DIET AND RISK OF CENTRAL NERVOUS SYSTEM TUMOURS



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Abstract

Existing evidence suggests diet may be associated with risk of central nervous system (CNS) tumours, but there is inconsistency between studies and limited knowledge of variation by tumour subtype. I present findings from the first systematic review and meta-analysis of the literature, and the first comprehensive analyses for the major subtypes of CNS tumours in large prospective studies with systematic coverage of dietary patterns, food groups, and nutrients.

Systematic review identified 37 epidemiological (predominantly case-control) studies, investigating risk of CNS tumours (predominantly glioma) in relation to 36 dietary factors in total. Meta-analyses of case-control studies showed some evidence for associations between vegetable or carotene intake and grains/cereal intake with decreased and increased glioma risk, respectively, and fruit intake and decreased meningioma risk, but these associations were not supported by the limited prospective evidence.

I investigated CNS tumour risk in relation to 29 food groups/nutrients and 3 dietary patterns, using data from the Million Women Study, NIH-AARP Study and PLCO Study for 2,313 cases of glioma, 750 of meningioma, 191 of pituitary tumours, and 174 of vestibular schwannoma, occurring during 15.4 million person-years follow-up. Using Cox regression, I found no significant association between any dietary factor and risk of any CNS tumour subtype, after applying a correction for multiple testing. For glioma, there were some borderline significant associations before correction, between increasing intakes of plant-based foods or increasing healthy diet scores and increasing risk, but these attenuated towards null in analyses accounting for reverse causation. For meningioma and vestibular schwannoma, the few significant associations found before correction for multiple testing may be chance findings. For pituitary tumours, there was no evidence of an association with diet.

This largest prospective analysis provides little evidence for any association of public health importance between diet and risk of the four major CNS tumour subtypes.

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List of Abbreviations

AHEI . . . . . The Alternative Healthy Eating Index

aMED Score . The Alternate Mediterranean Diet Score

ASR . . . . . Age-Standardised Rate

BMI . . . . . Body Mass Index

CA-125 . . . . Cancer Antigen 125

CBTRUS . . . Central Brain Tumor Registry of the United States

CI . . . . . Confidence Interval

CNS . . . . . Central Nervous System

DASH Score . The Dietary Approaches to Stop Hypertension Score

DRE . . . . . Digital Rectal Examination

EPIC . . . . . The European Prospective Investigation into Cancer and Nutrition Study

FFQ . . . . . Food Frequency Questionnaire

gs-CI . . . . . group-specific Confidence Interval

GPRD . . . . . General Practice Research Database

GWAS . . . . . Genome-Wide Association Study

HEI . . . . . The Healthy Eating Index

HES . . . . . Hospital Episode Statistics

HPFS . . . . . The Health Professionals Follow-Up Study

HRT . . . . . Hormone Replacement Therapy

IARC . . . . . The International Agency for Research on Cancer

ICD-10 . . . . International Classification of Diseases 10th revision

ICD-O-2 . . . International Classification of Diseases for Oncology, 2nd Edition

ICD-O-3 . . . International Classification of Diseases for Oncology, 3rd Edition

Iowa WHS . . The Iowa Women's Health Study

IQR . . . . . Interquartile Range

JPHC . . . . . The Japan Public Health Center-Based Prospective Study

KPMCP-NC . The Kaiser Permanente Medical Care Program of Northern California Study

MCCS . . . . . The Melbourne Collaborative Cohort Study

MED Score . . The Mediterranean Diet Score

MeSH . . . . . Medical Subject Headings

MWS . . . . . The Million Women Study

NCI . . . . . National Cancer Institute

NDI . . . . . National Death Index

NDNS . . . . . The National Diet and Nutrition Survey

NHS . . . . . National Health Service

NHS I . . . . . The Nurses' Health Study I

NHS II . . . . The Nurses' Health Study II

NIH-AARP . The National Institute of Health - AARP (formerly the American Association of Retired Persons) Study

OC . . . . . Oral Contraceptives

ONS . . . . . Office for National Statistics

OPCS . . . . . OPCS Classification of Interventions and Procedures

PBPP . . . . . Public Benefit and Privacy Panel for Health and Social Care

PHE . . . . . Public Health England

PLCO . . . . . The Prostate, Lung, Colorectal, Ovarian Cancer Screening Trial Study

PSA . . . . . Prostate Specific Antigen

RR . . . . . Relative Risk

SD . . . . . Standard Deviation

SES . . . . . Socioeconomic Status

SIR . . . . . Standardised Incidence Ratio

SMR . . . . . Scottish Morbidity Record

SNP . . . . . Single Nucleotide Polymorphism

TVU . . . . . Transvaginal Ultrasonography

UK . . . . . United Kingdom

US . . . . . United States of America

USDA CSFII US Department of Agriculture's Continuing Survey of Food Intakes by Individuals

vs . . . . . versus

WCRF/AICR World Cancer Research Fund/American Institute of Cancer Research

WHO . . . . . World Health Organization

1

Thesis Introduction

1.1 Introduction

This thesis studies the risk of central nervous system (CNS) tumours in relation to a variety of dietary factors including food groups, nutrients, and dietary patterns. In this thesis, I present findings from a systematic review and meta-analysis of the literature and from original analyses in a large cohort of UK women and two large cohorts of US men and women.

This chapter provides an overview of the thesis. It outlines the rationale for the thesis, namely that there is some evidence that diet may be associated with risk of CNS tumours, but there is inconsistency in evidence between studies and incomplete knowledge of the variation of risk factors between subtypes of CNS tumours. It also outlines the aims of the thesis – to summarise published evidence on diet and risk of CNS tumours systematically (Chapter 3) and to estimate reliably the risk of subtypes of CNS tumours in relation to diet in three very large cohorts (Chapters 6–8).

1.2 Rationale

CNS tumours are relatively uncommon in the UK, with 10,981 cases diagnosed and 5,223 deaths recorded in 2014.[1, 2] CNS tumours are one of the top three most lethal cancers in the UK, with an age-standardised five-year survival of 18.5% (95% CI 17.4–19.6%) during 2010–2011.[3] The poor survival of CNS tumours is attributable to a lack of effective treatment and, at least in part, to the predominantly late stage at diagnosis.[4, 5] The absence of both effective treatment and preclinical symptoms makes it important that risk factors of these tumours be identified.

Apart from some rare genetic factors (e.g. mutations that cause neurofibromatosis), the only well-established risk factor for CNS tumours is exposure to ionising radiation, despite the huge effort that has been invested into the investigation of risk factors for CNS tumours.[6, 7] These rare genetic factors and exposure to ionising radiation, however, account for only a very small proportion of CNS tumours in humans. Associations between modifiable lifestyle factors such as

tobacco smoking, alcohol intake, physical activity, or body mass index/obesity, and risk of CNS tumours have been investigated in many studies, although the evidence for many of the associations is not conclusive.[8–12] On the other hand, diet remains an understudied factor.

Many nutrients are essential in maintaining the function of the CNS and can therefore cross the blood brain barrier, which may have a role in preventing many harmful substances from reaching the CNS. Several dietary factors have been shown or suggested to be associated with risk of CNS tumours, but very few associations have been consistently reported.[13–16] These inconsistent findings may be due to study designs with retrospective ascertainment of exposure and consequent risk of bias, and/or the insufficient number of cases in many of the studies. Besides, foods and nutrients are consumed in combination, so the risk of CNS tumours in relation to the intake of a particular dietary item observed in a study may be confounded by other components of diet, due to complex interplay or correlation between dietary intakes. Furthermore, CNS tumours are a collection of tumours that have different origins (e.g. glial cells, meninges, endocrinal cells or nerve sheaths in the CNS [see Chapter 2]), and there has been increasing evidence that different subtypes of CNS tumours may have different risk factors, including dietary factors.[6, 17–21]

Thus, there is a need to study the risk of specific subtypes of CNS tumours in relation to diet in large prospective studies, which have sufficient numbers of cases of all subtypes, and have collected comprehensive dietary information before onset of disease.

1.3 Research Aims

Using very large cohort studies with prospectively collected dietary data and follow-up data via record linkage to cancer registries, this thesis aims to provide a detailed understanding of the association between diet and risk of subtypes of CNS tumours. This thesis will estimate the risk of subtypes of CNS tumours in relation to intakes of major food groups, nutrients, and dietary patterns using data from a total of 1.5 million individuals who provided dietary data from one study in the UK, the Million Women Study, and two studies from the US National Health Institutes – AARP (formerly the American Associations of Retired Persons) Diet and Health (NIH-AARP) Study, and the US Prostate, Lung, Colorectal, Ovarian Cancer Screening Trial (PLCO) Study. I also summarise evidence from published studies by undertaking a systematic literature review, and then compare and discuss all the available evidence.

1.4 Outline of this thesis

Chapter 2 reviews the epidemiology of CNS tumours and evidence for non-dietary risk factors. This chapter briefly introduces the central nervous system and CNS tumours, and provides possible explanations for variation in incidence, mortality and survival statistics for CNS tumours between countries, using the UK and US as examples. It also highlights non-dietary factors that have been suggested to be associated with CNS tumour risk, many of which may be confounders for the association between diet and risk of CNS tumours.

Chapter 3 systematically reviews evidence on the risk of CNS tumours and subtypes of CNS tumours in relation to diet, which includes major food groups, nutrients and dietary patterns. It outlines the search strategies and presents results from meta-analyses of the published studies subsequently obtained, summarising the current evidence for the association between diet and CNS tumour risk as well as discussing its limitations. This explains the need for the present study.

Chapter 4 introduces a large prospective cohort of UK women, the Million Women Study, which is one of the main data sources used for analyses in this thesis. This chapter also describes the development of the dietary data and dietary variables (in which I took a lead role) as well as CNS tumour variables, which were used in the analyses subsequently presented in this thesis (Chapters 6–8). In addition, this chapter outlines the basic characteristics of study participants including their baseline and re-survey dietary information.

Chapter 5 introduces two large prospective cohorts of US men and women, the NIH-AARP Study and the PLCO Study, which are the other main data sources used for analyses in this thesis. This chapter also shows the basic characteristics of these study participants including their baseline dietary information.

Chapter 6 investigates the risk of the most common subtype of CNS tumours, glioma, in relation to diet including major food groups, nutrients, and dietary patterns. This study is a prospective analysis in 3 cohorts: the Million Women Study cohort with 1,173 cases of glioma that had accrued by 31 December 2015; the NIH-AARP Study cohort with 1,005 cases of glioma that had accrued by 31 December 2011; and the PLCO Study cohort with 135 cases of glioma that had accrued by 31 May 2011.

Chapter 7 investigates the risk of the second most common subtype of CNS tumours, meningioma, in relation to diet including major food groups, nutrients, and dietary patterns. This study is a prospective analysis in the Million Women Study cohort with 750 cases of meningioma that had accrued by 31 December 2015.

Chapter 8 investigates the risk of CNS tumours other than glioma and meningioma in relation to diet including major food groups, nutrients, and dietary patterns. This study is a prospective analysis in the Million Women Study cohort with 174 cases of vestibular schwannoma, and 191 cases of pituitary tumours that had accrued by 31 December 2015.

Chapter 9 summarises the main findings of this thesis in the context of the existing literature. This chapter outlines the main results from chapters 6 to 8, discusses the strengths and limitations of the current study, and makes recommendations for future research.

1.4.1 Approximate word count

The approximate length of this thesis, excluding the bibliography, appendices, tables and figures is 42,000 words.

1.5 Role of the author in the preparation of this thesis

The work presented in this thesis is my own except as described below. Jane Green, Valerie Beral, and Amy Berrington de González led the original idea for a study of diet and risk of CNS tumours in the UK Million Women Study and the US NIH-AARP Study. Amy Berrington de González and Cari Kitahara suggested studying the association in the PLCO Study cohort. I was responsible for the subsequent design and conduct of all of the studies presented in this thesis.

The data for the study of diet and risk of CNS tumours in the UK Million Women Study are held by University of Oxford, Nuffield Department of Population Health, Cancer Epidemiology Unit. Valerie Beral, Jane Green, and Gillian Reeves agreed on the release of data for the analyses conducted in this thesis. Sau Wan Kan and Keith Shaw extracted anonymised data from the database and provided technical support for the access of the data. The data for the study of diet and risk of CNS tumours in the NIH-AARP Study and the PLCO Study in the US are held by National Institutes of Health, National Cancer Institute. I was responsible for drafting and submitting the proposals for the application for data from the NIH-AARP Study and the PLCO Study in the US. Jane Green, Siân Sweetland, Amy Berrington de González, and Cari Kitahara read, provided comments, and

approved the proposals. The review committees of both the NIH-AARP Study and PLCO Study agreed on the release of data for the analyses conducted in this thesis. Linda Liao and Michael Spriggs extracted anonymised data from the database and provided technical support for the access of data.

The dietary database in the UK Million Women Study was originally prepared by Paul Appleby, Andrew Roddam, Angela Balkwill, and Tim Key. The review and development of dietary data and dietary variables in the UK Million Women Study was done collaboratively by myself, Kathryn Bradbury, and Angela Balkwill. Valerie Beral, Jane Green, Tim Key, and Siân Sweetland advised and agreed on all of the proposed changes made to the dietary data.

Jane Green and Siân Sweetland acted as second reviewers for the systematic review of diet and risk of CNS tumours, and I conducted the meta-analysis with advice from both of them. The statistical analyses of risk of CNS tumours in relation to diet in the UK Million Women Study were designed collaboratively by myself, Jane Green, and Siân Sweetland, while the analyses in the US NIH-AARP Study and the PLCO Study were designed collaboratively by myself, Amy Berrington, and Cari Kitahara. I performed all of the analyses myself.

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2

The Epidemiology of Central Nervous System Tumours

2.1 The Central Nervous System (CNS) and CNS Tumours

The central nervous system (CNS), consisting of the brain and the spinal cord, is made up of neurons and supporting cells. Neurons process and transmit neuronal information while supporting cells, including mostly glial cells, provide structural, metabolic, and developmental support to neurons. The brain and spinal cord are covered by three layers of membranes called the meninges. Tumours that arise in the brain or spinal cord and the meninges are called primary CNS tumours whereas tumours that arise in other parts of the body and spread to the CNS are called secondary CNS tumours or CNS metastases. The epidemiology and distribution of CNS tumours by site and cell types vary greatly between adults and children and they are often discussed independently. In this thesis, I have concentrated on adult primary CNS tumours, both malignant and non-malignant forms, hereinafter referred to collectively as CNS tumours.

In the UK and the US, the vast majority (96%–97%) of CNS tumours occur in the brain.[1, 2] CNS tumours in adults have been historically classified into several major subtypes according to anatomical sub-site or cell type, of which the four most common subtypes are: glioma (27%–45%) that arises from glial cells; meningioma (21%–37%) that arises from meninges; pituitary tumours (8%–17%); and nerve sheath tumours or schwannomas (6%–8%) which are predominantly vestibular schwannoma (also known as acoustic neuroma).[1, 2] These four common subtypes constitute 79%–88% of CNS tumours, and consequently cause the biggest burden in adults.[1, 2] Other CNS tumours include embryonal tumours (germ cell tumours), craniopharyngioma, choroid plexus tumours, neuronal and mixed neuronal-glial tumours, tumours of the pineal region, and other rarer tumours. In England about 14% of CNS tumours registered in cancer registries are of unknown or unspecified type, while in the US this number is about 6%.[1, 2]

Unlike non-malignant tumours in most other parts of the body, non-malignant CNS tumours can cause damage that is often disabling, and sometimes life-

threatening, when they continue to grow and compress normal CNS tissue in the limited space internal to the hard skull or vertebra. Thus, they may impose similar harms to the individual, and costs to society due to medical care and/or productivity lost, as do malignant CNS tumours.

2.2 Incidence, Mortality, and Survival

Incidence rates for CNS tumours (global age-standardised rate [ASR] about 3.5 per 100,000) show considerable global variation, with higher incidence (ASR about 6 per 100,000) seen particularly within Europe, North America, Australasia or more developed countries, and lower incidence (ASR about 2 per 100,000) in Africa, South-Eastern Asia, South Asia or less developed countries.[3] The higher incidence of CNS tumours in developed countries when compared with less developed countries may reflect better diagnosis and registration of tumours. However, published incidence rates for CNS tumours must be interpreted with care because many national or regional incidence statistics do not include non-malignant tumours. Inclusion of non-malignant CNS tumours is important to allow fuller evaluation of the disease burden.

In the UK and the US in particular, where systematic collection of non-malignant CNS tumours by cancer registry at the national level has taken place since the 2000s,[1, 4] the ASRs of total incident CNS tumours are much higher at 18.0 (95% CI 17.7–18.4) per 100,000 UK population in 2014, and 22.0 (95% CI 21.9–22.1) per 100,000 US population annually during 2008–2012.[1, 2] Before systematic registration of non-malignant CNS tumours was initiated, two studies conducted in the UK (one was in England and the other one was in Scotland) in the 1990s that compared independently collected data from regional incidence studies with registrations from regional cancer registries showed that registrations of brain tumours were incomplete, particularly for non-malignant tumours.[5, 6] The regional study in England showed that only 42% of benign brain tumours were registered.[6] The regional study in Scotland showed that only 19% of meningiomas, which are

generally benign, were registered.[5] Although there was no information from these studies for overall CNS tumours, these statistics are likely to be applicable to CNS tumours, which are predominantly made up of brain tumours (see section 2.1). However, the extent of non-recording of non-biopsied CNS tumours (e.g. found in brain scans) in cancer registries at the current time is not known, and to what extent the incidence of CNS tumours is underestimated remains unclear.

Within the UK in 2014, CNS tumours were the eleventh most common incident cancer amongst men (ASR 18.4 [95% CI 17.9–18.9] per 100,000) and the ninth most common incident cancer amongst women (ASR 17.8 [17.3–18.2] per 100,000).[1, 7] The majority of UK patients with CNS tumours have higher grade tumours at diagnosis[1] (WHO grade III-IV)[8]. The estimated cumulative lifetime risks of incident CNS tumours in the UK are 1.35% for men and 1.37% for women.[1] In 2014 CNS tumours were the ninth most common cause of cancer mortality amongst men (ASR 10.4, [10.1–10.8] per 100,000) and the seventh amongst women (ASR 7.2, [7.0–7.5] per 100,000).[9, 10] Published data show that malignant CNS tumours are one of the top three most lethal cancers (after cancers of the pancreas and lung) in the UK, with age-standardised 5-year survivals of 17.8% (16.3–19.4) and 19.5% (17.9–21.1) in men and women, respectively.[11, 12] However, data for overall CNS tumours (malignant and non-malignant combined) were not published.

In the US, the Central Brain Tumor Registry of the United States was initiated in 1992 to provide complete and good quality statistical data on population-based malignant and non-malignant CNS tumours, and to establish awareness of the disease. The CBTRUS now includes data from 50 state cancer registries and the District of Columbia, and has been publishing CNS tumour statistical reports in journals since 2012.[2, 13] In the most recent report published in 2016, the annual ASRs of incident CNS tumours in 2009–2013 were 20.1 (20.0–20.2) and 24.5 (24.4–24.6) per 100,000 US men and women, respectively.[2, 14] These statistics rank CNS tumours as the eighth most common in men and fifth most common in women when compared with the incidence of other cancer sites published in the 2010–2014

United States Cancer Statistics report produced by the Centers for Disease Control and Prevention and the National Cancer Institute.[2, 14] These numbers are higher than those in UK populations because, at least in part, they included lymphoma and other haematopoietic cancers (ASR 0.44 per 100,000) and olfactory tumours of the nasal cavity (ASR 0.05 per 100,000) as CNS tumours. About 45% of US patients with CNS tumours have higher grade tumours (WHO grade III-IV) at diagnosis.[2] Information such as cumulative incidence, cancer mortality and survival data for CNS tumours in the US is only available for malignant tumours. The estimated cumulative lifetime risk of malignant CNS tumours in the US is 0.70% for men and 0.54% for women.[15] In 2010–2014 malignant CNS tumours were ranked as the eleventh most common cancer mortality in men (ASR, 5.3 per 100,000) and the tenth most common cancer mortality in women (ASR, 3.5 per 100,000).[15] For men and women in the US with malignant CNS tumours diagnosed in 2009, the age-standardised 5-year relative survivals were 34.8% and 37.6%, respectively.[15]

There is some variation in incidence of CNS tumours by sex and ethnicity. In the US, the incidence of glioma is higher in men (ASR 6.3 per 100,000) than women (ASR 5.4 per 100,000) whereas the incidence of meningioma is higher in women (ASR 11.1 per 100,000) than men (ASR 5.1 per 100,000); most gliomas are malignant (men 93.1%, women 92.6%) and most meningiomas are benign (men 97.0%, women 98.7%).[2] In the US, the vast majority of pituitary tumours (men 99.7%, women 99.8%) and nerve sheath tumours (men 99.2%, women 99.3%) are benign, and the incidence of these is rather similar between men and women (ASR in men vs women: pituitary 3.39 vs. 4.01 per 100,000; nerve sheath 1.82 vs. 1.83 per 100,000).[2] Published data on CNS tumour incidence in the UK is limited to overall estimates of malignant CNS tumour by sex and ethnicity and there are no incidence statistics by subtype. The incidence of malignant CNS tumours in the UK is higher in men than women and is higher in Whites (ASR range: men 8.2–8.7, women 5.3–5.6 per 100,000) than non-Whites (Asian ASR range: men 4.0–6.5 women 2.4–4.3; Black ASR range: men 2.9–5.4, women 2.1–4.1 per 100,000).[1] In the US, although incidence rates for overall CNS tumours are similar between Whites and African-Americans (both

ASR 22.5 per 100,000), incidence of gliomas and nerve sheath tumours is higher in Whites (glioma ASR 6.83 vs. 3.76 per 100,000, and nerve sheath tumour ASR 1.92 vs. 0.93 per 100,000 for Whites vs African-Americans respectively).[2] In contrast, incidence of meningioma and pituitary tumours is higher in African-Americans than in Whites (meningioma ASR 9.81 vs 8.11 per 100,000, and pituitary tumour ASR 5.93 vs 3.33 per 100,000, for African-Americans vs Whites respectively).[2] Variation of incidence by ethnicity may reflect differences in true incidence, or reporting, or diagnosis by socioeconomic status. A study in the US showed that there were significant associations between high levels of educational attainment or high income and increased risks of low-grade glioma and vestibular schwannoma (evidence for meningioma was mixed), and suggested that these associations may relate more to the diagnosis of tumours rather than to their inception.[16] A study in Sweden suggested that the increased glioma incidence associated with higher socioeconomic position (both higher educational attainment and income levels) found in their study may be due to detection bias and more complete cancer registration (i.e. seeking medical care earlier so more likely to have surgery and subsequent cancer registration).[17] The Swedish study also reported significant associations between higher educational attainment and increased meningioma incidence in women only and suggested that it may be due to detection bias as well as differences in reproductive factors and hormonal use (see next section).[17]

2.3 Risk factors

Associations reported in some studies for risk factors of CNS tumours are difficult to interpret for several reasons. Firstly, CNS tumours are relatively uncommon, particularly by subtypes. Many studies of risk factors for specific CNS tumours lack power, and often report relative risk estimates with wide confidence intervals. Secondly, many studies that investigate risk factors for CNS tumours are of case-control design. Recall bias in case-control studies of CNS tumours is a particular problem because CNS tumours may impair cognitive function, and are often rapidly

fatal. The proportion of proxy responses for recall of exposure data is often high; for instance, in the multicentre international case-control study coordinated by the International Agency for Research on Cancer (IARC), which investigated multiple risk factors including diet and occupational history for glioma, the proportion of proxy response in cases was 26.7%.[18, 19] Therefore, associations reported in case-control studies of CNS tumours may be unreliable. In addition, it is also important to consider reverse causality when interpreting associations because patients with CNS tumours may change their lifestyle (e.g. quit smoking) or may experience weight changes as a result of cognitive impairment or approaching the terminal state of the disease. Associations reported in large studies with prospective collection of information, which have many cases of CNS tumours even by subtypes, are more reliable.

Studies investigating risk factors for CNS tumours often do not have adequate statistical power to perform sex-specific analyses. Sex-specific results are more informative than estimates for men and women combined that are adjusted for sex. Incidence of the different subtypes of CNS tumours and the distribution of many factors including lifestyle and anthropometric measures may be very different between men and women. So, results from analyses examining incidence of CNS tumours in relation to these factors in men and women combined may still be subject to residual confounding by sex, even if they have adjusted for this factor. For example in the NIH-AARP cohort, the mean height of men (178.3cm) is much higher than women (163.3cm).[20] Analyses examining risk of CNS tumours in relation to height (in categories, e.g. >180cm vs. ≤160cm) in men and women combined would still be confounded by sex even after adjustment for sex. The distribution of sex across categories of height will be unequal; in particular there will be an insufficient number of women in the exposed (>180cm) category and an insufficient number of men in the reference (≤160cm) category. Besides, there is some evidence that use of menopausal hormones and female reproductive factors are associated with risk of CNS tumours.[21–23] These female-related factors may need to be taken account of in analyses in women.

Risk factors for CNS tumours, for which the distribution may be different between men and women, will be discussed separately in this section, where possible. This section reviews non-dietary risk factors for CNS tumours (summarised in Table 2.1), many of which may be confounders for the association between diet and risk of CNS tumours. Published evidence on dietary risk factors for CNS tumours, including alcohol intake, is summarised in Chapter 3.

2.3.1 Genetic factors

A number of genetic syndromes, which involved mutation of genes that control cell growth and/or cell division, are associated with increased risk of CNS tumours. In particular, neurofibromatosis 1 is associated with increased risks of glioma and schwannoma including vestibular schwannoma; neurofibromatosis 2 is associated with increased risks of glioma, meningioma, and vestibular schwannoma; tuberous sclerosis, Lynch syndrome, Li-Fraumeni syndrome, melanoma-neural system tumour syndrome and Maffucci syndrome are associated with an increased risk of glioma.[24–26] These monogenic Mendelian disorders are rare and account for only a very small proportion (about 1%) of CNS tumours at population level.[25, 27] Genome-wide association studies (GWAS) have identified germline DNA single nucleotide polymorphisms (SNPs) with relatively high allele frequency in a few genes (e.g. TERT, EGFR, CDKN2B, and RTEL1) that are associated with a small increased risk of glioma (range of RR: 1.20–1.50).[24] However, evidence from GWAS is limited by the small number of studies for any polymorphisms, and the relatively unclear biologic pathways of these polymorphisms.[24]

2.3.2 Ionising radiation

Ionising radiation may cause genomic instability (e.g. DNA double-strand break), which increases rate of mutation of genes.[28] Ionising radiation is the only non-genetic risk factor listed as a carcinogenic agent for the brain and central nervous system with sufficient evidence in humans (Group 1) by IARC,[29] based on

extensive study of atomic bomb survivors.[28] The study of atomic bomb survivors in Hiroshima and Nagasaki showed that increasing exposure to radiation was associated with increased incidence of glioma, meningioma, schwannoma, and pituitary tumours.[30–33] There were some linear associations between radiation exposure and risk of CNS tumours: the excess relative risk per Sievert (ERRSv) radiation exposure was statistically significant for schwannoma (ERRSv 4.5, 95% CI 1.9–9.2), borderline significant for meningioma (ERRSv 0.64, 95% CI -0.01–1.8), and not statistically significant for glioma (ERRSv 0.56, 95% CI -0.2–2.0) or pituitary tumours (ERRSv 0.98, 95% CI <-0.2–3.5).[30–33] There is also some evidence that therapeutic radiation exposure increases the risk of CNS tumours.[34, 35] In the past, radiation was once used for treatment of tinea capitis, a fungal disease of the scalp. A small study from Israel showed that, for patients who received cranial irradiation for tinea capitis, the risks of meningioma (RR 9.5, 95% CI 3.5–25.7) and nerve sheath tumours (RR 33.1, 95% CI 9.4–116.5) were significantly increased when compared with matched non-irradiated individuals or siblings (no significant association for glioma: RR 2.6, 95% CI 0.8–8.6).[34, 35] Evidence for risk of CNS tumours from other forms of radiation exposure, such as patients receiving other radiotherapy or radiation from diagnostic imaging examinations, or workers with occupational exposure to ionising radiation, is inconclusive.[24, 36, 37]

2.3.3 Non-ionising radiation

Radiofrequency electromagnetic fields, such as those emitted by mobile telephones, have been commonly discussed and investigated for their associations with brain tumours.[38–44] Such electromagnetic fields may induce biological changes such as small changes in protein structure that affect binding of ligands to receptor proteins, and were classified by the IARC as a carcinogenic agent for the brain with limited evidence in humans (Group 2B) in 2011.[45] The IARC summary report suggested that increased use of mobile phones may be associated with increased risks of glioma and vestibular schwannoma, while evidence for meningioma was insufficient to reach a conclusion.[45] However, this report was based on results mainly from

case-control studies (5 case-control studies[38, 41–44] and only 1 cohort[46]) and the interpretation remains debatable, for reasons given earlier at the beginning of section 2.3. Subsequently, an updated report published by a large Danish cohort study showed no significant associations between mobile phone use (subscribers vs. non-subscribers) and risk of glioma (RR in men 1.08, 95% CI 0.96–1.22; RR in women 0.98, 95% CI 0.69–1.40) or meningioma (RR in men 0.78, 95% CI 0.58–1.05; RR in women 1.02, 95% CI 0.71–1.47).[40] Results from the Million Women Study in the UK were consistent with those of the Danish study, in that no significant associations were found between mobile phone use (ever user vs never user) and risk of glioma (RR 0.91, 95% CI 0.76–1.08), or meningioma (RR 1.05, 95% CI 0.81–1.38), or pituitary tumours (RR 1.52, 95% CI 0.99–2.33).[39] Although a significant association between long duration use of a mobile phone (10+ years use vs. never user) and increased risk of vestibular schwannoma was shown in the initial report published by the Million Women Study (RR 2.46, 95% CI 1.07–5.64) (96 cases),[39] this association was no longer significant in the 2014 updated analysis with slightly more cases (RR 1.17, 95% CI 0.60–2.27) (total number of cases = 126).[47]

2.3.4 Occupational exposures

A large study in Nordic countries, which linked occupation information of 15 million people obtained from the census to cancer registry data, found that incidence rates of glioma and meningioma in physicians were increased when compared with age-and-sex-standardised rates in the general population.[48] These increased incidence rates/ratios, however, were only statistically significant for glioma in female physicians [standardised incidence ratio (SIR) 1.55, 95% CI 1.02–2.25] and for meningioma in male physicians (SIR 1.53, 95% CI 1.13–2.01).[48] Ascertainment bias may explain the increased incidence of CNS tumours in physicians. For instance, physicians may have an increased insight into neurological symptoms caused by CNS tumours, which may lead to an earlier diagnosis of the disease.

Some studies have also reported increased risks of glioma in firefighters and farmers, and increased risks of any brain tumours in pathologists and embalmers, suggesting that the elevated risks may be associated with occupational exposures to chemicals or inorganic solvents, which are carcinogenic.[24, 36, 37] Many studies have subsequently investigated risk of CNS tumours in relation to exposure to pesticides, petroleum products, or polycyclic aromatic hydrocarbons, but findings were inconsistent.[24, 36, 37] Amongst the more than 300 chemicals that have been classified by IARC as agents that are carcinogenic (group 1), probably (group 2A) or possibly (group 2B) carcinogenic to humans, none has been listed as a carcinogen (sufficient or limited evidence) for the brain or central nervous system.[29]

2.3.5 Personal history of allergies

It has been suggested that people with allergic phenotype have enhanced cellular immunity that may inhibit the development of glioma.[36] A systematic review and meta-analysis of observational studies (3 cohort and 9 case-control studies) has suggested an inverse relationship between allergy and risk of glioma: any allergic conditions summary RR 0.61, 95% CI 0.55–0.67; asthma summary RR 0.68, 95% CI 0.58–0.80; and eczema summary RR 0.69, 95% CI 0.58–0.82.[49] The meta-analysis did not find a significant association between any allergy conditions and meningioma (summary RR 0.93, 95% CI 0.72–1.19).[49] The significant associations between allergy and glioma reported in the meta-analysis were mainly driven by the results of the contributing case-control studies, which all reported statistically significant associations, whereas all cohort studies reported null or non-significant associations.[49] Therefore, these significant associations may be subject to selection bias and/or recall bias, and may not be reliable. Some studies have investigated the association between allergy-related SNPs and risk of glioma but the results were conflicting and inconclusive.[24, 36, 37]

2.3.6 Anthropometric factors

2.3.6.1 Height

Published evidence has suggested that increasing adult height is associated with increasing incidence of glioma.[50–53] In a 2012 pooled analysis of original data (with 1354 gliomas) from 13 prospective studies (including the PLCO study) and 2 case-control studies, Kitahara et al. found a non-linear association between height and risk of glioma in men (≥190cm vs. 170–174cm: RR 1.70, 95% CI 1.11–2.61; per 5-cm increase: RR 1.05, 95% CI 0.98–1.12), but not in women (≥175cm vs. 160–164cm: RR 1.06, 95% CI 0.70–1.62; per 5-cm increase: RR 1.02, 95% CI 0.94–1.10).[51] The authors of the pooled analysis acknowledged that their results were different from other previously published studies, particularly results for women in whom significant associations between height and risk of glioma had been reported.[50, 52] In the Million Women Study, each 10cm increase in height was associated with an increased risk of glioma (RR 1.24, 95% CI 1.09–1.40).[50] In the NIH-AARP Study, each 10 cm increase in height was associated with an increased risk of glioma in both women (RR 1.30, 95% CI 1.02–1.67) and men (RR 1.18, 95% CI 1.02–1.36).[52] A large Norwegian study, subsequently published in 2017, which linked measured body height of 1.8 million residents to cancer registry data, also reported that increasing height (per 10cm increase) was associated with increasing incidences of glioma in women (RR 1.25, 95% CI 1.15–1.35) and men (RR 1.21, 95% CI 1.14–1.28).[53]

Published evidence for the associations between height and risk of subtypes of CNS tumours other than glioma is limited. For meningioma, there was some evidence for an association between increasing height (per 10 cm increase) and risk of meningioma in the Million Women Study[50] (RR 1.11, 95% CI 0.94–1.31) and in the Norwegian database linkage study (men: RR 1.16, 95% CI 1.05–1.28; women: 1.14, 95% CI 1.06–1.22).[53] The Norwegian study also showed significant associations between increasing height (per 10cm increase) and increased incidence of pituitary adenoma in both men (RR 1.24, 95% CI 1.09–1.40) and women (RR

1.34, 95% CI 1.15–1.58), and of nerve sheath tumours in women (RR 1.33, 95% CI 1.12–1.58) but not men (RR 1.04, 95% CI 0.89–1.21).

Increased risk of CNS tumours in relation to height may be due to any or a combination of low-penetrant genetic variants, early-life environmental and nutritional exposures, and greater circulating growth factors.[51]

2.3.6.2 Body mass index

In 2016, IARC released an updated short report on body fatness and risk of cancer, and listed excess body fatness as a risk factor for meningioma with sufficient evidence in humans, but evidence for glioma was considered insufficient to reach a conclusion.[54] The report cited results for meningioma from a meta-analysis[55] published in 2015 that included 6 cohort studies (including the Million Women Study) and 3 case-control studies. The meta-analysis (no sex-specific results) showed increased risks of meningioma in relation to overweight (summary RR 1.21, 95% CI 1.01–1.43) and obesity (summary RR 1.54, 95% CI 1.32–1.79), and the results for obesity were not materially changed after restricting the analysis to cohort studies only (obesity summary RR 1.51, 95% CI 1.25–1.82; overweight summary RR 1.12, 95% CI 0.95–1.31). The study suggested increased meningioma risk in relation to BMI may be due to higher circulating growth factors, excess hormone produced by adipose tissue, and/or obesity-related chronic inflammation or oxidative stress.[55] Although evidence for glioma was considered as inconclusive in that IARC short report, in general the published evidence suggests that there is no association between body fatness and risk of glioma.[55] In a meta-analysis of glioma risk (5 cohort and 2 case-control studies) that included results from both the Million Women Study and the NIH-AARP Study, neither overweight nor obesity were significantly associated with risk of glioma (overweight summary RR: 1.06, 95% CI 0.94–1.20; obesity summary RR: 1.11, 95% CI 0.98–1.27) (no sex-specific results).[55] There is limited published evidence for the associations between BMI and pituitary tumours or vestibular schwannoma. A large Norwegian study, which linked measured body height and weight of 1.8 million residents to cancer registries found that BMI

(per 5 kg/m^2 increase) was associated with increased risk of pituitary adenoma in men (RR 1.29, 95% CI 1.12–1.47), whereas the association was not significant in women (RR 1.13, 95% CI 1.00–1.28).[53] The study also found a significant association between increasing BMI (per 5 kg/m^2 increase) and decreased risks of nerve sheath tumours in women (RR 0.85, 95% CI 0.74–0.99) but not in men (RR 0.93, 95% CI 0.76–1.12).[53] The Norwegian study also reported that there was no association between BMI (per 5 kg/m^2 increase) and risk of glioma (men: RR 1.03, 95% CI 0.96–1.10; women: RR 0.97, 95% CI 0.91–1.03).[53] This study found some evidence for an association between BMI (per 5 kg/m^2 increase) and risk of meningioma in men (RR 1.13, 95% CI 1.01–1.27) (women: RR 1.05, 95% CI 1.00–1.11), although they were not able to account for socioeconomic status and other potential confounders of the association.[53]

2.3.7 Lifestyle factors

2.3.7.1 Physical activity

Published evidence has suggested that a high level of physical activity is associated with decreased risk of meningioma,[50, 56–58] and may be associated with decreased risk of glioma.[50, 52, 57–59] In 2015, a meta-analysis (no sex-specific analysis) that summarised published evidence from 6 cohort studies (including results for glioma and meningioma from the Million Women Study, and for glioma from the NIH-AARP Study) and 3 case-control studies was published.[55] The meta-analysis suggested that a high level of physical activity was associated with decreased risk of meningioma (summary RR 0.73, 95% CI 0.61–0.88) and glioma (summary RR 0.86, 95% CI 0.76–0.97), when compared to the least level of physical activity.[55] However, when the meta-analysis was restricted to summarising results from cohort studies only, the decreased risk in relation to physical activity remained significant for meningioma (summary RR 0.72, 95% CI 0.58–0.89) but not for glioma (summary RR 0.91, 95% CI 0.77–1.07).[55] These results suggest that the significant association between physical activity and risk of glioma observed in the meta-analysis was

mainly driven by results from case-control studies, which may be subject to bias in selection of study participants, differential recall, and/or reverse causation. The study suggested that the decreased meningioma risk associated with physical activity may be due to reduced levels of circulating growth factors and/or enhanced anti-inflammatory and antioxidant properties.[55] To my best knowledge, there is no published evidence on risks associated with physical activity for either pituitary tumours or vestibular schwannoma.

2.3.7.2 Tobacco smoking

Published evidence suggests that tobacco smoking is not associated with risk of glioma.[50, 60–62] In 2016, a meta-analysis of risk of glioma (no sex-specific analysis) that included 6 studies with prospective collection of data (including the Million Women Study and the NIH-AARP Study) and 19 studies with retrospective collection of data was published.[60] The meta-analysis showed no evidence for an association between smoking (ever smoker vs. never smoker) and risk of glioma (summary RR 0.98, 95% CI 0.92–1.05), and the RRs were not materially changed after restricting the meta-analysis to evidence from studies with prospective collection of data only (summary RR 1.05, 95% CI 0.95–1.17).[60] Published evidence from prospective studies on smoking and CNS tumours other than glioma is limited. Smoking was shown not to be associated with risk of meningioma in the Million Women Study[50] (current smokers: RR 0.88, 95% CI 0.66–1.16; past smokers: RR 0.86, 95% CI 0.67–1.10, when compared with never smokers), or in a meta-analysis of 6 case-control studies (summary RR for ever smokers: 1.02, 95% CI 0.85–1.21 when compared with never smokers).[63] A subsequent large case-control study showed that sex modified the association between smoking (ever smokers vs. never smokers) and risk of meningioma (women: RR 0.80, 95% 0.70–0.90; men: RR 1.30, 95% CI 1.09–1.55),[64] but it is not known to what extent the associations were caused by differential recall between cases and control, an inherent bias of studies with retrospective collection of data.[64] Tobacco smoking (current smoker vs. never smoker) was shown to be associated with substantially decreased risks of vestibular

schwannoma in an international case-control study (RR 0.5, 95% CI 0.4–0.6)[65] and in the Million Women Study (RR 0.41, 95% CI 0.24–0.70)[66]. Similarly, a decreased risk of pituitary adenoma was found with tobacco smoking (smoking vs. non-smoking: RR 0.27, 95% CI 0.10–0.72) in a small cohort study with 5 exposed cases.[67] However, tobacco smoking has not been shown to be associated with risk of pituitary tumours in large studies such as the Million Women Study with 31 exposed cases[66] (current smoker vs. never smoker: RR 0.94, 95% CI 0.60–1.40), and a case-control study with 145 exposed cases[68] (regular smoking, yes vs. no: RR 1.2, 95% CI 0.9–1.7).

2.3.7.3 Menopausal hormones

Published evidence from prospective studies suggests increased risks of glioma, meningioma, and vestibular schwannoma in relation to use of menopausal hormones.[69–72] In 2015, an article that combined findings from an original analysis using data from the UK General Practice Research Database (GPRD) and published evidence from 7 other studies with prospective collection of data (including results for glioma, meningioma, and vestibular schwannoma from the Million Women Study, and for glioma from the NIH-AARP Study) was published.[21] The meta-analysis from the article showed that, when compared to never users, users of oestrogen-only menopausal hormones were at increased risk of glioma (summary RR 1.23, 95% CI 1.06–1.42), meningioma (summary RR 1.31, 95% CI 1.20–1.43), and vestibular schwannoma (summary RR 1.66, 95% CI 1.24–2.22); whereas users of oestrogen-progestogen menopausal hormones were not at significantly increased risk of glioma (summary RR 0.92, 95% CI 0.78–1.08), meningioma (summary RR 1.05, 95% CI 0.95–1.16), or vestibular schwannoma (summary RR 1.25, 95% CI 0.95–1.64).[21] Studies suggested that oestrogen receptors may be expressed in glioma and meningioma.[22, 69] Published evidence for pituitary tumours is limited: to my best knowledge, the study using UK GPRD data was the only prospective study that investigated menopausal hormone use and risk of pituitary tumours.[21] This study showed that users of any menopausal hormones (RR 1.35, 95% CI

0.99–1.85) or oestrogen-only menopausal hormones (RR 1.51, 95% CI 0.98–2.32) were not at significantly increased risk of pituitary tumours, but interpretation of the results is limited by the small number of cases (n=273).[21]

2.3.8 Female reproductive factors

Published evidence from prospective studies generally shows no associations between many reproductive factors and risk of glioma.[22, 23, 50] Although the NIH-AARP Study found a significant association between an older age at menarche and risk of glioma (≥15 vs. <13: RR 1.67, 95% CI 1.03–2.69), this significant association was not found in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort (>15 vs. <12: RR 0.88, 95% CI 0.47–1.63).[23] The Million Women Study[50], the NIH-AARP Study,[22] and the EPIC Study[23] found no significant increased or decreased risks for glioma in relation to parity, age of first birth, or use of oral contraceptives: the Million Women Study parity ≥3 vs. 0 (RR 0.96, 95% CI 0.68–1.35), age at first birth (≥25 vs. <20: RR 1.13, 95% CI 0.84–1.50), and use of oral contraceptives (≥5 years vs. never: RR 0.88, 95% CI 0.72–1.06)[50]; the NIH-AARP Study parity ≥3 vs. 0 (RR 0.83, 95% CI 0.54–1.26), age of first live birth (≥30 vs. <20: RR 0.87, 95% CI 0.54–1.40), and use of oral contraceptives (ever vs. never: RR 0.76, 95% CI 0.53–1.10)[22]; the EPIC Study parity ≥3 vs. 0 (RR 1.18, 95% CI 0.68–2.06), age of first full-term pregnancy (>30 vs. nulliparous: RR 1.42, 95% CI 0.71–2.84), and use of oral contraceptives (current vs. never: RR 1.23, 95% CI 0.53–2.83)[23], respectively.

Published evidence from prospective studies also suggests that there were no associations between similar reproductive factors and risk of meningioma.[23, 50, 71, 73] A meta-analysis of meningioma risk that included 6 studies with prospective collection of studies (including the Million Women Study) and 11 case-control studies showed that there were no increased or decreased risks in relation to use of oral contraceptives (summary RR: 0.93, 95% CI 0.83–1.03), age at menarche (summary RR 1.06, 95% CI 0.92–1.21), age at first birth (summary RR 0.94, 95% CI

0.80–1.10), or parity (summary RR 1.18, 95% CI 1.00–1.40).[73] The associations and relative risk estimates were not materially changed when the analyses were restricted to results from prospective studies only, with summary RRs (95% CIs) of 0.98 (0.92–1.05), 1.26 (0.92–1.21), 0.98 (0.76–1.26), and 1.11 (0.85–1.45), respectively.[73]

Published evidence for risk of pituitary tumours and vestibular schwannoma in relation to reproductive factors is very limited. An international case-control study showed that parity was associated with increased risk of vestibular schwannoma (parous vs nulliparous: RR 1.7, 95% CI 1.1–2.6) but there was no significant trend with increasing number of parity (p for trend = 0.3).[65] This case-control study also showed no association between age at menarche and risk of vestibular schwannoma (≥15 vs. <12: RR 1.1, 95% CI 0.7–1.8).[65] For pituitary tumours, a case-control study from the UK found an increased risk of pituitary tumours for age at first live birth <20 years old when compared with nulliparous (RR 3.4, 95% CI 1.4–8.4), but there was no significant trend with increasing age at first live birth (p for trend = 0.1).[68] There were no significant increased or decreased risks of pituitary tumours in relation to live births (yes vs. no: RR 1.2, 95% CI 0.7–2.1), age at menarche (≥15 vs. <12: RR 0.9, 95% CI 0.4–1.8), or use of oral contraceptives (RR 0.8, 95% CI 0.4–1.4).[68]

2.4 Summary

This chapter has briefly reviewed the epidemiology of CNS tumours and has described some evidence relating to many non-dietary risk factors for CNS tumours. Increased incidence of CNS tumours in developed countries when compared to developing countries, and in people with higher than lower socioeconomic status (level of educational attainment and income), may reflect better diagnosis and registration of CNS tumours rather than true increased incidence. In adults, glioma (generally malignant) and meningioma, vestibular schwannoma, and pituitary tumours (generally benign), are the four most common subtypes of CNS tumours.

CNS tumours are relatively uncommon, especially by subtypes, and many studies lack power. Evidence from case-control studies is often unreliable because of recall bias and high proxy response as a result of the nature of CNS tumours, which impair cognitive function and are rapidly fatal. Consequently, there is little evidence for risk factors of CNS tumours from previous studies. Some monogenic Mendelian genetic diseases or syndrome (e.g. neurofibromatosis and tuberous sclerosis) are established risk factors for CNS tumours but these diseases are rare and only account for about 1% of CNS tumours. For non-genetic factors, IARC has listed ionising radiation as a carcinogenic agent for the brain and CNS with sufficient evidence in humans, and excess body fatness as a risk factor for meningioma with sufficient evidence. Although IARC suggested that radiofrequency electromagnetic fields such as those emitted by mobile telephones may be associated with increased risks of glioma and vestibular schwannoma, prospective studies did not find strong evidence to support these associations.

Prospective studies have consistently reported associations between some non-genetic factors and risk of subtypes of CNS tumours. For glioma, factors that are associated with increased incidences include increasing height and use of menopausal hormone containing oestrogen only; for meningioma, increasing height and use of menopausal hormone containing oestrogen only are also associated with increased incidences while increasing level of physical activity is associated with decreased incidences. Published evidence for non-dietary risk factors of vestibular schwannoma and pituitary tumours from prospective studies is scarce.

An understanding of non-dietary risk factors and of variations in incidence of specific CNS tumour subtypes by ethnicity, socioeconomic status, and sex can be helpful in studying the associations between diet and risk of subtypes of CNS tumours. Diet is complex and it often correlates with many demographic and lifestyle factors. It is important that studies investigating dietary risk factors for CNS tumours are conducted in large cohorts with prospective collection of information on diet and many demographic and lifestyle factors. The following

analyses of diet and risk of CNS tumours (Chapter 6–8) will take into account these non-dietary factors as potential confounders, where possible.

2.5 Tables

Table 2.1: Non-dietary risk factors for central nervous system tumours

Potential risk factors	Associations reported in the literature	Possible mechanism for an association
Genetic factors	Neurofibromatosis type 1 and type 2, tuberous sclerosis, Lynch Syndrome, Li-Fraumeni Syndrome, and single nucleotide polymorphisms (e.g. *TERT, EGFR, CDKN2B,* and *RTEL1*) were associated with increased glioma risks; neurofibromatosis type 2 was associated with increased risks of meningioma and vestibular schwannoma	Involves mutation of genes that control cell growth and/or cell division
Ionising radiation	Atomic bomb survivors had increased risk of glioma, meningioma, schwannoma, and pituitary tumours; therapeutic radiation (cranial irradiation) was associated with increased risk of meningioma and nerve sheath tumours	Genomic instability caused by ionising radiation (e.g. DNA double-strand breaks) which increases rate of mutation of genes
Non-ionising radiation	Case-control studies reported associations between use of mobile phone and increased risk of glioma or vestibular schwannoma but these associations were not found in large prospective studies	Non-ionising radiation may induce biological changes such as small changes in protein structure that affect binding of ligands to receptor protein involved in signalling pathway
Occupational exposures	Increased incidence in glioma in female (but not male) physicians was reported in a database linkage study. Increased risks of glioma in firefighters and farmers and increased risks of any brain tumours in pathologist and embalmers were reported in case-control studies	There was ascertainment bias in physician; firefighters, farmers, pathologist, or embalmers were exposed to pesticides, petroleum products, or polycyclic hydrocarbons, which are carcinogenic
Personal history of allergies	Case-control studies reported an inverse association between allergies and glioma risk but these associations were not found in cohort studies; studies report null or non-significant associations between allergies and meningioma risk	People with allergic phenotype may have enhanced cellular immunity that inhibit the development of tumours

Table 2.1: Non-dietary risk factors for central nervous system tumours (continued)

Potential risk factors	Associations reported in the literature	Possible mechanism for an association
Anthropometric factors	Studies consistently reporting associations between increasing height and increased risk of glioma; there was some evidence for associations between increasing height and increased risk of meningioma, pituitary tumours, and nerve sheath tumours;	Increased CNS tumour risks in relation to height may be due to any or a combination of low-penetrant genetic variants, early-life environmental and nutritional exposures, and greater circulating growth factors;
	Studies consistently reporting associations between higher body mass index (BMI) and increased meningioma risks but not glioma risks; evidence for BMI and risk of pituitary tumours and vestibular schwannoma is limited	Increased meningioma risk in relation to BMI may be due to higher circulating growth factors, excess hormone produced by adipose tissue, and/or obesity-related chronic inflammation and oxidative stress
Lifestyle factors	Prospective studies suggested a high level of physical activity is associated with decreased risk of meningioma and not associated with glioma risks;	Decreased meningioma risk associated with physical activity may be due to reduced levels of circulating growth factors and/or enhanced anti-inflammatory and antioxidant properties;
	Smoking was shown to be associated with decreased risks of vestibular schwannoma and not associated with risks of glioma, meningioma, and pituitary tumour;	
	Studies reported use of oestrogen-only menopausal hormones was associated with risk of glioma, meningioma, and pituitary tumours.	Studies suggested oestrogen receptors may be expressed in glioma and meningioma
Female reproductive factors	Studies generally reported no associations between age at menarche, parity, age of first birth, or use of oral contraceptives and risk of glioma or meningioma	n/a

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3

A Systematic Review and Meta-analysis of Diet and Risk of Central Nervous System Tumours

3.1 Introduction

International variation in diet and in cancer incidence suggests that diet might play a role in the aetiology of cancer. Some studies have suggested that diet is second to tobacco smoking as a preventable cause of cancer.[1, 2] While some dietary factors have been extensively studied for their relationships with many cancers, they remain understudied risk factors for central nervous system (CNS) tumours.[3, 4] A focus of published reports is on dietary nitrites and nitrates. An early investigation into diet and risk of CNS tumours (for which dietary information was collected retrospectively) reported that dietary sources of nitrite were associated with increased risks, and suggested that nitrite may be converted into N-nitroso compounds, shown to be neuro-carcinogenic in animals through endogenous nitrosation in the gastrointestinal tract.[5] Subsequently, some (but not all) epidemiological studies, largely case-control, have reported increased CNS tumour risks in relation to intakes of nitrite-preserved meat or meat products while intakes of fruit or vegetables, which contain nitrosation inhibitors such as vitamin C or vitamin E, were associated with decreased risks.[6–8]

The 2007 Second Expert Report on diet, nutrition, physical activity and cancer published by the World Cancer Research Fund/American Institute of Cancer Research (WCRF/AICR)[3] suggested that CNS tumours were uncommon (ranked as the 18th most common cancer type in the report) and diverse, and that further investigation into their relationships with foods and nutrition would be unlikely to be fruitful, based on a narrative review of the limited available evidence. Evidence for CNS tumours was no longer examined in the 2018 Third Expert Report,[4] and no comprehensive systematic review of the literature on diet and tumours of the CNS has been published. Over the past 10 years, incidence of registered CNS tumours has increased, probably largely as a result of improved CNS tumour registration. In countries with good quality cancer registries such as the UK and the US, CNS tumours now rank among the top 10 most common incident cancers, with little known about potentially modifiable risk factors.[9, 10] New evidence from large

prospective studies has become available for both malignant and benign tumours. I therefore conducted a systematic review and meta-analysis of published literature, with the aim of systematically summarising the evidence on dietary factors and incidence of CNS tumours, including subtypes of CNS tumours where possible.

3.2 Methods

3.2.1 Databases, search strategy, and search terms

Multiple database searching has a broader coverage of archives, some of which may be unique to a particular database, and has a higher chance of retrieving relevant articles.[11] I decided to do the systematic searching for relevant articles in the Embase and Medline databases.

A systematic search for articles investigating the associations between diet and risk of CNS tumours is challenging. Both diet and CNS tumours are diverse terms; with the former comprising a wide range of items including foods, beverages, nutrients, and dietary patterns, and the latter consisting of glioma, meningioma, pituitary tumours, vestibular schwannomas, and many other rarer subtypes. The use of subject headings, which are comprehensive hierarchical summary terms with a good degree of reliability between relevant terms that are grouped together,[12] can effectively facilitate a systematic search of articles archived in bibliographic databases. These summary terms are known as 'Subject Headings' in Embase and 'Medical Subject Headings' (MeSH) in Medline. In Embase, there are appropriate Subject Headings for both diet ('nutrition') and CNS tumours ('central nervous system tumours'). In Medline, diet is summarised under the MeSH terms 'food and beverages' and 'diet', however there is no well-defined MeSH term for CNS tumours, so here the search terms need to combine all possible terms for CNS tumours ("central nervous system" OR "brain" OR "intracranial" OR "cerebral" OR "glioma" OR "meningioma" OR "astrocytoma" OR "glioblastoma" OR "pituitary" OR "neuroma, acoustic" OR "schwannoma"). In both database searches, 'alcohol' and 'lifestyle'

were added as search terms to capture articles that reported intakes of alcohol or alcoholic beverages and CNS tumour risk, and 'site-specific cancer' and 'all cancer' were added to capture articles that reported diet and risk of multiple cancer outcomes including CNS tumours, which would have otherwise not been captured.

In summary, Embase (1974 to 01 May 2018) was searched with terms ("nutrition" OR "alcohol" OR "lifestyle" OR "life-style") AND ("central nervous system tumour" OR "site-specific cancer" OR "all cancer"); and Medline (1946 to 01 May 2018) was searched with terms ("food and beverages" OR "diet" OR "alcohol drinking" OR "Life Style") AND ("neoplasms" OR "cancer" OR "malignan*" OR "carcinoma" OR "tumor" OR "tumour") AND ("central nervous system" OR "brain" OR "intracranial" OR "cerebral" OR "glioma" OR "meningioma" OR "astrocytoma" OR "glioblastoma" OR "pituitary" OR "neuroma, acoustic" OR "schwannoma" OR "site-specific" OR "all cancer"). No restriction on publication types and languages of articles was applied. Reference lists of eligible articles were reviewed to identify further relevant articles.

3.2.2 Inclusion criteria

3.2.2.1 Study design

Articles reporting associations between diet and risk of CNS tumours based on original research (cohort studies or case-control studies), which were published as full papers in peer-reviewed journals, were included.

3.2.2.2 Study participants

Only studies that were conducted in adult populations were included. Studies that examined associations between diet during childhood or maternal diet during pregnancy (carrying study participants) and risk of CNS tumours in study participants during adulthood after long follow-up were excluded.

3.2.2.3 Study exposures

Studies that reported foods, beverages, nutrients, and dietary patterns as specific exposures were included. Studies that investigated dietary supplements or serum metabolites were excluded.

3.2.2.4 Study outcomes

Studies that reported relative risks (RRs) and confidence intervals (CIs), with adjustment at least for age, for incidence of overall CNS tumours (a composite outcome) and/or subtypes of CNS tumours as specific outcomes were included. Studies that investigated CNS tumour mortality only were excluded. Studies that included nervous system tumours but failed to provide separate results for CNS tumours were excluded.

3.2.3 Data extraction

An electronic data abstraction form was used to record general study characteristics (study name, author, year of publication, duration of study), information on study population (country and sources of participants, number of participants, mean age), exposure (diet), follow-up duration, and outcome (incident/fatal CNS tumours, subtypes of CNS tumours, number of exposed). Maximally adjusted measures of RRs and 95% CIs corresponding to the longest period of follow-up were extracted. For studies with multiple reports, the report with the largest number of outcome events was used. Data were extracted by 3 independent researchers (myself, Jane Green, and Siân Sweetland), with any disagreement resolved by discussions.

3.2.4 Statistical analysis

For inclusion in the quantitative meta-analyses, studies were required to have a minimum of 5 CNS tumour cases in the exposed group and in the reference group. Where the risk of overall CNS tumours or particular subtypes of CNS tumour by a particular dietary factor was reported in at least 2 separate studies, summary RRs with 95% CIs were derived using inverse variance weighted random effects meta-analysis. Meta-analyses were conducted combining RRs which compared groups with the highest intake against those with the lowest, however these groups were defined in each study. For studies that had less than 5 CNS tumour cases in the highest intake categories by a specific dietary factor, RRs for the highest and second highest intake categories were combined, where possible, using a method for synthesis of correlated information in fixed-effect meta-analysis developed by Berrington and Cox.[13] For all meta-analyses, heterogeneity of results between studies was assessed by a χ^2 test.

