification resulted from a pilot study on 71 vegetarian women, who were asked to answer a FFQ and keep a FD for 7 days, contributing to additional information on typical vegetarian dishes and portion sizes. (Cade et al., 2004a).

Figure 3.2 shows an example section from the FFQ relating to frequency of consumption of some meats whilst the combined baseline questionnaires – for food frequency and lifestyle are found in Appendix V. A total of 217 food items made up the questionnaire; participants were asked to tick one of 10 pre-coded categories, indicating average consumption frequency of the specific item, ranging from never to 6 or more times daily, over the past 12 months.

***Figure 3.2 Section of the baseline FFQ related to intake of some meats***

| FOODS AND AMOUNTS | HOW OFTEN HAVE YOU EATEN THESE FOODS IN THE LAST 12 MONTHS? | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | NEVER | Less than once a month | 1-3 per month | once a week | 2-4 per week | 5-6 per week | once per day | 2-3 per day | 4-5 per day | 6+ per day |
| OTHER MEATS | | | | | | | | | | |
| **Chicken/Turkey** roast, slices | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Breadcrumbed e.g.chicken nuggets/kievs | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Chicken/Turkey in creamy sauce, curry | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| **Bacon** | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| **Ham** | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Corned Beef, Spam, Luncheon Meats | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |

This allowed an estimation of the number of portions consumed per day for each item. Portion weight was assigned to each food item – calculated as the average of three sources (Calvert et al., 1997). These included (1) FDs from the pilot study; (2) portion sizes for women from the National Diet and Nutrition Survey (NDNS, 1994); (3) other published values (Crawley, 1993). Nutrient intakes were then calculated using data from McCance & Widdowson's *The Composition of Foods* (5$^{th}$ edition) (Holland et al.,

1991), choosing foods to include all varieties and all possible cooking methods (Calvert et al., 1997).

### 3.4.2 Food diaries

When subjects were contacted a second time in phase 2, they were sent a booklet and asked to log all food and beverages consumed within a four-day period, as well as the physical activity performed on the third day. Participants were given instructions on how to complete the diary. They were asked to record food and to include a description of how it was prepared, to provide the nutritional information provided on the packet of any readymade foods consumed, to list recipes of items / meals made from scratch, and to give weighed or estimated portion sizes. Suggestions to use household measures such as tablespoons or cup measures if kitchen scales were not available were given. Instructions given included a half-day example on how to fill in the booklet, as depicted in Figure 3.3. The women were also asked to make note of any dietary supplements they took.

Following four days of recording food intake, participants were also asked some general questions about their diet, as a confirmation of facts, with the main aim of ensuring that the coding process is as accurate as possible. Examples of such questions included: *'How thickly did you spread your butter, margarine or spread on bread, crackers etc?'* and *'Did you add salt to your food during cooking?'.* A copy of the FD template is found in Appendix VI. Participants were also sent a questionnaire requesting additional information related to their eating habits, health and lifestyle. A copy of this questionnaire template is found in Appendix VII.

***Figure 3.3 Sample food log given to phase 2 participants to aid completion of food diary***

**EXAMPLE DAY - UP TO LUNCH**

| Date: 14 October 1998 Day of the week Friday | | |
|---|---|---|
| **Time of food or drink** | **Description of food or drink consumed (include brandname where possible)** | **amount** |
| 7.15 am | Filter Coffee | 1 cup (200ml) |
| | semi-skimmed milk | 3 tablespoons |
| 7.30 am | Sainsbury's orange juice, un-sweetened | 1 glass (150ml) |
| | Sainsbury's Bran flakes | 40g |
| | semi-skimmed milk | 180ml |
| 10.30am | Plain chocolate digestives (large biscuits) | 2 |
| | Earl Grey tea (weak) no milk | 1 cup |
| 11 am | banana (medium sized) | 95g |
| 11.30 am | London herb company Lemon Zester tea | 1 |
| 12.10 pm | Local bakery's wholemeal bread un-sliced loaf (cut thickly) | 1 slice 47g |
| | Tesco sunflower margarine | thinly spread |
| | home-made mushroom risotto (see recipe) | About 1/3 of recipe |
| | green seedless grapes | 32g |
| | Cox's Orange Pippin apple (medium) | 82g |
| | Sainsbury's wholemilk fruit yoghurt (150g) | 1 pot |
| | London herb company sweet berry tea | 1 |
| 2pm | Warburton's Carrot cake – with cream cheese topping (see nutritional information) | 1 slice – 75g (on packet) |

### 3.4.2.1 Food diary coding

Nutrient intakes from FD were calculated using Diet and Nutrition Tool for Evaluation (DANTE) – a Microsoft Access program developed by the University of Leeds Nutritional Epidemiology Group. This in-house package uses standard values from McCance & Widdowson's *The Composition of Foods* (5th edition) (Holland et al., 1991) as well as additional data from manufacturers and recipes. In cases where the portions sizes were missing, average portion sizes as listed in the Food Standards Agency *Food Portion Sizes* (3rd edition) (FSA, 1994) were assigned. Furthermore, recipes provided by the subjects were added to the package. This ensures entry of data is as accurate as possible.

Whilst recruiting participants willing to keep a detailed record of their food intake for several days is challenging, the processing of such recorded data – diary coding, is very labour intensive and not all diaries have been coded to date. The case-cohort method was thus used for the purpose of this research. FD of women identified as CRC cases through NHS Digital were handpicked and coded together with an equal number of random cohort controls chosen via a Microsoft Access query. Such controls are chosen from the full cohort and thus called the 'sub-cohort'. This was done to allow the coder to be blind, reducing coder bias. Control diaries were selected from the full sample of approximately 14 000 phase 2 subjects to ensure the sample is not skewed. Since some diaries (both cases and controls) had been previously coded for use in different research, the number of random control diaries chosen was greater than the number of cases to ensure sufficient control diaries and maintenance of coder blinding. The nutrient profile reports generated for all cases and controls respectively, together with previously generated reports available from investigations of other associations in the UKWCS were used in the analyses in order to consolidate findings. Diary coding details were logged on a tracking form within a Microsoft Access database to facilitate future research.

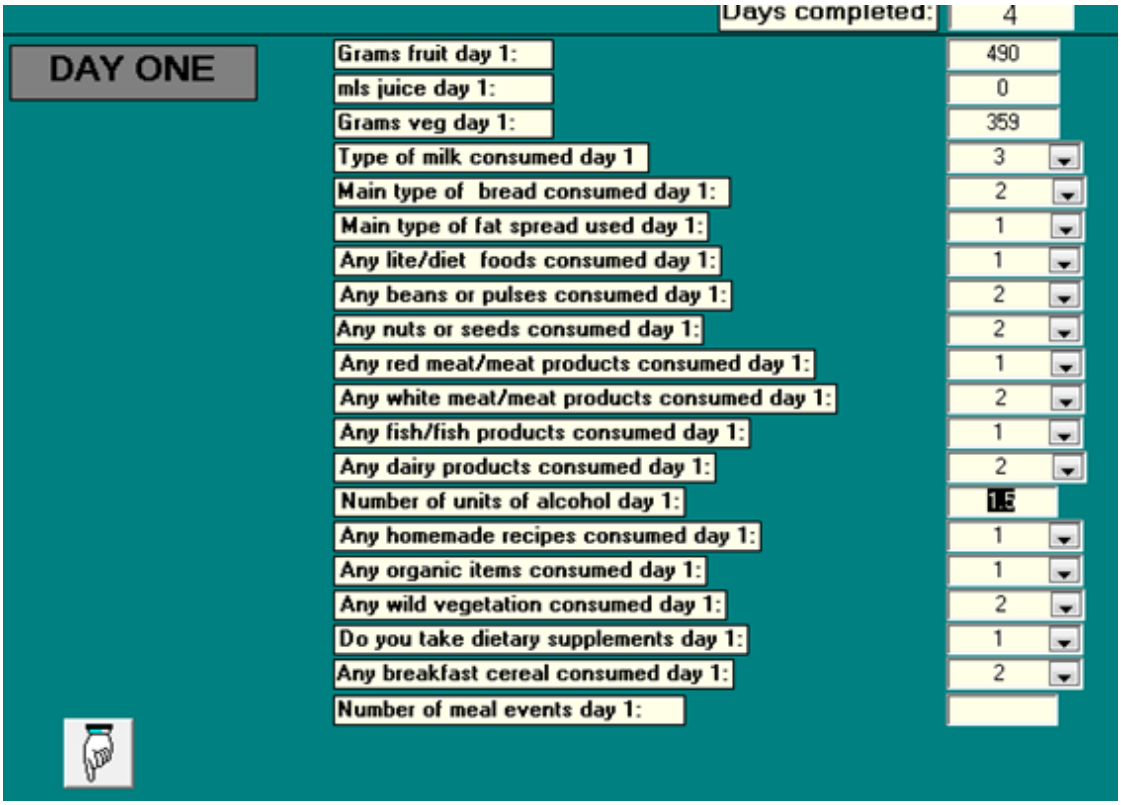
FD coding may include a percentage of coder subjectivity. To counteract this, a protocol to guide coders on the use of DANTE and on interpreting FD was prepared by the researcher to minimize coder variability (Refer to Appendix VIII). Coders were also initially trained in the use of the package and invited to query when in doubt or when they had any issues relating to specific food items. Protocol instructions specified food items to be entered into DANTE in the form eaten, such as the weight of cooked rather than raw pasta. This is crucial since participants tend to report the raw weight of consumed food, but in the case of say cereals, which absorb water during cooking, the food weight multiplies around four fold. On the other hand, protein foods such as meat decrease in mass during cooking. Coders were thus given access to an Excel spreadsheet, pre-programmed with cooking conversion multiplication factors; this would allow the raw weight to be entered, and it would be converted to the cooked weight. McCance & Widdowson's *The Composition of Foods* ($5^{th}$ edition) (Holland et al., 1991) was used to source conversion factors. This process helped to minimise

coding errors. Nevertheless, coded FDs were cross-checked between coders and edited as necessary.

#### 3.4.2.2 Quality checklist

Since resources do not allow for the full coding of all FDs, key information from all returned FD has been previously captured and the data entered onto a database - a quality checklist. The data captured includes type of bread, milk and fat spread consumed, grams of fruit and vegetables consumed, whether any meat, nuts, dairy products or supplements were consumed, amongst other information, as depicted in Figure 3.4, for all the days of completed FD. These key pieces of information provide an overall picture of the diet consumed by cohort members.

***Figure 3.4 Section of the food diary quality checklist, related to one day of consumption***

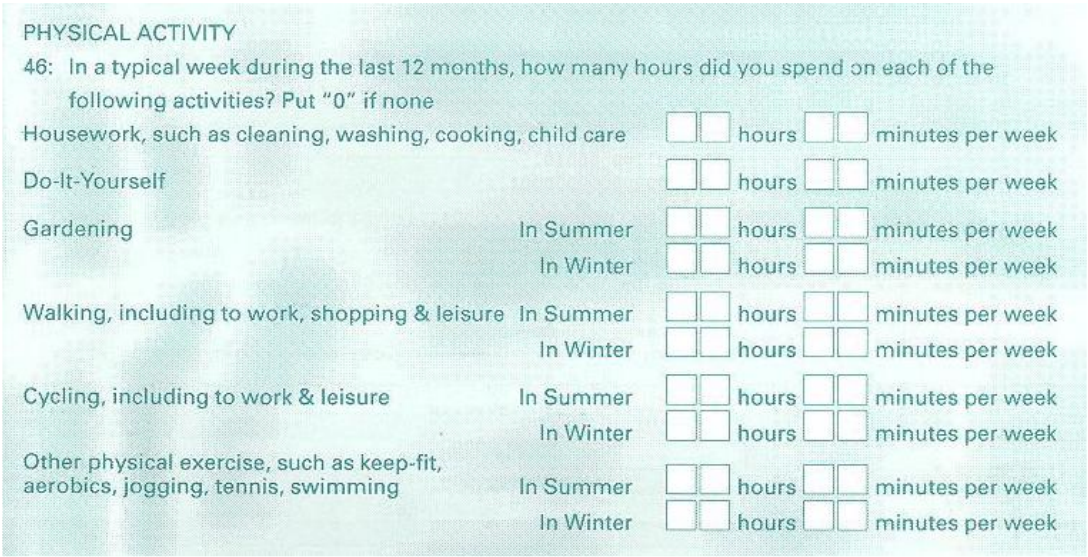



Baseline data extracted from the FFQ was used for the investigations detailed in chapters 4 & 5, whilst data extracted from FD and some of the data reported in the quality checklist was used for the study in chapter 6. FD with less than 3 full days completed were not coded and thus not included in the analysis.

## 3.5 Assessment of health & lifestyle

The questionnaire given at baseline also included questions on health and lifestyle, with questions on smoking, size, physical activity, illness, education, employment, menstrual and obstetric history following the FFQ and other food related questions. At phase 2, in conjunction with the FD, participants were also asked to fill in a questionnaire asking mostly about eating habits and cooking methods but also about smoking, weight and height, illnesses and family medical history, physical activity, medications, pregnancy, contraception and menstrual cycle and bowel movements. Figures 3.5 and 3.6 show sections of the baseline and phase 2 questionnaires respectively, related to some of the questions asked on physical activity. Some of the data in both these questionnaires was used to derive one of the dietary patterns – the WCRF/AICR score, as detailed in chapter 5, to exclude some participants from the analysis – such as people with a previous family history of cancer, and to adjust for potential confounding factors, as explained in section 3.9.2.2.

***Figure 3.5 Section of the baseline health & lifestyle questionnaire related to activity.***



PHYSICAL ACTIVITY

46: In a typical week during the last 12 months, how many hours did you spend on each of the following activities? Put "0" if none

| | | | |
|---|---|---|---|
| Housework, such as cleaning, washing, cooking, child care | | ☐☐ hours | ☐☐ minutes per week |
| Do-It-Yourself | | ☐☐ hours | ☐☐ minutes per week |
| Gardening | In Summer | ☐☐ hours | ☐☐ minutes per week |
| | In Winter | ☐☐ hours | ☐☐ minutes per week |
| Walking, including to work, shopping & leisure | In Summer | ☐☐ hours | ☐☐ minutes per week |
| | In Winter | ☐☐ hours | ☐☐ minutes per week |
| Cycling, including to work & leisure | In Summer | ☐☐ hours | ☐☐ minutes per week |
| | In Winter | ☐☐ hours | ☐☐ minutes per week |
| Other physical exercise, such as keep-fit, aerobics, jogging, tennis, swimming | In Summer | ☐☐ hours | ☐☐ minutes per week |
| | In Winter | ☐☐ hours | ☐☐ minutes per week |

***Figure 3.6 Section of the phase 2 questionnaire related to weekday activity.***

ACTIVITY

37. On an average **weekday** how is your day spent?

| | Number of hours & / or minutes in a 24 hour day spent doing the following activities? | |
|---|---|---|
| | Hours | Minutes |
| Sleeping | | |
| Sitting | | |
| Light activities (e.g. washing, dressing, eating) | | |
| Standing | | |
| Household chores (e.g. vacuuming, ironing) | | |
| Lifting heavy objects | | |
| Light exercise (e.g. walking, yoga, easy gardening) | | |
| Moderate exercise (e.g. fast walking, easy swimming, hill walking, easy cycling) | | |
| Strenuous exercise (e.g. running, vigorous swimming, high impact aerobics) | | |

## 3.6 Ethical considerations

The dataset from the UKWCS is the property of the Nutritional Epidemiology Group at the University of Leeds, available for this research and carries with it ethical approval that was granted at its initiation in 1993 from relevant research ethics committees (174 within the UK) (Cade et al., 2004a). Participants had consenting to the confidential use of collected data at baseline, in follow-up stages and from cancer registries for research purposes. A copy of one of the approval letters from a local ethics committee is found in Appendix IX. The National Research Ethics Committee (REC) for Yorkshire and the Humber - Leeds East have now taken on responsibility for the ongoing cohort (Cade et al., 2015). Whilst no new information was needed for the investigations carried out in this study and thus no additional ethical approval was necessary, the researcher made contacted the Committee and established a REC reference number for the UKWCS - 15/YH/0027. This will facilitate ethical approval for further research on the cohort, when necessary. The relevant communication related to this is found in Appendix X.

## 3.7 Outcome data, censor date & case definition

The cancer outcomes used in the analyses are incident malignant neoplasms of the colon (codes 153.0-153.9 or C18) and of the rectosigmoid junction and of the rectum (codes 154.0-154.1 or C19 and C20) of the International Statistical Classification of Diseases (ICD), 9th and 10th editions. The ICD-10 codes for malignant neoplasms are as specified for the CRC site in the GLOBOCAN 2012 database (WHO, 2010). Table 3.1 lists the relevant codes.

***Table 3.1 Colorectal neoplasms: ICD-9 and ICD-10 classification codes***

| ICD-9 Code | ICD-10 Code | Description | Category |
|---|---|---|---|
| ***Malignant neoplasm of the colon*** | | | |
| 153.4 | C18.0 | Caecum | Proximal |
| 153.5 | C18.1 | Appendix | Proximal |
| 153.6 | C18.2 | Ascending colon | Proximal |
| 153.0 | C18.3 | Hepatic flexure | Proximal |
| 153.1 | C18.4 | Transverse colon | Proximal |
| 153.7 | C18.5 | Splenic flexure | Proximal |
| 153.2 | C18.6 | Descending colon | Distal |
| 153.3 | C18.7 | Sigmoid colon | Distal |
| 153.8 | C18.8 | Overlapping lesion of colon | Colon general |
| 153.9 | C18.9 | Colon, unspecified | Colon general |
| ***Malignant neoplasms of the rectosigmoid junction and of the rectum*** | | | |
| 154.0 | C19 | Rectosigmoid junction | Rectum |
| 154.1 | C20 | Rectum | Rectum |

Regional cancer registries document cancer diagnoses under ICD codes; these are then collated by NHS Digital. Registrations of cancer diagnosis for women in the UKWCS are made available to the University of Leeds at least annually. These are made via record linkage of identification codes to the central register of NHS Digital. Any personal information enabling identification of the women is deleted before the data is made available for analysis. This data is available from baseline in 1995 until the 1st April 2014. The latter was used as the censor date for the purpose of this study, for both the baseline and the phase 2 datasets. 98% of baseline participants were successfully

traced to allow record linkage. The median time to cancer incidence or time to cancer date from the date the questionnaire was received was 17.4 years.

Cases were identified as patients who were cancer free, except for non-melanoma skin cancer, at the time of FFQ or FD completion and who developed CRC a minimum of 12 months after the start of dietary assessment. This was done since the presence of latent disease, though not formally diagnosed could have influenced the eating habits of women suspecting to be ill. Excluding all cancer patients, in favour of excluding only those with CRC results in the loss of a substantial number of cases. However several studies show that cancer diagnosis may motivate patients to alter their lifestyle habits, and a considerable number of patients change their dietary intake, exercise habits and supplement use following a cancer diagnosis. In a study of 250 women newly diagnosed with non-metastatic breast cancer, Maunsell and colleagues found that 41% of women reported dietary changes since diagnosis, with 77% of those decreasing their meat intake can 72% increasing their fruit and vegetable consumption (Maunsell et al., 2002). Similarly, a study on 260 women from New Mexico reported modest, significant dietary changes, namely decreases in total energy and macronutrients and an increased fat consumption as a percentage of diet, 2 years post breast cancer diagnosis, with decreases being greater in younger women (Wayne et al., 2004). Such findings were also reported in long-term breast cancer survivors; in a study on survivors on average 12 years post-diagnosis, 25% of participants reported making positive exercise and diet changes (Alfano et al., 2008). In the UK prospective multicentre study, DietCompLyf, consisting of a cohort of over 1,500 breast cancer patients, a significant increase in consumption of fruit and vegetables, whole grains and lean protein sources was reported post-diagnosis, whilst products high in fat and sugar, red meat, coffee, alcohol and refined grains were seen to decrease significantly (Velentzis et al., 2011).

In cases where no self-reported data of prior medical history was available (n=2585), women were assumed to be free from disease. Other participants who were excluded were those who reported very high (> 6000 kcal/day) or very low (< 500 kcal/day) total energy intake in the FFQ. Energy intake restriction helps to address issues of potential improper FFQ completion and over and under-reporters (Willett, 2012).

## 3.8 Dietary patterns

### 3.8.1 Choice of relevant dietary patterns

The WCRF/AICR 2011 report concluded that there is evidence, ranging from convincing to limited, for the association of various foods and nutrients increasing or decreasing the risk of CRC (WCRF/AICR, 2011) – this has been discussed at length in chapter 2. Whilst several dietary patterns have been linked to various health outcomes in the literature, no one dietary pattern has been specifically linked to CRC. For the purpose of this research, several factors were considered in choosing dietary patterns with the aim of choosing the ones that are potentially most relevant. Such factors include:

1. The foods listed in the WCRF/ AICR 2011 report as compared to the components making up the respective dietary patterns, with preference given to food and nutrients for which evidence of an association with increasing or decreasing CRC risk was convincing or probable as opposed to limited;
2. The nature of the recommendations on which the indices were based, that is on the prevention of CVD or general health, or on cancer prevention recommendations;
3. The fact that the UKWCS participants are British – preference was thus given to scores based on international dietary guidelines, rather than those specifically intended for the American population;
4. The variables present in the UKWCS and the ease of generation of the components making up the respective dietary patterns.

On the basis of the above factors, in particular the nature of the recommendations, and in view of the gap in the literature as highlighted in section 2.9.3 and in the introduction to chapter 5, the WCRF/AICR cancer prevention recommendations were chosen as one of the dietary patterns to be explored.

In choosing the second dietary pattern, the available scientific literature was consulted and the choice was narrowed down to four eating patterns commonly investigated in relation to chronic diseases – namely the HEI 2010, the 2005 Diet Quality Index (DQI), the MD Score and the Recommended Food Score (RFS).

Table 3.2 lists the different, relevant components making up these patterns considered for inclusion in the study and categorises them in relation to the foods and nutrients listed in the WCRF/AICR report. For instance, the report concluded that there was convincing evidence to show that 'foods containing dietary fibre' decreased the risk of CRC. In the HEI 2010, whole grains and refined grains were the two components affecting the total score that could be linked most closely to dietary fibre intake. Nutrients that were a component of the various dietary patterns, but that were not listed in the WCRF/AICR report as decreasing or increasing the risk associated with CRC, such as sodium – one of the twelve components in the HEI 2010 – were not included in the table.

The MD score was the dietary pattern that included most relevant components, listed in the WCRF/AICR 2011 report as being backed by convincing / probable evidence in the aetiology of CRC. Furthermore, its components could be easily generated from the variables present in the UKWCS database. It was thus chosen as the second dietary pattern to be investigated in relation to incidence of CRC.

*Table 3.2 Comparison of the HEI 2010, the DQI 2005, the MDS and the RFS in relation to conclusions from the WCRF/AICR, 2011*

| Dietary pattern | Healthy Eating Index 2010 | Diet Quality Index 2005 | Mediterranean Diet Score | Recommended Food Score |
|---|---|---|---|---|
| | (Guenther et al., 2013) | (Zamora et al., 2010) | (Trichopolou et al., 2003) | (Kant et al., 2000) |
| Number of components | 12 components | 10 components | 9 components | 23 components: 5 food groups |
| Basis of dietary pattern | Dietary Guidelines for Americans | Dietary Guidelines for Americans | Mediterranean diet | Dietary Guidelines for Americans |
| **WCRF/AICR, 2011** *Convincing / Probable evidence* | | | | |
| Foods containing dietary fibre | whole grains / refined grains | whole grains | cereals | whole grains |
| Red meat / Processed meat | protein foods / seafood, plant proteins | N/A | meat / fish | lean meat or meat alternates |
| Alcohol | empty calories | alcohol | alcohol | N/A |
| Garlic | N/A | N/A | N/A | N/A |
| Milk / Calcium | dairy | reduced fat milk & alternatives | dairy | low-fat dairy |
| *Limited - suggestive evidence* | | | | |
| Non-starchy vegetables | total vegetables / greens & beans | vegetables | vegetables | vegetables |
| Fruits | fruits | fruits | fruit & nuts | fruits |
| Foods containing Vitamin D | N/A | N/A | N/A | N/A |
| Foods containing Iron | N/A | N/A | N/A | N/A |
| Cheese | dairy | N/A | dairy | low-fat dairy |
| Foods containing animal fats | empty calories / fatty acids | total fat / saturated fat / cholesterol | Monounsaturated fat: Saturated fat | N/A |
| Foods containing sugars | empty calories | foods containing sugars | N/A | N/A |

### 3.8.2 Calculation of dietary pattern component values from dietary assessment sources

*FFQ*

Data from the FFQ used at baseline was converted into a Microsoft Access format to allow values for the different components making up the MD and the dietary components listed in the WCRF/AICR recommendations to be derived. Different FFQ items were grouped to generate one value for each component; details on the specific food items combined to form each food group and thus construct the MD and WCRF/AICR scores respectively are found in Appendix XI.

*FD*

The generation of the components making up the dietary patterns from the FD data proved to be more challenging than the process required to generate the same components from the FFQ. Some components were generated by combining food subcategories, as defined in The 5$^{th}$ Edition of McCance & Widdowson's *The Composition of Foods* (Holland et al., 1991). The specific categories included are listed in Appendix XII. Others were included in the quality checklist described in section 3.4.2.2, and thus the value could be derived from that dataset (Refer to Figure 3.4). Nutrient components were extracted from DANTE. Some of the components in the WCRF/AICR score are not food based; data from the phase 2 questionnaire was used where possible, whilst data from the baseline questionnaire was used in the case of breastfeeding where no relevant data was available at phase 2. Table 3.3 summarises the various sources used for generating the components making up both dietary patterns.

The derivation of some components was thus less straightforward than of others. In the WCRF/AICR cancer prevention recommendations, the 3$^{rd}$ recommendation relates to limiting foods and beverages that promote weight gain. For the purpose of operationalizing the WCRF/AICR score, this recommendation was divided into two sub-recommendations, namely limiting the consumption of energy dense foods and avoiding sugary drinks. Further details on score operationalization are given in Section 3.8.4 and Chapter 5. In deriving the energy density of the diet, the energy provided (kcal / 100g / day) by total food (solid, semi-solid and liquid foods such as soups), less

the energy content provided by beverages, divided by the total food weight was used to derive a value.

The main challenge was estimating nutrients from composite dishes. In determining the specific proportions of a composite dish, the same approach as is used in disaggregation of composite dishes in the National Diet and Nutrition Survey (NDNS) was taken, and thus several sources of information were used, in the following order:

- Information given by the product manufacturer;
- Recipes written by participants in their FD.
- Standard recipes from McCance & Widdowson's *The Composition of Foods* (Holland et al., 1991) (NDNS, 2014).

***Table 3.3 Different data sources used for generating dietary pattern components***

| **Dietary pattern components** | **Data source** |
|---|---|
| ***Mediterranean Diet Score*** | |
| Vegetables | Quality checklist |
| Legumes | McCance & Widdowson's (M&W) codes |
| Fruit & nuts | Fruit - Quality checklist; Nuts - M&W codes |
| Cereals | M&W codes |
| Fish | M&W codes |
| MUFA & PUFA: SFA | DANTE |
| Meat | M&W codes |
| Poultry | M&W codes |
| Dairy | M&W codes |
| Alcohol | Quality checklist |
| | |
| ***WCRF/AICR Score*** | |
| BMI | Phase 2 questionnaire |
| Physical activity | Phase 2 questionnaire |
| Energy dense foods | M&W codes |
| Sugary drinks | M&W codes |
| Fruit & vegetables | Quality checklist |
| Dietary fibre | DANTE |
| Red & processed meat | M&W codes |
| Alcohol | Quality checklist |
| Sodium | DANTE |
| Supplements | Quality checklist |
| Breastfeeding | Baseline questionnaire |

Furthermore, the Nutritional Epidemiology Group at the University of Leeds was in possession of an Excel file used in previous research on the UKWCS, using FD (Dahm et al., 2010). This contained a list of several composite dishes, with proportions of their components when disaggregated, and reference was made to it by the researcher where necessary. For dishes where none of the above sources were informative, reference to the composition of dishes with known proportions was made. A number of assumptions were thus made, some of which are outlined in Table 3.4. Homemade patties were assumed to be made of 77% minced beef or pork, and thus not considered to be processed meat, whilst canned, chilled or frozen ready-made meat products such as sausages, curries and stews were assumed to be processed.

***Table 3.4 Assumptions made with respect to food composition***

| Food item / dish | Assumptions made |
|---|---|
| Meat patties, homemade | 77% meat, not processed |
| Burgers with bun, retail | 25% meat, processed |
| Pies, retail | 30% meat or alternative |
| Sausages | 63% meat, processed |
| Casseroles, retail | 37% meat or alternative |
| Stews, retail | 37% meat or alternative |
| Curries, retail | 32% meat or alternative |
| Pate' / pastes | 30% meat or alternative |
| Protein & carbohydrate dish<br>eg: chicken & rice, beef & potato | 40% meat or alternative |
| Breaded / battered chicken / fish | 60% chicken or fish |
| Stir fry, with vegetables | 60% meat or alternative |
| Marzipan | 50% nuts |
| Mixed nuts and dried fruit, trail mix | 50% nuts |
| Bean / lentil & rice / nut dish | 50% nuts, beans or lentils |
| Yoghurt, fruit | 20% fruit |
| Custard | 80% dairy |

### 3.8.3 Calculating adherence to the Mediterranean diet

Bach and colleagues classified indexes evaluating adherence to the MD into three categories, based on the calculations used – (1) those based on positive and negative component scores; (2) those that add and subtract standardised components; (3) those based on a ratio between components. For the purpose of this study, an adherence score to the MD will be generated from the UKWCS data. The MD score used is a modified version of that by Trichopoulou and colleagues (Trichopoulou et al., 2003). This score has nine components, including both food and nutrients and that are scored dichotomously (0,1) with positive (+), positive in moderation (+m) and negative (-) scores. In view of the ease of its application, this score is the one used most extensively (Bach et al., 2006). It gives a logical coverage of food types and is representative of a typical MD.

The score indicating adherence to the MD as defined by Trichopoulou and colleagues in 2003 was modified with respect to three components - the lipid ratio (polyunsaturated: saturated fatty acids), meat and poultry with the last two being considered as separate categories. Monounsaturates were substituted as being a non-Mediterranean cohort, use of olive oil in the UKWCS is minimal. This approach was also taken in the EPIC multi-centre prospective cohort study where the MD score was used to calculate adherence to the Mediterranean dietary pattern in nine European countries (Trichopoulou et al., 2005). This resulted in 10 components, out of which for 9 of the components, a binary score of 0 or 1 was assigned, with the cohort median used as a cut-off. Thus, for components considered to have a beneficial effect – namely vegetables, legumes, fruit and nuts, cereal, fish and fatty acid ratio, women whose consumption was at or above the median were assigned a score of 1 whilst those whose intake was below the median were given a 0 value. Conversely, for components presumed to be detrimental – that is meat, poultry and dairy products, a score of 1 was assigned for intakes below and a score of 0 for intakes above the cut-off median respectively. For alcohol, the 10th component, daily intakes between 5 and 25g a value of 1 was assigned whilst women consuming intakes outside this range decreased their score by 1. As a result, the total MD score ranged from a minimal adherence score of 0 to a maximal adherence score of 10. Table 4.1 in chapter 4 lists

the components making up the UKWCS MD score and the cut-off median used for each component.

### 3.8.4 Calculating adherence to the WCRF/AICR cancer prevention recommendations

Developing an index from cancer prevention recommendations to assess a dietary pattern presents several research challenges. These include but are not limited to, which of the recommendations should be included for construction of the score based on the population under investigation, the method of assessing whether an individual meets a recommendation or not (Simmonds, 2015).

An adherence score to WCRF/AICR recommendations will be generated from the UKWCS database. The approach in constructing the score will reflect that taken by EPIC to predict cancer incidence (Romaguera et al., 2012) and mortality in women (Vergnaud et al., 2013). In these publications, seven out of ten components were operationalised in women, namely body fatness, physical activity, consumption of foods and drinks that promote weight gain, plant foods, animal foods, alcoholic drinks and breastfeeding. Some studies (Inoue-Choi et al., 2013; Nomura et al., 2016) that also generated a WCRF/AICR score operationalised an 8th recommendation, i.e. the limiting of salty foods and foods processed with salt, by using daily sodium intake as a variable. This data in relation to salt intake is available for the UKWCS. Notwithstanding the fact that in view of this dietary component being perceived to be less healthy, it is subject to under-reporting (Newby, 2003) and acknowledging that sodium data from a 24-hour urine collection would be more suitable, it was decided that for the purpose of this research, the 8th recommendation re sodium intake would be operationalised.

A maximum adherence score of 8 was possible for the UKWCS, with higher values indicating greater concordance with the recommendations. If the recommendation was met, the woman was assigned a score of 1, if not met a 0 was assigned and an intermediate category, resulting in a score of 0.5 was also created. Each major recommendation contributed equally to the final single score for each participant since WCRF/AICR recommendations were not ranked according to priority; for guidelines with more than one personal recommendation, an average of the allocated scores was

derived. Cut-offs used will be quantitative criteria as described in the WCRF/AICR recommendations. Further details on the operationalization of the recommendations and generation of the WCRF/AICR score are found in Table 5.1 in chapter 5.

## 3.9 Statistical analyses

This section will describe the statistical techniques common to chapters 4, 5 & 6, namely the use of descriptive statistics, survival analysis and the selection of covariates for adjustment. An overview of cubic splines used in chapter 4 and Kappa statistics and Bland Altman plots used in chapter 6 is given in the respective chapters. Statistical analyses were conducted using IC Stata 13 statistical software (StataCorp, 2013) and all tests calculated two sided *p* values and 95% confidence intervals (95% CI).

### 3.9.1 Descriptive statistics

The datasets were first explored and cleaned. Variables of interest were checked for errors. Histograms were drawn for continuous variables whilst the frequency of categorical variables was checked to enable the identification of potential outliers in the datasets. Descriptive statistics were used to describe the demographic, health, lifestyle and dietary characteristics of women within the cohort at baseline and phase 2, according to the Mediterranean and WCRF/AICR dietary patterns. Characteristics of cases and controls were explored separately to enable a better understanding of the studied population. Such information is tabulated in chapters 4, 5 and 6. Differences in characteristics of women at baseline and phase 2 are slight and have been previously reported (Cade et al., 2015).

### 3.9.2 Cox proportional hazards regression

The relationship between the MD score and the WCRF/AICR score and risk of CRC was estimated using survival analysis - Cox proportional hazards regression in chapters 4 and 5 respectively for baseline data, and in chapter 6 for both scores using phase 2 data. The time in the study was calculated as the time from completion of FFQ or FD to CRC incidence, censor date or to the date the participant was lost to follow up was measured, and such a variable was created in Stata and used as the time variable. A second variable flagging CRC incidence following completion of dietary assessment was

created. Cox proportional hazard ratios (HRs) and 95% CIs were used to estimate risk of CRC incidence in relation to dietary patterns. In such modelling, the key assumptions include an independence of the observations and a proportionality of hazards. The proportional hazards assumption may be checked graphically by log-log curves of survival for all terms in the model; continuous variables were first split into 3 groups. It was ensured that the proportional hazards assumption was not violated when the graph lines were roughly parallel.

#### 3.9.2.1 Re-weighting

As previously explained in section 3.3., the sampling scheme at recruitment was stratified, specifically to include a large number of vegetarians and fish-eaters. In order to account for this oversampling, re-weighting was used in statistical models, based on the inverse probability of being sampled, to reflect the actual proportions of vegetarians and fish-eaters in the UK. This ensures that estimates provided are more representative of the UK population. In view of the fact that there were nearly four times as many vegetarians sampled as there were vegetarians at the time, and around twice as many pescatarians in the UKWCS as there were in the general population, 0.27 and 0.43 were used to reweight vegetarians and pescatarians respectively.

#### 3.9.2.2 Modelling strategy and adjusting for confounders

An important step in obtaining valid estimates in exposure-outcome relationships is adjusting for confounders. This is particularly the case for cohort studies where potential confounders may affect the estimated risks if they are not controlled for. Such variables are associated with the exposure of interest, in this case the dietary pattern, but are also independent risk factors of the disease outcome, i.e. CRC incidence. *A priori confounders* are those identified from previous robust evidence – one approach considered suitable in identifying confounders and used in this research. A Directed Acyclic Graph (DAG) (Refer to Appendix XIII) was also generated for the UKWCS to provide a visual and rigorous summary of causal links between the different exposures and the outcome – incidence of CRC. It enabled a check of whether sufficient confounders have been selected for the adjustment, whilst ensuring that over-adjustment in models was avoided. Confounders were detected by identifying

common influences on exposures and outcome. Greenland and colleagues state that confounders on the same path are causally related and adjustment for just one represents the minimal sufficiency set (Greenland et al., 1999).

In building models to explore the associations of interest in this dissertation, unadjusted regression models were initially used. Age, considered as a confounder in view of it being a strong risk factor for CRC was then added to give a simple regression models. Evidence based confounding factors in the link between the respective dietary patterns of interest and CRC that may impact on findings that were identified from previous literature, as detailed in chapter 2, were taken into consideration. Fully-adjusted regression models were thus built for both dietary patterns respectively.

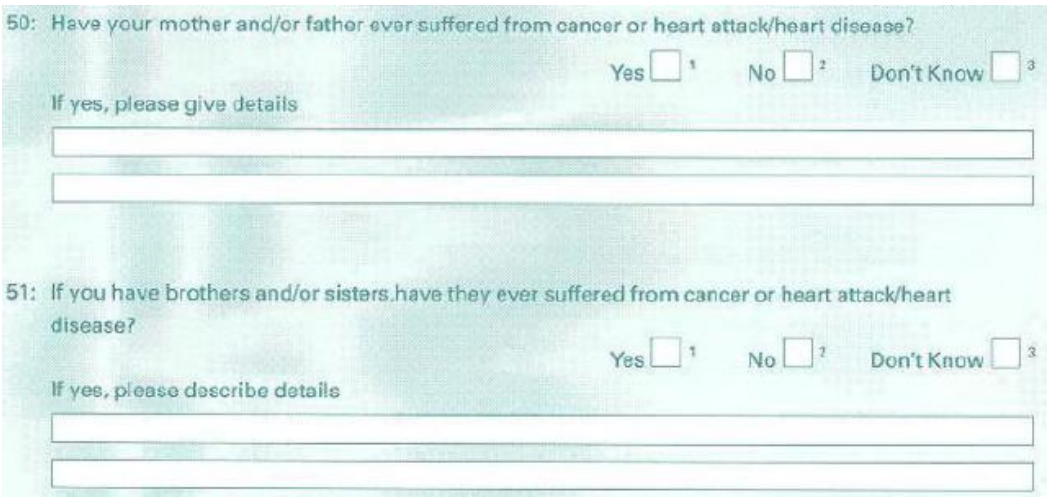
For the MD, the confounders included in the fully-adjusted model were age (years), BMI ($kg/m^2$), energy intake (kcal/day), physical activity (hr/day), smoking status (never, current or former smoker), family history of CRC in a first degree relative and socio-economic status (professional/ managerial, intermediate or routine and manual). For the WCRF/AICR dietary pattern, the fully-adjusted model included the following covariates: age (years), smoking status (never, current or former smoker), family history in a first degree relative and socio-economic status (professional/ managerial, intermediate or routine and manual). Potential confounders that were either included in the score derivation, such as BMI and physical activity, or were closely related to a score component, such as energy (kcal) to energy density were excluded from the adjusted analyses.

The UKWCS population were women and 98% were white; thus although gender and ethnicity are considered to confound the relationship between diet and CRC, they were not included as confounders. It could also be noted that only employment status as in the National Statistics Socio-Economic Classification (NS-SEC) measured for socio-economic position, a situation that could result in risking residual confounding. Education was considered and included as an additional confounder but 2668 women were lost due to missing data. A collinearity test between education and socio-economic status showed Pearson's correlation to be 0.417 which is admittedly moderate. It was thus decided to use a more parsimonious model and adjust only for

socio-economic status with respect to occupation. Whilst this may not be recommended for different populations, in a cohort of British middle-aged women, where 86% of the participants are married with children, it may be acceptable to make the assumption that socio-economic position is a sufficient measure.
Participants with incomplete data on any one of the chosen confounders were excluded from the analyses. Notwithstanding, confounding factors that had a substantial proportion of missing observations were not included in the fully adjusted model, particularly if another closely related variable was available. For instance, the socio-economic status variable rather than education was chosen as a confounder since the latter had more missing observations.

Women with a family history of CRC cancer are at an increased risk of CRC. Such women could be excluded from the analyses in order to provide a more accurate risk estimate for women with no family history. Alternatively, family history could be included as a confounding factor. The latter approach was adopted for this research to ensure that the maximum number of CRC cases possible are retained. Figure 3.7 shows the questions asked in the baseline questionnaire relating to family history of cancer. Family history was defined as having a first degree relative, namely a parent or sibling who had cancer. Participants were asked to provide further details on the type of cancer. This information was used to derive a variable relating to whether the women had a family history of CRC.

**Figure *3.7*** **Section of the baseline questionnaire relating to family history of cancer.**


50: Have your mother and/or father ever suffered from cancer or heart attack/heart disease?

Yes ☐ 1 No ☐ 2 Don't Know ☐ 3

If yes, please give details

51: If you have brothers and/or sisters have they ever suffered from cancer or heart attack/heart disease?

Yes ☐ 1 No ☐ 2 Don't Know ☐ 3

If yes, please describe details

#### 3.9.2.3 Sensitivity analyses

Section 3.8.4 described how 8 of the WCRF/AICR cancer prevention recommendations were operationalised to generate an adherence score for this dietary pattern. In chapter 5, sensitivity analyses were carried out operationalising a 9$^{th}$ recommendation relating to the recommendation on supplement use in the WCRF/AICR score.

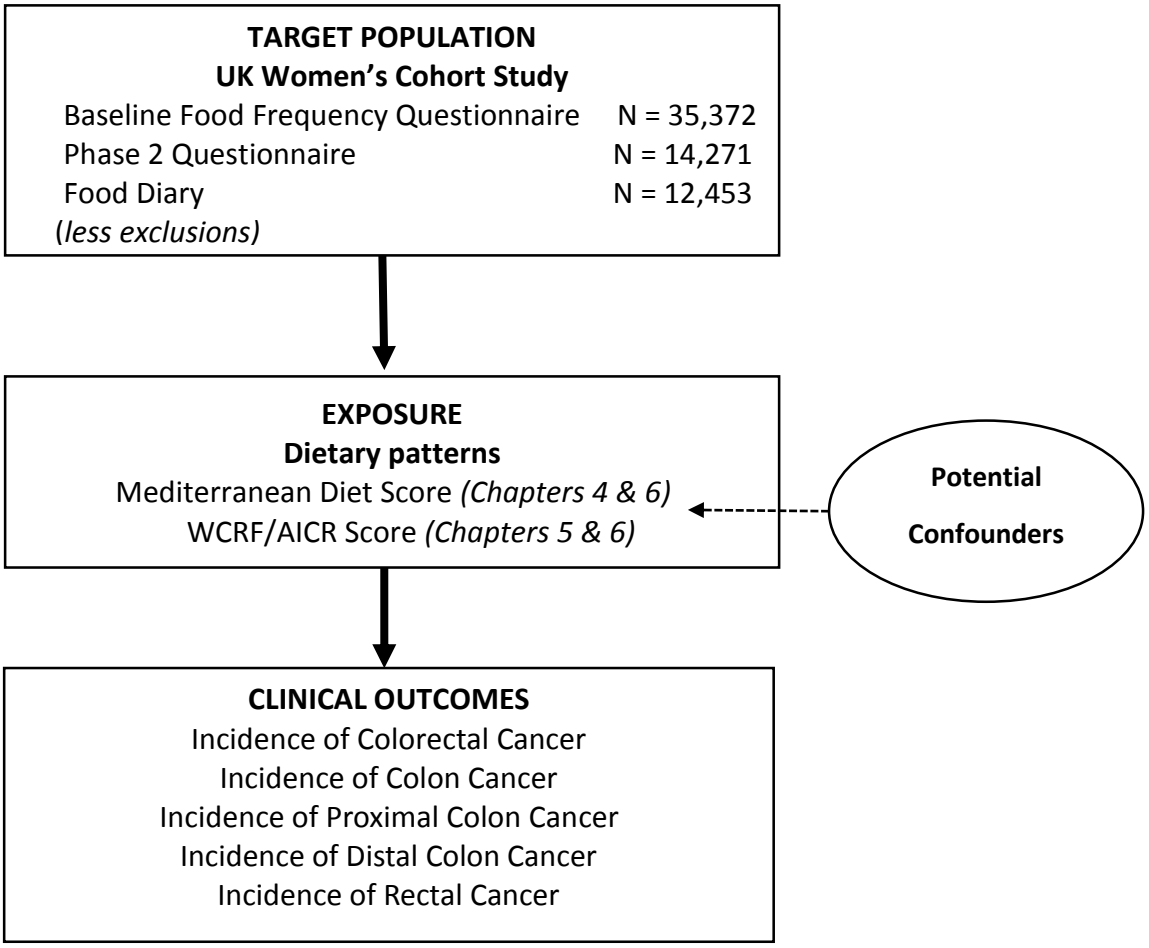
This approach was taken for several reasons. Firstly, there is evidence to show that supplement use is generally associated with having a healthier lifestyle profile and nutritional intake (Kirk et al., 1999). They are more likely to exercise regularly, maintain a healthy weight and avoid tobacco use (Dickinson and Mackay, 2014). The exclusion of supplement users from the main analysis thus reduces potential confounding and ensures estimations of dietary patterns and CRC incidence are more accurate.