3.3 Results

The systematic search identified 10,555 articles, of which 1196 were duplicates. 9204 were excluded based on title and abstract review, leaving 155 which were examined in full text review (Figure 3.1). An additional 4 articles were identified from the reference lists. A total of 159 articles were assessed against the inclusion criteria listed in section 3.2.2, and a further 97 articles were excluded for the following reasons: were not peer reviewed (n=1); investigated effects of dietary supplements from trials (n=2); were conducted in a population including children (n=2); investigated ecological associations between diet and CNS tumour risk (n=3); investigated diet and risk of CNS tumour mortality only (n=3); investigated risk of nervous system tumours but failed to provide separate results for CNS tumours (n=3); investigated associations between serum metabolites and CNS tumour risk (n=13); were conducted in a population of children only (n=29). Meta-analysis articles that were based on secondary analyses of published data (n=19) and narrative review articles (n=22) were also excluded (although the individual studies included in these studies were examined for inclusion here). The remaining 62 articles from 37 epidemiological studies (12 cohort studies and 25 case-control studies), with a total of 3,096,593 participants and 12,265 CNS tumours, were included in the final review.

The 37 studies (between them) investigated risk of CNS tumours (and of subtypes of CNS tumours) in relation to intakes of as many as 27 individual food groups or nutrients, as well as the Dietary Approaches to Stop Hypertension (DASH) score (see Chapter 4 section 4.4.4.1), vegetarian diet, organic food, glycaemic index, dietary nitrate, nitrite, aspartame, acrylamide, and haem iron. Overall CNS tumours (5 cohort studies and 5 case-control studies), glioma (11 cohort studies and 18 case-control studies), and meningioma (5 cohort studies and 8 case-control studies) were most extensively studied with respect to diet, and are described in the next section. For vestibular schwannoma, the search identified one relevant report only (from a case-control study), which found no significant association with alcohol consumption (RR comparing yes vs. no 1.78, 95% CI 0.87–3.66).[14] The search did not identify

any relevant reports which met the review inclusion criteria for pituitary tumours or any of the other rarer subtypes of CNS tumours, although one case-control study which included children (and so was not included in this review) found no significant associations between intakes of tea, wine, or fat and risk of pituitary tumours.[15]

Risks of overall CNS tumours, glioma, and meningioma in relation to diet including major food groups, nutrients, and dietary patterns as well as other compounds found in diet, stratified by the source of published evidence (case-control study or cohort study), are presented in Figure 3.2, Figure 3.3, and Figure 3.4, respectively, and are described below.

3.3.1 Food groups

3.3.1.1 Total fruit

Eleven published studies (9 case-control studies[6, 7, 16–22], 2 cohort studies[23, 24]) reported associations between total fruit intake and risk of CNS tumours (overall CNS tumours 3 studies[16, 20, 22]; glioma 7 studies[6, 7, 17–19, 23, 24]; meningioma 2 studies[16, 21]). For overall CNS tumours, a meta-analysis of 3 case-control studies[16, 20, 22] (1 reporting increased risk, 1 reporting decreased risk, 1 reporting a null association) showed no significant association with total fruit intake (summary RR 0.62, 95% CI 0.17–2.23), with significant heterogeneity between studies (p for heterogeneity <0.001). There was no prospective evidence for fruit intake and risk of CNS tumours. For glioma, a meta-analysis of 5 case-control studies[6, 7, 17–19] (1 decreased risk, 4 null) showed no significant association with total fruit intake (summary RR 0.89, 95% CI 0.58–1.35), with significant heterogeneity between studies (p=0.021); while a meta-analysis of 2 cohort studies[23, 24] (2 null) showed no significant association between total fruit intake and glioma risk (summary RR 1.23, 95% CI 0.99–1.54), with no significant heterogeneity between studies (p=0.424). For meningioma, a meta-analysis of 2 case-control studies[16, 21]) (2 decreased risk) showed a significantly decreased risk with total fruit intake

(summary RR 0.33, 95% CI 0.19–0.57), with no significant heterogeneity between studies (p=0.670); there was no prospective evidence.

3.3.1.2 Citrus fruit

Seven published studies (5 case-control studies[6, 8, 19, 25, 26], 2 cohort studies[24, 27]) reported associations between citrus fruit intake and risk of CNS tumours (overall CNS tumours 1 study[8]; glioma 7 studies[6, 8, 19, 24–27]; meningioma 1 study[8]). For overall CNS tumours, 1 case-control study[8] reported a significantly increased risk with citrus fruit intake (RR 1.40, 95% CI 1.10–1.70) (prospective evidence lacking). For glioma, a meta-analysis of 5 case-control studies[6, 8, 19, 25, 26] (1 increased risk, 1 decreased risk, 3 null) showed no significant association with citrus fruit intake (summary RR 1.16, 95% CI 0.83–1.63), with no significant heterogeneity between studies (p=0.052); and a meta-analysis of the 2 cohort studies[24, 27] (2 null) also showed no significant association with citrus fruit intake (summary RR 1.31, 95% CI 0.89–1.91), with no significant heterogeneity between studies (p=0.418). For meningioma, 1 case-control study[8] reported no significant association with citrus fruit intake (RR 1.10, 95% CI 0.70–1.70) (prospective evidence lacking).

3.3.1.3 Fruit juice

Two published studies (1 case-control study[7] and 1 cohort study[23]) reported no significant associations between fruit juice intake and risk of glioma (case-control: RR 1.00, 95% CI 0.60–1.50; cohort: RR 0.94, 95% CI 0.72–1.22). There was no published evidence at all for the association between fruit juice intake and risk of overall CNS tumours or meningioma.

3.3.1.4 Total vegetables

Twelve published studies (10 case-control studies[6–8, 16, 17, 19–22, 26], 2 cohort studies[23, 24]) reported associations between total vegetable intake and risk of CNS tumours (overall CNS tumours 4 studies[8, 16, 20, 22]; glioma 8 studies[6–8,

17, 19, 23, 24, 26]; meningioma 3 studies[8, 16, 21]). For overall CNS tumours, a meta-analysis of 4 case-control studies[8, 16, 20, 22] (1 decreased risk, 3 null) showed no significant association with total vegetable intake (summary RR 0.78, 95% CI 0.60–1.01) with no significant heterogeneity between studies (p=0.212); there was no prospective evidence. For glioma, a meta-analysis of 6 case-control studies[6–8, 17, 19, 26] (6 null) showed a significantly decreased risk with total vegetable intake (summary RR, 0.77; 95% CI, 0.64–0.94) with no significant heterogeneity between studies (p=0.382); while a meta-analysis of 2 cohort studies[23, 24] (2 null) showed no significant association with total vegetable intake (summary RR 1.17, 95% CI 0.93–1.46), with no heterogeneity between studies (p=1.000). For meningioma, a meta-analysis of 3 case-control studies[8, 16, 21] (2 decreased risk, 1 null) showed no significant association with total vegetable intake (summary RR 0.44, 95% CI 0.20–1.01), with significant heterogeneity between studies (p=0.013); there was no prospective evidence.

3.3.1.5 Nuts

Two published studies (2 case-control studies[6, 19], both null) reported the association between nuts intake and risk of glioma, for which a meta-analysis showed no significant association (RR 1.09, 95% CI 0.75–1.59), with no significant heterogeneity between studies (p=0.589); and there was no prospective evidence. There was no published evidence at all for the association between nuts intake and risk of overall CNS tumours or meningioma.

3.3.1.6 Grains/cereal

Five published studies (5 case-control studies[6, 8, 19, 20, 26]) reported associations between grains/cereal intake and risk of CNS tumours (overall CNS tumours 2 studies[8, 20]; glioma 4 studies[6, 8, 19, 26]; meningioma 1 study[8]). For overall CNS tumours, a meta-analysis of 2 case-control studies[8, 20] (both null) showed no significant association with grains/cereal intake (summary RR 1.17, 95% CI 0.96–1.43), with no significant heterogeneity between studies (p=0.330). For glioma,

a meta-analysis of 4 case-control studies[6, 8, 19, 26] (2 increased risk, 2 null) showed a significantly increased risk with grains/cereal intake (summary RR 1.37, 95% CI 1.07–1.74), with no significant heterogeneity between studies (p=0.216). For meningioma, 1 case-control study[8] reported no significant association with grains/cereal intake (RR 0.90, 95% CI 0.60–1.50). There was no published prospective evidence for the associations between grains/cereal intake and risk of overall CNS tumours, glioma, or meningioma.

3.3.1.7 Red meat

Six published studies (2 case-control studies[26, 28], 4 cohort studies[23, 29–31]) reported associations between red meat intake and risk of CNS tumours (overall CNS tumours 2 studies[28, 29]; glioma 4 studies[23, 26, 30, 31]; meningioma 0 study). For overall CNS tumours, 1 case-control study[28] and 1 cohort study[29] found no significant associations with red meat intake (case-control: RR 1.00, 95% CI 0.80–1.20; cohort: RR 0.85, 95% CI 0.63–1.15). For glioma, a case-control study[26] found no significant association with red meat intake (RR 0.90, 95% CI 0.50–1.60); and a meta-analysis of 3 cohort studies[23, 30, 31] (3 null) showed no significant association with red meat intake (summary RR 0.93; 95% CI, 0.78–1.12), with no significant heterogeneity between studies (p=0.629). There was no published evidence at all for the association between red meat intake and risk of meningioma.

3.3.1.8 Processed meat

Eleven published studies (7 case-control studies[6–8, 19, 22, 26, 32], 4 cohort studies[23, 29–31]) reported associations between processed meat intake and risk of CNS tumours (overall CNS tumours 4 studies[8, 22, 29, 32]; glioma 8 studies[6–8, 19, 23, 26, 30, 31]; meningioma 2 studies[7, 8]). For overall CNS tumours, a meta-analysis of 3 case-control studies[8, 22, 32] (3 null) showed no significant association with processed meat intake (summary RR 0.99, 95% CI 0.84–1.16), with no significant heterogeneity between studies (p=0.495); and 1 cohort study[29] also reported no significant association with processed meat intake (RR 0.88, 95%

CI 0.65–1.18). For glioma, a meta-analysis of 5 case-control studies[6–8, 19, 26] (1 increased risk, 4 null) showed no significant association with processed meat intake (summary RR 1.24, 95% CI 0.94–1.64), with no significant heterogeneity between studies (p=0.116); and a meta-analysis of 3 cohort studies[23, 30, 31] (3 null) also showed no significant association with processed meat intake (summary RR 1.07, 95% CI 0.88–1.29), with no significant heterogeneity between studies (p=0.855). For meningioma, a meta-analysis of 2 case-control studies[7, 8] (2 null) showed no significant association with processed meat intake (summary RR 1.25, 95% CI 0.64–2.47), with no significant heterogeneity between studies (p=0.103); and there was no prospective evidence.

3.3.1.9 White meat

Four published studies (3 case-control studies[20, 26, 28], 1 cohort study[33]) reported associations between white meat intake and risk of CNS tumours (overall CNS tumours 3 studies[20, 28, 33]; glioma 1 study[26]]; meningioma 0 study). For overall CNS tumours, a meta-analysis of 2 case-control studies[20, 28] (1 decreased risk, 1 null) showed no significant association with white meat intake (summary RR 0.78, 95% CI 0.32–1.93), with significant heterogeneity between studies (p=0.016); and 1 cohort study[33] also reported no significant association with white meat intake (RR 1.10, 95% CI 0.86–1.41). For glioma, 1 case-control study[26] reported no significant association with white meat intake (RR 0.80, 95% CI 0.40–1.50); there was no prospective evidence. There was no published evidence at all for the association between white meat intake and risk of meningioma.

3.3.1.10 Fish

Ten published studies (9 case-control studies[6–8, 16, 19, 20, 22, 26, 28], 1 cohort study[33]) reported associations between fish intake and risk of CNS tumours (overall CNS tumours 6 studies[8, 16, 20, 22, 28, 33]; glioma 5 studies[6–8, 19, 26]; meningioma 2 studies[8, 16]). For overall CNS tumours, a meta-analysis of 5 case-control studies[8, 16, 20, 22, 28] (2 decreased risk, 3 null) showed significantly

decreased risk with fish intake (summary RR 0.79, 95% CI 0.63–0.99), with no significant heterogeneity between studies (p=0.179); while 1 cohort study[33] reported no significant association with fish intake (RR 1.05, 95% CI 0.83–1.35). For glioma, a meta-analysis of 5 case-control studies[6–8, 19, 26] (5 null) showed no significant association with fish intake (summary RR 0.79, 95% CI, 0.60–1.04), with no significant heterogeneity between studies (p=0.153); and there was no prospective evidence. For meningioma, a meta-analysis of 2 case-control studies[8, 16] (2 null) showed no significant association with fish intake (summary RR 0.98, 95% CI 0.69–1.41), with no significant heterogeneity between studies (p=0.637); there was no prospective evidence.

3.3.1.11 Eggs

Five published studies (5 case-control studies[6, 8, 19, 20, 22]) reported associations between eggs intake and risk of CNS tumours (overall CNS tumours 3 studies[8, 20, 22]; glioma 3 studies[6, 8, 19]; meningioma 1 study[8]). For overall CNS tumours, a meta-analysis of 3 case-control studies[8, 20, 22] (1 decreased risk, 1 increased risk, 1 null) showed no significant association with eggs intake (summary RR 0.75, 95% CI 0.30–1.89), with significant heterogeneity between studies (p<0.001). For glioma, a meta-analysis of 3 case-control studies[6, 8, 19] (2 increased risk, 1 null) showed no significant association with eggs intake (summary RR 1.47; 95% CI 0.93–2.32), with no significant heterogeneity between studies (p=0.143). For meningioma, 1 case-control study[8] reported no significant association with eggs intake (RR 1.30, 95% CI 0.80–2.20). There was no published prospective evidence for the associations between eggs intake and risk of overall CNS tumours, glioma, or meningioma.

3.3.1.12 Dairy products

Three published studies (3 case-control studies[6, 17, 26], all null) reported the association between intake of dairy products and risk of glioma, for which a meta-analysis showed no significant association (RR 1.28, 95% CI 0.58–2.85), with significant heterogeneity between studies (p=0.037); there was no prospective

evidence. There was no published evidence at all for the association between intake of dairy products and risk of overall CNS tumours or meningioma.

3.3.1.13 Cheese

Two published studies (2 case-control studies[6, 22]) reported associations between cheese intake and risk of CNS tumours (overall CNS tumours 1 study[22]; glioma 1 study[6]; meningioma 0 study). For overall CNS tumours, 1 case-control study[22] showed no significant association with cheese intake (RR 0.84, 95% CI 0.48–1.47). For glioma, 1 case-control study[6] showed evidence for a borderline significant association with cheese intake (RR 0.40, 95% CI 0.10–1.00). There was no published evidence at all for the association between cheese intake and risk of meningioma, and no published prospective evidence for the association between cheese intake and risk of overall CNS tumours or glioma.

3.3.1.14 Alcohol

Fifteen published studies (10 case-control studies[16, 18, 20–22, 34–38], 5 cohort studies[39–43]) reported associations between alcohol intake and risk of CNS tumours (overall CNS tumours 4 studies[16, 20, 22, 40]; glioma 10 studies[18, 34–42]; meningioma 5 studies[16, 21, 38, 40, 43]). For overall CNS tumours, a meta-analysis of 3 case-control studies[16, 20, 22] (1 increased risk, 1 decreased risk, 1 null) showed no significant association with alcohol intake (summary RR 1.33, 95% CI 0.47–3.71), with significant heterogeneity between studies ($p<0.001$); and 1 cohort study[40] also reported no significant association with alcohol intake (RR 0.95, 95% CI 0.84–1.08). For glioma, a meta-analysis of 6 case-control studies[18, 34–38] (1 decreased risk, 5 null) showed no significant association with alcohol intake (summary RR 0.85, 95% CI 0.72–1.01), with no significant heterogeneity between studies ($p=0.596$); and a meta-analysis of 4 cohort studies[39–42] (1 increased risk, 1 decreased risk, 2 null) showed no significant association with alcohol intake (summary RR 0.96, 95% CI 0.64–1.44), with significant heterogeneity between studies ($p=0.006$). For meningioma, a meta-analysis of 3 case-control studies[16,

21, 38] (1 decreased, 2 null) showed no significant association with alcohol intake (summary RR 0.54, 95% CI 0.27–1.06), with no significant heterogeneity between studies (p=0.137); and a meta-analysis of 2 cohort studies[40, 43] (2 null) also showed no significant association with alcohol intake (summary RR 0.92, 95% CI 0.55–1.54), with no significant heterogeneity between studies (p=0.092).

3.3.1.15 Coffee

Nine published studies (3 case-control studies[25, 44, 45], 6 cohort studies[42, 46–50]) reported associations between coffee intake and risk of CNS tumours (overall CNS tumours 1 study[50]; glioma 8 studies[25, 42, 44–49]; meningioma 1 study[49]). For overall CNS tumours, 1 small cohort study[50] reported some evidence of a borderline association with coffee intake (RR 0.48, 95% CI 0.23–1.00); there was no evidence from case-control studies. For glioma, a meta-analysis of 3 case-control studies[25, 44, 45] (1 decreased risk, 2 null) showed no significant association with coffee intake (summary RR 0.52; 95% CI, 0.13–2.01), with significant heterogeneity between studies (p<0.001); and a meta-analysis of 5 cohort studies[42, 46–49] (5 null) showed no significant association with coffee intake (summary RR 0.93, 95% CI 0.77–1.14), with no significant heterogeneity between studies (p=0.367). For meningioma, 1 cohort study[49] reported no signification association with coffee intake (RR 0.71, 95% CI 0.46–1.08); there was no evidence from case-control studies.

3.3.1.16 Tea

Seven published studies (2 case-control studies[25, 45], 5 cohort studies[46–50]) reported associations between tea intake and risk of CNS tumours (overall CNS tumours 1 study[50]; glioma 7 studies[25, 45–50]; meningioma 2 studies[49, 50]). For overall CNS tumours, 1 cohort study[50] reported no significant association with tea intake (RR 1.07, 95% CI 0.70–1.62); there was no evidence from case-control studies. For glioma, a meta-analysis of 2 case-control studies[25, 45] (1 decreased risk, 1 null) showed no significant association with tea intake (summary RR 0.68; 95% CI,

0.18–2.52), with significant heterogeneity between studies (p=0.018); and a meta-analysis of 5 cohort studies[46–50] (5 null) showed no significant association with tea intake (summary RR 0.87, 95% CI 0.73–1.04), with no significant heterogeneity between studies (p=0.423). For meningioma, a meta-analysis of 2 cohort studies[49, 50] (2 null) reported no signification association with tea intake (summary RR 1.02, 95% CI 0.70–1.48), with no significant heterogeneity between studies (p=0.982); there was no evidence from case-control studies.

3.3.2 Nutrients

3.3.2.1 Carbohydrate

There was no published evidence at all for the association between carbohydrate intake and risk of overall CNS tumours, glioma, or meningioma.

3.3.2.2 Protein

Three published studies (3 case-control studies[22, 26, 51]) reported associations between protein intake and risk of CNS tumours (overall CNS tumours 1 study[22]; glioma 3 studies[22, 26, 51]; meningioma 1 study[22]). For overall CNS tumours, 1 case-control study[22] reported significantly increased risk with protein intake (RR 1.94, 95% CI 1.03–3.63). For glioma, a meta-analysis of 3 case-control studies[22, 26, 51] (3 null) showed no significant association with protein intake (summary RR 1.08, 95% CI 0.73–1.59), with no significant heterogeneity between studies (p=0.220). For meningioma, 1 case-control study[22] reported no significant association with protein intake (RR 2.23, 95% CI 0.91–5.45). There was no published prospective evidence for the associations between protein intake and risk of overall CNS tumours, glioma, or meningioma.

3.3.2.3 Total fat

Three published studies (3 case-control studies[22, 26, 51]) reported associations between total fat intake and risk of CNS tumours (overall CNS tumours 1 study;

glioma 3 studies[22, 26, 51]; meningioma 1 study[22]). For overall CNS tumours, 1 case-control study[22] reported no significant association with total fat intake (RR 0.76, 95% CI 0.45–1.26). For glioma, a meta-analysis of 3 case-control studies[22, 26, 51] (3 null) showed no significant association with total fat intake (summary RR 0.99, 95% CI 0.65–1.49), with no significant heterogeneity between studies (p=0.160). For meningioma, 1 case-control study[22] reported no significant association with total fat intake (RR 1.00, 95% CI 0.52–1.90). There was no published prospective evidence for the associations between total fat intake and risk of overall CNS tumours, glioma, or meningioma.

3.3.2.4 Saturated fat

Three published studies (3 case-control studies[22, 26, 51]) reported associations between saturated fat intake and risk of CNS tumours (overall CNS tumours 0 study; glioma 3 studies[22, 26, 51]; meningioma 1 study[22]). For glioma, a meta-analysis of 3 case-control studies[22, 26, 51] (3 null) showed no significant association with saturated fat intake (summary RR 1.12, 95% CI 0.75–1.68), with no significant heterogeneity between studies (p=0.204). For meningioma, 1 case-control study[22] reported a significantly increased risk with saturated fat intake (RR 2.34, 95% CI 1.11–4.90). There was no published evidence at all for the association between saturated fat intake and risk of overall CNS tumours, and no published prospective evidence for the associations between saturated fat intake and risk of glioma or meningioma.

3.3.2.5 Other fat

One case-control study reported no significant associations between non-saturated fat (non-specified type) intake and risk of glioma in men (RR 1.74, 95% CI 0.98–3.10) and women (RR 1.18, 95% CI 0.64–2.20) (results are not shown in the figures).[51] There was no published evidence at all for the associations between intakes of monounsaturated fat or polyunsaturated fat and risk of overall CNS tumours, glioma, or meningioma.

3.3.2.6 Fibre

Two published studies (2 case-control studies[22, 26]) reported associations between fibre intake and risk of CNS tumours (overall CNS tumours 0 study; glioma 2 studies[22, 26]; meningioma 1 study[22]). For glioma, a meta-analysis of 2 case-control studies[22, 26] (1 decreased risk, 1 null) showed no significant association with fibre intake (summary RR 1.02, 95% CI 0.33–3.18) with significant heterogeneity between studies (p=0.023). For meningioma, 1 case-control study[22] reported no significant association with fibre intake (RR 0.63, 95% CI 0.34–1.39). There was no published evidence at all for the association between fibre intake and risk of overall CNS tumours, and no published prospective evidence for the associations between fibre intake and risk of glioma or meningioma.

3.3.2.7 Carotene

Five published studies (4 case-control studies[19, 20, 26, 52], 1 cohort study[24]) reported associations between carotene intake and risk of CNS tumours (overall CNS tumours 1 study[20]; glioma 4 studies[19, 24, 26, 52]; meningioma 0 study). For overall CNS tumours, 1 case-control study[20] reported no significant association with carotene intake (RR 0.38, 95% CI 0.10–1.60), and there was no prospective evidence. For glioma, a meta-analysis of 3 case-control studies[19, 26, 52] (2 decreased risk, 1 null) showed significantly decreased risk with carotene intake (summary RR 0.72, 95% CI 0.58–0.90) with no significant heterogeneity between studies (p=0.362); while 1 cohort study[24] reported no significant association with carotene intake (RR 0.92, 95% CI 0.64–1.32). There was no published evidence at all for the association between carotene intake and risk of meningioma.

3.3.2.8 Vitamin C

Eight published studies (6 case-control studies[6, 7, 19, 20, 26, 52], 2 cohort studies[23, 30]) reported associations between vitamin C intake and risk of CNS tumours (overall CNS tumours 1 study[20]; glioma 7 studies[6, 7, 19, 23, 26, 30, 52];

meningioma 0 study). For overall CNS tumours, 1 case-control study[20] reported no significant association with vitamin C intake (RR 0.78, 95% CI 0.20–4.10), and there was no prospective evidence. For glioma, a meta-analysis of 5 case-control studies[6, 7, 19, 26, 52] (1 decreased risk, 4 null) showed no significant association with vitamin C intake (summary RR 0.89, 95% CI 0.68–1.18), with no significant heterogeneity between studies (p=0.153); and a meta-analysis of 2 cohort studies[23, 30] (2 null) also showed no significant association with vitamin C intake (summary RR 1.07, 95% CI 0.76–1.52), with no significant heterogeneity between studies (p=0.116). There was no published evidence for the association between vitamin C intake and risk of meningioma.

3.3.2.9 Vitamin E

Seven published studies (5 case-control studies[6, 19, 20, 26, 52], 2 cohort studies[23, 30]) reported associations between vitamin E intake and risk of CNS tumours (overall CNS tumours 1 study[20]; glioma 6 studies[6, 19, 23, 26, 30, 52]; meningioma 0 study). For overall CNS tumours, 1 case-control study[20] reported a significantly decreased risk with vitamin E intake (RR 0.16, 95% CI 0.10–0.50), and there was no prospective evidence. For glioma, a meta-analysis of 4 case-control studies[6, 19, 26, 52] (4 null) showed no significant association with vitamin E intake (summary RR 1.15, 95% CI 0.83–1.60), with no significant heterogeneity between studies (p=0.103); and a meta-analysis of 2 cohort studies[23, 30] (2 null) also showed no significant association with vitamin E intake (summary RR 1.10, 95% CI 0.89–1.37), with no significant heterogeneity between studies (p=0.453). There was no published evidence at all for the association between vitamin E intake and risk of meningioma.

3.3.2.10 Folate

One case-control study[26] reported no significant association between folate intake and risk of glioma (RR 0.90, 95% CI 0.50–1.50), and there was no prospective evidence. There was no published evidence at all for the associations between folate intake and risk of overall CNS tumours or meningioma.

3.3.2.11 Calcium

Two published studies (2 case-control studies[20, 51]) reported associations between calcium intake and risk of CNS tumours (overall CNS tumours 1 study[20]; glioma 1 studies[51]; meningioma 0 study). For overall CNS tumours, 1 case-control study[20] reported no significant association with calcium intake (RR 0.25, 95% CI 0.10–1.10). For glioma, one case-control study[51] reported no significant association between calcium intake and risk of glioma in (RR 0.69, 95% CI 0.36–1.32). There was no published evidence at all for the association between calcium intake and risk of meningioma, and no published prospective evidence for the associations between calcium intake and risk of overall CNS tumours or glioma.

3.3.2.12 Cholesterol

Four published studies (4 case-control studies[22, 26, 51, 53]) reported associations between cholesterol intake and risk of CNS tumours (overall CNS tumours 2 studies[22, 53]; glioma 3 studies[22, 26, 51]; meningioma 1 study[22]). For overall CNS tumours, meta-analysis of 2 case-control studies[22, 53] (1 decreased risk, 1 null) showed no significant association with cholesterol intake (summary RR 0.75, 95% CI 0.42–1.35), with no significant heterogeneity between studies (p=0.063). For glioma, a meta-analysis of 3 case-control studies[22, 26, 51] (3 null) showed no significant association with cholesterol intake (summary RR 1.31, 95% CI 0.72–2.36), with significant heterogeneity between studies (p=0.040). For meningioma, 1 case-control study[22] reported no significant association with cholesterol intake (RR 0.65, 95% CI 0.32–1.34). There was no published prospective evidence for the associations between cholesterol intake and risk of overall CNS tumours, glioma, or meningioma.

3.3.3 Dietary patterns

3.3.3.1 DASH score

One case-control study[17] reported that DASH score was associated with significantly decreased glioma risk (RR 0.28, 95% CI 0.13–0.57). There was no published

prospective evidence for the associations between DASH score and glioma risk, and no published evidence at all for the associations between DASH score and risk of overall CNS tumour or meningioma.

3.3.3.2 Vegetarian diet

One cohort study[54] reported that there was no significant association between vegetarian diet and overall CNS tumour risk (RR 1.31, 95% CI 0.79–2.17); there was no evidence from case-control studies. There was no published evidence at all for the association between vegetarian diet and risk of glioma or meningioma.

3.3.3.3 Glycaemic index

One case-control study[55] and one cohort study[56] reported that there was no significant association between glycaemic index and overall CNS tumour risk (RR 0.95, 95% CI 0.76–1.18 and 0.89, 95% CI 0.51–1.58, respectively). There was no published evidence at all for the association between glycaemic index and risk of glioma or meningioma.

3.3.3.4 Organic food

One cohort study[57] reported that there was no significant association between organic food consumption and overall CNS tumour risk (RR 1.16, 95% CI 0.97–1.40); there was no evidence from case-control studies. There was no published evidence at all for the association between organic food consumption and risk of glioma or meningioma.

3.3.4 Other dietary exposures

3.3.4.1 Dietary nitrite

Six published studies (4 case-control studies[6, 7, 19, 26], 2 cohort studies[23, 30]) reported associations between dietary nitrite intake and risk of glioma. For glioma, a meta-analysis of 4 case-control studies[6, 7, 19, 26] (4 null) showed

no significant association with dietary nitrite intake (summary RR 1.10, 95% CI 0.85–1.43), with no significant heterogeneity between studies (p=0.519); and a meta-analysis of 2 cohort studies[23, 30] (1 increased risk, 1 null) showed a significantly increased risk with dietary nitrite intake (summary RR 1.30, 95% CI 1.05–1.60), with no significant heterogeneity between studies (p=0.835). There was no published evidence at all for the associations between dietary nitrite intake and risk of overall CNS tumours or meningioma.

3.3.4.2 Dietary nitrate

Six published studies (4 case-control studies[6, 7, 19, 26], 2 cohort studies[23, 30]) reported associations between dietary nitrate intake and risk of glioma. For glioma, a meta-analysis of 4 case-control studies[6, 7, 19, 26] (4 null) showed no significant association with dietary nitrate intake (summary RR 0.81, 95% CI 0.62–1.05), with no significant heterogeneity between studies (p=0.408); and a meta-analysis of 2 cohort studies[23, 30] (2 null) also showed no significant association with dietary nitrate intake (summary RR 1.20, 95% CI 0.95–1.52), with no significant heterogeneity between studies (p=0.391). There was no published evidence at all for the associations between dietary nitrate intake and risk of overall CNS tumours or meningioma.

3.3.4.3 Aspartame

One case-control study[18] and one cohort study[58] reported that there was no significant association between aspartame intake and glioma risk (RR 1.02, 95% CI 0.57–1.85 and 0.73, 95% CI 0.46–1.15, respectively). There was no published evidence at all for the association between aspartame and risk of overall CNS tumours or meningioma.

3.3.4.4 Dietary acrylamide

One cohort study[59] reported no significant associations between dietary acrylamide intake and risk of overall CNS tumours (RR 0.87, 95% CI 0.54–1.41) and glioma (RR 0.78, 95% CI 0.43–1.42); there was no evidence from case-control studies. There was no published evidence at all for the association between dietary acrylamide intake and risk of meningioma.

3.3.4.5 Dietary haem iron

One cohort study[31] reported no association between dietary haem iron intake and risk of glioma (RR 0.96, 95% CI 0.73–1.26); there was no evidence from case-control studies. There was no published evidence at all for the associations between dietary haem iron intake and risk of overall CNS tumours and meningioma.

3.4 Discussion

This systematic review and meta-analysis included 62 published reports from 37 studies, which (between them) investigated risk of CNS tumours (predominantly glioma) in relation to intakes of 27 food groups or nutrients, as well as DASH score and other dietary patterns/indices, dietary nitrite, nitrate, acrylamide, aspartame, and haem iron. However, no firm conclusions could be drawn for any association between diet and CNS tumours. Generally, there is a lack of convincing and consistent evidence in the literature. Significant associations reported in individual studies largely became null when evidence from all available studies was combined using meta-analysis, indicating possible heterogeneity between studies (dietary exposures and statistical analysis) and possible selective reporting in some individual studies. Further, most evidence came from studies with retrospective collection of data, which can be susceptible to considerable bias. Firstly, bias caused by differential or inaccurate recall may be substantial because CNS tumours may impair cognitive function and are often rapidly fatal. Secondly, reliance on proxy

respondents for recall of information in retrospective studies of CNS tumours is also high (8%–76%) due to the same reasons. Thirdly, there is also a risk of selection bias because CNS tumour patients with more advanced diseases may be less likely to participate. So evidence from retrospective studies may be unreliable. Evidence from studies with prospective collection of dietary data is limited and patchy (summarised in Table 3.1). In general, there is a lack of an overview of the association between diet and risk of CNS tumours that is supported by reliable prospective evidence, a lack of studies that are able to study subtypes of CNS tumours other than glioma.

Studies that have used the composite outcome 'overall CNS tumours' (usually to maximise sample size) are likely to produce little useful evidence for the association between diet and CNS tumours. This is because CNS tumours are diverse. The two most common subtypes of CNS tumours, glioma and meningioma, are distinct from each other, whether it be embryonal origin, cellular histology, or epidemiological risk factors,[60–63] not to mention the differences with other rarer CNS tumour subtypes (see Chapter 2). Therefore, interpretation of results for overall CNS tumours is challenging because it reflects the summary effect of subtypes that may have different susceptibilities to the risk factors being studied. Besides, composition of 'overall CNS tumours' is expected to vary across different studies (and populations) due to differences in age structure, ethnic conformation, distribution of risk factors, diagnosis and registration of CNS tumours (especially for benign tumours), and many other unrecognised factors, which adds difficulty to the interpretation and comparison of results between studies. Results for overall CNS tumours are included in this review for completeness, but of greater interest are the studies which provide results for subtypes of CNS tumours separately.

Glioma is the most common subtype of CNS tumours as well as the most commonly reported subtype of CNS tumours for its relationship with diet in the literature (11 cohort studies and 18 case-control studies). However, published prospective evidence for the association between diet and risk of glioma is still limited (available for 12 food groups and nutrients only [total fruit, citrus fruit, fruit

juice, red meat, processed meat, alcohol, coffee, tea, carotene, vitamin C, vitamin E] plus dietary nitrite, nitrate, aspartame, acrylamide, and haem iron). There was some weak prospective evidence for a significant association between dietary nitrite intake and increased glioma risk (combining 2 studies with small numbers and with wide CIs for the risk estimate). Published evidence from case-control studies was available for 27 food groups or nutrients: total fruit, citrus fruit, fruit juice, total vegetable, nuts, grains/cereal, red meat, processed meat, poultry, fish, egg, dairy products, cheese, alcohol, coffee, tea, protein, fat (saturated fat, non-saturated fat), fibre, carotene, vitamin C, vitamin E, folate, calcium, cholesterol plus DASH score, dietary nitrite, nitrate, and aspartame. There was evidence from case-control studies for significant associations between intakes of 4 dietary factors and risk of glioma: total vegetable intake and decreased risk (combining 6 studies); grains/cereal intake and increased risk (combining 4 studies); carotene intake and decreased risk (combining 3 studies); and DASH score and decreased risk (1 individual study). However, none of the 4 significant associations with diet found in case-control studies was supported by prospective evidence: no significant association for total vegetable intake (after combining 2 published cohort studies); no published prospective evidence for grains/cereal; no significant association for carotene (1 published cohort study); and no published prospective evidence for the DASH score. Published prospective evidence for glioma is missing for many food groups, nutrients, and dietary patterns, and the number of cases for the current published prospective evidence is small – thus, more prospective evidence from large cohort studies is needed.

Published evidence for CNS tumours other than glioma is very limited. This is because CNS tumours other than glioma are generally non-malignant by nature and are not routinely registered in many countries. In the literature, there were 5 cohort studies and 8 case-control studies reporting associations between diet and risk of meningioma. Published prospective evidence for diet and risk of meningioma was only available for 3 food groups and nutrients (alcohol, coffee, and tea), for which no significant associations were found with meningioma risk. Published

evidence for meningioma from case-control studies was available for 13 food groups or nutrients: total fruit, citrus fruit, total vegetable, grains/cereal, processed meat, fish, egg, alcohol, protein, total fat (saturated fat), fibre, and cholesterol. For meningioma, there was some evidence from case-control studies for significantly decreased risk associated with total fruit intake (combining 2 studies) but there was no prospective evidence available. Prospective evidence is thus missing for the vast majority of food groups, nutrients, or dietary patterns for meningioma. As already noted, prospective evidence is also missing for all dietary factors for vestibular schwannoma and pituitary tumours.

Epidemiological research often uses quantitative or semi-quantitative questionnaires (e.g. food frequency questionnaires [FFQ]), which are designed to estimate an individual's usual intake over a longer period of time, rather than 24-hour dietary recall records or diet diaries which record actual daily intake. Measurements are, however, not without errors so investigating the association between diet and health by relating dietary data collected through questionnaires at baseline to health outcomes is challenging, especially when studying relatively rare neoplasms such as the CNS tumours. True relative risks (RRs) for the association between perfectly measured diet and health outcomes may be biased or attenuated by diet exposures with measurement errors. The likely extent of this can be partly 'quantified' by using methods such as the one proposed by Willett *et al.*: regressing the true dietary intakes (which can be approximated by data from multiple dietary records) on the measured dietary intakes (e.g. those collected using FFQ).[64] The regression coefficients for the measured intakes provide an estimation of 'validity' (also known as the 'attenuation factor') of the questionnaire used.[64] Willett *et al.* estimated that a true RR of 1.5 for the association between a particular dietary factor and CNS tumours will be attenuated to an observed RR of about 1.33 with a regression coefficient of 0.7 between the true and measured dietary intakes.[64] The corresponding observed RRs for regression coefficients of 0.6, 0.5, 0.4, 0.3, and 0.2 were 1.28, 1.22, 1.18, 1.13, and 1.08, respectively.[64] Therefore, the least number of cases needed to detect the observed RRs (given the true RR is 1.5) with 80% power

at 95% significance level, in epidemiologic studies, were about 390, 520, 800, 1150, 2100, and 5300 corresponding to regression coefficients between true and measured intakes of 0.7, 0.6, 0.5, 0.4, 0.3, and 0.2, respectively. The regression coefficients for a standardised FFQ usually fall between 0.3 and 0.5,[64, 65] so studies need to include about 800 to 2100 cases to be able to detect a true RR of 1.5 between a particular dietary factor and CNS tumour risk. The largest retrospective and prospective studies which have published on diet and subtypes of CNS tumours had about 1200 glioma cases (published in 2009 pooling data from 8 case-control studies with each using a different dietary questionnaire[8]) and 900 cases (published in 2012 using the NIH-AARP Study data[46]), respectively, and so may have been underpowered to detect public health relevant associations.

While the evidence was inconclusive, it was not unreasonable for the 2007 Second Expert Report on diet, nutrition, and physical activity[3] to suggest that further investigation into diet and CNS tumours was unlikely to be fruitful based on the context at the time: (1) the incidence of CNS tumours was underestimated due to incomplete registration of CNS tumours (ranked 18th most common cancer in the 2007 report) so the consequent impact of finding (modifiable) dietary factors with moderate RRs (e.g. true RR of 1.5 to 2.0) had been underestimated; (2) individual prospective studies with good quality dietary data, such as the NIH-AARP Study, may not be large enough to include an adequate number of cases for meaningful analyses; (3) and most published evidence for diet and CNS tumours before 2007 came from case-control studies which have varied categorisation of dietary exposures so meta-analysis of these published data may not provide convincing evidence. There is now an estimated lifetime risk of CNS tumours of about 1 in 74 in the UK,[66] and few known risk factors,[66] so finding dietary factors associated with a moderate effect may be of interest. Furthermore, using the newly available large prospective dietary data from the Million Women Study and pooling individual participant data from other large prospective studies into a combined analysis, thereby increasing statistical power and reducing heterogeneity in analysis between studies, should allow investigators to detect or exclude true RRs of moderate magnitude associated

with dietary intakes. Therefore, it is not appropriate to agree with the conclusion made in the 2007 Second Expert Report without further investigating into the association between diet and CNS tumours. Moreover, the current systematic review identified some significant associations of glioma risk with various dietary factors (citrus fruit[8, 25], total vegetables[19], grains/cereal[6, 8], processed meat[7], eggs[6, 8], alcohol[37], coffee[45], tea[45], fibre[26], carotene[26, 52], vitamin C[52], vitamin E[19], and DASH score[17]) and of meningioma risk with some dietary factors (total fruit[16, 21], total vegetables[16, 21], saturated fat[22]), although only a few dietary factors remained statistically significant after combining evidence from all published studies (total vegetables, grains/cereal, and carotene for glioma [1 published study for DASH score only]; and total fruit for meningioma [1 published study for saturated fat only]). There is also prospective evidence that suggests that high intake of fruit or vegetables may be associated with increased risk of glioma.[23, 24] Comprehensive analyses of diet using studies that include many cases of CNS tumours are warranted to clarify these associations.

3.4.1 Strengths and weaknesses

This is the first review that systematically summarises all published evidence on diet and risk of CNS tumours, and estimates summary relative risks by subtypes of CNS tumour for particular dietary exposures. This review gives an overview and summary of evidence, avoiding an over-interpretation of positive results from a single study or for a single dietary factor, and has greater statistical power than any of the included individual studies to detect a true association. The meta-analysis approach used here attempt to account for the different dietary measurement methods and reporting bias in each individual study by combining risk estimates comparing ranked dietary intakes (highest intake category versus lowest) rather than intakes estimated by the questionnaire used in each study. I included studies that reported the effect of diet on risk of CNS tumours in adults only. Studies that examined the effect of maternal diet during pregnancy (carrying study participants) or childhood diet and risk of CNS tumour in study participants during adulthood

after long follow-up were excluded. This ensured that our primary analysis was examining the effect of diet in adulthood that contributes to subsequent risk of CNS tumours, minimising between study heterogeneity.

This analysis has several limitations. Firstly, heterogeneity between studies identified in this review was high as a result variation in study design, and study population, as well as definitions of exposure and outcome. The meta-analysis approach used here could not fully take into account the varied categorisation of dietary variables (e.g. highest vs. lowest fifth in one study, consumer vs. non-consumer in another study), and this remains a major limitation of the approach used here and this meta-analysis of published evidence. In order to allow for this, findings between studies were combined using a random effect meta-analysis, which takes account of within- and between-studies variance, and generates conservative summary estimates with wider confidence intervals, keeping over-estimation of an association to the minimum, when compared with a fixed effect model.[67] Because results from case-control studies are expected to be subject to considerable bias related to differential recall and misreporting of data (impaired cognitive function, proxy respondents), summary results were also generated and presented, stratified by the source of evidence (case-control study or cohort study) to minimise heterogeneity of evidence. Secondly, CNS tumours are relatively rare when compared to other common cancers. The number of cases reported in many of the identified individual studies was small. A meta-analysis of these studies might still fail to detect a weak yet genuine association between diet and risk of CNS tumours.

3.4.2 Conclusions and recommendations

While many studies have investigated possible associations between diet and risk of CNS tumours, no firm conclusions could be drawn from this review for any particular dietary factor and for any particular subtypes of CNS tumours. The majority of published evidence came from case-control studies, which are generally unreliable for reasons discussed earlier. Published prospective evidence is limited

and patchy. Studies need to be large to include enough cases of CNS tumours by subtypes for detailed analyses, and they also need to have collected comprehensive information on diet and potential confounders using validated questionnaires. Such studies (for example the three studies briefly introduced next) are then able to reliably and systematically investigate the associations between diet and risk of subtypes of CNS tumours.

The Million Women Study (see Chapter 4) has information on both malignant and non-malignant CNS tumours, and has published very little on diet and risk of CNS tumours (alcohol and organic food only) (Table 3.1).[40, 57] The National Institutes of Health (NIH)-AARP (formerly the American Association of Retired Persons) Study (see Chapter 5) has information on malignant CNS tumours, and has published findings for malignant CNS tumours in relation to intakes of fruit, vegetable, red meat, processed meat, alcohol, coffee, tea, vitamin C and vitamin E as well as dietary nitrite, nitrate, and aspartame (Table 3.1).[23, 29, 33, 41, 46, 56, 58] The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO Study) (see Chapter 5) has information on glioma, and has published on the associations between intakes of coffee or tea and risk of glioma only (Table 3.1).[47] These three studies have collected comprehensive and reasonably good quality dietary data (regression coefficients of between 0.4 and 0.6 for the great majority of nutrient intakes) and had recorded large number of CNS tumours in the study follow-up (see Chapters 4–5), thus offering the opportunity with adequate statistical power to study the association between diet and CNS tumours.

3.5 Tables

Table 3.1: Published evidence from cohort studies for dietary risk factors of CNS tumour

Dietary exposures	Number of cohort studies published (1 or more studies from MWS/NIH-AARP/PLCO)		
	Glioma	Meningioma	Overall CNS tumour
Food groups			
Fruit	2 (NIH-AARP)	-	-
Citrus fruit	2	-	-
Fruit juice	1 (NIH-AARP)	-	-
Total vegetables	2 (NIH-AARP)	-	-
Nuts	-	-	-
Grains/cereal	-	-	-
Red meat	3 (NIH-AARP)	-	1 (NIH-AARP)
Processed meat	3 (NIH-AARP)	-	1 (NIH-AARP)
White meat	-	-	1 (NIH-AARP)
Fish	-	-	1 (NIH-AARP)
Eggs	-	-	-
Dairy Products	-	-	-
Cheese	-	-	-
Alcohol	4 (MWS/NIH-AARP)	2 (MWS)	1 (MWS)
Coffee	5 (NIH-AARP/PLCO)	1	1
Tea	5 (NIH-AARP/PLCO)	2	1
Nutrients			
Carbohydrate	-	-	-
Protein	-	-	-
Total Fat	-	-	-
Saturated	-	-	-
Monounsaturated fat	-	-	-
Polyunsaturated fat	-	-	-
Fibre	-	-	-
Carotene	1	-	-
Vitamin C	2 (NIH-AARP)	-	-
Vitamin E	2 (NIH-AARP)	-	-
Folate	-	-	-
Calcium	-	-	-
Cholesterol	-	-	-
Dietary Patterns/Indices			
MED/aMED score	-	-	-
HEI/AHEI	-	-	-
DASH score	-	-	-
Vegetarian diet	-	-	1
Glycaemic index	-	-	1 (NIH-AARP)
Organic Food	-	-	1 (MWS)
Others			
Nitrite	2 (NIH-AARP)	-	-
Nitrate	2 (NIH-AARP)	-	-
Aspartame	1 (NIH-AARP)	-	-
Acrylamide	1	-	1
Haem iron	1	-	-

MWS Million Women Study, NIH-AARP National Institutes of Health-AARP (formerly American Association of Retired Persons) Study, PLCO Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial Study, (a)MED score (alternate) Mediterranean Diet score, (A)HEI (Alternative) Healthy Eating Index, DASH score Dietary Approaches to Stop Hypertension score

3.6 Figures

Figure 3.1: Study selection flowchart

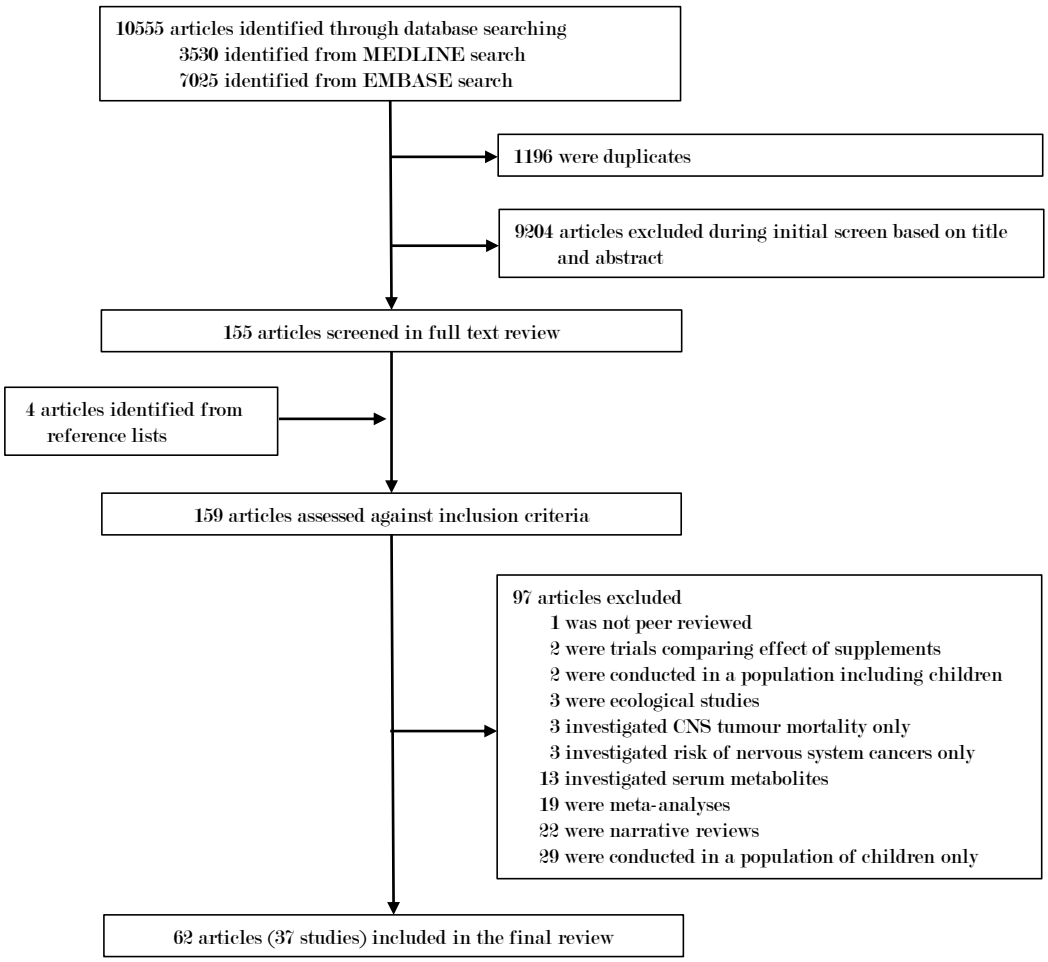
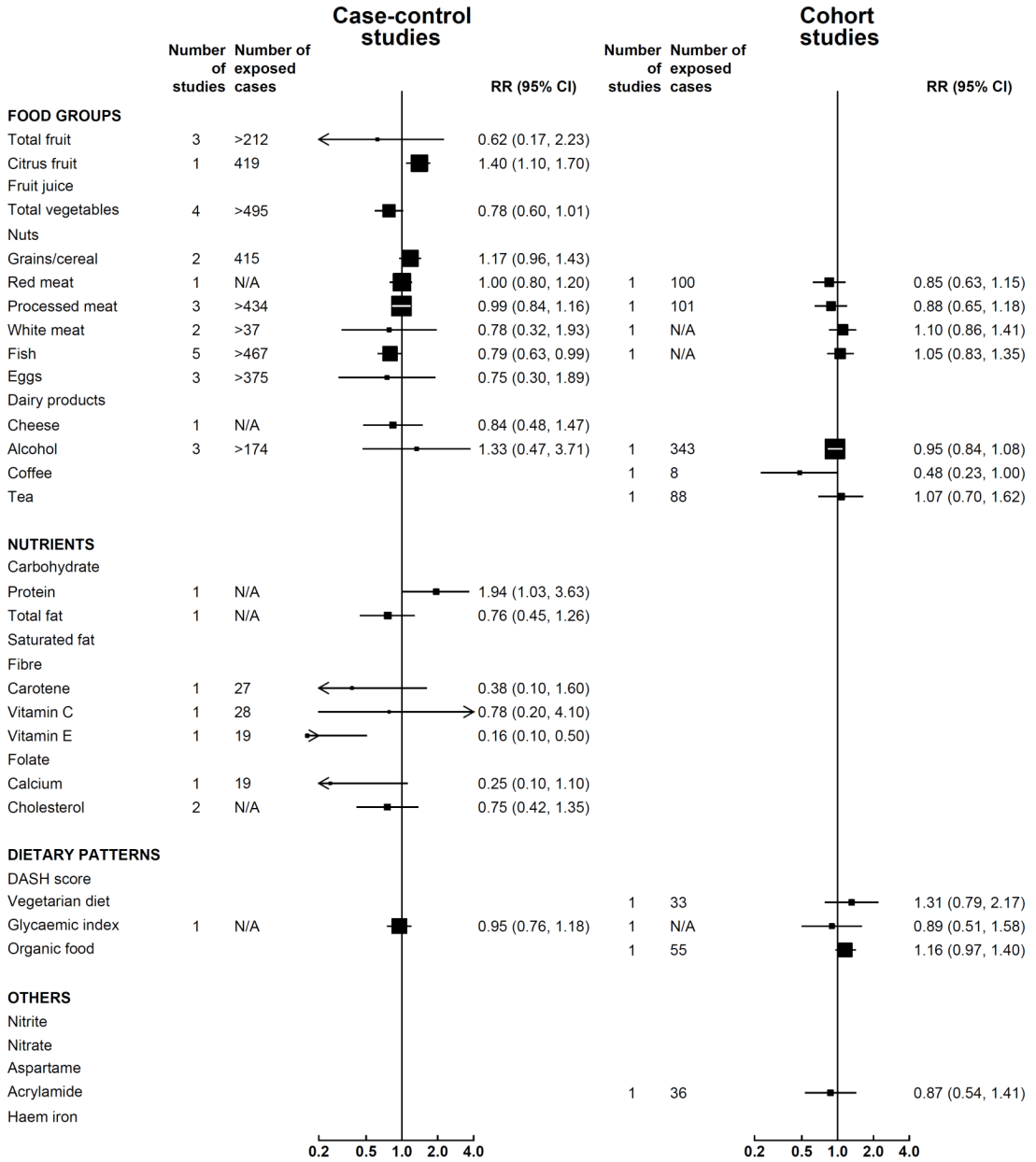
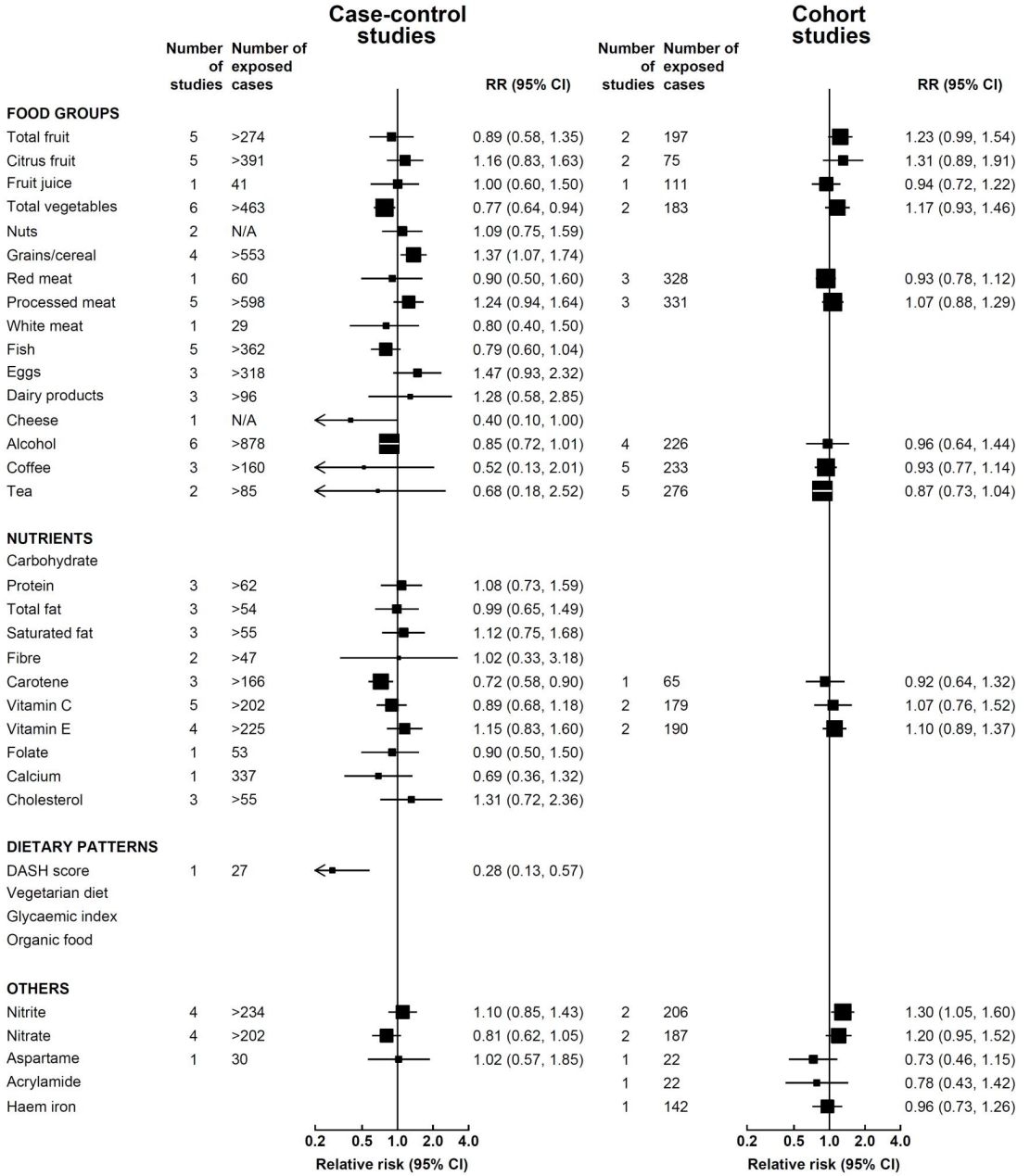


Figure 3.2: Diet and risk of overall CNS tumours



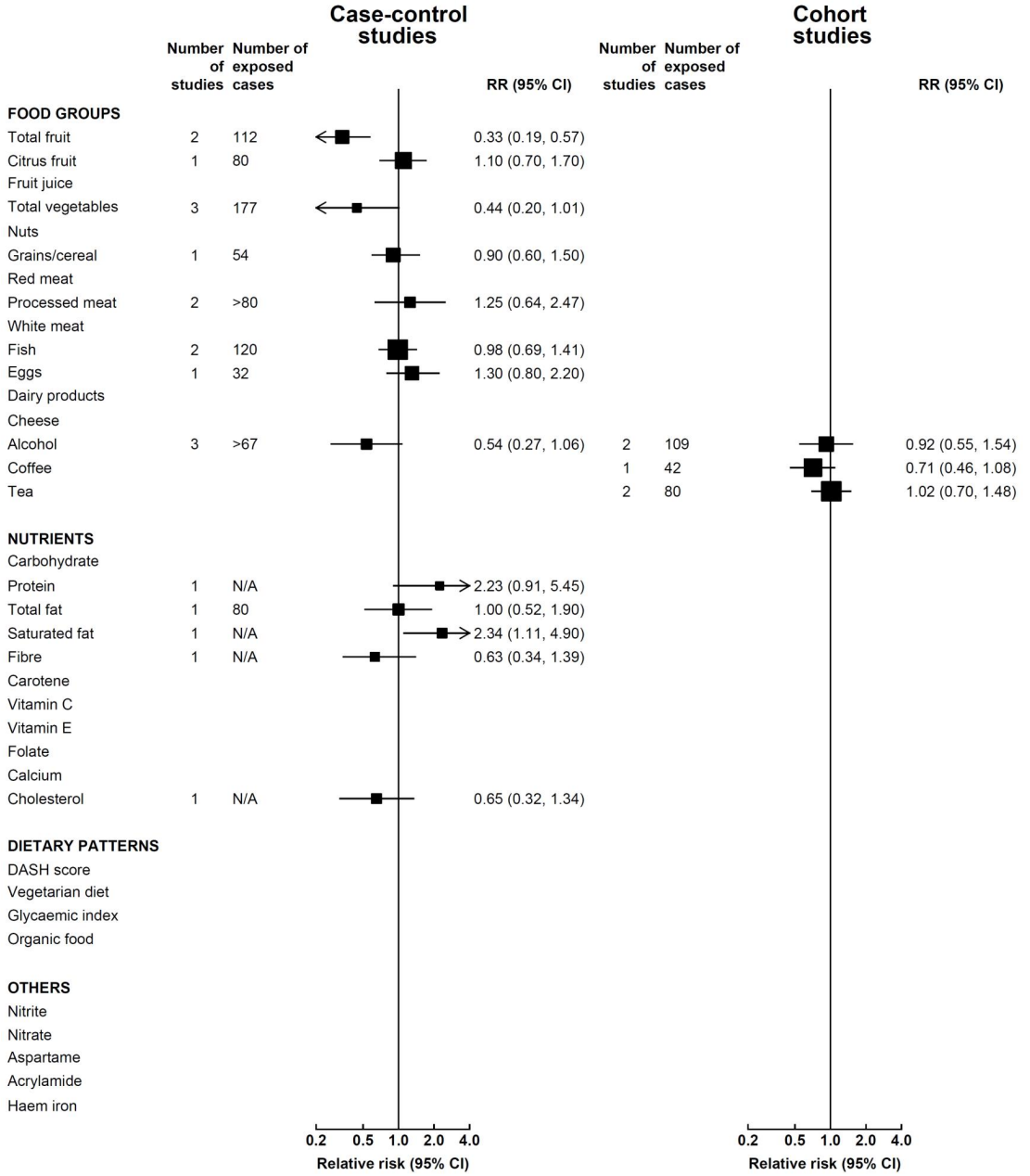
Number of exposed cases for the meta-analyses shown was the summation of number of exposed cases in each of the contributing studies. When the number of exposed cases is missing (not available, N/A) in one or more of the contributing studies, the total number was calculated summing the number from studies with information and the symbol '>' was added to indicate that the actual total number of exposed cases is greater than the number presented in the figure.

Figure 3.3: Diet and risk of glioma



Number of exposed cases for the meta-analyses shown was the summation of number of exposed cases in each of the contributing studies. When the number of exposed cases is missing (not available, N/A) in one or more of the contributing studies, the total number was calculated summing the number from studies with information and the symbol '>' was added to indicate that the actual total number of exposed cases is greater than the number presented in the figure.

Figure 3.4: Diet and risk of meningioma



Number of exposed cases for the meta-analyses shown was the summation of number of exposed cases in each of the contributing studies. When the number of exposed cases is missing (not available, N/A) in one or more of the contributing studies, the total number was calculated summing the number from studies with information and the symbol '>' was added to indicate that the actual total number of exposed cases is greater than the number presented in the figure.

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4

The Million Women Study

4.1 Introduction

This chapter introduces the Million Women Study, and describes the dietary data and central nervous system tumour data used in Chapters 6 to 8.

The Million Women Study is an open-ended ongoing study of the health of women, with prospective collection of data. More than 1.3 million women aged 50–64 years old who were invited to attend the National Health Service (NHS) Breast Cancer Screening Programme in England and Scotland between 1996 and 2001 were recruited into the study.[1] Originally, the main aim of the study was to investigate the association between hormone replacement therapy and risk of breast cancer. The study has subsequently investigated the risks and burden of many other diseases, such as other cancers, cardiovascular, neurodegenerative, musculoskeletal, and other diseases, in relation to many other factors, including demographic, diet, lifestyle, social, health, and other behavioural factors. Information on exposure measures, including dietary information, is collected using postal and online questionnaires. The large size and prospective nature of the Million Women Study provide a good opportunity to reliably study the association between diet and relatively rare tumours such as central nervous system (CNS) tumours.

4.2 Study design

4.2.1 Recruitment and participants

In 1996–2001, women aged 50–64 in England and Scotland who were registered with an NHS general practitioner in areas covered by the 66 participating breast screening units (Figure 4.1) and who were invited to attend the free routine NHS breast screening were also invited to join the study. Women were sent the recruitment questionnaire with their screening invitation and were asked to bring the completed questionnaire to their screening appointment. During the recruitment period, approximately three million invitations were sent out. About 70% of those receiving

invitations attended the screening and around 70% of those attending the screening agreed to participate in the study.[2, 3] At the end of recruitment, the number of women in the study was about 1.3 million, representing over 1 in 4 women in the UK in the target age group (or 1 in 2 in the recruitment areas). Women provided information on age, date and place of birth, level of education, home address, body size, lifestyle factors (such as smoking and drinking), medical history, hormone replacement therapy, reproductive history, and other characteristics through the recruitment questionnaire. Timings and contents of all the study questionnaires are summarised in Table 4.1. More information on the study is available at the Million Women Study website (www.millionwomenstudy.org).

4.2.2 Follow-up

4.2.2.1 Postal re-survey questionnaires

Since recruitment, re-survey questionnaires have been sent to surviving participants every 3–5 years to update information collected previously on body size, lifestyle, medical history, hormone replacement therapy, and other characteristics which may have changed over time, and to collect new information such as diet (see section 4.4 for details) and social factors. To date, four different postal re-survey questionnaires i.e. the 3-year, 8-year, 12-year, and 15-year re-survey questionnaires, have been sent, in addition to the recruitment questionnaire (Table 4.1). Some 80% of women in the cohort have responded to at least one of the four re-survey questionnaires. Data processing is complete for data collected through the 3-year, 8-year, and 12-year re-survey questionnaires while data collected through the 15-year re-survey questionnaire are not yet ready to be analysed.

4.2.2.2 Online questionnaires

Starting about 10 years after recruitment into the study, women who provided valid email addresses were also invited to complete online dietary questionnaires, consisting of an online 24-hour recall dietary questionnaire (the Oxford WebQ) and

an online food frequency questionnaire (the online FFQ) (Table 4.1). Since 2010, over 100,000 women have completed any 1 of the 2 online questionnaires at least once. More information on the dietary data can be found in section 4.4.

4.2.2.3 Linked outcomes

Women in the Million Women Study are followed up through electronic record linkage to routinely collected healthcare and health outcome data in England and Scotland. Follow-up remains virtually complete after 20 years, with about 1% loss to follow-up, mainly due to emigration.

Women are linked to the NHS Central Registers for cancer registrations, death registrations and changes in registration with the NHS since recruitment, and since 2005–2006 also for hospital admissions (Hospital Episode Statistics [HES] in England or Scottish Morbidity Record [SMR] data in Scotland). The sensitivities of the cancer registries for cancer case ascertainment were shown to be extremely good in both England (98%)[4] and Scotland (95%)[5]. The English data are provided by the Office for National Statistics (ONS)/NHS Digital while the Scottish data are provided by the Public Benefit and Privacy Panel (PBPP) for Health and Social Care, part of the NHS in Scotland. Linkages to other data include cancer screening data in England (provided by Public Health England [PHE]), data on cancer outcomes and services in England (provided by PHE), and primary care data for 100,000 women in each of England (provided by Clinical Practice Research Datalink) and Scotland (provided by PBPP Scotland). Details on data sources, data content, and dates the data were received are summarised in Table 4.2.

Information that is available in the cancer registration database includes cancer site (coded using the 9th or 10th revision of the International Classification of Diseases, ICD-9 or ICD-10)[6], tumour morphology (coded using the 2nd or 3rd edition of the International Classification of Diseases for Oncology, ICD-O-2 or ICD-O-3)[7], and date of cancer registration. Additional information for tumour characteristics such as stage and grade is also available for some women from

England, in a database managed by Public Health England. For death registrations and change in registration with the NHS, information on date of event (death, emigration or cancellation) and cause of death (coded using ICD-10) if any, is available. For hospital admissions, information on all inpatient and day-case hospital admissions, including dates of admission and discharge, diagnosis of clinical conditions (coded using ICD-9 or ICD-10), and all operations and procedures (coded using Classification of Interventions and Procedures version 4, OPCS-4)[8], is available.

4.2.3 Validation of self-reported information

Various validations have been carried out in subsets of participants to examine reporting error, regression dilution, and changes over time regarding participants' self-reported data. Some of this self-reported information, such as anthropometric data, reproductive factors, and hormonal use, has been compared with objective measures or routinely collected health records, and good agreements were found.[9–11] Repeatability of frequency of physical activity asked on two occasions (i.e. recruitment and 3-year re-survey) was assessed and good agreements were found.[12] Repeatability of dietary questionnaires and performance of dietary questionnaires in estimating nutrients were also assessed and will be discussed in detail in section 4.4.

4.3 Characteristics of study participants

4.3.1 Characteristics at recruitment and re-surveys

The 1.3 million participants in the study were born in a median year of 1942 (IQR 1938–1946). At recruitment: women had a mean age of 56.2; they had a mean height of 162.0 cm and BMI of 26.2 kg/m2; the mean alcohol intake was 4.1 drinks per week; 19.4% of women reported being current smokers; 38.7% of women reported doing strenuous exercise one or more times per week; 10.9% of women were nulliparous,

59.1% reported ever using oral contraceptives and 33.0% were current user of menopausal hormones; and 13.3% of women had a university degree (Table 4.3).

When compared with women of the entire cohort, responders to the first three postal re-surveys (3-year, 8-year, and 12-year re-surveys) appeared to have healthier lifestyles at recruitment, for instance: after standardisation to birth year and age group of the entire cohort, they were more likely to do strenuous exercise ≥1/week (41.8–43.8% of responders of the three postal re-surveys vs. 38.7% of the entire cohort), less likely to be a current smoker (13.4–15.6% vs. 19.4%); more likely to have a university degree (15.8–18.3% vs. 13.3%); and more likely to be from the least deprived third of social deprivation group (36.2–37.9% vs. 33.3%) (Table 4.3). This healthy responder bias is even more apparent in the Oxford WebQ responders: 51.6% did strenuous exercise ≥1/week, only 6.7% were current smokers, 41.8% had a university degree, and 44.1% were from the least deprived third of social deprivation group at recruitment (Table 4.3).

4.3.2 Health outcomes of study participants since recruitment

There were 185,233 deaths (up to 31 March 2017) and 201,988 incident cancers (up to 31 December 2015) recorded by the registries. About 1.13 million women had been admitted to hospital (up to 31 March 2017) at least once (Table 4.4). With a very large number of participants, the Million Women Study has substantial power to detect associations for many common outcomes, even by relevant subtypes of disease. The study may also have sufficient power to detect modest associations between extreme categories of a given exposure and relatively rare cancers such as CNS tumours and its subtypes. In women who provided dietary data and who had not reported changing diet at analysis baseline, a total of 2,612 CNS tumours cases (1,173 gliomas, 750 meningiomas, 191 pituitary tumours, 174 vestibular schwannomas, and 324 other subtypes) occurred during the study follow-up.

4.4 Dietary data

4.4.1 Dietary data collection

Comprehensive dietary information of study participants was collected through the 3-year re-survey questionnaires and the Oxford WebQ, as well as a 7-day diet diary in a reproducibility study (see section 4.4.2) and the online FFQ. The 8-year, 12-year, and 15-year re-survey questionnaires also collected dietary information, but had a focus on major components of a diet only. Data processing is complete for data collected through the 3-year, 8-year, and 12-year re-survey questionnaires, the 7-day diet diary, and the Oxford WebQ (online data received up till November 2017) while data collected through the 15-year re-survey questionnaire and the online FFQ are currently being prepared and are not yet ready to be analysed.

4.4.1.1 The 3-year re-survey questionnaire

The 3-year re-survey questionnaire asked the participants to report their diet during a typical week. To capture the main sources of variability in the diets of study participants, this questionnaire used semi-quantitative questions to collect dietary information. Generally, information was collected on frequency of intake of a number of foods (e.g. fruits, vegetables) and the detailed subtypes of food (e.g. apple, banana, carrot, broccoli) usually consumed (Table 4.5). Information on the portion size of consumption was not collected. Total energy intake and intakes of macronutrients and micronutrients in study participants were then derived by multiplying the consumption of standard portion(s)[13] of a particular food with the energy and nutrient composition of that particular food[14–23]. This questionnaire also collected information on dietary habits (e.g. never eat meat, type of cooking oil usually used, always remove fat from meat) (Table 4.5). A copy of the 3-year re-survey questionnaire is in Appendix A.1.

4.4.1.2 The 8-year and 12-year re-survey questionnaire

The 8-year and 12-year re-survey questionnaires asked the participants to update their frequency of intake of major food groups (i.e. fruit, vegetables, meat, fish, dairy products, bread, and cereal) and beverages (i.e. alcohol, coffee, and tea), with information on subtypes (e.g. tomatoes, broccoli) usually consumed (Table 4.5). When compared to the 3-year re-survey, dietary assessments in the 8-year and 12-year re-surveys are relatively limited and total energy intake and nutrient intake of participants were not derived from dietary data collected from these questionnaires.

4.4.1.3 The Oxford WebQ

Since 2010, women who are alive and who have provided valid email addresses (about 116,600 women) are invited to complete an online 24-hour dietary recall questionnaire, the Oxford WebQ (https://mws.ceu.ox.ac.uk/diet/). This online questionnaire aims to obtain information on the quantities of all foods and beverages consumed during the previous 24 hours, and could be subject to within person variations. Therefore, invitations were repeatedly sent to study participants so that an average daily dietary intake could be obtained and seasonal variations of dietary intakes could be assessed. Up to November 2017, more than 56,000 women had completed the questionnaire at least once (at least four times for over 24,000 women).

The Oxford WebQ is a more complete assessment of diet in collecting updated dietary information than the 8-and 12-year postal re-surveys. It is structured to record information about foods consumed from each of 21 food categories (e.g. meat or poultry, fish, bread, cereal) (Table 4.6). For the majority of questions for these food groups, individuals are first presented with a single question, 'e.g. did you eat any meat or poultry yesterday?' If a positive answer to the question (e.g. meat or poultry) is received, participants are then presented with an extended question revealing a list of commonly consumed items (e.g. sausage, beef, pork), and are asked to indicate the amount of consumption using standard categories (e.g. none, ½ serving, 1 serving). The definition of standard serving (portion size)

for each question can be found in the help section for each of the questions. Where appropriate, questions on particular dietary habits (e.g. did you remove skin/fat from the chicken or meat), are asked. Participants are required to have answered all questions in the same section before proceeding to the next section. Information on whether the reported diet was typical for the individual, reasons (e.g. ill, fasting, away from home and others) if the reported diet was atypical, and if the individual were following a special diet (e.g. vegetarian, vegan, gluten free), is also collected. In addition, the questionnaire also collects information on physical activity (i.e. frequency of light, moderate, and vigorous activity) during the previous 24 hours. At the end of the survey, individuals have a chance to review a summary of the reported diet and make necessary amendments. Total energy intake and intake of macronutrients and micronutrients in participants are derived automatically according to the dietary information provided on the Oxford WebQ by multiplying the consumption of standard portion(s)[13] of a particular food with the energy and nutrient composition of that particular food[14–23].

4.4.2 Performance of the dietary questionnaires

To study the short-term and long-term repeatability of the 3-year re-survey questionnaire in capturing dietary information and to assess its performance for estimating nutrient intakes, a reproducibility study was conducted between 2000 and 2002.[24] A random sample of about 12,000 women were either sent a second copy of the 3-year re-survey questionnaire at 3, 6, 12 or 24 months, or a 7-day diet diary 3 months after the initial 3-year re-survey questionnaire was completed. The study showed that 75% of the food group items had at least moderate agreement (kappa statistic 0.41–0.60) for all four time-point comparisons (3-, 6-, 12-, and 24-month).[24] The performance of the 3-year re-survey questionnaire for estimating nutrient intakes when compared with a 7-day diet diary was reasonably good.[24]

The performance of the Oxford WebQ in capturing food items eaten daily and for estimating nutrient intakes has also been assessed. Volunteers were recruited

and were asked to complete the Oxford WebQ, unassisted, and then complete a standardised 24-hour dietary recall assessment by two trained interviewers, who were blinded to the participants' dietary information recorded by the Oxford WebQ. When compared to the interviewer-administered dietary assessment, the majority of nutrients derived from the Oxford WebQ had a Spearman's correlation of between 0.5 and 0.9, and the great majority had a mean intake difference of less than 10%.[25]

Neither the dietary information collected through the 3-year re-survey questionnaire nor those through the Oxford WebQ has been compared with any biological markers of dietary intakes such as urinary nitrogen or doubly labelled water. So the performances of the two questionnaires including estimating nutrient intakes evaluated by using diet records (i.e. 7-day diary or interview) as the reference may be overestimated.

4.4.3 Preparation of dietary data

To prepare the baseline dietary data collected using the 3-year re-survey questionnaire for nutritional epidemiology analysis, the Million Women Study Diet Documentation Project was initiated. The work of the project includes, for each dietary intake question on the 3-year re-survey questionnaire, reviewing missing data and performing range check and consistency checks to identify errors related to data entry, reporting, or other forms of errors. Nutrient values and standard portion sizes that were assigned to each dietary item and procedures of nutrient calculation were also reviewed. The work was carried out by a dietary data committee in the Million Women Study made up of myself, Kathryn Bradbury, Angela Balkwill, and was overseen by Tim Key, Jane Green, Siân Sweetland, and Valerie Beral.

4.4.3.1 Missing data and imputation

The proportion of missing data was lower than 5% for commonly consumed dietary items such as fruit, vegetables, fish, and meat; 10%–15% for beverages such as alcohol, tea, and coffee; and higher than 20% for less commonly consumed dietary

items such as crisps, fizzy drinks, and others, possibly due to non-consumption. The dietary data committee found that it is possible to impute frequency of intake from missing to zero when participants reported never eating a particular dietary item and left the frequency of intake of that particular item blank for the following three dietary items: meat (n=9,474), fish (n=9,728), and eggs (n=2,830). No imputation for any other dietary items was performed.

4.4.3.2 Range check and review of original questionnaire

For some study participants with seemingly extreme or implausible intakes, their original questionnaires in which they reported their dietary intakes were reviewed. For instance, the questionnaires for women who reported regularly consuming all subtypes of vegetables (up to 27 subtypes) available on the questionnaire were reviewed (<0.1% of the entire cohort). There were actual errors on only a few of those questionnaires (e.g. women who crossed out the whole section had been read as ticking all boxes by the data reading machine). In summary, the number of errors was very small (<0.1% of the entire cohort) for each of the dietary items that were checked. The dietary data committee made a decision not to correct any of these data entry errors so that no differential correction was introduced because we were not able to check all questions on all questionnaires manually.

4.4.3.3 Consistency of reporting of dietary intakes

Consistency checks for reporting of dietary intakes were possible for some dietary items including fruit, vegetables, meat and fish. For instance, study participants were asked about their frequency of fish intake and subtypes of fish that are usually eaten, and were also asked about their dietary habits including indication of 'never eat fish'. Less than 0.1% of participants who reported 'never eat fish' had frequencies of fish intake that were greater than zero or provided information on subtypes of fish that are usually eaten. In summary, the proportions of inconsistency in reporting were small (<1.3%) for each dietary item. The dietary data committee recommended

that participants with inconsistency in reporting for a particular food are excluded when that particular food group is involved as the main analysis.

4.4.3.4 Calculation of intakes of dietary energy and nutrients

Intakes of total energy and nutrients in the Million Women Study were previously derived by Paul Appleby, Andrew Roddam, Angela Balkwill and Tim Key to compare the performance of the 3-year re-survey questionnaire in estimating energy and nutrient intakes against a 7-day diet diary in the reproducibility study.[24] The algorithm for these calculations was reviewed. Calculation of energy and nutrients in the Million Women Study involves four major steps, described below for beef intake as an example:

1. Select food codes that are associated with a particular dietary item e.g. beef: 90% of code 18049 (grilled lean beef or rump steak) and 10% of code 18005 (average cooked beef fat). Energy and nutrient contents of each food code can be found in McCance & Widdowson's The Composition of Foods (Fifth Edition).[14–23]

2. Select the standard portion size associated with a particular dietary item e.g. beef: medium average portion of minced or stewed beef is 140g while for fried or grilled beef or steak is 144g.[13]

3. Derive frequency of beef intake from crude dietary intake collected. Frequency of beef intake was derived from total amount of meat intake taking account of subtypes of meat reported as usually eaten. If participants reported '6' for frequency of total meat intake, and indicated that they usually eat beef, lamb, and sausages, then it is assumed that participants had 2 portions each of beef, lamb, and sausages in a week (total meat intake in portion divided equally by subtypes of meat that are usually eaten).

4. Generate programming codes that can calculate energy and nutrient intakes based on selected food codes, standard portion sizes, and frequency of intake.

The dietary data committee reviewed thoroughly all the procedures of energy and nutrient calculation in the Million Women Study and made a number of corrections. For selection of food codes, inappropriate selection of food codes such as energy and nutrient composition for egg intake was corrected from raw egg to boiled egg. For selection of standard portion sizes, inappropriate selection such as a standard portion of sausages was corrected from 120g to 80g. For frequency of intake, intake of a particular dietary item was corrected from the larger of frequency of intake or the sum of the number of subtypes of that particular item to the actual frequency of intake reported. For calculation of energy intake and nutrients, a few errors such as referencing the wrong food codes (e.g. referencing codes for Cod for Salmon) were corrected.

The agreements for energy and nutrient intake between the 3-year re-survey and the 7-day diet diary were compared after all corrections were incorporated (Table 4.7). Spearman's correlation for total energy intake and intakes of many nutrients including protein and carbohydrate between the two diet sources improved slightly while the correlation coefficients for some nutrients such as carotene and vitamin C decreased slightly after these corrections were made (Table 4.7).

4.4.4 Dietary variables

4.4.4.1 Food groups and nutrients

Food groups (e.g. total fruit, total vegetables) are a more standardised form of dietary data than crude data on intakes of dietary items (e.g. apple, lettuce) which are collected through questionnaires. Food group variables can be developed by converting crude dietary data using specific operational definitions and procedures. In the Million Women Study, food group variables were developed in accordance with the composition of food groups which was used in the UK National Diet and Nutrition Survey, and after agreements made among the Million Women Study dietary data committee and supervisors.[26] For instance, intake of total fruit in grams was a summation of the intakes of fresh fruit, dried fruit, and stewed/tinned

fruit. Table 4.8 lists all the food group variables which are used in nutritional epidemiology analysis in Chapters 6–8, and their compositions.

Intakes of foods and nutrients were standardised to total energy intake before they were used in the descriptive analysis shown in the next section, the nutritional epidemiology analyses in Chapters 6–8, and the derivation of dietary patterns. Standardisation to energy intake can partly reduce measurement errors related to under-or-over-reporting of dietary intakes because they were partly associated with total energy intake.[27] In the Million Women Study, daily intakes of food groups and nutrients (except for energy-contributing nutrients) were standardised to 1600 kcal/day, which was the approximate mean daily dietary energy intakes of women in the study as well as women of similar age in the UK (see 4.9) and in the US (see Chapter 5). This was done by dividing the intake of each particular food group or nutrient by the individual's daily dietary energy intake, and then multiplying by 1600 kcal. Intakes of energy contributing nutrients, namely carbohydrate, protein, total fat and fat subtypes (saturated, monounsaturated, and polyunsaturated) were expressed as percentage dietary energy intake from these nutrients. This was done by multiplying each individual's carbohydrate intake by 3.75 kcal/g; protein intake by 4 kcal/g; and fat or fat subtypes intake by 9 kcal/g, and then dividing it by the individual's dietary energy intake. Energy-standardised-intakes or percentage energy from intakes of foods or beverages or nutrients are used universally in this thesis unless otherwise specified.

4.4.4.2 Dietary patterns

Foods are consumed in combinations, so a measure of combinations of dietary intakes such as measuring adherence to a particular dietary pattern takes account of correlations between dietary intakes. Three common dietary patterns, namely the Dietary Approaches to Stop Hypertension, the Mediterranean diet, and the Healthy Eating Index were derived using energy-standardised-intakes of food groups and/or nutrients, as described below.

1. The Dietary Approaches to Stop Hypertension

The Dietary Approaches to Stop Hypertension (DASH) score measures adherence to the recommended dietary intakes to control and prevent hypertension promoted by the US National Heart, Lung, and Blood Institute of the NIH.[28] The DASH score measures adherence to the consumption of 8 dietary components, which have a range from 1 point to 5 points each. The total score for the DASH score ranges from 8 point (non-adherence) to 40 points (perfect adherence). For each of the following five components (total fruit and fruit juice, non-legume vegetables, nuts and legumes, dairy products, whole grains), participants were categorised into fifths according to their dietary intakes and scores of 1 to 5 points were assigned based on their ranking in fifths (e.g. 1 point for the lowest fifth, 5 points for the highest fifth). Scoring was reversed for the remaining three components: sugar-sweetened beverages, red and processed meats, and sodium. In the Million Women Study, scoring for sodium intake was based on added sodium, as asked in the question 'how often do you add salt to food' (5 points for never, 3 points for sometimes, 2 points for usually, and 1 point for always add salt to food).

2. The alternate Mediterranean diet score

The Mediterranean diet score measures adherence to the Mediterranean diet.[29] The alternate Mediterranean diet (aMED) score is a modified version of the original score, which includes only dietary components that have been consistently shown to be associated with risks of chronic diseases.[30, 31] The aMED score measures adherence to the consumption of nine dietary components with a possible range from 0 to 9 points. For each of seven components (fish, legumes, whole grains, non-legume vegetables, total fruit and fruit juice, nuts, ratio of monounsaturated fat to saturated fat) 1 point was assigned for intakes equal to or greater than the sex-specific median, and 0 points otherwise. Scoring was reversed for red and processed meats, so that 1 point was assigned for intakes below the sex-specific median, and 0 points otherwise. For alcohol intake, 1 point was assigned for moderate intakes (5–15g/day in women), and 0 points otherwise. Participants were categorised into 4

groups (0–2, 3–4, 5–6, 7–9 points) according to their total scores.

3. The alternative Healthy Eating Index

The 2010 Healthy Eating Index (HEI) measures the adherence to the recommended dietary intakes based on the 2010 Dietary Guidelines for Americans developed by the US Department of Agriculture.[32] The alternative Healthy Eating Index (AHEI) is a modified version of the HEI-2010 which includes only dietary components that have been consistently shown to be associated with risks of chronic diseases.[33] The AHEI comprises eleven components, which have a range from 0 to 10 points each. The total score for the AHEI ranges from 0 points (non-adherence) to 110 points (perfect adherence). For each of the following six components, intakes were scored proportionally from 0 to 10 points according to the range of recommended intakes: non-legume vegetables (0–5 servings/day), total fruit (0–4 servings/day), whole grains (0¬–75g/day in women), nuts and legumes (0–1 serving/day), energy from intake of polyunsaturated fat excluding omega 3 fatty acids (2%–10%/day), and omega-3 fatty acids (0–250mg/day); intakes below the recommended range were assigned with 0 points while intakes above the range were assigned with 10 points. Scoring was reversed for each of the following three components: sugar-sweetened beverages (0–1 serving/day), red and processed meats (0–1.5 servings/day), and energy from intake of trans-fat (0.5%–4%/day). For sodium, participants were usually categorised into tenths according to sodium intake and score was reversely assigned based on the rank of the tenths. In the Million Women Study, scoring for sodium was based on added salt (10 points for never, 6.7 points for sometimes, 3.3 points for usually, and 0 point for always add salt to food) For alcohol, 10 points were assigned to moderate intake (0.5–1.5 drinks/day in women); intakes were scored proportionally from 10 to 0 for intakes between 1.5–2.5 drinks/day in women; intakes greater than 2.5 drinks/day in women were assigned 0 point; and intakes <0.5 drinks/day was assigned 2.5 points.

4.4.5 Dietary intakes

4.4.5.1 Baseline dietary intakes

Approximately 867,000 participants (about 64% of the entire cohort) have provided information on dietary intake in the 3-year re-survey, which is the baseline for dietary information and for nutritional epidemiology analyses. Among them, about 170,000 were excluded from further analyses for several reasons, including: 577 women based on standard exclusions for the Million Women Study (see Figure 6.1); 123,937 women who reported having changed their diet in the past 5 years because of illness; 45,953 women who had prior cancer; 4,276 women who reported an implausible dietary intake (daily total energy intake outside 500–3,500 kcal); and 181 women who had neurofibromatosis or tuberous sclerosis.

The remaining 692,179 women, with a median age of 59 (IQR 55–63) at 3-year re-survey, reported a mean daily total energy intake of 1612 kcal, with 47.3%, 16.3%, 34.3%, and 2.4% of intake from carbohydrate, protein, total fat, and alcohol, respectively (Table 4.9). The non-energy standardised mean daily intakes of total fruit, total vegetables, total meat, fish, and fibre were 204g, 121g, 62g, 34g, and 13.4g, respectively. The majority of these numbers were not different from the findings in women of a similar age group (range of age 50–64) in the National Diet and Nutrition Survey (NDNS) 2002 (carried out in 2000–2001) (Table 4.9).[34] The NDNS 2002[34] used a 7-day food diary to record dietary intakes as opposed to a semi-quantitative food frequency questionnaire in the Million Women Study. Women in the NDNS reported a higher consumption (non-energy standardised) of total meat (119g), fish (43g), vegetables (143g), and fibre (14.0g), and a lower consumption of fruit (151g) when compared with women in the Million Women Study, but their total energy intake (1652 kcal), and mean percentages of energy intake from carbohydrate (46.4%), protein (16.8%), total fat (33.3%), and alcohol (3.7%) were similar.[34] It is unclear why the consumption of total meat was much higher in women in the NDNS than women in the Million Women Study.

4.4.5.2 Correlations between baseline intakes foods and nutrients

In the Million Women Study, spearman's correlations were greater than 0.50 for intakes of the following food groups and nutrients (categorised into fourths): total fruit and citrus fruit or fibre; total vegetables and carotene; total fruit, citrus fruit, or fruit juice and vitamin C; dairy products and calcium; eggs and cholesterol; polyunsaturated fat and vitamin E; and fibre and folate (Table 4.10). Percentage energy intake from carbohydrate was negatively correlated with percentage energy intakes from total fat and monounsaturated fat (correlation coefficients >0.65). There were moderate correlations between the three dietary patterns and some food groups and nutrients. Correlations were greater than 0.40 between DASH score and intakes of total fruit, total vegetables, fibre, or carotene; between aMED score and intakes of total fruit, total vegetables, fibre, or vitamin C; and between AHEI and fibre (results not shown).

4.4.5.3 Differences in baseline dietary intakes by participant's characteristics

There were some marked differences in dietary intakes by women's smoking status as well as some noteworthy differences in intakes of food groups by other participant's characteristics. Differences in intakes of nutrients by these factors were relatively modest. Differences in mean intakes of food groups were greater than 20%: between women who never smoked (reference group) and those who were current smokers for intakes of total fruit (-32.0%), citrus fruit (-27.8%), grains/cereal (-25.9%), alcohol (36.9%), coffee (63.7%), and tea (26.1%); between women who had <12 years of education (reference group) and those who had tertiary education for intakes of citrus fruit (25.6%), total vegetables (21.8%), nuts (41.8%), cheese (20.5%), alcohol (76.4%), and tea (-26.2%); between women with BMI<25 (reference group) and those with BMI≥30 for intakes of nuts (-28.9%), processed meat (21.9%), and alcohol (-35.3%); between women who never/rarely did strenuous exercise (reference group) and those who did strenuous exercise ≥2 per week for intakes of total fruit (21.0%), citrus fruit (22.9%), nuts (33.5%), and alcohol (26.0%); between women

from the lower third of social deprivation (reference group) and those from the upper third for intake of alcohol (27.9%); between non-drinkers (reference group) and those who had ≥1 alcoholic drinks per day for intakes of nuts (24.7%) and tea (-27.6%); between women who never used oral contraceptives (reference group) and those who had ever used them for intake of alcohol (49.8%); and between never users of menopausal hormones and current users for intake of alcohol (26.6%) (Table 4.11). Differences in mean nutrient intake were greater than 10%: between never vs. current smokers for percentage energy intake from saturated fat (10.4%), fibre (-17.5%), carotene (-14.8%), vitamin C (-20.0%); between levels of education (<12 years vs. tertiary) for intakes of carotene (26.0%) and vitamin C (17.3%); between levels of strenuous exercise (never/rarely vs. 2+ times/week) for intakes of carotene (13.4%) and vitamin C (15.4%); between levels of social deprivation (lower vs. upper third) for carotene intake (10.8%); and between levels of drinking (non-drinker vs. 1+ drinks/day) for percentage energy intake from carbohydrate (-13.6%) (Table 4.11). Details on mean intakes of all food groups and nutrients by levels of these characteristics are given in Supplementary Table B.1 in Appendix B.

4.4.5.4 Changes in dietary intakes over time and regression dilution ratios

Among these 692,179 women who completed the baseline dietary assessment in the 3-year re-survey, 42,121 provided dietary information subsequently through the Oxford WebQ about 10 years later (median year 2013, IQR 2012–2015) (median age during assessment 69, IQR 66–72). Updated dietary information provided by the Oxford WebQ responders is used in conjunction with baseline dietary information of all participants collected in the 3-year re-survey to improve measurement of diet by reducing the impact of regression dilution bias.[35] Although some non-dietary characteristics of the Oxford WebQ responders differed from those of all women in the cohort (e.g. level of educational attainment) (see section 4.3.1), their mean dietary intakes were representative of all women in the cohort, as described in the next paragraph.

Table 4.12 shows selected mean dietary intakes of all women at baseline, and of Oxford WebQ responders at baseline and at the time of completing the Oxford WebQ (Supplementary Table B.2 in Appendix B shows all dietary factors assessed). At baseline (the 3-year re-survey), overall mean intakes were different between Oxford WebQ responders and all women in the cohort for intakes of total fruit (235.0g vs. 206.8g), total vegetables (142.2g vs. 122.0g), red meat (31.2g vs. 30.3g), alcohol (8.1g vs. 5.4g), and percentage energy intake from carbohydrate (45.2% vs. 47.3%), protein (16.5% vs. 16.3%), and total fat (34.9% vs. 34.3%), but their mean intakes of these dietary factors by category of intake (fourths) were nearly identical. For instance, the baseline mean intakes of total fruit by category of consumption in fourths were not much different between the Oxford WebQ responders and all women: lowest fourth (65.1g vs. 60.0g), second fourth (137.9g vs. 136.3g), third fourth (220.3g vs. 219.2g), highest fourth (412.6g vs 411.7g), respectively. So, the differences in overall mean intakes between Oxford WebQ responders and all women are likely to be caused by the differential response rate to the Oxford WebQ dietary assessment rather than actual differences in intakes. For example, the higher overall baseline mean daily intake of total fruit in Oxford WebQ responders than all women was due to the higher Oxford WebQ response rate of women whose total fruit intakes were high at baseline (response rate: lowest fourth of total fruit intake at baseline 7152/166414 [4.3%], second fourth 9546/166414 [5.7%], third fourth 11903/166413 [7.2%], and highest fourth 13046/166413 [7.8%]). Although the overall mean intakes were biased by differential response rates to the Oxford WebQ, the mean intakes of the Oxford WebQ responders by level of consumption in fourths are likely to be representative of all women in the cohort.

When compared to baseline, the range of mean dietary intakes in fourths (mean of highest fourth minus mean of lowest fourth) re-measured at the Oxford WebQ dietary assessment narrowed markedly for intakes of the vast majority of dietary factors (e.g. total fruit: baseline 60.0–206.8; re-measured 135.8–206.9). The regression dilution ratios comparing intakes of Oxford WebQ with baseline for total fruit, total vegetables, red meat, and percentage energy intakes from carbohydrate,

protein, and total fat were 0.4, 0.6, 0.3, 0.4, 0.4, and 0.3, respectively (Table 4.12). Regression dilution ratios for the majority of food groups and nutrients were between 0.3 and 0.4 over the course of about 10 years (Supplementary Table B.2 in Appendix B). Only two dietary factors had regression dilution ratios of greater than 0.6: alcohol 0.8 and carotene 0.7. Differences between baseline and re-measured dietary intakes (either due to reporting errors or actual changes over time) may result in biased estimates of linear associations between exposures and outcomes due to regression dilution.[35] Consequently, linear associations between diet and risk of central nervous system tumours in the Million Women Study reported in Chapters 6–8 were corrected for regression dilution bias.

4.5 Central nervous system tumour data

4.5.1 Ascertainment of central nervous system tumours

Incident central nervous system (CNS) tumours in participants were ascertained using linked cancer incidence data provided by cancer registration databases (see section 4.2.2.3). CNS tumours were then classified into the four major subtypes (glioma, meningioma, pituitary tumours, and vestibular schwannoma), other rarer subtypes, or unspecified type. Incident glioma, meningioma, and vestibular schwannoma were ascertained by combining the ICD-10 codes for both malignant and benign CNS tumours (C70–C72, C75.1–C75.3, D32–D33, D35.2–35.4, D42–D43, and D44.3–D44.5) and ICD-O-3 tumour morphology codes for glioma (9380.3–9460.3), meningioma (9530.0–9539.1), or vestibular schwannoma (9560.0), respectively. Incident pituitary tumours were ascertained by combining ICD-10 codes for tumours of the pituitary gland (C75.1, D35.2, or D44.3) and ICD-O-3 morphology codes (8000.0–9992.3 excluding 9380.3–9460.3 and 9530.0–9539.1). The remainder were classified as other rarer subtypes if they were not unspecified type (ICD-O-3 codes 8000.0–8001.3).

4.5.2 Incident cases and incidence rates

Since recruitment, there were 5,773 first incident CNS tumours registered during the study follow-up period (up to 31 December 2015). There were 2,500 glioma (43.3%), 1,756 meningioma (30.4%), 444 pituitary tumours (7.7%), 397 vestibular schwannoma (6.9%), and 676 other or unspecified types (11.7%), the proportions of which were similar to the proportions of subtypes of CNS tumours in England in 2006–2010 (45% glioma, 21% meningioma, 8% pituitary tumours, 6% tumours of the nerves, 20% other or unspecified types).[36] In the Million Women Study, the incidence of overall CNS tumours increased with age, with the highest incidence rate being in older participants (Figure 4.2). Overall incidence of CNS tumours per 100,000 by age groups of participants (50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, ≥85) were 15.6 (95% CI 13.8–17.6), 21.2 (95% CI 19.8–22.7), 26.4 (95% CI 25.1–27.8), 31.1 (95% CI 29.6–32.6), 35.7 (95% CI 33.7–38.0), 41.1 (95% CI 37.8–44.7), 47.1 (95% CI 38.8–57.0), and 67.5 (95% CI 43.6–104.6), respectively. The incidence of overall CNS tumours in women in the Million Women Study was slightly lower than that in UK women of the same age groups in 2013–2015 (Figure 4.2).[36]

4.5.3 Incidence of subtypes of CNS tumours in relation to sociodemographic, anthropometric, and lifestyle factors

The Million Women Study has published findings on: incidence of glioma and meningioma in relation to height, body mass index (BMI), strenuous exercise, social deprivation, smoking, alcohol drinking, parity, oral contraceptive use, and menopausal hormones; and incidence of pituitary tumours and vestibular schwannoma in relation to smoking and menopausal hormones use[37–40] (see Chapter 2). Table 4.13 shows updated findings (based on more cases accrued since these papers were published) for these associations, and additional evidence from this prospective study for incidence of pituitary tumours and vestibular schwannoma in relation to height, BMI, strenuous exercise, social deprivation, alcohol drinking, parity, oral contraceptive use, and incidence of glioma, meningioma, pituitary tumours, and

vestibular schwannoma in relation to levels of educational attainment in study participants (see Appendix C.1 for methods).

There were significant associations between height and incidences of glioma [relative risk (RR) per 10cm increase 1.13, 95% confidence interval (CI) 1.06–1.20], meningioma (RR 1.18, 95% CI 1.10–1.27), pituitary tumours (RR 1.25, 95% CI 1.08–1.44), and vestibular schwannoma (RR 1.18, 95% CI 1.02–1.38). Significant associations were found between BMI and incidences of meningioma (RR per kg/m^2 increase 1.28, 95% CI 1.16–1.42) and pituitary tumours (RR 1.52, 95% CI 1.25–1.86). There was weak evidence that doing strenuous exercise was associated with a decreased meningioma incidence (RR for once per week vs. never/rarely 0.83, 95% CI 0.70–0.99). Smoking was associated with a markedly decreased incidence of vestibular schwannoma (RR for current vs. never smokers 0.36, 95% CI 0.25–0.53). There were significant associations between current use of menopausal hormones containing oestrogen only and incidences of glioma (RR for current vs. never users 1.16, 95% CI 1.03–1.30) and meningioma (RR 1.29, 95% CI 1.12–1.49). Significant associations were found between education and incidence of meningioma (RR for tertiary vs. <12 years of education 1.24, 95% CI 1.07–1.43) and pituitary tumours (RR 1.38, 95% CI 1.04–1.83).

Dietary intakes of study participants vary by many factors, including smoking, levels of educational attainment, and BMI (see section 4.4.5), which were in themselves associated with incidence of subtypes of CNS tumours. It is important to understand and take into account possible confounding by socio-demographic, anthropometric, and lifestyle factors when studying the association between diet and risk of CNS tumours in Chapters 6–8.

4.6 Tables

Table 4.1

Table 4.1: Timings and contents of the postal questionnaires and online surveys

Contents	Details	Postal questionnaires					Online questionnaires	
		Recruitment	3-year Re-survey	8-year Re-survey	12-year Re-survey	15-year Re-survey	Online FFQ	Oxford WebQ
Data processing		Complete	Complete	Complete	Complete	Pending	Pending	Ongoing
Date	Year questionnaire was completed, median (IQR)	1998 (1998–1999)	2001 (2000–2003)	2006 (2006–2006)	2011 (2010–2012)	Pending	Since 2010	Since 2010
	Years between recruitment and resurvey, mean	-	3.3 years	7.7 years	12.5 years	Pending	-	-
Number of Women		1,360,000	870,000	680,000	580,000	Pending	Pending	56,000 (up to Nov 2017)
Socio-demographic	Date of birth, place of birth, deprivation, education	•						
	Ethnicity, early life circumstances		•	•	•	•		
Body size	Height	•		•	•			
	Weight (and derived BMI)	•	•	•	•	•		
	Early life body size		•	•				
Lifestyle factors	Smoking	•	•	•	•	•		
	Alcohol drinking	•	•	•	•	•		
	Physical activity	•	•	•	•	•		•
Past health		•	•	•	•	•		
Family history		•	•	•	•	•		
Reproductive factors	Menarche, age at each birth, breastfeeding, use of oral contraceptives	•						
	Menopause, hysterectomy	•	•	•				
	Use of menopausal hormones	•	•	•	•	•		
Diet	Food and beverages		•	•	•	•	•	•
Well-being	Overall health, happiness, stress		•	•	•	•		
Falls	Including fractures		•	•	•	•		
Social & Occupational	Social participation		•	•	•	•		
	Work history, shift work		•	•	•	•		
	Marital status/bereavement		•	•	•	•		
	Sleeping, napping		•	•	•	•		

FFQ food frequency questionnaire, IQR interquartile range, BMI body mass index

Table 4.2: Record linkage to routinely collected health outcome data

Linked outcomes	**Data**	**Population with data**	**End of follow-up date**	**Provider**
Deaths	Causes of death (ICD codes)	Whole cohort	31 March 2017	England: ONS/NHS Digital Scotland: PBPP Scotland
Loss to follow-up	Emigration or other reasons and dates	Whole cohort	31 March 2017	England: ONS/NHS Digital Scotland: PBPP Scotland
Hospital admissions (inpatient and day-case)	Diagnosis (ICD codes) Procedures (OPCS codes)	Whole cohort	31 March 2017	England: HES/NHS Digital Scotland: PBPP Scotland
Cancer registrations	Cancer site (ICD codes) Tumour morphology (ICD-O codes)	Whole cohort	31 December 2015	England: ONS/NHS Digital Scotland: PBPP Scotland
Cancer screening data	Dates of invitations for screening and attendance (breast, cervix, and bowel)	Women in England only	31 December 2013	Public Health England
Cancer outcome and service data	Additional data on tumour characteristics (e.g. stage, grade)	Women in England only	31 December 2017	Public Health England
Primary care data	Diagnosis and prescribing	100,000 women in England	31 December 2013	England: Clinical Practice Research Datalink
	Dispensing of drugs prescribed in primary care	100,000 women in Scotland	31 December 2015	Scotland: PBPP Scotland

ONS Office of National Statistics, NHS National Health Service, PBPP Public Benefit and Privacy Panel, ICD International Classification of Diseases, ICD-O International Classification of Diseases for Oncology, HES Hospital Episode Statistics, OPCS Classification of Interventions and Procedures

Table 4.3: Characteristics of all women at recruitment, and those completing subsequent re-surveys, adjusted for age and year of birth

Questionnaires	Recruitment Survey	3-year re-survey	8-year re-survey	12-year re-survey	Oxford WebQ†
Number of women	1364374	866556	661588	586882	56188
Characteristics					
	Mean (SD)	**Mean (95% CI) adjusted for age and year of birth**			
Age	56.2 (4.9)	56.2 (56.2–56.2)	56.2 (56.2–56.2)	56.2 (56.2–56.2)	56.2 (56.2–56.2)
Height, cm	162.0 (6.6)	162.3 (162.3–162.3)	162.4 (162.4–162.4)	162.5 (162.5–162.5)	163.6 (163.6–163.7)
BMI, kg/m^2	26.2 (4.7)	26.1 (26.0–26.1)	26.0 (26.0–26.0)	25.9 (25.9–25.9)	25.3 (25.3–25.4)
Alcohol intake, drinks/week	4.1 (5.3)	4.2 (4.2–4.2)	4.2 (4.2–4.3)	4.3 (4.3–4.3)	5.7 (5.6–5.7)
	No. (%)	**% (95% CI) adjusted for age and year of birth**			
Least deprived third	453633 (33.5)	36.2 (36.1–36.3)	37.1 (36.9–37.2)	37.9 (37.8–38.0)	44.1 (43.8–44.5)
Nulliparous	147529 (10.9)	11.3 (11.2–11.4)	11.2 (11.1–11.3)	11.1 (11.0–11.2)	12.7 (12.5–13.0)
Strenuous exercise ≥1/week,	508970 (38.7)	41.8 (41.7–41.9)	43.0 (42.8–43.1)	43.8 (43.7–44.0)	51.6 (51.2–52.0)
Current smoker	262858 (19.4)	15.6 (15.5–15.7)	14.3 (14.3–14.4)	13.4 (13.3–13.5)	6.7 (6.4–7.0)
HRT current user	445251 (33.0)	34.1 (34.0–34.2)	34.9 (34.8–35.0)	34.9 (34.8–35.0)	39.4 (39.0–39.8)
Ever use oral contraceptives	797148 (59.1)	60.7 (60.6–60.8)	61.5 (61.4–61.6)	62.0 (61.9–62.2)	70.0 (69.6–70.4)
Had a university degree	175947 (13.3)	15.8 (15.7–15.9)	17.3 (17.2–17.4)	18.3 (18.2–18.4)	41.8 (41.6–42.1)

Until November 2017, † women who responded to the Oxford WebQ once or more

‡ age group at recruitment (48-49, 50-51, 52-53, 54-55, 56-57, 58-59, 60-61, 62-63, 64-65, ≥66); year of birth (≤1930, 1931, 1932, 1933, ..., 1948, 1949, ≥1950)

BMI body mass index, HRT hormone replacement therapy, SD standard deviation, CI confidence interval

Table 4.4: Follow-up for deaths, cancer registrations and hospital admissions notified as of March 2017

HEALTH OUTCOMES	**Number of women (%)**
Deaths (until 31 March 2017)	185,233 (14%)
At least one hospital admission (until 31 March 2017)	1,128,056 (85%)
Incident cancer registrations (until 31 December 2015):	
All sites (excluding non-melanoma skin cancer)	201,988 (15%)
Breast cancer	70,305 (5%)
Colorectal cancer	22,203 (2%)
Lung cancer	21,482 (2%)
Central nervous system tumours	5,773 (‹1%)
LOSS TO FOLLOW-UP (until 31 March 2017)	19,705 (1%)

Table 4.5: Content of dietary information collected through postal questionnaires in the Million Women Study

Content of dietary information	**3-year re-survey**	**8-year re-survey**	**12-year re-survey**
Number of times/ portions eaten a week or a day (open question)	Meat, fish, chips, potato, pasta, rice, cheese, egg, vegetables (cooked), vegetables (raw), fruit(fresh), fruit(dried), fruit (stewed), fruit juice, bread (white), bread (brown), crispbread, biscuit, chocolate, sweet, sauce, dairy, cake, nuts, crisps, jam, soup, cereal, alcohol, day drinking alcohol, tea, milk, fizzy drink, coffee, water, squash, sugar in drinks	Meat, fish, vegetables (cooked), vegetables (raw), fruit (fresh), fruit (dried), bread, alcohol, day drinking alcohol, tea, milk, coffee	Meat, poultry, processed meat, fish, tuna, oily fish, vegetables (cooked), vegetables (raw), 8 subtypes of vegetables, fruit (fresh), fruit (dried), fruit (stewed), fruit (tinned), 7 subtypes of fruits, bread (wholemeal), yogurt or dessert (dairy), yogurt or dessert (soya), 4 subtypes of cereal, alcohol, tea, milk, coffee
Eat about once a week or more often (binary)	10 subtypes of meat, 9 subtypes of fish, 27 subtypes of vegetables, 6 subtypes of fruit, 8 subtypes of spread, 12 subtypes of fat/oil, 4 subtypes of milk, 3 subtypes of cream, dairy ice cream	5 subtypes of meat, 2 subtypes of fish, 13 subtypes of vegetables, 8 subtypes of spread/oil/fat, 4 subtypes of milk, 8 subtypes of alcohol,	-
Never eat or use (binary)	Meat, fish, fats/oils in cooking, salad dressing/cream, beef, pork/ham, lamb, dairy products, kidney, liver/pate, sugar, wheat(products), salami, sausages, eggs, beef burgers, milk/cream	Meat, fish, beef, pork/ham, lamb, dairy products, liver/pate, sugar, wheat(products), sausages, eggs, beef burgers	Meat, fish, dairy, egg
Never, sometimes, usually or always eat or use (categorical)	Add milk in tea, add milk in coffee, add salt to food, remove fat from meat, eat organic food	Eat organic food, eat low fat food, eat yakult (probiotic products)	-
Others (categorical)	Subtypes of cereal usually eaten, spread thickness, add butter to food, changes to diet in last 5 years, drink alcohol with meals	Preference of temperature of drinks, subtypes of cereal usually eaten, subtypes of bread mainly eaten, changes to diet in last 5 years, drink alcohol with meals, reduced amount of alcohol, lactose intolerant, subtypes of artificial sweeteners usually used	Add into tea/coffee: milk, sugar, sweetener; preference of temperature of tea/coffee; subtypes of milk used, changes to diet in last 5 years,

Table 4.5: Content of dietary information collected through postal questionnaires in the Million Women Study (continued)

Content of dietary information	3-year re-survey	8-year re-survey	12-year re-survey
Derived nutrients	Total energy, carbohydrate, sugars, protein, total fat (saturated fat, monounsaturated fat, polyunsaturated fat), trans fat, omega-3 fatty acids, fibre, alcohol, calcium, retinol, carotene, vitamin B6, vitamin B12, vitamin C, vitamin D, vitamin E, thiamin, riboflavin, niacin, folate, cholesterol, magnesium, potassium, zinc, selenium, phosphorus	-	-

Table 4.6: Content of dietary information collected through the Oxford WebQ in the Million Women Study

Did you drink/eat a particular food yesterday (no, yes)	21 major food categories: Drinks (juice, coffee, tea/infusion, other non-alcoholic drinks, alcoholic drinks), breakfast cereal, bread or crackers, have butter or margarine on bread/crackers, pastry, yogurt or ice-cream, cakes/puddings/other desserts, biscuits/chocolate/sweets, crisps/nuts/savoury snacks, soup, pasta/rice/sushi/couscous, cheese, eggs, meat/poultry, fish/seafood, vegetarian alternatives to meat, spreads/sauces/dips/jams/honey, beans/lentils/potatoes/vegetables, fruits, vitamin/supplements
How much of the particular food did you eat? (fixed categories: e.g. none, 1/2, 1, ..., 6+ servings)	9 subtypes of drinks, 6 subtypes of coffee, 5 subtypes of tea/infusion, 5 subtypes of other non-alcoholic drinks, 7 subtypes of alcoholic drinks, 8 subtypes of breakfast cereal, 9 subtypes of bread, 7 subtypes of bread/crackers with butter or margarine (thickly/medium/thinly spread), 11 subtypes of pastry, yogurt/ice-cream, 9 subtypes of cakes/pudding/other desserts, 8 subtypes of chocolates/5 subtypes of biscuits or sweet snacks, 10 subtypes of crisps/nuts/savoury snacks, 3 subtypes of soup, 8 subtypes of pasta/rice/sushi/couscous, 11 subtypes of cheese, 5 subtypes of eggs, 10 subtypes of meat/poultry, 9 subtypes of fish/seafood, 4 subtypes of vegetarian alternatives to meat, 38 subtypes of beans/lentils/potatoes/vegetables, 19 subtypes of fruits,
How much of the following did you add (fixed categories)	Sugar added to coffee, sweetener added to coffee, sugar added to tea/infusion, sweetener added to tea/infusion, sugar/jam/honey/syrup added to cereal/porridge, sweetener added to cereal/porridge
Dietary habits (no, yes, varied)	Add milk/cream/whitener coffee, decaffeinated coffee, add milk to standard tea, decaffeinated standard tea, add milk to rooibos/redbush tea, cereal with dried fruit, add milk to your cereal, remove skin from chicken/poultry, remove fat from meats, add salt to food
Others	Serving size (smaller, average, larger), whether diet in the past 24 hours is typical (no, yes) and reasons (ill, fasting, away from home/work, others), special diet (gluten/wheat free, lactose intolerance, vegetarian, vegan, low calorie/weight controlled, high calorie to prevent weight loss, low fibre, others), cereal/porridge (made with water or milk), 10 subtypes of milk used most frequently or did not use milk or type unknown, 4 subtypes of flour ingredient for bread eaten, 8 subtypes of butter or margarine (ingredients: very low fat, low fat, normal fat, cholesterol lowering, don't know), soup ingredients (pea, meat, fish, vegetables, pasta, other), 19 subtypes of spreads/sauces/dips/jams/honey had, 14 subtypes of butter/margarine/oil used in cooking (ingredients: very low fat, low fat, normal, cholesterol lowering, don't know), 5 meal types (takeaway, restaurant, sandwiches, ready prepared, cooked at home), 21 subtypes of vitamin/supplements had
Derived nutrients	Total energy, carbohydrate, sugars, protein, total fat (saturated fat, monounsaturated fat, polyunsaturated fat), trans fat, omega-3 fatty acids, fibre, alcohol, calcium, retinol, carotene, vitamin B6, vitamin B12, vitamin C, vitamin D, vitamin E, thiamin, riboflavin, niacin, folate, cholesterol, magnesium, potassium, zinc, selenium, phosphorus

† The Oxford WebQ also collect information on physical activity (i.e. frequency of light, moderate, and vigorous activity) during the previous 24 hours

Table 4.7: Comparing the estimation of nutrient intake from the 3-year re-survey with the 7-day diary after incorporating all recommendations made

Nutrients	7-day diet diary	Dietary assessment in the 3-year re-survey			
		Before correction		*After correction*	
	median	*median*	*Spearman's correlation with diary*	*median*	*Spearman's correlation with diary*
Total energy, kcal	1746.0	1878.1	0.332	1679.3	0.342
Protein, g	70.0	71.3	0.355	67.0	0.381
Carbohydrate, g	212.4	204.5	0.518	203.7	0.519
Fat, g					
saturated, g	23.0	25.3	0.514	21.7	0.503
monounsaturated, g	21.1	32.4	0.297	22.4	0.315
polyunsaturated, g	10.1	16.1	0.181	11.0	0.191
Fibre, g	14.2	13.9	0.554	13.7	0.547
Alcohol, g	4.8	2.7	0.779	2.7	0.779
Calcium, mg	814.7	827.8	0.581	807.5	0.580
Retinol, ug	308.5	373.3	0.440	364.2	0.411
Carotene, ug	1964.9	1132.8	0.321	1075.2	0.282
Folate, ug	253.3	271.8	0.496	265.1	0.502
Vitamin D, ug	2.5	3.2	0.364	2.8	0.360
Vitamin E, mg	5.9	11.9	0.105	8.0	0.179
Thiamine, mg	1.5	1.4	0.389	1.3	0.409
Riboflavin, mg	1.6	1.9	0.600	1.8	0.592
Niacin, mg	17.5	19.1	0.332	17.9	0.360
Vitamin B12, ug	4.2	4.8	0.346	4.1	0.354
Vitamin C, mg	91.5	94.9	0.595	94.3	0.582
Cholesterol, mg	224.3	222.9	0.497	203.4	0.474

Table 4.8: Composition of selected food groups in the Million Women Study

Food groups	Dietary item(s) included
Total fruit	Fresh fruit (apples, bananas, oranges/satsumas, grapefruit, pears, stone fruit), dried fruit, stewed/tinned fruit
Citrus fruit	Oranges/satsumas, grapefruit
Fruit juice	Fruit juice
Total vegetables	Legumes, non-legume vegetables
Legumes	Cooked or raw vegetables (baked beans, soya meat/tofu, chick peas/lentils)
Non-legume vegetables	Cooked or raw vegetables (green peas, broccoli, cabbage, carrots, courgettes, beetroot, leeks, parsnip, lettuce, tomatoes, onions, garlic, swede, spinach, sweetcorn, avocado, aubergine, celery, green beans, cauliflower, green/red peppers, Brussels sprouts, mushrooms, cucumber)
Nuts	Nuts including peanut butter
Grains/cereal	Brown/wholemeal bread, crackers/crispbread breakfast type cereal (bran, biscuit, oat, muesli, other), rice
Whole grains	Brown/wholemeal bread, crackers/crispbread, breakfast type cereal (bran, biscuit, oat, muesli), brown rice
Red meat	Beef, lamb, pork, beef burger/hamburger, kidney, liver/pate
Processed meat	Bacon, ham, sausages
White meat	Chicken/poultry
Fish	Fish (tuna, sardines, trout, fish & chips, salmon, kippers/herring, cod/haddock/other white fish, mackerel, other seafood)
Eggs	Eggs including those in omelettes, quiches, cakes
Cheese	Cheese including those in pizzas, quiches, cheese sauce
Dairy products	Cheese, dairy desserts, total milk (including milk in milky drinks and those added to tea and coffee)
Alcohol	Wine, lager, spirits
Coffee	Coffee
Tea	Tea
Sugar sweetened beverages	Fruit juice, fruit squash, fizzy/soft drink