Secondly, the data available for supplement use at baseline was limited to a yes or no response to the question: *Do you take any vitamins, minerals, fish oils, fibre or other food supplements?* Women were also asked to give details on the name, brand and frequency of supplement use. Several women chose not to answer this question (n = 2778); including this recommendation in the original adherence score construction would have resulted in an unnecessary loss of CRC cases.

## 3.10 Analytical framework

Figure 3.8 depicts the UKWCS as the target population for this research and lists the maximum number of participants in each dataset. The research focused on the association between various dietary patterns as the exposure and CRC incidence as the outcome. The dietary patterns studied were determined using the MD score and the WCRF/AICR score.

*Figure 3.8 Analytical framework*




## 3.11 Summary

This chapter has given a background to the UKWCS study design and the process of data collection. It has described details of the two dietary assessment methods used in the different phases, namely the FFQ and the FD, and the coding process. Information on how the components making up the two respective dietary patterns were derived from both the FFQ and from the FD was given, as were details on how adherence scores were calculated. Statistical techniques common to several of the analyses were also discussed.

The subsequent two chapters, 4 and 5 will explore associations between incidence of CRC and the Mediterranean dietary pattern and WCRF/AICR dietary pattern respectively, using baseline data. Chapter 6 will investigate these same associations using data from phase 2, and the agreement between the two dietary assessment methods will be explored.

# CHAPTER 4 THE MEDITERRANEAN DIET AND RISK OF COLORECTAL CANCER IN THE UKWCS

## 4.1 Chapter overview

*Background:* Evidence from epidemiological studies investigating associations between adherence to the MD and CRC is inconsistent. The aim of this chapter is to assess whether adherence to the Mediterranean dietary pattern is associated with reduced incidence of cancers of the colon and rectum in the UKWCS.

*Method:* Primary data from the UKWCS was used to investigate the associations between adherence to the MD score and colorectal, colon and rectal cancer risk. A total of 35 372 women were followed for a median of 17.4 years. A 10-component score indicating adherence to the MD was generated for each cohort participant using a 217-item FFQ. The MD score ranged from 0 for minimal adherence to 10 for maximal adherence. Cox proportional hazards regression was used to provide adjusted HRs and 95% CIs for colon and rectal cancer risk.

*Results:* A total of 465 incident CRC cases were documented. A moderate, inverse, non-linear association was observed between adherence to the MD score and risk of CRC. In the multivariable-adjusted model, there was a statistically significant trend (HR=0.88, 95% CI: 0.78 to 0.99; $P_{trend}$ = 0.03) for a 2-point increment in the MD score. For rectal cancer, a 2-point increment in the MD score resulted in an HR (95% CI) of 0.69 (0.56 to 0.86) whilst a 62% linear reduced risk (HR 0.38; 95% CI: 0.20 to 0.74; $P_{trend}$ < 0.001) was observed for women within the highest vs. the lowest category of the MD score. Estimates for an association with colon cancer were weak ($P_{trend}$ = 0.41). While the estimates of the association were stronger for rectal than for colon cancer, the CI were wide potentially implying no difference between the sites.

*Conclusion:* Findings suggest women with a higher adherence to a Mediterranean dietary pattern compared to those with a lower adherence may have a lower risk of CRC, especially rectal cancer.

## 4.2 Introduction

CRC is the third most common cancer with 1.36 million cases diagnosed worldwide in 2012 (Ferlay et al., 2015). The MD has consistently been found to have a beneficial influence on total morbidity and mortality, as well as offering cardio protection and reduction in overall cancer incidence (Couto et al., 2011; Estruch et al., 2013; Sofi et al., 2014). It is traditionally characterised by a high intake of olive oil and nuts, cereals, fruit and vegetables, moderate intakes of fish, poultry and wine with meals, and low intakes of red and processed meats, dairy products and sweets (Willett et al., 1995).

However, studies exploring associations between the MD and risk of CRC are limited and have given inconsistent results. Fung and colleagues found no association between adherence to the MD and colorectal, colon or rectal cancers in a large cohort of middle-aged men and women (Fung et al., 2010). This was however inconsistent with findings from a large US cohort study (Reedy et al., 2008) and from the large European cohort, EPIC (Bamia et al., 2013), that both reported a reduced risk of CRC with adherence to the MD. Similar associations were reported for all CRC sites in the Italian section of EPIC (Agnoli et al., 2013). Notwithstanding, comparisons between studies should be made with caution in view of the variation in the derivation of the MD scores.

The aim of this chapter is to assess whether adherence to the Mediterranean dietary pattern is associated with reduced incidence of cancer of the colorectum, colon and rectum in a large UK cohort of women with a long follow up period.

## 4.3 Methods

### 4.3.1 Study design, study population and ethical approval

The UKWCS of 35 372 middle-aged women was formed from participants of a WCRF 1995 direct mail survey. Women completed a self-administered FFQ between 1995 and 1998, providing data for the baseline dataset. Information on diet, lifestyle and health was also provided. The cohort participants are mainly white, middle-class and well-educated with 27% having a degree and 86% married with children. Details of recruitment and the cohort profile have been reported in detail elsewhere (Cade et al.,

2004a; Cade et al., 2015) and are outlined in section 3.3. The study carries with it ethical approval granted at its initiation in 1993 as detailed in section 3.6.

### 4.3.2 Baseline characteristics and dietary information

Anthropometrics, lifestyle factors and socio-demographic information were self-reported. Information on physical activity was collected whilst socio-economic status was based on occupation. The FFQ used at baseline was developed from one used in EPIC (Riboli et al., 1997) and consisted of 217 food items and participants were asked to indicate average consumption frequency of food items over a 12 month period, with missing data assumed to be non-consumption. Standard portion weights were assigned and energy intake was derived using McCance & Widdowson's *The Composition of Foods* (5th Edition) (Holland et al., 1991).

### 4.3.3 Case definition

The cancer outcomes used in the analyses are incident malignant neoplasms of the colon (codes 153.0-153.9 or C18) and of the rectosigmoid junction and of the rectum (codes 154.0-154.1 or C19 and C20) of the ICD, 9th and 10th editions (AMA 2004; WHO, 2010). Registrations of cancer diagnosis for women in the UKWCS were made via record linkage of identification codes to the central register of NHS Digital. This data is available from baseline in 1995 until the 1st April 2014 for 98% of the cohort women.

### 4.3.4 Mediterranean diet score construction

A score indicating adherence to the MD was generated for each cohort participant. The definition used and the approach taken in constructing the score was as described by Trichopoulou and colleagues (Trichopoulou et al., 1995), though modified with respect to the lipid ratio as defined in a later study (Trichopoulou et al., 2005), in view of the non-Mediterranean British cohort under study. This resulted in 10 components, 9 of which had a binary score of 0 or 1 assigned, with the cohort median used as a cut-off. Thus, for components considered to have a beneficial effect – namely vegetables, legumes, fruit and nuts, cereal, fish and fatty acid ratio (sum of monounsaturated and polyunsaturated fats to saturated fat), women whose consumption was at or above

the median were assigned a score of 1 whilst those whose intake was below the median were given a 0 value. Conversely, for components presumed to be detrimental – that is meat, poultry and dairy products, a score of 1 was assigned for intakes below the median and a score of 0 for intakes above the cut-off median respectively. For alcohol, the 10th component, daily intakes between 5 and 25g a value of 1 was assigned whilst women consuming intakes outside this range decreased their score by 1. The MD score was thus calculated as the sum of the 0s and 1s assigned to the different components respectively, with the total ranging from a minimal adherence score of 0 to a maximal adherence score of 10. Details are given in Table 4.1.

***Table 4.1 Derivation of the Mediterranean diet score***

| MD Score Component | Indicator Value 1 | 0 |
|---|---|---|
| Vegetables (g/day) | ≥ 282 | < 282 |
| Legumes (g/day) | ≥ 31 | < 31 |
| Fruit & nuts (g/day) | ≥ 273 | < 273 |
| Cereals (g/day) | ≥ 226 | < 226 |
| Fish (g/day) | ≥ 24 | < 24 |
| MUFA + PUFA : SFA[1] | ≥ 1.53 | < 1.53 |
| Meat (g/day) | < 40 | ≥ 40 |
| Poultry (g/day) | < 13 | ≥ 13 |
| Dairy (g/day) | < 97 | ≥ 97 |
| Alcohol (g/day) | 5-25 | < 5 or > 25 |

[1] Ratio of the sum of monounsaturated fatty acids and polyunsaturated fatty acids to saturated fatty acids.

### 4.3.5 Statistical analysis

Statistical analysis were conducted using Stata version 13 statistical software (StataCorp, 2013). Descriptive statistics were used to describe lifestyle characteristics of participants. Survival analysis was conducted to explore the relationship between the MD score and colorectal, proximal colon, distal colon and rectal cancer risk. Cox proportional hazards regression was used to provide HRs and 95% CI for the estimation of relative risk of cancer. The proportional hazards assumption was tested graphically for all terms in the model. In order to account for the stratified sampling scheme at

recruitment, over-sampling vegetarians and fish-eaters, statistical models used weights based on the inverse probability of being sampled to provide estimates more representative of the UK population. The time variable used in the models was time in the study, calculated from the date of questionnaire receipt until either death or censor date (1st April 2014). Adherence to the MD score was modelled as categorical (0-2, 3, 4, 5-6 and 7-10), to create groups with similar numbers, with each category assigned a score 1, 2, 3, 4 & 5 respectively, and comparing each category to the lowest, reference category. Estimates per 2-point increment in the continuous MD score and tests for linear trend were also calculated. Analyses were carried out for CRC, and then for colon, proximal colon, distal colon and rectal cancer separately. The individual MD score components were split into thirds based on their tertiles, labelled as low, medium and high intakes and explored in association with incidence of colorectal, colon and rectal cancers, using the low intake as the reference category. Cox regression models were used to test for trend, using the continuous variable.

Risk factors for CRC previously identified in the literature were taken into consideration. Associations were estimated first as a simple age-adjusted model, and finally as a full model adjusting for age (years), BMI ($kg/m^2$), energy intake (kcal/day), physical activity (hr/day),, smoking status (never, current or former smoker), family history of CRC in a first degree relative and socio-economic status (professional/ managerial, intermediate or routine and manual). Participants with incomplete data on these variables were excluded. Education was included as an additional confounder in a third model, but several women were lost due to the missing data (n=2668) and no major differences were observed in the results. It was thus decided to use the more parsimonious model described above, adjusting only for occupation as a measure of socio-economic status, which is acceptable in our cohort. In the analysis exploring the association of the individual components of the MD score with colorectal, colon and rectal cancer, the same potential confounders as listed above were adjusted for. A consideration was given to the mutual adjustment of the other components in the score, but given that several foods were highly correlated, such as for instance vegetable intake and legume intake, adjusting for them in the same model was not deemed appropriate. Whilst it is understood that the correlation between other components, such as fish and cereals would be much lower, mutually adjusting for

some components but not for others in a range of models would be confusing. Furthermore, in view of the fact that the objective of the analysis was mainly to identify which, if any of the score components drove the association between the MD and CRC incidence, rather than whether any were independent predictors, adjustment for potential confounders was consistent for all the analyses involving the Mediterranean dietary pattern in this study. Restricted cubic splines based on three knots at 10, 50 and 90% through the distributions of the data were also used to explore potential deviation from linear associations in the continuous variables (Orsini & Greenland, 2011).

## 4.4 Results

### 4.4.1 Demographics

During a median follow-up time of 17.4 years (interquartile range (IQR) = 1.7), a total of 527 women in the UKWCS were diagnosed with incident CRC. Participants who did not provide sufficient data at baseline to allow flagging on NHS Digital (n=695), women self-reporting history of any previous malignant cancer at baseline, except for non-melanoma of the skin (n=2391), women who were diagnosed with CRC within one year of baseline (n=53) and women with energy intakes outside the plausible range of 500 to 6000kcal/day (n=79) were excluded. Following exclusions, 32 154 cohort participants were eligible for inclusion in the analysis with 465 CRC cases, of which 366 were located in the colon (173 in the proximal colon and 119 cases in the distal colon) and 154 cases were located in the rectum.

### 4.4.2 Adherence and baseline characteristics

Figure 4.1 depicts the proportion of UKWCS participants adhering to the Mediterranean dietary pattern, according to the individual scoring categories. The characteristics of study participants according to the 5 categories of the MD score are reported in Table 4.2. Women in the highest category of the score were likely to be younger, had a lower BMI and engaged in more physical activity compared to those in the lower categories. High adherers to the MD score tended to have a higher energy intake but lower alcohol intake, were more likely to be vegetarians and fish eaters and to take supplements than women with lower adherence scores. Women with scores

reflecting poor adherence tended to smoke and were less likely to have a degree or hold a managerial position.

***Figure 4.1 Proportion of UKWCS participants adhering to the Mediterranean dietary pattern***

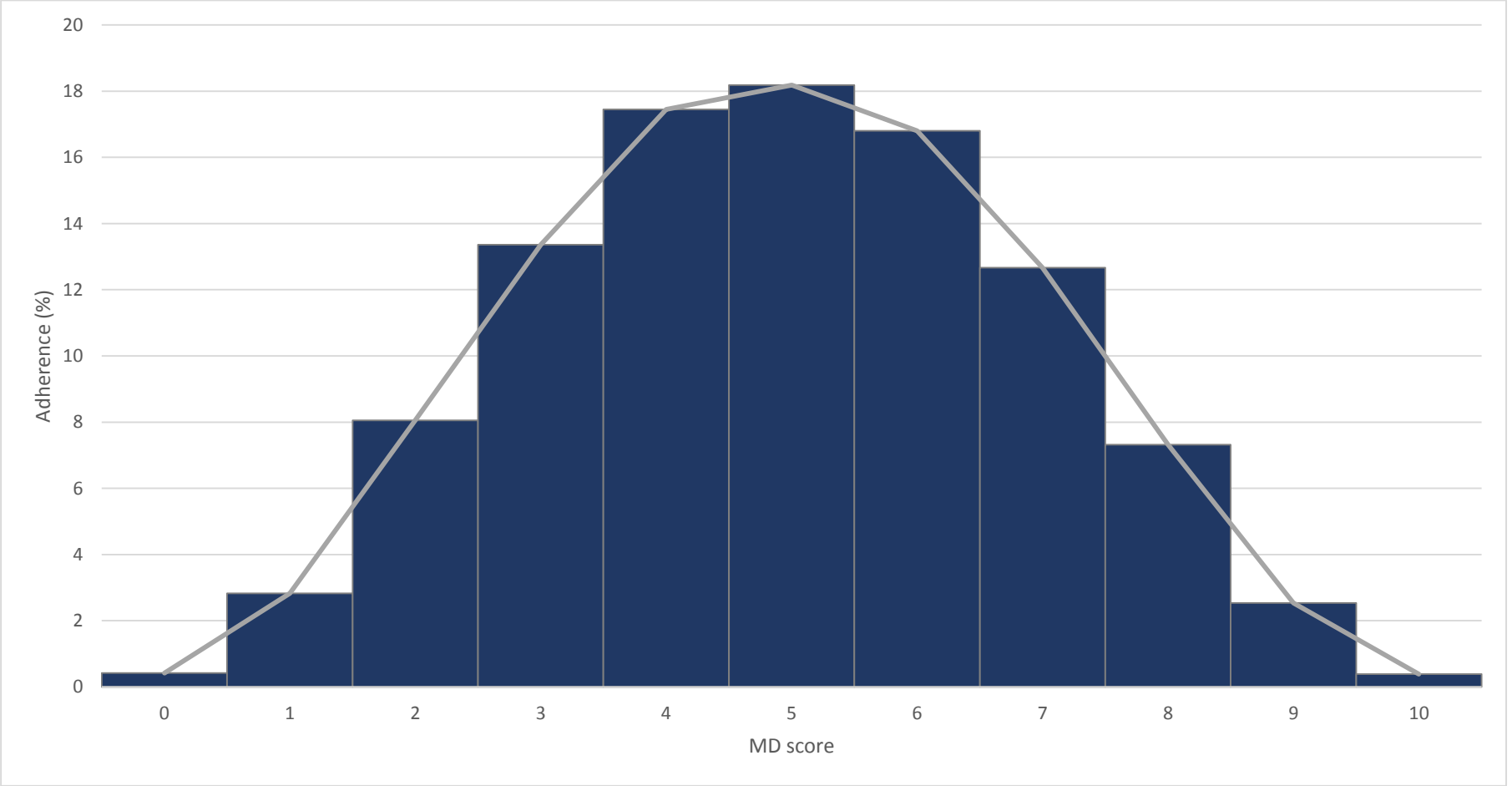


***Table 4.2 Baseline characteristics of women in the UKWCS according to adherence to the Mediterranean dietary pattern.[1]***

| | | Mediterranean diet score | | | | |
|---|---|---|---|---|---|---|
| | **Total** | **1** | **2** | **3** | **4** | **5** |
| MD score range (median) | 0 - 10 | 0-2 (2) | 3 | 4 | 5-6 (5) | 7-10 (7) |
| N (%) | 32154 (100) | 3631 (11.3) | 4295 (13.4) | 5610 (17.5) | 11245 (35.0) | 7373 (22.9) |
| Age (years) | | | | | | |
| *Mean* | 52.0 | 53.4 | 53.3 | 52.8 | 51.8 | 50.3 |
| *95% CI* | (51.9, 52.1) | (53.1, 53.7) | (53.1, 53.6) | (52.6, 53.0) | (51.6, 52.0) | (50.1, 50.5) |
| BMI (kg/m$^2$) | | | | | | |
| *Mean* | 24.4 | 25.6 | 25.0 | 24.8 | 24.3 | 23.5 |
| *95% CI* | (24.4, 24.5) | (25.5, 25.8) | (24.9, 25.1) | (24.6, 24.9) | (24.2, 24.4) | (23.4, 23.6) |
| Energy intake (kcal/day) | | | | | | |
| *Mean* | 2338 | 2104 | 2171 | 2236 | 2377 | 2575 |
| *95% CI* | (2331, 2348) | (2085, 2123) | (2152, 2190) | (2216, 2252) | (2362, 2391) | (2560, 2591) |
| Physical activity (hr/day) | | | | | | |
| *Mean* | 0.24 | 0.18 | 0.20 | 0.21 | 0.25 | 0.30 |
| *95% CI* | (0.23, 0.24) | (0.16, 0.19) | (0.18, 0.21) | (0.20, 0.22) | (0.24, 0.26) | (0.29, 0.31) |
| Ethanol (g/day) | | | | | | |
| *Median* | 5.5 | 1.9 | 3.6 | 4.8 | 6.1 | 8.0 |
| *IQR* | 11.8 | 6.8 | 10.8 | 11.8 | 12.1 | 11.6 |
| Current smoker | | | | | | |
| N (%) | 3484 (11.2) | 482 (13.7) | 571 (13.7) | 622 (11.4) | 1124 (10.3) | 685 (9.6) |
| Professional / Managerial SES | | | | | | |
| N (%) | 19956 (63.4) | 1976 (55.9) | 2401 (55.9) | 3357 (61.4) | 7145 (64.8) | 5077 (70.2) |
| Degree level of education | | | | | | |
| N (%) | 8862 (27.4) | 694 (18.9) | 906 (21.0) | 1421 (25.2) | 3213 (28.4) | 2605 (35.2) |

| | Total | Mediterranean diet score 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| Diet group | | | | | | |
| Meat-eaters, N (%) | 20663 (70.3) | 3111 (98.1) | 3440 (91.4) | 4149 (82.7) | 6989 (67.3) | 2974 (42.2) |
| Fish-eaters, N (%) | 4002 (13.6) | 16 (0.5) | 117 (3.1) | 321 (6.4) | 1388 (13.4) | 2160 (30.7) |
| Vegetarians, N (%) | 4712 (16.0) | 45 (1.4) | 207 (5.5) | 547 (10.9) | 2005 (19.3) | 1908 (27.1) |
| Supplement users | | | | | | |
| N (%) | 16815 (57.5) | 1542 (42.5) | 2023 (47.1) | 2810 (50.1) | 6067 (54.0) | 4373 (59.3) |
| Family history of colorectal cancer | | | | | | |
| N (%) | 1826 (6.0) | 217 (6.0) | 243 (5.7) | 329 (5.9) | 624 (5.5) | 413 (5.6) |

[1]UKWCS UK Women's Cohort Study, MD Mediterranean diet, Cl Confidence Interval, BMI Body mass index, SES Socioeconomic status

### 4.4.3 Survival analysis

The HRs and 95% Cls for incidence of colorectal, colon and rectal cancer across categories of adherence to the MD score are shown in Table 4.3. In the multivariable-adjusted model, compared to the reference intake, all categories had a lower risk of CRC. The test for trend was statistically significant where the risk estimate per 2-point increment in the MD score was 0.88 (0.78 to 0.99; $P_{trend}$ = 0.03). An inverse association for rectal cancer risk with adherence to the MD score was demonstrated, with a HR (95% CI) of 0.38 (0.20 to 0.74; $P_{trend}$ < 0.001) for women within the highest category of the score in comparison to the reference category. In the continuous model, a 2-point increase in the MD score resulted in an HR (95% CI) of 0.69 (0.56 to 0.86) for rectal cancer. No strong association for risk of colon, proximal colon or distal colon cancer with adherence to a Mediterranean dietary pattern was found, although the risk estimates in both the categorical and continuous models for colon cancer suggest a possible protective association. Notwithstanding, although estimates for rectal cancer were stronger than for colon cancer, the confidence intervals were wide; hence the possibility of no difference in association between the two sites exists.

***Table 4.3 Hazard ratios and 95% confidence intervals for incidence of colorectal, colon and rectal cancer according to adherence to the Mediterranean diet score.***

| Cancer site | Mediterranean diet score categories | Cases[1] | Age-adjusted HR (95% CI) | Multivariable-adjusted[2] HR (95% CI) |
|---|---|---|---|---|
| Colorectal | | 465 | | |
| | 1 | 74 | 1 | 1 |
| | 2 | 75 | 0.89 (0.65, 1.24) | 0.91 (0.64, 1.30) |
| | 3 | 88 | 0.80 (0.58, 1.10) | 0.82 (0.58, 1.15) |
| | 4 | 136 | 0.64 (0.48, 0.86) | 0.63 (0.45, 0.87) |
| | 5 | 92 | 0.76 (0.55, 1.06) | 0.82 (0.57, 1.17) |
| | Per 2 unit increment | | 0.86 (0.77, 0.96) | 0.88 (0.78, 0.99) |
| | $P_{trend}$ | | *0.007* | *0.030* |
| | | | | |
| Colon | | 336 | | |
| | 1 | 49 | 1 | 1 |
| | 2 | 54 | 0.98 (0.66, 1.44) | 0.98 (0.64, 1.51) |
| | 3 | 66 | 0.95 (0.65, 1.38) | 0.92 (0.60, 1.39) |
| | 4 | 100 | 0.72 (0.51, 1.02) | 0.70 (0.47, 1.04) |
| | 5 | 67 | 0.95 (0.65, 1.41) | 1.03 (0.67, 1.57) |
| | Per 2 unit increment | | 0.92 (0.81, 1.04) | 0.94 (0.82, 1.08) |
| | $P_{trend}$ | | *0.188* | *0.413* |
| | | | | |
| Proximal colon | | 173 | | |
| | 1 | 20 | 1 | 1 |
| | 2 | 35 | 1.55 (0.89, 2.70) | 1.67 (0.90, 3.10) |
| | 3 | 27 | 0.93 (0.52, 1.69) | 0.92 (0.47, 1.80) |
| | 4 | 53 | 0.97 (0.57, 1.64) | 1.06 (0.59, 1.91) |
| | 5 | 38 | 1.38 (0.78, 2.43) | 1.66 (0.89, 3.10) |
| | Per 2 unit increment | | 0.99 (0.83, 1.18) | 1.05 (0.87, 1.27) |
| | $P_{trend}$ | | *0.912* | *0.590* |
| | | | | |
| Distal colon | | 119 | | |
| | 1 | 18 | 1 | 1 |
| | 2 | 12 | 0.61 (0.29, 1.27) | 0.60 (0.26, 1.34) |
| | 3 | 35 | 1.39 (0.78, 2.48) | 1.38 (0.72, 2.62) |
| | 4 | 30 | 0.54 (0.29, 1.00) | 0.48 (0.24, 0.97) |
| | 5 | 24 | 0.89 (0.46, 1.72) | 0.86 (0.41, 1.79) |
| | Per 2 unit increment | | 0.89 (0.71, 1.10) | 0.87 (0.69, 1.11) |
| | $P_{trend}$ | | *0.272* | *0.255* |
| | | | | |

| Cancer site | Mediterranean diet score categories | Cases[1] | Age-adjusted HR (95% CI) | Multivariable-adjusted[2] HR (95% CI) |
|---|---|---|---|---|
| | | | | |
| Rectal | | 154 | | |
| | 1 | 30 | 1 | 1 |
| | 2 | 26 | 0.76 (0.45, 1.28) | 0.77 (0.44, 1.35) |
| | 3 | 26 | 0.52 (0.30, 0.90) | 0.58 (0.32, 1.02) |
| | 4 | 44 | 0.51 (0.32, 0.82) | 0.50 (0.29, 0.83) |
| | 5 | 28 | 0.41 (0.23, 0.72) | 0.38 (0.20, 0.74) |
| | Per 2 unit increment | | 0.72 (0.60, 0.87) | 0.69 (0.56, 0.86) |
| | $P_{trend}$ | | *0.001* | *0.001* |

[1] Case numbers apply to multivariable adjusted models.

[2] Adjusted for age, BMI, energy intake, physical activity, smoking status, socioeconomic status and family history of colorectal cancer.

The relationships portrayed in Table 4.3 were reflected in the restricted cubic spline models, depicted in Figures 4.2, 4.3 and 4.4. The bars indicate 95% CI derived from the 3-knot restricted cubic spline regression. A deviation from linearity was observed for the relationship between the MD score and CRC (Figure 4.2) and colon cancer (Figure 4.3) respectively, with adherence scores above 6 showing little risk reduction. The cubic spline model portraying the relationship between adherence to a MD and risk of rectal cancer showed no deviation from linearity (Figure 4.4). Figure 4.5 also depicts the estimates shown in Table 4.3: multi-variable adjusted hazard ratios of CRC incidence, by anatomical sub site are shown according to the level of adherence to the MD score. Adherence to the fourth score category of the MD reduced the risk of total CRC by 37% (95% CI = 0.45 to 0.87) and decreased the risk of rectal cancer by 50% (95% CI = 0.29 to 0.83).

***Figure 4.2 Restricted cubic spline for the association between colorectal cancer and the Mediterranean diet score.***

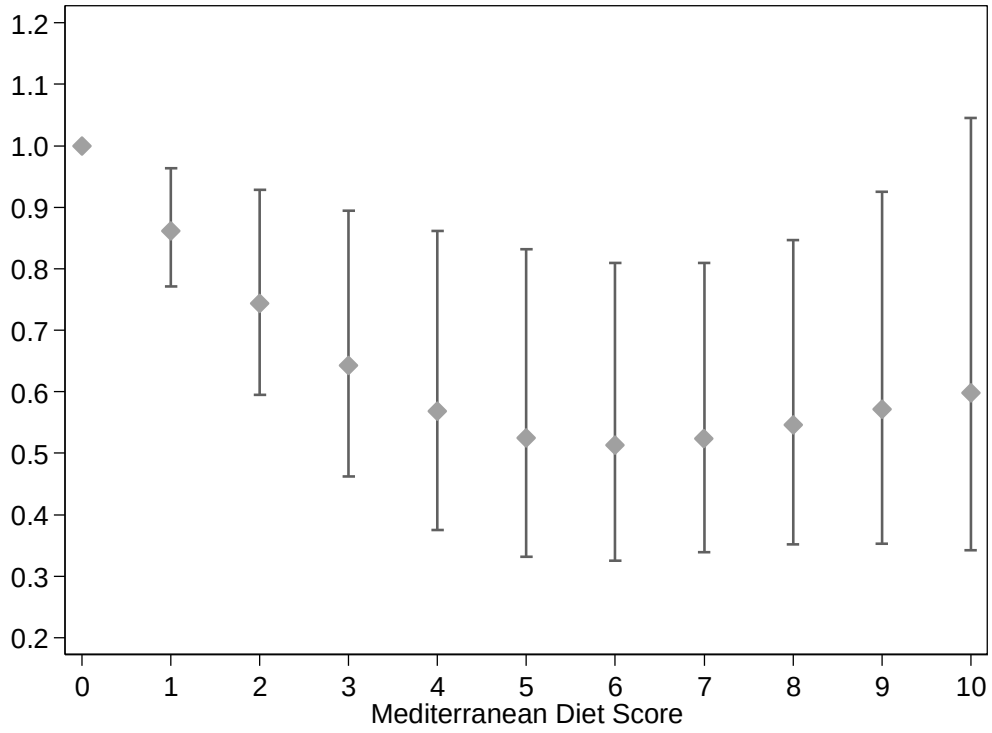



***Figure 4.3 Restricted cubic spline for the association between colon cancer and the Mediterranean diet score.***

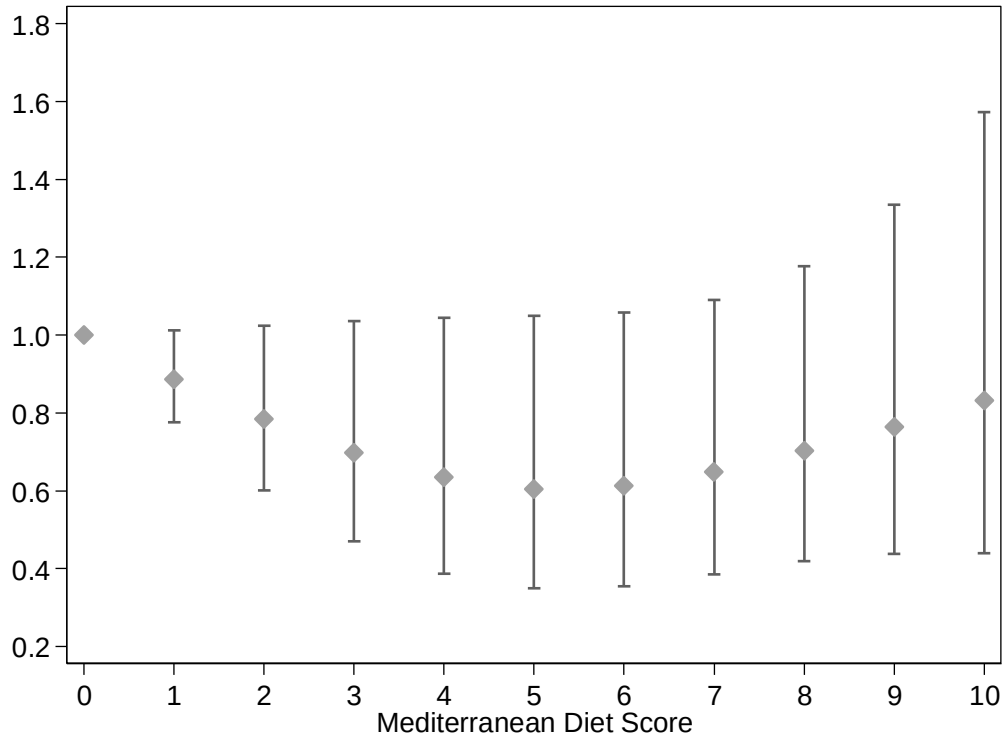


***Figure 4.4 Restricted cubic spline for the association between rectal cancer and the Mediterranean diet score.***

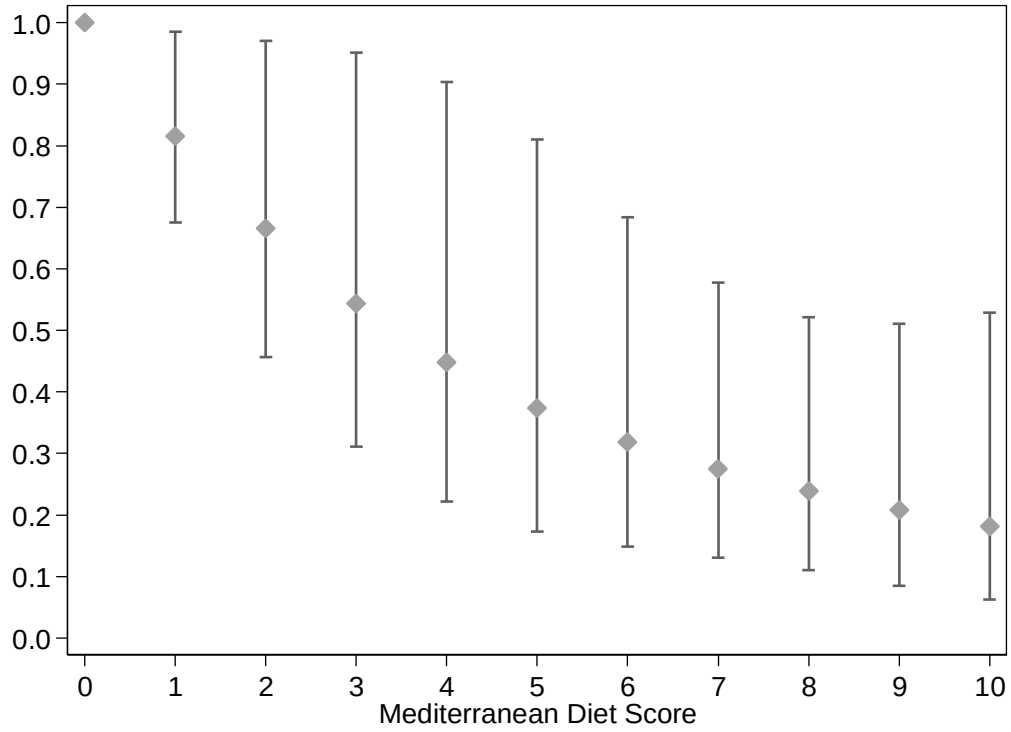
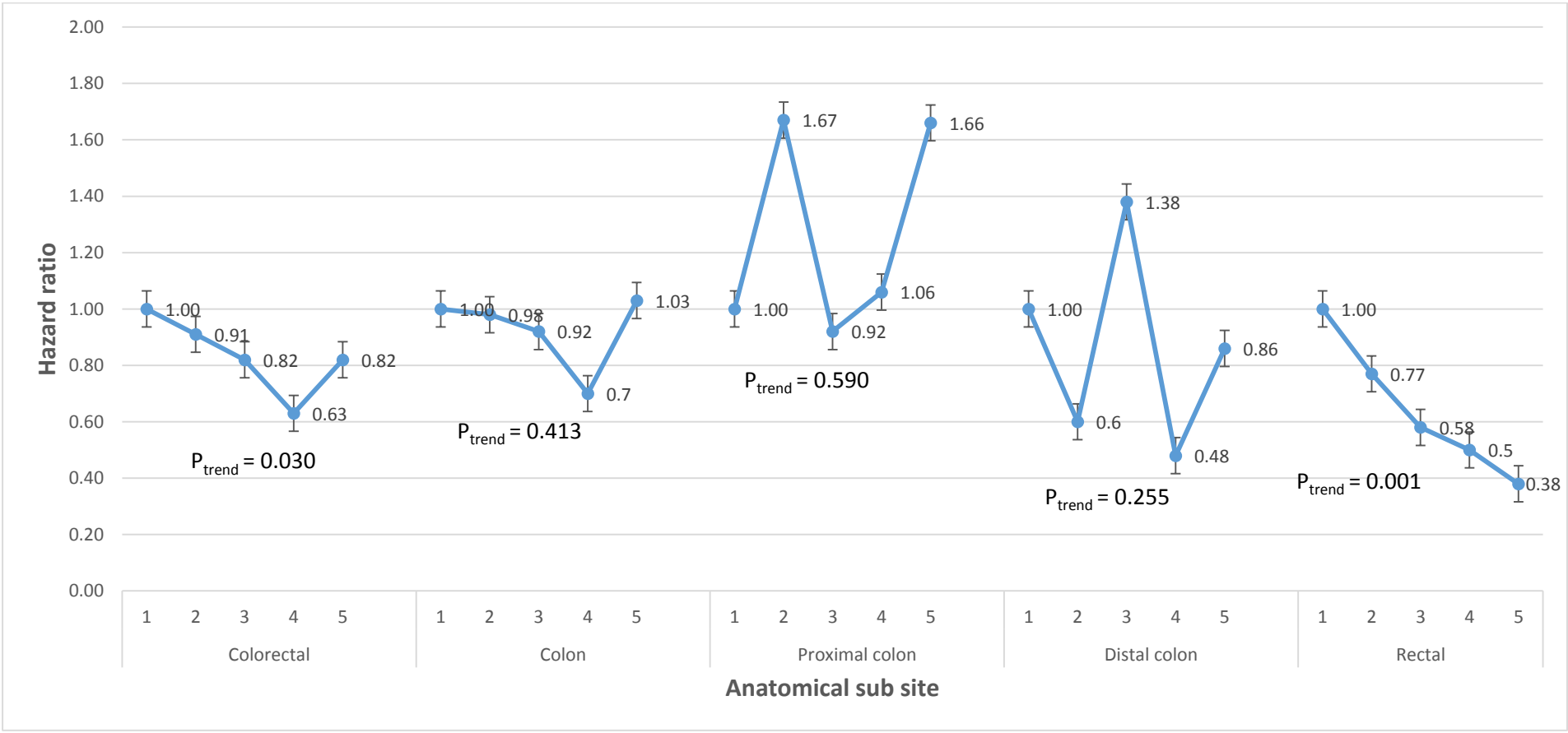



Table 4.4 shows the estimates of the separate components of the MD score with colorectal, colon and rectal cancer. The analysis found no association with CRC or colon cancer, whilst an inverse association was seen only for the high intake of legumes on rectal cancer risk, with a 44% lower risk (95% CI: 0.35 to 0.91; $P_{trend}$ = 0.02) when compared to the lowest reference intake. Estimated associations for legume intake and CRC risk, though weak, were in the expected direction.