Table 4.9: Daily dietary intakes of women in the Million Women Study compared with women of similar age in the National Diet and Nutrition Survey

	Million Women Study, 3-year re-survey	**NDNS 2002**
Number of women	692,179	242
Age, range	49–95	50–64
Age, median (IQR)	59 (55–63)	n/a
Year completed assessment	1998-2007	2000-2001
Dietary assessment method	Semi-quantitative questionnaire	7-day diet diary
Daily dietary intakes, mean (SD)		
Total energy, kcal	1,612 (430)	1,652 (n/a)
Total fruit, g	204 (147)	151 (n/a)
Total vegetables, g	121 (84)	143 (n/a)
Total meat, g	62 (36)	119 (n/a)
Fish, g	34 (22)	43 (n/a)
Carbohydrate, % energy	47.3 (7.0)	46.4 (n/a)
Protein, % energy	16.3 (2.6)	16.8 (n/a)
Total fat, % energy	34.3 (6.1)	33.3 (n/a)
Alcohol, % energy	2.4 (3.4)	3.7 (n/a)
Fibre, g	13.4 (4.8)	14.0 (n/a)

NDNS National Diet and Nutrition Survey, IQR interquartile range, SD standard deviation

Table 4.10: Correlations between intakes of selected foods and nutrients in the Million Women Study

Spearman's correlation	Total fruit	Citrus fruit	Fruit juice	Total vegetable	Eggs	Dairy products	Carbohydrate	Total fat	Saturated fat	MU fat	PU fat	Fibre	Carotene	Vitamin C	Vitamin E	Folate	Calcium	Cholesterol
Total fruit	1.00																	
Citrus fruit	0.55	1.00																
Fruit juice	0.08	0.10	1.00															
Total vegetables	0.30	0.17	0.02	1.00														
Eggs	-0.06	-0.01	‹0.01	-0.01	1.00													
Dairy products	-0.03	-0.01	-0.10	-0.12	-0.09	1.00												
Carbo-hydrate	0.24	0.11	0.17	-0.07	-0.15	0.17	1.00											
Total fat	-0.30	-0.16	-0.16	-0.06	0.15	-0.15	-0.74	1.00										
Saturated fat	-0.32	-0.17	-0.14	-0.19	0.12	-0.02	-0.50	0.72	1.00									
MU fat	-0.19	-0.10	-0.12	0.03	0.10	-0.21	-0.65	0.73	0.39	1.00								
PU fat	-0.13	-0.08	-0.07	0.07	0.06	-0.19	-0.32	0.38	‹0.01	0.24	1.00							
Fibre	0.60	0.36	0.04	0.45	-0.10	-0.05	0.25	-0.32	-0.39	-0.18	-0.05	1.00						
Carotene	0.37	0.20	0.03	0.74	-0.02	-0.12	-0.05	-0.05	-0.14	0.04	0.02	0.46	1.00					
Vitamin C	0.61	0.61	0.54	0.43	-0.03	-0.11	0.21	-0.29	-0.32	-0.18	-0.10	0.49	0.44	1.00				
Vitamin E	0.06	0.04	-0.03	0.18	0.05	-0.12	-0.16	0.15	-0.10	0.03	0.69	0.10	0.17	0.08	1.00			
Folate	0.33	0.30	0.15	0.42	0.02	0.07	0.19	-0.32	-0.33	-0.24	-0.09	0.51	0.38	0.48	0.04	1.00		
Calcium	0.09	0.10	-0.04	‹0.01	-0.01	0.70	0.16	-0.22	-0.05	-0.27	-0.25	0.06	0.02	0.06	-0.08	0.25	1.00	
Cholesterol	-0.15	-0.05	-0.06	-0.03	0.68	-0.11	-0.47	0.42	0.43	0.26	0.07	-0.24	0.02	-0.12	0.04	-0.07	-0.05	1.00

MU fat, monounsaturated fat; PU fat, polyunsaturated fat

Table 4.11: Differences in mean daily dietary intakes (%) by selected characteristics in the Million Women Study

Daily dietary intake	Height (170+ vs. ‹160 cm)	BMI (30+ vs. ‹25)	Exercise (2+times per week vs. Never /rarely)	Deprivation (Lower vs. upper third)	Smoking (Current vs. Never)	Alcohol (1+ drink/day vs. Non-drinkers)	Parity (Parous vs. Nulli-parous)	Oral contra-ceptive use (Ever vs Never)	Menopausal hormone use (Current vs. Never)	Education (Tertiary vs. ‹12 years)
Total fruit, g	4.8	-6.0	21.0	9.5	-32.0	-7.8	-3.5	1.7	-0.1	19.5
Citrus fruit, g	3.1	-8.1	22.9	8.0	-27.8	1.0	-2.4	4.9	-0.8	25.6
Fruit juice, g	-1.7	-4.3	7.7	0.6	-11.9	-1.8	0.3	-1.1	2.6	3.1
Total vegetables, g	6.2	-2.5	15.8	10.0	-12.1	10.5	-4.0	6.2	5.0	21.8
Nuts, g	11.0	-28.9	33.5	2.2	-4.8	24.7	-3.4	11.0	6.6	41.8
Grains/cereal, g	4.1	-10.7	16.4	6.3	-25.9	-3.6	-7.3	-3.1	-1.2	16.2
Red meat, g	-2.4	12.4	-5.5	4.5	7.0	13.5	2.2	5.7	2.4	3.3
Processed meat, g	-2.7	21.9	-13.4	-7.2	12.0	-7.5	8.9	-0.7	-6.4	-14.1
White meat, g	-3.0	0.6	1.7	5.4	-10.0	2.0	0.0	10.9	9.6	12.5
Fish, g	-2.6	1.1	9.9	3.6	-6.0	8.3	-3.2	-0.1	0.5	11.5
Eggs, g	2.8	15.9	-2.2	-6.3	12.6	3.8	3.4	2.7	2.0	-2.2
Dairy products, g	-3.9	2.9	-3.9	-3.8	2.0	-19.7	3.5	-4.7	-2.6	-12.6
Cheese, g	6.6	-11.2	3.7	1.9	2.3	9.5	-4.8	2.4	0.6	20.5
Alcohol, g	15.1	-35.3	26.0	27.9	36.9	n/a	-17.4	49.8	26.6	76.4
Coffee, g	-6.1	12.0	-10.2	-7.2	63.7	-1.4	1.1	6.0	-1.3	-10.4
Tea, g	-12.1	4.3	-13.3	-15.8	26.1	-27.6	5.2	-9.1	-3.4	-26.2
Carbohydrate, %E	-1.8	1.5	-0.8	-1.9	-3.7	-13.6	0.8	-2.6	-1.0	-6.4
Protein, %E	-0.8	2.7	1.0	1.8	-2.1	-1.9	0.7	1.1	0.7	2.0
Total fat, %E	1.8	-0.5	-1.0	0.1	4.1	0.0	0.0	0.4	-0.6	3.7
Saturated fat, %E	2.8	-2.1	-4.0	-1.2	10.4	-2.1	-1.4	-1.2	-1.9	3.2
Monounsaturated fat, %E	2.2	-1.9	1.2	2.1	1.3	4.5	-0.6	1.7	0.6	7.8
Polyunsaturated fat, %E	-1.0	4.3	-1.6	-2.2	3.3	-2.4	3.4	1.3	-0.1	-2.1
Fibre, g	2.2	-4.5	9.3	5.8	-17.5	-5.3	-2.6	-0.7	0.3	8.0
Carotene, µg	5.7	-5.7	13.4	10.8	-14.8	7.9	-5.3	4.5	1.7	26.0
Vitamin C, µg	2.8	-5.0	15.4	8.4	-20.0	1.9	-1.3	3.3	1.7	17.3
Vitamin E, mg	-1.2	6.2	-1.3	-2.5	5.7	-3.8	2.9	2.2	-0.8	-1.7
Folate, µg	-0.7	-0.2	2.9	1.3	-6.2	-4.7	-0.7	-1.4	0.2	-0.4
Calcium, mg	-0.6	0.1	-0.1	-0.8	-1.4	-10.4	0.7	-2.6	-1.9	-2.7
Cholesterol, mg	1.9	6.1	-1.5	-0.6	7.6	3.4	0.8	2.0	-0.1	4.6
DASH score, point	3.0	-4.8	9.2	5.5	-11.7	0.1	-1.6	1.0	0.0	10.0
aMED score, point	5.2	-9.3	21.6	11.9	-21.5	25.2	-2.8	5.1	3.5	24.0
AHEI, point	3.6	-5.7	10.4	6.5	-11.0	13.1	-1.7	3.1	0.9	13.1
Total energy intake, kcal	8.1	-1.0	4.2	4.6	-5.4	6.6	-0.3	-0.2	-1.1	7.5

%E, percentage energy intake; reference groups for calculating differences (%) were: height (‹160cm), BMI (‹25), exercise (never/rarely), deprivation (upper third), smoking (never), alcohol drinking (non-drinkers), parity (nulliparous), oral contraceptives use (never), menopausal hormones use (never), and education (‹12 years)

Table 4.12: Mean daily intakes of selected food groups and nutrients for all women and responders of the Oxford WebQ in the Million Women Study

		All women		Oxford WebQ Responders			
	Category of intake at baseline (fourth)	No. of women	Intake at baseline, mean (SD)	No. of women	Intake at baseline, mean (SD)	Intake at Oxford WebQ, mean (SD)	Regression dilution ratio
Total fruit (g)	1	166414	60.0 (30.8)	7152	65.1 (28.5)	135.8 (117.9)	
	2	166414	136.3 (20.0)	9546	137.9 (19.9)	173.8 (111.8)	
	3	166413	219.2 (29.3)	11903	220.3 (29.3)	210.2 (119.7)	
	4	166413	411.7 (140.1)	13046	412.6 (137.8)	269.2 (150.9)	
	Overall	665654	206.8 (150.4)	41647	235.0 (153.3)	206.9 (137.6)	0.4
Total vegetables (g)	1	167554	45.9 (15.1)	6235	49.8 (13.0)	157.3 (117.1)	
	2	167553	84.2 (10.1)	9673	84.8 (10.0)	184.1 (116.6)	
	3	167553	125.0 (14.5)	11807	125.9 (14.6)	213.1 (133.9)	
	4	167553	233.0 (90.9)	13896	237.4 (95.0)	260.3 (181.7)	
	Overall	670213	122.0 (84.2)	41611	142.2 (91.0)	213.9 (150.8)	0.6
Red meat (g)	1	161581	1.1 (2.9)	10489	0.6 (2.3)	22.0 (32.4)	
	2	161580	20.4 (4.8)	7936	20.7 (4.8)	27.7 (34.1)	
	3	161580	36.1 (4.8)	9546	36.4 (4.8)	32.7 (36.2)	
	4	161580	63.6 (18.7)	10805	63.9 (19.0)	38.0 (38.3)	
	Overall	646321	30.3 (25.0)	38776	31.2 (26.3)	28.4 (35.6)	0.3
Alcohol (g)	1	300162	0.0 (0.0)	9863	0.0 (0.0)	3.3 (7.7)	
	2	106756	2.4 (0.9)	7118	2.4 (0.9)	3.6 (5.7)	
	3	145199	6.7 (1.7)	11499	6.8 (1.7)	8.0 (8.3)	
	4	140059	17.9 (7.8)	13641	18.1 (7.6)	17.5 (13.5)	
	Overall	692176	5.4 (7.7)	42121	8.1 (8.6)	9.2 (11.6)	0.8
Carbohydrate (% energy)	1	173044	38.4 (4.4)	14950	38.0 (4.9)	41.3 (6.8)	
	2	173044	45.3 (1.3)	11367	45.2 (1.3)	44.4 (6.3)	
	3	173045	49.5 (1.3)	8940	49.4 (1.3)	45.8 (6.3)	
	4	173043	56.0 (3.6)	6864	55.6 (3.3)	47.6 (6.8)	
	Overall	692176	47.3 (7.0)	42121	45.2 (7.2)	44.1 (7.0)	0.4
Protein (% energy)	1	173045	13.1 (1.2)	8650	13.3 (1.1)	14.8 (3.0)	
	2	173043	15.4 (0.5)	10540	15.4 (0.5)	15.7 (2.9)	
	3	173044	17.0 (0.5)	11585	17.0 (0.5)	16.3 (3.0)	
	4	173044	19.7 (1.7)	11346	19.6 (1.7)	17.2 (3.3)	
	Overall	692176	16.3 (2.6)	42121	16.5 (2.5)	16.1 (3.2)	0.4
Total fat (% energy)	1	173044	26.6 (3.1)	9300	26.7 (3.1)	32.9 (6.4)	
	2	173045	32.4 (1.1)	10148	32.4 (1.1)	34.4 (6.0)	
	3	173043	36.1 (1.1)	10799	36.2 (1.1)	35.6 (6.0)	
	4	173044	41.9 (3.5)	11874	42.2 (3.9)	37.4 (6.1)	
	Overall	692176	34.3 (6.1)	42121	34.9 (6.2)	35.2 (6.4)	0.3

Regression dilution ratio = (range of re-measured mean intake at Oxford WebQ) / (range of mean intake at baseline)

Table 4.13: Differences in risk factors for subtypes of CNS tumours in the Million Women Study

Risk factors		Glioma		Meningioma		Pituitary tumours		Vestibular schwannoma	
	No. of women	No. of cases	RR (95% CI)	No. of cases	RR (95% CI)	No. of cases	RR (95% CI)	No. of cases	RR (95% CI)
Height (cm)									
‹160	430685	742	1.00 (reference)	511	1.00 (reference)	116	1.00 (reference)	111	1.00 (reference)
160–164	388948	768	1.15 (1.04–1.28)	506	1.11 (0.98–1.26)	146	1.43 (1.12–1.83)	110	1.07 (0.82–1.39)
165–169	289214	569	1.16 (1.04–1.30)	426	1.28 (1.12–1.46)	90	1.21 (0.91–1.59)	107	1.38 (1.05–1.81)
≥170	189533	385	1.22 (1.07–1.38)	281	1.30 (1.12–1.51)	85	1.76 (1.32–2.34)	65	1.28 (0.94–1.75)
per 10 cm increase			1.13 (1.06–1.20)		1.18 (1.10–1.27)		1.25 (1.08–1.44)		1.18 (1.02–1.38)
Body mass index (kg/m^2)									
‹25	582084	1081	1.00 (reference)	690	1.00 (reference)	148	1.00 (reference)	177	1.00 (reference)
25–29	444992	872	1.05 (0.96–1.15)	633	1.22 (1.10–1.36)	167	1.55 (1.24–1.93)	149	1.10 (0.88–1.37)
≥30	223031	418	1.04 (0.93–1.17)	329	1.32 (1.15–1.51)	94	1.84 (1.41–2.40)	52	0.77 (0.56–1.05)
per 10 kg/m2 increase			1.06 (0.97–1.16)		1.28 (1.16–1.42)		1.52 (1.25–1.86)		0.81 (0.64–1.03)
Strenuous exercise (times)									
Never/rarely	618961	1153	0.91 (0.80–1.03)	860	0.99 (0.85–1.15)	202	1.05 (0.77–1.43)	181	0.94 (0.69–1.27)
‹1 per week	157616	323	1.00 (reference)	226	1.00 (reference)	52	1.00 (reference)	56	1.00 (reference)
1 per week	227676	439	0.93 (0.81–1.08)	270	0.83 (0.70–0.99)	84	1.15 (0.82–1.63)	68	0.83 (0.58–1.18)
≥2 per week	265770	497	0.91 (0.79–1.04)	348	0.92 (0.78–1.09)	82	0.99 (0.70–1.40)	81	0.85 (0.60–1.19)
Social deprivation									
Lower third	438858	823	1.00 (reference)	573	1.00 (reference)	155	1.00 (reference)	146	1.00 (reference)
Middle third	434674	819	1.02 (0.93–1.12)	591	1.04 (0.92–1.16)	143	0.94 (0.75–1.19)	130	0.93 (0.73–1.18)
Upper third	436158	844	1.08 (0.97–1.19)	574	1.04 (0.92–1.18)	138	0.95 (0.75–1.21)	119	0.97 (0.75–1.24)
Smoking status									
Never smoker	634468	1275	1.00 (reference)	893	1.00 (reference)	239	1.00 (reference)	233	1.00 (reference)
Past smoker	352602	669	0.95 (0.87–1.05)	447	0.92 (0.82–1.03)	111	0.87 (0.69–1.09)	115	0.88 (0.70–1.11)
Current smoker	255302	429	0.91 (0.82–1.02)	338	1.06 (0.93–1.21)	72	0.88 (0.67–1.16)	33	0.36 (0.25–0.53)

RRs were mutually adjusted for all other variables in the table

Table 4.13: Content of dietary information collected through postal questionnaires in the Million Women Study (continued)

Risk factors		Glioma		Meningioma		Pituitary tumours		Vestibular schwannoma	
	No. of women	No. of cases	RR (95% CI)	No. of cases	RR (95% CI)	No. of cases	RR (95% CI)	No. of cases	RR (95% CI)
Alcohol drinking									
Non-drinkers	314665	579	0.96 (0.87–1.06)	469	1.17 (1.04–1.31)	111	1.06 (0.84–1.34)	98	1.21 (0.95–1.55)
‹1 drink per day	686198	1320	1.00 (reference)	893	1.00 (reference)	236	1.00 (reference)	205	1.00 (reference)
≥1 drinks per day	308054	580	1.03 (0.93–1.14)	385	0.99 (0.88–1.12)	91	0.92 (0.72–1.18)	93	1.05 (0.82–1.35)
Parity									
Nulliparous	141472	260	1.00 (reference)	170	1.00 (reference)	48	1.00 (reference)	36	1.00 (reference)
Parous	1172872	2229	1.01 (0.89–1.15)	1578	1.11 (0.94–1.30)	395	0.99 (0.73–1.34)	360	1.17 (0.83–1.66)
Oral contraceptive use									
Never	773753	1404	0.98 (0.90–1.07)	1010	0.99 (0.90–1.10)	251	0.94 (0.76–1.15)	256	1.24 (1.00–1.55)
Ever	530747	1065	1.00 (reference)	721	1.00 (reference)	186	1.00 (reference)	139	1.00 (reference)
Menopausal hormones									
Never user	647495	1244	1.00 (reference)	820	1.00 (reference)	222	1.00 (reference)	176	1.00 (reference)
Past user	220049	430	1.02 (0.91–1.14)	310	1.13 (0.99–1.29)	66	0.88 (0.67–1.16)	77	1.24 (0.94–1.62)
Current user (type)									
Unspecified	43822	75	0.91 (0.72–1.15)	60	1.13 (0.87–1.48)	18	1.25 (0.77–2.02)	14	1.13 (0.66–1.96)
Oestrogen-progestogen	226695	372	0.91 (0.81–1.03)	281	1.05 (0.92–1.21)	61	0.84 (0.63–1.12)	68	1.06 (0.79–1.40)
Oestrogen only	165524	359	1.16 (1.03–1.30)	263	1.29 (1.12–1.49)	72	1.29 (0.99–1.69)	56	1.18 (0.87–1.60)
Education									
‹12 years	777793	1513	1.00 (reference)	996	1.00 (reference)	245	1.00 (reference)	225	1.00 (reference)
Secondary	336004	606	0.93 (0.84–1.02)	458	1.10 (0.98–1.23)	121	1.19 (0.95–1.49)	104	0.95 (0.74–1.20)
Tertiary	169970	321	0.97 (0.85–1.10)	256	1.24 (1.07–1.43)	70	1.38 (1.04–1.83)	61	1.07 (0.79–1.44)

RRs were mutually adjusted for all other variables in the table

4.7 Figures

Figure 4.1: Location of NHS breast cancer screening clinics through which Million Women Study participants were recruited

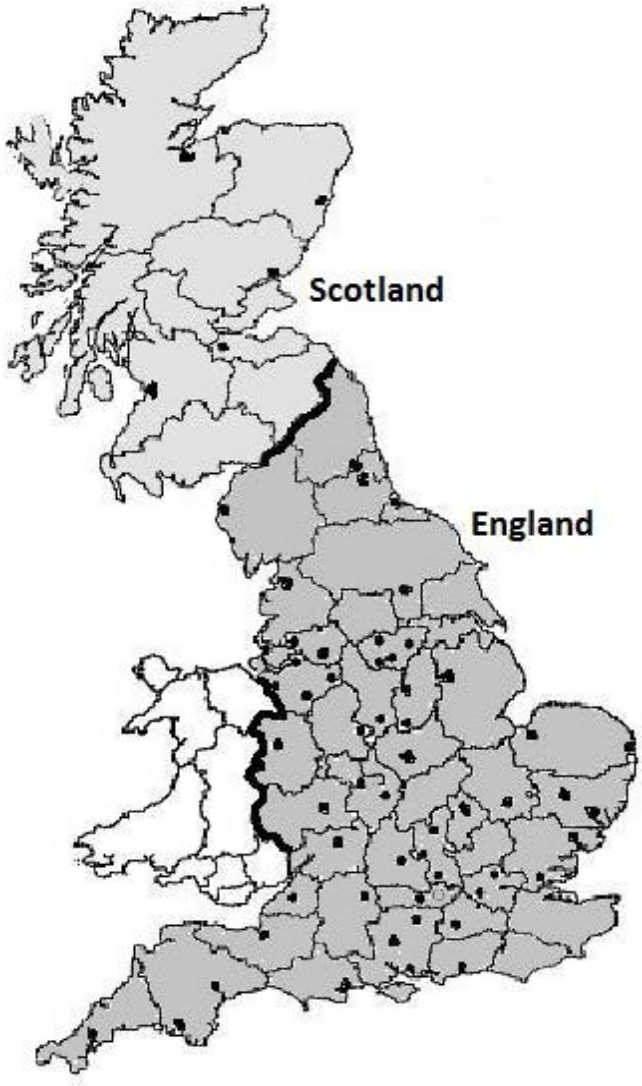
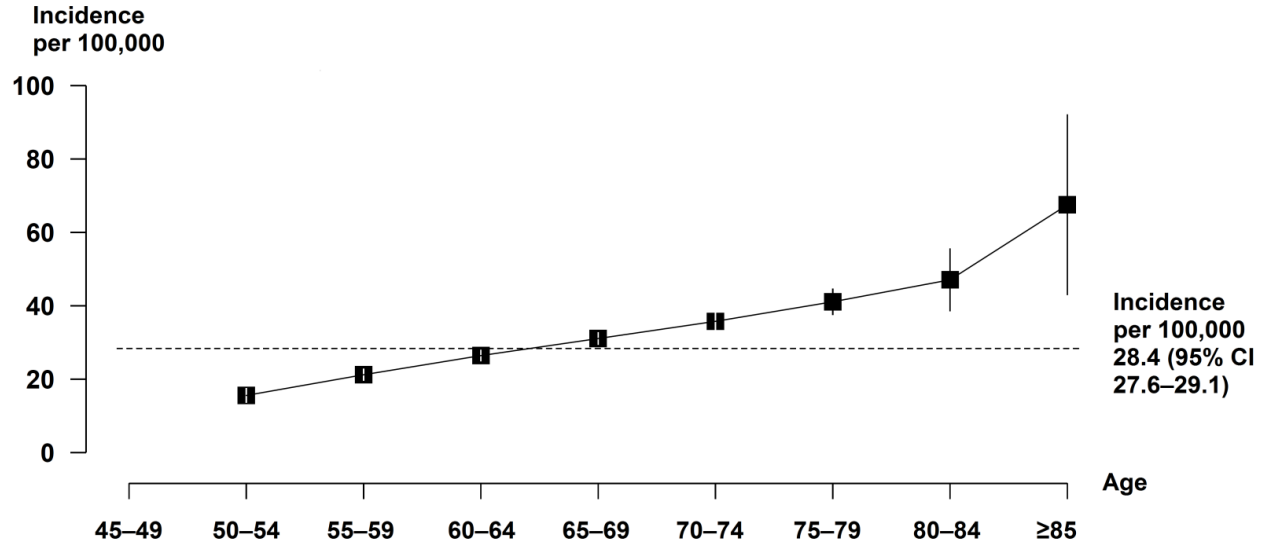


Figure adapted from Figure 1 of the original article "The Million Women Study Collaborative Group: The Million Women Study: design and characteristics of the study population [peer-reviewed research]. Breast Cancer Res 1999; 1: 73–80. The original article is an open access article distributed under the terms of the Creative Commons Attribution License [http://creativecommons.org/licenses/by/2.0], which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Figure 4.2: Central nervous system tumour incidence in Million Women Study participants, by age at diagnosis



Million Women Study	No. of cases	0	251	793	1391	1606	1069	539	104	20
	Person-years	13875	1612875	3740880	5265347	5169605	2990213	1312120	220955	29625
	Incidence per 100,000	0	15.6	21.2	26.4	31.1	35.7	41.1	47.1	67.5
	(95% CI)	n/a	(13.8–17.6)	(19.8–22.7)	(25.1–27.8)	(29.6–32.6)	(33.7–38.0)	(37.8–44.7)	(38.8–57.0)	(43.6–104.6)
UK Women	Incidence per 100,000	17.7	20.8	24.5	31.2	35.9	41.8	47.1	50.6	55.3

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5

The NIH-AARP Study and the PLCO Study

5.1 Introduction

This chapter introduces the National Institutes of Health (NIH) – AARP (formerly the American Association of Retired Persons) Study, and the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial (hereinafter referred to as the NIH-AARP Study and the PLCO Study), and describes the dietary data and glioma data used in Chapter 6.

The NIH-AARP Study and the PLCO Study are two large studies of US men and women with prospective collection of data. The NIH-AARP Study was set up to investigate the association between diet and cancer.[1] The PLCO Study was designed originally to assess the effect of cancer screening tests on mortality for cancers of the prostate, lung, colon and rectum, and ovary.[2] Both studies have also investigated risks of cancers in relation to many demographic and lifestyle factors, health-related behaviours, as well as other factors. Both the NIH-AARP study and the PLCO Study were coordinated by the National Cancer Institute (NCI) of the NIH, and used a nearly identical food frequency questionnaire, which was developed by the NCI, to collect comprehensive dietary information from their study participants. The large size and prospective nature of both the NIH-AARP Study and the PLCO Study provide a good opportunity to reliably study the association between diet and risk of relatively rare cancers such as glioma.

5.2 The NIH-AARP Study

5.2.1 Recruitment and participants

In 1995–1996, current members of the AARP aged 50–69 who resided in one of the six states (California, Florida, Pennsylvania, New Jersey, North Carolina, and Louisiana) or two metropolitan areas (Atlanta, Georgia and Detroit, Michigan) were sent the Baseline Questionnaire and were invited to join the study. The 8 particular areas were chosen because they were areas where completeness of

cancer case ascertainment from cancer registries was good (≥90%), areas with large AARP membership, and areas with large minority populations.[1] Approximately 3.5 million questionnaires were sent to AARP members in these areas, and about 567,000 (16.2%) were completed and returned.[1] Study participants provided comprehensive information on diet (see section 5.4 for details) as well as information on age, date and place of birth, ethnicity, level of education, marital status, body size, lifestyle factors (such as smoking and drinking), physical activity, medical history, hormone replacement therapy and reproductive history (women only), and other characteristics, through the Baseline Questionnaire (summarised in Table 5.1). More information on the study is available at the NIH-AARP Study website (https://dietandhealth.cancer.gov/).

5.2.2 Follow-up

5.2.2.1 Follow-up questionnaires

Two follow-up questionnaires were sent to surviving participants at various time points after recruitment. The Risk Factor Questionnaire sent in 1996–1997 collected information including early life diet (diet in 1986–1987 and at age 12-13), health-related behaviours (e.g. use of supplements and cancer screening exams undergone), and early life body size (e.g. height and weight at age 18). The Follow-up Questionnaire sent in 2005–2006 collected information on retirement as well as up to date information on physical activity, smoking, history of cancer, and other factors. This thesis aims to study the association between diet and risk of CNS tumours using prospectively collected data only, so dietary data collected retrospectively using the Risk Factor Questionnaire was not used in this thesis. To allow corrections for error in reporting of dietary intakes using the Baseline Questionnaire, a dietary questionnaire called the Calibration Questionnaire, was also sent to a subset of study participants in 1996–1998 (see section 5.4.2 for detail).

5.2.2.2 Linked data

Participants in the study were followed up to 31 December 2011 by various means. Firstly, changes in participants' addresses were obtained both from the National Change of Address database and through follow-up questionnaires. In the first 3 years of follow-up, only about 2% of participants were lost to follow-up due to emigration.[3] Secondly, study participants were linked to the US Social Security Administration's Death Master File for death registrations.[3] Surviving participants who did not move outside the study areas during the follow-up period were also followed up via linkage to state cancer registries for incident cancer registrations. The sensitivities of the cancer registries for cancer case ascertainment were shown in a pilot study (n= 12,000) to be very good (≥89.2%).[3] Information that is available in the cancer registration database includes cancer site (coded using the 10th revision of the International Statistical Classification of Diseases and Related Health Problems, ICD-10)[4] and tumour morphology (coded using the 3rd edition of the International Classification of Diseases for Oncology, ICD-O-3)[5] as well as date of cancer registration. Information on health outcome data that is available and its sources is summarised in Table 5.2.

5.2.3 Characteristics of study participants

5.2.3.1 Characteristics at recruitment

Approximately 567,000 participants were recruited into the study. Among them, about 96,000 were excluded from further analyses for several reasons, including 20,233 participants based on standard exclusions for the NIH-AARP Study (see Figure 6.1), 51,346 participants who had prior cancer and 24,039 participants who reported an implausible energy intake (daily total intake outside 500–3500 kcal for women and 800–4200 kcal for men).

Among the remaining 470,780 participants, 277,906 were men and 192,874 were women. At recruitment: female participants had a mean age of 61.3, a mean height and BMI of 163.3 cm and 26.8 kg/m^2, respectively; 14.5% of women reported being

current smokers; 60.3% of women reported doing strenuous exercise 1 or more times per week; 15.2% of women were nulliparous, 40.1% reported ever using oral contraceptives; 44.6% were current users of hormones; and 31.1% of women had a university degree (see Table **??**). Male participants had a mean age of 61.6, a mean height and BMI of 178.3 cm and 27.2 kg/m^2, respectively; 10.5% of men reported being current smokers; 71.5% of men reported doing strenuous exercise 1 or more times per week; and 46.3% of men had a university degree (see Table **??**).

5.2.3.2 Health outcomes

Up to 31 December 2011, there were 119,252 first cancers recorded by the study cancer registries. With a large number of participants, the NIH-AARP Study has adequate power to detect associations for many common cancers, even by relevant subtypes of cancers. The study may also have sufficient power to detect modest associations between extreme categories of a given exposure and relatively rare cancers such as glioma (1,005 cases).

5.3 The PLCO Study

5.3.1 Recruitment and participants

In 1993–2001, men and women aged 55–74 were invited (e.g. through direct mail, mass media, and/or outreach) to participate in the PLCO study through ten study centres across the US (Alabama, Michigan, Colorado, Hawaii, Wisconsin, Minnesota, Pennsylvania, Utah, Missouri, and Washington DC).[6] Potential participants were not eligible if they had a history of cancer (except basal or squamous cell skin cancer) or had a recent cancer screening test (e.g. prostate specific antigen (PSA) test, colonoscopy), a surgical resection of the prostate, lung, colon and rectum, or ovary (e.g. prostatectomy), or were using a hormonal therapy (e.g. finasteride, tamoxifen).[2] A total of about 155,000 eligible participants were randomized into the intervention and control arms. Participants in the intervention arm were

asked to provide blood specimens and were offered examinations to screen for prostate, lung, colorectal, and/or ovarian cancer, while participants in the control arm received routine health care.

At recruitment, all participants were given the Baseline Questionnaire, and about 96% of them provided information on age, date and place of birth, ethnicity, level of education, marital status, body size, lifestyle factors such as smoking, medical history, hormone replacement therapy and reproductive history (women only), and other characteristics through the questionnaire. A food frequency questionnaire, the Diet History Questionnaire, was administered to all study participants from December 1998, and was completed by about 77% of study participants. Table 5.1 summarises information collected by the Baseline Questionnaire and the Diet History Questionnaire. More information on the study and is available at the PLCO study website (https://biometry.nci.nih.gov/cdas/plco/).

5.3.2 Follow-up

Participants from both intervention and control arms were followed up to 31 December 2009 by various means including linked mortality data, questionnaires about cancer diagnosis administered to participants annually, and other follow-up questionnaires, which are described below. Additionally, participants in the intervention arm were offered various cancer screening examinations. Information on health outcome data that is available and the source of the information is summarised in Table 5.2.

5.3.2.1 Cancer screening examinations

Participants in the intervention arm were offered a series of exams to screen for prostate, lung, colorectal and ovarian cancer during the first 5 years after randomisation. These examinations included: chest radiography and flexible sigmoidoscopy in all participants; digital rectal examination (DRE) and PSA test in men; and transvaginal ultrasonography (TVU) and cancer antigen 125

(CA-125) test in women. Participants were not offered these exams when they had a cancer of the prostate, lung, colon and rectum (or adenoma), or ovary, or had any surgical removal of these organs (e.g. prostatectomy), or if they died during this 5-year period. Participants and their physicians were notified of positive results from these screening exams.

5.3.2.2 Linked mortality data

Participants in the PLCO study were followed up through the National Death Index (NDI) Plus searches for information on death. Death certificates for each death that occurred up to 31 December 2009 were obtained, and information on the underlying cause of death was derived by trained professionals.

5.3.2.3 The Annual Study Update

A cancer diagnosis questionnaire, the Annual Study Update, was sent to surviving participants annually for 13 years since randomisation or until 31 December 2009, whichever was earlier. The questionnaire collected information on cancer diagnosis, the type of cancer, date of diagnosis, place of diagnosis, physician contact information, use of finasteride (in men only), and death information (provided by the participant's relatives or friends). About 96% of the expected 1.7 million Annual Study Updates were completed and returned.

5.3.2.4 Other follow-up questionnaires

Participants in the intervention arm were also given another food frequency questionnaire, the Dietary Questionnaire, early into the study. Because the questionnaire is given to only a subset of study participants rather than the entire cohort and the dietary information is less comprehensive than the Diet History Questionnaire, dietary data collected using this questionnaire was not used in this thesis. Two other follow-up questionnaires, the Health Status Questionnaire and the Supplemental Questionnaire, were sent to participants at various time points after recruitment. The Health Status Questionnaire was sent to a random sample of the study participants

(about 1,000 each year during 1997–2003 and about 2,000 during 2004–2010) to assess the rate of cancer screening exams (e.g. PSA, DRE, CA-125, TVU, colonoscopy) and other medical exams (e.g. eye examination, blood cholesterol) that occurred outside the PLCO trial protocol. In total, approximately 13,000 Health Status Questionnaires were completed and returned. In 2006, the Supplemental Questionnaire was introduced to all participants to collect up-to-date information on demographic, lifestyle BMI, physical activity, and other characteristics (excluding diet). Approximately 104,000 participants (67% of the cohort) completed the Supplemental Questionnaire.

5.3.3 Cancer ascertainment

Information on incident cancer comes from the PLCO cancer screening exams (and subsequent diagnostic exams), the Annual Study Update, death certificates (cancer as a cause of death) and reports from the PLCO Death Review Committee (suspected death associated with cancer), and notifications by participants' relatives (although these were infrequent). For every suspected incident cancer that was identified, the participant's medical records were obtained and information on cancer diagnosis date and morphology (coded using international classification of diseases for oncology second revision [ICD-O-2][7]) was abstracted by specially trained and certified professionals. For prostate, lung, colorectal and ovarian cancer, additional information on cancer stage, histopathologic type, diagnostic procedures, and initial cancer treatment was also abstracted.

5.3.4 Characteristics of study participants

5.3.4.1 Characteristics at dietary assessment

Approximately 111,000 participants were recruited and have provided dietary information through the Diet History Questionnaire. Among them, about 12,000 were excluded from further analyses for several reasons, including: 55 participants based on standard exclusions for the PLCO Study (see Figure 6.1), 9,636 participants who

had prior cancer, and 2,573 participants who reported an implausible energy intake (daily total intake outside 500–3500 kcal for women and 800–4200 kcal for men).

Among the remaining 99,148 participants, 47,196 were men and 51,952 were women. At the time when the Diet History Questionnaire was completed: female participants had a mean age of 65.3, a mean height and BMI of 163.2 cm and 27.0 kg/m^2, respectively; 8.4% of women reported being current smokers; 7.3% of women were nulliparous, 55.6% reported ever using oral contraceptives; 52.7% were current users of hormones; and 30.8% of women had a university degree (see Table **??**). Male participants had a mean age of 65.8, a mean height and BMI of 177.9 cm and 27.5 kg/m^2, respectively; 9.9% of men reported being current smokers; and 42.5% of men had a university degree (see Table **??**).

5.3.4.2 Health outcomes since randomisation

Up till 31 December 2009, there were more than 28,900 first cancers recorded by the study database. The PLCO Study has adequate power to detect associations between many exposures and risks of many common cancers. The study may also have sufficient power to detect modest associations between extreme categories of a given exposure and relatively rare cancers such as glioma (135 cases).

5.4 Dietary data in the NIH-AARP Study and the PLCO Study

5.4.1 Data collection

The NIH-AARP Study and the PLCO Study have used a nearly identical food frequency questionnaire, which was developed by the US NCI, to collect comprehensive dietary information from their study participants. The main difference between the questionnaires used in the two studies is the format (grid-style questions in the NIH-AARP questionnaire versus ordinary text style in the PLCO questionnaire). Other differences include order of the questions, and a few extra questions on how

meats were usually cooked in the PLCO Study questionnaire which were not on the NIH-AARP Study questionnaire. Both questionnaires, namely the Baseline Questionnaire in the NIH-AARP Study and the Diet History Questionnaire in the PLCO Study, asked about the intakes of 124 food and beverage items, specific food choices, cooking practices, and use of supplements in the past 12 months (a copy of the Baseline Questionnaire of the NIH-AARP Study is in Appendix A.2; the nearly identical Diet History Questionnaire of the PLCO Study is not shown). Generally, information was collected on frequency (e.g. never, 1 time per day, 2+ times per day) and portion size (e.g. less than 1 fruit, 1 to 2 fruits) of intake by subtypes of foods (e.g. apples, pears, bananas).

5.4.2 Performance of the dietary questionnaires

To evaluate the performance of the Baseline Questionnaire in the NIH-AARP Study in estimating nutrient intake and to correct for measurement error of reporting of dietary data, a calibration study was carried out. About 2,800 participants were selected into the calibration study based on stratifications of intakes of fruits and vegetables, red meat, fibre, and energy from fat, captured using the Baseline Questionnaire.[8] Those selected were invited to complete a 24-hour dietary recall by telephone administered by trained interviewers, and were mailed the Calibration Questionnaire, which is a dietary questionnaire that is similar to the Baseline Questionnaire.[8] The calibration study showed that the vast majority of median daily intakes of nutrient or food groups captured by the Baseline Questionnaire and the Calibration questionnaire were similar.[8] The study also showed that nutrient intakes captured by the Baseline Questionnaire evaluated within a measurement error model had reasonably good correlations (0.36–0.76), when using the two 24-hour dietary recalls as the reference.[8] Because the Diet History Questionnaire in the PLCO Study is nearly identical to the Baseline Questionnaire in the NIH-AARP Study, it can be assumed that the performance of the PLCO Diet History Questionnaire will be similar to the NIH-AARP Baseline Questionnaire.

5.4.3 Dietary variables

5.4.3.1 Food groups and nutrients

Dietary variables in both the NIH-AARP Study and the PLCO Study were prepared by the US National Cancer Institute and were made available to me upon applications which were approved by the study steering committees. In both studies, food group variables were derived by combining intake of individual subtypes of foods that belong to that food group in accordance with the composition of food groups used in the US Department of Agriculture's (USDA) Continuing Survey of Food Intakes by Individuals (CSFII).[8, 9] Total energy intake and intakes of macronutrients and micronutrients in study participants were derived according to information on standard portion size and nutrient composition of a particular food obtained from the USDA CSFII databases.[8, 9] In both the NIH-AARP Study and the PLCO Study, intakes of foods and nutrients were standardised to total energy intake (1600 kcal/day in women and 2000 kcal/day in men, which were approximate mean energy intakes of women and men of similar age in the US and the UK) (intakes of energy contributing nutrients were expressed as percentage dietary energy intake from these nutrients) before they were used in the descriptive analysis shown in the next section, the nutritional epidemiology analyses in Chapter 6, and for the derivation of dietary patterns.

5.4.3.2 Dietary patterns

Three dietary pattern variables, namely the Dietary Approaches to Stop Hypertension (DASH) score, the alternate Mediterranean diet (aMED) score, and the Healthy Eating Index (HEI) were derived using standardised intakes of food groups and/or nutrients in both the NIH-AARP Study and the PLCO Study. The components and scoring criteria for each of the dietary pattern variables were identical for men and women, and have been described in detail in Chapter 4 section 4.4.4.2, except for differences in scoring criteria for men, which are described below.

For scoring of moderate alcohol intake in aMED score, 1 point was assigned for 10–25g/day in men. For scoring in AHEI, the range of recommended intake of whole grains is 0–90g/day in men; for scoring of alcohol intake in men, 10 points were assigned to 0.5–2.0 drinks/day and intakes were scored proportionally from 10 to 0 for intakes between 2.0 and 3.5 drinks/day while intakes greater than 3.5 drinks/day were assigned 0 point; and intakes <0.5 drinks/day was assigned 2.5 points.

5.4.4 Dietary intakes

5.4.4.1 Dietary intakes of participants in the NIH-AARP Study

Men in the NIH-AARP Study reported a mean daily total energy intake of 1974 kcal, with of 48.1%, 15.4%, 30.4%, and 5.0% intake from carbohydrate, protein, total fat, and alcohol, respectively, whereas the numbers were 1541 kcal, 51.1%, 15.5%, 30.0%, and 2.6%, respectively, in women (Tables 5.3 & 5.4 for men and women, respectively). Mean daily intakes of total fruit, total vegetables, total meat, fish, and fibre (non-energy standardised) in men were 232g, 246g, 139g, 21g, and 20.3g, respectively while in women were 243g, 240g, 101g, 17g, and 17.6g, respectively.

5.4.4.2 Dietary intakes of participants in the PLCO Study

Men in the PLCO Study reported a mean daily total energy intake of 1970 kcal, with of 47.1%, 15.3%, 32.3%, and 4.4% intake from carbohydrate, protein, total fat, and alcohol, respectively, whereas the numbers were 1493 kcal, 50.2%, 15.5%, 31.3%, and 2.4%, respectively, in women (Tables 5.3 & 5.4 for men and women, respectively). Mean daily intakes of total fruit, total vegetables, total meat, fish, and fibre (non-energy standardised) in men were 166g, 229g, 130g, 17g, and 19.2g, respectively, while in women were 191g, 233g, 95g, 14g, and 16.8g, respectively.

5.4.4.3 Dietary intakes of participants in the NIH-AARP Study and the PLCO Study, and of US populations in the USDA CSFII 1994–1996

Participants in the NIH-AARP Study and PLCO Study reported broadly similar dietary intakes (Table 5.3 & 5.4 for men and women, respectively). The two noticeable differences were that NIH-AARP participants (both men and women) reported a higher intake of fruit and a lower percent total energy intake from total fat than PLCO participants. Table Table 5.3 & 5.4 also shows mean intakes of total energy, energy-contributing nutrients, and some selected food groups (non-energy standardised) of US adults of similar age groups (50–59 and 60–69) from a nationwide dietary survey, the USDA CSFII, carried out in 1994–1996.[9] The USDA CSFII collected dietary information using 24-hour dietary recalls on 2 non-consecutive days by trained interviewers rather than a single administered food frequency questionnaire as used in both the NIH-AARP and the PLCO studies. When compared to participants in the USDA CSFII, participants in both the NIH-AARP Study and the PLCO Study reported lower total energy intakes, lower percentage energy intake from total fat, higher percentage energy intake from alcohol, and higher intakes of vegetables, dietary fibre, and total meat (Table 5.3 & 5.4).[9]

5.4.4.4 Correlations between dietary intakes

In the NIH-AARP Study, correlations between dietary intakes were very similar between men and women. For both men and women in the NIH-AARP Study, spearman's correlations were greater than 0.50 for intakes of the following food groups and nutrients (categorised in fourths): total fruit and citrus fruit; total fruit or total vegetables and fibre; total fruit or fruit juice and vitamin C; total vegetables and carotene; cholesterol and eggs; dairy products and calcium; total fat, saturated fat, monounsaturated fat, and cholesterol; polyunsaturated fat and vitamin E; and fibre and carotene or folate (Table 5.5 & 5.6 for men and women, respectively). Percentage of energy intake from carbohydrate was negatively correlated with percentage energy intakes from total fat, saturated fat, and monounsaturated fat

as well as intake of cholesterol (correlation coefficients >0.50) (Table 5.5 & 5.6). Correlations were greater than 0.40 between DASH score and intakes of fibre, vitamin C, folate, calcium, and percentage energy from carbohydrate; between aMED score and intakes of total vegetables, fibre, and carotene; between AHEI and intakes of total vegetables and fibre (results not shown). There were negative correlations (correlation coefficient greater than 0.40) between DASH score and intakes of red meat, processed meat, and cholesterol; and between aMED score and intake of saturated fat (results not shown).

In the PLCO Study, correlations between dietary intakes were very similar between men and women. For both men and women in the PLCO Study, spearman's correlations were greater than 0.50 for intakes of the following food groups and nutrients (categorised in fourths): total fruit and citrus fruit; total fruit or total vegetables and fibre; total fruit or fruit juice and vitamin C; total vegetables and carotene; cholesterol and eggs; dairy products and calcium; total fat, saturated fat, and cholesterol; and fibre and carotene or folate (Table 5.7 & 5.8). Percentage of energy intake from carbohydrate was negatively correlated with percentage energy intakes from total fat, saturated fat, and monounsaturated fat as well as intake of cholesterol (correlation coefficients >0.50) (Table 5.7 & 5.8). Correlations were greater than 0.40 between DASH score and intakes of total fruit, fibre, vitamin C, calcium, and percentage energy from carbohydrate; between aMED score and intakes of total vegetables, fibre, and carotene; between AHEI and intakes of nuts and vitamin E (results not shown). There were negative correlations (correlation coefficient greater than 0.40) between DASH score and intakes of red meat and cholesterol; and between aMED score and intake of saturated fat (results not shown).

5.4.4.5 Differences in dietary intakes by participant's characteristics

In the NIH-AARP Study, there were some marked differences in dietary intakes by participant's smoking status as well as some noteworthy differences by other participant's characteristics. In men, the difference in mean intakes of food groups or nutrients was greater than 30%: between men who never smoked (reference group)

and those who were current smokers for intakes of total fruit (-44.2%), citrus fruit (-48.0%), fruit juice (-34.3%), grains/cereal (-44.8%), eggs (41.8%), alcohol (93.3%), coffee (80.2%), carotene (-30.6%), and vitamin C (-30.3%); between men with BMI <25 (reference group) and those with BMI ≥30 for intakes of red meat (35.2%) and eggs (38.2%); between men who never/rarely did strenuous exercise (reference group) and those who did strenuous exercise ≥3 per week for intakes of total fruit (32.6%), citrus fruit (41.1%), grains/cereal (30.5%), and carotene (32.2%); between men who were non-drinkers (reference group) and those who had ≥1 alcoholic drinks per day for intakes of total fruit (-31.2%), grains/cereal (-40.8%), and tea (-31.7%); between non-White men (reference group) and White men for intakes of cheese (60.9%), alcohol (39.8%), and coffee (43.5%); and between men who had <12 years of education (reference group) and those who had tertiary education (i.e. had a university degree) for intakes of fish (32.3%) and alcohol (48.2%) (Table 5.9). In women, the difference in mean intakes was greater than 30%: between women who never smoked (reference group) and those who were current smokers for intakes of total fruit (-33.5%), citrus fruit (-39.6%), grains/cereal (-33.0%), alcohol (147.8%), and coffee (83.2%); between women whose height was <160cm (reference group) and those whose height was ≥170cm for intake of alcohol (33.6%); between women with BMI <25 (reference group) and those with BMI ≥30 for intakes of processed meat (35.3%) and alcohol (-56.5%); between women who never/rarely did strenuous exercise (reference group) and those who did strenuous exercise ≥3 per week for intakes of total fruit (34.1%), citrus fruit (49.4%), and carotene (42.1%); between women who were non-drinkers (reference group) and those who had ≥1 alcoholic drinks per day for intakes of total fruit (-32.9%), grains/cereal (-47.2%), and cheese (50.8%); between non-White women (reference group) and White women for intakes of dairy products (34.3%), cheese (74.4%), alcohol (87.9%), and coffee (59.7%); and between women who had <12 years of education (reference group) and those who had tertiary education for intakes of cheese (58.5%), alcohol (109.1%), and carotene (30.4%) (Table 5.10). Details on mean intakes of all food groups and

nutrients by levels of these characteristics are given in Supplementary Tables B.3 and B.4 in Appendix B (for men and women, respectively).

In the PLCO Study, there were also some marked differences in dietary intakes by participant's smoking status as well as some noteworthy differences by other participant's characteristics. In men, the difference in mean intakes of food groups or nutrients was greater than 30%: between men who never smoked (reference group) and those who were current smokers for intakes of total fruit (-44.5%), citrus fruit (-47.2%), fruit juice (-34.8%), grains/cereal (-43.8%), alcohol (79.6%), and coffee (101.1%); between men with BMI <25 (reference group) and those with BMI ≥30 for intakes of red meat (36.0%) and eggs (36.8%); between men who were non-drinkers (reference group) and those who had ≥1 alcoholic drinks per day for intakes of total fruit (-31.3%) and grains/cereal (-43.9%); between non-White men (reference group) and White men for intakes of dairy products (70.0%), cheese (126.2%) and coffee (39.7%); and between men who had <12 years of education (reference group) and those who had tertiary education for intakes of fruit juice (32.3%), nuts (39.8%), white meat (31.1%), cheese (31.1%), alcohol (34.2%), and tea (36.1%) (Table 5.11). In women, the difference in mean intakes was greater than 30%: between women who never smoked (reference group) and those who were current smokers for intakes of total fruit (-33.1%), citrus fruit (-37.5%), grains/cereal (-32.7%), alcohol (119.4%), and coffee (101.0%); between women with BMI <25 (reference group) and those with BMI ≥30 for intakes of processed meat (32.1%), eggs (39.1%), and alcohol (-54.6%); between women who were non-drinkers (reference group) and those who had ≥1 alcoholic drinks per day for intakes of total fruit (-30.7%), grains/cereal (-46.5%), cheese (56.0%), and coffee (56.3%); between non-White women (reference group) and White women for intakes of dairy products (75.7%), cheese (134.7%), alcohol (108.4%), and coffee (57.1%); and between women who had <12 years of education (reference group) and those who had tertiary education for intakes of nuts (33.5%), cheese (63.6%), alcohol (116.6%), and carotene (31.0%) (Table 5.12). Details on mean intakes of all food

groups and nutrients by levels of these characteristics are given in Supplementary Tables B.5 and B.6 in Appendix B (for men and women, respectively)

5.5 Glioma data

5.5.1 Ascertainment of glioma

In the NIH-AARP Study, incident gliomas in participants were ascertained using linked cancer incidence data provided by the study state cancer registries. Glioma was ascertained by combining the ICD-10 codes for malignant CNS tumours (C70–C72 and C75.1–C75.3) and ICD-O-3 tumour morphology codes for glioma (9380.3–9460.3). Information on non-malignant CNS tumours (ICD-10 codes D32–D33, D35.2–35.4, D42–D43, and D44.3–D44.5) was not available, so the number of meningioma (ICD-O-3 9530.0–9539.1) (n=27), vestibular schwannoma (ICD-O-3 9560.0) (n=6), and pituitary tumours (ICD-10 C75.1, D35.2, or D44.3) (n=0), which were generally benign, was small and these CNS tumours were not studied further.

In the PLCO Study, incident gliomas in participants were ascertained using data from the PLCO cancer database, which contains information on cancer site and tumour morphology abstracted from participant's medical records (see section 5.3.3). Glioma was ascertained by combining the ICD-10 codes for malignant CNS tumour (C70–C72 and C75.1–C75.3) and ICD-O-2 tumour morphology codes for glioma (9380–9460). The PLCO Study database contains no information on other subtypes of CNS tumours.

5.5.2 Incident cases and incidence rates

In the NIH-AARP Study, 1,005 first gliomas were registered by the cancer registries during the study follow-up period (up to 31 December 2011) since recruitment. The incidences of glioma per 100,000 by age groups of participants (45–54, 55–64, 65–74, 75–84, $\geq$85) were 10.3 (95% CI 6.2–17.1), 14.3 (12.6–16.2), 18.3 (16.9–20.0), 21.0 (CI 18.3–24.0), and 22.1 (CI 3.1–157.1), respectively (Table 5.13). Although

these numbers were slightly higher than the incidences of neuroepithelial tumours (of which the vast majority is glioma) of US general populations of the same age groups in 2009–2013 (Table 5.13), the 95% confidence intervals of the incidences generally overlapped.[10],

In the PLCO Study, 135 first gliomas were recorded by the study cancer database during the follow-up period (up to 31 December 2009) since the Diet History Questionnaire was introduced to the participants. The incidences of glioma per 100,000 by age groups of participants (55–64, 65–74, 75–84, ≥85) were 11.8 (7.9–17.6), 16.2 (12.8–20.6), 26.0 (19.1–35.3), and 47.1 (6.6–334.5), which were similar to that of the NIH-AARP Study and the US general populations[10] (Table 5.13).

5.5.3 Incidence of glioma in relation to sociodemographic, anthropometric, and lifestyle factors

The NIH-AARP Study has published findings on incidence of glioma in relation to height, BMI, physical activity, smoking, alcohol drinking, and use of menopausal hormones, parity, use of oral contraceptives (women only)[11–13] (see Chapter 2); and the PLCO Study has published findings on height and glioma incidence[14] (see Chapter 2). Table 5.14 & 5.15 shows updated findings (based on more cases accrued since these papers were published) for men and women, respectively, and additional evidence from the NIH-AARP Study for incidence of glioma in relation to ethnicity, marital status, and level of educational attainment; and from the PLCO Study for incidence of glioma in relation to BMI, smoking, alcohol drinking, ethnicity, marital status, level of educational attainment, and use of menopausal hormones, parity, use of oral contraceptives (women only) (see Appendix C.2 for methods).

In the NIH-AARP Study, there were significantly increased incidences of glioma in relation to ethnicity (relative risk [RR] for White vs. non-White 1.93, 95% confidence interval [CI] 1.26–2.96) and education (RR for tertiary vs. <12 years 1.74, 95% CI 1.12–2.70) in men only, and in relation to height (RR for ≥170 vs. <160cm 1.39, 95% CI 1.01–1.92) in women only. In the PLCO Study, there was

evidence that use of oral contraceptives was associated with an decreased glioma incidence (RR for ever vs. never 0.51, 95% CI 0.28–0.94).

Dietary intakes of study participants in both the NIH-AARP Study and the PLCO Study vary by many factors including ethnicity and levels of educational attainment (see section 5.4.3.5), which were also associated with glioma incidence. The possible confounding effect of socio-demographic factors as well as anthropometric and lifestyle factors will be taken into account when studying the association between diet and risk of glioma in Chapter 6.

5.6 Tables

Table 5.1: Timings and contents of the Baseline Questionnaire in the NIH-AARP Study and the Baseline Questionnaire and the Diet History Questionnaire in the PLCO Study

Contents	**Details**	**The NIH-AARP Study**	**The PLCO Study**	
		The Baseline Questionnaire	The Baseline Questionnaire	The Diet History Questionnaire
Date	Year questionnaire was completed, range	1995–1997	1993–2001	1998–2001
	Median year since recruitment	0	0	3
Number of participants		566,000	149,000	102,000
Socio-demographic	Date of birth	•	•	•
	Place of birth	•	•	
	Ethnicity	•	•	
	Education	•	•	
	Marital status	•	•	
Body size	Height, weight, and derived BMI	•	•	
Lifestyle factors	Smoking	•	•	
	Alcohol drinking	•		•
	Physical activity	•		
Well-being	Current health	•		
Past health		•	•	
Family history		•	•	
Reproductive factors	Menarche, age at first birth, use of oral contraceptives	•	•	
	Menopause, hysterectomy	•	•	
	Use of menopausal hormones	•	•	
Diet	Foods and beverages	•		•
Occupational	Work history		•	

Table 5.2: Health outcome data for participants in the NIH-AARP Study and the PLCO Study

	The NIH-AARP Study (up to 31 December 2011)		**The PLCO Study** (up to 31 December 2009)	
Health outcome data	**Data**	**Source of information**	**Data**	**Source of information** †
Cancer	Cancer site (ICD codes), Tumour morphology (ICD-O codes)	State cancer registries covered by the study	Cancer site (ICD codes), Tumour morphology (ICD-O codes)	PLCO Study cancer screening/ diagnostic examinations, PLCO Annual Study Update (self report), death certificate (cause of death), and notifications by participant's relatives or friends
Death	Cause of death (ICD codes)	US Social Security Administration's Death Master File	Cause of death (ICD codes)	National Death Index Plus and PLCO Annual Study Update (participant's relative or friend's report)
Emigration or loss to follow-up	Address change	National Change of Address database, follow-up questionnaires (self-report)	not available	Not available

† Medical record of participants with cancer in the PLCO Study was reviewed and information on cancer diagnosis and diagnosis date was abstracted by trained professional; death certificate for each death in the PLCO Study was obtained and reviewed.

Table 5.3: Dietary intakes of men in the NIH-AARP Study and PLCO Study compared with men of similar age in the US Department of Agriculture (USDA)'s 1994-1996 Continuing Survey of Food Intakes by Individuals (CSFII)

	NIH-AARP	**PLCO**	**USDA CSFII**	**USDA CSFII**
Number of participants	277,906	47,196	888	845
Age, range	50–71	54–83	50–59	60–69
Age, median (IQR)	62 (57–66)	65 (61–70)	n/a	n/a
Year completed assessment	1995–1997	1998–2001	1994–1996	1994–1996
Dietary assessment method	FFQ	FFQ	24-hour dietary recall	24-hour dietary recall
Daily dietary intakes, mean (SD)				
Total energy, kcal	1,974 (695)	1,970 (694)	2,270 (n/a)	2,072 (n/a)
Total fruit, g	232 (225)	166 (143)	162 (n/a)	175 (n/a)
Total vegetables, g	246 (176)	229 (168)	186 (n/a)	192 (n/a)
Total meat, g	139 (82)	130 (81)	114 (n/a)	94 (n/a)
Fish, g	21 (22)	17 (19)	19 (n/a)	18 (n/a)
Carbohydrate, % energy	48.1 (9.1)	47.1 (8.7)	48.7 (n/a)	49.3 (n/a)
Protein, % energy	15.4 (3.1)	15.3 (2.9)	16.3 (n/a)	16.6 (n/a)
Total fat, % energy	30.4 (7.6)	32.3 (7.4)	33.8 (n/a)	33.5 (n/a)
Alcohol, % energy	5.0 (8.2)	4.4 (7.1)	2.5 (n/a)	2.1 (n/a)
Fibre, g	20.3 (9.2)	19.2 (8.4)	18.5 (n/a)	18.5 (n/a)

IQR interquartile range, SD standard deviation

Table 5.4: Dietary intakes of women in the NIH-AARP Study and PLCO Study compared with women of similar age in the US Department of Agriculture (USDA)'s 1994-1996 Continuing Survey of Food Intakes by Individuals (CSFII)

	NIH-AARP	PLCO	USDA CSFII	USDA CSFII
Number of participants	192,874	51,952	864	789
Age, range	50–71	54–83	50–59	60–69
Age, median (IQR)	62 (57–66)	65 (60–70)	n/a	n/a
Year completed assessment	1995–1997	1998–2001	1994–1996	1994–1996
Dietary assessment method	FFQ	FFQ	24-hour dietary recall	24-hour dietary recall
Daily dietary intakes, mean (SD)				
Total energy, kcal	1,541 (576)	1,493 (541)	1,600 (n/a)	1,489 (n/a)
Total fruit, g	243 (219)	191 (153)	159 (n/a)	171 (n/a)
Total vegetables, g	240 (176)	233 (166)	156 (n/a)	162 (n/a)
Total meat, g	101 (66)	95 (62)	70 (n/a)	67 (n/a)
Fish, g	17 (20)	14 (17)	14 (n/a)	12 (n/a)
Carbohydrate, % energy	51.1 (8.9)	50.2 (8.6)	51.2 (n/a)	51.2 (n/a)
Protein, % energy	15.5 (3.2)	15.5 (2.9)	16.5 (n/a)	16.7 (n/a)
Total fat, % energy	30.0 (7.7)	31.3 (7.6)	33.3 (n/a)	33.5 (n/a)
Alcohol, % energy	2.6 (5.6)	2.4 (4.8)	1.6 (n/a)	1.3 (n/a)
Fibre, g	17.6 (8.5)	16.8 (7.6)	14.5 (n/a)	14.2 (n/a)

IQR interquartile range, SD standard deviation

Table 5.5: Correlations between intake of selected foods and nutrients in men in the NIH-AARP Study

Spearman's correlation	Total fruit	Citrus fruit	Fruit juice	Total vegetables	Eggs	Dairy products	Carbohydrate	Total fat	Saturated fat	MU fat	PU fat	Fibre	Carotene	Vitamin C	Vitamin E	Folate	Calcium	Cholesterol
Total fruit	1.00																	
Citrus fruit	0.54	1.00																
Fruit juice	0.15	0.18	1.00															
Total vegetables	0.28	0.24	0.05	1.00														
Eggs	-0.14	-0.05	-0.04	-0.12	1.00													
Dairy products	0.06	0.03	0.06	-0.05	-0.06	1.00												
Carbohydrate	0.49	0.22	0.23	0.18	-0.28	0.17	1.00											
Total fat	-0.34	-0.17	-0.22	-0.17	0.32	-0.12	-0.59	1.00										
Saturated fat	-0.35	-0.19	-0.19	-0.24	0.33	0.02	-0.54	0.82	1.00									
MU fat	-0.36	-0.18	-0.22	-0.19	0.32	-0.16	-0.58	0.92	0.76	1.00								
PU fat	-0.16	-0.05	-0.14	0.05	0.15	-0.20	-0.39	0.68	0.37	0.65	1.00							
Fibre	0.52	0.33	0.07	0.56	-0.23	0.08	0.46	-0.34	-0.42	-0.35	-0.08	1.00						
Carotene	0.36	0.30	0.11	0.69	-0.12	-0.01	0.24	-0.19	-0.25	-0.20	‹0.01	0.53	1.00					
Vitamin C	0.54	0.46	0.62	0.40	-0.15	0.06	0.47	-0.39	-0.38	-0.41	-0.19	0.42	0.43	1.00				
Vitamin E	0.15	0.16	-0.02	0.34	0.03	-0.06	-0.05	0.33	0.08	0.31	0.58	0.30	0.30	0.17	1.00			
Folate	0.32	0.23	0.23	0.41	-0.20	0.18	0.49	-0.38	-0.39	-0.38	-0.17	0.61	0.38	0.46	0.27	1.00		
Calcium	0.15	0.11	0.07	0.10	-0.10	0.85	0.25	-0.17	-0.04	-0.21	-0.21	0.24	0.14	0.18	0.04	0.33	1.00	
Cholesterol	-0.26	-0.11	-0.13	-0.14	0.66	-0.06	-0.51	0.56	0.62	0.53	0.24	-0.35	-0.14	-0.26	‹0.01	-0.29	-0.09	1.00

MU fat monounsaturated fat, PU fat polyunsaturated fat

Table 5.6: Correlations between intake of selected foods and nutrients in women in the NIH-AARP Study

Spearman's correlation	Total fruit	Citrus fruit	Fruit juice	Total vegetables	Eggs	Dairy products	Carbohydrate	Total fat	Saturated fat	MU fat	PU fat	Fibre	Carotene	Vitamin C	Vitamin E	Folate	Calcium	Cholesterol
Total fruit	1.00																	
Citrus fruit	0.54	1.00																
Fruit juice	0.11	0.16	1.00															
Total vegetables	0.26	0.25	‹0.01	1.00														
Eggs	-0.12	-0.03	‹0.01	-0.09	1.00													
Dairy products	0.06	0.05	0.05	-0.05	-0.05	1.00												
Carbohydrate	0.50	0.23	0.19	0.15	-0.26	0.17	1.00											
Total fat	-0.40	-0.21	-0.17	-0.19	0.26	-0.23	-0.73	1.00										
Saturated fat	-0.39	-0.21	-0.14	-0.26	0.26	-0.08	-0.64	0.81	1.00									
MU fat	-0.41	-0.23	-0.17	-0.23	0.26	-0.25	-0.70	0.92	0.74	1.00								
PU fat	-0.23	-0.10	-0.13	0.01	0.14	-0.27	-0.53	0.71	0.37	0.68	1.00							
Fibre	0.51	0.34	0.01	0.59	-0.17	0.07	0.46	-0.40	-0.45	-0.41	-0.16	1.00						
Carotene	0.35	0.30	0.04	0.68	-0.10	-0.01	0.23	-0.23	-0.28	-0.25	-0.07	0.56	1.00					
Vitamin C	0.55	0.48	0.54	0.42	-0.12	0.05	0.45	-0.42	-0.41	-0.44	-0.24	0.43	0.43	1.00				
Vitamin E	0.11	0.14	-0.04	0.36	0.03	-0.14	-0.17	0.32	0.07	0.30	0.56	0.26	0.29	0.17	1.00			
Folate	0.27	0.23	0.18	0.45	-0.13	0.13	0.44	-0.43	-0.43	-0.43	-0.23	0.59	0.39	0.45	0.23	1.00		
Calcium	0.13	0.12	0.04	0.10	-0.08	0.86	0.23	-0.30	-0.15	-0.33	-0.31	0.23	0.14	0.17	-0.06	0.27	1.00	
Cholesterol	-0.27	-0.12	-0.09	-0.13	0.63	-0.08	-0.58	0.51	0.56	0.48	0.23	-0.34	-0.15	-0.26	0.01	-0.27	-0.12	1.00

MU fat monounsaturated fat, PU fat polyunsaturated fat

Table 5.7: Correlations between intake of selected foods and nutrients in men in the PLCO Study

Spearman's correlation	Total fruit	Citrus fruit	Fruit juice	Total vege-tables	Eggs	Dairy prod-ucts	Carbo-hydrate	Total fat	Satu-rated fat	MU fat	PU fat	Fibre	Caro-tene	Vita-min C	Vita-min E	Folate	Cal-cium	Chole-sterol
Total fruit	1.00																	
Citrus fruit	0.56	1.00																
Fruit juice	0.17	0.17	1.00															
Total vege-tables	0.33	0.25	0.06	1.00														
Eggs	-0.14	-0.04	-0.04	-0.06	1.00													
Dairy products	0.07	0.05	0.09	-0.07	-0.07	1.00												
Carbo-hydrate	0.48	0.24	0.24	0.18	-0.28	0.19	1.00											
Total fat	-0.35	-0.18	-0.23	-0.17	0.29	-0.15	-0.63	1.00										
Saturated fat	-0.37	-0.20	-0.21	-0.26	0.28	0.03	-0.54	0.80	1.00									
MU fat	-0.35	-0.19	-0.23	-0.18	0.28	-0.19	-0.62	0.91	0.71	1.00								
PU fat	-0.14	-0.05	-0.14	0.06	0.16	-0.24	-0.38	0.65	0.30	0.61	1.00							
Fibre	0.60	0.34	0.12	0.55	-0.20	0.04	0.47	-0.36	-0.47	-0.35	-0.04	1.00						
Carotene	0.42	0.32	0.12	0.69	-0.09	-0.03	0.26	-0.22	-0.29	-0.23	‹0.01	0.55	1.00					
Vitamin C	0.53	0.43	0.60	0.45	-0.13	0.07	0.48	-0.41	-0.41	-0.42	-0.18	0.48	0.48	1.00				
Vitamin E	0.23	0.16	0.04	0.33	-0.02	-0.06	‹0.01	0.18	-0.08	0.19	0.48	0.40	0.31	0.26	1.00			
Folate	0.34	0.21	0.22	0.36	-0.17	0.13	0.49	-0.40	-0.45	-0.39	-0.12	0.59	0.38	0.48	0.36	1.00		
Calcium	0.13	0.09	0.08	0.06	-0.07	0.83	0.23	-0.17	0.01	-0.22	-0.24	0.16	0.09	0.17	0.05	0.24	1.00	
Cholesterol	-0.26	-0.12	-0.14	-0.11	0.71	-0.07	-0.49	0.51	0.57	0.47	0.19	-0.37	-0.14	-0.26	-0.11	-0.30	-0.07	1.00

MU fat monounsaturated fat, PU fat polyunsaturated fat

Table 5.8: Correlations between intake of selected foods and nutrients in women in the PLCO Study

Spearman's correlation	Total fruit	Citrus fruit	Fruit juice	Total vegetables	Eggs	Dairy products	Carbohydrate	Total fat	Saturated fat	MU fat	PU fat	Fibre	Carotene	Vitamin C	Vitamin E	Folate	Calcium	Cholesterol
Total fruit	1.00																	
Citrus fruit	0.55	1.00																
Fruit juice	0.09	0.13	1.00															
Total vegetables	0.32	0.24	<0.01	1.00														
Eggs	-0.11	-0.03	-0.03	-0.04	1.00													
Dairy products	0.06	0.05	0.09	-0.07	-0.05	1.00												
Carbohydrate	0.49	0.23	0.22	0.16	-0.27	0.20	1.00											
Total fat	-0.41	-0.22	-0.22	-0.20	0.24	-0.25	-0.75	1.00										
Saturated fat	-0.42	-0.23	-0.19	-0.28	0.23	-0.09	-0.63	0.79	1.00									
MU fat	-0.42	-0.22	-0.22	-0.21	0.23	-0.27	-0.72	0.91	0.72	1.00								
PU fat	-0.23	-0.11	-0.16	0.01	0.15	-0.31	-0.53	0.70	0.36	0.65	1.00							
Fibre	0.61	0.33	0.03	0.57	-0.15	0.04	0.48	-0.41	-0.49	-0.40	-0.15	1.00						
Carotene	0.41	0.30	0.05	0.66	-0.06	-0.01	0.25	-0.26	-0.32	-0.27	-0.08	0.56	1.00					
Vitamin C	0.52	0.43	0.54	0.44	-0.11	0.06	0.47	-0.46	-0.46	-0.47	-0.25	0.47	0.45	1.00				
Vitamin E	0.18	0.12	-0.03	0.33	-0.01	-0.09	-0.06	0.14	-0.10	0.14	0.41	0.35	0.27	0.21	1.00			
Folate	0.29	0.19	0.18	0.38	-0.12	0.13	0.45	-0.44	-0.48	-0.43	-0.19	0.57	0.36	0.45	0.36	1.00		
Calcium	0.12	0.09	0.07	0.07	-0.05	0.83	0.23	-0.31	-0.14	-0.34	-0.33	0.16	0.11	0.16	0.02	0.25	1.00	
Cholesterol	-0.27	-0.12	-0.12	-0.11	0.68	-0.11	-0.55	0.48	0.52	0.45	0.21	-0.35	-0.14	-0.27	-0.11	-0.28	-0.12	1.00

MU fat monounsaturated fat, PU fat polyunsaturated fat

Table 5.9: Differences in mean daily dietary intakes (%) by selected characteristics of men in the NIH-AARP Study

Daily dietary intake	Height (185+ vs. <175 cm)	BMI (30+ vs. <25)	Exercise (3+ times per week vs. never /rarely)	Smoking (Current vs. Never)	Alcohol (1+ drinks /day vs. non-drinkers)	Ethnicity (White vs. non-White)	Marital status (Married* vs. without partner)	Education (Tertiary vs. <12 years)
Total fruit, g	-7.7	-10.9	32.6	-44.2	-31.2	-23.8	-4	3.3
Citrus fruit, g	-10.7	-7.2	41.1	-48	-18.3	-19.6	1.2	8.1
Fruit juice, g	2.4	-5	15.9	-34.3	-0.3	-21.1	-8.2	25.2
Total vegetables, g	-1.9	-3.6	23.5	-19.8	-7.3	-4.6	-0.9	15.6
Nuts, g	12.3	-6.8	7.6	6.2	-14.7	15.3	-1.2	8.3
Grains/cereal, g	-4.3	-27.6	30.5	-44.8	-40.8	-19.9	-4.9	2.1
Red meat, g	5.5	35.2	-18.1	27.3	-2	16.3	4.5	-9.6
Processed meat, g	2	24.3	-16.4	25.6	-11.5	11.7	4.3	-18.9
White meat, g	-0.6	5.9	14.7	-22.6	-2.8	-5.5	3.4	24.3
Fish, g	0.5	2.9	15.8	-17.1	11.3	-8.6	-1.6	32.3
Eggs, g	4.8	38.2	-23.7	41.8	-10.8	-12.2	-13.2	-24.4
Dairy products, g	6.4	0	6.3	-10.5	-28.7	25.3	-4	0.4
Cheese, g	15.2	23.6	-5.5	13.1	19.4	60.9	-0.2	29.9
Alcohol, g	12.3	-16.9	-0.1	93.3	n/a	39.8	-18.3	48.2
Coffee, g	-3	4.6	-8.5	80.2	3.9	43.5	2.5	-6.2
Tea, g	-9.3	-0.2	-1.9	-18	-31.7	0.5	5.5	3.1
Carbohydrate, %E	-3.3	-6.9	5.8	-11.5	-17	-6.8	0.8	-0.8
Protein, %E	1.3	7.5	1.6	-4.3	-10.2	5.7	1.5	4.5
Total fat, %E	3.2	10.6	-8.4	10	-12	5	1.4	-6
Saturated fat, %E	4.1	12.6	-12	15.8	-12	8.1	-0.8	-8.1
Monounsaturated fat, %E	2.8	11.3	-9.3	11.3	-12.3	4.9	1.9	-7.3
Polyunsaturated fat, %E	2.9	6.7	-2.7	2.1	-11.6	1.8	3.5	-1.6
Fibre, g	-2.2	-9.7	21.4	-24.9	-14.9	-3.8	0.9	8.7
Carotene, ug	-3.7	-10.6	32.2	-30.6	-16.6	-14.2	-2.9	19.1
Vitamin C, ug	-1.6	-3.2	20.3	-30.3	-13.3	-15.2	-3.5	11.9
Vitamin E, mg	0	-1.4	5.7	-9.1	-13.4	-1	1.6	0.5
Folate, ug	-3.4	-7.9	12	-19.8	-12.7	-7.1	2.3	8.9
Calcium, mg	2.2	0.3	6.1	-9.5	-18.6	8.5	-1.2	2.7
Cholesterol, mg	4.5	22.2	-12.9	17.6	-7.8	1.2	-3	-8.7
DASH score, point	0.6	-5	10.6	-12.5	-2.5	1.2	-0.5	7.9
aMED score, point	0.8	-10.8	26	-24.4	3.3	-2.1	2.7	20.3
AHEI, point	0.8	-5	10.9	-8.6	9.5	-1.2	0.2	8.6
Total energy intake, kcal	8.2	4.8	0.5	10.5	12.7	1.6	-0.1	-6.3

*Married or living with a partner; %E, percentage energy intake; reference groups for calculating differences (%) were: height (<160cm), BMI (<25), exercise (never/rarely), smoking (never), alcohol drinking (non-drinkers), race (non-White), marital status (without partner), and education (<12 years)

Table 5.10: Differences in mean daily dietary intakes (%) by selected characteristics of women in the NIH-AARP Study

Daily dietary intake	Height (170+ vs. <160 cm)	BMI (30+ vs. <25)	Exercise (3+ times per week vs. never /rarely)	Smoking (Current vs. Never)	Alcohol (1+ drinks /day vs. non-drinkers)	Race (White vs. non-White)	Marital status (Married* vs. without partner)	Education (Tertiary vs. <12 years)	Parity (Parous vs. Nulli-parous)	Oral contra-ceptive use (Ever vs. Never)	Menopausal hormone use (Current vs. Never)
Total fruit, g	-3.9	-10	34.1	-33.5	-32.9	-25.2	-4	7.3	0.3	-6.9	-1.9
Citrus fruit, g	-8.5	-12.2	49.4	-39.6	-19.8	-19.9	-0.4	22.8	-3.2	-12.8	-4.8
Fruit juice, g	4	-11.3	9.8	-18.7	-1.2	-26.4	-9.2	2.9	-1.3	-7.4	-7.6
Total vegetables, g	-0.7	-6.4	28.8	-11.8	-3.9	0.3	2.1	21	0.2	-1	1.6
Nuts, g	11.2	-7.9	5.6	2.7	-16.4	0.7	-5.6	21.2	-6	0	2.6
Grains/cereal, g	-0.2	-11.8	22.5	-33	-47.2	-21.9	-10.7	-7.8	1.9	-9.2	3.7
Red meat, g	-0.1	28.5	-22.4	22.6	2.9	14.6	12.6	-19.1	4	2.8	-3.4
Processed meat, g	-1.5	35.3	-22.7	21.8	-8.7	-1.6	5.3	-26.8	-1.3	-3.2	-10.3
White meat, g	0.4	8.3	13.3	-10.8	2.2	-10.6	2.3	23.9	-1	3.7	3
Fish, g	0.1	3.1	13.7	-1.4	15.4	-12.3	4.1	27	-2.5	2.2	-0.1
Eggs, g	4.6	28.4	-16.6	22.5	2.6	7.3	-5.1	-6.5	-1.5	3	0
Dairy products, g	2.2	-4	13.9	-15.7	-24.6	34.3	-5.7	6	-1.6	-5.6	4.1
Cheese, g	20.6	10.2	-5.8	12.2	50.8	74.4	-6.3	58.5	-12.1	9.6	8.8
Alcohol, g	33.6	-56.5	11.1	147.8	n/a	87.9	1.4	109.1	-22	28.2	16.3
Coffee, g	-0.1	-18.4	-4	83.2	22.5	59.7	-4.8	-7.1	6.1	0	-1.5
Tea, g	-9.9	-3.1	1.6	-13.7	-26.6	26.4	-2.6	10.1	3.4	-1.7	-6.8
Carbohydrate, %E	-1.9	-3.7	6.2	-9.1	-18.3	-5.4	-1.3	0.9	0.2	-1.6	-0.1
Protein, %E	0	4.9	3.3	-3.5	-7.5	6.8	1.7	5.4	-0.2	0.2	1.6
Total fat, %E	1.1	9.9	-11.1	9.3	-8.3	2.4	1.2	-8.8	2	0.2	-1.8
Saturated fat, %E	2.1	10.7	-13.8	13.6	-7.1	7.3	-1	-9.3	1.4	0.4	-3.3
Monounsaturated fat, %E	0.6	10.9	-12.3	9.2	-9.3	1.5	2.2	-10.4	2.2	0.1	-1.9
Polyunsaturated fat, %E	0.8	7.4	-7.1	5.9	-8.2	-1.9	2.2	-6.8	2.7	0	0.1
Fibre, g	-1	-7.1	22.8	-19.6	-18.2	-2.6	0.3	11.6	-0.7	-2.6	3.8
Carotene, ug	-1.3	-12.2	42.1	-23.8	-14.3	-9.2	-1.5	30.4	-1.6	-3.2	1.7
Vitamin C, ug	-1	-6.4	22.3	-20	-13.2	-16.6	-3.4	9.7	0.1	-4.9	-3
Vitamin E, mg	-1.3	-1.1	4.4	-4.5	-10.6	-3.7	0.5	-0.9	0.8	-2.5	-0.1
Folate, ug	-2.4	-5.6	12.2	-13.4	-12.3	-2.9	0	9.5	-1.3	-1.5	2
Calcium, mg	0.9	-2.1	10.3	-9.8	-15.7	11.7	-3.4	6.4	-1.5	-2.7	2.1
Cholesterol, mg	2.3	17.6	-11.8	12.7	-1.3	3.3	0.4	-5.7	0.7	1.9	-2.1
DASH score, point	1.2	-5.5	11.6	-9.4	-2.7	1.9	-2	9.9	-1	-1.1	2.4
aMED score, point	1.9	-9.8	24.9	-16.7	-5.4	-3.9	1	21.4	-0.4	-0.1	6.1
AHEI, point	1.4	-5.6	10.5	-4.3	8.2	-0.3	0.3	10.1	-0.4	0.7	3.1
Total energy intake, kcal	5.5	6.6	-0.1	2.9	8.4	-5.7	2	-5.5	0.3	-0.3	-3.2

*Married or living with a partner; %E, percentage energy intake; reference groups for calculating differences (%) were: height (<160cm), BMI (<25), exercise (never/rarely), smoking (never), alcohol drinking (non-drinkers), race (non-White), marital status (without partner), education (<12 years), parity (nulliparous), oral contraceptives use (never), and menopausal hormones use (never)

Table 5.11: Differences in mean daily dietary intakes (%) by selected characteristics of men in the PLCO Study

Daily dietary intake	Height (170+ vs. ‹160 cm)	BMI (30+ vs. ‹25)	Smoking (Current vs. Never)	Alcohol (1+ drinks/day vs. non-drinkers)	Race (White vs. non-White)	Marital status (Married* vs. without partner)	Education (Tertiary vs. ‹12 years)
Total fruit, g	-7.1	-8.1	-44.5	-31.3	-10.7	2.3	2.9
Citrus fruit, g	-7.5	-9.5	-47.2	-21.9	0.3	4.6	1.2
Fruit juice, g	7.0	-11.3	-34.8	-6.5	-8.3	-9.5	32.3
Total vegetables, g	-2.5	-1.9	-17.7	-10.2	-7.0	-0.6	11.6
Nuts, g	3.5	-11.4	-11.9	-2.9	0.3	3.9	39.8
Grains/cereal, g	-2.8	-26.1	-43.8	-43.9	-16.9	0.0	-0.5
Red meat, g	5.6	36.0	22.8	3.1	21.7	1.4	-14.4
Processed meat, g	5.3	24.4	20.3	-8.1	14.4	-0.8	-17.2
White meat, g	-1.8	7.1	-17.9	-1.3	-15.5	-2.2	31.1
Fish, g	-6.2	3.6	-11.6	8.8	-29.3	-9.6	24.1
Eggs, g	0.2	36.8	29.3	-8.9	-5.4	-14.8	-20.4
Dairy products, g	11.4	-2.0	-13.6	-28.3	70.0	5.5	6.8
Cheese, g	26.0	27.1	1.6	14.5	126.2	6.4	31.1
Alcohol, g	3.6	-11.9	79.6	n/a	22.2	-14.7	34.2
Coffee, g	-7.4	0.4	101.1	25.9	39.7	-2.5	-15.2
Tea, g	-9.1	-7.1	-14.0	-25.9	-16.7	-0.8	36.1
Carbohydrate, %E	-2.7	-7.5	-10.0	-16.8	-5.6	1.0	-0.1
Protein, %E	1.6	7.7	-2.4	-8.4	5.6	0.8	3.7
Total fat, %E	3.2	9.6	7.7	-9.0	5.1	0.6	-4.6
Saturated fat, %E	5.3	12.5	13.1	-10.3	15.3	-0.3	-9.0
Monounsaturated fat, %E	2.6	9.7	8.3	-8.0	4.2	0.8	-4.9
Polyunsaturated fat, %E	1.3	5.0	0.3	-8.6	-5.8	1.8	2.8
Fibre, g	-1.9	-9.2	-22.7	-13.7	-2.4	2.9	9.8
Carotene, ug	-4.2	-11.1	-29.6	-17.0	-16.4	2.4	26.8
Vitamin C, ug	0.5	-4.9	-27.8	-15.6	-6.5	-3.7	13.8
Vitamin E, mg	0.6	-3.3	-11.6	-9.3	-1.8	1.2	12.8
Folate, ug	-4.3	-9.9	-16.9	-12.3	-13.7	2.1	12.6
Calcium, mg	5.2	0.0	-8.1	-17.2	21.9	1.9	5.0
Cholesterol, mg	3.1	24.0	15.9	-6.3	4.2	-4.9	-11.6
DASH score, point	1.0	-6.0	-12.5	-3.6	3.0	1.6	10.1
aMED score, point	-0.1	-11.2	-23.8	3.8	-6.9	3.2	25.6
AHEI, point	0.4	-4.1	-3.8	11.0	-4.0	0.4	8.4
Total energy intake, kcal	9.1	5.2	6.6	13.1	5.9	-0.9	-2.6

*Married or living with a partner; %E, percentage energy intake; reference groups for calculating differences (%) were: height (‹160cm), BMI (‹25), smoking (never), alcohol drinking (non-drinkers), race (non-White), marital status (without partner), and education (‹12 years)

Table 5.12: Differences in mean daily dietary intakes (%) by selected characteristics of women in the PLCO Study

Daily dietary intake	Height (170+ vs. ‹160 cm)	BMI (30+ vs. ‹25)	Smoking (Current vs. Never)	Alcohol (1+ drinks/ day vs. non-drinkers)	Race (White vs. non-White)	Marital status (Married* vs. without partner)	Education (Tertiary vs. ‹12 years)	Parity (Parous vs. Nulli-parous)	Oral contra-ceptives (Ever vs. Never)	Menopausal hormone use (Current vs. Never)
Total fruit, g	-6.0	-8.4	-33.1	-30.7	-15.9	-3.6	1.8	-1.4	-10.3	-3.3
Citrus fruit, g	-8.3	-10.4	-37.5	-15.8	-16.2	-2.2	10.4	-7.0	-15.1	-10.1
Fruit juice, g	4.9	-15.7	-21.8	-1.6	-16.7	-7.7	17.4	0.0	-7.0	-4.4
Total vegetables, g	-2.4	-3.9	-11.2	-5.2	-7.3	0.8	12.8	-2.2	-3.2	0.9
Nuts, g	9.2	-17.7	-14.6	-1.2	-4.0	-1.4	33.5	-4.6	4.7	11.4
Grains/cereal, g	-6.4	-11.7	-32.7	-46.5	-27.5	-13.2	-10.0	-3.3	-11.5	-3.4
Red meat, g	0.6	29.5	19.1	3.9	24.9	17.7	-18.6	8.5	6.0	-2.0
Processed meat, g	1.4	32.1	19.0	-8.0	4.1	7.6	-22.5	3.1	0.3	-7.3
White meat, g	-1.3	7.0	-4.1	8.1	-12.8	-0.8	30.0	-0.2	8.6	6.6
Fish, g	-4.5	3.3	0.6	24.3	-22.2	1.2	25.6	-1.3	3.8	2.8
Eggs, g	4.6	39.1	15.2	2.7	19.2	-7.2	-2.9	0.8	7.6	5.0
Dairy products, g	10.0	-8.4	-19.0	-25.1	75.7	-2.0	22.8	-2.5	-5.4	-0.4
Cheese, g	23.3	6.2	10.2	56.0	134.7	-3.9	63.6	-5.8	12.6	10.5
Alcohol, g	24.7	-54.6	119.4	n/a	108.4	5.1	116.6	-17.1	27.7	15.6
Coffee, g	-1.6	-15.9	101.0	56.3	57.1	-4.0	-24.0	2.3	1.2	-9.9
Tea, g	-8.4	-7.3	-6.3	-21.9	5.2	-3.7	17.6	-0.7	1.6	4.1
Carbohydrate, %E	-2.0	-3.7	-8.2	-18.6	-6.4	-1.7	-0.8	-1.1	-3.3	-1.5
Protein, %E	0.6	4.7	-2.2	-5.7	7.2	1.7	6.4	0.0	1.7	1.5
Total fat, %E	1.6	8.8	7.6	-6.2	4.1	1.6	-6.0	3.2	2.7	0.8
Saturated fat, %E	3.7	12.3	12.3	-6.8	14.6	0.1	-8.6	3.9	3.0	-0.6
Monounsaturated fat, %E	1.3	8.9	7.4	-5.5	3.0	2.8	-6.1	3.1	3.1	1.2
Polyunsaturated fat, %E	-0.3	4.2	3.2	-5.9	-5.3	1.5	-2.8	2.4	1.9	2.3
Fibre, g	-1.9	-7.5	-18.4	-17.1	-4.6	-0.4	8.0	-3.2	-3.9	1.5
Carotene, ug	-3.4	-12.3	-23.5	-12.4	-13.8	-1.3	31.0	-4.3	-4.1	2.5
Vitamin C, ug	-1.1	-6.8	-19.5	-12.3	-11.4	-4.0	8.8	-1.1	-5.2	-2.1
Vitamin E, mg	-0.5	-3.5	-6.8	-6.7	-2.8	-0.9	8.9	-1.6	1.0	4.8
Folate, ug	-4.0	-6.7	-12.2	-12.5	-11.1	-1.2	9.2	-3.3	-2.7	1.9
Calcium, mg	4.2	-3.2	-8.4	-13.6	21.3	-2.8	11.0	-1.9	-1.9	0.6
Cholesterol, mg	2.8	22.8	12.0	-0.6	11.0	0.1	-6.1	3.5	5.1	0.6
DASH score, point	1.1	-7.0	-10.4	-2.5	1.2	-2.1	10.4	-2.1	-1.7	1.9
aMED score, point	-0.2	-12.1	-18.4	-5.4	-8.7	0.0	21.9	-2.8	-1.1	5.3
AHEI, point	0.7	-4.9	-1.5	9.9	-2.8	-0.6	8.0	-1.2	1.1	2.8
Total energy intake, kcal	7.5	5.4	3.2	11.5	0.3	1.2	0.2	0.3	1.7	0.1

*Married or living with a partner; %E, percentage energy intake; reference groups for calculating differences (%) were: height (‹160cm), BMI (‹25), smoking (never), alcohol drinking (non-drinkers), race (non-White), marital status (without partner), education (‹12 years), parity (nulliparous), oral contraceptives use (never), and menopausal hormones use (never)

Table 5.13: Glioma incidence in the NIH-AARP Study and the PLCO Study, by age at diagnosis

Populations	Age	45–54	55–64	65–74	75–84	≥85
NIH–AARP Study	No. of cases	15	241	536	212	1
	Person-years	145,319	1,690,790	2,921,930	1,010,926	4,519
	Incidence per 100,000 (95% CI)	10.3 (6.2–17.1)	14.3 (12.6–16.2)	18.3 (16.9–20.0)	21.0 (18.3–24.0)	22.1 (3.1–157.1)
PLCO Study	No. of cases	0	24	69	41	1
	Person-years	3	203,125	424,836	157,880	2122
	Incidence per 100,000 (95% CI)	n/a	11.8 (7.9–17.6)	16.2 (12.8–20.6)	26.0 (19.1–35.3)	47.1 (6.6–334.5)
US population[11] †	Incidence per 100,000 (95% CI)	6.9 (6.8–7.0)	11.7 (11.6–11.9)	17.2 (16.9–17.4)	19.7 (19.3–20.0)	12.5 (12.1–12.9)

† Incidence of neuroepithelial tumours (of which the vast majority is glioma)

Table 5.14: Risk of glioma in relation to anthropometric, socio-demographic, and lifestyle factors in men in the NIH-AARP Study and the PLCO Study

Risk factors	NIH-AARP			PLCO		
	No. of men	No. of cases	RR (95% CI)	No. of men	No. of cases	RR (95% CI)
Height (cm)						
‹175	74924	172	**1.00** (reference)	13176	20	**1.00** (reference)
175–179	79163	185	**1.00 (0.81–1.23)**	13573	20	**0.93 (0.50–1.75)**
180–184	72884	194	**1.15 (0.93–1.41)**	12180	22	**1.15 (0.62–2.14)**
›185	47898	135	**1.23 (0.98–1.54)**	7861	18	**1.49 (0.77–2.85)**
per 10 cm increase			**1.09 (0.99–1.21)**			**1.19 (0.86–1.66)**
Body mass index (kg/m^2)						
‹25	80986	189	**1.00** (reference)	12123	23	**1.00** (reference)
25–29	134702	350	**1.12 (0.94–1.34)**	23718	39	**0.91 (0.54–1.54)**
›30	57211	144	**1.13 (0.91–1.41)**	10673	18	**1.04 (0.55–1.96)**
per 10 kg/m^2 increase			**1.01 (0.84–1.21)**			**0.86 (0.47–1.55)**
Strenuous exercise (times)						
Never/rarely	40682	96	**1.06 (0.79–1.42)**	n/a	n/a	n/a
‹1 per week	36107	89	**1.00** (reference)	n/a	n/a	n/a
1 per week	61019	154	**0.99 (0.76–1.29)**	n/a	n/a	n/a
›3 per week	137767	349	**0.98 (0.77–1.24)**	n/a	n/a	n/a
Smoking status						
Never smoker	81572	234	**1.00** (reference)	17856	40	**1.00** (reference)
Past smoker	157652	389	**0.91 (0.77–1.08)**	24639	36	**0.68 (0.43–1.08)**
Current smoker	28028	47	**0.75 (0.55–1.04)**	4691	6	**0.72 (0.30–1.74)**
Alcohol drinking						
Non-drinkers	57399	134	**0.95 (0.78–1.16)**	10965	20	**0.91 (0.52–1.62)**
‹1 drink per day	141499	376	**1.00** (reference)	23283	40	**1.00** (reference)
›1 drinks per day	79008	180	**0.87 (0.72–1.04)**	12948	22	**1.06 (0.63–1.80)**
Ethnicity						
Non-White	16832	22	**1.00** (reference)	4238	5	**1.00** (reference)
White	258086	662	**1.93 (1.26–2.96)**	42935	77	**1.25 (0.40–3.91)**
Marital status						
No partner	39109	82	**1.00** (reference)	6840	8	**1.00** (reference)
Married or living with a partner	237155	606	**1.13 (0.90–1.43)**	40251	74	**1.44 (0.69–2.99)**
Education						
‹12 years	15624	22	**1.00** (reference)	3184	6	**1.00** (reference)
12 years/high school	42767	104	**1.64 (1.03–2.59)**	8579	9	**0.58 (0.21–1.64)**
Post high school training	25756	59	**1.53 (0.94–2.51)**	5954	11	**1.04 (0.38–2.85)**
Some college	61377	149	**1.64 (1.05–2.58)**	9353	16	**0.92 (0.35–2.38)**
Tertiary – had a university degree	125373	335	**1.74 (1.12–2.70)**	20023	40	**1.01 (0.41–2.45)**

Table 5.15: Risk of glioma in relation to anthropometric, socio-demographic, and lifestyle factors in women in the NIH-AARP Study and the PLCO Study

Risk factors	NIH-AARP			PLCO		
	No. of women	No. of cases	RR (95% CI)	No. of women	No. of cases	RR (95% CI)
Height (cm)						
<160	49320	78	1.00 (reference)	12914	12	1.00 (reference)
160–164	54858	85	0.98 (0.72–1.33)	15600	14	0.97 (0.45–2.12)
165–169	51359	74	0.92 (0.66–1.26)	13985	13	1.05 (0.47–2.32)
≥170	35393	77	1.39 (1.01–1.92)	9179	14	1.77 (0.80–3.90)
per 10 cm increase			1.09 (0.92–1.28)			1.13 (0.74–1.72)
Body mass index (kg/m^2)						
<25	83149	140	1.00 (reference)	21036	24	1.00 (reference)
25–29	60851	101	0.99 (0.77–1.29)	17937	16	0.78 (0.41–1.49)
≥30	42873	66	0.98 (0.72–1.33)	12368	12	0.94 (0.46–1.93)
per 10 kg/m^2 increase			0.98 (0.80–1.20)			1.29 (0.78–2.14)
Strenuous exercise (times)						
Never/rarely	42747	68	0.82 (0.58–1.18)	n/a	n/a	n/a
<1 per week	27586	56	1.00 (reference)	n/a	n/a	n/a
1 per week	40579	65	0.78 (0.55–1.12)	n/a	n/a	n/a
≥3 per week	79526	123	0.74 (0.54–1.03)	n/a	n/a	n/a
Smoking status						
Never smoker	84948	137	1.00 (reference)	29766	31	1.00 (reference)
Past smoker	74211	121	1.07 (0.83–1.37)	17806	18	1.11 (0.61–2.03)
Current smoker	26954	45	1.22 (0.86–1.72)	4377	4	1.14 (0.39–3.33)
Alcohol drinking						
Non-drinkers	56619	83	0.91 (0.70–1.19)	16014	19	1.26 (0.68–2.33)
<1 drink per day	111789	190	1.00 (reference)	29826	29	1.00 (reference)
≥1 drinks per day	24466	42	0.99 (0.70–1.39)	6112	5	0.83 (0.32–2.18)
Ethnicity						
Non-White	17040	18	1.00 (reference)	4523	2	1.00 (reference)
White	172980	291	1.53 (0.94–2.47)	47417	51	2.55 (0.40–16.37)
Marital status						
No partner	105245	158	1.00 (reference)	14534	15	1.00 (reference)
Married or living with a partner	85813	152	1.21 (0.96–1.52)	37342	38	1.11 (0.59–2.09)
Education						
<12 years	11529	16	1.00 (reference)	2665	3	1.00 (reference)
12 years/high school	48682	89	1.25 (0.73–2.14)	14490	17	1.00 (0.29–3.45)
Post high school training	20627	28	0.94 (0.51–1.76)	6851	3	0.40 (0.08–2.00)
Some college	47824	79	1.16 (0.67–2.01)	11877	14	1.08 (0.30–3.82)
Tertiary – had a university degree	58004	101	1.22 (0.71–2.09)	15981	16	0.89 (0.25–3.16)

Table 5.15: Risk of glioma in relation to anthropometric, socio-demographic, and lifestyle factors in women in the NIH-AARP Study and the PLCO Study (continued)

Risk factors	NIH-AARP			PLCO		
	No. of women	No. of cases	RR (95% CI)	No. of women	No. of cases	RR (95% CI)
Parity						
Nulliparous	28952	53	**1.00** (reference)	3800	7	**1.00** (reference)
Parous	161804	260	**0.87 (0.64–1.18)**	48060	46	**0.57 (0.25–1.32)**
Oral contraceptive use						
Never	113838	202	**1.00** (reference)	23063	34	**1.00** (reference)
Ever	76152	109	**0.81 (0.63–1.04)**	28835	19	**0.51 (0.28–0.94)**
Menopausal hormone use						
Never user	89368	144	**1.00** (reference)	16238	15	**1.00** (reference)
Past user	17250	31	**1.13 (0.76–1.67)**	8172	6	**0.89 (0.34–2.30)**
Current user	85766	140	**1.01 (0.79–1.30)**	27247	32	**1.73 (0.90–3.30)**

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6

Diet and Risk of Glioma in Three Cohorts in the UK and US

6.1 Introduction

Observational epidemiological studies have investigated risk of glioma in relation to at least 27 food groups or nutrients, as well as the Dietary Approaches to Stop Hypertension (DASH) score, dietary nitrate, nitrite, aspartame, acrylamide, and haem iron, but no firm conclusions could be drawn for any particular dietary factors (see Chapter 3). The majority of published evidence came from studies with retrospective collection of dietary data, which is a particular problem for the study of glioma, because glioma may impair cognitive function and is rapidly fatal. Prospective studies have published evidence for 12 out of the 27 food groups or nutrients only, and were also limited by the small number of studies with few exposed cases for each particular dietary factor, and the inability to take account of reverse causality between diet and glioma.

In this chapter, I report on the association between diet and risk of glioma, combining data from one large cohort of UK women (the Million Women Study) and two large cohorts of US men and women (the National Institutes of Health [NIH]-AARP [formerly the American Association of Retired Persons]) Study and the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial [the PLCO Study]). In order to provide an overview for the risk of glioma in relation to diet (covering major components), I examined 26 out of the 27 food groups or nutrients that were discussed in Chapter 3 (non-saturated fat, which is non-specific was not examined), plus carbohydrate, monounsaturated fat, and polyunsaturated fat. Because foods and beverages are consumed in combination, I also investigated the associations of 3 common dietary patterns and risk of glioma. In summary, risk of glioma in relation to the 29 food groups and nutrients (total fruit, citrus fruit, fruit juice, total vegetables, nuts, grains/cereal, red meat, processed meat, white meat, fish, egg, dairy products, cheese, coffee, tea, carbohydrate, protein, total fat [saturated, monounsaturated, and polyunsaturated], fibre, carotene, vitamin C, vitamin E, folate, calcium, cholesterol, alcohol) and 3 dietary patterns (the DASH score, the alternate Mediterranean diet score, and the Alternative Healthy Eating Index) was

examined. Meta-analyses combining the results from the 3 studies examined in this chapter with those from relevant published prospective studies, were also performed.

6.2 Methods

The methods of recruitment, data collection, follow-up, development of dietary variables, and ascertainment of glioma for the Million Women Study, and for the NIH-AARP and PLCO Study have been described in detail in Chapters 4 and 5, respectively.

6.2.1 Exposure variables

Daily intakes of food groups and nutrients were derived from information collected through dietary questionnaires. In the NIH-AARP Study and the PLCO Study, intake was assumed zero when information reported by participants was missing whereas in the Million Women Study, intake remained missing when reported information was missing. Daily intakes of the 29 food groups and nutrients were standardised to 1600 kcal/day in women and to 2000 kcal/day in men (intakes of carbohydrate, protein, total fat and fat subtypes were expressed as percentage energy intake from these nutrients) (see Chapters 4 and 5 for details). Energy-standardised-intakes or percentage energy from intakes of food groups or nutrients were used in all analyses reported here unless otherwise specified. These energy-standardised dietary intakes were also used to derive the DASH score (8 dietary components with a total of 8–40 points), the alternate Mediterranean Diet (aMED) score (9 dietary components with a total of 0–9 points), and the Alternative Healthy Eating Index (AHEI) (11 dietary components with a total of 0–110 points) previously described in Chapter 4 (section 4.4.4.2). Participants in each study (stratified by sex) were categorised into fourths according to their intakes at baseline of the 29 food groups and nutrients, the DASH score, and the AHEI. For the aMED score, participants were categorised into four categories: 0–2, 3–4, 5–6, and 7–9 points.

6.2.2 Outcome

The outcome of interest was glioma. This was ascertained by combining ICD-10 codes for central nervous system (CNS) tumours (C70–C72, C75.1–C75.3, D32–D33, D35.2–35.4, D42–D43, D44.3–D44.5) and ICD-O-2 (PLCO Study) or ICD-O-3 (Million Women and NIH-AARP Study) morphology codes for glioma (9380.3–9460.3).

6.2.3 Statistical analysis

In the Million Women Study, women were excluded under standard rules if they had no corresponding follow-up information, or had missing information on date of birth, date of follow-up, or date of dietary assessment. In the NIH-AARP Study, participants were excluded under standard rules if information about participants was provided by proxy respondents, or they had missing information on follow-up, or had conflicted information on sex, or on cancer diagnosis (e.g. had a cancer diagnosis from death records but not cancer registries). In the PLCO Study, participants were excluded under standard rules if they had missing information on follow-up time. Participants in all three studies were excluded from these analyses if they had been diagnosed with any invasive cancer (ICD-10: C00–C97) other than non-melanoma skin cancer (ICD-10: C44) prior to dietary assessment, or if they reported an implausible energy intake through the baseline dietary questionnaire (<500 or >3500 kcal/day in women; <800 or >4200 kcal/day in men). In the Million Women Study, women were also excluded if they had been diagnosed with any benign CNS tumours (ICD-10: D32–D33, D35.2–35.4, D42–D43, D44.3–D44.5) or neurofibromatosis (ICD-10: Q85.0) or tuberous sclerosis (ICD-10: Q85.1) or reported having changed their diet because of illness within 5 years prior to dietary assessment (to reduce the impact of reverse causation because participants may have changed their diet as a result of preclinical disease). Equivalent information was not available in the NIH-AARP Study and the PLCO Study.

The remaining study participants contributed person-years from the date of completing dietary assessment until date of registration of glioma, date of registration of other malignant cancers except non-melanoma skin cancer (also the date of any benign CNS tumour in the Million Women Study), date of death, date of loss to follow-up, or last date of follow-up (31 December 2015 in the Million Women Study; 31 December 2011 in the NIH-AARP Study; and 31 December 2009 in the PLCO Study), whichever was earliest. The proportions of loss to follow-up were about 1% in the Million Women Study (by the end of follow-up)[1], 2% in the NIH-AARP Study (during the first 3 years into the study)[2] (both mainly due to emigration to areas not covered by study cancer registries), and about 4% in the PLCO Study (by the end of follow-up) (mainly due to the lack of response to the annual questionnaire which asked about current health status)[3].

Initial results were calculated for each study (as described below) and for men and women separately to explore potential differences and to take account of differences in study design. However, there was little heterogeneity of results by study and by sex as assessed by a χ^2 test and I^2 statistics (Table 6.2), so the results were combined for the main analyses. Summary RRs for each dietary factor were derived using inverse-variance-weighted meta-analysis of the individual study results.

For each of the three studies, RRs and 95% confidence intervals (CIs) for glioma in relation to the 29 food groups or nutrients and 3 dietary patterns were calculated using Cox regression models with time in the study as the underlying time variable. RRs were calculated using the lowest fourth category as the reference group (the group with 0–2 points for the aMED score). Analyses were conducted using the multivariate nutrient density method[4], in which energy-standardised dietary intakes (and dietary patterns derived using energy-standardised intakes) were used as the primary exposures and dietary energy intake was added into the statistical model in addition to other relevant adjustment variables. This method partly reduces error related to reporting of dietary intakes (primary exposures), and the coefficient for the primary exposure in the statistical model has a substitution

interpretation (e.g. the effect of an increase in intake of 1 unit of the primary exposure while maintaining the total energy intake constant).[4] For these analyses, to allow any two exposure categories to be compared (even if neither is the reference group), RRs were treated as floated absolute risks and group-specific confidence intervals (gs-CIs) were estimated[5, 6] and are presented in figures. Conventional 95% CIs are given in tables and in the text. There was no strong evidence to suggest that the proportional hazards assumption was violated, as assessed by tests based on Schoenfeld residuals.

In the Million Women Study, for analyses of the 3 dietary patterns, linear trend across the four categories of scores was assessed by Wald's test statistics by modelling the baseline categorical variables as continuous variables in the model. For the analyses of the 29 food groups and nutrients, to correct for regression dilution bias, which may result in biased estimates of a linear association,[7] linear trend was estimated using re-measured dietary intakes collected from the Oxford WebQ. This was achieved by substituting the mean intakes of the food groups and nutrients by levels of consumption in fourths at baseline with means of re-measured dietary intakes from participants from the same baseline consumption categories who subsequently completed the Oxford WebQ. The mean dietary intakes of women who responded to the Oxford WebQ were shown to be representative of all women in the cohort (see Chapter 4 section 4.4.5.3). In the Million Women Study, analyses were stratified by year of birth and year of dietary assessment, and adjusted for standard variables: height ($<$160, 160–164.9, 165–169.9, $\geq$170 cm), body mass index ($<$25, 25–29.9, $\geq$30 kg/m^2), strenuous exercise (never/rarely, $<$1, $\geq$1 times per week), social deprivation (thirds based on Townsend deprivation index), smoking status (never, past, current), alcohol intake ($<$1, $\geq$1 drinks per day) (except for the analysis of alcohol and glioma risk), parity (nulliparous, parous), oral contraceptive use (never, ever), use of menopausal hormones (never, past, current), and region of residence (nine geographical regions in England, plus Scotland). In this thesis, all nutritional epidemiological analyses were further adjusted for total energy intake (fourths) (for the multivariate nutrient density method) and level of educational

attainment (<12 years, secondary, tertiary – had a university degree) because it was shown to be a potential confounder of the association in Chapters 4–5.

In the NIH-AARP Study and the PLCO Study, linear trend was estimated using baseline dietary intake data for all food groups and nutrients (continuous) and dietary patterns (similarly modelling the categorical variables as continuous variables) because no re-measured values were available. All analyses in both studies were stratified by sex, and adjusted for dietary energy intake (sex-specific fourths) (for the multivariate nutrient density method), level of educational attainment (<12 years, secondary, tertiary) (as a potential confounder), and standard adjustment variables in both studies as described below: age at baseline (continuous), height (in men: <175, 175–179.9, 180–184.9, ≥185 cm; in women: <160, 160–164.9, 165–169.9, ≥170 cm), body mass index (BMI <25, 25–29.9, ≥30 kg/m^2), ethnicity (non-Hispanic Whites, others), marital status (married/living with a partner, others), smoking status (never, past, current), alcohol intake (<1, ≥1 drinks per day) (except for the analysis of alcohol and glioma risk), region of residence (8 states in the NIH-AARP Study; 10 states in the PLCO Study); with additional adjustment for for parity (nulliparous, parous), oral contraceptive use (never, ever), and use of menopausal hormones (never, past, current) in women. In the NIH-AARP Study, all analyses were also adjusted for strenuous exercise (never/rarely, <1, ≥1 times per week), which is not available in the PLCO Study.

In all three studies, participants with a missing value for any of the adjustment variables were assigned a separate category for that variable to ensure that the same participants were compared in all analyses. Information was either missing or reported as unknown for <4% of participants for each of the adjustment variables in the Million Women Study apart from BMI (7.5%) and alcohol intake (12.4%).

In order to control the risk of type I error due to multiple testing, a Bonferroni correction[8] was applied by multiplying nominal p values by 32 (the total number of dietary factors assessed). Statistical significance was defined as a two-sided p value of less than 0.05 after applying the Bonferroni correction. All analyses were

also stratified by follow-up time (<5 and ≥5 years) to assess potential biases related to changes of diet before ascertainment of glioma.

6.2.4 Meta-analysis of results from the current analysis and published reports

Published prospective studies for risk of glioma in relation to dietary factors were identified from a systematic search on Medline and Embase databases up to 1 May 2018 (see Chapter 3). Prospective studies were those in which dietary information was provided before the onset of glioma. For dietary factors for which evidence was available from published prospective studies which have a minimum of 5 exposed glioma cases, meta-analyses were conducted combining the most informative and independent published evidence with results from the current three prospective studies. RRs which compared groups with the highest intake against those with the lowest intake for each particular dietary factor in each study were combined using inverse-variance-weighted meta-analysis. Heterogeneity of results between studies was assessed by a χ^2 test and I^2 statistics.

All analyses were performed in Stata Statistical Software: Release 15 (StataCorp, College Station, TX USA). Figures were drawn in R version 3.3.3 (The R Foundation for Statistical Computing).

6.3 Results

6.3.1 Study populations and baseline characteristics for the three studies

Figure 6.1 shows three flowcharts describing exclusions of study participants in the 3 prospective studies. This analysis included 692,176 women in the Million Women Study, 470,780 participants (277,906 men and 192,874 women) in the NIH-AARP Study, and 99,148 participants (47,196 men and 51,952 women) in the PLCO Study. A total of 1,173 gliomas were registered after a mean 12.7-year follow up in the

Million Women Study (8.8 million person-years); 1,005 gliomas were registered after a mean 12.3-year follow-up in the NIH-AARP Study (5.8 million person-years); and 135 gliomas were ascertained after a mean 7.9-year of follow-up in the PLCO Study (0.8 million person-years). Table 6.1 shows the baseline characteristics, dietary energy intake, and intakes of energy contributing macronutrients for each of the study populations. When compared with participants in the Million Women Study, participants in the two US prospective studies were more likely to have had tertiary education, had somewhat higher BMIs and the women were more likely to be current users of hormone replacement therapy. Participants in the two US studies had similar sex-specific mean dietary energy intakes and percentage energy intakes from carbohydrate, protein, and total fat, whereas women in the Million Women Study reported a higher mean dietary energy intake with higher percentage energy intake from total fat and lower percentage energy intake from carbohydrate (Supplementary Table B.7 and B.8 in Appendix B shows all dietary factors assessed in this chapter for men and women, respectively).

6.3.2 Combined analysis of the three prospective studies

The combined analysis showed no significant associations between the 29 food group or nutrient factors or the 3 dietary patterns and risk of glioma after applying a Bonferroni correction for multiple testing. Before correction, there was some weak evidence for associations between risk of glioma and increasing consumption of some dietary items (including mostly plant-based foods [e.g. total fruit] or nutrients abundantly found in plant-based foods [e.g. fibre]), or healthy dietary patterns (such as those measured by high DASH score), as described below. Adjustment for each of the potential confounding variables made little or no difference to the RRs estimated.

Figures 6.2 and 6.3 show linear trends for glioma risk (summary RRs) associated with 29 food groups and nutrients, respectively, and Figure 6.4 shows summary RRs associated with dietary pattern scores (categorical), each combining results from the three prospective studies. Overall, without multiple testing correction, there

was some evidence for increased glioma risks associated with increasing intakes of total fruit (RR per 100g increase 1.03, 95% CI 1.00–1.06, $p_{uncorrected}$ for trend = 0.048), citrus fruit (RR per 50g increase 1.04, 95% CI 1.00–1.08, $p_{uncorrected}$ for trend = 0.043), carbohydrate (RR per 1% energy intake increase 1.01, 95% CI 1.00–1.01, $p_{uncorrected}$ for trend = 0.033), or fibre (RR per 5g increase 1.08, 95% CI 1.02–1.15, $p_{uncorrected}$ for trend = 0.008), or high versus low DASH score (RR 1.19, 95% CI 1.05–1.34, $p_{uncorrected}$ = 0.006), aMED score (RR 1.24, 95% CI 1.05–1.46, $p_{uncorrected}$ = 0.012), or AHEI (RR 1.14, 95% CI 1.01–1.28, $p_{uncorrected}$ = 0.037) (Figures 6.2–6.4 left panel). Similar results were seen when the risk of glioma was estimated using intakes of food groups or nutrients in fourths rather than examining linear trends (Table 6.2 left panel). When combining results from the three studies, the only difference between studies was among RRs comparing highest versus lowest fourth for cholesterol intake (I^2 = 63.5%, χ^2=11.0, df=4, p=0.027) (Table 6.2 left panel). Results for each of the prospective studies are in Supplementary Figures B.12–B.16 in Appendix B.

Sensitivity analyses were conducted to assess whether finer adjustment for covariates such as energy intake, height, and/or BMI (in continuous rather than categorical form) changed the results but this had little or no effect on the results. Sensitivity analyses were also conducted to assess the change in association when any two potentially correlated dietary factors were mutually adjusted for each other in the statistical model; even before correction for multiple testing, none of the dietary factors remained statistically significant and the log of RRs attenuated markedly (e.g. log of RRs for fibre intake and DASH score attenuated >20% when mutually adjusted for each other).

In the analyses stratified by follow-up time (<5, ≥5 years), there were some notable differences of results between the two time periods. In particular, potential associations with dietary factors found in the analyses using all follow-up time remained statistically significant (before correction for multiple testing only) in analyses including the first 5 years of follow-up (having about a third of all glioma

cases), but not in analyses including ≥5 years of follow-up (having about two thirds of all glioma cases), as described below.

In analyses including the first 5 years of follow-up only, there was some evidence for increased glioma risks associated with increasing intakes of total fruit (RR per 100g increase 1.06, 95% CI 1.02–1.11, $p_{uncorrected}$ for trend = 0.008), citrus fruit (RR per 50g increase 1.06, 95% CI 1.00–1.13, $p_{uncorrected}$ for trend = 0.035), grains/cereal (RR per 50g increase 1.08, 95% CI 1.01–1.16, $p_{uncorrected}$ for trend = 0.029), or fibre (RR per 5g increase 1.13, 95% CI 1.02–1.24, $p_{uncorrected}$ for trend = 0.015), and high versus low DASH score (RR 1.38, 95% CI 1.12–1.71, $p_{uncorrected}$ = 0.003), aMED score (RR 1.37, 95% CI 1.03–1.81, $p_{uncorrected}$ = 0.028), or AHEI (RR 1.31, 95% CI 1.07–1.61, $p_{uncorrected}$ = 0.010); and for decreased glioma risks associated with increasing intakes of red meat (RR per 50g increase 0.86, 95% CI 0.75–0.98, $p_{uncorrected}$ for trend = 0.026) (Figures 6.2–6.4 and Table 6.2 middle panels).

In analyses excluding the first 5 years of follow-up, there was little or no association between any food groups, nutrients, or dietary patterns and risk of glioma, and there was a tendency for the point estimates of the summary RRs for the associations reported earlier to move towards 1.00: total fruit (RR per 100g increase 1.01, 95% CI 0.97–1.05, $p_{uncorrected}$ for trend = 0.562), citrus fruit (RR per 50g increase 1.03, 95% CI 0.98–1.08, $p_{uncorrected}$ for trend = 0.309), grains/cereal (RR per 50g increase 1.00, 95% CI 0.94–1.07, $p_{uncorrected}$ for trend = 0.978), red meat (RR per 50g increase 1.01, 95% CI 0.92–1.10, $p_{uncorrected}$ for trend = 0.908), carbohydrate (RR per 1% energy intake increase 1.01, 95% CI 1.00–1.02, $p_{uncorrected}$ for trend = 0.190), or fibre (RR per 5g increase 1.06, 95% CI 0.98–1.14, $p_{uncorrected}$ for trend = 0.121), and high versus low DASH score (RR 1.10, 95% CI 0.95–1.28, $p_{uncorrected}$ = 0.197), aMED score (RR 1.17, 95% CI 0.95–1.45, $p_{uncorrected}$ = 0.132), or AHEI (RR 1.06, 95% CI 0.91–1.23, $p_{uncorrected}$ = 0.478) (Figures 6.2–6.4 and Table 6.2 right panels). Results for analyses stratified by follow-up time were similar when the risk of glioma was estimated using intakes of food groups or nutrients in fourths rather than examining linear trends (Table 6.2 middle and right panels).