***Figure 4.5 Association between colorectal cancer incidence, by anatomical sub site, and adherence to the Mediterranean diet score categories[1]***




[1] Cox regression model adjusted by age, BMI, energy intake, physical activity, smoking status, socioeconomic status and family history of colorectal cancer

***Table 4.4 Multivariate-adjusted hazard ratios of colorectal, colon and rectal cancer incidence according to intake of the Mediterranean diet score components***

| Mediterranean diet score components | Median intake (g/day) | Colorectal Cancer | | | Colon Cancer | | | Rectal Cancer | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Cases[1] | Age-adjusted HR (95% CI) | Multivariate-adjusted[2] HR (95% CI) | Cases[1] | Age-adjusted HR (95% CI) | Multivariate-adjusted[2] HR (95% CI) | Cases[1] | Age-adjusted HR (95% CI) | Multivariate-adjusted[2] HR (95% CI) |
| Vegetables | | | | | | | | | | |
| Low | 164 | 174 | 1 | 1 | 129 | 1 | 1 | 52 | 1 | 1 |
| Medium | 281 | 145 | 0.82 (0.65, 1.03) | 0.85 (0.66, 1.09) | 106 | 0.80 (0.61, 1.05) | 0.80 (0.60, 1.08) | 50 | 0.98 (0.65, 1.46) | 1.07 (0.69, 1.65) |
| High | 452 | 146 | 0.82 (0.65, 1.03) | 0.87 (0.68, 1.13) | 101 | 0.79 (0.60, 1.04) | 0.88 (0.65, 1.18) | 52 | 0.90 (0.60, 1.36) | 0.90 (0.57, 1.40) |
| $P_{trend}$ | | | 0.078 | 0.286 | | 0.080 | 0.370 | | 0.623 | 0.657 |
| Legumes | | | | | | | | | | |
| Low | 12 | 194 | 1 | 1 | 138 | 1 | 1 | 65 | 1 | 1 |
| Medium | 31 | 151 | 0.84 (0.67, 1.05) | 0.80 (0.63, 1.02) | 111 | 0.89 (0.68, 1.15) | 0.83 (0.62, 1.10) | 49 | 0.78 (0.53, 1.15) | 0.78 (0.51, 1.18) |
| High | 73 | 120 | 0.83 (0.64, 1.06) | 0.78 (0.60, 1.02) | 87 | 0.91 (0.68, 1.21) | 0.87 (0.64, 1.20) | 40 | 0.72 (0.47, 1.11) | 0.56 (0.35, 0.91) |
| $P_{trend}$ | | | 0.103 | 0.052 | | 0.455 | 0.330 | | 0.117 | 0.017 |
| Fruit & nuts | | | | | | | | | | |
| Low | 134 | 148 | 1 | 1 | 105 | 1 | 1 | 50 | 1 | 1 |
| Medium | 271 | 166 | 0.98 (0.77, 1.23) | 1.05 (0.81, 1.37) | 123 | 1.00 (0.76, 1.31) | 1.08 (0.79, 1.46) | 55 | 0.99 (0.66, 1.47) | 1.05 (0.67, 1.65) |
| High | 485 | 151 | 0.86 (0.68, 1.09) | 0.95 (0.73, 1.25) | 108 | 0.86 (0.65, 1.14) | 0.93 (0.67, 1.28) | 49 | 0.81 (0.53, 1.23) | 0.93 (0.57, 1.51) |
| $P_{trend}$ | | | 0.201 | 0.719 | | 0.286 | 0.609 | | 0.314 | 0.754 |
| Cereals | | | | | | | | | | |
| Low | 132 | 172 | 1 | 1 | 125 | 1 | 1 | 56 | 1 | 1 |
| Medium | 227 | 158 | 0.99 (0.79, 1.24) | 1.05 (0.81, 1.37) | 108 | 0.94 (0.72, 1.22) | 0.95 (0.69, 1.29) | 61 | 1.15 (0.79, 1.68) | 1.31 (0.83, 2.08) |
| High | 354 | 135 | 0.90 (0.71, 1.14) | 0.97 (0.72, 1.31) | 103 | 0.99 (0.75, 1.30) | 1.02 (0.72, 1.45) | 37 | 0.67 (0.43, 1.05) | 0.74 (0.42, 1.33) |
| $P_{trend}$ | | | 0.380 | 0.858 | | 0.910 | 0.910 | | 0.105 | 0.383 |

| Mediterranean diet score components | Colorectal Cancer | | | | Colon Cancer | | | Rectal Cancer | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Median intake (g/day) | Cases[1] | Age-adjusted HR (95% CI) | Multivariate-adjusted[2] HR (95% CI) | Cases[1] | Age-adjusted HR (95% CI) | Multivariate-adjusted[2] HR (95% CI) | Cases[1] | Age-adjusted HR (95% CI) | Multivariate-adjusted[2] HR (95% CI) |
| Fish | | | | | | | | | | |
| Low | 3 | 140 | 1 | 1 | 92 | 1 | 1 | 54 | 1 | 1 |
| Medium | 23 | 158 | 0.86 (0.67, 1.10) | 0.89 (0.68, 1.17) | 118 | 0.93 (0.69, 1.25) | 0.98 (0.70, 1.36) | 48 | 0.72 (0.47, 1.09) | 0.75 (0.49, 1.17) |
| High | 47 | 167 | 0.86 (0.67, 1.10) | 0.87 (0.66, 1.14) | 126 | 0.92 (0.69, 1.24) | 1.03 (0.74, 1.43) | 52 | 0.76 (0.51, 1.15) | 0.68 (0.43, 1.07) |
| $P_{trend}$ | | | 0.265 | 0.360 | | 0.620 | 0.804 | | 0.273 | 0.112 |
| MUFA & PUFA: SFA[3] | | | | | | | | | | |
| Low | 1.20 | 159 | 1 | 1 | 114 | 1 | 1 | 55 | 1 | 1 |
| Medium | 1.53 | 166 | 1.16 (0.93, 1.46) | 1.10 (0.87, 1.42) | 117 | 1.15(0.88, 1.50) | 1.04 (0.78, 1.40) | 56 | 1.11 (0.76, 1.63) | 1.12 (0.75, 1.68) |
| High | 1.96 | 140 | 0.98 (0.77, 1.25) | 0.99 (0.76, 1.29) | 105 | 1.09(0.82, 1.44) | 1.14 (0.84, 1.54) | 43 | 0.76 (0.49, 1.17) | 0.67 (0.42, 1.08) |
| $P_{trend}$ | | | 0.984 | 0.975 | | 0.510 | 0.416 | | 0.241 | 0.130 |
| Meat | | | | | | | | | | |
| Low | 0 | 113 | 1 | 1 | 72 | 1 | 1 | 46 | 1 | 1 |
| Medium | 40 | 185 | 1.30 (1.00, 1.68) | 1.35 (1.02, 1.80) | 143 | 1.63 (1.20, 2.22) | 1.61 (1.15, 2.27) | 49 | 0.80 (0.51, 1.27) | 0.99 (0.60, 1.61) |
| High | 93 | 167 | 1.17 (0.89, 1.52) | 1.17 (0.86, 1.58) | 121 | 1.37 (1.00, 1.89) | 1.29 (0.90, 1.85) | 59 | 0.98 (0.63, 1.53) | 1.13 (0.67, 1.90) |
| $P_{trend}$ | | | 0.699 | 0.795 | | 0.474 | 0.752 | | 0.747 | 0.566 |
| Poultry | | | | | | | | | | |
| Low | 0 | 122 | 1 | 1 | 86 | 1 | 1 | 42 | 1 | 1 |
| Medium | 11 | 179 | 1.11 (0.86, 1.43) | 1.13 (0.85, 1.50) | 141 | 1.13 (0.84, 1.52) | 1.15 (0.83, 1.60) | 45 | 0.97 (0.61, 1.56) | 1.06 (0.64, 1.76) |
| High | 34 | 164 | 1.02 (0.79, 1.32) | 1.04 (0.79, 1.38) | 109 | 0.89 (0.65, 1.22) | 0.95 (0.68, 1.33) | 67 | 1.39 (0.91, 2.13) | 1.38 (0.86, 2.22) |
| $P_{trend}$ | | | 0.848 | 0.968 | | 0.200 | 0.450 | | 0.057 | 0.141 |

| Mediterranean diet score components | Colorectal Cancer | | | | Colon Cancer | | | Rectal Cancer | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Median intake (g/day) | Cases[1] | Age-adjusted HR (95% CI) | Multivariate-adjusted[2] HR (95% CI) | Cases[1] | Age-adjusted HR (95% CI) | Multivariate-adjusted[2] HR (95% CI) | Cases[1] | Age-adjusted HR (95% CI) | Multivariate-adjusted[2] HR (95% CI) |
| Dairy | | | | | | | | | | |
| Low | 41 | 154 | 1 | 1 | 111 | 1 | 1 | 49 | 1 | 1 |
| Medium | 97 | 153 | 0.96 (0.76, 1.21) | 1.09 (0.84, 1.43) | 114 | 0.96 (0.73, 1.26) | 1.08 (0.80, 1.46) | 51 | 1.04 (0.69, 1.58) | 1.14 (0.71, 1.83) |
| High | 180 | 158 | 0.93 (0.73, 1.17) | 1.00 (0.76, 1.31) | 111 | 0.87 (0.66, 1.14) | 0.89 (0.65, 1.22) | 54 | 1.07 (0.71, 1.62) | 1.18 (0.73, 1.92) |
| $P_{trend}$ | | | 0.515 | 0.954 | | 0.307 | 0.433 | | 0.739 | 0.505 |
| Alcohol | | | | | | | | | | |
| Low | 0.40 | 161 | 1 | 1 | 110 | 1 | 1 | 59 | 1 | 1 |
| Medium | 5.51 | 157 | 1.06 (0.84, 1.34) | 1.04 (0.81, 1.34) | 120 | 1.17 (0.89, 1.54) | 1.14 (0.84, 1.53) | 50 | 0.96 (0.65, 1.44) | 1.02 (0.66, 1.59) |
| High | 16.96 | 147 | 1.09 (0.86, 1.37) | 1.14 (0.88, 1.48) | 106 | 1.15 (0.87, 1.53) | 1.18 (0.87, 1.60) | 45 | 0.90 (0.59, 1.37) | 1.06 (0.66, 1.69) |
| $P_{trend}$ | | | 0.488 | 0.334 | | 0.309 | 0.283 | | 0.634 | 0.821 |

[1] Case numbers apply to multivariable adjusted models.

[2] Adjusted for age, BMI, energy intake, physical activity, smoking status, socioeconomic status and family history of colorectal cancer.

[3] Ratio of the sum of monounsaturated fatty acids and polyunsaturated fatty acids to saturated fatty acids.

## 4.5 Discussion

This study evaluated adherence to the Mediterranean dietary pattern in relation to risk of CRC in a UK cohort of middle-aged women, followed up for a median of 17.4 years. 465 cases of CRC were included in the analysis. The MD score chosen for this analysis was deemed most suitable for this British cohort. It gives a logical coverage of food types and its components were variables in the UKWCS database, allowing generation of the MD adherence score. The overall MD score was inversely associated with incidence of colorectal and rectal cancer; with the magnitude of the association being stronger for rectal cancer risk, whilst little association was seen for risk of colon cancer alone in multivariate adjusted analyses. Investigation of the separate score components showed that legume intake offered a degree of protection against risk of rectal cancer. No evidence of an association was found for the intake of any other individual component of the MD score with either site of the colorectum.

Several prospective studies have investigated the association between the MD and CRC risk (Fung et al., 2010; Reedy et al., 2008; Bamia et al., 2013; Agnoli et al., 2013), although results were not consistent. A meta-analysis of 21 cohort and 12 case-control studies reported a 14% reduced risk of CRC with high adherence to MD (Schwingshackl et al., 2014), which is comparable to the 18% decrease in risk reported for this cohort. The results of this study are in part in agreement with those of Agnoli and colleagues who also reported a reduction in risk of developing colorectal and rectal cancer, but differed to the results of this cohort in finding evidence of an inverse association also for distal colon cancer (Agnoli et al., 2013), although our study may have been limited by small numbers for sub-site analysis. In contrast, no association for either cancer site in women was observed in the NIH-AARP Diet and Health Study (Reedy et al., 2008). The cubic spline for MD score and CRC (Figure 4.2) portrays a non-linear association above MD score 6, with a plateau being reached, potentially implying that the MD does not offer added benefit with respect to cancer risk reduction above this level of adherence. Conversely, for rectal cancer, the cubic spline (Figure 4.4) shows no deviation from linearity across the MD score, reflecting the strong inverse association inferred in the results. If a true difference exists between different anatomic sub sites of the colorectum, the heterogeneity in estimates could be attributed to the different microbial composition, molecular features and biochemical environment of the colonic

lumen (Song et al., 2015). Nevertheless, the apparent difference in associations may be due to the relatively small sub site numbers.

Whilst the magnitude of the association for CRC in this study is similar to that observed in the EPIC study (Bamia et al., 2013), in the latter a strong inverse association was evident for colon cancer whilst that for rectal cancer was much weaker. Fung and colleagues found no association between conformity to the MD and risk of CRC and colorectal adenomas, respectively, in women (Fung et al., 2010). This inconsistency in results from different studies may be due to different researchers' interpretation of what constitutes a Mediterranean dietary pattern, the variation in the scores used to assess adherence to it including cut-points for intake that may vary by sex, dietary measurement error resulting in the attenuation of modest associations as well as potential false reporting of interactions by sex and anatomical site. (Nieuwenhuis et al., 2011). For instance, authors may falsely declare that exposure to a particular eating pattern is associated with CRC in males but not in females, when the CI between both sexes overlap and the interaction by sex is not statistically significant. Furthermore, a lower number of cases in studies that differentiate categories according to sex may result in weaker risk estimates for women.

The beneficial effect of the MD on risk of CRC may be due to the predominantly plant based nature of this dietary pattern, characterised by foods high in dietary fibre, including fruit, vegetables, nuts and legumes, and a low intake of red meat, specifically processed. The potential of an increased fibre (Aune et al., 2011b; Murphy et al., 2012) and fish consumption (Wu et al., 2012; Norat et al., 2005) to decrease CRC risk have been previously reported as has the association of high intakes of red and processed meat with increased risk of colorectal, colon and rectal cancers (Chan et al., 2011). Notwithstanding, a systematic review and meta-analysis by Magalhaes and colleagues reported a higher risk of proximal and distal colon but not of rectal cancer in subjects with high consumption of red meat and low consumption of fruit and vegetables (Magalheas et al., 2012). In EPIC, inverse associations were observed for cereal fibre and colon and rectal cancer, whilst fibre from cereals but not from fruit and vegetables was associated with decreased rectal cancer (Murphy et al., 2012). The estimated associations for vegetables, legumes, fish and red meat reported in Table 4.4, though

not all strong, are in the expected directions and support the implication that such components are mediating the associations observed for adherence to the MD. Despite the standard MD adherence score (Trichopoulou et al., 2005) as used in this study attributing a detrimental effect to poultry and dairy products, recent evidence shows that poultry (Shi et al., 2015) and milk (Aune et al., 2012b) moderately reduce CRC incidence, whilst the association with yoghurt warrants further investigation (Song et al., 2015).

The exact mechanisms underlying the association between the MD and CRC remain unclear. In a review, Song *et al.* states that diet affects CRC carcinogenesis directly through immune responsiveness and inflammation, indirectly through excess weight which is itself a risk factor and may result in insulin resistance and also attributes a role to the gut microbiota (Song et al., 2015). Several relevant hypotheses have linked red meat consumption to CRC; it is a source of saturated fat and heme iron, the latter may induce the formation of the carcinogenic N-nitroso compounds, whilst the production of heterocyclic amines and polycyclic aromatic hydrocarbons during prolonged cooking at high temperatures may also be responsible for the association (Chan et al., 2010; Song et al., 2015). The anti-inflammatory and antineoplastic role of omega-3 polyunsaturated fatty acids (PUFAs) mainly through the reduction of prostaglandin E2 synthesis and/or synthesis of anti-inflammatory resolvins has been proposed as a mechanism (Cockbain et al., 2012) inversely relating PUFAs and thus fish consumption to CRC. Fibre from legume and vegetable intake in a MD may function in reducing CRC risk by diluting carcinogens from faeces and binding to carcinogenic bile acids, reducing colonic transit time and pH and may be fermented into beneficial SCFAs (Kritchevsky et al., 1995; Lipkin et al., 1999).

Strengths of this study include the large size of this UK cohort, its design and the long follow up, cancer registry confirmed diagnosis and the ability to control for non-dietary potential confounding factors. Some limitations have also been identified. The single FFQ administered at baseline is the only method of assessment of dietary information, leaving potential changes in diet throughout follow-up unaccounted for. The use of a dietary score in itself has its limitations (Michels & Schulze, 2005; Hu et al., 2002). In this study, the scoring system gave each component an equal weighting which may not

equate to potential mechanisms of effect and limits the dietary advice that can be given. Furthermore, the small number of cases in the analyses by sub site results in limited power.

In conclusion, this study has given evidence of a non-linear relationship between the MD and CRC, and of a strong, linear risk reduction between the MD and rectal cancer. Women adhering to a MD pattern may have a lower risk of CRC.

# CHAPTER 5 DOES ADHERENCE TO THE WCRF/AICR CANCER PREVENTION GUIDELINES REDUCE RISK OF COLORECTAL CANCER IN THE UK WOMEN'S COHORT STUDY?

## 5.1 Chapter overview

*Background:* Evidence on adherence to diet related cancer prevention guidelines and associations with CRC risk is limited and conflicting. The aim of this cohort analysis is to evaluate associations between adherence to the WCRF/AICR 2007 recommendations and incident CRC.

*Method:* The UKWCS comprises over 35,372 women who filled in a FFQ at baseline in 1995. They were followed up for CRC incidence for a median of 17.4 years, an individual score linking adherence to eight of the WCRF/AICR recommendations was constructed. Cox proportional hazards regression provided HRs and 95% CIs for the estimation of CRC risk, adjusting for confounders.

*Results:* Following exclusions, 444 CRC cases were identified. In the multivariate adjusted model, women within the second and third (highest) categories of the WRCF/AICR score had HRs (95% CIs) of 0.79 (0.62-1.00) and 0.73 (0.48-1.10) respectively for CRC compared with those in the lowest, reference category. The overall linear trend across the categories was not significant (p=0.17). No significant associations were observed between the WCRF/AICR score and proximal colon, distal colon and rectal cancers separately. Of the individual score components, a BMI within the normal weight range was borderline significantly protective only for rectal cancer in the fully adjusted model.

*Conclusion:* In view of the likely different causes of CRC subtypes, further research is needed to identify the optimal dietary patterns associated with reducing colon and rectal cancer risk respectively.

## 5.2 Introduction

CRC is the third most common cancer in men and the second in women, with about 694 000 annual deaths estimated worldwide, accounting for 8.5% of deaths from cancer. With respect to incidence, almost 55% of cases are reported in the more developed countries and occurrence differs 10-fold in both men and women, between countries (Ferlay et al., 2012). This wide geographical variation in incidence supports the theory that diet and nutrition may have a role in the aetiology of CRC and are thus considered modifiable risk factors (Center et al., 2009).

Although the role of diet in relation to CRC risk has been widely investigated, the synergistic effect and complex interactions of food components make the analysis of dietary patterns better at capturing disease risk than individual foods or nutrients (Ocke', 2013). Furthermore, dietary data combined with data on lifestyle choices represents a more complete picture. Guidelines promoting lifestyles to reduce cancer risk have been issued by both the ACS (Kushi et al., 2006) and the WCRF and the AICR (WCRF/AICR, 2007). Both sets of guidelines include recommendations targeting a healthy diet and body weight, low alcohol consumption, if any, and more physical activity for cancer prevention whilst the WCRF/AICR also makes two special recommendations to encourage breastfeeding where possible and for cancer survivors to follow guidelines for cancer prevention (WCRF/AICR, 2007). Several studies have operationalised a set of these guidelines to explore the association between concordance to the guidelines and reduced risk of chronic diseases, all-cause cancer and mortality (Cerhan et al., 2004; Inoue-Choi et al., 2013; Vergnaud et al., 2013).

With respect to reduced risk of incidence of cancers of the colon and rectum, studies have mainly explored adherence to ACS guidelines (Thomson et al., 2014; Kabat et al., 2015) or the Dietary Guidelines for Americans (Harnack et al., 2002), and others have looked at incidence of total CRC rather than differentiated between the colon and rectal cancer-sites (Makarem et al., 2015; Romaguera et al., 2012; Hastert & White, 2016; Nomura et al., 2016). Furthermore, results of the latter studies are conflicting. Further studies operationalising the WCRF/AICR guidelines and looking at the association between CRC, and exploring colon and rectal cancer separately are

needed. In fact, the 2017 WCRF/AICR CUP report stated that due to the limited evidence on this association, no conclusion can be made (WCRF/AICR, 2017).

The aim of this study is to assess whether adherence to the WCRF/AICR cancer prevention recommendations released in 2007, related to body fatness, physical activity, nutrition and breastfeeding is associated with reduced incidence of cancer of the colorectum, colon and rectum in a large UK cohort of women with a long follow up period.

## 5.3 Methods

### 5.3.1 Study design and population

The UKWCS of 35 372 middle-aged women was initiated in 1995 with the aim of exploring diet and chronic disease associations. Dietary information at baseline was obtained using a postal questionnaire - a FFQ and questions on lifestyle and health. Participants with varied dietary patterns were chosen for inclusion in the cohort in order to increase the explorative power of the cohort with respect to diet and disease outcomes. The cohort women have a mean (standard deviation, s.d.) age of 52.3 (9.4) years at baseline, are mainly middle-class and 86% have children. They are generally well-educated and health conscious with only 8% reporting that they smoke daily and a mean BMI in the normal range. Further details on the cohort profile have been reported in section 3.3.

### 5.3.2 Baseline characteristics and dietary information

Values for age, weight, height and waist circumference were self-reported. Additional information on medical history, smoking habit, supplement use and breastfeeding was also self-described, as was socio-demographic information such as marital status. Participants were asked about the time spent on vigorous activities to collect information on physical activity whilst their socio-economic status was classified based on their occupation. Women were grouped as either (a) professional / managerial; (b) intermediate; (c) routine / manual as defined by the UK NS-SEC (Rose et al., 2005). Although collected, ethnicity data was not used since over 99% of cohort participants were Caucasian.

The FFQ sent to participants at baseline was developed from one used by the Oxford arm of the EPIC (Riboli et al., 1997), and adapted to better suit the high proportion of vegetarians in the UKWCS. A total of 217 food items made up the questionnaire; participants were asked to tick one of 10 pre-coded categories, indicating average consumption frequency of the specific item over a 12 month period and ranging from never to 6 portions/day or more. The estimated number of portions were assigned a standard portion weight and the energy intake from macronutrients and alcohol was derived using McCance & Widdowson's *The Composition of Foods* (5th Edition) (Holland et al., 1991). In the case of missing data on food consumption, non-response was assumed to imply non-consumption.

### 5.3.3 Ethical approval

Ethical approval was granted at the initiation of the UKWCS in 1995 from 174 individual UK local ethics committees for the study to follow participants for cancer and other diseases. Participants were considered consenting to the confidential use of collected data at baseline, in follow-up stages and from cancer registries for research purposes when they returned a completed questionnaire. The back page of the questionnaire asked for access to participants' medical records via an NHS number and a general practitioner's address and outlined the aim of the study as that of examining 'the occurrence of certain diseases such as cancer which are registered by the NHS'.

### 5.3.4 Cancer case definition

The cancer outcomes used in the analyses are incident malignant neoplasms of the colon (as identified by codes 153.0-153.9 or C18) and of the rectosigmoid junction and of the rectum (as identified by codes 154.0-154.1 or C19 and C20) of the International Statistical Classification of Diseases (ICD, 9th and 10th revisions) (AMA, 2004, WHO, 2010). Cases were defined as patients who were cancer free, except for non-melanoma skin cancer, at the time of FFQ completion and who developed CRC, as reported through the NHS Digital, a minimum of 12 months after the dietary assessment to ensure the absence of latent disease that may otherwise have

influenced the women's dietary habits. Women who did not self-report prior medical history (n=2585) were assumed to be free from disease.

### 5.3.5 WCRF/AICR score construction

An adherence score to WCRF/AICR recommendations for cancer prevention was generated from the UKWCS database for each cohort participant. The approach taken in constructing the score was to operationalise eight out of ten WCRF/AICR recommendations, namely body fatness, physical activity, foods and drinks that promote weight gain, plant foods, animal foods, alcoholic drinks, consumption of salty foods and breastfeeding. All recommendations for which data was available were operationalized in an attempt to allow the evaluation of adherence to the dietary pattern formed as a whole, in relation to CRC risk. The recommendation to avoid the use of dietary supplements for cancer protection was explored in sensitivity analyses since data in the cohort related only to whether supplements were taken or not, and no information was available on whether supplements were taken to reduce cancer risk. The recommendation for cancer survivors was not applicable to this population.

A maximum adherence score of 8 was therefore possible for the UKWCS, with higher values indicating greater concordance with the recommendations. If the recommendation was met, the woman was assigned a score of 1, if not met a 0 was assigned and an intermediate category for partially met, resulting in a score of 0.5 was also created. Each major recommendation contributed equally to the final single score for each participant since WCRF/AICR recommendations were not ranked according to priority. For guidelines with more than one sub recommendation, namely energy density and plant foods, each sub recommendation was scored separately and an average of the allocated scores was derived. Where quantitative criteria were described in the WCRF/AICR recommendations, these were used as cut-offs. This was the case for body fatness, physical activity, energy density, consumption of fruit and vegetables, dietary fibre intake, consumption of animal food, alcohol intake, sodium intake and breastfeeding. With respect to the consumption of sugary drinks, the recommendation is avoidance of drinks with added sugars; for this study subjects were considered non-adherent if they reported consuming more than one sugary drink a

day (>250g/day) in the FFQ. Participants with missing data on BMI were dropped from the analysis, those with missing information on physical activity (n=1928) and breastfeeding (n=9533) were assumed to not have undertaken physical activity or breastfed respectively, whilst missing data on food and drinks was assumed to imply non-consumption. Details of the score operationalization are given in Table 5.1. The WCRF/AICR scores for participants were categorised into three groups, to indicate low, medium and high adherence to the recommendations (i.e. 0 to ≤ 3, >3 to ≤ 5, > 5to 8).

***Table 5.1 Classification and operationalization of the WCRF/AICR cancer prevention recommendations and the percentage adherence in the UKWCS[1]***

| WCRF/AICR recommendation | Personal recommendations | Operationalization | Scoring | UKWCS adherents (%) | CRC cases adherents (%) |
|---|---|---|---|---|---|
| 1. Body fatness<br>*Be as lean as possible within the normal range of body weight.* | (a) Ensure that body weight through childhood and adolescent growth projects towards the lower end of the normal BMI range at 21 | Insufficient data available | NA | NA | NA |
| | (b) Maintain body weight within the normal range from age 21 | BMI (kg/m$^2$): 18.5-24.9<br>BMI: 25-29.9<br>BMI: <18.5 or ≥30 | 1<br>0.5<br>0 | 62.4<br>25.6<br>12.0 | 55.6<br>26.8<br>17.6 |
| | (c) Avoid weight gain and increases in waist circumference throughout adulthood | Insufficient data available | NA | NA | NA |
| 2. Physical activity<br>*Be physically active as part of everyday life.* | (a) Be moderately physically active, equivalent to brisk walking, for ≥ 30 min every day. | >30 min/d of vigorous PA<br>15-30 min/d of vigorous PA<br><15 min/d of vigorous PA | 1<br>0.5<br>0 | 13.8<br>19.4<br>66.8 | 12.6<br>17.1<br>70.3 |
| | (b) As fitness improves, aim for ≥60 min of moderate or for ≥ 30 min of vigorous physical activity every day. | Insufficient data available | NA | NA | NA |
| | (c) Limit sedentary habits such as watching television. | Insufficient data available | NA | NA | NA |

| WCRF/AICR recommendation | Personal recommendations | Operationalization | Scoring | UKWCS adherents (%) | CRC cases adherents (%) |
|---|---|---|---|---|---|
| 3. Foods and beverages that promote weight gain *Limit consumption of energy dense foods; avoid sugary drinks.* | (a) Consume energy-dense foods sparingly | ED: ≤125 kcal/100 g/d | 1 | 32.8 | 33.3 |
| | | ED: >125 to <175 kcal/100 g/d | 0.5 | 57.9 | 59.0 |
| | | ED: >175 kcal/100 g/d | 0 | 9.3 | 7.7 |
| | (b) Avoid sugary drinks | Sugary drinks: 0 g/d | 1 | 4.8 | 5.2 |
| | | Sugary drinks: ≤250 g/d | 0.5 | 83.5 | 84.0 |
| | | Sugary drinks: >250 g/d | 0 | 11.7 | 10.8 |
| | (c) Consume fast foods sparingly, if at all. | Insufficient data available | NA | NA | |
| 4. Plant foods *Eat mostly foods of plant origin.* | (a) Eat ≥ 5 portions/servings (≥400 g) of a variety of nonstarchy vegetables and of fruit every day. | F&V: ≥400 g/d | 1 | 24.5 | 23.4 |
| | | F&V: 200 to <400 g/d | 0.5 | 41.1 | 42.8 |
| | | F&V: <200 g/d | 0 | 34.4 | 33.8 |
| | (b) Eat relatively unprocessed cereals (grains) and / or pulses (legumes) with every meal. | Dietary fibre: ≥25 g | 1 | 7.5 | 7.0 |
| | | Dietary fibre: 12.5 to <25 g/d | 0.5 | 50.4 | 50.2 |
| | | Dietary fibre: <12.5g/d | 0 | 42.1 | 42.8 |
| | (c) Limit refined starchy foods. | Insufficient data available | NA | NA | NA |
| | (d) People who consume starchy roots or tubers as staples should also ensure sufficient intake or nonstarchy vegetables, fruit and pulses (legumes). | Not applicable to this population | NA | NA | NA |
| 5. Animal foods *Limit intake of red meat and avoid processed meat.* | People who eat red meat should consume <500 g / wk and very few, if any, processed meats | RPM <500 g/wk and PM <3 g/d | 1 | 36.0 | 27.3 |
| | | RPM <500 g/wk and PM 3 to <50 g/d | 0.5 | 48.8 | 53.8 |
| | | RPM ≥500 g or PM ≥50 g/d | 0 | 15.2 | 18.9 |
| 6. Alcohol *Limit alcoholic drinks.* | If alcoholic drinks are consumed, limit consumption to ≤2 drinks/d for men and 1 drink/d for women. | Ethanol: ≤10 g/d | 1 | 66.3 | 68.2 |
| | | Ethanol: >10-20 g/d | 0.5 | 21.1 | 19.4 |
| | | Ethanol: >20 g/d | 0 | 12.6 | 12.4 |

| WCRF/AICR recommendation | Personal recommendations | Operationalization | Scoring | UKWCS adherents (%) | CRC cases adherents (%) |
|---|---|---|---|---|---|
| 7. Preservation, processing, preparation<br>*Limit consumption of salt; avoid mouldy cereals (grains) or pulses (legumes).* | (a) Avoid salt-preserved, salted or salty foods; preserve foods without using salt. | Insufficient data available | NA | NA | NA |
| | (b) Limit consumption of processed foods with added salt to ensure an intake of <6g (2.4g sodium) every day. | Sodium: ≤ 1.5 g/d<br>Sodium: >1.5 to 2.4 g/d<br>Sodium: >2.4 g/d | 1<br>0.5<br>0 | 3.5<br>23.3<br>73.2 | 3.36<br>23.2<br>73.2 |
| | (c) Do not eat mouldy cereals (grains) or pulses (legumes). | Insufficient data available | NA | NA | NA |
| 8. Dietary supplements<br>*Aim to meet nutritional needs through diet alone.* | Dietary supplements are not recommended for cancer prevention. | Not applicable to this population | NA | NA | NA |
| *WCRF/AICR special recommendations* | | | | | |
| S1. Breastfeeding (BF)<br>*Mothers to breastfeed; children need to be breastfed.* | Aim to breastfeed infants exclusively up to 6 months and continue with supplementary feeding thereafter. | Cumulative BF: ≥6 months<br>Cumulative BF: >0 to <6 months<br>No breastfeeding | 1<br>0.5<br>0 | 38.2<br>26.4<br>35.4 | 37.6<br>28.8<br>33.6 |
| S2. Cancer survivors<br>*Follow the recommendations for cancer prevention.* | (a) All cancer survivors should receive nutritional care from an appropriately trained professional. | Not applicable to this population | NA | NA | NA |
| | (b) If able to do so, and unless otherwise advised, aim to follow the recommendations for diet, healthy weight, and physical activity. | Not applicable to this population | NA | NA | NA |

[1]BMI, body mass index; NA, not applicable; PA, physical activity; ED, energy density; F&V, fruit and vegetables; wk, week; d, day; RPM, red and processed meat; PM, processed meat

### 5.3.6 Statistical analysis

Descriptive statistics were used to describe baseline characteristics of participants. Survival analysis was conducted using the Cox proportional hazards regression model to estimate cancer risk in the form of HRs and 95% CI. The relationship between adherence to WCRF/AICR guidelines and CRC was explored as the primary outcome, whilst some exploratory analysis was carried out on distal and proximal colon cancers and on rectal cancer as secondary outcomes. Probability weighting, described in detail in section 3.9.2.1, was used to account for the large proportion of vegetarians and fish eaters in the cohort and to reflect the inverse probability of being sampled, thus increasing the cohort's external validity. The time variable used in the models was time in the study (person years), calculated from the date of questionnaire receipt until either cancer diagnosis, death or censor date (01 April 2014). Assumptions for proportional hazards were tested graphically for all terms in the model.

The risk of cancer as adherence to the WCRF/AICR score increased was determined by comparing each group of participants, to the lowest adherence, reference group. Risk estimates were calculated per one-point increment in the continuous WCRF/AICR score and by the three score categories; linear trend was also calculated. Risk factors for CRC previously identified in the literature were taken into consideration. Potential confounders that were either included in the score derivation, such as BMI and physical activity, or were closely related to a score component, such as energy (kcal) to energy density were excluded from the adjusted analyses, as were those that had considerable missing observations, particularly if a strongly related variable was available. Associations were estimated for CRC, and then for colon, proximal colon, distal colon and rectal cancer separately. Results are presented for an age-adjusted model, and then for a full model adjusting for age (years), smoking status (never, current or former smoker), family history in a first degree relative and socio-economic status (professional/ managerial, intermediate or routine and manual). Sensitivity analyses were carried out operationalising a 9$^{th}$ recommendation relating to supplement use in the WCRF/AICR score. Stata version 13.0 statistical software (StataCorp, 2013) was used for all analyses and a 2-sided p-value ≤0.05 was considered statistically significant.

## 5.4 Results

### 5.4.1 Demographics

During a mean (s.d.) follow up time of 18.7 (0.8) years, 527 incident CRC cases were documented for women in the UKWCS. This is equivalent to approximately 28.2 new cases of CRC yearly in the cohort, i.e. 79.6 cases per 100,000 women. In 2015, the age-standardised rate of CRC incidence was 57.2 per 100,000 UK female population (Office for National Statistics, 2017). The directly age-standardised rate of CRC in UKWCS is 63 per 100,000 women (95% CI: 58, 68), standardized to the European Standard Population for women aged 35 and over. Although the two rates are not directly comparable as the women in the cohort are over 35 years, the incidence rate in the cohort is broadly consistent with that reported in the general UK population.

From the total cohort (n=35 372), participants who did not provide sufficient data at baseline to allow flagging on NHS Digital (n=695), women self-reporting history of any previous malignant cancer at baseline, except for non-melanoma of the skin (n=2391), women who were diagnosed with CRC within one year of baseline (n=53), women with energy intakes outside the plausible range of 500 to 6000kcal/day (n=79), and women with missing data for BMI (n=1191) were excluded. Following exclusions, a total of 30 963 cohort participants, followed for a median of 17.4 years (IQR=1.7) were eligible for inclusion in the analysis with 444 CRC cases, of which 322 were located in the colon (164 in the proximal colon and 115 cases in the distal colon) and 146 cases were of rectal cancer.

### 5.4.2 Baseline characteristics

The baseline characteristics of total study participants, women diagnosed with CRC and according to the level of adherence to the WCRF/AICR recommendations are reported in Table 5.2. Women who were in the highest adherence category of the score were likely to be younger and less likely to smoke or eat meat when compared to those in low and medium adherence categories. Lower adherers were less likely to possess a degree qualification or to hold a managerial position. Figure 5.1 depicts the proportion of UKWCS participants adhering to the individual recommendations, in comparison with the proportion of CRC cases. The greatest differences in proportion

are for red meat and BMI, where CRC cases are less adherent. Table 5.3 depicts the baseline characteristics of CRC cases and non-cases for UKWCS participants when the 9$^{th}$ recommendation to avoid supplements for cancer prevention is included in the WCRF score. Cases tended to be older, have a higher BMI and were less likely to hold a managerial position or to have a degree level of education than non-cases. They were also more likely to eat meat, although their median alcohol intake was lower than that that of women without a CRC diagnosis.

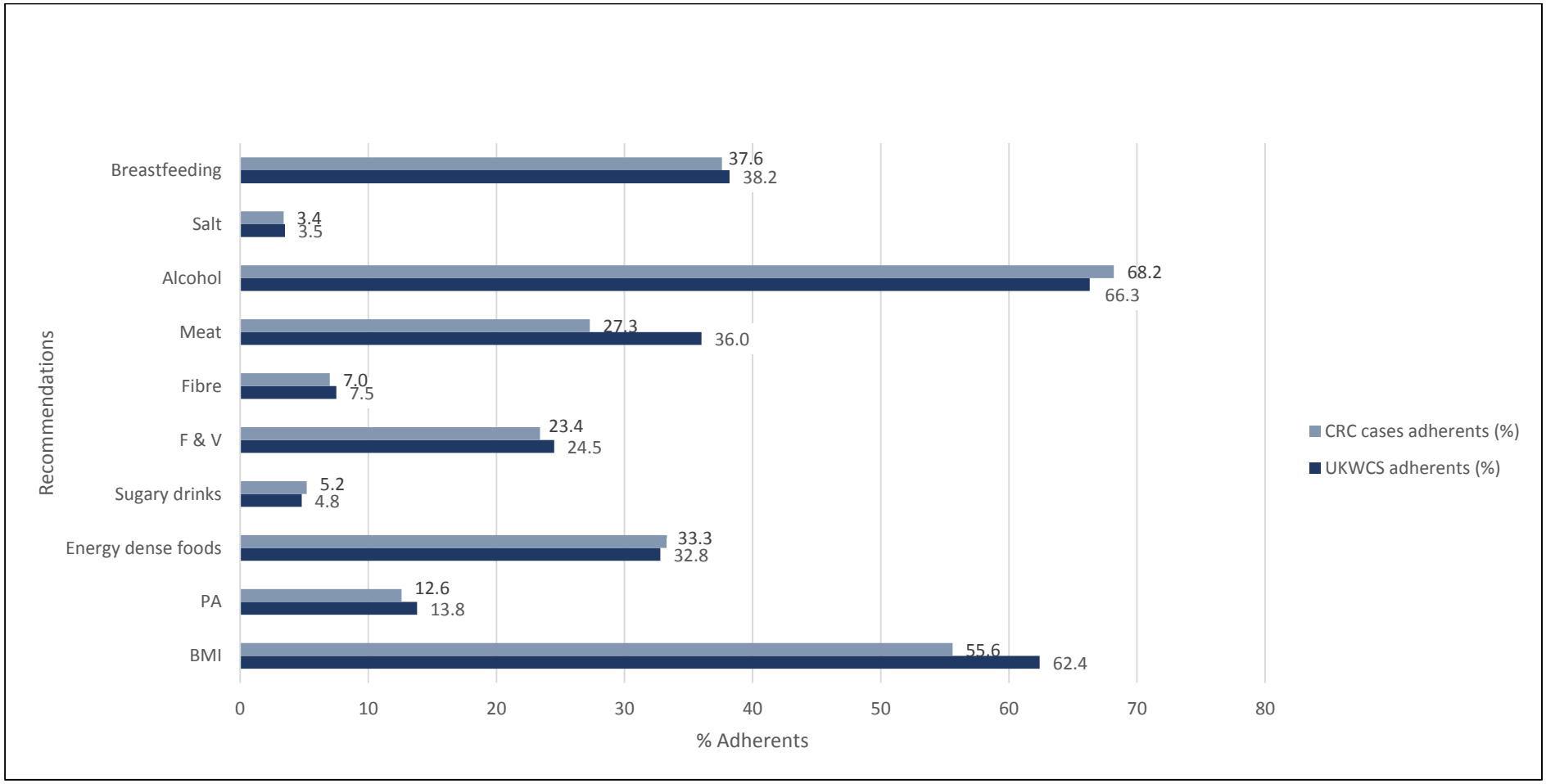
*Table 5.2 Characteristics of colorectal cancer cases and across WCRF/AICR score categories for participants in the UKWCS[1]*

| Variable | Total | CRC cases | WCRF/AICR score categories 1 | 2 | 3 |
|---|---|---|---|---|---|
| Observations N (%) | 30963 | 444 (1.4) | 6319 (20.4) | 20978 (67.7) | 3671 (11.9) |
| WCRF/AICR score range | 0-8 | | 0-3 | 3.25-5 | 5.25-8.0 |
| Age (years) | | | | | |
| Mean | 52.0 | 57.7 | 52.8 | 52 | 50.6 |
| 95% CI | (51.9, 52.1) | (56.9, 58.6) | (52.6, 53.0) | (51.9, 52.1) | (50.3, 50.9) |
| BMI ($kg/m^2$) | | | | | |
| Mean | 24.4 | 25.1 | 26.9 | 24 | 22.5 |
| 95% CI | (24.4, 24.5) | (24.6, 25.5) | (26.8, 27.0) | (24.0, 24.1) | (22.4, 22.5) |
| Energy intake (kcal/day) | | | | | |
| Mean | 2342 | 2355 | 2450 | 2326 | 2247 |
| 95% CI | (2334, 2350) | (2285, 2425) | (2433, 2468) | (2317, 2335) | (2222, 2272) |
| Ethanol (g/day) | | | | | |
| Median | 5.54 | 4.73 | 11.88 | 5.23 | 2.21 |
| IQR | 11.8 | 11.74 | 20.23 | 10.8 | 6.64 |
| Physical activity (hr/day) | | | | | |
| Mean | 0.24 | 0.22 | 0.1 | 0.23 | 0.56 |
| 95% CI | (0.24, 0.25) | (0.18, 0.26) | (0.09, 0.11) | (0.22, 0.24) | (0.54, 0.58) |

| | | | WCRF/AICR score categories | | |
|---|---|---|---|---|---|
| **Variable** | **Total** | **CRC cases** | **1** | **2** | **3** |
| Smoking status | | | | | |
| Current smoker N (%) | 3361 (11.2) | 42 (9.8) | 985 (16.0) | 2106 (10.3) | 270 (7.6) |
| Former smoker N (%) | 9240 (30.7) | 136 (31.6) | 2006 (32.5) | 6146 (30.2) | 1088 (30.6) |
| Never smoker N (%) | 17501 (58.14) | 252 (58.6) | 3177 (51.5) | 12129 (59.5) | 2195 (61.8) |
| Socio-economic status | | | | | |
| Professional / Managerial N (%) | 19298 (63.6) | 247 (57.0) | 3688 (59.6) | 13039 (63.5) | 2571 (71.5) |
| Intermediate N (%) | 8298 (27.4) | 139 (32.1) | 1825 (29.5) | 5734 (27.9) | 739 (20.5) |
| Routine and manual N (%) | 2736 (9.0) | 47 (10.9) | 675 (10.9) | 1773 (8.6) | 288 (8.0) |
| Education level | | | | | |
| No qualifications N (%) | 4656 (16.4) | 98 (24.8) | 1215 (21.2) | 3020 (15.7) | 421 (12.2) |
| Non-degree qualifications N (%) | 15983 (56.2) | 205 (51.8) | 3209 (55.9) | 10920 (56.8) | 1854 (53.6) |
| Degree N (%) | 7789 (27.4) | 93 (23.5) | 1312 (22.9) | 5293 (27.5) | 1184 (34.2) |
| Diet group | | | | | |
| Meat-eaters N (%) | 19919 (70.3) | 317 (78.5) | 5162 (92.2) | 13408 (69.8) | 1349 (38.3) |
| Fish-eaters N (%) | 3860 (13.6) | 39 (9.7) | 181 (3.2) | 2699 (14.1) | 980 (27.8) |
| Vegetarians N (%) | 4543 (16.0) | 48 (11.9) | 254 (4.5) | 3095 (16.1) | 1194 (33.9) |
| Supplement users N (%) | 16244 (57.6) | 236 (58.3) | 2972 (51.2) | 11129 (58.3) | 2143 (65.3) |
| Family history of colorectal cancer N (%) | 1755 (6.0) | 35 (8.3) | 326 (5.5) | 1238 (6.3) | 191 (5.6) |

[1]WCRF/AICR, World Cancer Research Fund/ American Institute of Cancer Research; BMI, body mass index; CRC, colorectal cancer; IQR, interquartile range

***Figure 5.1 Proportion of UKWCS respondents and colorectal cancer cases meeting each recommendation or sub-recommendation[1]***




[1] F&V, fruit and vegetables; BMI, body mass index; PA, physical activity

***Table 5.3 Characteristics of colorectal cancer cases and non-cases for participants in the UKWCS at baseline including a 9th (supplement use) recommendation[1]***

| Variable | Total | Cases | Non-cases |
|---|---|---|---|
| Observations N (%) | 28185 | 405 (1.4) | 27780 (98.6) |
| Age (years) | | | |
| Mean | 52.0 | 57.7 | 51.9 |
| 95% CI | (51.9, 52.1) | (56.9, 58.6) | (51.8, 52.0) |
| BMI (kg/m$^2$) | | | |
| Mean | 24.4 | 25.1 | 24.4 |
| 95% CI | (24.4, 24.5) | (24.6, 25.5) | (24.4, 24.5) |
| Energy intake (kcal/day) | | | |
| Mean | 2342 | 2355 | 2342 |
| 95% CI | (2334, 2350) | (2285, 2425) | (2334, 2350) |
| Ethanol (g/day) | | | |
| Median | 5.54 | 4.73 | 5.54 |
| IQR | 11.8 | 11.74 | 11.8 |
| Physical activity (hr/day) | | | |
| Mean | 0.24 | 0.22 | 0.24 |
| 95% CI | (0.24, 0.25) | (0.18, 0.26) | (0.24, 0.25) |
| Smoking status | | | |
| Current smoker N (%) | 3361 (11.2) | 42 (9.8) | 3319 (11.2) |
| Former smoker N (%) | 9240 (30.7) | 136 (31.6) | 9104 (30.7) |
| Never smoker N (%) | 17501 (58.14) | 252 (58.6) | 17249 (58.1) |
| Socio-economic status | | | |
| Professional / Managerial N (%) | 19298 (63.6) | 247 (57.0) | 19051 (63.7) |
| Intermediate N (%) | 8298 (27.4) | 139 (32.1) | 8159 (27.3) |
| Routine and manual N (%) | 2736 (9.0) | 47 (10.9) | 2689 (9.0) |
| Education level | | | |
| No qualifications N (%) | 4656 (16.4) | 98 (24.8) | 4558 (16.3) |
| Non-degree qualifications N (%) | 15983 (56.2) | 205 (51.8) | 15778 (56.3) |
| Degree N (%) | 7789 (27.4) | 93 (23.5) | 7696 (27.5) |
| Diet group | | | |
| Meat-eaters N (%) | 19919 (70.3) | 317 (78.5) | 19602 (70.2) |
| Fish-eaters N (%) | 3860 (13.6) | 39 (9.7) | 3821 (13.7) |
| Vegetarians N (%) | 4543 (16.0) | 48 (11.9) | 4495 (16.1) |
| Supplement users N (%) | 16244 (57.6) | 236 (58.3) | 16008 (57.6) |
| Family history of CRC N (%) | 1755 (6.0) | 35 (8.3) | 1720 (6.0) |

[1]BMI, body mass index; IQR, interquartile range; CRC, colorectal cancer

### 5.4.3 Survival analysis

The HRs (95% Cls) for incidence of colorectal, colon and rectal cancer according to the three different adherence categories of the WCRF/AICR score are shown in Table 5.4 and depicted in Figure 5.2. In the age-adjusted model, those within the second and third adherence categories had HRs (95% CI) for CRC of 0.76 (0.61, 0.95) and 0.66 (0.45, 0.99) (p=0.05) respectively, compared with those in the lowest adherence category, with a 1-unit increment in the WCRF/AICR score corresponding to a 10% decrease in risk of CRC (HR=0.90, 95% CI 0.81-1.00). However, further adjustment for smoking, socioeconomic status and family history of CRC in a first degree relative rendered the overall linear trend across the categories for the association non-statistically significant (p=0.17). Although HRs suggested an inverse relationship between the WCRF/AICR score and cancers of the colon and rectum respectively, no significant associations were observed in multivariate adjusted models. Sensitivity analyses operationalising the recommendation for dietary supplements did not significantly change the results, as depicted in Table 5.5.