When combining results from the three studies that were stratified by follow-up time, there was some evidence for heterogeneity of results for a few dietary factors only: among RRs from analyses including the first 5 years for cheese (I^2 = 68.6%, χ^2=12.7, df=4, p=0.013); and among RRs from analyses excluding the first 5 years of follow-up for red meat (I^2 = 74.8%, χ^2=15.9, df=4, p=0.003), dairy products (I^2 = 62.5%, χ^2=10.7, df=4, p=0.030), and calcium (I^2 = 65.7%, χ^2=11.7, df=4, p=0.020) (Table 6.2 middle and right panels). Results for each of the prospective studies stratified by follow-up time are in Supplementary Figures B.12–B.16 in Appendix B.

6.3.3 Diet and risk of glioma: meta-analysis of all available prospective evidence

Independent evidence from published prospective studies was found for 11 dietary factors: fruit (1 study)[9], citrus fruit (2 studies)[9, 10], vegetables (1 study)[9], red meat (2 studies)[11, 12], processed meat (2 studies)[11, 12], tea (3 studies)[13–15], coffee (3 studies)[13, 14, 16], alcohol (2 studies)[16, 17], vitamin C (1 study)[11], vitamin E (1 study)[11], and carotene (1 study)[9] (Figure 6.5). None of the published studies had reported results that were stratified by follow-up time, so results extracted from published studies were combined with results from analyses of all follow-up time of all participants in the three studies here. However, the number of exposed cases in each of the published prospective studies was small (n≤155), so the inclusion of published prospective studies adds little to the evidence already presented here. Summary RRs (combining the RR which compared highest versus lowest intake in each study) for glioma in relation to the 11 dietary factors were: alcohol (1.04, 95% CI 0.93–1.17), total fruit (1.19, 95% CI 1.06–1.33), citrus fruit (1.14, 95% CI 1.02–1.27), total vegetables (1.16, 95% CI 1.03–1.30), red meat (0.95, 95% CI 0.85–1.06), processed meat (0.92, 95% CI 0.82–1.03), tea (0.99, 95% CI 0.89–1.11), coffee (1.00, 95% CI 0.89–1.12), vitamin C (1.04, 95% CI 0.93–1.16), vitamin E (1.03, 95% CI 0.92–1.15), and carotene (1.14, 95% CI 1.01–1.28) (Figure **??**). There was no significant heterogeneity for RRs in relation to any of the 11 dietary factors between the Million Women Study, the NIH-AARP

Study, the PLCO Study, and the published literature when their results were combined using meta-analysis.

6.4 Discussion

Prospective evidence from a systematic investigation into diet using combined data from three large studies in the UK and the US shows little evidence for an association between diet and risk of glioma. In analyses without correction for multiple testing, there were some generally borderline significant associations, namely increased risks of glioma in relation to increasing intakes of plant-based products including total fruit, citrus fruit, carbohydrate, and fibre, or of high DASH score, aMED score, or AHEI when compared to low intake or low score, but none of these associations remained statistically significant after applying a Bonferroni correction. Exploratory analyses showed limited heterogeneity of results between studies and between sexes, confirming the validity of combining results from the three studies for maximum statistical power. My analyses were able to take into account major confounding factors and to address possible reverse causation bias.

The analyses reported in this chapter contribute substantially to the current evidence. My analysis is based on more than double the number of exposed cases than the current available prospective evidence for all 12 dietary factors (total fruit, citrus fruit, fruit juice, total vegetables, red meat, processed meat, alcohol, coffee, tea, carotene, dietary vitamin C, and dietary vitamin E); provides the first prospective evidence for 18 dietary factors (nuts, grains/cereal, white meat, fish, eggs, dairy products, cheese, carbohydrate, protein, total fat, saturated fat, monounsaturated fat, polyunsaturated fat, fibre, folate, calcium, cholesterol, and DASH score); and provides novel and prospective evidence for 2 dietary patterns (aMED score and AHEI). However, it is important to note that there are previous publications on diet and risk of glioma from all three studies: the NIH-AARP Study has previously published on 10 dietary factors (total fruit, fruit juice, total vegetables, red meat, processed meat, alcohol, coffee, tea, vitamin C, and vitamin

E)[18–22]; the PLCO Study has published on coffee and tea[23]; and the Million Women Study has published on alcohol and risk of glioma[24]. So the addition to the current evidence for these dietary factors mainly comes from new cases accrued since these papers were published and/or from the other (one or two) prospective studies. With more exposed glioma cases, results generated from the analyses in this chapter are consistent with the null or non-significant results shown in previously published reports using data from these three prospective studies, and are generally consistent with those from other small prospective studies (exposed glioma cases $\leq$155 in each study) which have published on diet and risk of glioma (Figure 6.5). None of the small prospective studies were able to take account of reverse causation, so their results can be difficult to interpret, although the inclusion of independent evidence from these small studies did not add much to the total evidence now available, as seen in Figure 6.5.

Results generated in this chapter are not entirely consistent with those reported in studies with retrospective collection of dietary data. Retrospective studies have reported significant associations between: high intake of total vegetables or carotene or high DASH score and decreased risks of glioma; and high intakes of grains/cereal or dairy products and increased risks of glioma (see Chapter 3). I did not find any evidence that supports these associations in the analyses presented in this chapter. However, it is not known to what extent these results were subject to selective reporting commonly seen in nutritional epidemiology studies[25] as well as differential recall of dietary exposure or inaccurate recall caused by underlying glioma which may impair cognitive function. Besides, glioma is rapidly fatal so the reliance on proxy respondents in these studies was high (range 8%–76% in the 8 studies that reported this information)[26–33], making these results generally unreliable.

Some prospective studies (but not all) have reported significant associations between combined intakes of some foods or beverages and risk of glioma. In particular: significantly increased glioma risk in relation to high intake of total fruit and vegetables was found in the NIH-AARP Study[22] but not in the combined

analysis of the Health Professionals Follow-up Study (HPFS), the Nurses' Health Study I (NHS I), and the Nurses' Health Study II (NHS II)[9]; and significantly decreased glioma risk in relation to high intake of total coffee and tea was found in the combined analysis of the HPFS, the NHS I, and the NHS II[13] but not in the NIH-AARP Study[21] or the European Prospective Investigation into Cancer and Nutrition (EPIC) Study[14]. Combining results from the Million Women Study, the NIH-AARP Study, and the PLCO Study, statistically significantly increased risk of glioma was found for intake of total fruit and vegetables (summary RR comparing highest against lowest fourth 1.19, 95% CI 1.05–1.35) in the analysis of all follow-up time but not in the analysis excluding the first 5 years of follow-up (summary RR 1.12, 95% CI 0.96–1.30) (Supplementary Table B.9 in Appendix B). I found no significant association between total intake of coffee and tea and risk of glioma, either in analyses of all follow-up time (summary RR comparing highest against lowest fourth 1.10, 95% CI 0.97–1.25) or in analyses excluding the first 5 years of follow-up (summary RR 1.15, 95% CI 0.98–1.34) (Supplementary Table B.10 in Appendix B).

I have chosen to use a fairly stringent correction for multiple testing – the Bonferroni method.[8] In the case of no correction for multiple testing and using 0.05 as the critical significance level, the probability of getting at least one significant result in the analyses here is $1 - 0.95^{32} = 0.81$ while the expected number of spurious significant results is $32 \times 0.05 = 1.6$. Correcting nominal p values using the Bonferroni method allows the rate of type I error (falsely rejecting the null hypothesis) to remain at the 0.05 level.[8] However, there are two potential downfalls with the Bonferroni method: 1) it may overcorrect the associations under examination, thereby increasing the rate of type II error (failing to reject the null hypothesis); 2) it does not account for dependence between testing (correlations between dietary variables). For these reasons, I also explored other methods to account for multiple testing: 1) a less stringent correction method – the false discovery rate method with Benjamini-Hochberg procedures, which control the proportion of falsely rejected null hypotheses through sequential Bonferroni-type correction[34]; 2) a method correcting for multiplicity accounting for correlations between exposure variables

by adjusting for the number of 'effective exposures' calculated using a principal component regression (here, n=20 or n=25 explained >95% or >99% of the total variance in the dietary variables, respectively) rather than correcting for the total number of exposure variables.[35] Neither method changed the conclusion of the analyses presented here. It is not surprising that different methods of correction for multiple testing did not change the results because the present analysis did not find strong evidence for an association between any dietary factors and glioma risks even before correction (the two dietary factors with the strongest evidence to reject the null hypothesis were high DASH score and fibre with uncorrected p values of 0.006 and 0.008, respectively).

My results suggest that the associations observed between diet and risk of glioma before correction for multiple testing may be partly explained by reverse causation. The increased risks of glioma in participants with higher intakes of plant-based products or healthier dietary patterns remained statistically significant in analyses including the first 5 years of follow-up but not in analyses excluding the first 5 years of follow-up (having about two third of all glioma cases) in which there was a tendency for the point estimates to move towards null. It is important to note that the analyses that were stratified by time have weaker statistical power to detect associations than analyses using all follow-up time, and although there were some differences between the two time periods, the 95% CIs for the point estimates generally overlapped. About 14% of women in the Million Women Study who reported making major changes to their diet due to illness in the previous 5 years prior to baseline dietary assessment were excluded from these analyses, as another way to minimise reverse causation due to changes of diet related to preclinical disease, but this information is not available in the NIH-AARP Study and the PLCO Study. So, it is also important for future studies to collect this information and exclude participants who reported dietary changes at baseline to reduce the impact of reverse causation.

The increased risk of glioma associated with high folate intake particularly in women after excluding the first 5 years of follow-up may simply be a chance finding or may be due to ascertainment bias. A study in the US suggests that the higher glioma incidence in individuals with higher levels of education when compared to lower levels was more related to the diagnosis of tumour rather than inception.[36] Folate intake was higher in participants with tertiary education than those without in the NIH-AARP Study and the PLCO Study, and was higher in non-current smokers than current smokers in each of the three prospective studies. Besides, folate intakes were positively correlated with fibre intakes and DASH score (Spearman's correlation coefficient >0.5 and 0.4, respectively) in each of the three prospective studies. Women with high folate intake may be those who are more health conscious (highly educated, never-smokers, and/or eat a healthy diet), so may be subject to ascertainment bias.

Dietary intakes varied markedly by smoking status. To remove residual confounding and any ascertainment bias related to smoking status, sensitivity analyses were conducted in never smokers. The great majority of the RRs were not materially changed (results not shown).

6.4.1 Strengths and weaknesses

This analysis has several strengths. The three prospective studies have collected detailed information on diet and many other factors, allowing for a systematic investigation into diet and risk of glioma as well as for statistical adjustment for many potential confounding variables. The prospective collection of dietary data helps prevent differential recall of dietary intakes between participants with and without glioma, and avoids the use of proxy responders, which is usually common in glioma studies. The use of electronically linked health outcome data for ascertainment of glioma and for follow-up in the Million Women Study and the NIH-AARP Study reduces non-participation of individuals with rapidly fatal cancers or more aggressive cancers (the vast majority of diagnosed gliomas), who

may not otherwise be included in retrospective studies. In addition, the use of routinely collected health outcome data also minimises loss of participants to follow-up other than that due to emigration, which is low in the Million Women Study (1%) and the NIH-AARP Study (3%). Although electronically linked cancer data is not available for PLCO study participants, the various approaches used to ascertain incident cancer (including annual update questionnaires with only a 4% non-response rate during the entire follow-up period, cancer screening/diagnosis tests, death certificates, and NDI Plus search) minimises participants' being lost to follow-up. With the large sample size, number of cases, and the prospective nature of data collection, these analyses were able to explore the effect of excluding the first 5 years of follow-up to minimise the impact of potential reverse causality on the association between diet and risk of glioma.

The main limitation of the present analyses is that of statistical power. A true small to moderate increased or decreased risk associated with diet might not have been detected because of the relatively small number of cases, despite this study being by far the largest study for diet and risk of glioma, with over 1.2 million participants (over 0.9 million women and 0.3 million men) and 2,313 incident glioma cases (1541 cases in women, 774 cases in men) over about 15.4 million person-years of follow-up. The number of cases in this study is more than twice as many as the largest published prospective study, the NIH-AARP Study, which has previously published on risk of glioma in relation to 10 dietary factors included here as well as dietary nitrites and nitrates, aspartame, and acrylamide.[18–22, 37, 38] The number of cases in this study is also more than the largest study ever published on diet and risk of glioma (with about 1185 glioma cases), which is an international multicentre study with retrospective collection of dietary data coordinated by the International Agency for Research on Cancer.[33] This study has 80% power with 95% significance to detect an observed RR of $\leq$0.85 or $\geq$1.18 in analyses of all follow-up time, and of $\leq$0.82 or $\geq$1.12 in analyses excluding the first 5 years of follow-up. Even when allowance is made for measurement error, as described in Chapter 3, this analysis has 80% power with 95% significance to detect true RRs of less than 2, ($\leq$0.66 to $\leq$0.76

or ≥1.32 to ≥1.51 in analyses of all follow-up time, and ≤0.60 to ≤0.71 or ≥1.66 to ≥1.70 in analyses excluding the first 5 years of follow-up), allowing us to conclude that risks of potential public health significance should not have been missed. Power to detect 'true' risks was estimated using regression coefficients of 0.6–0.4, which were coefficients for the great majority of dietary data in the three studies.

Another limitation of this study is that information on dietary nitrite, particularly from plant sources, which was shown to be associated with increased risks of glioma in men in the NIH-AARP Study in a previously published report (p for trend across fifths = 0.003)22, is not available in the Million Women Study or the PLCO Study. Evidence for dietary nitrite and risk of glioma, thus, remains limited. With over 400 additional glioma cases accrued since the previous report, the significant linear association between plant-source nitrite and an increased glioma risk in men in the NIH-AARP Study was reproduced (p for trend across fifths = 0.036) (RR highest vs. lowest fifths: 1.37, 95% CI 1.05–1.79) (Supplementary Table B.11 in Appendix B). However, in analyses excluding the first 5 years of follow-up, there was no longer a linear association between plant-source nitrite and risk of glioma (p for trend across fifths = 0.273), and the RR for highest vs. lowest fifth attenuated noticeably (1.19, 95% CI 0.87–1.63). Hord *et al.* suggested that about 80% of dietary nitrate, which can be reduced into nitrite by commensal bacteria in the mouth and gastrointestinal tract, comes from vegetable intake.[39] Therefore, it is not unexpected that the results for dietary nitrite resemble that of total vegetables (RR for highest versus lowest fourth: all follow-up time 1.24, 95% CI 1.07–1.44; excluding first 5 years of follow-up 1.16, 95% CI 0.97–1.39).

6.4.2 Conclusion

This study, the largest prospective study to date, suggests that there is little evidence for an association between diet and risk of glioma. Analysis excluding the first 5 years of follow-up further strengthens this conclusion by reducing the impact of reverse causation. These conclusions are also reinforced by the limited

heterogeneity between men and women, and among the three prospective studies, regardless of differences in the populations studied (UK and US), the assessment of diet (different dietary questionnaires), and the statistical analysis models used (stratification of study populations and control for potential confounders). With the rarity of glioma, the statistical power of this study, and the systematic investigation into diet carried out in this study, which covers many major components of diet, it is unlikely that any association between diet and risk of glioma of major public health concern has been overlooked.

6.5 Tables

Table 6.1: Baseline characteristics of participants in the Million Women Study, the NIH-AARP Study, and the PLCO Study

	Million Women Study	NIH-AARP Study		PLCO Study	
	Women	Men	Women	Men	Women
Number of participants	692176	277906	192874	47196	51952
Characteristics at baseline					
Age, mean (SD)	59.4 (4.9)	61.6 (5.4)	61.3 (5.4)	65.8 (5.7)	65.3 (5.7)
Height (cm), mean (SD)	162.4 (6.5)	178.3 (7.5)	163.3 (6.9)	177.9 (6.9)	163.2 (6.5)
BMI (kg/m^2), mean (SD)	25.9 (4.4)	27.2 (4.3)	26.8 (6.0)	27.5 (4.1)	27.0 (5.4)
Alcohol intake (drink/day), mean (SD)	0.7 (0.8)	1.1 (2.1)	0.4 (1.0)	0.9 (1.8)	0.4 (0.8)
Least deprived third, n (%)	229126 (33.3)	n/a	n/a	n/a	n/a
Education - Tertiary, n (%)	109712 (16.2)	125373 (46.3)	58004 (31.1)	20023 (42.5)	15981 (30.8)
Race - White, non-Hispanic, n (%)	676318 (99.1)	258086 (93.9)	172980 (91.0)	42935 (91.0)	47417 (91.3)
Married/living with a partner, n (%)	550460 (81.0)	237155 (85.8)	85813 (44.9)	40251 (85.5)	37342 (72.0)
Strenuous exercise ≥1/week, n (%)	289676 (43.0)	198786 (71.5)	120105 (60.3)	n/a	n/a
Current smoker, n (%)	84540 (12.4)	28028 (10.5)	26954 (14.5)	4691 (9.9)	4377 (8.4)
Nulliparous, n (%)	78093 (11.3)	n/a	28952 (15.2)	n/a	3800 (7.3)
HRT current user, n (%)	189962 (28.1)	n/a	85766 (44.6)	n/a	27247 (52.7)
Ever use OC, n (%)	420220 (61.2)	n/a	76152 (40.1)	n/a	28835 (55.6)
Daily dietary intakes, mean (SD)					
Total energy (kcal)	1612 (430)	1974 (695)	1540 (576)	1970 (694)	1493 (541)
Carbohydrate (% energy)	47.3 (7.0)	48.1 (9.1)	51.1 (8.9)	47.1 (8.7)	50.2 (8.6)
Protein (% energy)	16.3 (2.6)	15.4 (3.1)	15.5 (3.2)	15.3 (2.9)	15.5 (2.9)
Total fat (% energy)	34.3 (6.1)	30.4 (7.6)	30.0 (7.7)	32.3 (7.4)	31.3 (7.6)

SD standard deviation, BMI body mass index, HRT hormone replacement therapy, OC oral contraceptives

Table 6.2: Risk of glioma in relation to diet: combined analysis of the Million Women Study, the NIH-AARP Study, and the PLCO Study

		All follow-up time						First 5 years of follow-up						5+ years of follow-up					
Dietary factor	**Intake category**	**No. of cases**	**Summary RR (95% CI)**	**P value**	**Heterogeneity**			**No. of cases**	**Summary RR (95% CI)**	**P value**	**Heterogeneity**			**No. of cases**	**Summary RR (95% CI)**	**P value**	**Heterogeneity**		
					I^2 (%)	**X^2**	**P value**				**I^2 (%)**	**X^2**	**P value**				**I^2 (%)**	**X^2**	**P value**
Total fruit	Lowest fourth	534	1.00 (reference)	n/a	n/a	n/a	n/a	168	1.00 (reference)	n/a	n/a	n/a	n/a	366	1.00 (reference)	n/a	n/a	n/a	n/a
	Second fourth	527	0.96 (0.85–1.08)	0.499	0.0	3.0	0.556	173	1.00 (0.80–1.24)	0.978	29.8	5.7	0.223	354	0.94 (0.81–1.09)	0.423	0.0	3.6	0.468
	Third fourth	572	1.03 (0.91–1.17)	0.605	0.0	2.9	0.579	209	1.17 (0.95–1.45)	0.132	0.0	1.7	0.793	363	0.97 (0.83–1.12)	0.667	0.0	2.6	0.626
	Highest fourth	635	1.17 (1.03–1.32)	0.012	10.6	4.5	0.346	217	1.23 (0.99–1.52)	0.056	14.5	4.7	0.322	418	1.14 (0.98–1.32)	0.090	0.0	1.0	0.917
	Linear trend (per 100g)	*2268*	*1.03 (1.00–1.06)*	*0.048*	*28.5*	*5.6*	*0.232*	*767*	*1.06 (1.02–1.11)*	*0.008*	*30.2*	*5.7*	*0.221*	*1501*	*1.01 (0.97–1.05)*	*0.562*	*0.0*	*3.5*	*0.481*
Citrus fruit	Lowest fourth	605	1.00 (reference)	n/a	n/a	n/a	n/a	197	1.00 (reference)	n/a	n/a	n/a	n/a	408	1.00 (reference)	n/a	n/a	n/a	n/a
	Second fourth	418	0.87 (0.77–0.99)	0.039	0.0	2.5	0.638	142	0.89 (0.72–1.11)	0.310	0.0	0.9	0.927	276	0.86 (0.74–1.01)	0.072	14.2	4.7	0.324
	Third fourth	584	1.06 (0.94–1.19)	0.337	0.0	1.5	0.826	196	1.07 (0.87–1.31)	0.520	0.0	1.2	0.882	388	1.05 (0.91–1.21)	0.473	0.0	3.7	0.443
	Highest fourth	617	1.13 (1.00–1.26)	0.043	0.0	1.1	0.898	218	1.16 (0.95–1.42)	0.144	21.3	5.1	0.279	399	1.11 (0.96–1.28)	0.148	0.0	3.4	0.492
	Linear trend (per 50g)	*2224*	*1.04 (1.00–1.08)*	*0.043*	*4.9*	*4.2*	*0.379*	*753*	*1.06 (1.00–1.13)*	*0.035*	*0.0*	*1.0*	*0.911*	*1471*	*1.03 (0.98–1.08)*	*0.309*	*35.9*	*6.2*	*0.182*
Fruit juice	Lowest fourth	514	1.00 (reference)	n/a	n/a	n/a	n/a	187	1.00 (reference)	n/a	n/a	n/a	n/a	327	1.00 (reference)	n/a	n/a	n/a	n/a
	Second fourth	550	1.05 (0.93–1.19)	0.421	0.0	0.7	0.947	185	0.97 (0.79–1.19)	0.759	0.0	0.6	0.959	365	1.10 (0.95–1.28)	0.220	0.0	0.6	0.961
	Third fourth	519	0.97 (0.86–1.10)	0.646	1.4	4.1	0.398	182	0.92 (0.74–1.13)	0.408	27.0	5.5	0.242	337	1.00 (0.86–1.17)	0.956	0.0	3.5	0.481
	Highest fourth	526	0.98 (0.87–1.11)	0.775	0.0	2.3	0.680	174	0.90 (0.73–1.12)	0.347	11.8	4.5	0.338	352	1.03 (0.88–1.20)	0.740	0.0	1.2	0.879
	Linear trend (per 100g)	*2109*	*1.00 (0.97–1.03)*	*0.879*	*0.0*	*2.3*	*0.685*	*728*	*0.96 (0.90–1.02)*	*0.160*	*0.0*	*2.1*	*0.718*	*1381*	*1.02 (0.98–1.06)*	*0.355*	*0.0*	*1.5*	*0.821*
Total vegetables	Lowest fourth	504	1.00 (reference)	n/a	n/a	n/a	n/a	167	1.00 (reference)	n/a	n/a	n/a	n/a	337	1.00 (reference)	n/a	n/a	n/a	n/a
	Second fourth	580	1.12 (0.99–1.26)	0.066	47.3	7.6	0.108	194	1.13 (0.91–1.39)	0.265	39.9	6.7	0.155	386	1.12 (0.96–1.29)	0.146	0.0	3.8	0.438
	Third fourth	598	1.15 (1.02–1.29)	0.024	0.0	1.7	0.784	203	1.16 (0.95–1.43)	0.153	0.0	3.2	0.531	395	1.14 (0.98–1.32)	0.088	0.0	2.3	0.689
	Highest fourth	595	1.16 (1.02–1.31)	0.020	0.0	3.2	0.526	207	1.20 (0.97–1.48)	0.087	25.2	5.3	0.254	388	1.13 (0.97–1.32)	0.105	0.0	1.6	0.800
	Linear trend (per 100g)	*2277*	*1.03 (0.99–1.06)*	*0.098*	*0.0*	*2.8*	*0.590*	*771*	*1.03 (0.98–1.09)*	*0.276*	*0.0*	*2.0*	*0.744*	*1506*	*1.03 (0.99–1.07)*	*0.194*	*0.0*	*1.8*	*0.780*
Nuts	Lowest fourth	701	1.00 (reference)	n/a	n/a	n/a	n/a	236	1.00 (reference)	n/a	n/a	n/a	n/a	465	1.00 (reference)	n/a	n/a	n/a	n/a
	Second fourth	468	1.14 (1.01–1.29)	0.034	0.0	3.7	0.449	160	1.08 (0.88–1.34)	0.449	25.0	5.3	0.255	308	1.18 (1.01–1.37)	0.034	40.6	6.7	0.151
	Third fourth	387	0.99 (0.87–1.13)	0.884	0.0	1.6	0.809	135	0.96 (0.76–1.20)	0.702	44.4	7.2	0.126	252	1.01 (0.86–1.20)	0.879	61.7	10.5	0.033
	Highest fourth	403	1.08 (0.94–1.23)	0.279	0.0	2.3	0.680	149	1.09 (0.88–1.36)	0.418	0.0	3.6	0.458	254	1.07 (0.91–1.27)	0.416	29.7	5.7	0.224
	Linear trend (per 10g)	*1959*	*1.03 (0.97–1.08)*	*0.353*	*0.0*	*2.6*	*0.619*	*680*	*1.04 (0.95–1.13)*	*0.397*	*0.0*	*2.4*	*0.659*	*1279*	*1.02 (0.95–1.09)*	*0.549*	*0.0*	*2.6*	*0.635*

Summary RRs were calculated using inverse-variance weighted meta-analysis combining fully-adjusted RRs from the Million Women Study, the NIH-AARP Study, and the PLCO Study. Heterogeneity of results between studies was assessed by a χ^2 test and I^2 statistics. All analyses were also stratified by follow-up time (<5 and ≥5 years) to explore potential reverse causation. All p values shown here were uncorrected.

Table 6.2: Risk of glioma in relation to diet: combined analysis of the Million Women Study, the NIH-AARP Study, and the PLCO Study (continued)

		All follow-up time						First 5 years of follow-up						5+ years of follow-up					
Dietary factor	**Intake category**	**No. of cases**	**Summary RR (95% CI)**	**P value**	**Heterogeneity**			**No. of cases**	**Summary RR (95% CI)**	**P value**	**Heterogeneity**			**No. of cases**	**Summary RR (95% CI)**	**P value**	**Heterogeneity**		
					I^2 (%)	**X^2**	**P value**				**I^2 (%)**	**X^2**	**P value**				**I^2 (%)**	**X^2**	**P value**
Grains/ cereal	Lowest fourth	543	1.00 (reference)	n/a	n/a	n/a	n/a	180	1.00 (reference)	n/a	n/a	n/a	n/a	363	1.00 (reference)	n/a	n/a	n/a	n/a
	Second fourth	566	1.01 (0.90–1.14)	0.875	0.0	1.4	0.847	189	1.00 (0.81–1.23)	0.991	0.0	3.9	0.419	377	1.01 (0.88–1.17)	0.864	0.0	2.8	0.593
	Third fourth	572	1.00 (0.89–1.13)	0.972	37.9	6.4	0.168	193	1.00 (0.82–1.24)	0.965	0.0	2.5	0.645	379	1.00 (0.86–1.16)	0.997	21.6	5.1	0.277
	Highest fourth	617	1.08 (0.96–1.22)	0.204	38.6	6.5	0.164	215	1.10 (0.89–1.35)	0.365	55.2	8.9	0.063	402	1.07 (0.92–1.24)	0.369	0.0	1.9	0.763
	Linear trend (per 50g)	*2298*	*1.03 (0.98–1.08)*	*0.205*	*0.0*	*0.7*	*0.947*	*777*	*1.08 (1.01–1.16)*	*0.029*	*0.0*	*3.1*	*0.538*	*1521*	*1.00 (0.94–1.07)*	*0.978*	*0.0*	*0.8*	*0.932*
Red meat	Lowest fourth	573	1.00 (reference)	n/a	n/a	n/a	n/a	200	1.00 (reference)	n/a	n/a	n/a	n/a	373	1.00 (reference)	n/a	n/a	n/a	n/a
	Second fourth	607	1.05 (0.93–1.18)	0.426	56.5	9.2	0.056	210	1.02 (0.84–1.24)	0.849	30.0	5.7	0.221	397	1.06 (0.92–1.23)	0.401	15.0	4.7	0.319
	Third fourth	533	0.93 (0.82–1.05)	0.223	28.0	5.6	0.235	190	0.93 (0.76–1.14)	0.501	0.0	3.7	0.446	343	0.92 (0.80–1.07)	0.297	0.0	2.5	0.644
	Highest fourth	530	0.94 (0.83–1.06)	0.307	28.5	5.6	0.232	161	0.81 (0.66–1.01)	0.058	0.0	0.6	0.963	369	1.00 (0.86–1.16)	0.968	65.4	11.6	0.021
	Linear trend (per 50g)	*2243*	*0.94 (0.87–1.02)*	*0.133*	*0.0*	*3.4*	*0.487*	*761*	*0.86 (0.75–0.98)*	*0.026*	*0.0*	*1.8*	*0.766*	*1482*	*1.01 (0.92–1.10)*	*0.908*	*74.8*	*15.9*	*0.003*
Processed meat	Lowest fourth	657	1.00 (reference)	n/a	n/a	n/a	n/a	239	1.00 (reference)	n/a	n/a	n/a	n/a	418	1.00 (reference)	n/a	n/a	n/a	n/a
	Second fourth	500	1.03 (0.91–1.16)	0.644	0.0	1.5	0.831	159	0.87 (0.71–1.07)	0.178	0.0	3.4	0.498	341	1.12 (0.97–1.30)	0.122	0.0	3.3	0.514
	Third fourth	582	1.01 (0.90–1.13)	0.835	0.0	2.0	0.728	193	0.90 (0.74–1.09)	0.286	0.0	3.5	0.483	389	1.08 (0.93–1.24)	0.306	0.0	1.7	0.783
	Highest fourth	504	0.89 (0.79–1.00)	0.057	0.0	2.8	0.592	170	0.80 (0.65–0.98)	0.030	0.0	2.7	0.617	334	0.95 (0.82–1.09)	0.453	33.0	6.0	0.202
	Linear trend (per 10g)	*2243*	*0.98 (0.95–1.01)*	*0.216*	*0.0*	*2.2*	*0.706*	*761*	*0.97 (0.92–1.03)*	*0.339*	*24.3*	*5.3*	*0.260*	*1482*	*0.99 (0.95–1.03)*	*0.538*	*0.0*	*3.7*	*0.444*
White meat	Lowest fourth	552	1.00 (reference)	n/a	n/a	n/a	n/a	195	1.00 (reference)	n/a	n/a	n/a	n/a	357	1.00 (reference)	n/a	n/a	n/a	n/a
	Second fourth	594	1.06 (0.94–1.19)	0.326	0.0	4.0	0.406	200	1.01 (0.83–1.23)	0.909	0.0	1.8	0.775	394	1.09 (0.94–1.26)	0.260	0.0	3.0	0.553
	Third fourth	564	1.01 (0.89–1.13)	0.916	42.6	7.0	0.137	176	0.91 (0.74–1.12)	0.376	0.0	1.8	0.773	388	1.06 (0.91–1.22)	0.454	34.0	6.1	0.195
	Highest fourth	533	0.96 (0.85–1.09)	0.529	0.0	1.6	0.816	190	1.01 (0.82–1.25)	0.906	21.2	5.1	0.280	343	0.94 (0.80–1.09)	0.400	0.0	3.0	0.550
	Linear trend (per 50g)	*2243*	*0.97 (0.91–1.04)*	*0.375*	*0.0*	*0.7*	*0.947*	*761*	*1.01 (0.91–1.12)*	*0.884*	*42.4*	*6.9*	*0.139*	*1482*	*0.96 (0.89–1.05)*	*0.382*	*0.0*	*2.5*	*0.641*
Fish	Lowest fourth	542	1.00 (reference)	n/a	n/a	n/a	n/a	195	1.00 (reference)	n/a	n/a	n/a	n/a	347	1.00 (reference)	n/a	n/a	n/a	n/a
	Second fourth	589	1.07 (0.95–1.21)	0.256	58.4	9.6	0.047	205	1.04 (0.86–1.27)	0.673	25.3	5.4	0.253	384	1.09 (0.94–1.26)	0.268	42.1	6.9	0.141
	Third fourth	573	1.03 (0.92–1.16)	0.614	69.8	13.2	0.010	184	0.93 (0.76–1.14)	0.492	10.5	4.5	0.346	389	1.08 (0.94–1.26)	0.278	63.9	11.1	0.026
	Highest fourth	542	0.98 (0.87–1.11)	0.771	10.1	4.4	0.349	186	0.95 (0.77–1.16)	0.607	0.0	1.6	0.814	356	1.00 (0.86–1.16)	0.981	28.4	5.6	0.232
	Linear trend (per 50g)	*2246*	*0.97 (0.84–1.12)*	*0.701*	*12.8*	*4.6*	*0.332*	*770*	*1.00 (0.80–1.25)*	*0.991*	*26.4*	*5.4*	*0.245*	*1476*	*0.98 (0.82–1.17)*	*0.847*	*9.6*	*4.4*	*0.351*

Summary RRs were calculated using inverse-variance weighted meta-analysis combining fully-adjusted RRs from the Million Women Study, the NIH-AARP Study, and the PLCO Study. Heterogeneity of results between studies was assessed by a χ^2 test and I^2 statistics. All analyses were also stratified by follow-up time (<5 and ≥5 years) to explore potential reverse causation. All p values shown here were uncorrected.

Table 6.2: Risk of glioma in relation to diet: combined analysis of the Million Women Study, the NIH-AARP Study, and the PLCO Study (continued)

		All follow-up time						First 5 years of follow-up						5+ years of follow-up					
Dietary factor	**Intake category**	**No. of cases**	**Summary RR (95% CI)**	**P value**	**Heterogeneity**			**No. of cases**	**Summary RR (95% CI)**	**P value**	**Heterogeneity**			**No. of cases**	**Summary RR (95% CI)**	**P value**	**Heterogeneity**		
					I^2 (%)	**X^2**	**P value**				**I^2 (%)**	**X^2**	**P value**				**I^2 (%)**	**X^2**	**P value**
Eggs	Lowest fourth	567	1.00 (reference)	n/a	n/a	n/a	n/a	199	1.00 (reference)	n/a	n/a	n/a	n/a	368	1.00 (reference)	n/a	n/a	n/a	n/a
	Second fourth	535	0.93 (0.83–1.05)	0.256	0.0	1.1	0.901	187	0.92 (0.75–1.13)	0.446	6.0	4.3	0.372	348	0.94 (0.81–1.09)	0.411	0.0	2.8	0.600
	Third fourth	613	1.07 (0.95–1.20)	0.263	0.0	2.3	0.687	197	0.99 (0.81–1.21)	0.918	32.6	5.9	0.204	416	1.11 (0.97–1.28)	0.141	0.0	2.3	0.686
	Highest fourth	575	1.04 (0.92–1.17)	0.547	14.2	4.7	0.324	192	0.98 (0.80–1.20)	0.857	31.7	5.9	0.210	383	1.07 (0.92–1.24)	0.368	0.0	1.3	0.869
	Linear trend (per 10g)	*2290*	*0.99 (0.95–1.03)*	*0.762*	*51.3*	*8.2*	*0.084*	*775*	*0.98 (0.91–1.05)*	*0.507*	*43.4*	*7.1*	*0.132*	*1515*	*1.01 (0.96–1.06)*	*0.783*	*0.0*	*3.1*	*0.542*
Dairy products	Lowest fourth	552	1.00 (reference)	n/a	n/a	n/a	n/a	192	1.00 (reference)	n/a	n/a	n/a	n/a	360	1.00 (reference)	n/a	n/a	n/a	n/a
	Second fourth	587	1.01 (0.90–1.14)	0.819	54.5	8.8	0.067	207	1.03 (0.84–1.26)	0.765	25.9	5.4	0.249	380	1.00 (0.87–1.16)	0.987	33.4	6.0	0.198
	Third fourth	602	1.04 (0.92–1.16)	0.558	0.0	2.2	0.700	202	1.00 (0.82–1.23)	0.979	0.0	3.6	0.466	400	1.05 (0.91–1.21)	0.512	0.0	2.2	0.700
	Highest fourth	572	0.99 (0.87–1.11)	0.822	0.0	1.6	0.812	181	0.91 (0.73–1.12)	0.358	19.3	5.0	0.292	391	1.02 (0.88–1.19)	0.746	0.0	3.6	0.459
	Linear trend (per 100g)	*2313*	*1.00 (0.98–1.02)*	*0.959*	*3.5*	*4.1*	*0.386*	*782*	*1.01 (0.98–1.05)*	*0.409*	*0.0*	*1.8*	*0.772*	*1531*	*1.00 (0.97–1.02)*	*0.748*	*62.5*	*10.7*	*0.030*
Cheese	Lowest fourth	546	1.00 (reference)	n/a	n/a	n/a	n/a	184	1.00 (reference)	n/a	n/a	n/a	n/a	362	1.00 (reference)	n/a	n/a	n/a	n/a
	Second fourth	536	0.97 (0.86–1.09)	0.583	0.0	1.7	0.783	178	0.94 (0.76–1.16)	0.571	0.0	2.4	0.660	358	0.98 (0.85–1.14)	0.791	0.0	2.4	0.657
	Third fourth	534	0.96 (0.85–1.09)	0.541	0.0	1.1	0.890	179	0.96 (0.78–1.19)	0.725	0.0	1.6	0.800	355	0.96 (0.83–1.12)	0.637	13.6	4.6	0.327
	Highest fourth	591	1.07 (0.95–1.20)	0.264	0.0	3.3	0.505	210	1.14 (0.93–1.40)	0.216	60.2	10.1	0.039	381	1.04 (0.89–1.20)	0.643	0.0	2.5	0.638
	Linear trend (per 10g)	*2207*	*1.03 (0.96–1.11)*	*0.373*	*32.5*	*5.9*	*0.204*	*751*	*1.05 (0.94–1.18)*	*0.367*	*68.6*	*12.7*	*0.013*	*1456*	*1.02 (0.94–1.11)*	*0.602*	*0.0*	*1.6*	*0.816*
Alcohol	Lowest fourth	791	1.00 (reference)	n/a	n/a	n/a	n/a	274	1.00 (reference)	n/a	n/a	n/a	n/a	517	1.00 (reference)	n/a	n/a	n/a	n/a
	Second fourth	456	1.00 (0.89–1.13)	0.971	18.1	4.9	0.299	159	0.96 (0.78–1.19)	0.728	0.0	2.3	0.672	297	1.02 (0.88–1.19)	0.762	44.7	7.2	0.124
	Third fourth	554	1.05 (0.94–1.18)	0.386	0.0	0.7	0.947	171	0.91 (0.75–1.12)	0.382	0.0	2.2	0.694	383	1.13 (0.98–1.29)	0.093	0.0	0.3	0.987
	Highest fourth	512	1.02 (0.91–1.15)	0.723	0.0	1.5	0.828	178	1.00 (0.82–1.22)	0.994	0.0	2.0	0.736	334	1.03 (0.89–1.20)	0.658	0.0	2.2	0.694
	Linear trend (per 10g)	*2313*	*0.97 (0.94–1.01)*	*0.117*	*11.8*	*4.5*	*0.338*	*782*	*0.98 (0.93–1.03)*	*0.404*	*0.0*	*1.8*	*0.781*	*1531*	*0.97 (0.94–1.01)*	*0.186*	*0.0*	*3.1*	*0.542*
Coffee	Lowest fourth	529	1.00 (reference)	n/a	n/a	n/a	n/a	182	1.00 (reference)	n/a	n/a	n/a	n/a	347	1.00 (reference)	n/a	n/a	n/a	n/a
	Second fourth	539	1.02 (0.90–1.15)	0.795	0.0	1.2	0.877	192	1.10 (0.89–1.35)	0.386	0.0	1.9	0.749	347	0.97 (0.84–1.14)	0.740	0.0	3.0	0.563
	Third fourth	549	1.03 (0.91–1.17)	0.644	47.9	7.7	0.104	190	1.09 (0.88–1.35)	0.436	41.9	6.9	0.142	359	1.00 (0.86–1.17)	0.977	0.0	3.0	0.553
	Highest fourth	517	1.01 (0.89–1.16)	0.840	0.0	3.3	0.514	163	0.97 (0.77–1.21)	0.771	0.0	1.9	0.758	354	1.04 (0.89–1.22)	0.617	0.0	1.5	0.831
	Linear trend (per 100g)	*2134*	*1.00 (0.99–1.01)*	*0.560*	*0.0*	*3.4*	*0.490*	*727*	*0.99 (0.98–1.00)*	*0.169*	*0.0*	*2.1*	*0.712*	*1407*	*1.01 (1.00–1.02)*	*0.067*	*0.0*	*1.0*	*0.914*

Summary RRs were calculated using inverse-variance weighted meta-analysis combining fully-adjusted RRs from the Million Women Study, the NIH-AARP Study, and the PLCO Study. Heterogeneity of results between studies was assessed by a χ^2 test and I^2 statistics. All analyses were also stratified by follow-up time (<5 and ≥5 years) to explore potential reverse causation. All p values shown here were uncorrected.

Table 6.2: Risk of glioma in relation to diet: combined analysis of the Million Women Study, the NIH-AARP Study, and the PLCO Study (continued)

		All follow-up time						First 5 years of follow-up						5+ years of follow-up					
Dietary factor	**Intake category**	**No. of cases**	**Summary RR (95% CI)**	**P value**	**Heterogeneity**			**No. of cases**	**Summary RR (95% CI)**	**P value**	**Heterogeneity**			**No. of cases**	**Summary RR (95% CI)**	**P value**	**Heterogeneity**		
					I^2 (%)	**X^2**	**P value**				**I^2 (%)**	**X^2**	**P value**				**I^2 (%)**	**X^2**	**P value**
Tea	Lowest fourth	542	1.00 (reference)	n/a	n/a	n/a	n/a	179	1.00 (reference)	n/a	n/a	n/a	n/a	363	1.00 (reference)	n/a	n/a	n/a	n/a
	Second fourth	557	1.00 (0.89–1.13)	0.992	25.1	5.3	0.254	201	1.13 (0.92–1.39)	0.227	0.0	2.6	0.632	356	0.94 (0.81–1.08)	0.376	0.0	3.4	0.497
	Third fourth	545	0.97 (0.86–1.09)	0.620	0.0	1.4	0.842	184	1.04 (0.84–1.28)	0.723	0.0	3.3	0.503	361	0.94 (0.81–1.09)	0.390	24.3	5.3	0.259
	Highest fourth	563	1.01 (0.89–1.14)	0.925	0.0	1.6	0.812	176	1.02 (0.82–1.27)	0.863	0.0	1.8	0.772	387	1.00 (0.86–1.16)	0.955	0.0	2.0	0.739
	Linear trend (per 100g)	*2207*	*1.00 (0.99–1.01)*	*0.866*	*0.0*	*1.9*	*0.753*	*740*	*1.01 (0.99–1.03)*	*0.450*	*0.0*	*2.2*	*0.691*	*1467*	*1.00 (0.98–1.01)*	*0.845*	*0.0*	*2.4*	*0.658*
Carbo-hydrate	Lowest fourth	515	1.00 (reference)	n/a	n/a	n/a	n/a	173	1.00 (reference)	n/a	n/a	n/a	n/a	342	1.00 (reference)	n/a	n/a	n/a	n/a
	Second fourth	581	1.10 (0.97–1.24)	0.130	0.0	1.8	0.769	185	1.06 (0.86–1.31)	0.573	0.0	1.2	0.882	396	1.12 (0.96–1.29)	0.148	6.8	4.3	0.368
	Third fourth	604	1.13 (1.00–1.28)	0.049	28.8	5.6	0.229	223	1.28 (1.04–1.58)	0.020	3.6	4.1	0.386	381	1.06 (0.91–1.23)	0.482	41.9	6.9	0.142
	Highest fourth	613	1.17 (1.03–1.33)	0.018	0.0	1.5	0.832	201	1.18 (0.94–1.48)	0.148	48.9	7.8	0.098	412	1.15 (0.99–1.35)	0.073	28.3	5.6	0.233
	Linear trend (per 1% energy)	*2313*	*1.01 (1.00–1.01)*	*0.033*	*0.0*	*2.1*	*0.719*	*782*	*1.01 (1.00–1.02)*	*0.072*	*18.0*	*4.9*	*0.300*	*1531*	*1.01 (1.00–1.01)*	*0.190*	*25.3*	*5.4*	*0.253*
Protein	Lowest fourth	588	1.00 (reference)	n/a	n/a	n/a	n/a	207	1.00 (reference)	n/a	n/a	n/a	n/a	381	1.00 (reference)	n/a	n/a	n/a	n/a
	Second fourth	585	0.97 (0.86–1.08)	0.550	0.0	1.6	0.817	215	1.00 (0.83–1.21)	0.986	0.0	1.5	0.830	370	0.94 (0.82–1.09)	0.431	0.0	2.6	0.633
	Third fourth	598	0.98 (0.87–1.10)	0.757	0.0	1.5	0.823	193	0.90 (0.74–1.10)	0.306	0.0	3.2	0.525	405	1.03 (0.89–1.18)	0.726	0.0	3.5	0.475
	Highest fourth	542	0.90 (0.80–1.01)	0.079	0.0	2.4	0.668	167	0.80 (0.64–0.98)	0.035	39.5	6.6	0.158	375	0.95 (0.82–1.10)	0.515	0.0	1.4	0.848
	Linear trend (per 1% energy)	*2313*	*0.99 (0.97–1.01)*	*0.301*	*0.0*	*2.8*	*0.592*	*782*	*0.98 (0.95–1.01)*	*0.228*	*45.9*	*7.4*	*0.117*	*1531*	*1.00 (0.97–1.02)*	*0.725*	*0.0*	*1.1*	*0.902*
Total fat	Lowest fourth	590	1.00 (reference)	n/a	n/a	n/a	n/a	192	1.00 (reference)	n/a	n/a	n/a	n/a	398	1.00 (reference)	n/a	n/a	n/a	n/a
	Second fourth	584	0.98 (0.87–1.10)	0.689	0.0	0.3	0.990	203	1.02 (0.84–1.25)	0.827	0.0	0.4	0.986	381	0.96 (0.83–1.10)	0.527	0.0	0.8	0.937
	Third fourth	565	0.95 (0.84–1.07)	0.388	1.3	4.1	0.399	185	0.93 (0.75–1.14)	0.469	10.5	4.5	0.346	380	0.96 (0.83–1.11)	0.592	0.0	3.2	0.523
	Highest fourth	574	0.98 (0.87–1.11)	0.777	0.0	2.9	0.576	202	1.01 (0.82–1.25)	0.906	0.0	3.5	0.481	372	0.97 (0.84–1.12)	0.675	5.0	4.2	0.378
	Linear trend (per 1% energy)	*2313*	*1.00 (0.99–1.01)*	*0.661*	*0.0*	*1.2*	*0.870*	*782*	*1.00 (0.98–1.01)*	*0.493*	*7.3*	*4.3*	*0.365*	*1531*	*1.00 (0.99–1.01)*	*0.969*	*0.0*	*2.2*	*0.708*
Saturated fat	Lowest fourth	572	1.00 (reference)	n/a	n/a	n/a	n/a	195	1.00 (reference)	n/a	n/a	n/a	n/a	377	1.00 (reference)	n/a	n/a	n/a	n/a
	Second fourth	588	1.02 (0.91–1.15)	0.739	0.0	1.3	0.862	197	0.98 (0.81–1.20)	0.878	0.0	2.2	0.701	391	1.04 (0.90–1.20)	0.598	0.0	0.4	0.984
	Third fourth	576	1.00 (0.89–1.13)	0.975	0.0	3.9	0.424	188	0.94 (0.76–1.15)	0.528	37.9	6.4	0.169	388	1.04 (0.90–1.20)	0.612	0.0	3.5	0.485
	Highest fourth	577	1.02 (0.90–1.15)	0.789	9.3	4.4	0.353	202	1.01 (0.82–1.25)	0.914	0.0	3.4	0.493	375	1.02 (0.88–1.19)	0.802	15.2	4.7	0.317
	Linear trend (per 1% energy)	*2313*	*1.00 (0.98–1.02)*	*0.709*	*0.0*	*3.3*	*0.515*	*782*	*0.99 (0.96–1.02)*	*0.483*	*27.0*	*5.5*	*0.241*	*1531*	*1.00 (0.98–1.03)*	*0.943*	*0.0*	*3.9*	*0.423*
MU fat	Lowest fourth	595	1.00 (reference)	n/a	n/a	n/a	n/a	188	1.00 (reference)	n/a	n/a	n/a	n/a	407	1.00 (reference)	n/a	n/a	n/a	n/a
	Second fourth	589	0.98 (0.87–1.10)	0.728	0.0	0.9	0.929	203	1.05 (0.86–1.28)	0.627	0.0	1.2	0.872	386	0.95 (0.82–1.09)	0.450	0.0	0.4	0.986
	Third fourth	577	0.96 (0.86–1.08)	0.522	0.0	1.7	0.798	200	1.03 (0.84–1.27)	0.763	13.0	4.6	0.331	377	0.93 (0.81–1.07)	0.328	0.0	3.6	0.457
	Highest fourth	552	0.94 (0.83–1.06)	0.328	0.0	0.3	0.990	191	0.99 (0.80–1.22)	0.903	0.0	3.8	0.434	361	0.92 (0.79–1.07)	0.273	0.0	2.8	0.590
	Linear trend (per 1% energy)	*2313*	*0.99 (0.97–1.01)*	*0.496*	*0.0*	*1.0*	*0.909*	*782*	*0.98 (0.95–1.02)*	*0.311*	*0.0*	*4.0*	*0.410*	*1531*	*1.00 (0.97–1.02)*	*0.944*	*0.0*	*3.9*	*0.425*

Summary RRs were calculated using inverse-variance weighted meta-analysis combining fully-adjusted RRs from the Million Women Study, the NIH-AARP Study, and the PLCO Study. Heterogeneity of results between studies was assessed by a χ^2 test and I^2 statistics. All analyses were also stratified by follow-up time (<5 and ≥5 years) to explore potential reverse causation. All p values shown here were uncorrected. MU fat monounsaturated fat.

Table 6.2: Risk of glioma in relation to diet: combined analysis of the Million Women Study, the NIH-AARP Study, and the PLCO Study (continued)

		All follow-up time						First 5 years of follow-up						5+ years of follow-up					
Dietary factor	**Intake category**	**No. of cases**	**Summary RR (95% CI)**	**P value**	**Heterogeneity**			**No. of cases**	**Summary RR (95% CI)**	**P value**	**Heterogeneity**			**No. of cases**	**Summary RR (95% CI)**	**P value**	**Heterogeneity**		
					I^2 (%)	**X^2**	**P value**				**I^2 (%)**	**X^2**	**P value**				**I^2 (%)**	**X^2**	**P value**
PU fat	Lowest fourth	562	**1.00** (reference)	n/a	n/a	n/a	n/a	188	**1.00** (reference)	n/a	n/a	n/a	n/a	374	**1.00** (reference)	n/a	n/a	n/a	n/a
	Second fourth	615	1.07 (0.96–1.21)	0.220	31.1	5.8	0.214	192	0.99 (0.80–1.21)	0.886	44.9	7.3	0.123	423	1.12 (0.97–1.29)	0.122	5.4	4.2	0.376
	Third fourth	561	0.98 (0.87–1.11)	0.776	23.7	5.2	0.263	197	1.02 (0.83–1.25)	0.875	4.6	4.2	0.381	364	0.96 (0.83–1.12)	0.631	0.0	2.2	0.707
	Highest fourth	575	1.02 (0.91–1.15)	0.748	0.0	2.9	0.574	205	1.07 (0.87–1.31)	0.521	35.9	6.2	0.182	370	1.00 (0.86–1.15)	0.959	0.0	1.0	0.913
	Linear trend (per 1% energy)	*2313*	*1.00 (0.98–1.03)*	*0.835*	*0.0*	*3.2*	*0.523*	*782*	*1.02 (0.98–1.07)*	*0.386*	*37.9*	*6.4*	*0.169*	*1531*	*0.99 (0.96–1.03)*	*0.743*	*0.0*	*0.7*	*0.951*
Fibre	Lowest fourth	513	**1.00** (reference)	n/a	n/a	n/a	n/a	160	**1.00** (reference)	n/a	n/a	n/a	n/a	353	**1.00** (reference)	n/a	n/a	n/a	n/a
	Second fourth	566	1.06 (0.94–1.20)	0.319	0.0	3.1	0.540	196	1.17 (0.95–1.45)	0.137	0.0	2.9	0.582	370	1.01 (0.87–1.17)	0.869	0.0	3.3	0.505
	Third fourth	605	1.12 (1.00–1.27)	0.060	50.7	8.1	0.088	202	1.19 (0.96–1.48)	0.108	0.0	2.8	0.598	403	1.09 (0.94–1.27)	0.234	48.8	7.8	0.099
	Highest fourth	629	1.17 (1.04–1.33)	0.011	0.0	3.9	0.423	224	1.33 (1.08–1.66)	0.009	0.0	3.9	0.422	405	1.10 (0.95–1.28)	0.210	37.1	6.4	0.174
	Linear trend (per 5g)	*2313*	*1.08 (1.02–1.15)*	*0.008*	*0.0*	*2.3*	*0.680*	*782*	*1.13 (1.02–1.24)*	*0.015*	*0.0*	*1.3*	*0.863*	*1531*	*1.06 (0.98–1.14)*	*0.121*	*2.9*	*4.1*	*0.390*
Carotene	Lowest fourth	523	**1.00** (reference)	n/a	n/a	n/a	n/a	166	**1.00** (reference)	n/a	n/a	n/a	n/a	357	**1.00** (reference)	n/a	n/a	n/a	n/a
	Second fourth	623	1.16 (1.03–1.31)	0.013	39.1	6.6	0.160	192	1.10 (0.89–1.36)	0.372	0.0	3.9	0.419	431	1.19 (1.03–1.37)	0.018	44.2	7.2	0.127
	Third fourth	549	1.02 (0.91–1.16)	0.707	45.5	7.3	0.119	189	1.07 (0.86–1.33)	0.532	0.0	3.3	0.508	360	1.00 (0.86–1.16)	0.999	22.7	5.2	0.270
	Highest fourth	618	1.16 (1.03–1.31)	0.013	0.0	1.8	0.773	235	1.34 (1.09–1.65)	0.005	0.0	3.2	0.527	383	1.08 (0.93–1.25)	0.330	0.0	2.9	0.566
	Linear trend (per 1000ug)	*2313*	*1.03 (0.96–1.09)*	*0.415*	*0.0*	*3.0*	*0.559*	*782*	*1.09 (0.99–1.21)*	*0.094*	*31.0*	*5.8*	*0.215*	*1531*	*1.00 (0.92–1.08)*	*0.982*	*0.0*	*2.3*	*0.685*
Vitamin C	Lowest fourth	549	**1.00** (reference)	n/a	n/a	n/a	n/a	184	**1.00** (reference)	n/a	n/a	n/a	n/a	365	**1.00** (reference)	n/a	n/a	n/a	n/a
	Second fourth	541	0.95 (0.84–1.07)	0.412	17.5	4.8	0.303	180	0.93 (0.76–1.15)	0.516	0.0	1.8	0.780	361	0.96 (0.83–1.12)	0.623	37.3	6.4	0.173
	Third fourth	626	1.09 (0.97–1.23)	0.141	0.0	0.3	0.990	214	1.09 (0.89–1.33)	0.415	0.0	1.7	0.794	412	1.09 (0.95–1.26)	0.230	0.0	2.3	0.674
	Highest fourth	597	1.06 (0.94–1.19)	0.347	0.0	0.7	0.956	204	1.06 (0.86–1.30)	0.605	0.0	1.6	0.817	393	1.06 (0.92–1.23)	0.432	0.0	3.1	0.544
	Linear trend (per 50mg)	*2313*	*1.02 (0.99–1.05)*	*0.282*	*0.0*	*1.3*	*0.864*	*782*	*1.01 (0.96–1.06)*	*0.702*	*0.0*	*3.0*	*0.556*	*1531*	*1.02 (0.99–1.06)*	*0.242*	*0.0*	*2.2*	*0.700*
Vitamin E	Lowest fourth	555	**1.00** (reference)	n/a	n/a	n/a	n/a	179	**1.00** (reference)	n/a	n/a	n/a	n/a	376	**1.00** (reference)	n/a	n/a	n/a	n/a
	Second fourth	579	1.02 (0.90–1.14)	0.798	31.2	5.8	0.213	196	1.06 (0.86–1.30)	0.607	57.1	9.3	0.053	383	0.99 (0.86–1.15)	0.936	0.0	3.8	0.436
	Third fourth	594	1.04 (0.93–1.17)	0.503	0.0	3.5	0.475	209	1.12 (0.92–1.37)	0.269	30.2	5.7	0.220	385	1.00 (0.87–1.16)	0.986	0.0	1.9	0.751
	Highest fourth	585	1.04 (0.92–1.16)	0.564	0.0	1.6	0.817	198	1.07 (0.87–1.32)	0.504	0.0	2.6	0.625	387	1.02 (0.88–1.18)	0.815	0.0	3.0	0.566
	Linear trend (per 5mg)	*2313*	*1.01 (0.93–1.09)*	*0.872*	*0.0*	*1.2*	*0.884*	*782*	*0.97 (0.84–1.11)*	*0.664*	*0.0*	*0.8*	*0.943*	*1531*	*1.03 (0.94–1.13)*	*0.508*	*0.0*	*3.2*	*0.518*

Summary RRs were calculated using inverse-variance weighted meta-analysis combining fully-adjusted RRs from the Million Women Study, the NIH-AARP Study, and the PLCO Study. Heterogeneity of results between studies was assessed by a χ^2 test and I^2 statistics. All analyses were also stratified by follow-up time (<5 and ≥5 years) to explore potential reverse causation. All p values shown here were uncorrected. PU fat polyunsaturated fat.