Table 5.6 shows the results for the independent association between the separate components of the WCRF/AICR score and risk of colorectal, colon and rectal cancer, whilst Figure 5.3 depicts the HRs of CRC associated with meeting each recommendation or sub-recommendation individually. In the age-adjusted models, women who met the recommendation for body fatness had a statistically significant reduced risk of colorectal and rectal cancer (HR (95% CI) of 0.69 (0.53, 0.91; p=0.03) and 0.53 (0.33, 0.83; p=0.004)) respectively, compared to those who did not. Women who met the recommendation for animal foods had a statistically significant 32% reduced risk of colon cancer incidence when compared to the non-adherent (HR (95% CI) 0.68 (0.48, 0.96; p=0.03)). These associations were however attenuated; the association between body fatness and rectal cancer did not reach statistical significance (p=0.07), associations were not statistically significant for any of the other components in the fully adjusted multivariate models.

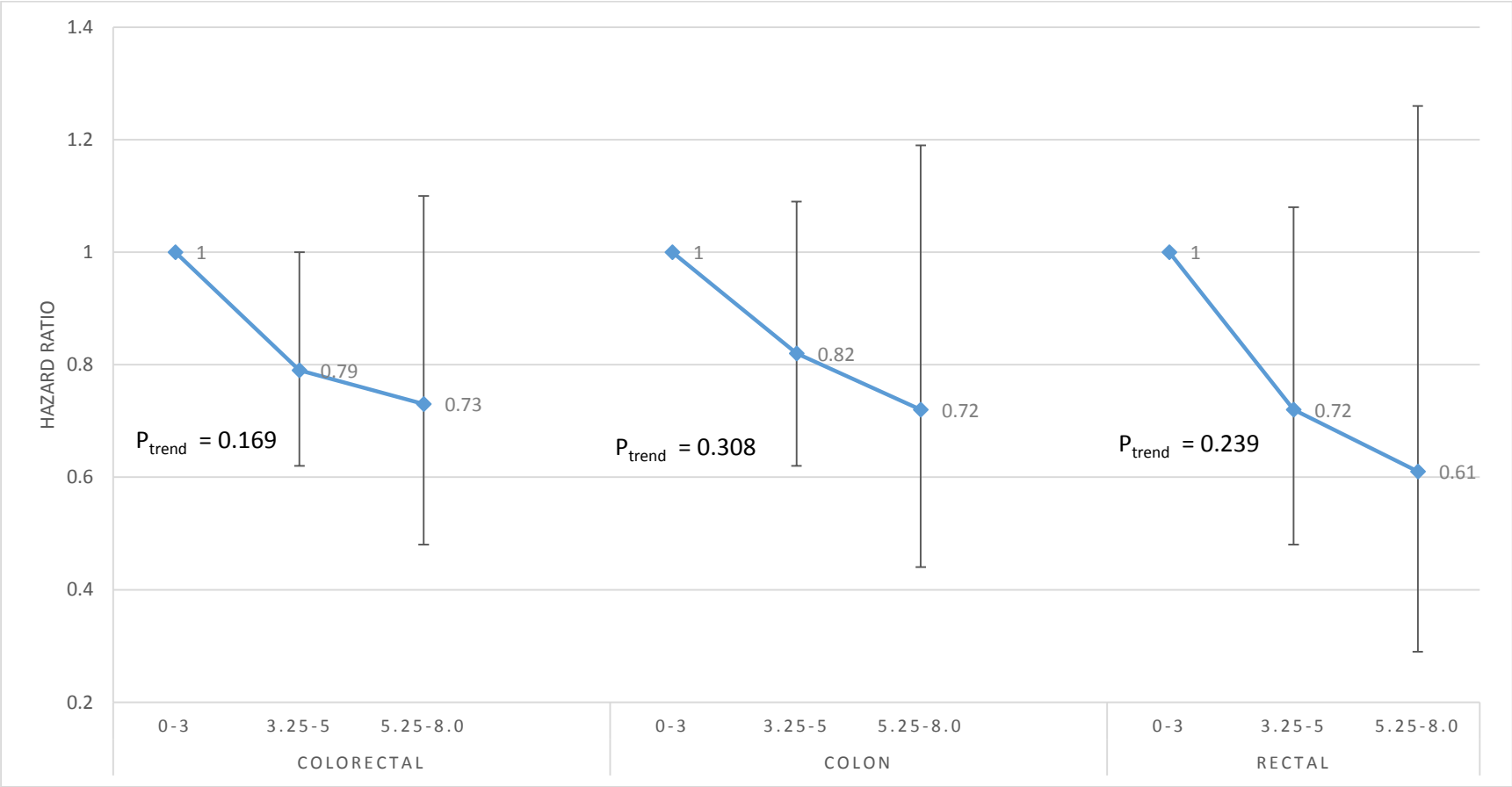
***Table 5.4 Hazard ratios and 95% confidence intervals for incidence of colorectal, colon and rectal cancer according to categories of the WCRF/AICR score***

| Cancer site | WCRF/AICR score categories | Cases[1] | Age-adjusted HR (95% CI) | Multivariable-adjusted[2] HR (95% CI) |
|---|---|---|---|---|
| Colorectal | | 444 | | |
| | 1 | | 1.0 | 1.0 |
| | 2 | | 0.76 (0.61, 0.95) | 0.79 (0.62, 1.00) |
| | 3 | | 0.66 (0.45, 0.99) | 0.73 (0.48, 1.10) |
| | Per 1 unit increment | | 0.90 (0.81, 1.00) | 0.92 (0.82, 1.03) |
| | $P_{trend}$ | | 0.046 | 0.169 |
| Colon | | 322 | | |
| | 1 | | 1.0 | 1.0 |
| | 2 | | 0.79 (0.61, 1.02) | 0.82 (0.62, 1.09) |
| | 3 | | 0.61 (0.38, 0.99) | 0.72 (0.44, 1.19) |
| | Per 1 unit increment | | 0.89 (0.79, 1.01) | 0.93 (0.82, 1.07) |
| | $P_{trend}$ | | 0.065 | 0.308 |
| Proximal colon | | 164 | | |
| | 1 | | 1.0 | 1.0 |
| | 2 | | 0.71 (0.50, 1.02) | 0.75 (0.51, 1.10) |
| | 3 | | 0.69 (0.36, 1.31) | 0.83 (0.43, 1.60) |
| | Per 1 unit increment | | 0.90 (0.76, 1.06) | 0.93 (0.77, 1.12) |
| | $P_{trend}$ | | 0.212 | 0.441 |
| Distal colon | | 115 | | |
| | 1 | | 1.0 | 1.0 |
| | 2 | | 1.01 (0.65, 1.59) | 0.96 (0.58, 1.58) |
| | 3 | | 0.41 (0.17, 0.99) | 0.41 (0.16, 1.07) |
| | Per 1 unit increment | | 0.91 (0.76, 1.09) | 0.93 (0.76, 1.14) |
| | $P_{trend}$ | | 0.290 | 0.504 |
| Rectal | | 146 | | |
| | 1 | | 1.0 | 1.0 |
| | 2 | | 0.72 (0.49, 1.06) | 0.72 (0.48, 1.08) |
| | 3 | | 0.65 (0.33, 1.28) | 0.61 (0.29, 1.26) |
| | Per 1 unit increment | | 0.90 (0.75, 1.09) | 0.88 (0.72, 1.08) |
| | $P_{trend}$ | | 0.291 | 0.239 |

[1]Case numbers apply to multivariable adjusted models.

[2]Adjusted for age, smoking status, socioeconomic status and family history of colorectal cancer.

***Figure 5.2 Association between the WCRF/AICR score and risk of total colorectal, colon and rectal cancer[1]***




[1] Cox regression model adjusted by age, smoking status, socioeconomic status and family history of colorectal cancer.

***Table 5.5 Hazard ratios and 95% confidence intervals for incidence of colorectal, colon and rectal cancer according to categories of the WCRF/AICR score, including a 9th (supplement use) recommendation***

| Cancer site | WCRF/AICR score categories | Cases[1] | Age-adjusted HR (95% CI) | Multivariable-adjusted[2] HR (95% CI) |
|---|---|---|---|---|
| Colorectal | | 405 | | |
| | 1 | | 1.0 | 1.0 |
| | 2 | | 0.79 (0.60, 1.04) | 0.81 (0.60, 1.08) |
| | 3 | | 0.70 (0.37, 1.34) | 0.79 (0.40, 1.55) |
| | Per 1 unit increment | | 0.93 (0.84, 1.03) | 0.95 (0.86, 1.06) |
| | $P_{trend}$ | | 0.155 | 0.391 |
| Colon | | 293 | | |
| | 1 | | 1.0 | 1.0 |
| | 2 | | 0.84 (0.60, 1.16) | 0.89 (0.63, 1.27) |
| | 3 | | 0.65 (0.28, 1.49) | 0.79 (0.34, 1.84) |
| | Per 1 unit increment | | 0.91 (0.81, 1.02) | 0.94 (0.83, 1.07) |
| | $P_{trend}$ | | 0.102 | 0.344 |
| Proximal colon | | 149 | | |
| | 1 | | 1.0 | 1.0 |
| | 2 | | 0.70 (0.45, 1.08) | 0.75 (0.47, 1.20) |
| | 3 | | 0.48 (0.15, 1.61) | 0.60 (0.18, 2.02) |
| | Per 1 unit increment | | 0.88 (0.75, 1.04) | 0.91 (0.76, 1.08) |
| | $P_{trend}$ | | 0.135 | 0.265 |
| Distal colon | | 105 | | |
| | 1 | | 1.0 | 1.0 |
| | 2 | | 1.38 (0.72, 2.66) | 1.30 (0.65, 2.61) |
| | 3 | | 0.13 (0.02, 1.00) | 0.14 (0.02, 1.10) |
| | Per 1 unit increment | | 0.94 (0.80, 1.09) | 0.93 (0.79, 1.12) |
| | $P_{trend}$ | | 0.389 | 0.465 |
| Rectal | | 134 | | |
| | 1 | | 1.0 | 1.0 |
| | 2 | | 0.77 (0.48, 1.25) | 0.71 (0.43, 1.16) |
| | 3 | | 0.73 (0.26, 2.06) | 0.70 (0.23, 2.10) |
| | Per 1 unit increment | | 0.97 (0.81, 1.17) | 0.96 (0.79, 1.16) |
| | $P_{trend}$ | | 0.775 | 0.647 |

[1]Case numbers apply to multivariable adjusted models.
[2]Adjusted for age, smoking status, socioeconomic status and family history of colorectal cancer.

***Table 5.6 Age and fully-adjusted hazard ratios and 95% confidence intervals for colorectal, colon and rectal cancers per component of the WCRF/AICR score[1]***

| | Colorectal Cancer | | | | Colon Cancer | | | | Rectal Cancer | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Age-adjusted HR (95% CI) | $P_{trend}$ | Multivariate-adjusted HR (95% CI) | $P_{trend}$ | Age-adjusted HR (95% CI) | $P_{trend}$ | Multivariate-adjusted HR (95% CI) | $P_{trend}$ | Age-adjusted HR (95% CI) | $P_{trend}$ | Multivariate-adjusted HR (95% CI) | $P_{trend}$ |
| 1. Body fatness (BMI) | | | | | | | | | | | | |
| 0[2] | 1.0 | 0.032 | 1.0 | 0.102 | 1.0 | 0.390 | 1.0 | 0.391 | 1.0 | 0.004 | 1.0 | 0.070 |
| 0.5 | 0.69 (0.51, 0.93) | | 0.70 (0.51, 0.97) | | 0.69 (0.48, 0.99) | | 0.66 (0.45, 0.96) | | 0.75 (0.46, 1.22) | | 0.85 (0.50 1.46) | |
| 1 | 0.69 (0.53, 0.91) | | 0.72 (0.54, 0.97) | | 0.78 (0.57, 1.07) | | 0.76 (0.55, 1.07) | | 0.53 (0.33, 0.83) | | 0.66 (0.40, 1.09) | |
| 2. Physical activity | | | | | | | | | | | | |
| 0 | 1.0 | 0.859 | 1.0 | 0.886 | 1.0 | 0.721 | 1.0 | 0.965 | 1.0 | 0.677 | 1.0 | 0.815 |
| 0.5 | 0.97 (0.74, 1.26) | | 0.97 (0.73, 1.28) | | 1.00 (0.74, 1.37) | | 1.07 (0.77, 1.48) | | 0.63 (0.51, 1.36) | | 0.62 (0.36, 1.08) | |
| 1 | 0.99 (0.73, 1.34) | | 0.99 (0.72, 1.36) | | 0.92 (0.64, 1.33) | | 0.97 (0.66, 1.43) | | 1.22 (0.75, 1.98) | | 1.12 (0.67, 1.87) | |
| 3. Foods that promote weight gain | | | | | | | | | | | | |
| 0 | 1.0 | 0.492 | 1.0 | 0.644 | 1.0 | 0.656 | 1.0 | 0.860 | 1.0 | 0.487 | 1.0 | 0.563 |
| 0.25 | 0.85 (0.31, 2.34) | | 0.76 (0.28, 2.11) | | 1.18 (0.28, 4.90) | | 1.01 (0.24, 4.21) | | 0.60 (0.14, 2.57) | | 0.58 (0.14, 2.46) | |
| 0.5 | 0.74 (0.27, 1.98) | | 0.67 (0.25, 1.80) | | 1.07 (0.26, 4.33) | | 0.98 (0.24, 3.97) | | 0.49 (0.12, 2.00) | | 0.44 (0.11, 1.79) | |
| 0.75 | 0.79 (0.34, 2.13) | | 0.75 (0.28, 2.03) | | 1.10 (0.27, 4.47) | | 1.03 (0.25, 4.23) | | 0.56 (0.14, 2.30) | | 0.54 (0.13, 2.20) | |
| 1 | 0.52 (0.17, 1.79) | | 0.42 (0.11, 1.55) | | 0.83 (0.17, 4.15) | | 0.62 (0.11, 3.35) | | 0.19 (0.02, 2.07) | | 0.20 (0.02, 2.21) | |

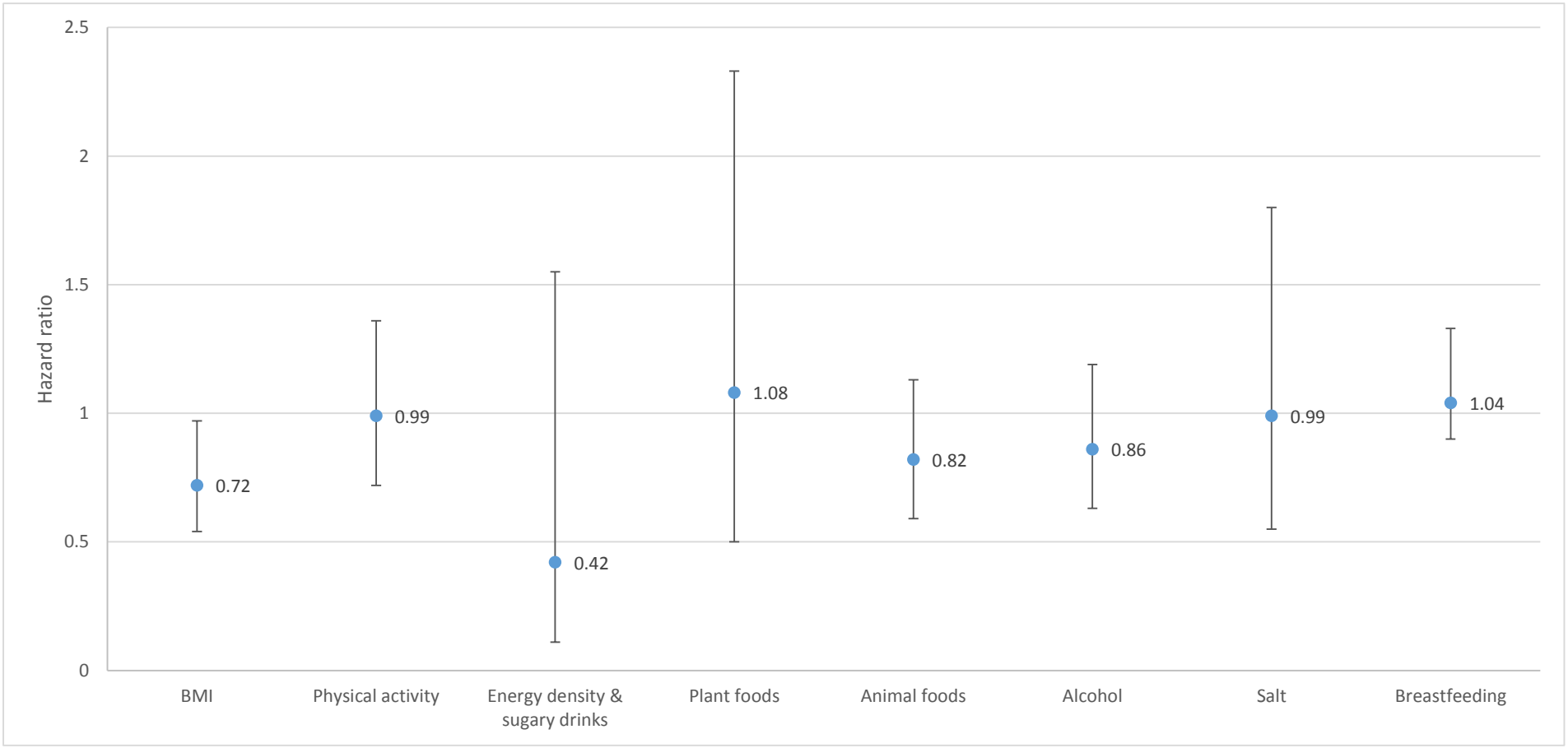
| | Colorectal Cancer | | | | Colon Cancer | | | | Rectal Cancer | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Age-adjusted HR (95% CI) | $P_{trend}$ | Multivariate-adjusted HR (95% CI) | $P_{trend}$ | Age-adjusted HR (95% CI) | $P_{trend}$ | Multivariate-adjusted HR (95% CI) | $P_{trend}$ | Age-adjusted HR (95% CI) | $P_{trend}$ | Multivariate-adjusted HR (95% CI) | $P_{trend}$ |
| 4. Plant foods | | | | | | | | | | | | |
| 0 | 1.0 | 0.529 | 1.0 | 0.891 | 1.0 | 0.727 | 1.0 | 0.787 | 1.0 | 0.551 | 1.0 | 0.532 |
| 0.25 | 0.88 (0.66, 1.17) | | 0.88 (0.64, 1.20) | | 0.93 (0.66, 1.31) | | 0.96 (0.66, 1.39) | | 0.71 (0.42, 1.18) | | 0.69 (0.40, 1.17) | |
| 0.5 | 1.02 (0.78, 1.35) | | 1.05 (0.78, 1.41) | | 1.02 (0.73, 1.41) | | 1.10 (0.77, 1.58) | | 1.09 (0.69, 1.74) | | 0.97 (0.59, 1.60) | |
| 0.75 | 0.79 (0.56, 1.11) | | 0.84 (0.58, 1.21) | | 0.81 (0.54, 1.22) | | 0.88 (0.57, 1.36) | | 0.64 (0.34, 1.19) | | 0.67 (0.36, 1.27) | |
| 1 | 0.92 (0.43, 1.97) | | 1.08 (0.50, 2.33) | | 1.23 (0.56, 2.75) | | 1.51 (0.68, 3.39) | | 0.50 (0.10, 2.59) | | 0.55 (0.11, 2.85) | |
| 5. Animal foods | | | | | | | | | | | | |
| 0 | 1.0 | 0.065 | 1.0 | 0.236 | 1.0 | 0.030 | 1.0 | 0.167 | 1.0 | 0.477 | 1.0 | 0.433 |
| 0.5 | 0.87 (0.68, 1.11) | | 0.94 (0.72, 1.22) | | 0.83 (0.62, 1.10) | | 0.89 (0.66, 1.21) | | 0.82 (0.53, 1.26) | | 0.89 (0.56, 1.41) | |
| 1 | 0.75 (0.56, 1.01) | | 0.82 (0.59, 1.13) | | 0.68 (0.48, 0.96) | | 0.76 (0.52, 1.11) | | 0.83 (0.50, 1.39) | | 0.80 (0.45, 1.40) | |
| 6. Alcohol | | | | | | | | | | | | |
| 0 | 1.0 | 0.561 | 1.0 | 0.360 | 1.0 | 0.685 | 1.0 | 0.703 | 1.0 | 0.827 | 1.0 | 0.702 |
| 0.5 | 0.91 (0.64, 1.30) | | 0.92 (0.63, 1.34) | | 1.10 (0.72, 1.67) | | 1.11 (0.71, 1.74) | | 0.69 (0.37, 1.31) | | 0.72 (0.38, 1.36) | |
| 1 | 0.90 (0.67, 1.22) | | 0.86 (0.63, 1.19) | | 0.98 (0.68, 1.42) | | 0.99 (0.66, 1.47) | | 0.92 (0.55, 1.55) | | 0.82 (0.47, 1.41) | |
| 7. Preservation, processing and preparation | | | | | | | | | | | | |
| 0 | 1.0 | 0.769 | 1.0 | 0.821 | 1.0 | 0.814 | 1.0 | 0.940 | 1.0 | 0.824 | 1.0 | 0.833 |
| 0.5 | 0.99 (0.79, 1.26) | | 0.96 (0.75, 1.24) | | 0.94 (0.71, 1.24) | | 0.89 (0.66, 1.20) | | 1.11 (0.75, 1.64) | | 1.13 (0.75, 1.71) | |
| 1 | 1.16 (0.69, 1.96) | | 0.99 (0.55, 1.80) | | 1.32 (0.75, 2.35) | | 1.30 (0.71, 2.40) | | 0.86 (0.29, 2.50) | | 0.38 (0.08, 1.91) | |

| | Colorectal Cancer | | | | Colon Cancer | | | | Rectal Cancer | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Age-adjusted HR (95% CI) | $P_{trend}$ | Multivariate-adjusted HR (95% CI) | $P_{trend}$ | Age-adjusted HR (95% CI) | $P_{trend}$ | Multivariate-adjusted HR (95% CI) | $P_{trend}$ | Age-adjusted HR (95% CI) | $P_{trend}$ | Multivariate-adjusted HR (95% CI) | $P_{trend}$ |
| 8. Breastfeeding | | | | | | | | | | | | |
| 0 | 1.0 | 0.730 | 1.0 | 0.719 | 1.0 | 0.317 | 1.0 | 0.780 | 1.0 | 0.694 | 1.0 | 0.627 |
| 0.5 | 0.99 (0.77, 1.27) | | 0.96 (0.74, 1.25) | | 0.90 (0.68, 1.20) | | 0.90 (0.66, 1.49) | | 1.18 (0.76, 1.82) | | 1.04 (0.65, 1.65) | |
| 1 | 0.96 (0.76, 1.21) | | 1.04 (0.90, 1.33) | | 0.87 (0.66, 1.14) | | 0.96 (0.72, 1.28) | | 1.09 (0.72, 1.65) | | 1.11 (0.73, 1.69) | |

[1]WCRF/AICR, World Cancer Research Fund/ American Institute of Cancer Research; BMI, body mass index.

[2]0 is assigned if the recommendation is not met, 0.5 is assigned for partly met recommendations and 1 is assigned for met recommendations.

***Figure 5.3 Fully adjusted hazard ratios of colorectal cancer associated with meeting each recommendation or sub-recommendation individually[1].***




[1] Cox regression model adjusted by age, smoking status, socioeconomic status and family history of colorectal cancer.

## 5.5 Discussion

This study evaluated adherence to the WCRF/AICR cancer prevention recommendations in relation to risk of CRC in a UK cohort of middle-aged women. The overall score related to operationalization of eight recommendations was not significantly associated with incidence of colorectal, colon or rectal cancer in multivariate adjusted analyses. Investigation of the separate score components showed adherence to the body fatness and animal foods recommendations to potentially offer a degree of protection against risk of cancers of the colorectum and rectum and of the colon, respectively.

Few studies have looked at the WCRF/AICR recommendations and CRC incidence. Findings from this study are consistent with those from the Framingham Offspring cohort (Makarem et al., 2015) and in the Black Women's Health Study (Nomura et al., 2016) where the overall WCRF/AICR score was not significantly associated with CRC incidence. Conversely, a one-point increment in the WCRF/AICR score was significantly associated with a 12% (95% CI: 9% to 16%) decreased CRC risk in the EPIC cohort (Romaguera et al., 2012) and a 13% (95% CI: 5% to 20%) decreased risk of CRC in the VITAL cohort (Hastert & White, 2016). However, the EPIC and VITAL cohorts (Romaguera et al., 2012; Hastert & White, 2016) operationalized a total of 7 and 6 recommendations respectively, rather than 8 score components as operationalized in this cohort. Notwithstanding, an evaluation of our results using a similar composite to the EPIC and VITAL cohorts (Romaguera et al., 2012; Hastert & White, 2016) to facilitate comparison, by dropping first the recommendation in relation to salt-preserved food, and secondly dropping two recommendations – those related to salt-preserved food and to breastfeeding, did not significantly change the results, as depicted in Table 5.7. Thomson and colleagues also reported a statistically significant decreased risk of CRC in the Women's Health Initiative (WHI) Observational Study but the ACS cancer prevention guidelines were operationalized for the study and associations were weakest amongst whites, which may partly explain the inconsistency in findings when compared to this study where most women are white (Thomson et al., 2014). Associations for colon and rectal cancers were not investigated separately in any of the previous cohort studies operationalising the WCRF/AICR guidelines.

***Table 5.7 Age and fully-adjusted hazard ratios and 95% confidence intervals for colorectal cancer operationalising a different number of recommendations of the WCRF/AICR cancer prevention guidelines***

| UKWCS Composite | WCRF/AICR score categories | Cases[1] | Age-adjusted HR (95% CI) | Multivariable-adjusted[2] HR (95% CI) |
|---|---|---|---|---|
| EPIC Cohort composite & score categories (7 recommendations) | | 444 | | |
| | 1 (0-3) | 137 | 1.0 | 1.0 |
| | 2 (>3 to <4) | 121 | 0.75 (0.58, 0.97) | 0.80 (0.61, 1.05) |
| | 3 (4 to <5) | 132 | 0.70 (0.54, 0.89) | 0.77 (0.59, 1.00) |
| | 4 (5 to 7) | 54 | 0.86 (0.61, 1.21) | 0.99 (0.70, 1.42) |
| | Per 1 unit increment | | 0.89 (0.80, 0.99) | 0.92 (0.82, 1.04) |
| | $P_{trend}$ | | 0.037 | 0.174 |
| | | | | |
| VITAL Cohort composite (6 recommendations) | Per 1 unit increment | | 0.87 (0.77, 0.99) | 0.89 (0.80, 1.02) |
| | $P_{trend}$ | | 0.029 | 0.089 |
| | | | | |

[1]Case numbers apply to multivariable adjusted models.
[2]Adjusted for age, smoking status, socioeconomic status and family history of colorectal cancer.

Two studies evaluating associations for risk of colon and rectal cancer separately looked at adherence to the Dietary Guidelines for Americans (Harnack et al., 2002) and to the ACS recommendations (Kushi et al., 2006) respectively. A statistically significant decrease in colon cancer risk was reported with greater adherence in both studies (Kabat et al., 2015; Harnack et al., 2002). In agreement with results from this cohort, data from the Iowa Women's Health Study, a population-based cohort of postmenopausal women reported inverse, but not significant decreased rectal cancer incidence with increased adherence to cancer prevention guidelines (Harnack et al., 2002).

The different strengths of associations for the colon and for the rectal cancer sites may be due to the different biological characteristics of the mucosa in that part of the colorectum or to the different mechanisms in oncogenesis (Kapiteijn et al., 2001). Notwithstanding this plausible explanation, the estimation of the association between the WCRF/AICR recommendations and cancer incidence by site should be considered

as being of an exploratory nature due to the smaller sample size. The cohort comprises relatively health conscious women when compared to the general population. Furthermore, the source of diet assessment was a single FFQ measured at baseline that is not only prone to recall bias and under-reporting, but also may not be fully representative of eating patterns long term. Nevertheless, dietary patterns in the UKWCS have been previously shown to be relatively stable over time and using groupings of dietary patterns in contrast to energy and nutrient intake, reduces bias caused by such measurement error (Greenwood et al., 2003). Although women who died within one year of dietary assessment were excluded to reduce reverse causation, anthropometric and lifestyle factors were self-reported, there is no data on their validity and thus potentially contributed to measurement error. No data was available on whether women were previously screened for CRC; this would have been an important confounding factor. These factors may have led to an attenuation of results suggesting that the association between risk of cancer at different sites of the colorectum and some dietary factors is probably stronger than stated in this cohort. Further discrepancies in results between different studies may be explained by differences in the treatment of the individual recommendations, the cut-offs chosen and the number of components used during the WCRF/AICR score operationalization.

An assessment of the contribution of the individual components to the overall score showed body fatness, assessed by BMI to be the strongest predictor of cancer of both the colon and rectum, as well as animal foods being a predictor of colon cancer. This is in line with findings from the VITAL cohort (Hastert & White, 2016) who also reported body fatness and red and processed meat intake to be the recommendations most strongly associated with higher CRC risk for women. Despite inverse associations of these components with cancer incidence in this cohort, associations after adjusting for confounders were not significant although borderline significance was noted for BMI and rectal cancer. BMI was similarly reported to be the strongest predictor of all cancer incidence in the NIH_AARP cohort (Kabat et al., 2015) whilst almost all components of the WCRF/AICR score were associated with total cancer incidence in the EPIC study (Romaguera et al., 2012). The lack of statistical significance in this study with respect to BMI and animal foods could be explained by insufficient statistical

power of the sample, or in the case of BMI, closely related measurements such as that of visceral fat may have been a better indicator of body fatness and a better predictor of CRC (Larsson & Wolk, 2007). The association may also be stronger in men than in women, which could potentially explain the stronger links reported in other cohorts including both sexes (Kabat et al., 2015; Romaguera et al., 2012). Men have higher rates of CRC than women, with rectal cancer being higher in men and proximal colon cancer higher in women. Hormonal factors could protect women from distal cancers (Gao et al., 2008). Other score components – such as breastfeeding, are unlikely to be on the direct causal pathway for cancer of the colorectum and thus, the fact that the scoring system used gives equal weighting to every recommendation is considered a limitation of this study.

Although the exact mechanisms linking body fatness to CRC are yet unclear, some possibilities have been put forward. Insulin / IGF and the adipokines, adiponectin and leptin are two hormonal systems that have been hypothesized to mediate the association (Ma et al., 2013). Adipose tissue is metabolically active and could produce inflammatory molecules that modulate carcinogenesis – cytokines, sex steroids and adipokines (Song et al., 2015). Thus, as adiposity increases, concentrations of IGF-binding protein-1 and adiponectin decrease, resulting in elevated levels of free IGF-1 and serum leptin that have been associated with increased CRC risk (Larsson and Wolk, 2007).

Strengths of this prospective cohort include its design, the long follow-up period, the potential to adjust for several confounding variables and the size of the study population. The latter enabled for the first time, a separate investigation of the colon and rectal sites in relation to the score derived from the WCRF/AICR cancer prevention guidelines and its individual components.

In conclusion, there were no statistically significant trends shown between adherence to the WCRF/AICR cancer prevention guidelines and risk of CRC. Of the individual score components, a BMI within the normal weight range was borderline significantly protective in the fully adjusted model, emphasising the importance of this for cancer

prevention. A better understanding of different dietary components on this health outcome may permit higher or lower WCRF/AICR score component weighting. In view of the likely different causes of CRC subtypes, further research is needed to identify the optimal dietary patterns associated with reducing colon and rectal cancer risk respectively.

# CHAPTER 6 COMPARISON OF DIETARY PATTERNS FROM FOOD DIARIES AND FOOD FREQUENCY QUESTIONNAIRES IN RELATION TO COLORECTAL CANCER RISK

## 6.1 Chapter overview

*Background:* Studies comparing dietary patterns derived from two different assessment methods, in relation to diet and disease are limited. The aims of this study are to assess the agreement between dietary patterns derived from FFQ and FD and to compare the associations between the Mediterranean dietary pattern and the WCRF/AICR dietary pattern in relation to incidence of CRC.

*Method:* The study population included 2276 healthy middle-aged women – participants of the UKWCS. A case-cohort study design was used. Energy and nutrient intakes, derived from 4-day FDs and from a 217-item FFQ were compared. A 10-component score and an 8-component score indicating adherence to the MD and to the 2007 WCRF/AICR cancer prevention recommendations respectively were generated. Agreement was assessed by weighted Kappa statistics and the Bland-Altman method. Cox regression was used to estimate HRs for CRC risk for both the FD and the FFQ patterns, for each score separately.

*Results:* The Bland-Altman method showed higher energy intake of -525 kcal (95% CI -556, -493) by the FFQ in comparison to the FD. Agreement between the two methods was slight for the MD score (K=0.15; 95% CI: 0.14, 0.16) and fair for the WCRF/AICR score (K=0.38; 95% CI: 0.37, 0.39). A total of 173 incident cases of CRC were documented. In the multi-variable adjusted models for FD patterns, the estimates for an association with CRC were weak. For a 1-unit increment in the MD score HR 0.94; 95% CI: 0.83 to 1.06; $P_{trend}$ 0.32, and HR 1.01; 95% CI: 0.83 to 1.24; $P_{trend}$ 0.87 for a 1-unit increment in the WCRF/AICR score. For scores derived from the FFQ, estimates were inverse, but weak ($P_{trend}$=0.06 for the MD score & $P_{trend}$=0.13 for the WCRF/AICR score respectively).

*Conclusion:* There is insufficient evidence of an association of CRC risk with the Mediterranean dietary pattern or with the WCRF/AICR cancer prevention recommendations, irrespective of the dietary assessment method.

## 6.2 Introduction

Dietary patterns are used as measures of exposure in studies exploring diet disease associations and have been shown to predict, though modestly, disease incidence, mortality and related biomarkers (Waijers et al., 2007). FFQs and FDs are the most common dietary assessment methods. Most dietary pattern analyses have used FFQ data for large population studies (Crozier et al., 2008), whilst FD tend to be used with smaller datasets and followed up for shorter terms, restricting the possibility of a direct comparison between the two. Studies comparing the two assessment methods in relation to diet and disease are limited, and those that do have given inconsistent results as discussed below. No studies have looked at dietary patterns in evaluating the agreement between results derived from FFQ and FD in the same cohort.

It has been previously suggested that reported associations between diet and disease are affected by the method of diet assessment used and that FD may be superior to an FFQ in evaluating such relationships. Strong significant associations have been reported between biomarkers for certain nutrients, and intakes as assessed via FD, but not FFQ in a study exploring associations with heart disease (Bingham, 2008). Dietary measurement error in an FFQ has furthermore been implied as potentially obscuring the true relationship between dietary fat and breast cancer risk, whilst a positive association was seen when fat intake was measured via a FD (Bingham 2003; Freedman et al 2006). Dahm and colleagues also argue that the inconsistency in results from epidemiological studies looking at diet and cancer may be due to measurement error and methodological differences. The authors who were looking at the relationship between dietary fibre and CRC incidence reported a statistically significant association when intake was ascertained via FD, as opposed to no statistical significance following analysis of data obtained from FFQ (Dahm et al., 2010). In contrast, in the UK Dietary Cohort Consortium, which uses pooled data from 4 prospective UK based studies and thus boasts a relatively large sample size, no

association between fat and breast cancer risk was reported, irrespective of whether diet was measured via FFQ or FD (Key et al., 2011). Different studies use different FFQs, which all vary in the number and type of foods included, the frequency of consumption of foods reported, the description of portion size used and the method of administration, amongst other differences (Cade et al., 2004b). This may partly explain the discrepancies in the different studies discussed above.

The aim of this study is two-fold. It aims to assess the agreement between dietary patterns derived from the FFQ and from FD in the UKWCS. Secondly, it aims to compare the associations between the Mediterranean dietary pattern and the WCRF/AICR dietary pattern respectively, derived from the two different dietary assessment methods, in relation to incidence of CRC, in order to determine whether associations vary with the method of assessment.

## 6.3 Methods

### 6.3.1 Study design and study population

The UKWCS participants at baseline were 35 372 women. Five years following baseline data collection, participants were re-contacted and asked to complete a four day FD, a one day exercise diary and to once again provide information linked to diet, health and lifestyle. Around 35% of the participants at baseline returned completed FD (n=12,625) and were included in the follow up phase of the cohort study. Health and lifestyle characteristics and mean (95% CI) intake of energy, selected nutrients and non-nutrients for total cohort women at baseline, for those who responded at phase 2, and split by those who were CRC cases or non-cases at are reported in Table 6.1.

Diary coding is extremely time consuming and only a fraction (n=2276) of the returned FD have been coded to date. For this study, a case-cohort approach was used: completed FD of women identified as CRC cases through NHS Digital were coded together with an equal number of random cohort controls chosen via a Microsoft Access query. Pairs of diaries were given to the coder and thus the latter was unaware of which diaries were controls or cases in order to minimize individual coder bias. The FFQs of the same participants who also had a coded FD were also used in the analysis.

***Table 6.1 Sample lifestyle characteristics and daily mean (95% CI) intake of energy, selected nutrients and non-nutrients as recorded by all women in the UKWCS at baseline, by phase 2 respondents and for CRC cases and non-cases.[1]***

| Variable | Baseline Food Frequency Questionnaire | Food Diary respondents at baseline | Colorectal cancer cases | Non-cases |
|---|---|---|---|---|
| Number of participants | 35,372 | 2,276 | 173 | 2,103 |
| Age (years) | | | | |
| Mean | 52.3 | 54.5 | 57.6 | 54.3 |
| 95% CI | (52.2, 52.4) | (54.1, 54.9) | (56.3, 58.9) | (53.9, 54.7) |
| BMI (kg/m$^2$) | | | | |
| Mean | 24.5 | 24.3 | 24.6 | 24.2 |
| 95% CI | (24.4, 25.5) | (24.1, 24.4) | (23.8, 25.3) | (24.1, 24.4) |
| Physical activity (hr/day) | | | | |
| Mean | 0.25 | 0.25 | 0.25 | 0.25 |
| 95% CI | (0.25, 0.26) | (0.23, 0.27) | (0.17, 0.32) | (0.23, 0.27) |
| Current smoker | | | | |
| N (%) | 3810 (10.8) | 192 (8.5) | 15 (8.7) | 177 (8.4) |
| Professional / Managerial SES | | | | |
| N (%) | 21852 (63.2) | 1442 (64.8) | 98 (56.6) | 1344 (63.9) |
| Degree level of education | | | | |
| N (%) | 8787 (27.2) | 597 (28.9) | 44 (25.4) | 553 (26.3) |
| Diet group | | | | |
| Meat-eaters, N (%) | 24738 (69.9) | 1539 (67.8) | 128 (74.0) | 1411 (67.1) |
| Fish-eaters, N (%) | 4156 (11.8) | 272 (12.0) | 21 (12.1) | 251 (11.9) |
| Vegetarians, N (%) | 6478 (18.3) | 459 (20.2) | 24 (13.9) | 435 (20.7) |
| Family history of CRC | | | | |
| N (%) | 2044 (6.1) | 145 (6.8) | 17 (9.8) | 128 (6.1) |
| Energy intake (kcal/day) | | | | |
| Mean | 2352 | 2357 | 2423 | 2350 |
| 95% CI | (2340, 2360) | (2323, 2390) | (2287, 2560) | (2316, 2386) |
| Protein (g/day) | | | | |
| Mean | 89.8 | 89.8 | 90.1 | 89.8 |
| 95% CI | (89.4, 90.1) | (88.3, 91.4) | (85.5, 94.7) | (88.2, 91.5) |
| Carbohydrate (g/day) | | | | |
| Mean | 312.7 | 314.3 | 319.7 | 313.9 |
| 95% CI | (311.6, 313.9) | (309.8, 318.9) | (299.5, 339.8) | (309.2, 318.5) |
| Dietary fibre (g/day) | | | | |
| Mean | 25.6 | 26.3 | 26.9 | 26.3 |
| 95% CI | (25.5, 25.7) | (25.8, 26.8) | (24.9, 28.8) | (25.8, 26.8) |

| Variable | Baseline Food Frequency Questionnaire | Food Diary respondents at baseline | Colorectal cancer cases | Non-cases |
|---|---|---|---|---|
| Sugars (g/day) | | | | |
| Mean | 149.7 | 150.9 | 154.7 | 150.6 |
| 95% CI | (149.0, 150.4) | (148.3, 153.5) | (143.6, 165.7) | (148.0, 153.3) |
| Fat (g/day) | | | | |
| Mean | 85.0 | 85.3 | 89.6 | 84.9 |
| 95% CI | (84.7, 85.4) | (83.7, 86.8) | (83.8, 95.4) | (83.3, 86.5) |
| SFA (g) | | | | |
| Mean | 29.5 | 29.3 | 30.4 | 29.2 |
| 95% CI | (29.3, 29.6) | (28.7, 29.9) | (28.3, 32.6) | (28.6, 29.9) |
| Iron | | | | |
| Mean | 18.2 | 18.5 | 18.8 | 18.5 |
| 95% CI | (18.1, 18.3) | (18.2, 18.8) | (17.6, 20.1) | (18.1, 18.8) |
| Sodium | | | | |
| Mean | 3.10 | 3.11 | 3.13 | 3.11 |
| 95% CI | (3.09, 3.11) | (3.06, 3.16) | (2.94, 3.32) | (3.06, 3.16) |
| Ethanol (g/day) | | | | |
| Median | 8.71 | 8.11 | 9.25 | 8.01 |
| IQR | 0.22 | 0.81 | 3.86 | 0.81 |

[1] BMI, body mass index; SES, socioeconomic status; CRC, colorectal cancer; SFA, saturated fatty acids; IQR interquartile range

### 6.3.2 Dietary assessment methods

The FFQ used at baseline consisted of 217 food items and participants were asked to indicate their average intake of food items over the past year. Further details on the FFQ are found in section 3.4.1.

When subjects were contacted a second time in the follow up phase, they were asked to log all food and beverages consumed within a four-day period, and give weighed or estimated portion sizes. Nutrient intakes from FD were calculated using DANTE – a Microsoft Access program containing food data from McCance & Widdowson's *The Composition of Foods* (5th edition) (Holland et al., 1991). Coders were initially trained in the use of the package and were asked to follow a coding protocol prepared by the researcher, on the use of DANTE and on interpreting FD (Appendix VIII). In cases where the portions sizes were missing, average portion sizes as listed in the Food Standards

Agency *Food Portion Sizes* (3rd edition) (FSA, 2002) were assigned. Furthermore, recipes provided by participants were added to DANTE. Nutrients in the form of supplements were not considered. Estimation of the intake of some nutrients from FD proved challenging since not all items are found in British food tables. This was especially the case for composite dishes, and in fact a number of assumptions with respect to various constituents of cooked dishes were made. For instance, pies were assumed to contain 30% of meat, poultry, fish or vegetarian alternative respectively whilst for burgers this percentage was 40%. Chicken or fish in batter or crumbs was assumed to contain a 60% protein portion. Homemade patties were assumed to be made of 77% minced beef or pork, and thus not considered to be processed meat, whilst canned or chilled ready-made meat products were assumed to be processed. Details are found in section 3.8.2. Coded diaries were checked for errors and edited as necessary. Such a practice reduces coder variability.

### 6.3.3 Case definition

Details are found in section 3.7.

### 6.3.4 Construction of the MD score and of the WCRF/AICR score

Adherence scores were calculated for each of the two dietary patterns – Mediterranean (FFQ & FD) and WCRF/AICR (FFQ & FD) for each of the women in the UKWCS who completed both phases of the study. Details on how a 10-component adherence score to the MD was generated for women who filled in an FFQ have been previously given in section 4.3.4. The same approach was taken in constructing a MD score for women in the cohort who filled in a FD.

In constructing the WCRF/AICR score for women at baseline, eight out of ten WCRF/AICR recommendations, namely body fatness, physical activity, foods and drinks that promote weight gain, plant foods, animal foods, alcoholic drinks, consumption of salty foods and breastfeeding were operationalized. The recommendation on avoiding the use of supplements for cancer prevention and the recommendation for cancer survivors were not applicable to this population and thus not operationalized. This resulted in a maximum adherence score of eight, with higher values indicating greater

adherence to the recommendations. Further details on how this score was operationalised for women who filled in the FFQ are reported in section 5.3.5. The same approach was used for women who filled in a FD and details of the score operationalization, and of the percentage adherents to the score at baseline and at phase 2 are given in Table 6.2 and depicted in Figure 6.1. For women with missing data on BMI at phase 2 (n=512), BMI from phase 1 was used when this was available. Since no data on breastfeeding was collected at phase 2, the data used at phase 1 was used for score derivation.

### 6.3.5 Statistical analysis

Statistical analysis were conducted using Stata version 13 statistical software (StataCorp, 2013). The significance level was two-sided and a p value of ≤ 0.05 was considered statistically significant. Descriptive statistics were used to describe the participants' characteristics and intake of selected nutrients. The continuous variable mean energy intake (kcal/day) was compared graphically using a Bland-Altman plot (Bland & Altman, 1986) to describe the agreement between the FFQ and FD methods. The mean difference (FFQ – FD) of the two quantitative measurements was plotted against the mean of both measures for each woman, and the components of bias and precision were assessed by using the limits of agreement (2 standard deviations of the mean difference) between methods.

A linear weighted Kappa (K) was used to evaluate the agreement between the two methods of assessing diet in the UKWCS, namely the baseline FFQ and the phase 2 FD, over and above that which would be expected by chance, and to account for the level of disagreement between the methods. Each kappa statistic was compared with recognised standards of agreement as follows: *'no agreement'* (K<0.0); *'slight'* (K=0.0-0.20); *'fair'* (K=0.21-0.40); *'moderate'* (K=0.41-0.60); *'substantial'* (K=0.61-0.80); and *'almost perfect'*K=0.81–1.00) (Landis & Koch, 1977).

Survival analysis was conducted to explore the relationship between the Mediterranean dietary pattern and the WCRF/AICR score and CRC risk respectively, using data derived from FDs and the corresponding FFQs. Cox proportional hazards

regression was used to provide HRs and 95% CIs for the estimation of relative risk of cancer. The proportional hazards assumption was tested graphically for all terms in the model. A weighting factor was used in statistical models, based on the inverse probability of being sampled, to account for the stratified sampling scheme at recruitment including over-sampling of vegetarians and fish-eaters and thus ensuring the provided estimates are more representative of the UK population. The time variable used in the models was time in the study, calculated from the date of either FD or FFQ receipt until either death or censor date (01$^{st}$ April 2014).

Adherence to the MD score was categorically modelled in tertiles of the score, whilst four similarly sized categories of the WCRF/AICR score were categorically modelled. Each category was then compared to the lowest, reference category. Estimates per 1-point increment in the continuous scores and tests for linear trend were also calculated. Risk factors for CRC previously identified in the literature were taken into consideration. Potential confounders that were closely related to a score component or explicitly included in the score derivation, such as BMI and physical activity in the WCRF/AICR score were excluded from the analyses. For both scores, associations were estimated first as a simple age-adjusted model, and finally as a fully-adjusted model. For the MD score, adjustments were made for age (years), BMI (kg/m$^2$), energy intake (kcal/day), physical activity (hr/day), smoking status (never, current or former smoker), family history of CRC in a first degree relative and socio-economic status (professional/ managerial, intermediate or routine and manual), whilst the WCRF/AICR score was adjusted for age, smoking status, family history of CRC in a first degree relative and socio-economic status.

***Table 6.2 Classification and operationalization of the WCRF/AICR cancer prevention recommendations and the percentage adherence in the UKWCS at baseline and at phase 2[1]***

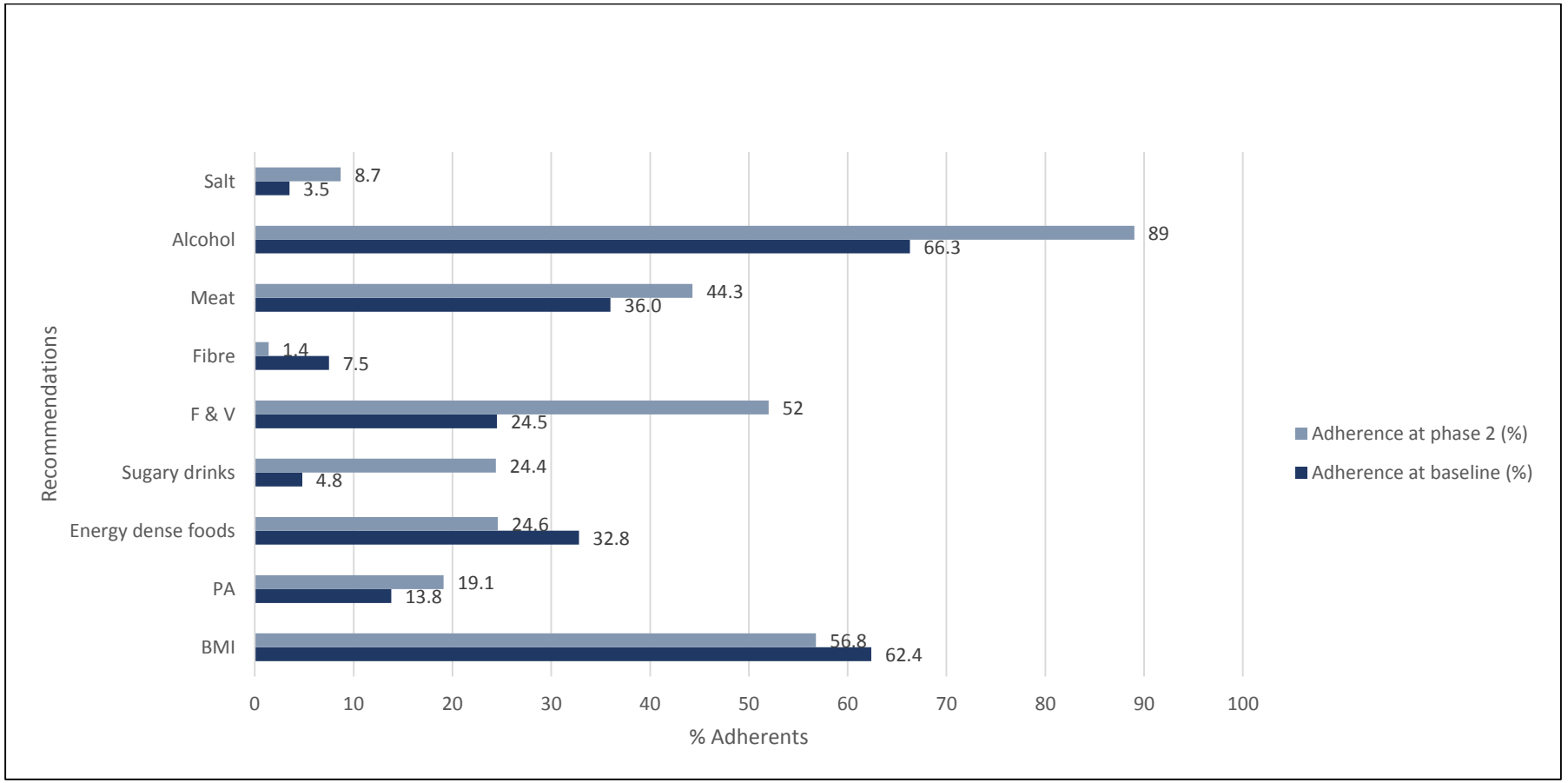
| WCRF/AICR recommendation | Personal recommendations | Operationalization | Scoring | Adherence at baseline (%) | Adherence at phase 2 (%) |
|---|---|---|---|---|---|
| 1. Body fatness<br>*Be as lean as possible within the normal range of body weight.* | (a) Ensure that body weight through childhood and adolescent growth projects towards the lower end of the normal BMI range at 21 | Insufficient data available | NA | NA | NA |
| | (b) Maintain body weight within the normal range from age 21 | BMI (kg/m$^2$): 18.5-24.9<br>BMI: 25-29.9<br>BMI: <18.5 or ≥30 | 1<br>0.5<br>0 | 62.4<br>25.6<br>12.0 | 56.8<br>30.2<br>13.0 |
| | (c) Avoid weight gain and increases in waist circumference throughout adulthood | Insufficient data available | NA | NA | NA |
| 2. Physical activity<br>*Be physically active as part of everyday life.* | (a) Be moderately physically active, equivalent to brisk walking, for ≥ 30 min every day. | >30 min/d of vigorous PA<br>15-30 min/d of vigorous PA<br><15 min/d of vigorous PA | 1<br>0.5<br>0 | 13.8<br>19.4<br>66.8 | 19.1<br>24.1<br>56.8 |
| | (b) As fitness improves, aim for ≥60 min of moderate or for ≥ 30 min of vigorous physical activity every day. | Insufficient data available | NA | NA | NA |
| | (c)Limit sedentary habits such as watching television. | Insufficient data available | NA | NA | NA |

| WCRF/AICR recommendation | Personal recommendations | Operationalization | Scoring | Adherence at baseline (%) | Adherence at phase 2 (%) |
|---|---|---|---|---|---|
| 3. Foods and beverages that promote weight gain *Limit consumption of energy dense foods; avoid sugary drinks.* | (a) Consume energy-dense foods sparingly | ED: ≤125 kcal/100 g/d<br>ED: >125 to <175 kcal/100 g/d<br>ED: >175 kcal/100 g/d | 1<br>0.5<br>0 | 32.8<br>57.9<br>9.3 | 24.6<br>56.3<br>19.1 |
| | (b) Avoid sugary drinks | Sugary drinks: 0 g/d<br>Sugary drinks: ≤250 g/d<br>Sugary drinks: >250 g/d | 1<br>0.5<br>0 | 4.8<br>83.5<br>11.7 | 24.4<br>59.2<br>16.4 |
| | (c) Consume fast foods sparingly, if at all. | Insufficient data available | NA | NA | NA |
| 4. Plant foods *Eat mostly foods of plant origin.* | (a) Eat ≥ 5 portions/servings (≥400 g) of a variety of non-starchy vegetables and of fruit every day. | F&V: ≥400 g/d<br>F&V: 200 to <400 g/d<br>F&V: <200 g/d | 1<br>0.5<br>0 | 24.5<br>41.1<br>34.4 | 52.0<br>36.9<br>11.1 |
| | (b) Eat relatively unprocessed cereals (grains) and / or pulses (legumes) with every meal. | Dietary fibre: ≥25 g<br>Dietary fibre: 12.5 to <25 g/d<br>Dietary fibre: <12.5g/d | 1<br>0.5<br>0 | 7.5<br>50.4<br>42.1 | 1.4<br>51.6<br>47.0 |
| | (c) Limit refined starchy foods. | Insufficient data available | NA | NA | NA |
| | (d) People who consume starchy roots or tubers as staples should also ensure sufficient intake or non-starchy vegetables, fruit and pulses (legumes). | Not applicable to this population | NA | NA | NA |
| 5. Animal foods *Limit intake of red meat and avoid processed meat.* | People who eat red meat should consume <500 g/wk and very few, if any, processed meats | RPM <500 g/wk and PM <3 g/d<br>RPM <500 g/wk and PM 3 to <50 g/d<br>RPM ≥500 g or PM ≥50 g/d | 1<br>0.5<br>0 | 36.0<br>48.8<br>15.2 | 44.3<br>34.4<br>21.4 |
| 6. Alcohol *Limit alcoholic drinks.* | If alcoholic drinks are consumed, limit consumption to ≤2 drinks/d for men and 1 drink/d for women. | Ethanol: ≤10 g/d<br>Ethanol: >10-20 g/d<br>Ethanol: >20 g/d | 1<br>0.5<br>0 | 66.3<br>21.1<br>12.6 | 89.0<br>9.3<br>1.7 |

| WCRF/AICR recommendation | Personal recommendations | Operationalization | Scoring | Adherence at baseline (%) | Adherence at phase 2 (%) |
|---|---|---|---|---|---|
| 7. Preservation, processing, preparation<br>*Limit consumption of salt; avoid mouldy cereals (grains) or pulses (legumes).* | (a) Avoid salt-preserved, salted or salty foods; preserve foods without using salt. | Insufficient data available | NA | NA | NA |
| | (b) Limit consumption of processed foods with added salt to ensure an intake of <6g (2.4g sodium) every day | Sodium: ≤ 1.5 g/d<br>Sodium: >1.5 to 2.4 g/d<br>Sodium: >2.4 g/d | 1<br>0.5<br>0 | 3.5<br>23.3<br>73.2 | 8.7<br>41.0<br>50.3 |
| | (c) Do not eat mouldy cereals (grains) or pulses (legumes). | Insufficient data available | NA | NA | NA |
| 8. Dietary supplements<br>*Aim to meet nutritional needs through diet alone.* | Dietary supplements are not recommended for cancer prevention. | Not applicable to this population | NA | NA | NA |
| *WCRF/AICR special recommendations* | | | | | |
| S1. Breastfeeding<br>*Mothers to breastfeed; children need to be breastfed.* | Aim to breastfeed infants exclusively up to 6 months and continue with supplementary feeding thereafter. | Cumulative BF: ≥6 months<br>Cumulative BF: >0 to <6 months<br>No breastfeeding | 1<br>0.5<br>0 | 38.2<br>26.4<br>35.4 | 38.3<br>26.5<br>35.2 |
| S2. Cancer survivors<br>*Follow the recommendations for cancer prevention.* | (a) All cancer survivors should receive nutritional care from an appropriately trained professional. | Not applicable to this population | NA | NA | NA |
| | (b) If able to do so, and unless otherwise advised, aim to follow the recommendations for diet, healthy weight, and physical activity. | Not applicable to this population | NA | NA | NA |

[1] WCRF/AICR, World Cancer Research Fund / American Institute of Cancer Research; BMI, body mass index; NA, not applicable; PA, physical activity; ED, energy density; F&V, fruit and vegetables; RPM, red and processed meat; PM, processed meat.

***Figure 6.1 Proportion of UKWCS respondents meeting each WCRF/AICR recommendation or sub-recommendation at baseline and at phase 2[1]***




[1] F&V, fruit and vegetables; BMI, body mass index; PA, physical activity

## 6.4 Results

### 6.4.1 Sample characteristics

By the 1st April 2014, a total of 173 women who participated in the UKWCS at phase 2 were diagnosed with incident CRC. The MD score and WCRF/AICR score respectively were derived for all the 2276 women participating at phase 2 for whom a FD had been coded. Women not flagged on NHS Digital (n=21) and women self-reporting history of any previous malignant cancer, except for non-melanoma of the skin (n=232) were excluded. Thus following exclusions, 2023 phase 2 respondents, with a coded FD were eligible for inclusion in the analysis, resulting in 134 CRC cases. In deriving the WCRF/AICR score, cases with missing BMI data that was also not available at baseline were also lost (n=2), resulting in 132 CRC cases. When considering the same phase 2 respondents, this time at baseline, 154 and 153 CRC cases following derivation of the MD score and WCRF/AICR score were eligible for inclusion in the analysis.

The health and lifestyle characteristics, mean energy, nutrient and non-nutrient intake of the total cohort participants at baseline compared with the total respondents at follow up phase, those diagnosed with CRC and non-CRC cases are reported in Table 6.1. Difference in baseline characteristics by response status were small. Women who responded at phase 2 had a slightly lower BMI, were less likely to smoke, more likely to have reached a degree level of education and to hold a managerial position than non-respondents. They were also slightly less likely to eat red meat, more dietary fibre and to consume less alcohol. Those diagnosed with CRC tended to be older, were more likely to hold a managerial position and a greater percentage had a family history of CRC than cancer-free phase 2 respondents. Their total energy intake, meat and alcohol intake was also higher.

Table 6.2 reports the percentage of adherents to the WCRF/AICR guidelines at baseline and at phase 2. In the follow-up phase, where dietary assessment was made through a FD, a higher adherence to the WCRF/AICR recommendations was recorded. Whilst participants were less likely to maintain their weight within the normal range at phase 2 than at baseline, they tended to be more physically active. A higher consumption of fruit and vegetables was reported through the FFQ than through the FD; participants

also reported consuming fewer animal foods, fewer sugary drinks including alcohol, fewer salt preserved foods but a diet higher in dietary fibre at phase 2 compared with the intake reported at baseline via FFQ. Notwithstanding, the overall energy density of the diet was calculated to be lower for the majority of the participants at baseline than for those at phase 2.

### 6.4.2 Agreement between FFQ and FD

The daily energy intakes of the UKWCS women as calculated from the FFQ and from the FD were compared using a Bland-Altman distribution as depicted in Figure 6.1. The FFQ gave a higher energy intake compared to the FD; the bias (mean difference) between the two methods was -525 kcal (95% CI -556, -493) with limits of agreement whereby the two methods broadly agree being within a range of -2032 to 982 kcal. A positive trend seems to be evident from the plot; although, the positive bias seems to be due to measurements greater than 2500 kcal, whilst for other energy intakes the data points are closer to each other.

***Figure 6.2 Bland-Altman plot for agreement between individuals' daily energy intake (kcal) as recorded by FFQ and FD (n=2276)***

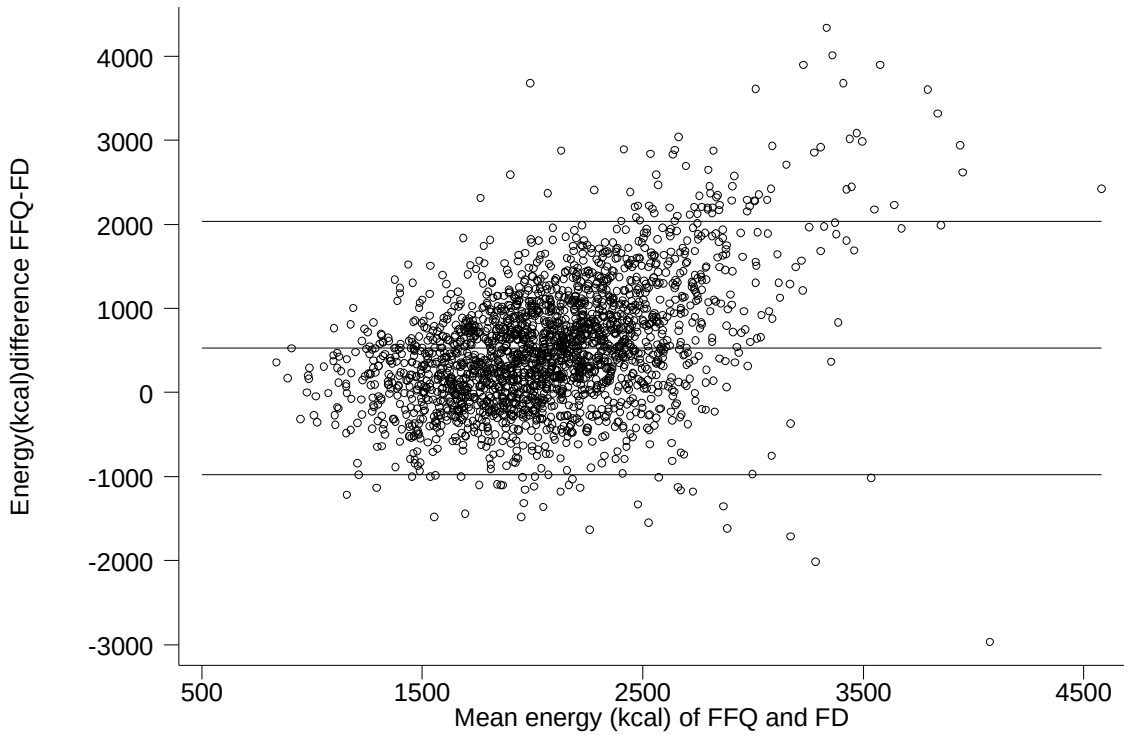


Table 6.3 shows the daily nutrient intake data and the Kappa agreements between the MD score and its respective components as derived via FFQ and as derived via FD**.** A number of differences were noted between nutrient intakes as estimated from the FFQ and FD. The overall agreement in the MD score between the two methods of assessing diet was 72%, and varied depending on the specific component making up the score. Agreement for the different components ranged from 62% for legume intake to 83% for red meat. Using kappa statistics, the measurement of agreement between the two methods of capturing diet varied between slight agreement for the overall MD score (K=0.15; 95% CI: 0.14, 0.16) to substantial agreement for red meat intake (K=0.62; 95% CI: 0.60, 0.64).

Kappa agreements between the two dietary assessment methods for the overall WCRF/AICR score and the recommendations from which it is derived are found in Table 6.4. Only fair agreement (K=0.38; 95% CI: 0.37, 0.39) occurred when comparing the overall WCRF/AICR score derived from the FFQ to that from the FD. Notwithstanding, the strength of agreement varies from fair for physical activity, energy density, sugary drinks, processed meat and alcohol to substantial for BMI (K=0.73; 95% CI: 0.73, 0.74) when considering the separate score components.

*Table 6.3 Kappa agreements between the MD score and its respective components derived via FFQ and that derived via FD[1]*

| Score / Component | FFQ median (IQR) | FD median (IQR) | Difference | Agreement (%) | Weighted Kappa (95% CI) | Strength of agreement |
|---|---|---|---|---|---|---|
| MD Score | 5 (3) | 3 (2) | 2 | 72 | 0.15 (0.14, 0.16) | Slight |
| Vegetables (g/ d) | 300 (203) | 195 (142) | 105 | 64 | 0.19 (0.17, 0.20) | Slight |
| Legumes (g/ d) | 31 (36) | 0 (30) | 31 | 62 | 0.21 (0.19, 0.21) | Fair |
| Red Meat (g/ d) | 33 (71) | 25 (60) | 8 | 83 | 0.62 (0.60, 0.64) | Substantial |
| Dairy (g/ d) | 111 (102) | 242 (220) | -131 | 63 | 0.16 (0.14, 0.17) | Slight |
| Poultry (g/ d) | 9 (22) | 6 (43) | 3 | 73 | 0.43 (0.41, 0.45) | Moderate |
| Cereals(g/ d) | 230 (153) | 140 (92) | 90 | 63 | 0.18 (0.16, 0.19) | Slight |
| Fruit & nuts (g/ d) | 292 (239) | 207 (194) | 85 | 69 | 0.30 (0.27, 0.31) | Fair |
| Fish (g/ d) | 24 (28) | 18 (43) | 6 | 71 | 0.35 (0.32, 0.38) | Fair |
| MUFA + PUFA : SFA[2] | 1.55 (0.54) | 1.34 (0.57) | 0.21 | 66 | 0.24 (0.21, 0.25) | Fair |
| Alcohol (g/ d) | 5.1 (11.0) | 1.6 (6.0) | 3.5 | 80 | 0.55 (0.54, 0.58) | Moderate |

[1] MD, Mediterranean diet; FFQ, food frequency questionnaire; FD, food diary; IQR, interquartile range.

[2] Ratio of the sum of monounsaturated fatty acids and polyunsaturated fatty acids to saturated fatty acids.

### 6.4.3 Survival analysis

The HRs and 95% Cls for incidence of CRC according to tertiles of adherence to the MD score as derived by both FD and FFQ are shown in Table 6.5. For women at phase 2, in the multivariable-adjusted model, compared to the reference intake, the third category had a lower risk of CRC but the test for trend was not statistically significant and the risk estimate for a 1-point increment in the MD score was 0.94 (0.83 to 1.06; $P_{trend}$ = 0.32). An inverse association for CRC risk with adherence to the MD score in the fully-adjusted model was demonstrated in phase 1 for women assessed via FFQ. Although the risk estimates in both the categorical and continuous models suggest a possible protective association, with a 1-point increment in the MD score resulting in an HR of 0.90 (0.80 to 1.00; $P_{trend}$ = 0.06), the association was non-significant.

Analysis of the WCRF/AICR score derived from FD filled in by women at phase 2, found no association with CRC with $P_{trend}$ = 0.87 in the multivariable-adjusted model, as recorded also in Table 6.5. Conversely, estimated associations for the score as derived from FFQ at phase 1, were inverse, though weak and only statistically significant in the age-adjusted model ($P_{trend}$ = 0.04); in the multi-variable adjusted model the significance of the overall trend was lost ($P_{trend}$ = 0.13). Such associations are also depicted in Figure 6.3.

*Table 6.4 Kappa agreements between the WCRF/AICR score and the respective recommendations derived via FFQ and that derived via FD[1]*

| Score / Recommendation | FFQ median (IQR) | FD median (IQR) | Difference | Agreement (%) | Weighted Kappa (95% CI) | Strength of agreement |
|---|---|---|---|---|---|---|
| WCRF/AICR Score | 4.5 (1.25) | 4.75 (1.5) | -0.25 | 90 | 0.38 (0.37, 0.39) | Fair |
| BMI (kg/m$^2$) | 23.5 (4.5) | 24.0 (5.0) | -0.5 | 93 | 0.73 (0.73, 0.74) | Substantial |
| Physical activity (min/d) | 9 (26) | 10 (26) | -1 | 80 | 0.21 (0.19, 0.23) | Fair |
| Energy density (kcal/ 100g/ d) | 135 (33) | 146 (43) | -11 | 74 | 0.23 (0.22, 0.24) | Fair |
| Sugary drinks (g/d) | 78 (131) | 92 (192) | -14 | 76 | 0.21 (0.20, 0.22) | Fair |
| Fruit and vegetables (g/ d) | 599 (387) | 412 (266) | 187 | 71 | 0.19 (0.17, 0.20) | Slight |
| Dietary fibre (g/ d) | 14 (9) | 13 (6) | 1 | 73 | 0.19 (0.18, 0.20) | Slight |
| Red meat (g/ wk) | 131 (346) | 175 (418) | -44 | 81 | 0.47 (0.45, 0.49) | Moderate |
| Processed meat (g/ day) | 7 (18) | 6 (23) | 1 | 79 | 0.38 (0.35, 0.39) | Fair |
| Alcohol (g/ d) | 5.0 (11.0) | 1.6 (6.0) | 3.4 | 80 | 0.40 (0.39, 0.41) | Fair |
| Sodium (g/ d) | 3.0 (1.3) | 2.4 (1.0) | 0.6 | 68 | 0.11 (0.09, 0.11) | Slight |

[1] WCRF/AICR, World Cancer Research Fund / American Institute of Cancer Research; BMI, Body Mass Index, FFQ, food frequency questionnaire; FD, food diary, IQR, interquartile range.

***Table 6.5 Hazard ratios and 95% confidence intervals for incidence of colorectal cancer according to tertiles of the Mediterranean diet score and to quartiles of the WCRF/AICR score for two dietary assessment methods***

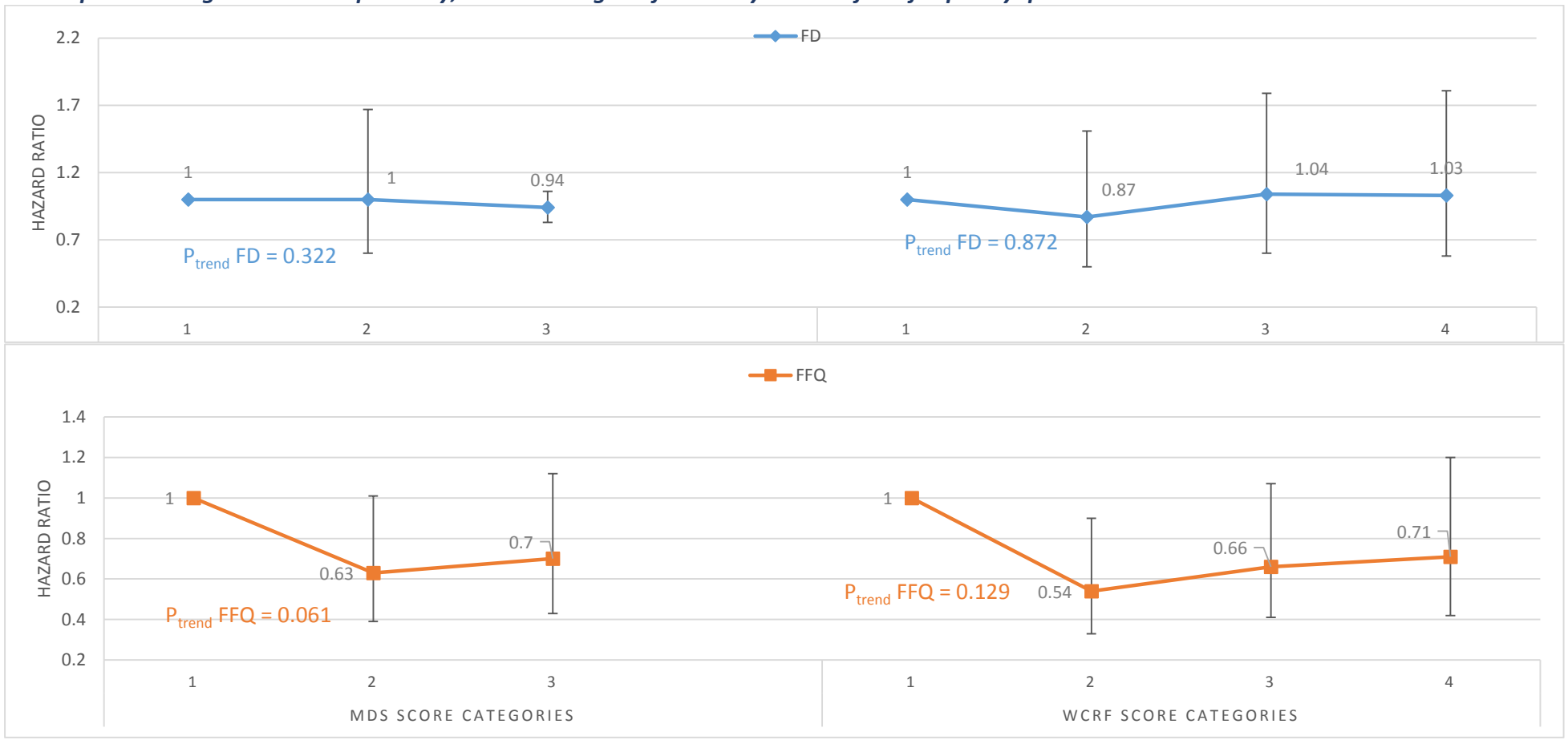
| Dietary pattern | Score categories | Food diaries | | | Food frequency questionnaires | | |
|---|---|---|---|---|---|---|---|
| | | Cases[1] | Age-adjusted HR (95% CI) | Multivariable-adjusted HR (95% CI) | Cases[1] | Age-adjusted HR (95% CI) | Multivariable-adjusted HR (95% CI) |
| **Mediterranean diet score[2]** | | 134 | | | 154 | | |
| | 1 | 42 | 1.0 | 1.0 | 40 | 1.0 | 1.0 |
| | 2 | 50 | 0.92 (0.59, 1.41) | 1.00 (0.60, 1.67) | 51 | 0.72 (0.47, 1.10) | 0.63 (0.39, 1.01) |
| | 3 | 42 | 0.74 (0.46, 1.20) | 0.75 (0.42, 1.32) | 63 | 0.82 (0.54, 1.25) | 0.70 (0.43, 1.12) |
| | Per 1 unit increment | | 0.96 (0.86, 1.06) | 0.94 (0.83, 1.06) | | 0.94 (0.85, 1.03) | 0.90 (0.80, 1.00) |
| | $P_{trend}$ | | *0.374* | *0.322* | | *0.190* | *0.061* |
| | | | | | | | |
| **WCRF/AICR score[3]** | | 132 | | | 153 | | |
| | 1 | 37 | 1.0 | 1.0 | 47 | 1.0 | 1.0 |
| | 2 | 31 | 0.86 (0.52, 1.40) | 0.87 (0.50, 1.51) | 33 | 0.49 (0.31, 0.77) | 0.54 (0.33, 0.90) |
| | 3 | 33 | 0.93 (0.57, 1.53) | 1.04 (0.60, 1.79) | 42 | 0.58 (0.38, 0.90) | 0.66 (0.41, 1.07) |
| | 4 | 31 | 0.97 (0.58, 1.61) | 1.03 (0.58, 1.81) | 31 | 0.64 (0.40, 1.03) | 0.71 (0.42, 1.20) |
| | Per 1 unit increment | | 1.00 (0.84, 1.19) | 1.01 (0.83, 1.24) | | 0.82 (0.67, 0.99) | 0.84 (0.67, 1.05) |
| | $P_{trend}$ | | *0.975* | *0.872* | | *0.041* | *0.129* |

[1] Case numbers apply to multivariable adjusted models.

[2] Adjusted for age, BMI, energy intake, physical activity, smoking status, socioeconomic status and family history of CRC.

[3] Adjusted for age, smoking status, socioeconomic status and family history of CRC.

***Figure 6.3 Association between colorectal cancer incidence, by anatomical sub site, and adherence to the Mediterranean diet[1] and WCRF/AICR cancer prevention guidelines[2] respectively, derived using the food diary and the food frequency questionnaire***




[1] Cox regression adjusted for age, BMI, energy intake, physical activity, smoking status, socioeconomic status and family history of CRC.

[2] Cox regression adjusted for age, smoking status, socioeconomic status and family history of CRC.

## 6.5 Discussion

Accurately assessing habitual dietary intake is vital in studies aimed at determining the role of diet in cancer prevention, but difficult to achieve. In this study, we assessed the agreement between adherence scores of two dietary patterns, the Mediterranean dietary pattern and the WCRF/AICR cancer prevention guidelines, by comparing the scores derived from a 217-item FFQ and a 4-day FD. We also looked at the association of the named dietary patterns derived from the different dietary assessment methods and CRC risk in the UKWCS.

The agreement between scores showing adherence to the MD was poorer than that between scores for the WCRF/AICR score. For all components of the MD score except dairy, the median intake in the FFQ was higher than in the FD, whilst for the dietary components of the WCRF/AICR score, only for sugary drinks and red meat intake was the FFQ median lower than the FD median. Overestimation of fruit and vegetable intake (Neville et al., 2017), and of fruit and nut intake (Carlsen et al., 2010) via FFQ when compared to FD has been previously reported, as is underestimation of added sugar (Carlsen et al., 2010) and of soft drinks and cheese (Vereecken & Maes, 2003) from the FFQ compared with the FD.

The relative bias in energy intake between the two dietary assessment methods was considerable, with energy intakes -525 kcal (95% CI -556, -493) higher with FFQs compared to mean energy intake estimated from FD. Higher energy intake by FFQ in comparison to FD has been reported in several previous studies (Brunner et al., 2001; Kowalkowska et al., 2013; Fernandez-Ballart et al., 2010). Such discrepancies in energy and nutrient intake between the two methods may be related to several factors, including inadequate participant estimation of frequency and food portion sizes, incorrect choice of food item by coder from database or use of an inaccurate dish recipe during FD coding and the FFQ structure with respect to the number and choice of food items (Cade et al., 2004b). For instance, overestimation of fruit and vegetable intake when assessed via FFQ compared to other dietary assessment methods may be attributed to the fact that these items are listed individually resulting in a reported magnified intake. Brunner and colleagues also noted such a finding in the Whitehall II

study and stated it could be related to the numerous items on the FFQ used (Brunner et al., 2001). Furthermore, in this study the FD was completed approximately 5 years after the FFQ was administered, a period during which participants may have altered their eating habits. Although the difference in energy intake was substantial, the values for energy density were closer on comparison of methods, with a difference of 11 kcal/100g/d. In fact, considering both the FFQ and FD medians, the women's diet is said to be borderline between low to medium energy density (BNF, 2009).

In this female UK cohort, CRC risk was not associated with a higher adherence to the Mediterranean dietary pattern or to the WCRF/AICR cancer prevention guidelines as derived from FFQs or FD. Estimates of the associations of CRC with scores generated from the FFQ though not statistically significant were protective for both dietary patterns, when compared to those generated from the FD, suggesting attenuation, potentially due to the relatively small numbers of cases. In fact, in the study reported in chapter 4, which included a larger number of CRC cases, a 12% decreased risk of CRC was reported (HR=0.88; 95% CI 0.78 to 0.99; $P_{trend}$ = 0.03) with a 2-point increment in the MD score.

In line with findings from this study, two other studies in women: the NIH-AARP Diet and Health Study (Reedy et al., 2007) and the Nurses' Health Study (Fung et al., 2010) also reported no statistically significant association between the MD and CRC in women. Notwithstanding, a recent systematic review and meta-analysis of 11 observational studies reported an 18% reduced risk of CRC for high adherers to a Mediterranean dietary pattern (Schwingshack et al., 2017). Whilst the discrepancy in findings may be partly attributed to the different methods of dietary assessment, other variations in studies that may contribute to the inconsistencies include different definitions of the MD and the components included in the score and the choice of cut-off points determining adherence according to intake. Studies investigating the association between the WCRF/AICR cancer prevention recommendations and CRC incidence have reported inconsistent findings, with those from the Black Women's Health Study (Nomura et al., 2016) and from the Framingham Offspring cohort (Makarem et al., 2015) reporting no significant association in agreement with results of this study. In contrast, both the EPIC (Romaguera et al., 2012) and VITAL cohort

(Hastert & White, 2016) reported reduced CRC risk with increased adherence to the WCRF/AICR recommendations for cancer prevention. However, none of the mentioned cohort studies used FD for dietary assessment and thus comparison is limited. The number of guidelines operationalized varies between studies; this may explain in part the inconsistencies.

Our findings do thus not support previous research that suggests FD are preferable at estimating risk in cohort studies of diet and cancer (Bingham et al., 2003; Freedman et al., 2006). Non-consecutive repeated 24-hour recalls are considered the gold standard for assessing usual intake (Biro et al., 2002). In comparison, although appropriately filled in FDs result in a more accurate assessment, the less laborious FFQ seems to be a better predictor of both habitual intake as well as at predicting items that are commonly not consumed on a daily basis, such as alcohol. For such items, the FFQ median reflects the consumption patterns better; the discrepancy of 3.5g / day of alcohol between the FFQ and the FD is substantial. Participants burdened with recording their food intake for a period of time may lead healthier lifestyles, may report foods that are considered more socially acceptable or may alter their food intake to simplify recording of diet (Baranowski, 2013).

The key strength of this study is that scores for the two dietary patterns being explored could be derived from both FFQ and FD. Whilst the advantages and disadvantages of the two different dietary assessment methods have been previously extensively reviewed (Cade et al., 2002), the fact that both methods are used in the same cohort gives a broader overview of dietary patterns in relation to CRC in this cohort. The prospective nature of the study also reduces selected recall bias. The long follow-up period is considered a strength, as is the adjustment of several potential non-dietary confounding factors. The case-cohort design allows the processing of data for only a proportion of the non-case participants. Although the relatively small number of CRC cases is the main limitation of this study, it was still considered of interest to explore since studies looking at cancer risk and using FD for dietary assessment are scarce. The small numbers create uncertainty around estimates making it challenging to determine whether true associations exist and are being masked by wider confidence intervals. Furthermore, limitations characteristic of a methodology based on using dietary scores

can also be attributed to this study, where the adherence scores for both dietary patterns were generated by scoring all components equally.

The results of this exploratory case-cohort study on dietary patterns derived from FFQ and FD respectively, and CRC do not suggest that the MD or the WCRF/AICR cancer prevention guidelines are associated with CRC risk in this British cohort of middle-aged women. Further studies with larger sample sizes, using FD for diet assessment are warranted.

# CHAPTER 7 SUMMARY AND CONCLUSIONS

## 7.1 Chapter overview

Findings from the three main parts of this thesis have been individually reported, compared with previous studies and their implications discussed in chapters 4, 5 and 6 respectively. This chapter aims to provide a summary of the key results across the separate studies, bringing together the different elements of this work in an overall discussion. It attempts to critically reflect on the research carried out, highlighting how effectively the work conducted met the central aim identified at the initial stages of the research, namely:

***'To explore the relationship between dietary pattern exposures and CRC incidence as an outcome using data from the UKWCS'.***

A number of points of specific interest will be targeted for an expanded discussion in section 7.2, whilst the strengths and limitations of the overall study will be considered in section 7.3. Areas where further research is warranted will be highlighted in section 7.4 and public health recommendations based on the research findings will be made in section 7.5. Section 7.6 concludes the chapter.

## 7.2 Summary discussion

The analyses presented in this thesis have used data from the UKWCS, a large population based British cohort designed to assess associations between diet and chronic diseases. Dietary information from this cohort which was previously assessed via a FFQ at baseline, and in the 2$^{nd}$ follow-up phase of the study via a FD, was combined with CRC incidence records obtained from NHS Digital. This allowed the exploration of an association between incidence of total CRC, and the different anatomical sub sites of the colorectum, in UK women in relation to dietary patterns derived from different dietary assessment methods. The investigation also sought to determine whether the associations from the FD derived patterns are in agreement with FFQ derived patterns. Not only was such data from phase 2 previously unexploited in relation to CRC in the UKWCS, but exploring associations between dietary patterns and cancer using FD derived data in addition to FFQ data has not been

previously reported in the literature. Studies differentiating associations by sub site are also very few. This originality of this work is thus highlighted.

The dietary patterns chosen for investigation in this study were the *a priori* Mediterranean dietary pattern and the 2007 WCRF/AICR cancer prevention recommendations. This alternative approach of studying dietary factors in relation to CRC risk was chosen in favour of emphasizing the effects of single foods or nutrients. The latter approach has given several inconclusive results, as discussed in chapter 2 whilst dietary pattern analysis allows an investigation of the consumption of foods in combination, portraying a more realistic scenario. The cancer protective effect of dietary patterns may be more pronounced than that of individual components due to interactions between the latter resulting in health benefits being more apparent. Furthermore, dietary indices may overcome issues of confounding factors and of collinearity between components, and allow the evaluation of the extremes of cumulative exposure. The use of studies looking at dietary patterns to assess cancer incidence is thus truly justified (Verberne et al., 2010).

The thesis successfully addressed the following research objectives, as stated in Chapter 1:

- An advanced literature review was conducted to identify observational studies reporting associations between diet, nutrients and dietary patterns and risk of CRC, and reported in Chapter 2.
- A 10-component adherence score to the Mediterranean dietary pattern and an 8-component adherence score to the WCRF/AICR cancer prevention recommendations for UKWCS participants were constructed. Characteristics of low and high adherers, as estimated using FFQs and FD are presented in Chapters 4, 5 and 6 respectively.
- The association between the Mediterranean dietary pattern derived from diet assessed via FFQ, and incident CRC risk, including consideration of the proximal colon, distal colon and rectal anatomical sub-sites respectively was explored using survival analysis and is presented in Chapter 4.

- *A total of 527 incident CRC cases were reported since baseline and the MD score was associated with a significantly lower risk of CRC and of rectal cancer, whilst estimates for an association with colon cancer were weak but suggested a protective association. Notwithstanding, the confidence intervals for estimates for colon and rectal cancer were wide, potentially suggesting the difference in association between the two anatomical sub sites was due to chance.*

- The association between adherence to the WCRF/AICR cancer prevention recommendations, derived from a FFQ, and risk of total CRC, colon and rectal cancer was also assessed using survival analysis and is presented in Chapter 5.
  - *A total of 444 incident CRC cases were included in the analysis, following exclusions; the WCRF/AICR score was not significantly associated with a lower risk of colon or rectal cancer. Although a protective association from CRC was also seen with the highest adherence category of the score, the overall linear trend across categories was not significant.*
- Finally, the agreement between the MD and the WCRF/AICR scores derived from the different dietary assessment methods, namely the FFQ and the FD was evaluated using a Bland-Altman plot and Kappa statistics; the associations of the named dietary patterns derived from FD with risk of CRC was explored, using a case-cohort study design using in Chapter 6.
  - *FD for a total of 2276 women were available, of which a total of 173 CRC cases were documented. Estimates for an association with CRC were weak with both the MD score and the WCRF/AICR score, though case numbers were small. The energy intake from the FFQ was considerably higher than that from the FD. Agreement between the two methods was slight for the MD score and fair for the WCRF/AICR score.*

The combination of these objectives ensured that adherence to the two chosen dietary patterns in relation to CRC risk in this cohort of women had been thoroughly investigated and that the overarching aim of this thesis has been successfully reached. A wealth of information was added to research on dietary patterns and risk of CRC, and the study gave invaluable insight into the potentially different associations of diet

with the separate anatomical sub sites of the colorectum. Whilst the first two objectives listed above used only baseline data of the UKWCS, the third objective used data from both the first and second phases of the study. Women were followed up for incidence of CRC from phase 1 for over 17 years.