Table 6.2: Risk of glioma in relation to diet: combined analysis of the Million Women Study, the NIH-AARP Study, and the PLCO Study (continued)

		All follow-up time						First 5 years of follow-up						5+ years of follow-up					
Dietary factor	**Intake category**	**No. of cases**	**Summary RR (95% CI)**	**P value**	**Heterogeneity**			**No. of cases**	**Summary RR (95% CI)**	**P value**	**Heterogeneity**			**No. of cases**	**Summary RR (95% CI)**	**P value**	**Heterogeneity**		
					I^2 (%)	**X^2**	**P value**				**I^2 (%)**	**X^2**	**P value**				**I^2 (%)**	**X^2**	**P value**
Folate	Lowest fourth	529	**1.00** (reference)	n/a	n/a	n/a	n/a	190	**1.00** (reference)	n/a	n/a	n/a	n/a	339	**1.00** (reference)	n/a	n/a	n/a	n/a
	Second fourth	566	**1.04** (0.92–1.17)	**0.569**	**0.0**	**1.3**	**0.867**	193	**0.98** (0.80–1.20)	**0.820**	**0.0**	**2.6**	**0.628**	373	**1.07** (0.92–1.24)	**0.390**	**0.0**	**2.5**	**0.651**
	Third fourth	597	**1.08** (0.96–1.22)	**0.201**	**0.0**	**0.1**	**0.999**	203	**1.02** (0.83–1.25)	**0.849**	**0.0**	**2.4**	**0.658**	394	**1.11** (0.96–1.29)	**0.153**	**0.0**	**1.5**	**0.832**
	Highest fourth	621	**1.13** (1.00–1.27)	**0.054**	**0.0**	**0.4**	**0.983**	196	**0.99** (0.80–1.22)	**0.924**	**0.0**	**3.1**	**0.547**	425	**1.21** (1.04–1.40)	**0.015**	**0.0**	**2.7**	**0.614**
	Linear trend (per 50ug)	*2313*	***1.01 (0.99–1.03)***	***0.176***	***0.0***	***2.0***	***0.742***	*782*	***1.01 (0.98–1.04)***	***0.432***	***0.0***	***2.6***	***0.622***	*1531*	***1.01 (0.99–1.04)***	***0.211***	***48.2***	***7.7***	***0.102***
Calcium	Lowest fourth	565	**1.00** (reference)	n/a	n/a	n/a	n/a	195	**1.00** (reference)	n/a	n/a	n/a	n/a	370	**1.00** (reference)	n/a	n/a	n/a	n/a
	Second fourth	576	**0.98** (0.87–1.10)	**0.687**	**1.4**	**4.1**	**0.398**	198	**0.97** (0.79–1.18)	**0.742**	**0.0**	**3.6**	**0.462**	378	**0.98** (0.85–1.13)	**0.758**	**58.5**	**9.6**	**0.047**
	Third fourth	576	**0.97** (0.86–1.09)	**0.580**	**0.0**	**0.3**	**0.987**	202	**0.98** (0.80–1.20)	**0.830**	**0.0**	**2.8**	**0.584**	374	**0.96** (0.83–1.11)	**0.602**	**0.0**	**3.2**	**0.517**
	Highest fourth	596	**1.00** (0.89–1.13)	**0.985**	**0.0**	**1.4**	**0.846**	187	**0.90** (0.73–1.11)	**0.321**	**19.2**	**4.9**	**0.293**	409	**1.06** (0.92–1.23)	**0.428**	**56.7**	**9.2**	**0.056**
	Linear trend (per 100mg)	*2313*	***1.00 (0.98–1.02)***	***0.831***	***0.0***	***3.7***	***0.452***	*782*	***1.01 (0.98–1.04)***	***0.612***	***0.0***	***3.0***	***0.550***	*1531*	***1.00 (0.98–1.02)***	***0.915***	***65.7***	***11.7***	***0.020***
Cholesterol	Lowest fourth	576	**1.00** (reference)	n/a	n/a	n/a	n/a	194	**1.00** (reference)	n/a	n/a	n/a	n/a	382	**1.00** (reference)	n/a	n/a	n/a	n/a
	Second fourth	598	**1.03** (0.92–1.15)	**0.642**	**0.0**	**3.8**	**0.436**	217	**1.09** (0.90–1.33)	**0.373**	**0.0**	**3.0**	**0.561**	381	**0.99** (0.86–1.14)	**0.890**	**32.4**	**5.9**	**0.205**
	Third fourth	581	**1.01** (0.89–1.13)	**0.929**	**0.0**	**0.6**	**0.968**	193	**0.97** (0.79–1.19)	**0.778**	**20.5**	**5.0**	**0.284**	388	**1.02** (0.89–1.18)	**0.758**	**0.0**	**3.1**	**0.537**
	Highest fourth	558	**1.00** (0.88–1.12)	**0.935**	**63.5**	**11.0**	**0.027**	178	**0.91** (0.74–1.12)	**0.375**	**39.6**	**6.6**	**0.157**	380	**1.04** (0.90–1.20)	**0.618**	**56.2**	**9.1**	**0.058**
	Linear trend (per 100mg)	*2313*	***0.96 (0.90–1.03)***	***0.268***	***57.0***	***9.3***	***0.054***	*782*	***0.91 (0.81–1.02)***	***0.094***	***31.8***	***5.9***	***0.209***	*1531*	***1.00 (0.92–1.09)***	***0.990***	***35.5***	***6.2***	***0.185***
DASH score	Lowest fourth	562	**1.00** (reference)	n/a	n/a	n/a	n/a	175	**1.00** (reference)	n/a	n/a	n/a	n/a	387	**1.00** (reference)	n/a	n/a	n/a	n/a
	Second fourth	591	**1.05** (0.93–1.18)	**0.436**	**0.0**	**1.0**	**0.912**	198	**1.13** (0.92–1.39)	**0.255**	**0.0**	**2.1**	**0.717**	393	**1.01** (0.88–1.17)	**0.862**	**0.0**	**2.5**	**0.647**
	Third fourth	585	**1.17** (1.04–1.32)	**0.011**	**45.5**	**7.3**	**0.119**	199	**1.27** (1.03–1.56)	**0.027**	**0.0**	**2.4**	**0.670**	386	**1.12** (0.97–1.30)	**0.123**	**52.3**	**8.4**	**0.078**
	Highest fourth	575	**1.19** (1.05–1.34)	**0.006**	**0.0**	**0.3**	**0.990**	210	**1.38** (1.12–1.71)	**0.003**	**0.0**	**3.4**	**0.490**	365	**1.10** (0.95–1.28)	**0.197**	**44.5**	**7.2**	**0.125**
aMED score	0–2 points	418	**1.00** (reference)	n/a	n/a	n/a	n/a	138	**1.00** (reference)	n/a	n/a	n/a	n/a	280	**1.00** (reference)	n/a	n/a	n/a	n/a
	3–4 points	912	**1.12** (0.99–1.26)	**0.066**	**64.4**	**11.2**	**0.024**	312	**1.14** (0.93–1.39)	**0.220**	**0.0**	**3.8**	**0.433**	600	**1.10** (0.96–1.28)	**0.176**	**57.2**	**9.3**	**0.053**
	5–6 points	743	**1.12** (0.99–1.27)	**0.072**	**18.5**	**4.9**	**0.297**	242	**1.05** (0.84–1.31)	**0.651**	**46.0**	**7.4**	**0.116**	501	**1.15** (0.99–1.34)	**0.070**	**61.8**	**10.5**	**0.033**
	7–9 points	240	**1.24** (1.05–1.46)	**0.012**	**42.7**	**7.0**	**0.137**	90	**1.37** (1.03–1.81)	**0.028**	**0.0**	**2.7**	**0.616**	150	**1.17** (0.95–1.45)	**0.132**	**51.1**	**8.2**	**0.085**
AHEI	Lowest fourth	536	**1.00** (reference)	n/a	n/a	n/a	n/a	172	**1.00** (reference)	n/a	n/a	n/a	n/a	364	**1.00** (reference)	n/a	n/a	n/a	n/a
	Second fourth	578	**1.06** (0.94–1.19)	**0.325**	**0.0**	**0.3**	**0.990**	178	**1.01** (0.82–1.25)	**0.928**	**0.0**	**3.7**	**0.447**	400	**1.08** (0.94–1.25)	**0.270**	**0.0**	**3.9**	**0.415**
	Third fourth	574	**1.05** (0.93–1.18)	**0.448**	**0.0**	**3.8**	**0.431**	198	**1.11** (0.90–1.37)	**0.313**	**0.0**	**2.2**	**0.700**	376	**1.01** (0.88–1.18)	**0.849**	**26.6**	**5.4**	**0.244**
	Highest fourth	625	**1.14** (1.01–1.28)	**0.037**	**0.0**	**3.3**	**0.501**	234	**1.31** (1.07–1.61)	**0.010**	**53.5**	**8.6**	**0.072**	391	**1.06** (0.91–1.23)	**0.478**	**35.1**	**6.2**	**0.187**

Summary RRs were calculated using inverse-variance weighted meta-analysis combining fully-adjusted RRs from the Million Women Study, the NIH-AARP Study, and the PLCO Study. Heterogeneity of results between studies was assessed by a χ^2 test and I^2 statistics. All analyses were also stratified by follow-up time (<5 and ≥5 years) to explore potential reverse causation. All p values shown here were uncorrected. DASH score the Dietary Approaches to Stop Hypertension score, aMED score the Alternate Mediterranean Diet score, AHEI the Alternative Healthy Eating Index.

6.6 Figures

Figure 6.1: Participants inclusion/exclusion flow diagram in the Million Women Study, the NIH-AARP Study, and the PLCO Study

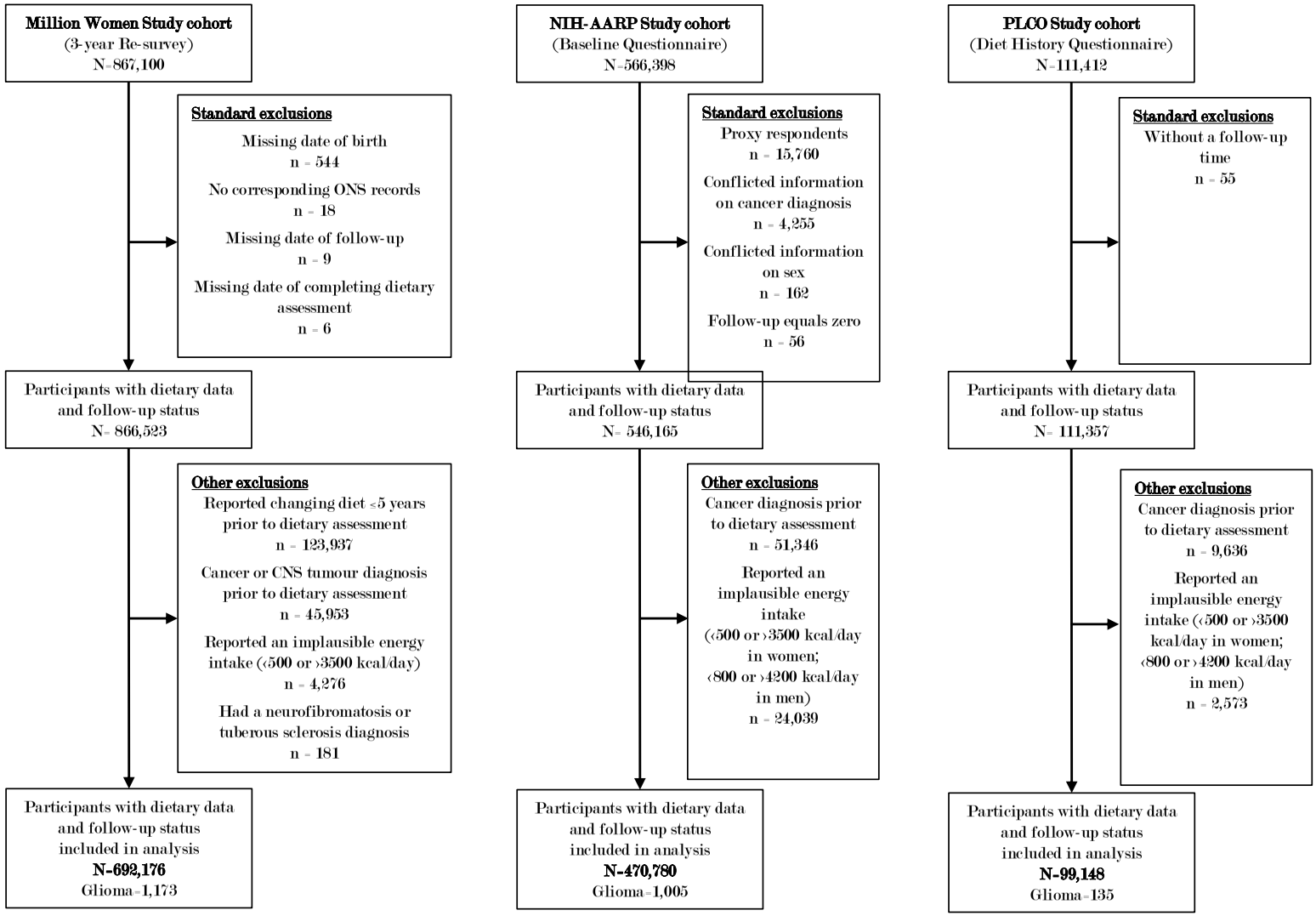
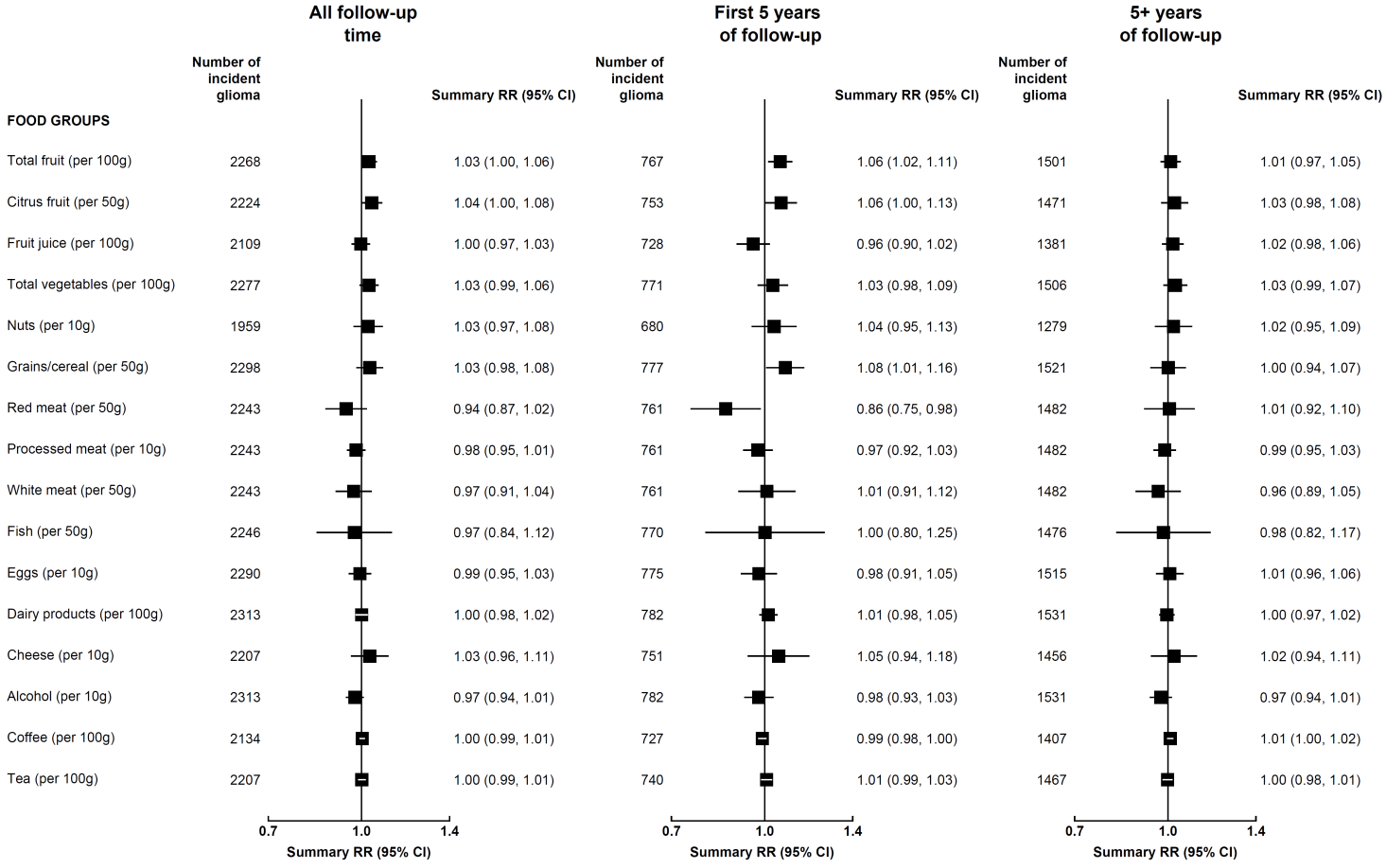
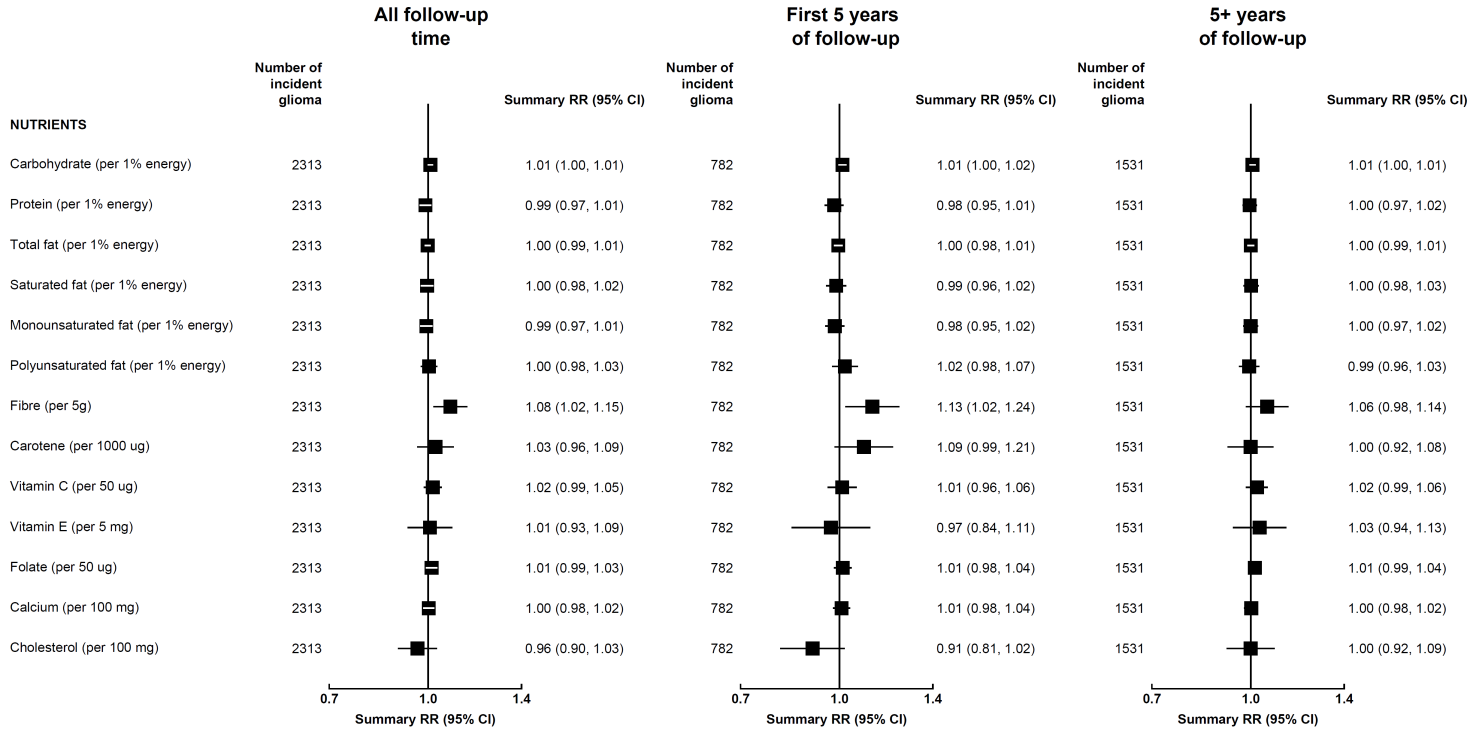


Figure 6.2: Risk of glioma in relation to increasing intakes of food groups in the Million Women Study, the NIH-AARP Study, and the PLCO Study



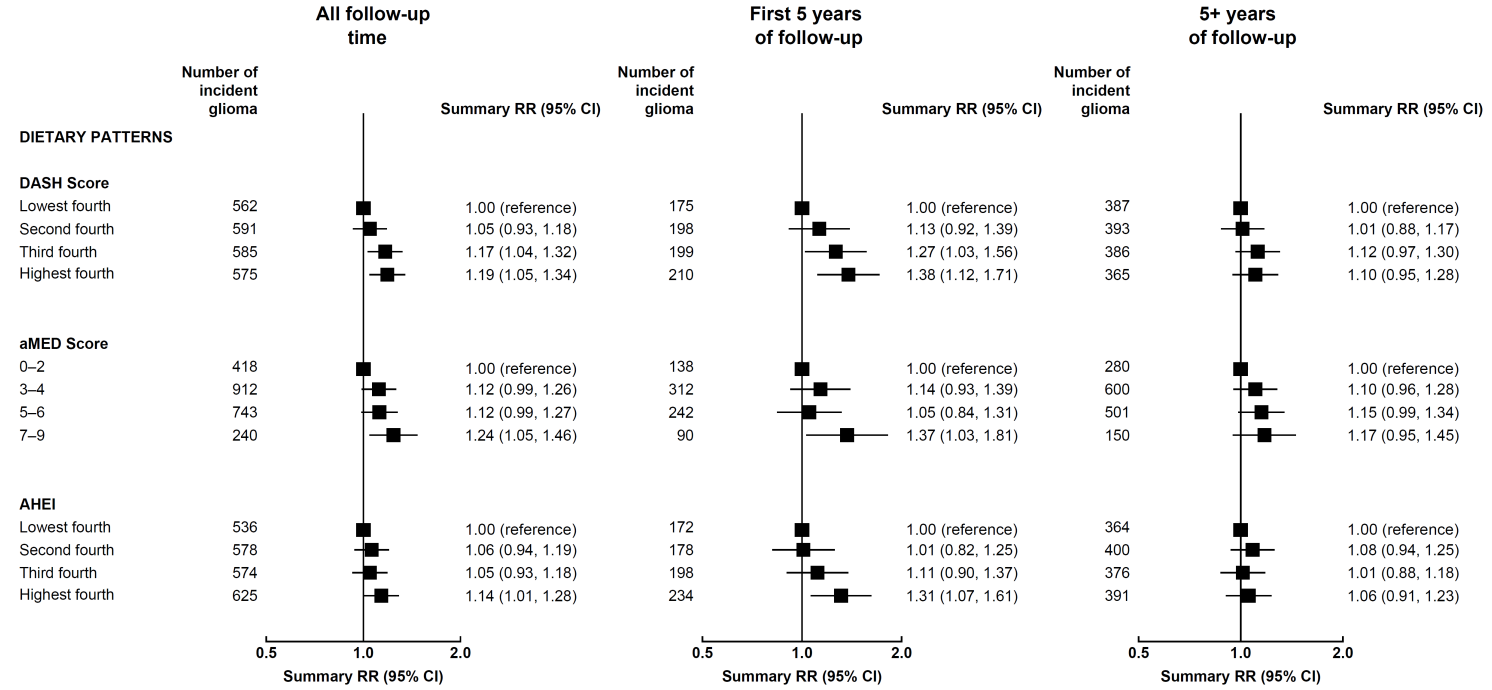
Summary RRs were calculated uring inverse-variance weighted meta-analysis combining fully-adjusted RRs of linear trend for glioma in relation to each food group from the Million Women Study, the NIH-AARP Study, and the PLCO Study. All analyses were also stratified by follow-up time (first 5 years, 5+ years) to explore potential reverse causation. All p values shown here were uncorrected.

Figure 6.3: Risk of glioma in relation to increasing intakes of nutrients in the Million Women Study, the NIH-AARP Study, and the PLCO Study



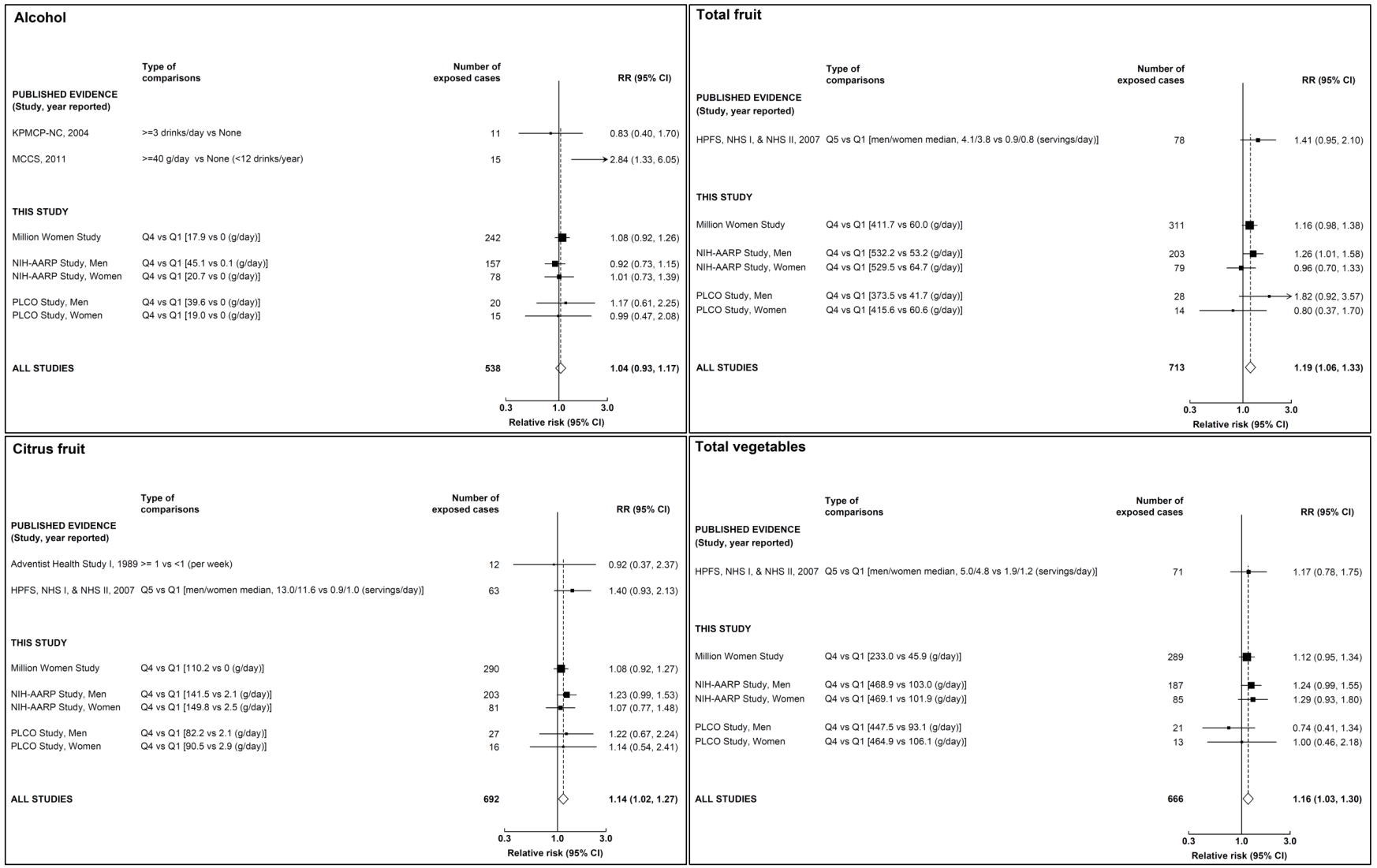
Summary RRs were calculated uring inverse-variance weighted meta-analysis combining fully-adjusted RRs of linear trend for glioma in relation to each nutrient from the Million Women Study, the NIH-AARP Study, and the PLCO Study. All analyses were also stratified by follow-up time (first 5 years, 5+ years) to explore potential reverse causation. All p values shown here were uncorrected.

Figure 6.4: Risk of glioma in relation to dietary patterns in the Million Women Study, the NIH-AARP Study, and the PLCO Study



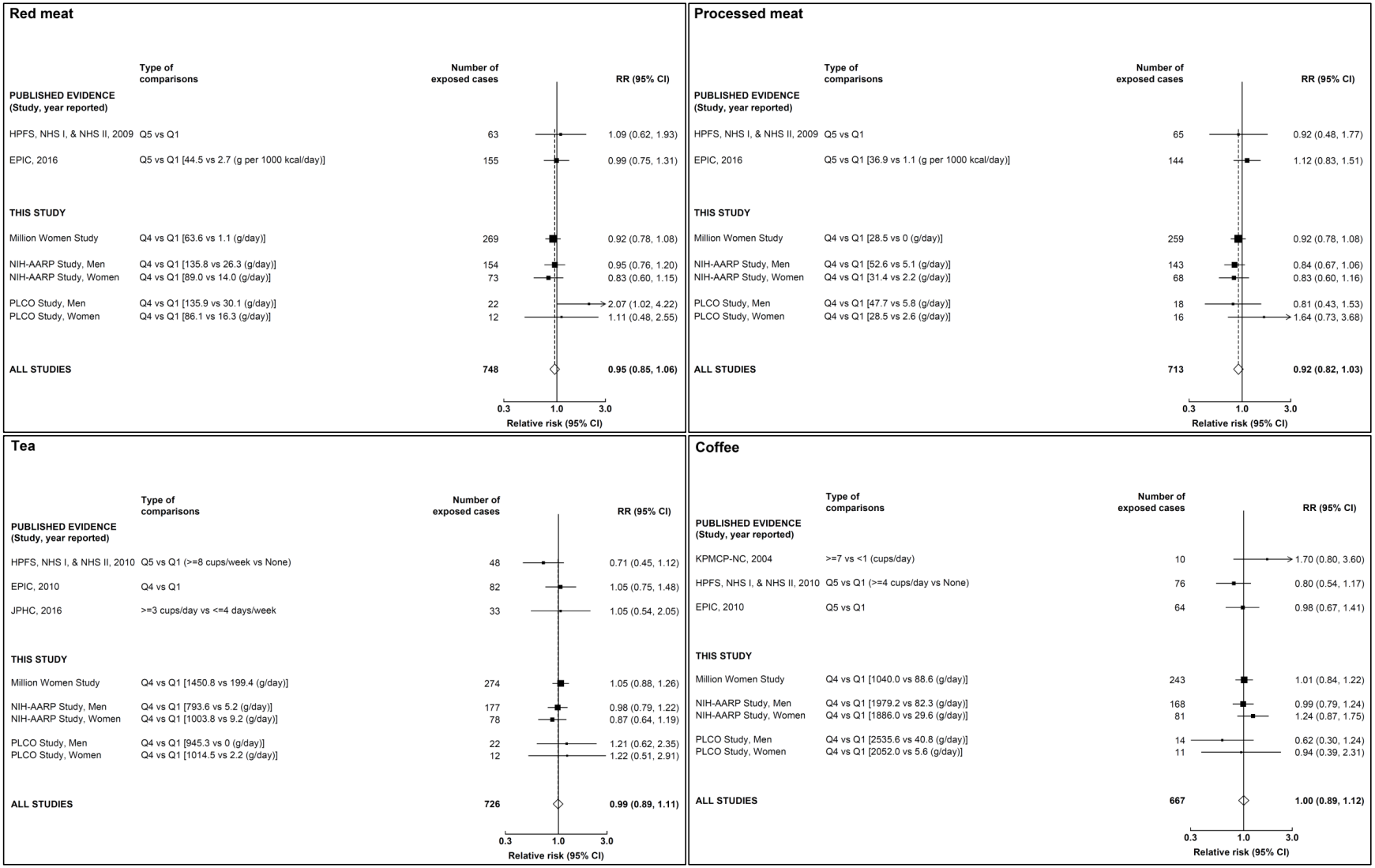
Summary RRs were calculated uring inverse-variance weighted meta-analysis combining fully-adjusted RRs of glioma in relation to specific categories of dietary patterns from the Million Women Study, the NIH-AARP Study, and the PLCO Study. All analyses were also stratified by follow-up time (first 5 years, 5+ years) to explore potential reverse causation. All p values shown here were uncorrected. DASH score the Dietary Approaches to Stop Hypertension score, aMED score the Alternate Mediterranean Diet score, AHEI the Alternative Healthy Eating Index.

Figure 6.5: Meta-analysis showing risk of glioma in relation to 11 dietary factors using independent evidence from published prospective studies



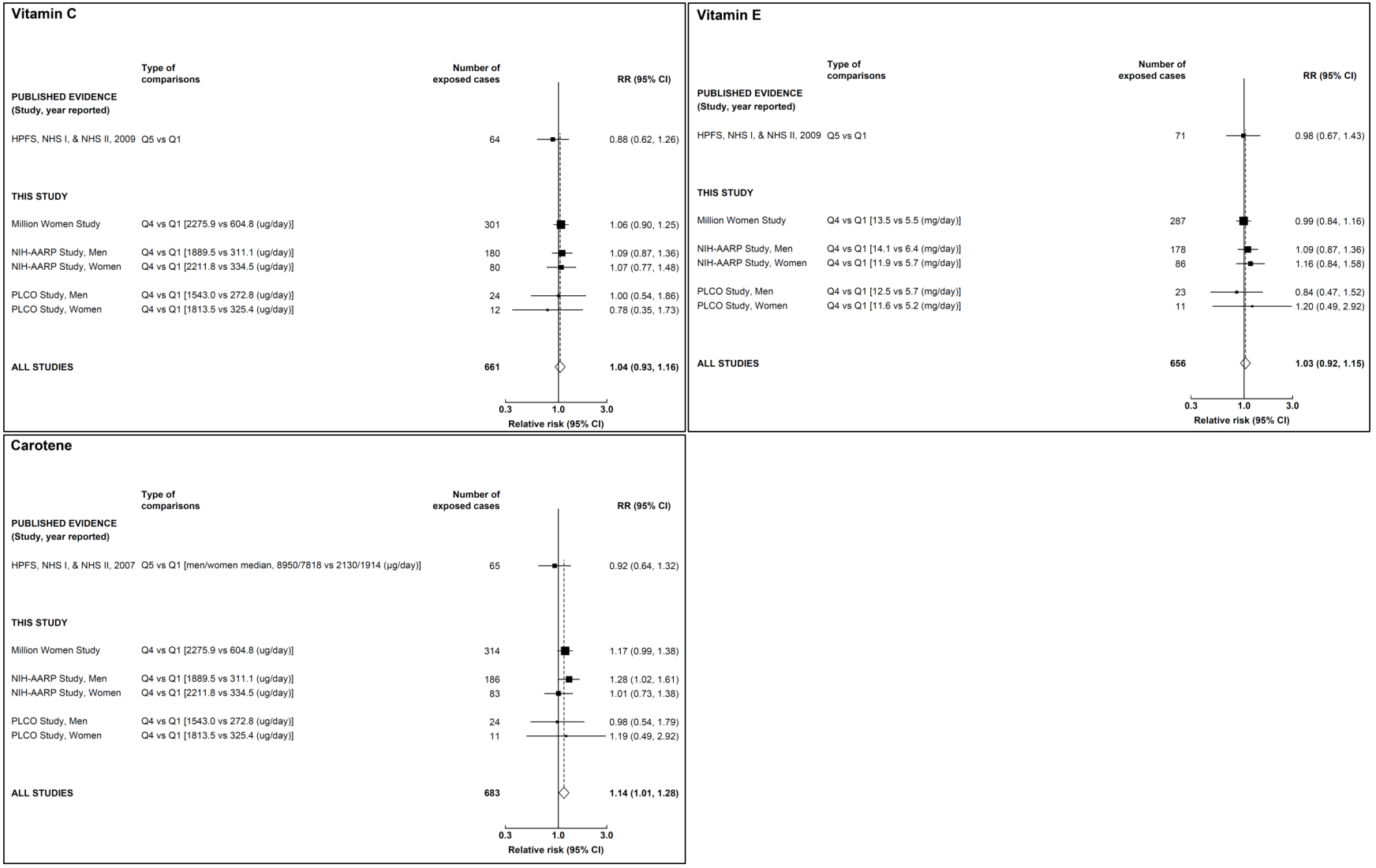
KPMCP-NC The Kaiser Permanente Medical Care Program of Northern California Study, MCCS The Melbourne Collaborative Cohort Study, HPFS The Health Professionals Follow-Up Study, NHS I The Nurses' Health Study I, NHS II The Nurses' Health Study II

Figure 6.10: Meta-analysis showing risk of glioma in relation to 11 dietary factors using independent evidence from published prospective studies (continued)



HPFS The Health Professionals Follow-Up Study, NHS I The Nurses' Health Study I, NHS II The Nurses' Health Study II, EPIC The European Prospective Investigation into Cancer and Nutrition Study, JPHC The Japan Public Health Center-Based Prospective Study, KPMCP-NC The Kaiser Permanente Medical Care Program of Northern California Study, MCCS The Melbourne Collaborative Cohort Study

Figure 6.10: Meta-analysis showing risk of glioma in relation to 11 dietary factors using independent evidence from published prospective studies (continued)



HPFS The Health Professionals Follow-Up Study, NHS I The Nurses' Health Study I, NHS II The Nurses' Health Study II

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7

Diet and Risk of Meningioma in the UK Million Women Study Cohort

7.1 Introduction

Both meningioma and glioma are central nervous system (CNS) tumours, but they arise from different cells in the CNS, and they have been shown to have different epidemiological risk factors (see Chapter 2). Therefore, it is worthwhile to investigate the risk of meningioma in relation to the 32 dietary factors examined for glioma in Chapter 6, despite the little evidence for an association between diet and glioma previously shown. Unlike glioma which is mostly malignant, meningioma is generally benign. There is a lack of registration of benign CNS tumours including meningioma in many countries. Observational epidemiological studies often rely on meningioma patients who were recruited from health institutions and matched controls in studying risk factors for meningioma, using exposure data which are collected retrospectively. For diet and risk of meningioma, published evidence is limited by the lack of prospective evidence (published prospective findings were available for alcohol, tea, and coffee only), the lack of statistical power in each study to detect an association (range of number of cases: 10–390), the small number of studies investigating each particular dietary factor (1–2 studies), and not being able to take account of reverse causation (see Chapter 3).

In this chapter, I report on the risk of meningioma in relation to 29 food groups and nutrients (total fruit, citrus fruit, fruit juice, total vegetables, nuts, grains/cereal, red meat, processed meat, white meat, fish, egg, dairy products, cheese, coffee, tea, carbohydrate, protein, total fat [saturated, monounsaturated, and polyunsaturated], fibre, carotene, vitamin C, vitamin E, folate, calcium, cholesterol, alcohol) and 3 dietary patterns (the Dietary Approaches to Stop Hypertension, the alternate Mediterranean diet score, and the Alternative Healthy Eating Index) in the UK Million Women Study cohort. Meta-analyses combining results from this study with those from relevant published prospective studies, were performed.

7.2 Methods

The methods of recruitment, data collection, follow-up, development of dietary variables, and ascertainment of meningioma have been described in detail in Chapter 4

7.2.1 Exposure variables

Exposure variables have been described in detail in Chapter 4 (section 4.4.3). In brief, energy-standardised-intakes or percentage energy from intakes of 29 food groups or nutrients were used in all analyses reported here unless otherwise specified. The Dietary Approaches to Stop Hypertension (DASH) score, the alternate Mediterranean Diet (aMED) score, and the Alternative Healthy Eating Index (AHEI) were also derived using these energy-standardised dietary intakes. Women were categorised into fourths according to their baseline intakes of the 29 dietary items and nutrients, AHEI, and DASH score. For aMED score, women were categorised into 4 groups: 0–2, 3–4, 5–6, 7–9 points.

7.2.2 Outcome

The outcome of interest was meningioma. This was ascertained by combining ICD-10 codes for central nervous system (CNS) tumours (C70–C72, C75.1–C75.3, D32–D33, D35.2–35.4, D42–D43, D44.3–D44.5) and ICD-O-3 morphology codes for meningioma (9530.0–9539.1).

7.2.3 Statistical analysis

Women were excluded under standard rules if they had no corresponding follow-up information (n=18), or had missing information on date of birth (n=544), date of follow-up (n=9), or date of dietary assessment (n=6). Women were also excluded if they had, prior to the baseline dietary assessment, any cancer or any benign CNS tumours (n=45,953) (ICD-10 C00–C97 [except non-melanoma skin cancer ICD-10 C44] and ICD-10 D32–D33, D35.2–35.4, D42–D43, D44.3–D44.5, respectively], or any diagnosis of neurofibromatosis or tuberous sclerosis (n=181) (ICD-10 Q85.0

and ICD-10 Q85.1, respectively); or reported having changed their diet because of illness within 5 years prior to the baseline dietary assessment (n=123,937); or reported an implausible energy intake (<500 or >3500 kcal/day) in the baseline dietary assessment (n=4,276) (Figure 6.1). The remaining women (N=692,176) contributed person-years from the date of baseline dietary assessment until the earliest of the date of registration of meningioma or any CNS tumour or any cancer (except non-melanoma skin cancer), date of death, date of loss to follow-up (about 1% of the entire cohort), or the last date of follow-up (31 December 2015).

Risk of meningioma (relative risks [RRs] and 95% confidence intervals [CIs]) in relation to the 29 food groups or nutrients and 3 dietary patterns were calculated using Cox regression models with time in the study as the underlying time variable, stratified by year of birth and year of baseline dietary assessment. RRs were calculated using the lowest fourth category as the reference group (the group with 0–2 points for the aMED score). RRs were treated as floated absolute risks and group-specific confidence intervals (gs-CIs) were estimated and are presented in figures,[1, 2] while conventional 95% CIs are given in tables and in the text. For the three dietary patterns, linear trend across the four categories of scores was assessed by Wald's test statistics by modelling the baseline categorical variables as continuous variables in the model. For the 29 food groups or nutrients, linear trend was estimated using re-measured dietary intakes collected from the Oxford WebQ to correct for regression dilution bias (mean intakes of food groups or nutrients by level of consumption in fourths at baseline were substituted by means of re-measured intakes).

Analyses were conducted using the multivariate nutrient density method[3]. Energy-standardised dietary intakes and derived dietary patterns were used as the primary exposures, and all analyses were adjusted for dietary energy intake (fourths), height (<160, 160–164.9, 165–169.9, ≥170 cm), body mass index (<25, 25–29.9, ≥30 kg/m^2), strenuous exercise (never/rarely, <1, ≥1 times per week), social deprivation (thirds based on Townsend deprivation index), level of educational attainment (<12 years, secondary, tertiary – had a university degree), smoking

status (never, past, current), alcohol intake (<1, ≥1 drinks per day) (except of the analysis of alcohol and meningioma risk), parity (nulliparous, parous), oral contraceptive use (never, ever), use of menopausal hormones (never, past, current), and region of residence (nine geographical regions in England, plus Scotland). Information was missing (or reported as unknown) for <2.7% for each of the adjustment variables apart from BMI (7.5%) and alcohol intake (12.4%). To ensure that the same women were compared in all analyses, women with a missing value for any of the adjustment variables were assigned a separate category. A Bonferroni correction[4] was applied (by multiplying the nominal p value by 32) to correct for multiple testing. Statistical significance was defined as a two-sided p value of less than 0.05 after applying the Bonferroni correction. All analyses were also stratified by follow-up time (first 5 years and 5 or more years) to explore possible reverse causation between diet and risk of meningioma.

7.2.4 Meta-analysis

Published prospective studies reporting associations between diet and risk of meningioma were identified from a systematic search on Medline and Embase databases up to 1 May 2018 (see Chapter 3). Meta-analyses were conducted combining RRs comparing the highest versus lowest for each particular dietary factor from the Million Women Study and those from published studies which have a minimum of 5 exposed meningioma cases, where available. Heterogeneity of results between studies was assessed by a χ^2 test.

All analyses were performed in Stata Statistical Software: Release 15 (StataCorp, College Station, TX USA). Figures were drawn in R version 3.3.3 (The R Foundation for Statistical Computing).

7.3 Results

7.3.1 Study populations and baseline characteristics

This analysis included 692,176 women. A total of 750 meningiomas (of which 729 [97.2%] were non-malignant) were registered after a mean 12.7-year follow-up (8.8 million person-years). Baseline characteristics, dietary energy intake, and intakes of energy contributing macronutrients of all women are shown in Table 6.1 (Supplementary Table B.8 in Appendix B shows all dietary factors assessed in this chapter).

7.3.2 Diet and risk of meningioma in the Million Women Study

There were no significant linear associations between any of the 29 food groups or 3 dietary patterns and risk of meningioma after applying a Bonferroni correction for multiple testing. Before correction, there were some weak linear associations between intakes of some dietary factors and risk of meningioma, as described below.

Before correction for multiple testing and in analyses of all follow-up time, there was weak evidence for an increased risk of meningioma in relation to increasing percentage energy intake from monounsaturated fat ($p_{uncorrected}$ for trend = 0.037) (Figure 7.1 left panel). In analyses including the first 5 years of follow-up only, there was some evidence for increased risk of meningioma in relation to increasing consumption cholesterol ($p_{uncorrected}$ for trend = 0.016), and decreased meningioma risk in relation to increasing consumption of citrus fruit ($p_{uncorrected}$ for trend = 0.013) and vitamin C ($p_{uncorrected}$ for trend = 0.001) (Figure 7.1 middle panel). In analyses excluding the first 5 years of follow-up, there was weak evidence for a decreased risk in relation to increasing consumption of white meat ($p_{uncorrected}$ for trend = 0.050) (Figure 7.1 right panel).

7.3.3 Diet and risk of meningioma: meta-analysis of all available prospective evidence

Independent evidence from published prospective studies was found for 3 dietary factors: alcohol (1 study)[5], coffee (1 study)[6], and tea (2 studies)[6, 7]. None of the published studies had reported results that were stratified by follow-up time, so results extracted from published studies were combined with results from analyses of all follow-up time presented here. The number of exposed cases in each of the published prospective studies was small (n≤52), so the inclusion of published prospective studies adds little to the evidence already presented here (Figure 7.2). Summary RRs (combining RRs which compared highest versus lowest intake in each study) for meningioma in relation to the 3 dietary factors were: alcohol (0.93, 95% CI 0.77–1.13), coffee (0.94, 95% CI 0.76–1.15), and tea (1.02, 95% CI 0.84–1.24). There was no significant heterogeneity for RRs in relation to any of the 3 dietary factor between the Million Women Study and the published literature when their results were combined using meta-analysis.

7.4 Discussion

There is little prospective evidence for an association between diet and risk of meningioma as shown in the systematic investigation into diet presented here. Initially, there were some weak linear associations between increasing energy percentage from consumption of monounsaturated fat and increased meningioma risk but they were not statistically significant after correction for multiple testing. Analyses were also done by stratifying follow-up time to explore possible reverse causation. In the analyses including the first 5 years of follow-up, initially, significantly increased meningioma risk was found for increasing consumption of cholesterol, and decreased risk was found for increasing consumption of citrus fruit, or of vitamin C, but none were statistically significant after correction for multiple testing, and RRs of these associations largely attenuated towards the null with all 95% CIs including 1.00 in the analyses excluding the first 5 years of follow-up.

Published evidence for diet and risk of meningioma is very limited. The Million Women Study and the Iowa Women's Health Study have investigated risk of meningioma in relation to alcohol intake[5, 8] while the European Prospective Investigation into Cancer and Nutrition (EPIC) Study and the Japan Public Health Center-Based Prospective (JPHC) Study have investigated the association between tea and/or coffee intake and risk of meningioma[6, 7]; however none of them report any significant findings. Prospective evidence for other food groups, all nutrients, and dietary patterns is lacking. Based on more exposed cases for alcohol and more than triple the number of exposed cases for coffee and tea than in the published evidence, the analysis in this chapter did not find any significant associations between intakes of alcohol, coffee, or tea and risk of meningioma either. My analyses provide the first prospective evidence for 12 dietary factors (total fruit, citrus fruit, total vegetable, grains/cereal, processed meat, fish, eggs, protein, total fat, saturated fat, fibre, and cholesterol), and novel and prospective evidence for 14 dietary factors (fruit juice, nuts, red meat, poultry, dairy products, cheese, carbohydrate, monounsaturated fat, polyunsaturated fat, carotene, vitamin C, vitamin E, folate, and calcium), as well as DASH score, aMED score, and AHEI. The results were not changed when correction for multiple testing was conducted using the FDR method with Benjamini-Hochberg procedures[9] or a method correcting for the number of 'effective exposure'[10].

Results presented here are not entirely consistent with those reported in retrospective studies. Retrospective studies have reported significant associations between: high intake of saturated fat and increased risk of glioma; and high intake of total fruit and decreased risk of meningioma (see Chapter 3). I did not find any significant associations between intakes of saturated fat or total fruit and risk of meningioma (even before correction for multiple testing), either in analyses of all follow-up time or in analyses excluding the first 5 years of follow-up. It is not known to what extent these published significant findings were due to selective reporting commonly seen in nutritional epidemiology studies[11] as well as differential recall of exposure and bias in selection of study participants, as often seen in retrospective studies. Biases caused by proxy responses in retrospective studies of diet and

meningioma risk could be relatively low compared to studies of glioma as seen in one study which reported the proportion of proxy responders as 11.9%,[12] whereas this proportion ranged from 8%-76% in glioma studies[13–20], because meningioma is generally benign and not rapidly fatal.

The potential associations found between diet and risk of meningioma may be explained by reverse causation. The association between monounsaturated fat intake and risk of meningioma found in analyses including all follow-up time (although not significant after correction for multiple testing) attenuated in the analyses excluding the first 5 years of follow-up. However, the analyses that excluded the first 5 years of follow-up (having about 70% of all meningioma cases) has weaker statistical power than analyses using all follow-up time. It is important for future studies explore potential reverse causation as well as to collect information on dietary changes and exclude those who reported making major changes to diet due to illness prior to baseline dietary assessment to reduce the impact of reverse causation because the proportion of individuals reporting making major changes to diet due to illness prior to dietary assessment in the Million Women Study (which was excluded from further analyses) is not low (14%).

Although there were no significant linear associations between any dietary factors and risk of meningioma in analyses excluding the first 5 years of follow-up, there were some weak significant associations for the RR comparing highest versus lowest fourth for intakes of nuts (RR 1.41, 95% CI 1.04–1.89, p = 0.025) and white meat (RR 0.74, 95% CI 0.57–0.96, p = 0.024) before correction for multiple testing. The risk of meningioma associated with intakes of nuts or white meat may simply be chance findings, and the association with nuts may be due to residual confounding from education: women with tertiary education had a 42% higher intake of nuts (see Table 4.11 in Chapter 4) and a significantly increased risk for meningioma (RR 1.24, 95% CI 1.07-1.43) when compared with women with <12 years of education (see Table 4.13 in Chapter 4). Although all analyses were adjusted for level of education, residual confounding from education cannot be excluded.

7.4.1 Strengths and weaknesses

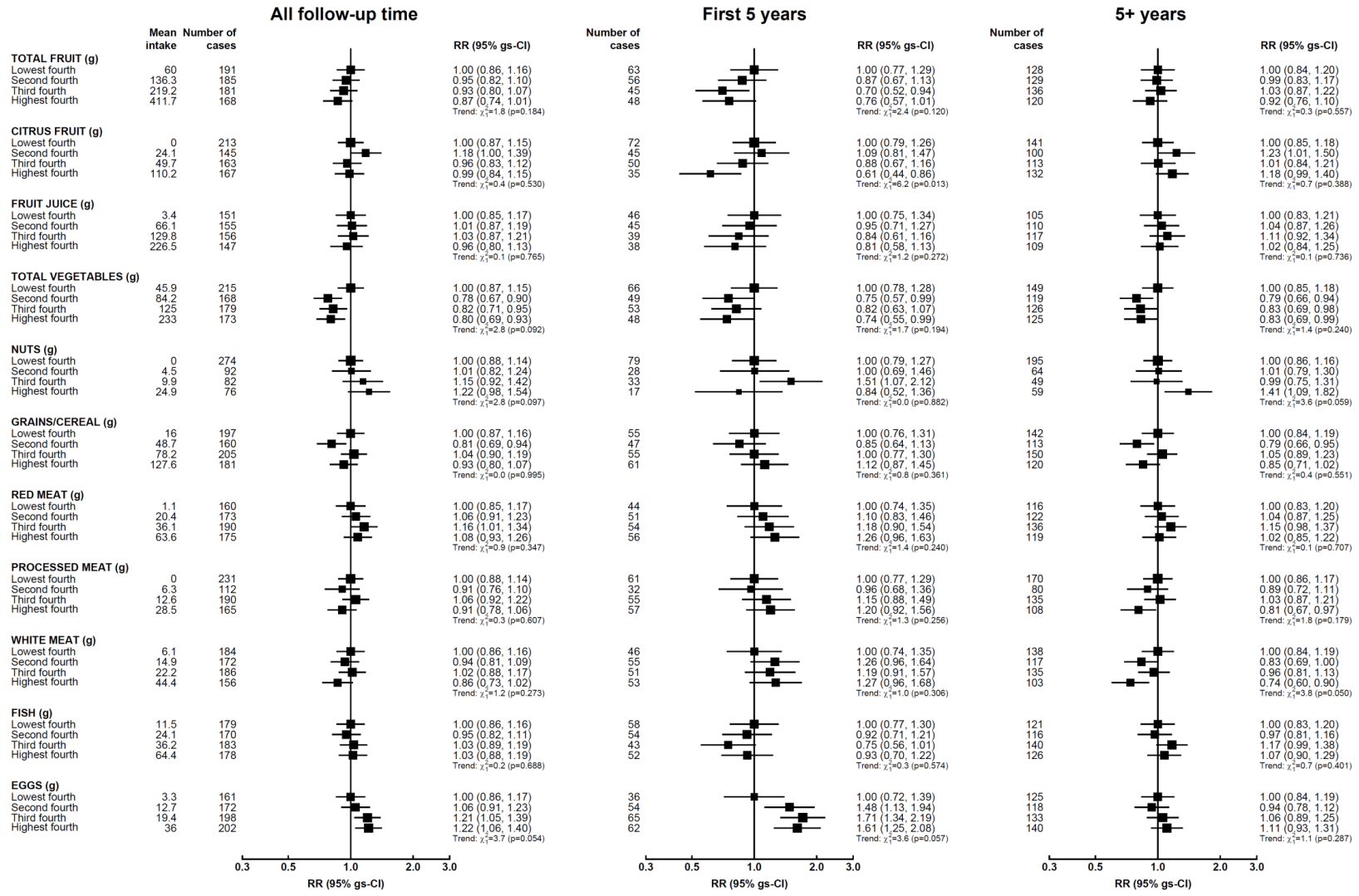
As discussed in Chapter 6, the strengths of the Million Women Study include its collection of comprehensive information on dietary and non dietary data (allowing systematic investigation into diet and statistical adjustment for many potential confounders), prospective design (preventing biases common in retrospective studies as discussed previously), electronic linkage for follow-up (limiting differential loss to follow-up), and large size (with many cases for rare tumours). This is the largest study for diet and risk of meningioma thus far with 0.7 million participants and 750 incident cases over about 8.8 million person-years of follow-up (the previous largest study published had 332 cases)[20]. The NIH-AARP Study has information on malignant meningioma (which is extremely rare) only while the PLCO Study has no information on meningioma. Despite being the largest, this study is still underpowered to detect or exclude moderate increased or decreased risks (RR 2.0-2.5) associated with diet. This Million Women Study analysis has 80% power with 95% significance to detect an observed RR comparing extreme fourths of dietary intakes of $\leq$0.75 or $\geq$1.34 in analyses of all follow-up time, and $\leq$0.71 or $\geq$1.41 in analyses excluding 5 years of follow-up. When allowance is made for measurement errors, this analysis have 80% power with 95% significance to detect a true RR of $<$2.5 ($\leq$0.49 to $\leq$0.62 or $\geq$1.62 to $\geq$2.06 in analyses of all follow-up time, and $\leq$0.42 to $\leq$0.56 or $\geq$1.78 to $\geq$2.37 in analyses excluding 5 years of follow-up) (estimated using regression coefficients of 0.6–0.4 between true and measured dietary intakes as described in Chapter 3).Another limitation of this analysis is that it was carried out in a women-only cohort, so results from this analysis do not contribute to the evidence for diet and risk of meningioma in men, which is extremely limited. It is, however, important to note that meningioma is rare and the incidence of meningioma in men is about half that of women in the US[21] (there is no information on the incidence of meningioma by sex in the UK).

7.4.2 Conclusion

This is the largest prospective study to date and suggests that there is little evidence for an association between diet and risk of meningioma of moderate to large magnitude, at least in women. This conclusion was further strengthened by the analysis excluding the first 5 years of follow-up, which reduces the impact of reverse causation. Given that meningioma is relatively rare and the investigation into diet carried out here was systematic and thorough, this report is unlikely to have overlooked any association between diet and risk of meningioma that is of major public health concern.