Drawing together the available evidence, the Mediterranean dietary pattern appears to be associated with reduced CRC risk, but the associations tend to be more consistent with rectal cancer and total CRC rather than for colon cancer. The differential associations between the Mediterranean dietary patterns and the two different anatomical sites of the colorectum support the notion that the pathology of these conditions may differ and the different food components of a MD potentially exert a different influence on the process of cancer development. A different aetiology was also noted between the proximal and distal colon, and although both associations were not significant, the difference may be explained on the lines of their distinct biological characteristics. These anatomical differences may stem in part from embryological origin and partly from modification during postnatal development; one may argue that they thus elicit a varied response to the same environmental factors (Glebov et al., 2003).

On looking at the associations of the individual components making up the MD, legumes stood out among the different components as being one of the key food groups driving the decrease in risk of rectal cancer and to some extent of CRC. Whilst attributing this to their high dietary fibre content is biologically plausible, a systematic review and meta-analysis of 25 prospective observational studies reported a reduced risk of CRC with a high fibre intake but on analysis by fibre subtype, the RR for legume fibre was not significant (Aune et al., 2011b). Although a high legume intake was also associated with a decreased risk of colorectal and other cancers in a multi-site case-control study, the authors acknowledged the need for investigating this association in prospective cohort studies (Aune et al., 2009). It is worth mentioning that in view of the high percentage of vegetarians in the UKWCS, the cohort's mean legume intake is expected to be higher than of the general UK population – this has been confirmed in a previous study looking at legume intake in the UKWCS (Aldwairji, 2013). Women with higher legume consumption could potentially have a lower intake of red meat, may

lead healthier lifestyles overall and have lower BMIs. Such factors have all been linked to a lower risk of CRC. Notwithstanding, legumes may reduce CRC via several mechanisms, including their fibre content, their role in weight management in view of their impact on satiety as well as their polyphenolic content. Legume fibre, in particular blue lupin kernel fibre has been shown to improve colonic function and to have beneficial effects on faecal mass and pH, transit time, SCFA – all risk factors for CRC (Fechner et al., 2013).

Olive oil is an integral component of the MD and high in polyphenols. However, since the population under study is a non-Mediterranean British cohort, olive oil is unlikely to be the main source of unsaturated fatty acids and thus the total amount of unsaturated fats was used in lieu of MUFAs to derive the MD score in this study. There is some epidemiological evidence to show that dietary omega-3 fatty acids are associated with a reduced CRC risk (Cockbain et al., 2012). Fish is a natural source of the eicosapentaenoic acid and docosahexaenoic acid. Epidemiological data in general report a small decrease in incidence of CRC with increased fish consumption (Norat et al., 2005; Cockbain et al., 2012; Wu et al., 2012). The WCRF/AICR 2017 CUP report supports this view and concluded the evidence for an association with fish consumption is suggestive, but limited; they could not come to a conclusion on the association with omega-3 fats from fish (WCRF/AICR, 2017). Epidemiological studies using FFQ to assess diet may be hindered by lack of discrimination between oily and lean fish, and processed and non-processed fish (Cockbain et al., 2012), thus potentially failing to reveal an association between fish intake and CRC risk. Estimates for fish reported in this study though weak are in the expected direction, thus supporting the implication that fish, partly due to its omega-3 content, is one component of the MD mediating the observed association. One may thus hypothesise that the type of fat in the diet has a role in cancer progression and is to a degree responsible for the decreased CRC incidence observed with a higher adherence to the MD. Pauwels (2011) also describes an added benefit of fish and olive oil consumption; together with red wine they aid in the consumption of legumes and vegetables.

Other components of the MD that have consistently been associated with reduced CRC risk include vegetables and fruits and whole grain foods. Conversely, the MD is characterised by a low consumption of red meat and dairy products. Estimated associations reported for vegetables and red meat consumption in this study, though not strong, were also in the expected directions. Verberne and colleagues describe the beneficial effect of the MD on cancer risk as being mediated through chronic inflammation and oxidative stress amongst other numerous biological mechanisms (Verberne et al., 2010). The Mediterranean dietary pattern is rich in antioxidants such as vitamin C and E, flavonoids and phenols and associated with low levels of low density lipoprotein cholesterol and may be said to be anti-inflammatory. While polyphenols from olive oil, resveratrol from red wine and lycopene from tomatoes have been shown to obstruct molecular cancer pathways (Farinetti et al., 2017). The fibre content may compensate for the effect of N-nitroso compounds by scavenging nitrite whilst the omega-3 fats may play a role in cancer initiation and progression (Verberne et al., 2010). The adequate omega-6 and omega-3 fatty acid ratio, the low trans fatty acid intake, the high fibre content and the high intake of antioxidants and polyphenols resulting from adherence to a MD lead to beneficial effects on human health (Tyrovolas & Panagiotakos, 2010).

In relation to the association between adherence to the WCRF/AICR cancer prevention guidelines and CRC incidence in the UKWCS, there was no evidence of statistically significant associations in any of the analyses carried out as part of this thesis. The generally null association was seen both when the data to generate the adherence score was derived via FFQ as described in chapter 5 and also with the FD derived pattern reported in chapter 6. Operationalizing a ninth recommendation on supplement use in sensitivity analysis did not change the results. The several differences in the food components making up the Mediterranean dietary pattern and those mentioned in the WCRF/AICR cancer prevention guidelines, such as fish, nuts, dairy, alcohol and sodium may be to an extent mediating the difference in associations. Notwithstanding, such observations are in line with findings from some studies, but not with others, as discussed at length in chapters 5 and 6. They may be explained by a true lack of association between this specific dietary pattern and cancer

or by the low case numbers in the case of FD derived dietary patterns. Alternatively, methodological limitations in dietary assessment and in data collection, especially based on self-reported dietary intake, and challenges such as the ones related to measurement error as discussed above may lead to misclassification of individuals vis-à-vis adherence to one or more recommendations; this may account for the null findings. Another issue relates to a potentially inadequate variation in dietary pattern adherence across the UKWCS. Notwithstanding the fact that the variation in adherence to the WCRF/AICR cancer prevention guidelines across the UKWCS was considerable, the women in this study may be healthier than the general UK population. This implies that the participants may on average have greater adherence levels to such recommendations in comparison to other British women; the proportion of women with low adherence would thus be insufficient to reveal an increased risk of CRC, if one existed. For instance only around 20% of the women in the UKWCS baseline analyses had an adherence score of 3 or less, which is relatively low compared to the 50% of the EPIC study participants who scored 3 or less in a similar study (Romaguera et al., 2012). Another potential reason for finding a null result is also related to the methods of dietary assessment. Both the FFQ and the 4-day FD methods may be too imprecise to measure some score components, such as sodium, accurately. In view of the fact that the recommendations are given to prevent all-cause cancer, some of them may not be directly applicable to CRC risk; this may attenuate the true associations resulting in null findings.

The statistically significant association between adherence to the MD and CRC incidence reported in Chapter 4 using baseline data was however not seen when phase 2 FD recorded data was used in the analyses as described in Chapter 6. Estimates though inverse, were weak and non-significant. One plausible explanation for the null observation is the relatively small number of cases by comparison to the over 400 CRC cases documented with baseline data. It may also be argued that the difference in results is due to the different dietary assessment methods. The data indicates reasonable validity of the FFQ-based dietary pattern estimates long-term, justifying the use of such an assessment method in studies of diet and cancer associations. This implies the FFQ may be considered more appropriate for recording habitual intake.

Although the FD is an accurate method of assessment, the use of short term dietary data for estimating usual intake is associated with several challenges. Such measurements are for instance expected to be prone to substantial within-person error: a combination of variation around one's usual intake, together with measurement error (Kipnis et al., 2003). Such dietary measurement error attenuates disease risk estimates, thus reducing the power to detect statistical significance. Findings from this study, and similar nutritional epidemiological investigations should be interpreted with caution considering that important diet disease associations may be masked.

## 7.3 Strengths and limitations

The choice of studying the role of well-established dietary patterns as opposed to that of individual foods or nutrients in the development of CRC may be considered one of the key strengths of this thesis. The interaction of different nutrients may affect their bioavailability whilst a single nutrient may be present in several foods. An above average intake of a particular food item in one's diet typically results in a low intake of another food (Michels & Schulze, 2005). Such factors make linking of nutrients and foods to disease outcomes complex. Studying dietary patterns allows different dietary exposures that may be associated with disease risk to be captured, though it has been argued that if the effect on disease outcome is that of a single exposure, it may be diluted with dietary pattern analysis (Michels & Schulze, 2005). Nevertheless, because dietary patterns encompass the overall diet, they allow public health recommendations to be easily translated into eating habits and a healthy diet to be achieved in several ways (Cespedes & Hu, 2015).

The dietary patterns used in this thesis to investigate the diet CRC association were both predefined diet quality scores. The MD score describes a dietary pattern including the consumption of a number of food groups, but it does not give a comprehensive diet pattern. Other limitations of using dietary indices include variation in the individual score components selected for inclusion in the score and in the definition of their respective cut-off points between different studies (Hu, 2002). Furthermore, a dietary index is generated using the knowledge available on the diet disease

association at the time of the study, and is thus limited by that understanding. Dietary recommendations used to build a dietary pattern for instance may not be updated in accordance to the latest available scientific evidence (Hu, 2002). The WCRF/AICR cancer prevention guidelines used in generating the WCRF/AICR score for this research, as described in chapter 5, were published in 2007. This is considered a limitation since scientific research is ongoing; new evidence is systematically reviewed as part of the WCRF CUP, evaluated and used to make conclusions – in fact a review of the recommendations is expected to be published in the near future (WCRF International, n.d.).

*A posteriori* methods for defining eating patterns have also been used in the literature where the dietary data available is manipulated using statistical techniques, with the most commonly used being principal component analysis. Reduced rank regression is different in that it targets the dietary pattern to a specific disease outcome by using both available data as well as prior knowledge. Although it is a more targeted approach, it is novel in comparison to other methods and thus has been used less in the literature (Michels & Schulze, 2005). Using mixed methods to study dietary patterns in this thesis, each method with its strengths and limitations, may have provided a more comprehensive approach in answering the research question. On the other hand, a major strength of this thesis is the use of multiple methods of dietary assessment to derive dietary patterns. Whilst most studies of dietary patterns use the FFQ, dietary data for the analyses was also derived from FD and explored in relation to CRC risk, thus contributing better to an understanding of the diet and disease relationship.

A key strength of this work is the study population – the UKWCS is a high quality cohort of a large size. Its prospective nature minimized recall and responder bias. The large proportion of vegetarians recruited allowed a greater spectrum of dietary intakes to be explored, making this cohort unique in that sense. Still, the cohort was reweighted by the percentage of vegetarians and fish-eaters, as detailed in section 3.9.2.1. This ensures the results are more applicable to women in the general UK population, although the extent of this is unknown. The large size of the cohort gave

the analyses undertaken using baseline data substantial power, and also allowed an exploration of the associations with different anatomical sub sites. Although the smaller number of CRC cases available for inclusion in the analyses at phase 2 is a limitation of this study, no other studies have used FD derived data to look at an association between dietary patterns risk of CRC, which makes the study novel. Another advantage of the UKWCS study design are the health and lifestyle questionnaires filled in by the participants, both at baseline and at phase 2. Although self-reporting of anthropometric data is not ideal, the questionnaires enabled several factors to be captured. Those that were potential confounders could be adjusted for in survival analyses. No adjustment could however be made for screening of CRC since this data was not available. CRC screening could have been a probable confounding factor for several reasons: the process is likely to identify cases sooner, health aware participants such as those in the UKWCS were more likely to attend screening, and such women tended to have a stronger family history of CRC and a higher risk of CRC themselves.

## 7.4 Future research

### 7.4.1 Using the UKWCS

The data used for analyses in this thesis could be explored further via sensitivity analyses. Family history is a strong risk factor for CRC and excluding women with a family history would allow a potential different association to be investigated. It was also mentioned in Chapter 2 that some patients have a hereditary type of CRC known as HNPCC which develops at around 44 years (Wang & Dubois, 2010). A sensitivity analysis excluding all cases before 50 years would exclude such hereditary cases. People with adenomatous polyps have an increased risk of CRC and risk factors for their development are likely to be similar to those for CRC. Sensitivity analysis could be conducted to exclude people reporting a history of polyps at baseline as their dietary choices may have been influenced.

The work in this study focused on two dietary patterns. The association between several other dietary patterns, such as Western, prudent, DASH, Dietary Inflammatory Index and low-fat amongst others could be investigated in relation to the incidence of

CRC. Different health outcomes available for the UKWCS could also be examined in relation to the Mediterranean and WCRF/AICR dietary patterns. Some examples include adenomatous polyps, total cancer incidence, cancer mortality and cancers at different anatomical sites.

In relation to the WCRF/AICR pattern, the adherence score as generated in this and similar studies assumes each score component is equally important in relation to health. The total unweighted score has been compared with specific cancers or all-cause cancers in several publications. It is however worth considering a score weighting where a greater emphasis on specific recommendations is made, developing weights potentially on the relative risk reported for CRC. For instance, the breastfeeding component is unlikely to be related to CRC risk (Parkin et al., 2011). Furthermore, the WCRF/AICR cancer prevention guidelines are expected to be updated very soon as part of the CUP. It would be interesting to see the association between cancer incidence and adherence to the new recommendations.

A future follow up study would result in a later censor date from NHS Digital, giving a greater number of documented CRC cases. This would allow re-analyses, with greater power and would be especially valuable for sub site analysis (proximal colon, distal colon and rectal) and for dietary pattern derived from FD. As previously discussed, only a fraction of the available FD have been coded to date. With a greater number of FD, one could create a new grouping of women whose FD and FFQ scores are in agreement, and investigate whether the associations with CRC incidence were stronger.

### 7.4.2 Other studies

Chapter 2 discussed the several existing studies assessing the association between diet and CRC. Those focusing on dietary patterns are fewer and in their majority conducted in Europe or in the US. Evidence on the associations of dietary patterns with different anatomical sites of the colorectum is very limited and the 2017 WCRF/AICR CUP report could thus make no conclusion on this association (WCRF/AICR, 2017). Further studies in varied population groups are thus needed. Such research should ideally be of a

longitudinal design, with large numbers, or dietary pattern interventions. Large cohort studies would allow associations for colon and rectal cancer to be studied separately. Long-term trials are rare for several reasons, mainly related to cost and poor adherence to the diet. The only intervention trial – the Lyon Heart Trial was carried out on a much smaller scale and results are thus only suggestive (de Lorgeril et al., 1998). The PREDIMED trial (Martinez-Gonzalez et al., 2015) is an exception – it is a landmark trial that included over 7000 participants with risk factors for CVD who were advised to follow either a low fat control diet or a Mediterranean-style diet; the latter were provided with either nuts or olive oil. After an approximate 4 year follow-up, both intervention groups experienced an approximate 30% reduction in CVD events compared with the control group. In view of the observational evidence on the association between higher adherence to the MD and decreased CRC incidence from this study, and from other cohorts, similar trials with cancer as an outcome are needed. Such interventions would lend support on the benefits of the MD in primary prevention of cancer and provide tangible scenarios that may guide policies on public health.

Chapter 2 reviewed the numerous modes of action of various dietary components on incidence of CRC. It is apparent that a better understanding of the complex mechanisms by which diet influences the development and progression of CRC is crucial if the prevention of cancer is to be addressed. This should be one of the focal points of future research. Furthermore, individuals' genetic variation may affect the way food is processed, nutrients effect the expression of an individual's genes and a number of nutritional factors may protect the genome from damage. The interaction between nutrition and genes is termed nutrigenomics and is in summary the impact of dietary components on the genome (Mead, 2007). Research evidence from nutrigenomics to the treatment and prevention of disease is very likely the way forward in the prevention of CRC, amongst other chronic diseases.

Dietary assessment is associated with several challenges as discussed in previous chapters. A recent systematic review on the validity of dietary assessment methods (Walker et al., 2017) concluded that research is necessary to support the development

and validation of accurate dietary assessment methods, specifically considering innovative technologies. Dietary data to examine diet and cancer risks may be collected using on-line assessment methods such as 24hr recall questionnaires and FFQs, via smartphone applications, and other emerging technologies such as image-assisted dietary assessment methods. In the latter, handheld devices or wearable cameras are used to capture images (Gemming et al., 2015). Advantages of such technologies include real-time recording, reduction in self-report bias, less time spent collecting data and coding, thus reducing also coding errors. Such tools enhance the accuracy of self-report dietary assessment and potentially, being less burdensome on participants, simply their recruitment enabling larger cohorts to be studied.

## 7.5 Public health policy implications

Dietary patterns are an alternative approach to individual foods and nutrients for informing public health recommendations (Cespedes & Hu, 2015). Whilst the WCRF/AICR 2017 CUP review on CRC reported limited and inconclusive evidence for dietary patterns, a very recent review on dietary patterns and CRC risk (Tabung et al., 2017) reported that *'consuming a dietary pattern high in fruits and vegetables and low in meats and sweets is protective against CRC risk.'* This is to an extent in line with findings from this study as the characteristics of the dietary pattern reported are similar to those of the MD. Furthermore, the review reported stronger associations in men than in women and more significant findings from case-control studies in comparison to cohort studies (Tabung et al., 2017). The current results suggest that adherence to the Mediterranean dietary pattern reduces risk of CRC, especially of rectal cancer. Legumes seem particularly beneficial for lowering risk and based on this study results, their importance should thus be emphasised.

Public health messages should thus continue to encourage adherence to the MD, not only because it is beneficial in preventing heart disease (Estruch et al., 2013), but also to reduce risk of CRC. These findings are positive as the public needs consistent dietary advice as primary prevention for a range of chronic diseases; they do not say choose to protect themselves against CVD but not cancer. Furthermore, results from Chapter 4 show that health benefits in the sense of risk reduction are not seen only

in women with full adherence to the Mediterranean dietary patterns, but also in those who are partially adherent. This is encouraging as it implies that even a few changes to one's eating patterns may have a positive influence on disease risk. Unfortunately dietary habits of southern European countries have changed over the past five decades, and recommendations should focus on supporting people in reversing the trend and consume the traditional MD of the 1960s (Tourlouki et al., 2013).

As reported in chapters 5 and 6, no protective effect of adhering to the WCRF/AICR cancer prevention guidelines was found in terms of CRC risk. While this is in line with results from smaller studies, it does not support previous research from larger cohort studies such as EPIC (Romaguera et al., 2012) and VITAL (Hastert & White, 2016). Nevertheless, on looking at the association with individual WCRF/AICR recommendations, results were indicative of body fatness as potentially driving the association between WCRF/AICR and CRC risk. Although further research is necessary to support this, the importance of maintaining one's weight within what is considered a normal, healthy range should thus be emphasised for CRC prevention. Thus, despite the evidence from this thesis, when considering the limitations in self-reported dietary assessment, it is difficult to regard findings from this single study as definitive.

The public health message to adhere to cancer prevention guidelines should remain, especially since there is no evidence of detrimental effects. Furthermore, many of the food related recommendations for cancer prevention are in line with a typical MD, such as consuming high intakes of fruit and vegetables, increasing dietary fibre consumption via whole grains, eating less red meat and avoiding sugary foods. However, more promotion and implementation of such dietary recommendations is needed to reach the general public. A number of YouGov surveys help to give an insight into the public's habits. A 2012 YouGov survey for the WCRF, of over 2100 participants found that only one in five Britons eat the recommended five portions of fruit and vegetables a day (YouGov, 2012a) whilst another survey showed 64% of Britons said they will not change their eating habits following a report that red meat increases risk of heart disease and cancer (Gardiner, 2012). A third survey reported

that whilst 88% are aware that a high sugar diet is a health risk, only a third check the sugar content of a food on the label (Dahlgreen, 2014).

In view of the above, the strategy for reducing the cancer burden should thus not be restricted to behaviour change on an individual level. Factors affecting individuals' food choice decisions are complex. In a qualitative study aimed at exploring the public's willingness to reduce red meat consumption reported people associated meat consumption with pleasure and linked it to social, personal and cultural values (MacDiarmid et al., 2016). A review investigating factors affecting fruit and vegetable consumption listed sensory appeal, familiarity and habit, social interactions, cost, availability, time constraints, personal ideology, media and advertising and health as affecting food choice (Pollard et al., 2002). Such barriers need to be addressed in order to increase adherence to healthy dietary patterns and public health initiatives and policy initiatives are necessary at higher national and international levels.

## 7.6 Conclusion

In this population of health-conscious, middle-aged, British women, a higher adherence to the Mediterranean dietary pattern, derived from a FFQ, was associated with a reduced risk of CRC; this association was particularly apparent with rectal cancer. Conversely, no significant association was found between adhering to the WCRF/AICR cancer prevention guidelines and CRC, which is contrary to results of larger cohorts, and which may be in part attributed to the relatively higher adherence scores of the women in our cohort in comparison to those in other cohorts and to the general UK population. For the first time this thesis investigated the associations between dietary patterns derived using FD data in relation to CRC incidence. The FDs reported a lower energy intake than the FFQs. Estimates for both the Mediterranean dietary pattern and for the WCRF/AICR guidelines, derived from FDs were non-significant, though case numbers were small, implying potential attenuation of associations.

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# APPENDICES

## APPENDIX I WCRF/AICR 2007 judgement on CRC prevention and causation

### FOOD, NUTRITION, PHYSICAL ACTIVITY, AND CANCERS OF THE COLON AND THE RECTUM

In the judgement of the Panel, the factors listed below modify the risk of cancers of the colon and the rectum. Judgements are graded according to the strength of the evidence.

| | DECREASES RISK | INCREASES RISK |
|---|---|---|
| **Convincing** | **Physical activity[1,2]** | **Red meat[3,4]**<br>**Processed meat[4,5]**<br>**Alcoholic drinks (men)[6]**<br>**Body fatness**<br>**Abdominal fatness**<br>**Adult attained height[7]** |
| **Probable** | **Foods containing dietary fibre[8]**<br>**Garlic[9]**<br>**Milk[10,11]**<br>**Calcium[12]** | **Alcoholic drinks (women)[6]** |
| Limited — suggestive | Non-starchy vegetables[9]<br>Fruits[9]<br>Foods containing folate[8]<br>Foods containing selenium[8]<br>Fish<br>Foods containing vitamin D[8,13]<br>Selenium[14] | Foods containing iron[4,8]<br>Cheese[10]<br>Foods containing animal fats[8]<br>Foods containing sugars[15] |
| Limited — no conclusion | Cereals (grains) and their products; potatoes; poultry; shellfish and other seafood; other dairy products; total fat; fatty acid composition; cholesterol; sugar (sucrose); coffee; tea; caffeine; total carbohydrate; starch; vitamin A; retinol; vitamin C; vitamin E; multivitamins; non-dairy sources of calcium; methionine; beta-carotene; alpha-carotene; lycopene; meal frequency; energy intake | |
| **Substantial effect on risk unlikely** | None identified | |

1 Physical activity of all types: occupational, household, transport, and recreational.
2 Much of the evidence reviewed grouped colon cancer and rectal cancer together as 'colorectal' cancer. *The Panel judges* that the evidence is stronger for colon than for rectum.
3 The term 'red meat' refers to beef, pork, lamb, and goat from domesticated animals.
4 Although red and processed meats contain iron, the general category of 'foods containing iron' comprises many other foods, including those of plant origin.
5 The term 'processed meat' refers to meats preserved by smoking, curing, or salting, or addition of chemical preservatives.
6 The judgements for men and women are different because there are fewer data for women. Increased risk is only apparent above a threshold of 30 g/day of ethanol for both sexes.
7 Adult attained height is unlikely directly to modify the risk of cancer. It is a marker for genetic, environmental, hormonal, and also nutritional factors affecting growth during the period from preconception to completion of linear growth (see chapter 6.2.1.3).
8 Includes both foods naturally containing the constituent and foods which have the constituent added (see chapter 3.5.3). Dietary fibre is contained in plant foods (see box 4.1.2 and chapter 4.2).
9 Judgements on vegetables and fruits do not include those preserved by salting and/or pickling.
10 Although both milk and cheese are included in the general category of dairy products, their different nutritional composition and consumption patterns may result in different findings.
11 Milk from cows. Most data are from high-income populations, where calcium can be taken to be a marker for milk/dairy consumption. *The Panel judges* that a higher intake of dietary calcium is one way in which milk could have a protective effect.
12 The evidence is derived from studies using supplements at a dose of 1200 mg/day.
13 Found mostly in fortified foods and animal foods.
14 The evidence is derived from studies using supplements at a dose of 200 µg/day. Selenium is toxic at high doses.
15 'Sugars' here means all 'non-milk extrinsic' sugars, including refined and other added sugars, honey, and as contained in fruit juices and syrups. It does not include sugars naturally present in whole foods such as fruits. It also does not include lactose as contained in animal or human milks.

For an explanation of all the terms used in the matrix, please see chapter 3.5.1, the text of this section, and the glossary.

## APPENDIX II WCRF/AICR 2011 judgement on CRC prevention and causation

### FOOD, NUTRITION, PHYSICAL ACTIVITY AND CANCERS OF THE COLON AND THE RECTUM 2011

| | DECREASES RISK | INCREASES RISK |
|---|---|---|
| **Convincing** | **Physical activity[1,2]**<br>**Foods containing dietary fibre[3]** | **Red meat[4,5]**<br>**Processed meat[4,6]**<br>**Alcoholic drinks (men)[7]**<br>**Body fatness**<br>**Abdominal fatness**<br>**Adult attained height[8]** |
| **Probable** | Garlic<br>Milk[9]<br>Calcium[10] | **Alcoholic drinks (women)[7]** |
| **Limited - suggestive** | Non-starchy vegetables<br>Fruits<br>Foods containing vitamin D[3,12] | Foods containing iron[3,4]<br>Cheese[11]<br>Foods containing animal fats[3]<br>Foods containing sugars13 |
| **Limited - no conclusion** | Fish; glycaemic index; folate; vitamin C; vitamin E; selenium; low fat; dietary pattern | |
| **Substantial effect on risk unlikely** | None identified | |

1 Physical activity of all types: occupational, household, transport and recreational.
2 The Panel judges that the evidence for colon cancer is convincing. No conclusion was drawn for rectal cancer.
3 Includes both foods naturally containing the constituent and foods which have the constituent added. Dietary fibre is contained in plant foods.
4 Although red and processed meats contain iron, the general category of 'foods containing iron' comprises many other foods, including those of plant origin.
5 The term 'red meat' refers to beef, pork, lamb, and goat from domesticated animals.
6 The term 'processed meat' refers to meats preserved by smoking, curing, or salting, or addition of chemical preservatives.
7 The judgements for men and women are different because there are fewer data for women. For colorectal and colon cancers the effect appears stronger in men than in women.
8 Adult attained height is unlikely directly to modify the risk of cancer. It is a marker for genetic, environmental, hormonal, and also nutritional factors affecting growth during the period from preconception to completion of linear growth (see chapter 6.2.13 – Second Expert Report).
9 Milk from cows. Most data are from high-income populations, where calcium can be taken to be a marker for milk/dairy consumption. The Panel judges that a higher intake of dietary calcium is one way in which milk could have a protective effect.
10 The evidence is derived from studies using supplements at a dose of 1200mg/day.
11 Although both milk and cheese are included in the general category of dairy products, their different nutritional composition and consumption patterns may result in different findings.
12 Found mostly in fortified foods and animal foods.
13 'Sugars' here means all 'non-milk extrinsic' sugars. Including refined and other added sugars, honey, and as contained in fruit juices and syrups. It does not include sugars naturally present in whole foods such as fruits. It also does not include lactose as contained in animal or human milks.

# APPENDIX III WCRF/AICR 2017 judgement on CRC prevention and causation

| 2017 | DIET, NUTRITION, PHYSICAL ACTIVITY AND COLORECTAL CANCER 2017 | | |
|---|---|---|---|
| | | DECREASES RISK | INCREASES RISK |
| STRONG EVIDENCE | Convincing | Physical activity[1,2] | Processed meat[3]<br>Alcoholic drinks[4]<br>Body fatness[5]<br>Adult attained height[6] |
| | Probable | Wholegrains<br>Foods containing dietary fibre[7]<br>Dairy products[8]<br>Calcium supplements[9] | Red meat[10] |
| LIMITED EVIDENCE | Limited – suggestive | Foods containing vitamin C[11]<br>Fish<br>Vitamin D[12]<br>Multivitamin supplements[13] | Low intakes of non-starchy vegetables[14]<br>Low intakes of fruits[14]<br>Foods containing haem iron[15] |
| | Limited – no conclusion | Cereals (grains) and their products; potatoes; animal fat; poultry; shellfish and other seafood; fatty acid composition; cholesterol; dietary n-3 fatty acid from fish; legumes; garlic; non-dairy sources of calcium; foods containing added sugars; sugar (sucrose); coffee; tea; caffeine; carbohydrate; total fat; starch; glycaemic load; glycaemic index; folate; vitamin A; vitamin B6; vitamin E; selenium; low fat; methionine; beta-carotene; alpha-carotene; lycopene; retinol; energy intake; meal frequency; dietary pattern | |
| STRONG EVIDENCE | Substantial effect on risk unlikely | | |

1 Physical activity of all types: occupational, household, transport and recreational.
2 The Panel judges that the evidence for colon cancer is convincing. No conclusion was drawn for rectal cancer.
3 The term 'processed meat' refers to meats preserved by smoking, curing, or salting, or addition of chemical preservatives.
4 Based on evidence for alcohol intakes above approximately 30 grams per day (about two drinks a day).
5 Body fatness marked by body mass index (BMI), waist circumference or waist-hip ratio.
6 Adult attained height is unlikely to directly influence the risk of cancer. It is a marker for genetic, environmental, hormonal and nutritional growth factors affecting growth during the period from preconception to completion of linear growth.
7 Includes both foods naturally containing the constituent and foods that have the constituent added. Dietary fibre is contained in plant foods.
8 Includes evidence from total dairy, milk, cheese and dietary calcium intakes.
9 The evidence is derived from supplements at a dose of 200 – 1,000 mg per day.
10 The term 'red meat' refers to beef, pork, lamb, and goat from domesticated animals.
11 The Panel judges that the evidence for colon cancer is limited. No conclusion was drawn for rectal cancer.
12 Includes evidence from foods containing vitamin D, serum vitamin D, and supplemental vitamin D.
13 Definitions and categorisation of multivitamin supplements are not standardised.
14 Increased risk observed at low intakes (below 100 grams per day).
15 Foods include red and processed meat, fish and poultry.

## APPENDIX IV WCRF/AICR cancer prevention sub-recommendations

| Recommendation | Sub-recommendations (personal recommendations) |
|---|---|
| 1) Be as lean as possible without becoming underweight | 1.1) Ensure that body weight through childhood and adolescent growth projects3 towards the lower end of the normal BMI range at age 21<br>1.2) Maintain body weight within the normal range from age 21<br>1.3) Avoid weight gain and increases in waist circumference throughout adulthood |
| 2) Be physically active for at least 30 minutes every day | 2.1) Be moderately physically active, equivalent to brisk walking, for at least 30 minutes every day<br>2.2) As fitness improves, aim for 60 minutes or more of moderate, or for 30 minutes or more of vigorous, physical activity every day<br>2.3) Limit sedentary habits such as watching television |
| 3) Limit consumption of energy-dense foods | 3.1) Consume energy-dense foods sparingly<br>3.2) Avoid sugary drinks<br>3.3) Consume 'fast foods' sparingly, if at all |
| 4) Eat more of a variety of vegetables, fruits, wholegrains, & pulses such as beans | 4.1) Eat at least five portions/servings (at least 400 g or 14 oz) of a variety of non-starchy vegetables and of fruits every day<br>4.2) Eat relatively unprocessed cereals (grains) and/or pulses (legumes) with every meal<br>4.3) Limit refined starchy foods<br>4.4) People who consume starchy roots or tubers as staples also to ensure intake of sufficient non-starchy vegetables, fruits, and pulses (legumes) |
| 5) Limit consumption of red meats (such as beef, pork and lamb) and avoid processed meats | 5.1) People who eat red meat to consume less than 500 g (18 oz) a week, very little if any to be processed |
| 6) If alcoholic drinks are consumed, limit consumption to no more than two drinks a day for men and one drink a day for women | 6.1) If alcoholic drinks are consumed, limit consumption to no more than two drinks a day for men and one drink a day for women |

| Recommendation | Sub-recommendations (personal recommendations) |
|---|---|
| 7) Limit consumption of salt & avoid mouldy grains and cereals | 7.1) Avoid salt-preserved, salted, or salty foods; preserve foods without using salt<br>7.2) Limit consumption of processed foods with added salt to ensure an intake of less than 6g (2.4g sodium) a day<br>7.3) Do not eat mouldy cereals (grains) or pulses (legumes). |
| 8) Aim to meet nutritional needs through diet alone | 8.1) Dietary supplements are not recommended for cancer prevention |
| 9) It is best for mothers to breastfeed exclusively for up to 6 months and then add other liquids & foods | 9.1) Breastfeeding protects both mother and child<br>9.2) 'Exclusively' means human milk only, with no other food or drink, including water<br>9.3) In accordance with the UN Global Strategy on Infant and Young Child Feeding |
| 10) After treatment, cancer survivors should follow the recommendations for cancer prevention | 10.1) Cancer survivors are people who are living with a diagnosis of cancer, including those who have recovered from the disease<br>10.2) This recommendation does not apply to those who are undergoing active treatment, subject to the qualifications in the text<br>10.3) This includes all cancer survivors, before, during, and after active treatment |

(Source: Romageura et al., 2016.

www.wcrf.org/sites/default/files/Session-Presentation-WCC-romaguera.pptx)

FOOD INTAKE:

Listed below are food items divided into sections according to food type. Please put a tick (✓) in the box to indicate how often, on average, you have eaten the specified amount of each food during the last 12 months.

Example: White bread, so if you eat 4 or 5 slices a day, you should put a tick in the column headed "4-5 day".

| FOODS AND AMOUNTS | HOW OFTEN HAVE YOU EATEN THESE FOODS IN THE LAST 12 MONTHS? | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | NEVER | Less than once a month | 1-3 per month | once a week | 2-4 per week | 5-6 per week | once per day | 2-3 per day | 4-5 per day | 6+ per day |
| BREAD | | | | | | | | | | |
| White slices or rolls | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8✓ | 9 |

Example: For seasonal fruit such as strawberries, if you eat strawberries about once a week when in season you should put a tick in the column headed "once a week".

| FOODS AND AMOUNTS | HOW OFTEN HAVE YOU EATEN THESE FOODS WHEN IN SEASON? | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | NEVER | Less than once a month | 1-3 per month | once a week | 2-4 per week | 5-6 per week | once per day | 2-3 per day | 4-5 per day | 6+ per day |
| FRUIT | | | | | | | | | | |
| Strawberries | 0 | 1 | 2 | 3✓ | 4 | 5 | 6 | 7 | 8 | 9 |

If you make a mistake and put a tick in the wrong box just cross through the tick as shown below, and put another tick in the correct box.

Example: If you eat apples twice a week, but ticked the "2-3 times daily" box instead, just cross this through as shown, and tick in the "2-4 per week" box instead.

| FOODS AND AMOUNTS | HOW OFTEN HAVE YOU EATEN THESE FOODS IN THE LAST 12 MONTHS? | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | NEVER | Less than once a month | 1-3 per month | once a week | 2-4 per week | 5-6 per week | once per day | 2-3 per day | 4-5 per day | 6+ per day |
| FRUIT | | | | | | | | | | |
| Apples | 0 | 1 | 2 | 3 | 4✓ | 5 | 6 | 7✓ | 8 | 9 |

CONFIDENTIAL

UNIVERSITY OF LEEDS

# The UK Women's Nutrition & Lifestyle Survey

This questionnaire is mostly about your usual food intake over the last year. It is designed for both vegetarians and non-vegetarians, so some questions may not seem relevant to you. There are also some questions about other topics such as smoking and exercise.

Please answer every question. If you are uncertain about how to answer a question then do the best you can, but please do not leave a question blank. Don't be put off once you've started! It may be quite lengthy but it is straightforward and quick to work your way through.

We want to find out about the relationship of nutrition with the occurrence of certain diseases. Please complete this questionnaire and return it in the pre-paid envelope as soon as possible. Your answers will be treated as strictly confidential and will be used only for medical research.

Please estimate how often you eat the following foods, and please answer every question.

## PLEASE PUT A TICK(✓) ON EVERY LINE

| FOODS AND AMOUNTS | HOW OFTEN HAVE YOU EATEN THESE FOODS IN THE LAST 12 MONTHS? | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | NEVER | Less than once a month | 1-3 per month | once a week | 2-4 per week | 5-6 per week | once per day | 2-3 per day | 4-5 per day | 6+ per day |
| **BREAD/SAVOURY BISCUITS** | | | | | | | | | | |
| White bread & rolls | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Brown bread & rolls | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Wholemeal bread & rolls | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Chapatis, Nan, Paratha | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Papadums | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Tortillas | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Pitta Bread | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Crispbread e.g. Ryvita | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Cream crackers, cheese biscuits | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| **BREAKFAST CEREALS** | | | | | | | | | | |
| Porridge, Ready-brek | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Sugar coated cereals e.g. Sugar Puffs | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Non-sugar coated cereals e.g. Cornflakes, Rice Krispies | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Muesli | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| All Bran, Bran Flakes | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Weetabix, Shredded Wheat | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| **POTATOES, RICE & PASTA** | | | | | | | | | | |
| Potatoes e.g. boiled, mashed | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Chips | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Jacket Potato | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Roast Potatoes | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Potato Salad | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| White Pasta e.g. Spaghetti, Green Pasta, Red Pasta, Noodles | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Wholemeal Pasta, Brown Spaghetti | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| White Rice | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Brown Rice | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Wild Rice | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Macaroni Cheese | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |



Please estimate how often you eat the following foods, and please answer every question.

PLEASE PUT A TICK(✓) ON EVERY LINE

| FOODS AND AMOUNTS | HOW OFTEN HAVE YOU EATEN THESE FOODS IN THE LAST 12 MONTHS? | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | NEVER | Less than once a month | 1-3 per month | once a week | 2-4 per week | 5-6 per week | once per day | 2-3 per day | 4-5 per day | 6+ per day |
| **DAIRY & NON-DAIRY PRODUCTS** | | | | | | | | | | |
| Thick & Creamy Yoghurt (125g carton) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Low fat Yoghurt (125g carton) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Diet Yoghurt (125g carton) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Greek Yoghurt (125g carton) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Fromage Frais/Creme Fraiche (125g carton) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Dairy Desserts (125g carton) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Single/Sour Cream (tablespoon) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Double/Clotted Cream (tablespoon) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Icecream | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Milk Puddings | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Low-fat Cheese | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Cheese e.g. Cheddar, Brie, Edam | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Cottage Cheese | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Cheese and Onion Pastie | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Soya Cheese | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Soya Yoghurt | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| **MARGARINES/BUTTERS & SPREADS** | | | | | | | | | | |
| Butter (enough for 1 slice of bread) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Block Margarine e.g. Stork, Krona, NOT in tub (enough for 1 slice of bread) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Polyunsaturated Margarine e.g. Flora, Sunflower, Granose, in tub (enough for 1 slice of bread) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Other soft Margarine, Dairy spreads e.g. Blue Band, Clover, in tub (enough for 1 slice of bread) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Low fat spread e.g. Outline, Gold, Flora Lite, in tub (enough for 1 slice of bread) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Very low fat spread, in tub e.g. St Ivel Lowest Fat Spread (enough for 1 slice of bread) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Monounsaturated Margarine eg. Mono, Olivio (enough for 1 slice of bread) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |

Please estimate how often you eat the following foods, and please answer every question

## PLEASE PUT A TICK(✓) ON EVERY LINE

| FOODS AND AMOUNTS | HOW OFTEN HAVE YOU EATEN THESE FOODS IN THE LAST 12 MONTHS? | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | NEVER | Less than once a month | 1-3 per month | once a week | 2-4 per week | 5-6 per week | once per day | 2-3 per day | 4-5 per day | 6+ per day |
| **SPREADS** | | | | | | | | | | |
| Marmite/Bovril/Vegemite | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Peanut Butter | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Chocolate/Chocolate & Nut Spread | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Jam/Marmalade | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Honey | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Vegetable paté | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Nut Paté | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| **SAUCES & SOUPS** | | | | | | | | | | |
| Low Calorie Salad Cream (tablespoon) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Mayonnaise, Salad Cream Type Dressing (tablespoon) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| French Type Dressing (tablespoon) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Sauces e.g. white/cheese/Cook In/curry | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Tomato Ketchup (tablespoon) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Pickles/Chutney/Pesto sauce | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Packet Soups - Meat & Veg (Bowl) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Other - Vegetable Soups (Bowl) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Other - Meat Soups (Bowl) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Low Calorie Soups (Bowl) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| **GRAINS (Medium serving)** | | | | | | | | | | |
| Barley | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Oats | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Bulgar Wheat | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Wheat Germ (tablespoon) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Cous-cous | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| White Rice | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Brown Rice | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| **NUTS & SEEDS** | | | | | | | | | | |
| Peanuts/Pistachio Nuts | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Cashew Nuts & Almonds | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Pecan Nuts/Walnuts | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Sunflower Seeds/ Sesame Seeds | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |



Please estimate how often you eat the following foods, and please answer every question

PLEASE PUT A TICK(✓) ON EVERY LINE

| FOODS AND AMOUNTS | HOW OFTEN HAVE YOU EATEN THESE FOODS IN THE LAST 12 MONTHS? | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | NEVER | Less than once a month | 1-3 per month | once a week | 2-4 per week | 5-6 per week | once per day | 2-3 per day | 4-5 per day | 6+ per day |
| **PULSES (include when used in recipes)** | | | | | | | | | | |
| Lentils, dals | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Chick Peas, Chanas | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Hummus | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Baked beans | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Mung Beans & Red Kidney Beans | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Bean Sprouts | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Black Eyed Beans | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Butter Beans/Broad Beans | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| **EGGS/EGG DISHES** | | | | | | | | | | |
| Boiled/ Poached egg | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Omelette, Scrambled egg | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Fried egg | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Quiche | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| **VEGETABLE DISHES** | | | | | | | | | | |
| Quorn | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Textured vegetable protein/ Sosmix/burger mix/soya sausages | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Vegetarian Chilli/Vegetable Curry | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Mixed Bean Casserole/Ratatouille | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Stir-fry vegetables | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Vegetable - Lasagne/Moussaka/Ravioli/ filled pasta with sauce | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Vegetable Pizza | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| **MEAT** | | | | | | | | | | |
| Beef e.g. roast, steak | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Beef Stew/Casserole/Mince/Curry | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Beefburger/Hamburger | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Pork e.g. Roast, Chops, Slices | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Pork Stew/Casserole | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Lamb e.g. Roast, Chops | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Lamb Stew/Casserole | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |

Please estimate how often you eat the following foods, and please answer every question.

## PLEASE PUT A TICK(✓) ON EVERY LINE

| FOODS AND AMOUNTS | HOW OFTEN HAVE YOU EATEN THESE FOODS IN THE LAST 12 MONTHS? | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | NEVER | Less than once a month | 1-3 per month | once a week | 2-4 per week | 5-6 per week | once per day | 2-3 per day | 4-5 per day | 6+ per day |
| **OTHER MEATS** | | | | | | | | | | |
| **Chicken/Turkey** roast, slices | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Breadcrumbed e.g.chicken nuggets/kievs | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Chicken/Turkey in creamy sauce, curry | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| **Bacon** | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| **Ham** | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Corned Beef, Spam, Luncheon Meats | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Sausages e.g. Beef Pork | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Pies/Pasties/Sausage Rolls | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| **Offal** e.g. Liver, Kidney | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Liver Pâté/Sausage, Salami | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Meat - Lasagne/Moussaka/Ravioli/ filled pasta with sauce | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Meat Pizza | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| **FISH** | | | | | | | | | | |
| Fish fingers/cakes | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Fried fish in batter (as in fish and chips) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| White fish e.g. Cod, Haddock, Plaice, Sole, Halibut (fresh or frozen) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Oily fish e.g. Mackerel, Kippers, Tuna, Salmon, Sardines, Herring | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Shellfish e.g. Crab, Prawns, Mussels | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Fish Roe, Taramasalata | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Fish Pie/Fish Lasagne | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| **VEGETABLES** | | | | | | | | | | |
| Beetroot | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Broccoli, Spring Greens, Kale | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Brussel Sprouts | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Cabbage | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Carrots | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Cauliflower | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Celery | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |



Please estimate how often you eat the following foods, and please answer every question.

PLEASE PUT A TICK(✓) ON EVERY LINE

| FOODS AND AMOUNTS | HOW OFTEN HAVE YOU EATEN THESE FOODS IN THE LAST 12 MONTHS? | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | NEVER | Less than once a month | 1-3 per month | once a week | 2-4 per week | 5-6 per week | once per day | 2-3 per day | 4-5 per day | 6+ per day |
| **VEGETABLES (continued)** | | | | | | | | | | |
| Coleslaw | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Low-calorie Coleslaw | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Courgettes, Marrow, Squash | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Cucumber | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Garlic | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Green Beans, Runner Beans | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Leeks | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Lettuce | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Mushrooms | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Aubergine, Okra/Ladies Finger | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Olives | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Parsnips | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Peas, Mushy peas, Mange-tout | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Peppers - Red, Green, Yellow, Black etc. | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Swedes | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Sweetcorn | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Tomatoes - raw/canned/sauce | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Turnip | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Watercress, Mustard & Cress | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| **FRUIT** | | | | | | | | | | |
| Apples | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Avocado | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Bananas | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Grapes | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Kiwi Fruit | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Mangoes | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Oranges, Satsumas, Grapefruit, etc | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Papaya | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Pears | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Pineapple | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |

Please estimate how often you eat the following foods, and please answer every question.

PLEASE PUT A TICK(✓) ON EVERY LINE

| FOODS AND AMOUNTS | HOW OFTEN HAVE YOU EATEN THESE FOODS IN THE LAST 12 MONTHS? | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | NEVER | Less than once a month | 1-3 per month | once a week | 2-4 per week | 5-6 per week | once per day | 2-3 per day | 4-5 per day | 6+ per day |
| **SEASONAL FRUIT** How often have you eaten these fruits, when they are in season? | | | | | | | | | | |
| Apricots | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Melon | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Nectarines | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Peaches | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Plums | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Raspberries | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Red currants/Black currants | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Rhubarb | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Strawberries | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| **DRIED FRUIT** | | | | | | | | | | |
| Dates | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Figs | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Prunes | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Mixed Dried Fruit e.g. Apricots, Apples, Pears, Mangoes | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Currants, Raisins, Sultanas | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| **SWEET SNACKS** | | | | | | | | | | |
| Cereal Bars/Flapjacks (one) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Fruit bars (one) eg Apricot, Date | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Chocolate Snack Bars e.g. Mars, Crunchie (1 bar) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Mini chocolate snack bars, Chocolates - singles or squares (1) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Boiled Sweets, Toffees, Mints | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| **SAVOURY SNACKS** | | | | | | | | | | |
| Crisps (1 bag) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Other fried snacks e.g. Wotsits (1 bag) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Low fat or baked snacks e.g. Low-fat Crisps (1 bag) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Bombay Mix (small handful) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Peanuts/Pistachio Nuts (small handful) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Mixed Nuts and Raisins (small handful) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |



Please estimate how often you eat the following foods, and please answer every question.

PLEASE PUT A TICK(✓) ON EVERY LINE

| FOODS AND AMOUNTS | HOW OFTEN HAVE YOU EATEN THESE FOODS IN THE LAST 12 MONTHS? | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | NEVER | Less than once a month | 1-3 per month | once a week | 2-4 per week | 5-6 per week | once per day | 2-3 per day | 4-5 per day | 6+ per day |
| **BEVERAGES** | | | | | | | | | | |
| Tea (cup) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Herbal Tea (cup) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Coffee - instant/ground (cup) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Coffee - decaffeinated (cup) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Coffee substitute e.g Caro/Bambu (cup) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Coffee whitener (teaspoon) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Cocoa, Hot Chocolate (cup) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Horlicks, Ovaltine (cup) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Low Calorie/Low-fat Horlicks, Ovaltine, Hot Chocolate, (cup) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Orange Juice (Pure Fruit) (glass) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Other (100%) Pure fruit juices (glass) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Fruit Squash/Cordial - diluted (glass) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Fizzy soft drinks e.g. Coke, Lemonade (glass/can) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Low Calorie/Diet Soft Drinks (glass/can) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| **ALCOHOLIC BEVERAGES** | | | | | | | | | | |
| Wines (wineglassful) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Beer, Lager (half pint) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Cider (half pint) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Port, Sherry, Liqueurs (glass) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Spirits e.g. Whisky, Gin, Vodka, Brandy (single/1 measure) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| **BISCUITS, SWEETS & PUDDINGS** | | | | | | | | | | |
| Plain Biscuits e.g. Marie, Nice, Digestive (one) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Chocolate Biscuits (one) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Sandwich/Cream Biscuits (one) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Fruitcake (1 slice) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Sponge cakes (1 slice) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Buns/Pastries e.g. Croissants, Doughnuts, Tray Bakes, (one) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Scones/Pancakes/Muffins/Crumpets (1) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Fruit Pies, Tarts, Crumbles, (1 slice) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| Sponge Puddings (1 serving) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |

1: **Other Foods**

Are there any other foods which you eat more than once a week? Yes [ ] 1 No [ ] 2

If yes, please list below

| Food | Usual serving size | Number of times eaten each week |
|---|---|---|
| | | |
| | | |
| | | |

2: Would you describe yourself as a vegetarian? Yes [ ] 1 No [ ] 2

If yes, how long have you been vegetarian? [ ][ ] years.

Would you describe yourself as a vegan? Yes [ ] 1 No [ ] 2

If yes, how long have you been vegan? [ ][ ] years.

3: Do you use herbs and spices at least once per week when cooking food? Yes [ ] 1 No [ ] 2

Which fresh herbs and spices would you use at least once a week? Please list here

Which dried herbs and spices would you use at least once a week? Please list here

PORTION SIZE:

4: Compared to other people would you describe your typical average portion size of foods as?

Small? [ ] 1 Medium? [ ] 2 Large? [ ] 3

PULSES:

5: Do you eat pulses e.g. beans, peas, lentils etc. Yes [ ] 1 No [ ] 2

**If no,** please go to question 7.

6: Can you please indicate how much of the Pulses you eat are Fresh, Frozen, Canned or Dried. Please tick the appropriate boxes, e.g. 1/4 Dried, 3/4 Frozen.

| | Proportion | | | | |
|---|---|---|---|---|---|
| | Never | 1/4 | 1/2 | 3/4 | All |
| Fresh | 1 | 2 | 3 | 4 | 5 |
| Frozen | 1 | 2 | 3 | 4 | 5 |
| Dried | 1 | 2 | 3 | 4 | 5 |
| Canned | 1 | 2 | 3 | 4 | 5 |

How do you usually cook pulses? Tick all applicable.

| | | | |
|---|---|---|---|
| Steaming/Boiling/Pressure Cooking | [ ] 1 | Stewing/Casseroling/Baking | [ ] 4 |
| Microwaving | [ ] 2 | Stir Frying/Frying | [ ] 5 |
| Roasting | [ ] 3 | Raw/soaked/Raw-sprouted | [ ] 6 |



VEGETABLES:

7: How many servings of vegetables or vegetable containing dishes, (excluding potatoes) do you usually eat each week? [ ][ ]

8: Can you please indicate how much of the vegetables you eat are Fresh, Frozen, Canned or Dried. Please tick the appropriate boxes, e.g. 1/4 Dried, 3/4 Frozen.

| | Proportion | | | | |
|---|---|---|---|---|---|
| | Never | 1/4 | 1/2 | 3/4 | All |
| Fresh | 1 | 2 | 3 | 4 | 5 |
| Frozen | 1 | 2 | 3 | 4 | 5 |
| Dried | 1 | 2 | 3 | 4 | 5 |
| Canned | 1 | 2 | 3 | 4 | 5 |

9: Do you ever eat raw vegetables apart from salad vegetables? Yes [ ] 1 No [ ] 2

10: How do you usually cook your vegetables.? (Excluding potatoes). Tick more than one box if necessary.

| | |
|---|---|
| Boiling | [ ] |
| Steaming | [ ] |
| Grilling/Barbecuing/Baking/Roasting (Cooked dry or using a small amount of oil) | [ ] |
| Stir Frying/Frying/Sauté | [ ] |
| Microwaving | [ ] |
| Deep frying - including in batter | [ ] |
| Casseroling/Baking in sauce | [ ] |
| Other | [ ] |

Please describe

FRUIT:

11: How many servings of fruit or fruit containing dishes do you usually eat each week? [ ][ ]

Can you please indicate how much of the fruit you eat is Fresh, Canned, Dried or Stewed.

Please tick the appropriate boxes e.g. 1/4 Fresh, 3/4 Canned

| | Proportion | | | | |
|---|---|---|---|---|---|
| | Never | 1/4 | 1/2 | 3/4 | All |
| Fresh | 1 | 2 | 3 | 4 | 5 |
| Stewed | 1 | 2 | 3 | 4 | 5 |
| Dried | 1 | 2 | 3 | 4 | 5 |
| Canned | 1 | 2 | 3 | 4 | 5 |

12: Do you ever cook the fruit you eat? Yes [ ] 1 No [ ] 2

13: If so, how do you usually cook your fruit?

| | | | |
|---|---|---|---|
| Stewing | [ ] 1 | Poaching/Steaming | [ ] 2 |
| Baking | [ ] 3 | Microwaving | [ ] 4 |
| Other | [ ] 5 | | |

Please describe

MEAT: (If you **never** eat meat please go to question 16)

14: How many servings of meat or meat containing dishes do you usually eat each week? ☐☐

What do you do with the visible fat on your meat?
- Eat all/most of the fat ☐ 1
- Eat some of the fat ☐ 2
- Eat as little as possible/none ☐ 3

15: How do you usually cook meat? Tick more than one box if necessary.
- Grilling/Barbecuing/Baking/Roasting (Cooked dry or using a small amount of oil) ☐ 1
- Stir Frying/Frying ☐ 2
- Microwaving ☐ 3
- Deep frying - including in batter ☐ 4
- Casseroling/Baking in sauce ☐ 5
- Other ☐ 6

Please describe

16: How many servings of fish or fish containing dishes do you usually eat each week? ☐☐

How do you usually cook fish. Tick more than one box if necessary.
- Boiling ☐ 1
- Steaming ☐ 2
- Grilling/Barbecuing/Baking/Roasting (Cooked dry or using a small amount of oil) ☐ 3
- Stir Frying/Frying ☐ 4
- Microwaving ☐ 5
- Deep frying - including in batter ☐ 6
- Casseroling/Baking in sauce ☐ 7
- Other ☐ 8

Please describe

MILK:

17. What type of milk do you use most often? Select one only

| | | | |
|---|---|---|---|
| Full cream (Silver Top) | ☐ 1 | Semi-skimmed (Red/White Top) | ☐ 2 |
| Skimmed/fat free | ☐ 3 | Channel Islands (Gold Top) | ☐ 4 |
| Dried Milk | ☐ 5 | Soya | ☐ 6 |
| Sterilised | ☐ 7 | None | ☐ 8 |

Other ☐ 9 Specify

If you used soya milk, please describe brand and type

18: How much milk do you drink each day, including milk with tea, coffee, milky drinks, cereals etc?

| | | | |
|---|---|---|---|
| None | ☐ 1 | ¼ Pint | ☐ 2 |
| ½ Pint | ☐ 3 | ¾ Pint | ☐ 4 |
| 1 Pint | ☐ 5 | More than 1 Pint | ☐ 6 |



BREAKFAST:

19: Are there any breakfast cereals that you normally eat that were not mentioned earlier? Yes ☐ 1 No ☐ 2

If yes, which brand and type of breakfast cereal, do you usually eat?

List the types most often used

| Brand | Type |
|---|---|
| | |
| | |
| | |

20: Do you usually take sugar on your breakfast cereal? Yes ☐ 1 No ☐ 2

If yes, how many teaspoons? ☐☐ teaspoons

21: Do you usually take sugar/honey in tea, herbal tea, coffee or coffee substitute? Yes ☐ 1 No ☐ 2

If Yes, please write the number of teaspoons per cup.

- Sugar/honey in tea ☐☐ teaspoons
- Sugar/honey in herbal tea ☐☐ teaspoons
- Sugar/honey in coffee ☐☐ teaspoons
- Sugar/honey in coffee substitute ☐☐ teaspoons

Do you use sweeteners instead of sugar or honey, Yes ☐ 1 No ☐ 2

Which brand of sweetener do you use, please specify

If yes how many tablets per day, or how many teaspoons of powder per day? ☐☐

22: On days when you eat bread, how many slices of bread or rolls do you eat ? ☐☐ slices/rolls per day

USE OF FATS:

23: Do you usually spread butter/margarine on your bread?

Yes ☐ 1 No ☐ 2 Sometimes ☐ 3

How many slices of bread/rolls/crackers do you have with spread each day? ☐☐

How much spread do you use?
- Just a scrape/thinly spread ☐ 1
- medium ☐ 2
- Thickly spread ☐ 3

24: What kind of fat do you most often use for frying, roasting, grilling etc?

Tick more than one if applicable
- Butter ☐ 1
- Lard/Dripping ☐ 2
- Vegetable Oil ☐ 3
- Solid White Vegetable Fat ☐ 4
- Margarine ☐ 5
- None ☐ 6

If you used vegetable oil, or margarine, please give type e.g. corn, sunflower

25: What kind of fat do you most often use for baking cakes etc.? Tick more than one if applicable

Butter ☐ 1 — Solid White Vegetable Fat ☐ 2

Lard/Dripping ☐ 3 — Margarine ☐ 4

Vegetable Oil ☐ 5 — None ☐ 6

If you use margarine, please give Brand e.g. Flora, Stork

USE OF SALT:

26: How often do you add salt to food while cooking?

Always ☐ 1 — Usually ☐ 2

Sometimes ☐ 3 — Rarely ☐ 4

Never ☐ 5

27: How often do you add salt to any food at the table?

Always ☐ 1 — Usually ☐ 2

Sometimes ☐ 3 — Rarely ☐ 4

Never ☐ 5

28: Do you regularly use a salt substitute (e.g. Lo-salt)? Yes ☐ 1 No ☐ 2

If yes, which brand?

USE OF SUPPLEMENTS:

29: Do you take any vitamins, minerals, fish oils, fibre or other food supplements? Yes ☐ 1 No ☐ 2

If yes, please fill in details below.

| Name and Brand of Supplements | How much do you take at a time | How often do you take these? | | | |
|---|---|---|---|---|---|
| | | Daily | Weekly | Monthly | Less often |
| | | 1 | 2 | 3 | 4 |
| | | 1 | 2 | 3 | 4 |
| | | 1 | 2 | 3 | 4 |

SPECIAL DIETS:

30: I) Have you changed your diet over the last 12 months? Yes ☐ 1 No ☐ 2

If yes, please indicate if the change was for any of the reasons listed below?

Tick more than one box if applicable

High Blood Pressure ☐ 8 — Stomach problems (e.g. ulcer or gastritis) ☐ 1

Bowel problems (e.g. irritable bowel or diverticulitis) ☐ 2 — Concern over eating a healthy Diet ☐ 3

Concern over a family history of illness ☐ 4 — High Blood Cholesterol/Lipids ☐ 5

Overweight/Obesity ☐ 6 — Diabetes ☐ 7

Allergies (e.g. skin rash) ☐ 9 — Other ☐ 9

Specify



II) Describe below how your diet has changed

Do you currently follow any of these diets? Tick more than one box if necessary.

Low fat ☐ 1 — Low salt ☐ 2 — Diabetic ☐ 3

Slimming ☐ 4 — Gluten free ☐ 5 — High fibre ☐ 6

Other ☐ 7 — Please give details

CONSUMPTION OF ALCOHOL:

31: How often, if ever do you drink alcohol?

More than once a week ☐ 1 — Once a week ☐ 2

Less than once a week ☐ 3 — Never drink alcohol ☐ 4

32: In a typical week, how much do you drink?

Beer or cider ☐☐ pints each week

Wine ☐☐ glasses each week

Sherry/Fortified Wines ☐☐ glasses each week

Spirits ☐☐ glasses (singles) each week

33: Five years ago, how many alcoholic drinks did you have each week?

Beer or cider ☐☐ pints each week

Wine ☐☐ glasses each week

Sherry/Fortified Wines ☐☐ glasses each week

Spirits ☐☐ glasses (singles) each week

SMOKING:

34: Which one of the following best describes you?

I smoke every day ☐ 1 — I smoke occasionally, but not every day ☐ 2

I used to smoke every day, but do not smoke at all now ☐ 3 — I have never smoked ☐ 4

If you have never smoked, please go to question 37.

35: Do/did you smoke?

Cigarettes ☐ 1

Cigars ☐ 2

A combination of the above ☐ 3

If you currently smoke or used to smoke cigarettes how many do/did you smoke each day?

☐☐ cigarettes

If you currently smoke or used to smoke cigarettes which brand of cigarettes do/did you usually smoke?

36: If you have stopped smoking for what period of time have you been a non-smoker?

1 year or less ☐ 1 2-5 years ☐ 2

6-10 years ☐ 3 Over 10 years ☐ 4

SIZE:

37: Approximately how much did you weigh when you were born?

☐☐ lbs or ☐☐ Kg or Don't Know ☐

38: Approximately how much did you weigh when you were 20 years old?

☐☐ stones ☐☐ pounds or ☐☐☐ Kg or Don't Know ☐

39: Approximately how much do you weigh at present?

☐☐ stones ☐☐ pounds or ☐☐☐ Kg or Don't Know ☐

40: Have you lost more than half a stone in the last year? Yes ☐ 1 No ☐ 2

Have you gained more than half a stone in the last year?
(Please ignore weight gained during pregnancy.) Yes ☐ 1 No ☐ 2

41: What is your present waist size? ☐☐ inches or ☐☐☐ centimetres or Don't Know ☐ 1

42: What is your present hip size? ☐☐ inches or ☐☐☐ centimetres or Don't Know ☐ 1

43: What is your present height? ☐ ft ☐☐ inches or ☐☐☐ centimetres or Don't Know ☐ 1

44: What size of blouse do you wear? Size ☐☐

45: What size of skirt do you wear? Size ☐☐

PHYSICAL ACTIVITY

46: In a typical week during the last 12 months, how many hours did you spend on each of the following activities? Put "0" if none

| | | | |
|---|---|---|---|
| Housework, such as cleaning, washing, cooking, child care | | ☐☐ hours | ☐☐ minutes per week |
| Do-It-Yourself | | ☐☐ hours | ☐☐ minutes per week |
| Gardening | In Summer | ☐☐ hours | ☐☐ minutes per week |
| | In Winter | ☐☐ hours | ☐☐ minutes per week |
| Walking, including to work, shopping & leisure | In Summer | ☐☐ hours | ☐☐ minutes per week |
| | In Winter | ☐☐ hours | ☐☐ minutes per week |
| Cycling, including to work & leisure | In Summer | ☐☐ hours | ☐☐ minutes per week |
| | In Winter | ☐☐ hours | ☐☐ minutes per week |
| Other physical exercise, such as keep-fit, aerobics, jogging, tennis, swimming | In Summer | ☐☐ hours | ☐☐ minutes per week |
| | In Winter | ☐☐ hours | ☐☐ minutes per week |



47: In a normal week, do you do any of these activities vigorously enough to cause sweating or a faster heartbeat? Yes ☐ 1 No ☐ 2

If yes, for how long each week do you do such vigorous physical activity? ☐☐ hours ☐☐ minutes per week

ILLNESS:

48: Have you ever been told by a doctor that you have, or had, any of the following conditions?
Please tick all which apply and give the age at which each condition was first diagnosed.

| | | | |
|---|---|---|---|
| Heart attack, coronary thrombosis, myocardial infarction | Yes ☐ 1 | No ☐ 2 | at age ☐☐ yrs old |
| Angina | Yes ☐ 1 | No ☐ 2 | at age ☐☐ yrs old |
| Stroke | Yes ☐ 1 | No ☐ 2 | at age ☐☐ yrs old |
| High Blood Pressure (Hypertension) | Yes ☐ 1 | No ☐ 2 | at age ☐☐ yrs old |
| High Blood Cholesterol, Hyperlipidaemia | Yes ☐ 1 | No ☐ 2 | at age ☐☐ yrs old |
| Diabetes | Yes ☐ 1 | No ☐ 2 | at age ☐☐ yrs old |
| Gallstones | Yes ☐ 1 | No ☐ 2 | at age ☐☐ yrs old |
| Polyps in the large intestine | Yes ☐ 1 | No ☐ 2 | at age ☐☐ yrs old |
| Cancer | Yes ☐ 1 | No ☐ 2 | at age ☐☐ yrs old |

If yes, what type of cancer? _____

Any other illnesses or operations?
Do not include hysterectomy or breast surgery. These are covered later in the questionnaire.

| Condition/ operation / disease | Age first diagnosed |
|---|---|
| | ☐☐ yrs old |
| | ☐☐ yrs old |
| | ☐☐ yrs old |
| | ☐☐ yrs old |

49: Are you currently receiving long-term treatment for any illness or condition? Yes ☐ 1 No ☐ 2

If yes, please give details of treatment. If no please go to question 50:

| Illness or condition | Treatment | Dose | Frequency |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| | | | |

50: Have your mother and/or father ever suffered from cancer or heart attack/heart disease?

Yes ☐ 1 No ☐ 2 Don't Know ☐ 3

If yes, please give details

51: If you have brothers and/or sisters, have they ever suffered from cancer or heart attack/heart disease?

Yes ☐ 1 No ☐ 2 Don't Know ☐ 3

If yes, please describe details

EDUCATION:

52: How old were you when you finished your full time education? ☐☐ yrs old

53: Do you have any of the following qualifications? Tick all applicable

| | | | |
|---|---|---|---|
| CSE | ☐ 1 | "A" Level, Highers | ☐ 4 |
| GCE "O" Level | ☐ 2 | Teaching diploma, HNC | ☐ 5 |
| City & Guilds | ☐ 3 | Degree | ☐ 6 |
| Other ☐ 7 describe | | None of these | ☐ 8 |

EMPLOYMENT:

54: Have you ever had a paid job? Yes ☐ 1 No ☐ 2

**If yes,** please answer for your current or most recent job

What is/was your job title?

What do/did you do in your job?

What does/did the organisation you work for make or do?

Are/were you a Manager? ☐ 1 Foreman/woman? ☐ 2

Supervisor? ☐ 3 None of these? ☐ 4

Are/were you self-employed? Yes ☐ 1 No ☐ 2



Do you have a paid job at present? Yes ☐ 1 No ☐ 2

If no, how would you describe yourself?

Housewife ☐ 1 Unemployed ☐ 2

Retired ☐ 3 Student ☐ 4

Other ☐ 5 describe

When did you last have paid employment 19☐☐ (year) or Never ☐ 1

55: What is your marital status?

Married or living as married ☐ 1 Divorced ☐ 2

Widowed ☐ 3 Single ☐ 4

Separated ☐ 5

If you are not married or living as married, please go to question 57.

PARTNER'S EMPLOYMENT:

56: If married or living as married, has your partner ever had a paid job? Yes ☐ 1 No ☐ 2

If yes, please answer for your partner's current or most recent job.

What is/was your partner's job title?

What does/did the organisation your partner works for make or do?

Is/was your partner a Manager? ☐ 1 Foreman/woman? ☐ 2

Supervisor? ☐ 3 None of these? ☐ 4

Is/was your partner self-employed? Yes ☐ 1 No ☐ 2

Does your partner have a paid job at present? Yes ☐ 1 No ☐ 2

If no, how would you describe your partner?

House-husband ☐ 1 Student ☐ 2

Unemployed ☐ 3 Retired ☐ 4

Other ☐ 5 describe

57: Which of these groups would you consider you belong to?

White ☐ 1 Bangladeshi ☐ 2

Indian ☐ 3 Chinese ☐ 4

Pakistani ☐ 5 Black - Caribbean ☐ 6

Black - other ☐ 7

Other ☐ 8

MENSTRUAL & OBSTETRIC HISTORY:

58: How old were you when you had your first menstrual period ☐☐ years old

59: What is the usual length of your menstrual cycle?

(i.e. from the first day of one period to the first day of the next period e.g. 26 days)? ☐☐ days.

60: Have you ever been pregnant? Yes ☐ 1 No ☐ 2

Are you pregnant at the moment? Yes ☐ 1 No ☐ 2

How many times have you been pregnant? ☐☐

Have you ever had a miscarriage/still birth? Yes ☐ 1 No ☐ 2

If you have had children, please go to question 61. If not please go to question 63.

61: Have you had any children? Yes ☐ 1 No ☐ 2

If yes, how old were you when your first child was born ☐☐ years

If yes, how many children have you had? ☐☐ children

If none please go to question 63.

Please can you write in each child's sex and approximate birthweight.

| Child | Sex of Child | Approximate Birthweight | Child's D.O.B |
|---|---|---|---|
| CHILD 1: | | | 19☐☐ |
| CHILD 2: | | | 19☐☐ |
| CHILD 3: | | | 19☐☐ |
| CHILD 4: | | | 19☐☐ |
| CHILD 5: | | | 19☐☐ |

62: Did you ever breast feed any of your children? Yes ☐ 1 No ☐ 2

If yes, for those children you breast-fed, please describe how long you continued breast feeding after each birth, (even only occasional breast feeding). Tick the appropriate box.

| | 1–6 days | 1–4 weeks | 1–3 months | 4–6 months | 6+ months | 12+ months |
|---|---|---|---|---|---|---|
| CHILD 1: | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 | ☐ 6 |
| CHILD 2: | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 | ☐ 6 |
| CHILD 3: | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 | ☐ 6 |
| CHILD 4: | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 | ☐ 6 |
| CHILD 5: | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 | ☐ 6 |

63: Have you ever seen a doctor because of fertility problems? Yes ☐ 1 No ☐ 2

If yes, has a doctor ever told you that you were infertile? Yes ☐ 1 No ☐ 2

64: Have you ever used oral contraceptives (the pill)? Yes ☐ 1 No ☐ 2

If yes, how old were you when you first started to use the pill? ☐☐ years old

For how long altogether did you use the pill? ☐☐ years

Are you currently using the pill? Yes ☐ 1 No ☐ 2

If no, how old were you when you last used it? ☐☐ years old



65: Have you ever used a coil or intra-uterine device (IUD)? Yes ☐ 1 No ☐ 2

If yes, do you have a coil or IUD at present? Yes ☐ 1 No ☐ 2

66: How many "natural" menstrual periods have you had in the last 12 months?

Do not count bleeding while using the pill or HRT (Hormone Replacement Therapy)

None ☐ 1

1 to 3 ☐ 2

4 to 5 ☐ 3

6 to 9 ☐ 4

10 or more ☐ 5

Not applicable because using the Pill or HRT or currently pregnant ☐ 6

67: When did you last have a "natural" menstrual period? Do not count bleeding while using the pill or HRT (Hormone Replacement Therapy). Record as fully as possible

Date: ☐☐/☐☐/19☐☐ or age ☐☐ years old Don't know ☐

68: Have you ever used HRT (Hormone Replacement Therapy) for menopause? Yes ☐ 1 No ☐ 2

If yes, how old were you when you first used HRT? ☐☐ years old

For how long altogether have you used HRT? years ☐☐ and months ☐☐

Are you currently using HRT? Yes ☐ 1 No ☐ 2

If no, how old were you when you last used HRT? ☐☐ years old

69: Have you had a hysterectomy ? If no please go to question 71.

Yes ☐ 1 Age at time of operation ☐☐ years old No ☐ 2 Don't know ☐ 3

70: Have you had an operation to remove one or both your ovaries?

Yes ☐ 1 No ☐ 2 Don't know ☐ 3

If yes, how old were you? ☐☐ years old

Were one or both ovaries removed? One ☐ 1 Both ☐ 2 Don't know ☐ 3

71: Have you ever had a breast biopsy (minor surgery to remove tissue from your breast for diagnostic purposes)? Yes ☐ 1 No ☐ 2 Don't know ☐ 3

If yes, how old were you (first occurrence)? ☐☐ years old

***This page has perforations down the side so that as soon as we receive this questionnaire we will remove this sheet and keep it securely separately from the rest of the questionnaire so that the information you have given is kept anonymously.***

72: Can you please give us these other details : DATE OF BIRTH

FIRST NAME(s)/FORENAME(s)

OTHER NAME(s)/FORENAME(s)

SURNAME AT BIRTH/(MAIDEN NAME)

CURRENT SURNAME/LAST NAME

73: One of the objectives of this study is to establish the relationship of nutrition with the occurrence of certain diseases such as cancer which are registered by the National Health Service (NHS). To do this we need to know your NHS number if you know it, and also details about your GP. It would be very helpful if you could fill in your NHS number (this is on your medical card). If you were born between 1939 and 1952 this is your National Identity number.

Example:

| NHS NUMBER | U | N | A | Z | | / | 4 | 6 | 4 |
|---|---|---|---|---|---|---|---|---|---|

| NHS NUMBER | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|

74: Please could you also fill in your G.P.'s Name and Address.

G.P. Name:

Address:

Postcode:

Telephone Number:

CONTACTING YOU:

75: If we have any queries about your answers to this questionnaire, we would like to contact you. Can you please give us your telephone number

Telephone : Dialling Code: Number: Daytime ☐

Dialling Code: Number: Evening ☐

76: We would like to write to you again about the progress of our research and to find out more information about your typical food intake.

In case you change your address and we lose contact with you, could you give us the name of two friends or relatives who would know your new address? Please inform them that you have done this.

Contact Name (1):

Contact Address:

Postcode:

Telephone Number:

Contact Name (2):

Contact Address:

Postcode:

Telephone Number:

***Please will you check the name and address label overleaf, and correct the details as necessary.***

**Thank you for your help filling out this questionnaire and helping us with our research.**

**Please send your completed questionnaire in the stamped addressed envelope to:**

**Amanda Woodhouse,**
**Division of Public Health,**
**The Nuffield Institute for Health,**
**71–75 Clarendon Road, Leeds LS2 9PL.**

**Please phone 0113 233 4862**
**if you have any queries about this questionnaire.**

**Please write any changes to the details on the label in the spaces below**

**First name**

**Surname**

**Address**

**Postcode**

UNIVERSITY OF LEEDS

UK Women's Cohort Study

# FOOD AND ACTIVITY DIARY

We would be grateful if you could record all your food and drink for 4 consecutive days and your physical activity on day 3. You can find full instructions in the diary.

Please complete and return this diary at your convenience, but preferably within one month. We appreciate that completing this diary will take some time and we wish to take this opportunity to thank you for your contribution to our research.

**If you have any queries, please contact a member of the team on 0113 343 7452 or email** cohorteam@leeds.ac.uk

**Thank you very much for your help.**

## INSTRUCTIONS ON HOW TO COMPLETE THIS DIARY

This diary is designed for you to record everything you eat and drink for four days, plus one day for physical activity.

To give us an accurate picture, please fill out the diary in as much detail as possible. It is very important that you do not change what you eat and drink, or the physical activities that you carry out just because you are keeping a record.

### FOOD DIARY

- Please date your record when you start your diary.
- Please record the time you had something to eat or drink in the left-hand column marked **"Time of food/drink"**.
- In the column marked **"Description of food or drink consumed"**, please give a full record of the food/drink and how it was prepared (cooking method). If possible, please record each individual food and drink item separately **(see example on page 4)**.
- In the last column, please record the **amount of food or drink you consumed** by giving the weight if on the packet or carton e.g. 150g pot of yoghurt, 56g bar of milk chocolate. For other foods we would like you to weigh the foods you consume. If you do not have scales at home, or if you are eating food away form the home, then describe the food you eat using household measures e.g. tablespoons, cups, large glass etc. Please document what you ate & drank in as much detail as possible.

- To establish that your weighing scales are accurate, please weigh ***at least*** one of the following foods in (grams) and record your results in the boxes below :

**1 raw egg (still in the shell)** □□g
**1 large tin of baked beans (420g)** □□□g
**1 full bag of flour** □□□□g

- At the end of the third page, there is space to write down all recipes and if more than one serving, how much was consumed by you. Also use this space to record details of any foods/drinks eaten away from home and to record the brand of any manufactured products.

- If you eat ready made foods that have the nutritional information on the packet, then please could you write down this information in the space provided on the fourth page. It is important to state if the information is for either per serving, or per 100 grams. If it is for a serving, then please write down the serving size that you had.

- At the end of the diary section are a few questions about your diet in general over the four days you have recorded. Please remember to complete these before returning your food diary.

## PHYSICAL ACTIVITY DIARY

We would like to find about your physical activity for one full day. **Please fill in the physical activity diary on day three.**

Please refer to the specific instructions, which are situated just before the physical activity diary.

## EXAMPLE DAY - UP TO LUNCH

| Date: 14 October 2005 | Day of the week Friday | |
|---|---|---|
| **Time of food or drink** | **Description of food or drink consumed (Include brand name where possible)** | **Amount** |
| 7.15 am | Filter Coffee | 1 cup (200m1) |
| | semi-skimmed milk | 3 tablespoons |
| 7.30 am | Sainsbury's orange juice, un-sweetened | 1 glass (150ml) |
| | "Sainsbury's Bran flakes | 40g |
| | semi-skimmed milk | 180ml |
| 10.30am | Plain chocolate digestives (large biscuits) | 2 |
| | Earl Grey tea (weak) no milk | 1 cup |
| 11 am | banana (medium sized) | 95g |
| 11.30 am | London herb company Lemon Zester tea | 1 |
| 12.10 pm | Local bakery's wholemeal bread un-sliced loaf (cut thickly) | 1 slice 47g |
| | Tesco sunflower margarine | thinly spread |
| | home made mushroom risotto (see recipe) | About $^1/_3$ of recipe |
| | green seedless grapes | 32g |
| | Cox's Orange Pippin apple (medium) | 82g |
| | Sainsbury's wholemilk fruit yogurt (150g) | 1 pot |
| | London herb company sweet berry tea | 1 |
| 2pm | Warburton's Carrot cake - with cream cheese topping (see nutritional information) | 1 slice - 75g (on packet) |

**EXAMPLE - CONTINUED**

**Recipes/description of foods eaten away from home/ any other comments**

Home made mushroom risotto
2 Tablespoons of olive oil
3 oz Butter
1 Clove of garlic
1lb Button Mushrooms
10oz Rice (long grain rice)
1 large onion
1 ½ Pints of vegetable stock
Pinch of salt & pepper
Pinch of rosemary, thyme & chilli powder.

Fry onion & garlic in butter & olive oil until soft. Add chilli & mushrooms, cook gently for approx 5 mins. Add all of the rice, then add stock ladle by ladle until completely absorbed, this should take around 20 mins.

Usually approx 3 servings from this of equal proportion

**EXAMPLE - CONTINUED**

**Nutritional Information for Ready Made / Packaged foods**
**Please state, if the information is for a serving or per 100g**

| Food | Serving size | per 100g | Energy kcal | Protein | Carbohydrate | Fat | Fibre |
|---|---|---|---|---|---|---|---|
| Carrot cake | | ✓ | 490 | 4.5 | 52.4 | 30.6 | 0.7 |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |

**Any extras not already recorded, e.g. sweets/snacks/drinks?**

2 polo mints during morning at work, & pack of Salt & Vinegar crisps (Walkers 28g) on way home

**END OF EXAMPLE**

CONFIDENTIAL

# UK Women's Cohort Study

This study is looking at the relationship of diet with the occurrence of certain diseases. The questionnaire is mostly about your eating habits, lifestyle and health. Some questions may not seem relevant to you but please try to answer every question as best you can.

Please complete this questionnaire and return it in the pre-paid envelope. Your answers will be treated in the **strictest confidence.**

A summary of this research will be sent to all participants.

## WHAT YOU EAT

1. Would you describe yourself as a vegetarian?
   Yes ☐ 1 No ☐ 2 Used to be ☐ 3

2. If yes, or used to be, how long in total have you been vegetarian? ☐☐ years.
   If never, please write 0.

3. Would you describe yourself as a vegan?
   Yes ☐ 1 No ☐ 2 Used to be ☐ 3

4. If yes, or used to be, how long in total have you been vegan? ☐☐ years.
   If never, please write 0.

5. What proportion of the food you eat is organically produced?
   *(all foods including fruit & vegetables, meat, bread, cereals, etc.)*

| None/rarely | ¼ (some/little) | ½ (half) | ¾ (most) | All |
|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 |

6. What proportion of the food you eat is home grown?
   *(all foods including fruit & vegetables, meat, bread, cereals, etc.)*

| None/rarely | ¼ (some/little) | ½ (half) | ¾ (most) | All |
|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 |

7. How many servings of vegetables or dishes containing vegetables **(excluding potatoes)** do you usually eat in an average week? ☐☐

8. How many servings of fruit or dishes containing fruit do you usually eat in an average week? ☐☐

9. How many servings of red meat or dishes containing red meat do you usually eat in an average week e.g. beef, lamb, pork? (If never please write 0) ☐☐

10. How many servings of white meat or dishes containing white meat do you usually eat in an average week e.g. chicken, turkey, and other poultry? (If never please write 0) ☐☐

11. How many servings of fish or dishes containing fish do you usually eat each week? (If never please write 0) ☐☐

12. How many servings of nuts or dishes containing nuts do you usually eat each week? (If never please write 0) ☐☐

**16. HOW OFTEN HAVE YOU EATEN THESE FOODS IN THE LAST 12 MONTHS?**
Please put a tick (✓) on every line.

| FOOD | Never | Less than once a month | About once a month | Once a week | 2-4 per week | 5-6 per week | Once per day | More than once a day |
|---|---|---|---|---|---|---|---|---|
| Soya bread (e.g. Burgen) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Soya sauce | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Soya Milk | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Tofu as part of a main meal | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Brown rice | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Peanuts | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Textured vegetable protein (TVP) as part of a main meal | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Tempeh | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Miso | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Rape seed, sunflower, peanut or soya bean oil | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |

**17. COOKING METHODS**

How often do you eat foods cooked by the following methods?
Please put a tick (✓) on every line

| FOOD AND COOKING METHOD | Never | Less than once a month | About once a month | Once a week | 2-4 per week | 5-6 per week | Once per day | More than once a day |
|---|---|---|---|---|---|---|---|---|
| **Roasted / Baked** | | | | | | | | |
| Meat | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Fish | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Potatoes | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Vegetables | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Cheese or cheese containing dishes | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| **Fried** | | | | | | | | |
| Meat | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Fish | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Potatoes | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Vegetables | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |



13. How many servings of beans or pulses or dishes containing beans or pulses do you usually eat each week? (If never please write 0) ☐☐

14. Have you taken any vitamins, minerals, fish oils, fibre or other food supplements at all in the last year?
Yes ☐ 1 No ☐ 2

15. Do you presently use dietary supplements
Yes ☐ 1 No ☐ 2

**If yes,** please indicate which supplements you use. Please look at the list of dietary supplements & list in the box below how often you use them. See example

**1** = Vitamin C
**2** = Vitamin B complex
**3** = Vitamin B12
**4** = Folic Acid
**5** = Antioxidants
**6** = Multivitamins with minerals
**7** = Multivitamins without minerals
**8** = Other single vitamins
**9** = Iron
**10** = Calcium
**11** = Selenium
**12** = Zinc
**13** = Other Minerals
**14** = Fish Oils (Cod / halibut liver oils)
**15** = Evening Primrose/Starflower Oils
**16** = Garlic supplements
**17** = Other supplements

| Supplement number | How often do you take the Dietary Supplement – please tick ✓ | | | | |
|---|---|---|---|---|---|
| | More than once a day | Daily | Weekly | Monthly | Less than once a month |
| e.g. 3 | 1 | 2 ✓ | 3 | 4 | 5 |
| | 1 | 2 | 3 | 4 | 5 |
| | 1 | 2 | 3 | 4 | 5 |
| | 1 | 2 | 3 | 4 | 5 |
| | 1 | 2 | 3 | 4 | 5 |
| | 1 | 2 | 3 | 4 | 5 |
| | 1 | 2 | 3 | 4 | 5 |
| | 1 | 2 | 3 | 4 | 5 |
| | 1 | 2 | 3 | 4 | 5 |
| | 1 | 2 | 3 | 4 | 5 |
| | 1 | 2 | 3 | 4 | 5 |
| | 1 | 2 | 3 | 4 | 5 |

| FOOD AND COOKING METHOD | Never | Less than once a month | About once a month | Once a week | 2-4 per week | 5-6 per week | Once per day | More than once a day |
|---|---|---|---|---|---|---|---|---|
| **BBQ'd** | | | | | | | | |
| Meat | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Fish | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Vegetables | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| **Grilled & Char-grilled** | | | | | | | | |
| Meat | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Fish | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Potatoes | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Vegetables | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Toast | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Cheese dishes e.g. cheese on toast | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |

**18. On average how well cooked do you like the following foods?**

Please put a tick (✓) on every line

| FOOD | Lightly cooked, very pale brown | Medium, slightly browned | Medium to well done, mid-dark brown | Very well done, dark brown & crispy | Never eat this food |
|---|---|---|---|---|---|
| Beef | 1 | 2 | 3 | 4 | 5 |
| Chicken or Turkey | 1 | 2 | 3 | 4 | 5 |
| Pork | 1 | 2 | 3 | 4 | 5 |
| Lamb | 1 | 2 | 3 | 4 | 5 |
| Other Meats | 1 | 2 | 3 | 4 | 5 |
| Meat products e.g. sausages/burgers | 1 | 2 | 3 | 4 | 5 |
| Fish (if fried / chargrilled etc.) | 1 | 2 | 3 | 4 | 5 |
| Cheese dishes – e.g. macaroni cheese, cheese on toast | 1 | 2 | 3 | 4 | 5 |
| Toast | 1 | 2 | 3 | 4 | 5 |
| Potatoes- (roasted / fried/ sautéed) | 1 | 2 | 3 | 4 | 5 |
| Vegetables (char-grilled / grilled / roasted / fried) | 1 | 2 | 3 | 4 | 5 |



## ALCOHOL

19. How often do you drink alcohol?

| | | | |
|---|---|---|---|
| More than once a day | ☐ 1 | Once a day | ☐ 2 |
| A few times a week | ☐ 3 | Once a week | ☐ 4 |
| A couple of times a month | ☐ 5 | Once a month | ☐ 6 |
| Less than once a month | ☐ 7 | Never drink alcohol | ☐ 8 |

20a. In a typical week, how much do you drink?
**IF less** than once per week then go to question 20b

| | |
|---|---|
| Beer or cider | ☐☐ Half pints each week |
| Wine | ☐☐ glasses each week |
| Sherry/Fortified Wines | ☐☐ glasses each week |
| Spirits | ☐☐ glasses (singles) each week |

20b. In a typical month how much do you drink ?

| | |
|---|---|
| Beer or cider | ☐☐ Half pints each month |
| Wine | ☐☐ glasses each month |
| Sherry/Fortified Wines | ☐☐ glasses each month |
| Spirits | ☐☐ glasses (singles) each month |

## SMOKING

21. Have you ever smoked as much as one cigarette a day for as long as a year?
Yes ☐ 1 No ☐ 2

**If No, please go to question 35.**

22. If Yes, how old were you when you started smoking cigarettes regularly? ☐☐ years old

23. Did you smoke at the following ages? If so, how many cigarettes did you smoke and were they usually filter cigarettes?

| | | | | |
|---|---|---|---|---|
| Age 20 ☐☐☐ cigs per day | Filter ☐ | No filter ☐ | Non-smoker ☐ |
| Age 30 ☐☐☐ cigs per day | Filter ☐ | No filter ☐ | Non-smoker ☐ |
| Age 40 ☐☐☐ cigs per day | Filter ☐ | No filter ☐ | Non-smoker ☐ |
| Age 50 ☐☐☐ cigs per day | Filter ☐ | No filter ☐ | Non-smoker ☐ |
| Age 60 ☐☐☐ cigs per day | Filter ☐ | No filter ☐ | Non-smoker ☐ |

24. Did you smoke cigarettes a year ago? Yes ☐ 1 No ☐ 2

How many cigarettes did you smoke each day? ☐☐☐ cigarettes

Did you usually smoke filter cigarettes? Yes ☐ 1 No ☐ 2

Did you usually smoke low tar cigarettes? Yes ☐ 1 No ☐ 2

Which brand did you normally smoke? ☐

How deeply did you inhale? Deeply into the lungs ☐ 1 A little ☐ 2 Not at all ☐ 3

25. If you have stopped smoking, how old were you when you last smoked? ☐☐ years old

26. Could you please estimate the total number of years and months you have smoked for?
(Exclude periods when you gave up smoking) ☐☐ years ☐☐ months

27. Do you currently smoke cigarettes ? Yes ☐ 1 No ☐ 2

How many cigarettes do you smoke each day? ☐☐☐ cigarettes

Do you usually smoke filter cigarettes? Yes ☐ 1 No ☐ 2

Do you usually smoke low tar cigarettes? Yes ☐ 1 No ☐ 2

Which brand do you normally smoke? ☐

## WEIGHT & HEIGHT

28. Approximately how much do you weigh at present?

☐☐ stones ☐☐ pounds OR ☐☐☐ Kilogrammes (to nearest kg) ☐ Don't Know

29. Please fill in your approximate weight at the stated age **where applicable.**

**Weight at 20 years**
☐☐ stones ☐☐ pounds OR ☐☐☐ Kilogrammes (to nearest kg) ☐ Don't Know

**Weight at 30 years**
☐☐ stones ☐☐ pounds OR ☐☐☐ Kilogrammes (to nearest kg) ☐ Don't Know

**Weight at 40 years**
☐☐ stones ☐☐ pounds OR ☐☐☐ Kilogrammes (to nearest kg) ☐ Don't Know

**Weight at 50 years**
☐☐ stones ☐☐ pounds OR ☐☐☐ Kilogrammes (to nearest kg) ☐ Don't Know



**Weight at 60 years**
☐☐ stones ☐☐ pounds OR ☐☐☐ Kilogrammes (to nearest kg) ☐ Don't Know

**Weight at 70 years**
☐☐ stones ☐☐ pounds OR ☐☐☐ Kilogrammes (to nearest kg) ☐ Don't Know

30. Are you a frequent 'dieter' whose weight fluctuates regularly? Yes ☐ 1 No ☐ 2

## HEIGHT

31. What is your present height? ☐ ft ☐☐ inches or ☐☐☐ cms or ☐ Don't Know

## ILLNESSES

32. Has a doctor ever told you that you have, or have had, any of the following conditions?
(Please exclude conditions relating to pregnancy only).

| Condition | Yes | year of diagnosis | No |
|---|---|---|---|
| Heart attack, coronary thrombosis, myocardial infarction | 1 | | 2 |
| Angina | 1 | | 2 |
| Stroke | 1 | | 2 |
| High Blood Pressure (Hypertension) | 1 | | 2 |
| High Blood Cholesterol, Hyperlipidaemia | 1 | | 2 |
| Diabetes | 1 | | 2 |
| Gallstones | 1 | | 2 |
| Polyps in the large intestine | 1 | | 2 |
| Cancer | 1 | | 2 |
| Diabetes | 1 | | 2 |
| Stomach (e.g. ulcer or gastritis) | 1 | | 2 |
| Irritable bowel syndrome | 1 | | 2 |
| Haemorrhoids | 1 | | 2 |
| Diverticular disease | 1 | | 2 |
| Anal fissure | 1 | | 2 |
| Ulcerative colitis | 1 | | 2 |
| Arthritis | 1 | | 2 |
| Anorexia Nervosa | 1 | | 2 |
| Bulimia Nervosa | 1 | | 2 |

33. Have you ever been told you have the following types of cancer?

| Type (site of cancer) | Yes | Year of diagnosis | No |
|---|---|---|---|
| Breast | 1 | | 2 |
| Skin | 1 | | 2 |
| Lung | 1 | | 2 |
| Colon and rectum | 1 | | 2 |
| Ovary | 1 | | 2 |
| Stomach | 1 | | 2 |
| Cervix | 1 | | 2 |
| Uterus | 1 | | 2 |
| Pancreas | 1 | | 2 |

## FAMILY MEDICAL HISTORY

34. We would like to find out about your family's medical history so that we can explore any possible links with your own health. Please look at the list of medical conditions listed below and document whether or not any of your family members have ever had any of these conditions. Please include the age at diagnosis if known. If you are adopted or if your parents remarried, please give details of blood relatives only.

**Codes for Medical Conditions:**

1. Heart Attack, coronary thrombosis or myocardial infarction
2. Angina
3. Stroke
4. High blood pressure (hypertension)
5. High blood cholesterol or hyperlipidaemia
6. Diabetes
7. Polyps in the large intestine
8. Stomach-ulcer or gastritis
9. Irritable bowel syndrome
10. Ulcerative Colitis
11. Anal fissure
12. Arthritis
13. Anorexia Nervosa
14. Bulimia Nervosa

Please only use one line for each family member with a condition.

| Code | Mother | Father | Sister | Brother | Aunt | Uncle |
|---|---|---|---|---|---|---|
| E.g. 4 | ✓ 65yrs | | | | | |
| 4 | | | ✓ 60yrs | | | |
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**Family Medical History Cont.**

35. We would like to find out about your family's history of cancer. Please look at the list of different types of cancer listed below and document whether or not any of your family members have ever had any of these types of cancer. Please include the age at diagnosis if known. If you are adopted or if your parents remarried, please give details of blood relatives only.

**Codes for Cancer**

1. Breast
2. Skin
3. Lung
4. Colon & rectum
5. Ovary
6. Stomach
7. Cervix
8. Uterus
9. Pancreas
10. Prostate

| Code | Mother | Father | Sister | Brother | Aunt | Uncle |
|---|---|---|---|---|---|---|
| E.g. 10 | | ✓ 72 | | | | |
| E.g. 1 | | | ✓ 61 | | | |
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## Your Children's Medical History

36. How many children do you have?

sons ☐☐ daughters ☐☐ none ☐

**If none** then please go to question 37.

How old are your children?

| Son or daughter please tick (✓) Son | Daughter | Year of birth | Were you a vegetarian during your pregnancy please tick (✓) Yes | No | Were you a vegan during your pregnancy please tick (✓) Yes | No |
|---|---|---|---|---|---|---|
| E.g. | ✓ | 1982 | ✓ | | | |
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Were any of your children born with the following conditions?

| Condition | Son(s) Yes | Son(s) No | Daughter(s) Yes | Daughter(s) No |
|---|---|---|---|---|
| Hypospadias (misplaced opening of penis) | | | | |
| Undescended testicles | | | | |
| Neural tube defects (e.g. Spina Bifida) | | | | |
| Renal (kidney) abnormalities | | | | |
| Cardiac (heart) abnormalities | | | | |
| Imperforate anus (sealed back passage) | | | | |
| Gastroschisis/Omphalocoele (exposed stomach not covered by skin) | | | | |
| Any other congenital abnormalities Please give details in the space below | | | | |

Details of any congenital abnormalities



## ACTIVITY

37. On an average **weekday** how is your day spent?

| | Number of hours & / or minutes in a 24 hour day spent doing the following activities? | |
|---|---|---|
| | Hours | Minutes |
| Sleeping | | |
| Sitting | | |
| Light activities (e.g. washing, dressing, eating) | | |
| Standing | | |
| Household chores (e.g. vacuuming, ironing) | | |
| Lifting heavy objects | | |
| Light exercise (e.g. walking, yoga, easy gardening) | | |
| Moderate exercise (e.g. fast walking, easy swimming, hill walking, easy cycling) | | |
| Strenuous exercise (e.g. running, vigorous swimming, high impact aerobics) | | |

38. On an average **weekend day** how is your day spent?

| | Number of hours & / or minutes in a 24 hour day spent doing the following activities? | |
|---|---|---|
| | Hours | Minutes |
| Sleeping | | |
| Sitting | | |
| Light activities (e.g. washing, dressing, eating) | | |
| Standing | | |
| Household chores (e.g. vacuuming, ironing) | | |
| Lifting heavy objects | | |
| Light exercise (e.g. walking, yoga, easy gardening) | | |
| Moderate exercise (e.g. fast walking, easy swimming, hill walking, easy cycling) | | |
| Strenuous exercise (e.g. running, vigorous swimming, high impact aerobics) | | |

39. Which of the following four activity classes best describes your present weekly activity?

No weekly physical activity ☐ 1

Only light/moderate physical activity in most weeks ☐ 2

Vigorous activity for at least 20 minutes once or twice a week. ☐ 3
(vigorous activity causes shortness of breath, rapid heart rate and sweating)

Vigorous physical activity at least 20 minutes three or more times per week ☐ 4

40. Compared with yourself 10 years ago, how would you describe your activity levels?

More active ☐ 1 About the same ☐ 3

Less active ☐ 2 Don't know ☐ 4

41. On a scale from 1-10 please indicate how much of your time you spend fidgeting.
1 would represent "no fidgeting at all" and 10 would represent "Constant fidgeting "

Time spent fidgeting 1-10 ☐☐

**MEDICATIONS**

42. Have you taken painkillers, such as aspirin, on a regular basis for periods of three months or longer?

Yes ☐ 1 No ☐ 2 Don't know ☐ 3

43. Apart from aspirin, we are interested in 'anti-inflammatory drugs' taken for conditions such as rheumatoid arthritis, for example: Ibuprofen, naproxen, diclofenac, indomethacin and pyroxicam
Have you taken any of these, on a regular basis for periods of three months or longer?

Yes ☐ 1 No ☐ 2 Don't know ☐ 3



44. If Yes, can you provide the name of the drug, frequency with which you used it, the strength and the dates (month/year) when you used it?

| Name of Drug | Pills per day | Strength | Date started | Date finished | How often did you take the drug Please Tick (✓) | | |
|---|---|---|---|---|---|---|---|
| | | | | | Daily | Most days | Intermittently |
| Aspirin | | | | | 1 | 2 | 3 |
| Ibuprofen | | | | | 1 | 2 | 3 |
| Naproxen | | | | | 1 | 2 | 3 |
| Diclofenac | | | | | 1 | 2 | 3 |
| Indomethacin | | | | | 1 | 2 | 3 |
| Pyroxicam | | | | | 1 | 2 | 3 |

**MEDICAL APPOINTMENTS**

45. In the last 12 months how often have you visited any of the following on your own behalf (excluding routine antenatal visits during pregnancy)?

| | Number of occasions over last 12 months ? |
|---|---|
| General Practitioner (NHS) | |
| Private medical practitioner | |
| Hospital Doctor | |
| Alternative Practitioner e.g. homeopath | |

46. Do you go for routine health checks/ screening e.g. smear-tests, well women clinics?

Yes ☐ 1 No ☐ 2

## PREGNANCY, CONTRACEPTION & MENSTRUAL CYCLE

47. Are you pregnant at the moment? Yes ☐ 1 No ☐ 2

48. Have you ever taken Folic acid supplements prior to conception or in early pregnancy?
Yes ☐ 1 No ☐ 2

49. How many times have you been pregnant? ☐☐

50. Have you ever used oral contraceptives (the pill)? Yes ☐ 1 No ☐ 2

**If Yes,** how old were you when you first used the pill? ☐☐ years old

For how long altogether did you use the pill? ☐☐ years

Are you currently using the pill? Yes ☐ 1 No ☐ 2

**If no,** how old were you when you last used it? ☐☐ years old

51. How many "natural" menstrual periods have you had in the last 12 months?
Do not count bleeding while using the pill or HRT (Hormone Replacement Therapy)

None ☐ 1 1 to 3 ☐ 2 4 to 5 ☐ 3 6 to 9 ☐ 4 10 or more ☐ 5

Not applicable (using the Pill or HRT or currently pregnant) ☐

If none, how old were you when you had your last "natural" menstrual period? ☐☐ years old
Do not count bleeding while using the pill or HRT (Hormone Replacement Therapy).

52. Have you ever used HRT (*hormone replacement therapy for menopause*)?
Yes ☐ 1 No ☐ 2

**If Yes,** how old were you when you first used HRT? ☐☐ years old

Are you currently using HRT? Yes ☐ 1 No ☐ 2

**If no,** how old were you when you last used HRT? ☐☐ years old

53. Have you ever had a hysterectomy *(womb removed)*? Yes ☐ 1 No ☐ 2
Age at time of operation ☐☐ years old

54. Have you had an operation to remove one or both your ovaries? Yes ☐ 1 No ☐ 2 Don't know ☐ 3

**If yes,** how old were you? ☐☐ years old

Were one or both ovaries removed? One ☐ 1 Both ☐ 2 Don't know ☐ 3



## BOWEL MOVEMENTS

55. How often do you open your bowels?

| | | | |
|---|---|---|---|
| Less than once a week | ☐ 1 | Once a week | ☐ 2 |
| 2-3 times a week | ☐ 3 | 4-6 times a week | ☐ 4 |
| Every day | ☐ 5 | 2-3 times a day | ☐ 6 |
| More than 3 times a day | ☐ 7 | | |

56. What is the usual consistency of your stools?

Hard ☐ 1 Formed but not hard ☐ 2 Semi formed ☐ 3 Liquid ☐ 4

Have you taken any medication as treatment for constipation? Yes ☐ 1 No ☐ 2

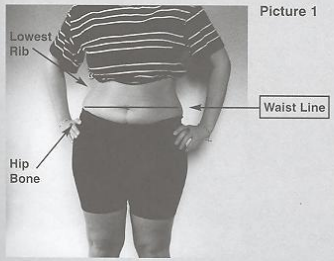
### Waist and Hip measurements

**We would like you to measure your waist and hips using a household tape measure. Please refer to the pictures on the next page in order to be sure of the correct positioning of the tape for waist and hip measurements.**

You may find it easier to measure your waist and hips if you stand in front of a mirror. It is important that you are not wearing heavy or thick clothing, ideally you should measure your waist and hips directly against your skin. Stand relaxed and try not to hold your breath when taking the measurements.

If you find these measurements tricky in any way, then perhaps you could ask a relative or friend to assist you.

**Step 1. Waist**
Feel for your natural waist line, it is between your lowest ribs and your hip bones. Take the tape measure and place around your natural waist line as shown on picture 1. Try not to pull the tape measure too tight, stand relaxed and breathe out gently. Measure your waist to the nearest millimetre.

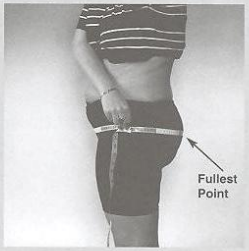



Picture 1

57. Waist Measurement ☐☐☐ **cm.** ☐ **mm** or ☐☐ . ☐ **inches**

**Step 2. Hips**

Please refer to **pictures 2 & 3**
You will find it easier to measure your hips if you are standing next to a long mirror to help you make the measurement. Stand relaxed and with feet shoulder width apart. Find the fullest point around your buttocks, keep the tape measure horizontal, and try not to pull too tight. Measure your hips again to the nearest millimetre.


Pictures 2 & 3

58. Hips measurement ☐☐☐ **cm.** ☐ **mm** or ☐☐ . ☐ **inches**

It is not easy to obtain accurate measurements of the waist and hip. Therefore, could you please repeat the measurements following the instructions exactly as before.

59. Repeated Waist Measurement ☐☐☐ **cm.** ☐ **mm** or ☐☐ . ☐ **inches**

60. Repeated Hips measurement ☐☐☐ **cm.** ☐ **mm** or ☐☐ . ☐ **inches**

***Thank you for your help filling out this questionnaire and helping us with our research.***



Please send your completed questionnaire and food diary in the postage paid envelope enclosed to: (please note you do not need to affix a postage stamp)

**Alyson Greenhalgh**
**UK Women's Nutrition and Lifestyle Survey team**
**Division of Public Health**
**Nuffield Institute for Health**
**University of Leeds**
**Leeds**
**LS2 9PL**

Please telephone one of the study team on 0113 233 4866 if you have any queries about this questionnaire.

As part of our ongoing research, we would like to perhaps contact you in the future for a blood sample. Would you be willing to go to your own doctor for a blood sample to be taken?

Yes ☐ [1] No ☐ [2]

This study is looking at the long-term relationship between diet and health. We would like to write to you again about the progress of our research and to look at changes in your diet and lifestyle. In case you change your address and we lose contact with you, could you give us the name of someone who would know your new address? Please inform them that you have done this. Thank you.

Contact Name: _____

Contact Address: _____

_____

_____

Postcode: _____

Telephone Number: _____

Please will you check the name and address label on this questionnaire and correct the details as necessary.

Please write any changes to the details on the label in the spaces below

First name _____

Surname _____

Address _____

_____

_____

_____

Postcode _____

Telephone number _____

# DIARY CODING PROTOCOL

***Background***

This research is related to one of the UK's largest population-based prospective studies, designed to explore relationships between diet and chronic disease - the UK Women's Cohort Study (UKWCS). For such exploration, the diet must be recorded. The women in Phase 2 or the UKWCS have all completed a four day food diary. Your role in this research is to code some of these diaries using the diet and nutrition tool for evaluation (DANTE). This will generate a nutrient profile report for the subjects, thus contributing information to a larger dataset which may then be analysed.

***General Information***

- Diaries are kept in the NEG Office – you may either code diaries on site or photocopy them and code elsewhere. Diaries should never be taken out of the school.

- Diaries are bundled into sets of 2 and should be coded as such.
  Each student will code 16 x 2 = 32 diaries.

- You will also check each other's diaries once they are coded.
  Each student will check 16 x 2 = 32 diaries.

- You should keep a record of the diaries that you have coded and checked.

- *Coding, Checking & Editing system*
  1. Code 2 diaries & check 2 diaries
     Complete edits for checked diaries

  2. Code 4 diaries & check 4 diaries
     Complete edits for checked diaries

  3. Code 4 diaries & check 4 diaries
     Complete edits for checked diaries etc.

- Make a note of your queries.
  Discuss them with fellow coders or send me an email on fspci@leeds.ac.uk.

- We will meet on Tuesday 12th November 2013 at 12pm to discuss your progress.
  You should have coded and checked 8 x 2 = 16 diaries by then.
  This is an average of a 4 diaries / week.

- All diaries should be coded and checked by Friday 13th December, 2013.

- You will be given a dataset in January 2014. Kindly note that students who fail to complete the coding and checking exercise in the stipulated time frame will NOT be given a dataset.



***Finding DANTE and Getting Started***

Start \ Computer \ shared (\\ds.leeds.ac.uk) (N:) \ MAPS \ Research \ PRC \ NEG \ 03. Dietary Assessment Tools \ DANTE \ Diary Coding 2013 \ Dante.mdb

- Each coder will have their user ID on DANTE. Pick username from dropdown list, password is your first name: Press **'Login'**. If nothing happens, close the dialog box, press the **'Options'** tab in the security warning bar and choose **'Enable this content'**.

- Click **'Next ID'** and type the ID No. for your diary – found on the back cover of the diary.
  (*Note:* occasionally there is a fault and ID 11 appears in the list. Overtype 11 with the correct ID, press Next ID again and type the ID in once more. Watch out for any that are listed as ID 11).

- Click **'SEARCH'** to begin entering foods for day 1
  *(see detailed section below on how to search for foods)*

- Press **'Next day'** for each following day
  *(if you forgot to do this you can overtype on the main screen to make sure each food is listed for the correct day)*

  *Note how many days appear to be correctly filled in; sometimes people give up recording half way through the fourth day. In this case only complete 3 days and make a note that you did this because the fourth day looked incomplete.*

- **'Reset Default'** button sets the day back to 1

- At the end of the diary, print a summary of your diary to be checked.
  - Press 'Close'
  - Select 'Open reporting' from the 'Study Information' window
  - Select 'Open form' from the 'UKWCS Diary Coding' study
  - Select 'Report of info entered'
  - Enter the ID of the diary you just completed and select 'OK'
    *(Ensure the print preview icon is selected at the bottom right of the access screen)*
  - Print a copy of the output
  - Fold and put printout inside diary for checking

***Checking other coders' diaries***

1. Select someone else's food diary which is ready for checking.
2. Check the food diary against the print out. Make notes of any questions / suggestions / errors on the print out and return to the source to perform the edits.
3. Record the ID which you have checked on your checking record

***Analysing a Food Diary***

1. Check back pages of diary for additional questions about spreads, milk types, type of bread used etc. and any further comments. (If subject puts butter on toast, add it even if not mentioned).

2. Enter the subject ID number (diary back cover).

3. Begin data entry for each day, taking care to enter EVERYTHING recorded, including water, condiments, herbs etc.

4. Break each food into components where possible (e.g. record a sandwich as bread, spread, cheese etc. rather than using the composite code 'cheese sandwich').

5. Enter weight of food item consumed in grams as recorded by the subject. (If in doubt, refer to the FSA book on Food Portion Sizes to help you decide if portion size recorded looks reasonable.)

6. Decide on the correct food within the food tables to give the best possible 'fit'. (If unclear in DANTE, refer to the Paul and Southgate Food Tables and supplements if more detail about the food code is needed e.g. whether the food code refers to a manufactured dish or home-made recipe, or the concentrate versus diluted beverage).

7. If unsure what the food is or which code to select from similar foods:
   (a) check the additional questions section and other pages of the diary to see if the food has been recorded again with more detail;
   (b) look up the standard coding assumption on the excel database (e.g. if subject has just recorded 'bacon', assume was 'bacon rasher, lean only, grilled'). These are standard coding assumptions allocated by the nutrition researchers to ensure that inter-observer error in coding foods is minimized.

   *Coding assumptions.xls*
   (N:) \ MAPS \ Research \ PRC \ NEG \ 03. Dietary Assessment Tools \DANTE \ Diary Coding 2013 \ Coding Assumptions.xls

8. Follow the general coding guidelines below that refer to default cooking methods; familiarisation with these procedures helps to minimize errors.

***Queries List***

1. If no default code exists, record the subject ID, day and description of the food on a queries list. Put a 'post-it' note on the diary itself to indicate it is incomplete.

2. When the query has been resolved, the person coding that diary must enter the allocated code(s) into the correct diary period on the DANTE file.

3. Once entry is complete, print out the list of foods entered for each diary as a paper data backup.



***Searching for Foods***

There are 4 key ways:

1. **Main:** The main search allows searching for the first word in the description (e.g. typing 'milk' will bring up any listing beginning with milk but not where milk appears elsewhere in the item description).

2. **Any:** This will look for the typed food item anywhere in the listed foods.

3. **Group:** If you can't find the food item (eg: unusual cake) click on the group it belongs to (cake) and find something similar in the system.

4. **Recipe:** These have been added when people have provided their recipe for something specific. In general do not use recipe items if there is a standard recipe in the system but use only if it is the closest thing you can find. (*Note: do not use the add recipe button).*

- **[Full detail]** button on search page will list nutrients - use this to match a food up to something similar if it's missing from the system.

- **[Convert]** button – used for converting imperial into metric.

- Data is automatically saved in access and you do not need to 'save' the file whilst entering data.

***Entering Food Items – Cooked or Raw?***

- Foods that are eaten cooked, such as meat and pasta, should be entered cooked – do not enter raw codes.

- Use the **Raw to cooked calculator**:

1. To convert dry foods (pasta, rice, legumes) which have been weighed dry to their cooked weight – *weight increases*;
2. To convert the weight of raw meat and fish to the cooked weight – *weight decreases.*

- *Raw to cooked calculator.xlsx*
  (N:) \ MAPS \ Research \ PRC \ NEG \ 03. Dietary Assessment Tools \DANTE \ Diary Coding 2013 \ Raw to cooked calculator.xlsx

- DO NOT edit column C in this file, add your weight into column B

- **Fat Spreads**

Check diary back pages for fat spreads used.
Only assume the 'diet' version was used if this is stated clearly.
Margarines are included in food tables as 'margarine' and 'fat spreads'.
To match brand names with codes, use Coding Assumptions spreadsheet.

| Subject record | Code as |
|---|---|
| Butter | Butter, salted |
| Margarine | Margarine, soft, not polyunsaturated |
| 'Spread' | 70-80% fat, not polyunsaturated |
| Reduced fat spread | Fat spread, 70-80% fat not polyunsaturated |
| Low fat spread | Fat spread, 40% fat, not polyunsaturated |
| Very low fat spread | Fat spread 20-25% fat, not polyunsaturated |

- **Fruit**

Assume weighed with core and any other inedible bits
Use code 'average raw, weighed with core'
Subtract weight for uneaten portion if supplied

| Subject record | Code as |
|---|---|
| Fruit juice | 'Orange juice, unsweetened' |
| Stewed fruit | 33% rhubarb, 33% apple and 33% plum stewed with sugar |
| Fruit pie | Fruit pie, pastry top and bottom |

- **Meats**

Code as cooked product, according to method used
Take care with any bones, skin and other inedible bits - choose appropriate code
Assume the portion given is all edible, unless otherwise stated

| Subject record | Code as |
|---|---|
| Steak | Beef sirloin, grilled, medium rare, lean and fat |
| Bacon | Rashers, lean only, grilled |
| Beefburger | Beefburger, economy frozen, grilled<br>*(coding as beefburger takeaway includes the bun & trimmings)* |
| Sausages, cocktail | Sausages, pork, grilled |
| Sausages, type unknown | Sausages, pork, grilled |

- **Miscellaneous**

| Subject record | Code as |
|---|---|
| Gravy | Instant gravy granules, made up |
| Stock | Stock cube weight + water (OR) Bone & vegetable broth |
| Bovril | Beef extract |
| Marmite | Yeast extract |
| Sweeteners | Ignore, they are not found in DANTE |



***Specific procedures for coding defaults***

- **Beverages**

| Subject record | Code as |
|---|---|
| Tea | Infusion e.g. black, herbal or green<br>(do not include weight for tea leaves or bag) |
| Tea with milk | Black infusion, with whole milk<br>(if type of tea & milk are unknown) |
| Coffee | Instant, made up with water<br>(do not use granules) |
| Filter coffee | Coffee, average infusion |
| Hot chocolate drink | Drinking chocolate<br>(this is the dry powder only - add milk or water) |
| Squash / cordial type | Use the code for 'made-up' unless subject has recorded concentrate and water separately |
| Carbonated drinks | If unspecified, code as standard, not diet |
| Diet carbonated drinks | Code as 'diet coke' |

*Remember to code for milk added to tea / coffee separately.*

- **Breads**

Assume white, medium, sliced if no information is given in the back pages

- **Breakfast cereals**

Assume consumed with milk if milk is stated on some of the days but not on others
Check the type of milk in the back pages

- **Cooking methods**

Always code 'as eaten' - If meat was weighed raw, convert using calculator and code as cooked
Assume the cooked item was weighed (unless otherwise stated)
Check that the portion size for cereals looks appropriate for a cooked weight. *An average raw portion of pasta might be 75g.*

*Eg: Chicken wing quarter, raw weight = 100g*
*Enter 100g into raw and cooked calculator (= 73g)*
*Code as chicken wing quarter, roasted, meat and skin 73g*

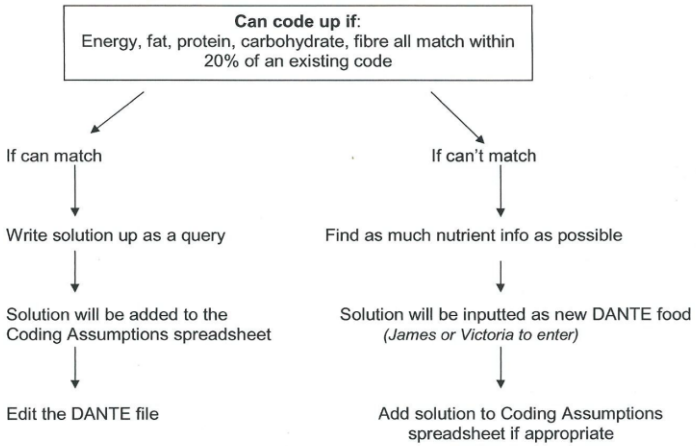
If no code exists for a grilled food, code as 'oven baked' (and vice versa)
Code microwaved food as 'grilled' or 'oven baked'
Code vegetables as 'boiled in unsalted water' (unless otherwise stated)
Code steamed / microwaved vegetables as 'boiled'
Code fried / roasted food as 'fried in blended or vegetable oil'

***Strategy for Coding Queries***

1. If food is unknown to coder – ask other cohort team members for details. If name is not found in DANTE or in the Coding Assumptions spreadsheet, find the nutrient content from:

- Packaging / nutrient information provided by subject
- Searching the internet (supermarket websites, USDA etc.)
- Phone manufacturer
- Visit shops

2. Compare to a similar food in DANTE to see if it can be matched






- **Milk**

Check diary back pages for fat content of milk.

| Subject record | Code as |
|---|---|
| Consumed at home | Semi skimmed |
| Consumed away from home | Whole |

If no serving size is given, use the following portions:

| | |
|---|---|
| Whole, in 1 cup tea / coffee | 25g |
| Whole, in 1 mug tea / coffee | 30g |
| Semi-skimmed, in 1 cup tea / coffee | 30g |
| Semi-skimmed, in 1 mug tea / coffee | 40g |
| Skimmed, in 1 cup tea / coffee | 35g |
| Skimmed, in 1 mug tea / coffee | 50g |
| Dried milk, 1 teaspoon | 3g |
| Coffee whitener, 1 teaspoon | 3g |

- **Pizza**

| Subject record | Code as |
|---|---|
| Pizza, unspecified | Cheese and tomato |
| Pizza in restaurant (not retail) | Homemade pizza & add other toppings separately |

- **Sandwiches**

Break down into components - bread, spread, cheese etc.
Assume commercial sandwiches are spread with margarine, soft, not polyunsaturated

- **Soups**

Assume tinned unless otherwise indicated

- **Vegetables**

Code vegetables as 'boiled in unsalted water' (unless otherwise stated in the back pages that salt is added during cooking)

| Subject record | Code as |
|---|---|
| Carrots | Old, boiled in unsalted water |
| Green beans | Green /French beans, boiled in unsalted water |
| Mashed potatoes | Mashed potatoes, mashed with butter |
| Chips from takeaway | Retail, fried in blended vegetable oil |
| Potatoes | Old, boiled in unsalted water |

***Sources of DANTE food codes***

The first two digits of the DANTE code number indicate which book or book supplement the food information is taken from:

50 McCance and Widdowson, 5th Edition
11 Cereal and cereal products
12 Milk products and eggs
13 Vegetables, herbs and spices
14 Fruit and nuts
15 Vegetable dishes
16 Fish and fish products
17 Miscellaneous Foods
18 Meat, poultry and game
19 Meat products and dishes

***Weight & Portion Size Queries***

- Assume 1g = 1ml
- If no weight for a food / drink item is given:

1. Check other pages of the diary to see if the food & weight is recorded on another day.
2. If food is a pre-set unit (e.g. McVities Go-Ahead Cake Bar), search for item within the FSA Food Portion Sizes book or the manufacturer's /supermarket website or search in the shop and note weight on packaging.
3. If food is not a unit item – select medium portion size from DANTE or FSA Food Portion Sizes.

***Dealing with Recipe dishes***

1. If a recipe closely matches a recipe dish already in DANTE (e.g. Fruit Scones), choose this in preference to entering a new recipe. Ensure code selected is a recipe dish rather than a commercial product –recipe is found at the back of McCance & Widdowson.
2. If the subject has clearly broken the recipe down into its components and it is straight forward to enter each component individually with weight consumed, choose this approach rather than adding a new recipe
3. If the subject has consumed this recipe item repeatedly, add as a new recipe within DANTE. Make sure the recipe name clearly identifies where it came from. If cooking is used, incorporate water loss by selecting a similar recipe from McCance & Widdowon for a weight loss %.
4. Select codes to reflect food AS EATEN. (e.g. Green pepper, should be 'peppers, green, boiled in salted water' for a recipe where peppers are cooked)
5. Number of portions = 1 if recipe will be used per 100g or if no. of portions made is unknown.





***Contacts for Nutrient Information***
(numbers may have changed)

| | |
|---|---|
| • COCA COLA SCWEPPES | 0208 302 2600 |
| • GINSTERS PIES/PASTIES | 01579 386200 |
| • KELLOGGS | 0161 869 2268 |
| • CADBURY | 0121 458 2000 |
| • BIRDS EYE WALLS | 01932 228888 |
| • BASS | 01283 511000 |
| • HEINZ | 0208 5737757 |
| • VAN DEN BURGH | 01293 648000 |
| • SMITH KLINE BEECHAM | 0208 5605151 |
| • PROCTER AND GAMBLE | 0800 146412 |
| • MARS | 01753 550055 |
| • MCCAIN | 01723 584141 |
| • ST IVEL | 01793 848444 |
| • MCVITIES | 0500 011 710 |
| • NESTLE | 01904 604604 |
| • BAXTERS | 01343 820286 |

***Useful Websites***

**Asda**
http://www.asda.com
No nutrient information, but unit weights and some food descriptions

***Clearspring***
http://www.clearspring.co.uk
Health foods and Japanese products

***Goodness direct***
http://www.goodnessdirect.co.uk
A mail-order web site for health foods and supplements
Many products have nutrient info or ingredient listings
Also useful links to other related web sites

***Heinz***
http://www.heinz.co.uk
Good site - Nutrient info for Heinz products and also Weight Watchers and John West brands

**Iceland**
http://www.icelandstore.co.uk
Enter as 'guest'. Nutrient information and unit weights for own brand and other frozen foods

***Nabisco***
http://www.cerealpartners.co.uk
Breakfast cereal nutrition info

***Provamel***
http://www.provamel.com
Soya products including milk, yoghurts, desserts. Nutrient info as displayed on packaging

**Sainsburys**
http://www.sainsburystoyou.com
username: v.j.burley@leeds.ac.uk
password: cohort
Lots of nutrient information for own brand items and others

**Tesco**
http://www.tesco.com
username: 14727366
password: cohort
Useful site with nutrients and descriptions for some foods

***USDA***
http://www.nal.usda.gov/fnic/cgi-bin/nut_search.pl
Takes you to the search section for the USDA Food Composition Tables

**Waitrose**
http://www.waitrose.com/food
No need to register as user – photos of foods, and some ingredient listings, but no nutrients

**North Worcestershire Health Authority**

**LOCAL RESEARCH ETHICS COMMITTEE**

Chairman:
**Michael A Spittle**

The Croft
Sutton Park Road
Kidderminster
Worcs., DY11 6LJ
Telephone: (01562) 824711
Fax: (01562) 822695

KG 180995 14th September 1995

Amanda Woodhouse
Division of Public Health
The Nuffield Institute for Health
71-75 Clarendon Road
Leeds, LS2 9PL

Dear Ms Woodhouse

Protocol for Research:
LREC: 3/95 (February 1995) - The UK Women's Nutrition and Lifestyle Survey

Following the meeting of the Local Research Ethics Committee on the 12th September 1995, we write to confirm that, with the revised questionnaire now received, the Committee has given approval to the above project. Concern was, however, expressed regarding the length of the questionnaire and the time it would take for completion.

In keeping with the Committee's protocol, would you please inform us of the results of the study when it is completed.

Yours sincerely

Kath Garrad

**Kath Garrad**
Secretary to the Local Research Ethics Committee

WARRINGTON LREC

141294

NCH
NORTH CHESHIRE HEALTH
Lister Road, Astmoor West Estate
Runcorn, Cheshire WA7 1TW
Tel: 01928 593000 Fax: 01928 569532
Tel: 0928 592200 Fax: 0928 569532

**Our Ref:** W94/33 (Filename JCade)
**Please quote Ref No on all correspondence**

**Direct Line 0928 593050**

6 December, 1994

Dr Janet Cade
Principal Investigator
Nuffield Institute for Health
71-75 Clarendon Road
Leeds
LS2 9PL

Dear Dr Cade

**The UK Women's Nutrition and Lifestyle Survey - Reg Ref: W94/33**

Thank you for your application to the local Research Ethical Committee to carry out the above study. I am pleased to tell you that at the meeting on 1st December, 1994 ethical approval was given for the study to proceed.

I would point out the requirement to refer proposed amendments to the protocol to the LREC for further review and to obtain LREC approval prior to implementation (except only in cases of emergency were the welfare of the subject is paramount). If applicable the LREC should be informed should the research be discontinued or any subject withdrawn.

**Investigators should furnish the LREC with details of the progress of the research periodically (eg 6 monthly).**

Yours sincerely

**Dr D Pearson**
**Chairman Warrington LREC**

WORLD AIDS DAY 1 DECEMBER
An initiative by North Cheshire Health in support of WADD

Incorporating
North Cheshire Health Authority and the North Cheshire Division of Cheshire Family Health Services Authority

Yours sincerely

**Jade Robinson**
**REC Administrative Assistant**

E-mail: nrescommittee.yorkandhumber-leedseast@nhs.net



NHS
**Health Research Authority**
**NRES Committee Yorkshire & The Humber - Leeds East**
Room 001
Jarrow Business Centre
Rolling Mill Road
Jarrow
Tyne and Wear
NE32 3DT

Tel: 0191 428 3467

23 January 2015

Professor Janet Cade
Professor of Nutritional Epidemiology and Public Health and Head of Nutritional Epidemiology Group
The University of Leeds
Nutritional Epidemiology Group
Division of Epidemiology
Room 001a, Level 8, Worsley Buildin
LS2 9JT

Dear Professor Cade

| | |
|---|---|
| **Study title:** | **The UK Women's Diet and Lifestyle Cohort Study** |
| **REC reference:** | **15/YH/0027** |
| **IRAS project ID;** | |

This study was given a favourable ethical opinion by the Committee on 04 August 1995.

Research Ethics Committees are required to keep a favourable opinion under review in the light of progress reports and any developments in the study. You should submit a progress report for the study 12 months after the date on which the favourable opinion was given, and then annually thereafter. Our records indicate that a progress report is overdue. It would be appreciated if you could complete and submit the report by no later than one month from the date of this letter.

Guidance on progress reports and a copy of the standard NRES progress report form is available from the Health Research Authority website.

The Health Research Authority website also provides guidance on declaring the end of the study.

| | |
|---|---|
| **15/YH/0027:** | **Please quote this number on all correspondence** |

# APPENDIX XI FFQ items contributing to the dietary patterns

The following food groups list the items from the baseline FFQ which have been chosen to contribute to the various components making up the Mediterranean dietary pattern. The 'meat' component was used to generate both the Mediterranean dietary pattern and the WCRF/AICR dietary pattern, whist sugary drinks is a component only of the latter. Separate FFQ items are indicated with '|', whilst some lines in the FFQ list multiple foods, such as oranges, satsumas, grapefruit etc.

**Mediterranean dietary pattern**

***Vegetables include the following FFQ items:***

Quorn | Textured vegetable protein, sosmix, burgermix, soya sausages | Vegetarian chilli, vegetable curry | Mixed bean casserole, ratatouille | Stir-fry vegetables| Vegetable – lasagna, moussaka, ravioli, filled pasta with sauce | vegetable pizza | Beetroot| Broccoli, spring greens, kale| Brussels sprouts| Cabbage| Carrots | Cauliflower| Celery| Coleslaw (low calorie coleslaw)| Courgettes, marrow, squash| Cucumber| Garlic| Green beans, runner beans| Leeks | Lettuce | Mushrooms| Aubergine, okra, ladies finger| Parsnips| Peas, mushy peas, mange-tout| Peppers – red, green, yellow, black etc.| Swede| Sweet corn| Tomatoes (raw, canned, sauce)| Turnip| Watercress, mustard & cress.

***Legumes include the following FFQ items:***

Lentils, dahls| Chick peas, chanas| Hummus| Baked beans| Mung beans & red kidney beans| Bean sprouts | Black eyed beans| Butter beans and broad beans.

***Fruit & nuts include the following FFQ items:***

Apples | Avocado| Bananas| Grapes| Kiwi| Mangoes| Oranges, satsumas, grapefruit etc.| Papaya| Pears| Pineapple| Apricots| Melon| Nectarines| Peaches| Plums| Raspberries| Currants red and black| Rhubarb| Strawberries| Dates| Figs| Prunes| Mixed dried fruit| Raisins and sultanas |Fruit tarts, pies and crumbles| Bombay mix |Peanuts and pistachio| Mixed nuts |Cashews and almonds| Pecans and walnuts| Sunflower and sesame seeds.

***Cereals include the following FFQ items:***

White bread & rolls| Brown bread & rolls| Wholemeal bread & rolls| Chapattis, Nan, Paratha| Papadums| Tortillas| Pitta bread| Crispbread e.g. Ryvita| Cream crackers, cheese biscuits| Porridge, readybrek| Sugar coated cereals e.g. sugar puffs| Non-sugar coated cereals e.g. cornflakes, rice krispies| Muesli| All bran, bran flakes| Weetabix, shredded wheat| White pasta e.g. spaghetti, green pasta, red pasta, noodles| Wholemeal pasta, brown spaghetti| White rice| Brown rice| Wild rice| Macaroni cheese | Barley| Bulgar wheat| Wheat germ| Couscous.

***Fish includes the following FFQ items:***

Fish fingers & cakes | Fried fish in batter | White fish e.g. cod, haddock, plaice, sole, halibut | Oily fish e.g. mackerel, kippers, tuna, salmon, sardines, herring | Shellfish e.g. crab, prawns, mussels | Fish roe & taramasalata | Fish pie & lasagne.

***Meat includes the following FFQ items:***

Beef e.g. roast, steak | Beef stew, casserole, mince, curry | Beefburger, hamburger | Pork e.g. roast, chops, slices | Pork stew, casserole | Lamb e.g. roast, chops | Lamb stew, casserole | Bacon | Ham | Corned beef, spam, luncheon meats | Sausages e.g. beef pork | Pies, pasties, sausage rolls | Offal e.g. liver, kidney | Liver pate', sausage & salami | Meat lasagne, moussaka, ravioli, filled pasta with sauce | Meat pizza.

***Poultry includes the following FFQ items:***

Chicken / Turkey roast, slices | Breadcrumbed chicken nuggets, kievs | Chicken, turkey in cream sauce, curry.

***Dairy includes the following FFQ items:***

Thick and creamy yoghurt | Low fat yoghurt | Diet yoghurt | Greek yoghurt | Fromage frais, crème fraiche | Dairy desserts | Single, sour cream | Double, clotted cream | Icecream | milk puddings | Low-fat cheese | Cheese e.g. Cheddar, Brie, Edam | Cottage cheese | Cheese & onion pastie | Butter.

**WCRF/AICR dietary pattern**

***Sugary drinks include:***

Orange juice (pure fruit) | 100% Pure fruit juices | Fizzy soft drinks e.g. Coke, Lemonade.

# APPENDIX XII Food subcategories for the generation of dietary patterns from food diaries

The following is a list of the different food subcategories, as found in McCance & Widdowson's *The Composition of Foods* (Holland et al., 1991), that have been combined to generate the different components of the Mediterranean dietary pattern, from FD data. The 'meat' component was used to generate both the Mediterranean dietary pattern and the WCRF/AICR dietary pattern, whist sugary drinks is a component only of the latter.

**Mediterranean dietary pattern**

1. **Legumes**

- Beans and lentils
- Vegetable dishes (beanburgers, curries, dahl, falafel, lentil cutlets, lentil roast etc.)

2. **Nuts**

- Nuts and seeds, general

3. **Cereals & cereal products**

- Flours, grains & starches
- Rice
- Pasta
- Breads
- Rolls
- Breakfast cereals
- Biscuits (oatcakes, water biscuits, matzos)

4. **Fish & fish products**

- White fish
- Fatty fish
- Crustacea
- Molluscs
- Fish products (caviar, crabsticks, fishcakes, fish fingers etc.)
- Fish dishes (pies, pasta etc.)

5. **Meat & meat products**

- Beef
- Veal
- Lamb
- Pork

- Venison
- Offal (except chicken)
- Bacon
- Meat products (hams, salamis, burgers, sausages etc.)
- Meat dishes (pies, curries, stews, ribs etc.)

### 6. Poultry (meat and meat products)

- Chicken
- Duck
- Turkey
- Goose
- Hare
- Partridge
- Pheasant
- Pigeon
- Offal (chicken)
- Meat products (nuggets, kievs etc.)
- Meat dishes (pies, curries, stir-fries etc.)

### 7. Dairy (milk and milk products)

- Milk and milk based drinks
- Creams
- Cheeses
- Yoghurts
- Ice-creams
- Puddings and chilled desserts
- Savoury dishes and sauces

## WCRF/AICR dietary pattern

### 8. Sugary drinks

- Fruit juices
- Carbonated drinks (low calorie excluded)

## APPENDIX XIII Directed Acyclic Graph for the variables associated with dietary patterns and colorectal cancer