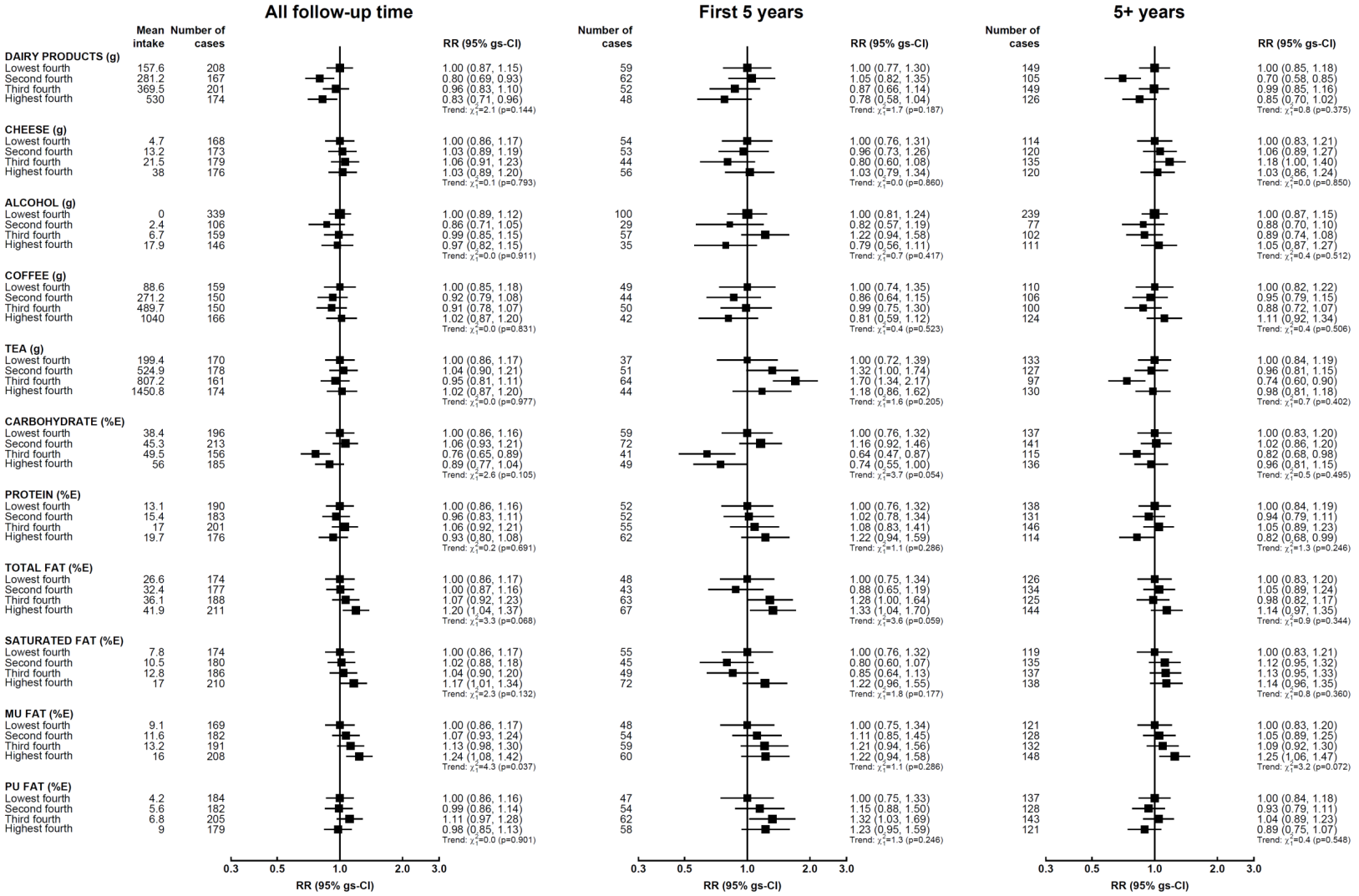
7.5 Figures

Figure 7.1: Diet and risk of meningioma in the Million Women Study



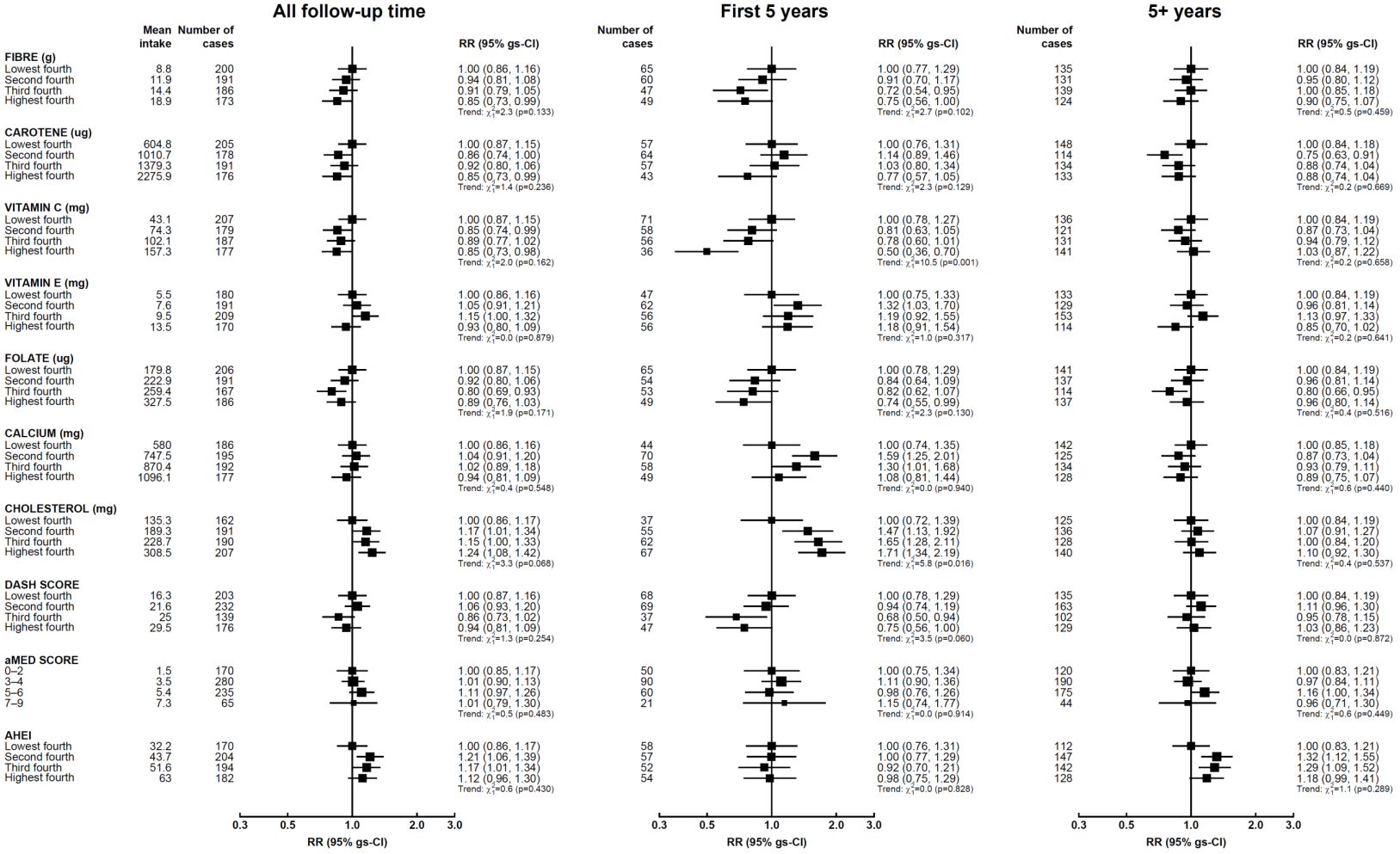
All analyses were stratified by year of birth and year of dietary assessment, and adjusted for dietary energy intake (fourths), height (<160, 160–164.9, 165–169.9, ≥170 cm), body mass index (<25, 25–29.9, ≥30 kg/m^2), strenuous exercise (never/rarely, <1, ≥1 times per week), social deprivation (thirds based on Townsend deprivation index), education (<12 years, secondary, tertiary), smoking status (never, past, current), alcohol intake (<1, ≥1 drinks per day) (except of the analysis of alcohol and meningioma risk), parity (nulliparous, parous), oral contraceptive use (never, ever), use of menopausal hormones (never, past, current), and region of residence (nine geographical regions in England, and Scotland). All p values for trend shown here were uncorrected.

Figure 7.1: Diet and risk of meningioma in the Million Women Study (continued)



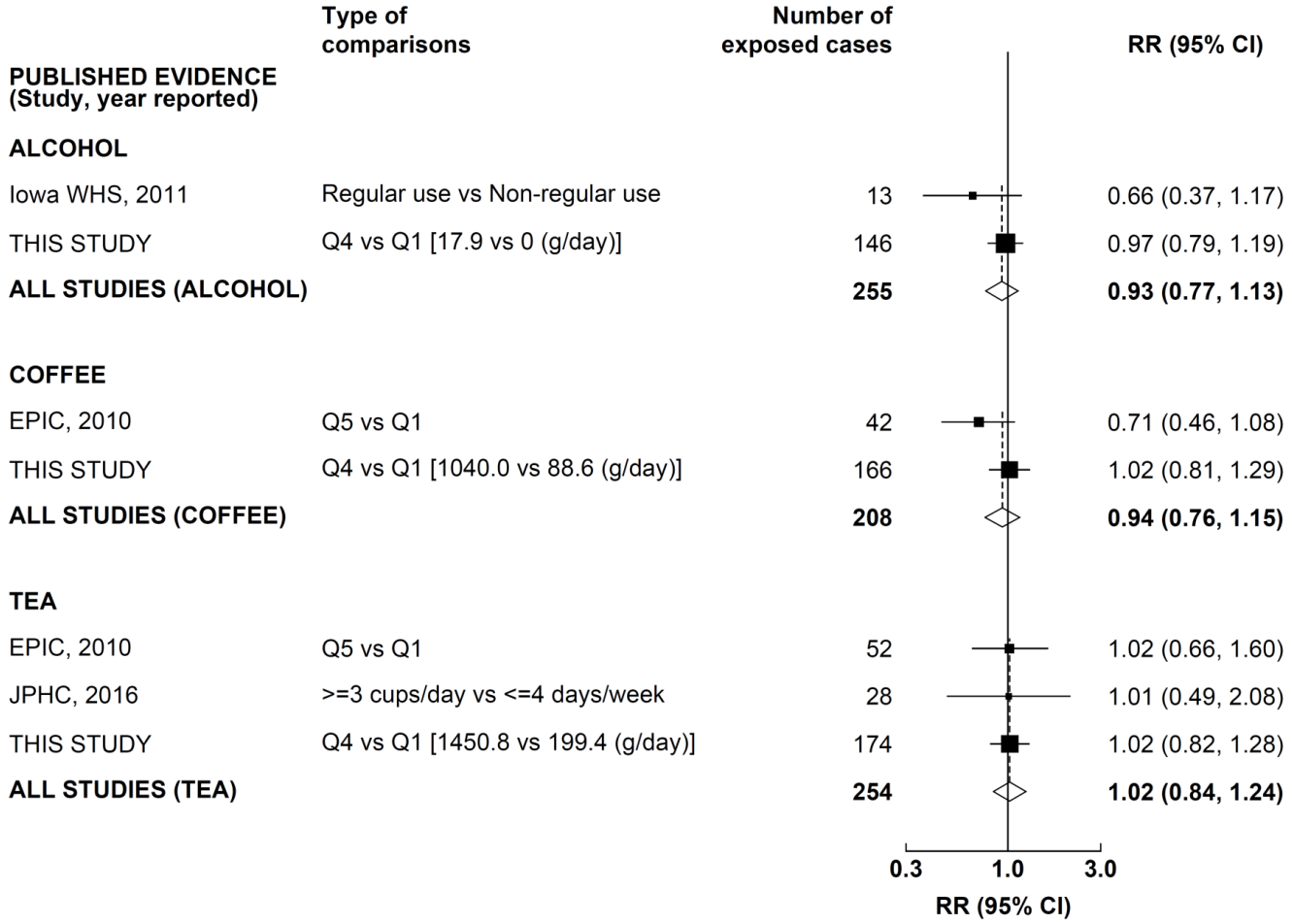
All analyses were stratified by year of birth and year of dietary assessment, and adjusted for dietary energy intake (fourths), height (<160, 160–164.9, 165–169.9, ≥170 cm), body mass index (<25, 25–29.9, ≥30 kg/m^2), strenuous exercise (never/rarely, <1, ≥1 times per week), social deprivation (thirds based on Townsend deprivation index), education (<12 years, secondary, tertiary), smoking status (never, past, current), alcohol intake (<1, ≥1 drinks per day) (except of the analysis of alcohol and meningioma risk), parity (nulliparous, parous), oral contraceptive use (never, ever), use of menopausal hormones (never, past, current), and region of residence (nine geographical regions in England, and Scotland). All p values for trend shown here were uncorrected.

Figure 7.1: Diet and risk of meningioma in the Million Women Study (continued)



All analyses were stratified by year of birth and year of dietary assessment, and adjusted for dietary energy intake (fourths), height (<160, 160–164.9, 165–169.9, ≥170 cm), body mass index (<25, 25–29.9, ≥30 kg/m^2), strenuous exercise (never/rarely, <1, ≥1 times per week), social deprivation (thirds based on Townsend deprivation index), education (<12 years, secondary, tertiary), smoking status (never, past, current), alcohol intake (<1, ≥1 drinks per day) (except of the analysis of alcohol and meningioma risk), parity (nulliparous, parous), oral contraceptive use (never, ever), use of menopausal hormones (never, past, current), and region of residence (nine geographical regions in England, and Scotland). All p values for trend shown here were uncorrected.

Figure 7.2: Meta-analysis showing risk of meningioma in relation to 3 dietary factors with independent evidence from published prospective studies



Iowa WHS The Iowa Women's Health Study, EPIC The European Prospective Investigation into Cancer and Nutrition Study, JPHC The Japan Public Health Center-Based Prospective Study

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8

Diet and Risk of Pituitary Tumours and Vestibular Schwannoma in the UK Million Women Study Cohort

8.1 Introduction

Both pituitary tumours and vestibular schwannoma are rare central nervous system (CNS) tumours, which are generally benign and not always registered by cancer registries. In the literature, there is very limited evidence with regards to epidemiological risk factors as well as dietary risk factors for the two tumours (see Chapters 2&3). The Million Women Study has accrued about 200 cases for each of the tumours since the 3-year re-survey and has the best statistical power thus far to systematically study their associations with diet.

In this chapter, I report on the risk of pituitary tumours and risk of vestibular schwannoma in relation to 29 food groups and nutrients (total fruit, citrus fruit, fruit juice, total vegetables, nuts, grains/cereal, red meat, processed meat, white meat, fish, egg, dairy products, cheese, coffee, tea, carbohydrate, protein, total fat [saturated, monounsaturated, and polyunsaturated], fibre, carotene, vitamin C, vitamin E, folate, calcium, cholesterol, alcohol) and 3 dietary patterns (the Dietary Approaches to Stop Hypertension, the alternate Mediterranean diet score, and the Alternative Healthy Eating Index) in the UK Million Women Study cohort.

8.2 Methods

The methods of recruitment, data collection, follow-up, development of dietary variables, and ascertainment of pituitary tumours and of vestibular schwannoma have been described in detail in Chapter 4.

8.2.1 Exposure variables

The exposure variables have been described in detail in Chapter 4 (section 4.4.4). In brief, energy-standardised-intakes or percentage energy from intakes of 29 food groups or nutrients were used in all analyses reported here unless otherwise specified. Dietary Approaches to Stop Hypertension (DASH) score, the alternate Mediterranean Diet (aMED) score, and the Alternative Healthy Eating Index

(AHEI) were also derived using these energy-standardised dietary intakes. Women were categorised into fourths according to their intakes at baseline of the 29 dietary items and nutrients, AHEI, and DASH score. For aMED score, women were categorised into 4 groups: 0–2, 3–4, 5–6, 7–9 points.

8.2.2 Outcome

The outcomes of interest were pituitary tumours and vestibular schwannoma. Pituitary tumours were ascertained by combining ICD-10 codes for tumours of the pituitary gland (C75.1, D35.2, or D44.3) and ICD-O-3 morphology codes (8000.0–9992.3 excluding 9380.3–9460.3 and 9530.0–9539.1). Vestibular schwannoma was ascertained by combining ICD-10 codes for central nervous system (CNS) tumours (C70–C72, C75.1–C75.3, D32–D33, D35.2–35.4, D42–D43, D44.3–D44.5) and ICD-O-3 morphology codes (9560.0).

8.2.3 Statistical analysis

Women were excluded under standard rules if they had no corresponding follow-up information (n=18), or had missing information on date of birth (n=544), date of follow-up (n=18), or date of dietary assessment (n=6). Women were also excluded if they had, prior to the baseline dietary assessment, any cancer or any benign CNS tumours (n=45,953) (ICD-10 C00–C97 [except non-melanoma skin cancer ICD-10 C44] and ICD-10 D32–D33, D35.2–35.4, D42–D43, D44.3–D44.5, respectively], or any diagnosis of neurofibromatosis or tuberous sclerosis (n=181) (ICD-10 Q85.0 and ICD-10 Q85.1, respectively); or reported having changed their diet because of illness within 5 years prior to the baseline dietary assessment (n=123,937); or reported an implausible energy intake (<500 or >3500 kcal/day) in the baseline dietary assessment (n=4,276) (see Figure 6.1). The remaining women (N=692,176) contributed person-years from the date of baseline dietary assessment until the earliest of the date of registration of pituitary tumours (for the analysis of pituitary tumours) or vestibular schwannoma (for the analysis of vestibular schwannoma)

or any CNS tumour or any cancer (except non-melanoma skin cancer), date of death, date of loss to follow-up (about 1% of the entire cohort), or the last date of follow-up (31 December 2015).

Relative risks (RRs) and 95% confidence intervals (CIs) of pituitary tumours and of vestibular schwannoma in relation to the 29 food groups or nutrients and 3 dietary patterns were calculated using Cox regression models with time in the study as the underlying time variable, stratified by year of birth and year of baseline dietary assessment. RRs were calculated using the lowest fourth category as the reference group (the group with 0–2 points for the aMED score). RRs were treated as floated absolute risks and group-specific confidence intervals (gs-CIs) were estimated and are presented in figures,[1, 2] while conventional 95% CIs are given in tables and in the text. For the three dietary patterns, linear trend across the four categories of scores was assessed by Wald's test statistics by modelling the baseline categorical variables as continuous variables in the model. For the 29 food groups or nutrients, linear trend was estimated using re-measured dietary intakes collected from the Oxford WebQ to correct for regression dilution bias (mean intakes of food groups or nutrients by level of consumption in fourths at baseline were substituted by means of re-measured intakes).

Analyses were conducted using the multivariate nutrient density method.[3] Energy-standardised dietary intakes and derived dietary patterns were used as the primary exposures, and all analyses were adjusted for dietary energy intake (fourths), height (<160, 160–164.9, 165–169.9, ≥170 cm), body mass index (<25, 25–29.9, ≥30 kg/m^2), strenuous exercise (never/rarely, <1, ≥1 times per week), social deprivation (thirds based on Townsend deprivation index), education (<12 years, secondary, tertiary), smoking status (never, past, current), alcohol intake (<1, ≥1 drinks per day) (except of the analysis of alcohol and risk of pituitary tumours and vestibular schwannoma), parity (nulliparous, parous), oral contraceptive use (never, ever), use of menopausal hormones (never, past, current), and region of residence (nine geographical regions in England, plus Scotland). Information was

missing (or reported as unknown) for <2.7% for all adjustment variables apart from BMI (7.5%) and alcohol intake (12.4%). To ensure the same women were compared in all analyses, women with a missing value for any of the adjustment variables were assigned a separate category. A Bonferroni correction[4] was applied (by multiplying the nominal p value by 32) to correct for multiple testing. Statistical significance was defined as a two-sided p value of less than 0.05 after applying the Bonferroni correction. All analyses were also stratified by follow-up time (first 5 years and 5 or more years) to explore possible reverse causation between diet and risk of pituitary tumours or vestibular schwannoma.

There was no published prospective evidence for any dietary factor and risk of pituitary tumours or vestibular schwannoma, and so no meta-analysis was performed.

All analyses were performed in Stata Statistical Software: Release 15 (StataCorp, College Station, TX USA). Figures were drawn in R version 3.3.3 (The R Foundation for Statistical Computing).

8.3 Results

8.3.1 Study populations and baseline characteristics

These analyses included 692,176 women. A total of 191 pituitary tumours (of which 186 [97.4%] were non-malignant) and 174 vestibular schwannomas (all were non-malignant) were registered after a mean 12.7-year follow-up (8.8 million person-years). Baseline characteristics, dietary energy intake, and intakes of energy contributing macronutrients of all women are shown in Table 6.1 (Supplementary Table B.8 in Appendix B shows all dietary factors assessed in this chapter).

8.3.2 Diet and risk of pituitary tumours in the Million Women Study

There were no significant linear associations between any of the 29 food groups, nutrients, or 3 dietary patterns and risk of pituitary tumours in either analyses

including all follow-up time or analyses stratified by follow-up time (first 5 year, 5 or more years), both before and after correction for multiple testing (Figure 8.1). When comparing the highest fourth against the lowest fourth for the intakes of the 29 food groups and nutrients, or the 3 dietary patterns (7–9 vs. 0–2 points for aMED score), there were similarly no significant associations with risk of pituitary tumours.

8.3.3 Diet and risk of vestibular schwannoma in the Million Women Study

There were no significant linear associations between any of the 29 food groups and nutrients, or 3 dietary patterns and risk of vestibular schwannoma after applying a Bonferroni correction for multiple testing (Figure 8.2). Before correction, there were some linear associations between intakes of some dietary factors and risk of vestibular schwannoma, as described below.

Before correction for multiple testing and in analyses of all follow-up time, there was some evidence for an increased risk of vestibular schwannoma in relation to increasing consumption of processed meat ($p_{uncorrected}$ for trend = 0.004) and cheese ($p_{uncorrected}$ for trend = 0.025) (Figure 8.2 left panel). In analyses including the first 5 years of follow-up only, there was some evidence for increased risk of vestibular schwannoma in relation to increasing consumption of fibre ($p_{uncorrected}$ for trend = 0.036) (Figure 8.2 middle panel). In analyses excluding the first 5 years of follow-up, there was some evidence for increased risk of vestibular schwannoma in relation to increasing consumption of processed meat ($p_{uncorrected}$ for trend = 0.009), and decreased risk of vestibular schwannoma in relation to increasing consumption of grains/cereal ($p_{uncorrected}$ for trend = 0.026), fibre ($p_{uncorrected}$ for trend = 0.044), and carotene (0.041) (Figure 8.2 right panel).

8.4 Discussion

This systematic investigation into diet presented in this chapter shows that there is little prospective evidence for an association between diet and risk of pituitary tumours or vestibular schwannoma. For pituitary tumours, there were no significant linear associations with diet in any of the analyses presented here. For vestibular schwannoma, there were, initially, some linear associations between increasing consumption of animal-based products such as processed meat or cheese and increased vestibular schwannoma risk, and between increasing consumption of plant-based products such as grains/cereal or carotene and decreased vestibular schwannoma risk. Increasing consumption of fibre was associated with increased vestibular schwannoma risk in the analysis including the first 5 years of follow-up but with decreased risk in the analysis excluding first 5 years of follow-up. However, none of the associations found between diet and risk of vestibular schwannoma were statistically significant after correction for multiple testing.

Published evidence for diet (including alcohol) and risk of pituitary tumours or vestibular schwannoma is extremely limited. There was one published report for the association between alcohol intake and risk of vestibular schwannoma from a small case-control study (44 cases), in which no significant association was found.[5] There is no published evidence for other dietary factors and risk of vestibular schwannoma, either in studies with retrospective or prospective collection of data. For pituitary tumours, there was one published case-control study reporting no significant associations with intakes of tea, wine, or fat, but the study included children in the study population and was not included in the review in Chapter 3.[6] My analysis provides the largest evidence thus far for associations between the 29 food groups and nutrients and the 3 dietary patterns assessed here and risk of pituitary tumours and vestibular schwannoma. The results were not changed when other multiple testing correction methods, such the FDR method with Benjamini-Hochberg procedures[7] or a method correcting for the number of 'effective exposure'[8] were used.

The association between increasing consumption of fibre and increased risk of vestibular schwannoma found in the analyses including the first 5 years of follow-up only (although not significant after correction for multiple testing) may be due to reverse causation (correlation between total fruit and fibre = 0.6). It is important for prospective studies investigating dietary risk factors for CNS tumours including vestibular schwannoma to explore reverse causation by performing analyses stratified by follow-up time (statistical power weakened) and to exclude participants who reported making major changes to diet due to illness prior to baseline dietary assessment, as was possible in the present study.

In analyses excluding the first 5 years of follow-up (having about 55% of all cases), the association between increasing consumption of processed meat and increased risk of vestibular schwannoma, and associations between increasing consumption of grains/cereal, fibre, or carotene (correlation between fibre and both grains/cereal or carotene >0.45) and decreased vestibular schwannoma risk before correction for multiple testing may simply be chance findings and/or residual confounding from physical activity: women who reported doing strenuous exercise twice or more per week had lower intake of processed meat (-13.4%), and higher intakes of grains/cereal (+16.4%), fibre (+9.3%), and carotene (+13.4%), and in the analyses excluding first 5 years of follow-up they had 25% decreased vestibular schwannoma risk when compared to women who reported never/rarely doing exercise (results not shown). Although all analyses were adjusted for level of physical activity (strenuous exercise), residual confounding from physical activity cannot be excluded.

8.4.1 Strengths and weaknesses

As discussed in Chapter 6, the strengths of the current analyses include the systematic investigation into diet and statistical adjustment for many potential confounders, the prospective design which prevents the forms of bias occurring in retrospective studies discussed previously, electronic linkage for follow-up (limiting differential loss to follow-up), and large size. One limitation of the current analysis

is that results were generated from analyses using data in a women-only cohort, so they do not contribute to evidence in men. Nonetheless, this is the largest study thus far for diet and risk of pituitary tumours and vestibular schwannoma. The NIH-AARP Study has information on malignant pituitary tumours and vestibular schwannoma (which are extremely rare) only while the PLCO Study do not have information on pituitary tumours and vestibular schwannoma. Despite being the largest, this study is still underpowered to detect a moderate to large increased or decreased risk (RR 3-5) associated with diet. This study has 80% power with 95% significance to detect an observed RR comparing extreme fourths of dietary intakes for pituitary tumours of $\leq$0.56 or $\geq$1.77 in analyses of all follow-up time, and of $\leq$0.51 or $\geq$1.96 in analyses excluding 5 years of follow-up; and for vestibular schwannoma of $\leq$0.55 or $\geq$1.82 in analyses of all follow-up time, and of $\leq$0.45 or $\geq$2.24 in analyses excluding 5 years of follow-up. Because of measurement errors, the study may have 80% power with 95% significance to detect a true RR for pituitary tumours of $\leq$0.24 to $\leq$0.38 or $\geq$2.60 to$\geq$4.19 only in analyses of all follow-up time; and $\leq$0.19 to $\leq$0.32 or $\geq$3.08 to $\geq$5.40 only in analyses excluding 5 years of follow-up; and for vestibular schwannoma of $\leq$0.22 to $\leq$0.37 or $\geq$2.72 to $\geq$4.49 only in analyses of all follow-up time; and $\leq$0.13 to $\leq$0.26 or $\geq$3.82 to $\geq$7.47 only in analyses excluding 5 years of follow-up (estimated using regression coefficients of 0.6–0.4 between true and measured dietary intakes as described in Chapter 3).

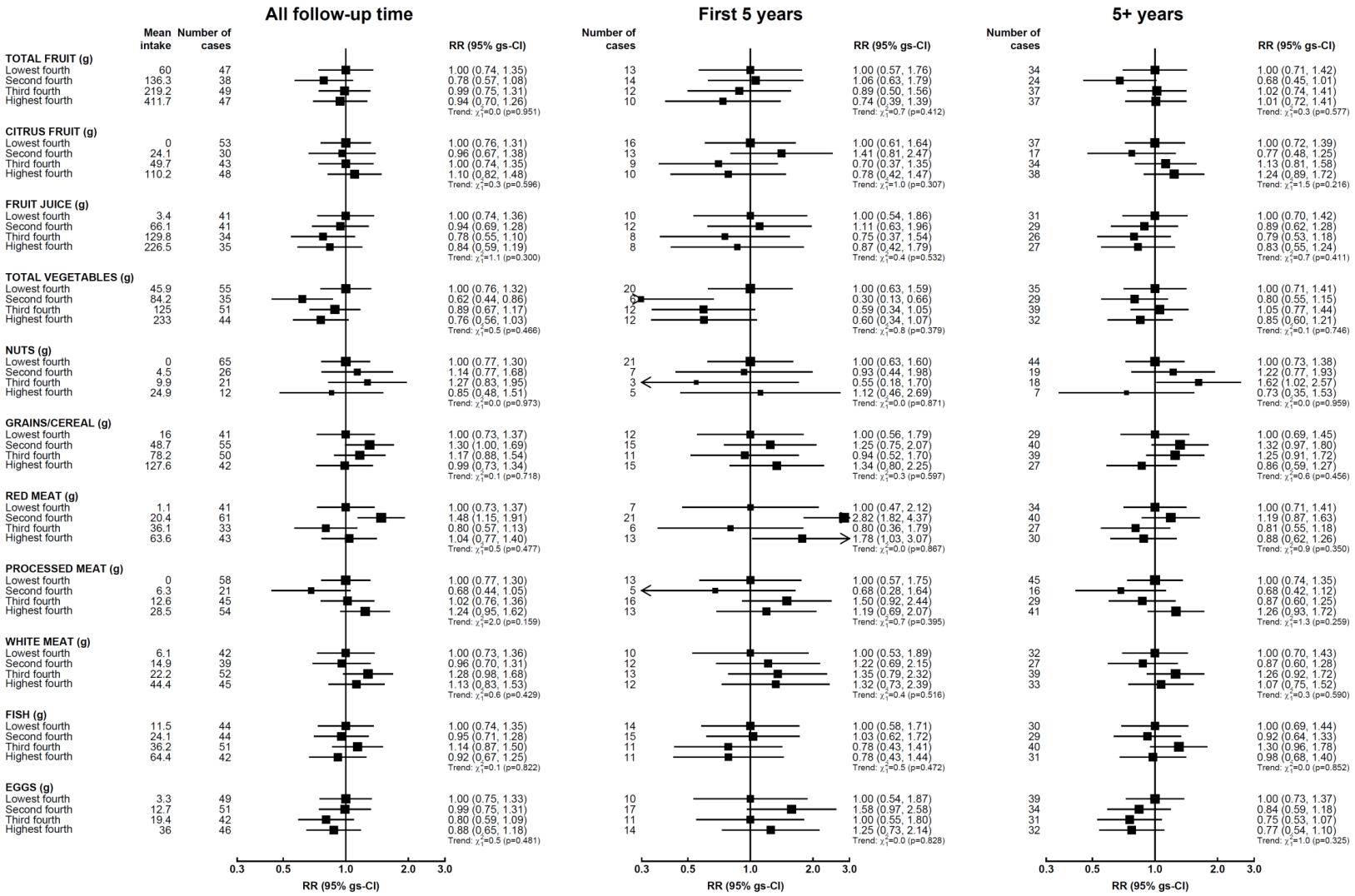
8.4.2 Conclusion

Despite being the largest prospective study to date, this study has inadequate statistical power to detect even a moderate to large increased or decreased risk of pituitary tumours or vestibular schwannoma associated with diet. The limited evidence presented here suggests there is little evidence for substantial relative risks of pituitary tumours and vestibular schwannoma in relation to diet, at least in women. Given the systematic investigation into diet carried out here and the fact that pituitary tumours and vestibular schwannoma are rare and mostly

benign, this report is unlikely to have overlooked any association with diet that is of public health concern.

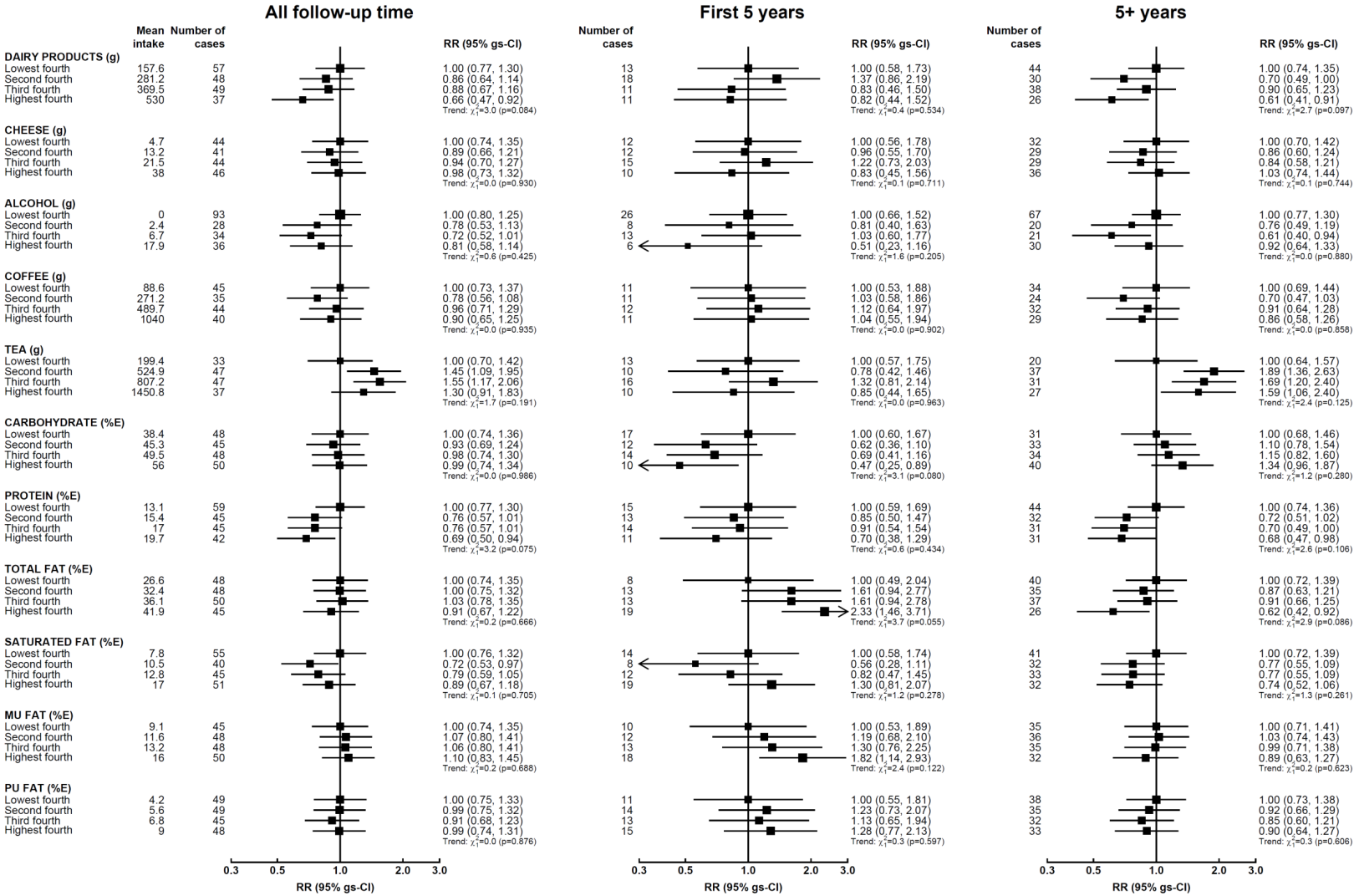
8.5 Figures

Figure 8.1: Diet and risk of pituitary tumours in the Million Women Study



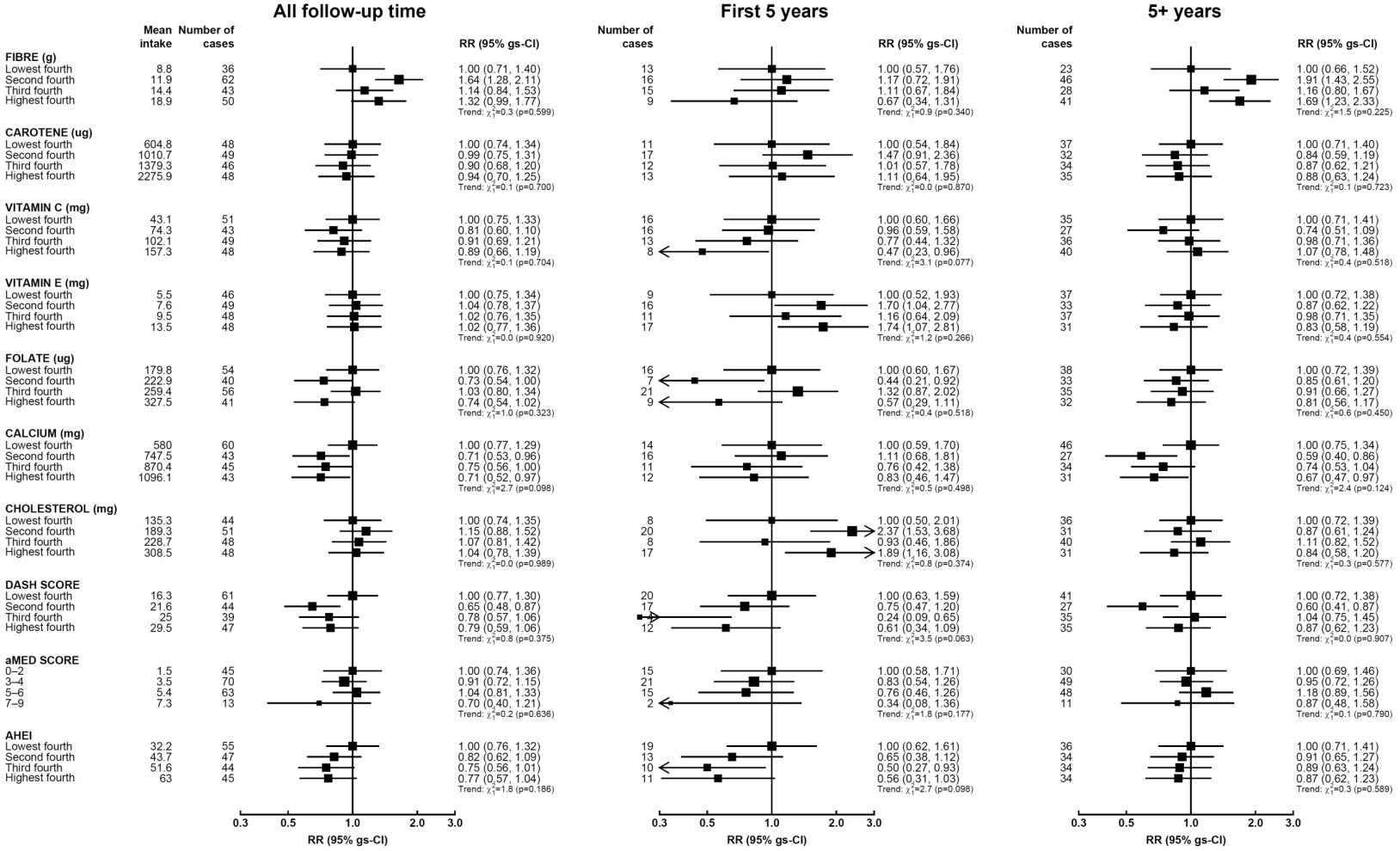
All analyses were stratified by year of birth and year of dietary assessment, and adjusted for dietary energy intake (fourths), height (<160, 160–164.9, 165–169.9, ≥170 cm), body mass index (<25, 25–29.9, ≥30 kg/m^2), strenuous exercise (never/rarely, <1, ≥1 times per week), social deprivation (thirds based on Townsend deprivation index), education (<12 years, secondary, tertiary), smoking status (never, past, current), alcohol intake (<1, ≥1 drinks per day) (except of the analysis of alcohol and pituitary tumour risk), parity (nulliparous, parous), oral contraceptive use (never, ever), use of menopausal hormones (never, past, current), and region of residence (nine geographical regions in England, and Scotland). All p values for trend shown here were uncorrected.

Figure 8.1: Diet and risk of pituitary tumours in the Million Women Study (continued)



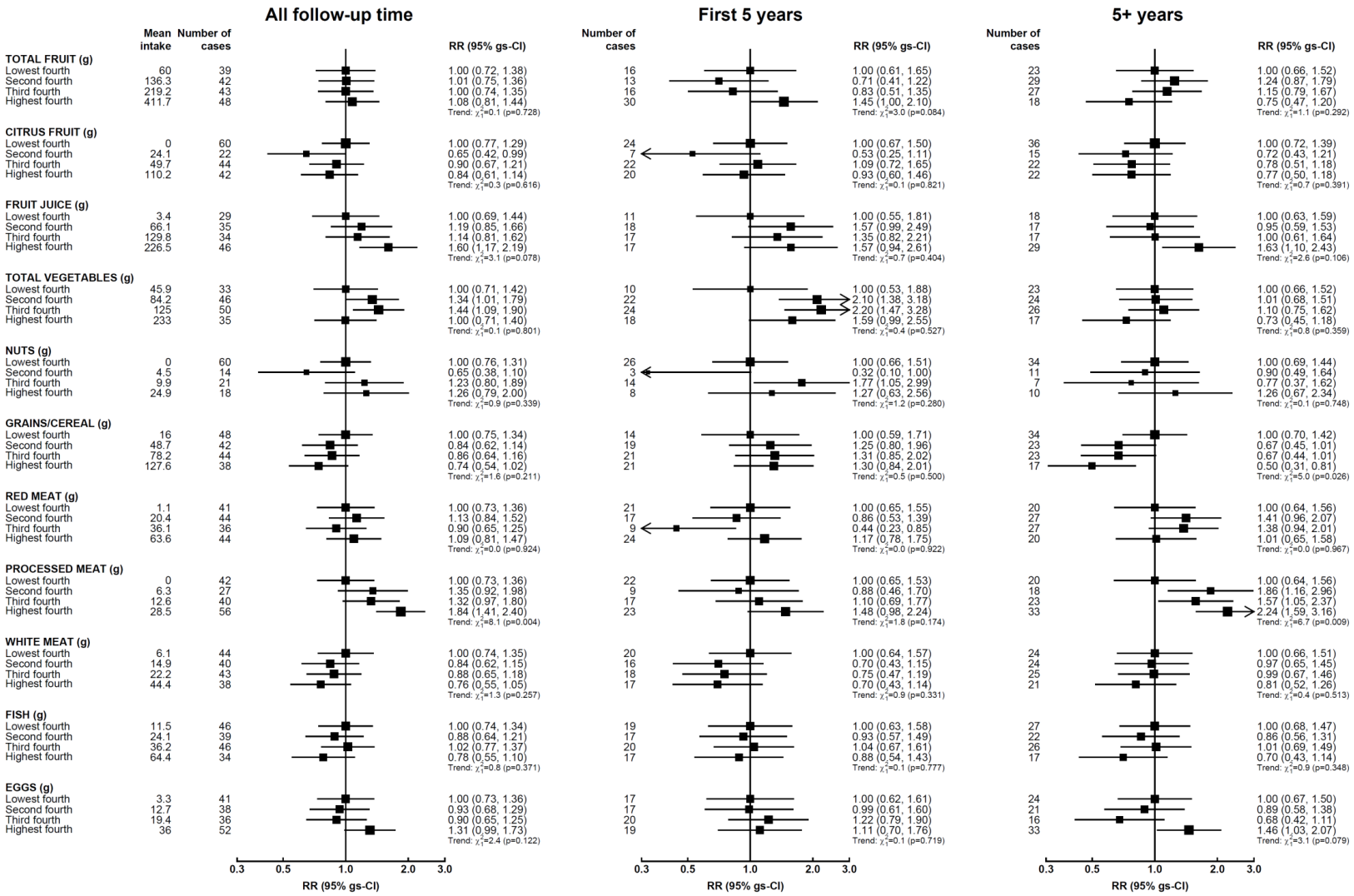
All analyses were stratified by year of birth and year of dietary assessment, and adjusted for dietary energy intake (fourths), height (<160, 160–164.9, 165–169.9, ≥170 cm), body mass index (<25, 25–29.9, ≥30 kg/m^2), strenuous exercise (never/rarely, <1, ≥1 times per week), social deprivation (thirds based on Townsend deprivation index), education (<12 years, secondary, tertiary), smoking status (never, past, current), alcohol intake (<1, ≥1 drinks per day) (except of the analysis of alcohol and pituitary tumour risk), parity (nulliparous, parous), oral contraceptive use (never, ever), use of menopausal hormones (never, past, current), and region of residence (nine geographical regions in England, and Scotland). All p values for trend shown here were uncorrected.

Figure 8.1: Diet and risk of pituitary tumours in the Million Women Study (continued)



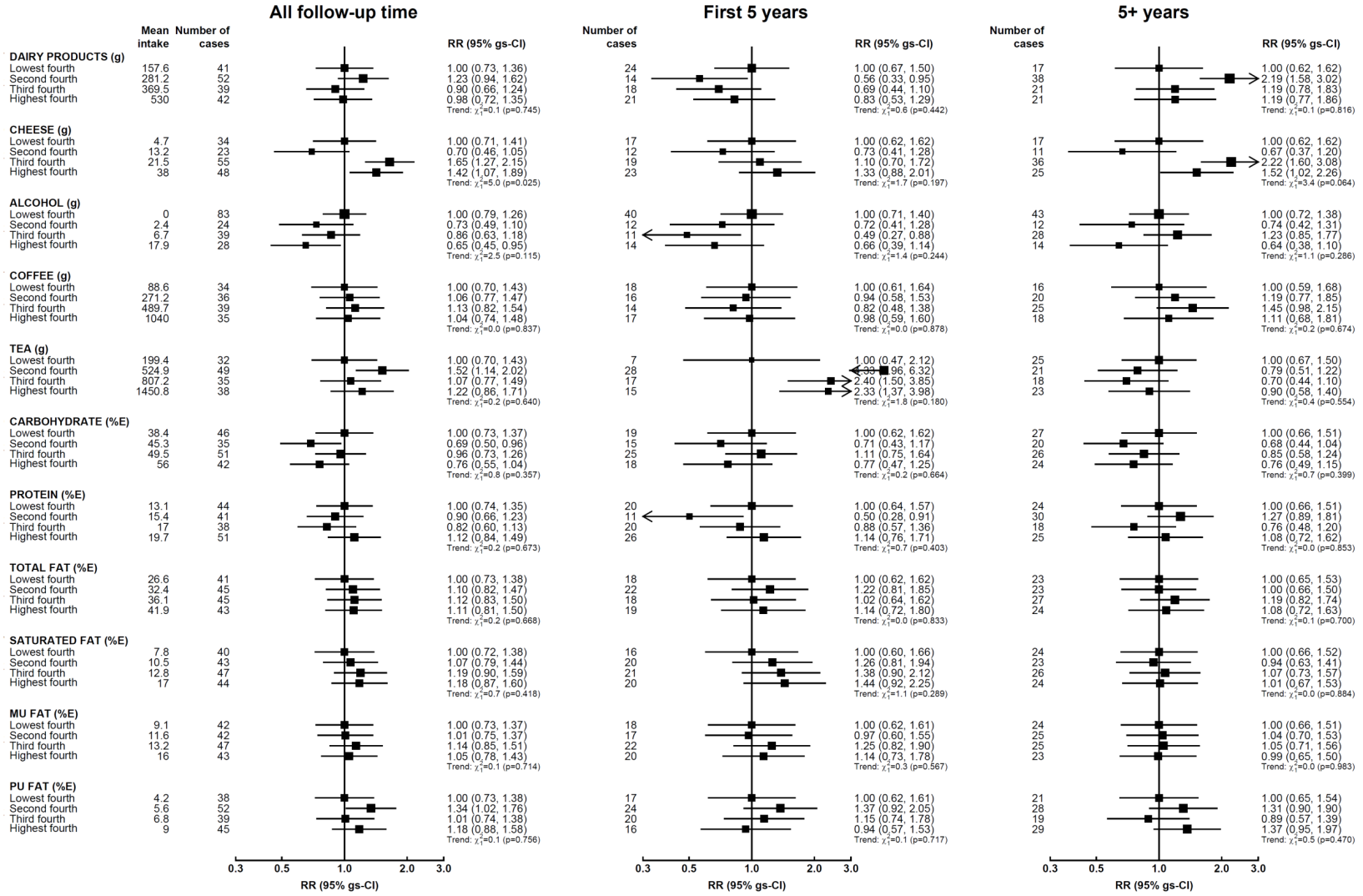
All analyses were stratified by year of birth and year of dietary assessment, and adjusted for dietary energy intake (fourths), height (<160, 160–164.9, 165–169.9, ≥170 cm), body mass index (<25, 25–29.9, ≥30 kg/m^2), strenuous exercise (never/rarely, <1, ≥1 times per week), social deprivation (thirds based on Townsend deprivation index), education (<12 years, secondary, tertiary), smoking status (never, past, current), alcohol intake (<1, ≥1 drinks per day) (except of the analysis of alcohol and pituitary tumour risk), parity (nulliparous, parous), oral contraceptive use (never, ever), use of menopausal hormones (never, past, current), and region of residence (nine geographical regions in England, and Scotland). All p values for trend shown here were uncorrected.

Figure 8.2: Diet and risk of vestibular schwannoma in the Million Women Study



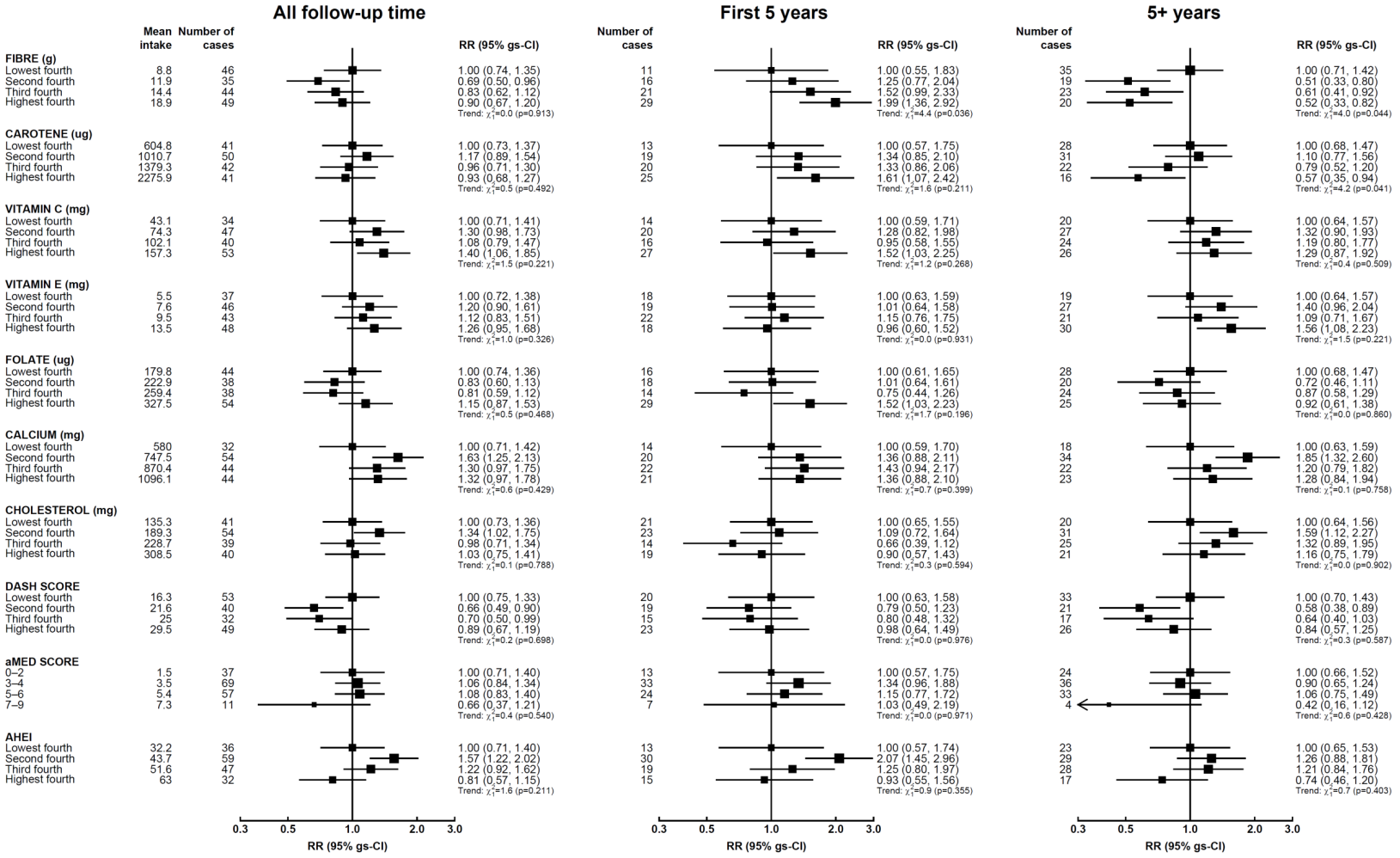
All analyses were stratified by year of birth and year of dietary assessment, and adjusted for dietary energy intake (fourths), height (<160, 160–164.9, 165–169.9, ≥170 cm), body mass index (<25, 25–29.9, ≥30 kg/m^2), strenuous exercise (never/rarely, <1, ≥1 times per week), social deprivation (thirds based on Townsend deprivation index), education (<12 years, secondary, tertiary), smoking status (never, past, current), alcohol intake (<1, ≥1 drinks per day) (except of the analysis of alcohol and vestibular schwannoma risk), parity (nulliparous, parous), oral contraceptive use (never, ever), use of menopausal hormones (never, past, current), and region of residence (nine geographical regions in England, and Scotland). All p values for trend shown here were uncorrected.

Figure 8.2: Diet and risk of vestibular schwannoma in the Million Women Study (continued)



All analyses were stratified by year of birth and year of dietary assessment, and adjusted for dietary energy intake (fourths), height (<160, 160–164.9, 165–169.9, ≥170 cm), body mass index (<25, 25–29.9, ≥30 kg/m^2), strenuous exercise (never/rarely, <1, ≥1 times per week), social deprivation (thirds based on Townsend deprivation index), education (<12 years, secondary, tertiary), smoking status (never, past, current), alcohol intake (<1, ≥1 drinks per day) (except of the analysis of alcohol and vestibular schwannoma risk), parity (nulliparous, parous), oral contraceptive use (never, ever), use of menopausal hormones (never, past, current), and region of residence (nine geographical regions in England, and Scotland). All p values for trend shown here were uncorrected.

Figure 8.2: Diet and risk of vestibular schwannoma in the Million Women Study (continued)



All analyses were stratified by year of birth and year of dietary assessment, and adjusted for dietary energy intake (fourths), height (<160, 160–164.9, 165–169.9, ≥170 cm), body mass index (<25, 25–29.9, ≥30 kg/m^2), strenuous exercise (never/rarely, <1, ≥1 times per week), social deprivation (thirds based on Townsend deprivation index), education (<12 years, secondary, tertiary), smoking status (never, past, current), alcohol intake (<1, ≥1 drinks per day) (except of the analysis of alcohol and vestibular schwannoma risk), parity (nulliparous, parous), oral contraceptive use (never, ever), use of menopausal hormones (never, past, current), and region of residence (nine geographical regions in England, and Scotland). All p values for trend shown here were uncorrected.

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9
Discussion

9.1 Summary of findings

Existing evidence on diet and risk of central nervous system (CNS) tumours was limited and inconsistent. There is a lack of published prospective studies that include the large numbers of CNS tumour cases required for generating reliable evidence in nutritional epidemiology analysis, so drawing firm conclusions based on existing evidence would have been inappropriate. Combining data from three large prospective studies, including new data on both malignant and benign CNS tumours from the Million Women Study, provides the best current epidemiological evidence on associations between diet, including major food groups, nutrients, or common dietary patterns, and risk of the four most common subtypes of CNS tumours (glioma, meningioma, pituitary tumours, and vestibular schwannoma). Despite being the largest, some limitations remain; these studies used dietary data collected through questionnaire at baseline and measurement errors may distort true underlying associations. The observed generally null findings thus do not entirely exclude the possibility of a true association. However, the large size of the current analysis allows us to conclude that it is unlikely that any association of public health importance has been missed. In this chapter the findings for each CNS tumour subtype are summarised, followed by a discussion of relevant methodological issues and interpretation of the results, and suggestions for future work.

9.1.1 Diet and risk of glioma

In the literature, some individual case-control studies found significantly decreased glioma risks with intakes of citrus fruit[1, 2], total vegetables[3], alcohol[4], coffee[5], tea[5], fibre[6], carotene[6, 7], vitamin C[7], vitamin E[3], or DASH score[8]); and significantly increased risk with intakes of grains/cereal[2, 9], processed meat[10], or eggs[2, 9]. In the meta-analyses reported here, combining all published evidence from case-control studies, the associations with total vegetables, grains/cereal, carotene, and DASH score (there was only 1 published study for DASH score) remained statistically significant (Chapter 3). On the contrary, there was some prospective

evidence from the combined analysis of the Health Professionals Follow-Up Study and Nurses' Health Study I II (HPFS, NHS I, NHS II) and a previously published report from the NIH-AARP Study that suggested that high intakes of total fruit or total vegetables may be associated with increased glioma risk, with a possible 'disease mechanism' suggested in the latter study being pesticide residues left on fresh produce.[11, 12] Including a large number of gliomas (2313 cases), in my analyses in the three cohorts I did not find decreased glioma risks associated with intakes of total vegetables or carotene or DASH score; or increased risks associated with intakes of grains/cereal (nor other significant associations found in case-control studies). Rather, my analyses showed little evidence for an association between diet and risk of glioma, with little heterogeneity of results by study or by sex. Initially, there were some generally borderline significant associations between increasing intakes of total fruit like those suggested by recently published prospective studies[11, 12] or other plant-based foods or nutrients (e.g. citrus fruit or fibre), or healthy dietary patterns (e.g. high DASH score), and increasing glioma risk, but none were statistically significant after applying a Bonferroni correction for multiple testing. Using other correction methods (i.e. the false discovery rate method with Benjamini-Hochberg procedures[13] and multiplicity adjustment based on number of 'effective exposure'[14]) to account for multiple testing did not change the conclusion of the analyses. I have also explored potential reverse causation, whereby preclinical disease affects dietary intake, by performing analyses stratified by follow-time (<5, ≥ 5 years) and found that some evidence of differences for the results between the two time periods. In particular, potential associations with dietary factors found in the analyses using all follow-up time remained statistically significant (before correction only) in the analyses of first 5 years of follow-up (having about one third of all cases) but not in analyses of 5+ years of follow-up (having about two third of all cases). So it is important for studies to explore potential reverse causation.

The generally null results presented here provide the best current evidence to suggest that associations found in case-control studies may well be biased by differential recall and participation between cases and controls; and that those

suggested in prospective studies with relatively small number of cases (e.g. total fruit associated with increased glioma risks) could be due to reverse causation, whereby preclinical diseases affects dietary intakes. With the large number of gliomas included in the current analyses, the generally null results suggest that diet is unlikely to be associated with observed RRs for glioma of $\geq$1.18 (or $\leq$0.85) with 80% power at 95% significance level comparing extreme fourth intakes, corresponding to true RRs of about 1.32 to 1.51 (or 0.76 to 0.66) provided that regression coefficients were 0.6 to 0.4 between true and measured dietary intakes, which were coefficients for the great majority of dietary data estimated by questionnaires used in the three studies. Dietary data measured by food frequency questionnaire were subject to measurement errors which may distort the underlying true associations with disease risk so studies need to accrue large number of cases to be able to detect true RRs of moderate magnitude as discussed in Chapter 3. Nevertheless, the combined analysis presented here has included a sufficiently large number of glioma cases to conclude that it is unlikely that any association with diet of moderate to large magnitude (e.g. true RR $\geq$1.5 to 2.0) has been missed and that further investigation using dietary data collected through conventional questionnaire at baseline is unlikely to find an association with glioma risks of major public health importance. RRs of small to moderate magnitude may be detected by combining more data or by improving measurement of dietary data significantly (e.g. use a 7-day diet diary at baseline), which is logistically difficult for large scale epidemiological studies that use conventional questionnaires to collect dietary data, but may be possible with the help of advanced technology (e.g. imaging capabilities of mobile devices; see section 9.3.2). Studying the associations with serum metabolomics which have a more direct effect on the organ system including the CNS than dietary intakes which are subject to variability in digestion (serum biomarker measurements are also more objective than self-reported dietary data) may in turn provide some hint for the role of diet on development of glioma.

9.1.2 Diet and risk of meningioma

In the literature, some individual case-control studies reported significantly decreased meningioma risk with intakes of total fruit[15, 16] and total vegetables[15, 16]; and significantly increased risk with intake of saturated fat[17]. In my meta-analyses combining all published evidence from case-control studies, the associations with total fruit and saturated fat (1 published study only) intake remained statistically significant (Chapter 3). Prospective evidence was scarce and there was no published prospective evidence to support the significant associations found in case-control studies. My analyses in the Million Women Study, which are based on the largest number of meningioma cases (750 cases) thus far, show little evidence for an association between any dietary factor and risk of meningioma. Initially, there was weak evidence for an increased meningioma risk in relation to increasing intakes of monounsaturated fat but it was not statistically significant after applying a Bonferroni correction. The results were not changed when correction for multiple testing were conducted using the FDR method with Benjamini-Hochberg procedures[13] or a method correcting for the number of 'effective exposure'[14]. In analyses excluding the first 5 years of follow-up to reduce potential reverse causation, there was weak evidence for a decreased meningioma risk associated with increasing white meat intake (before correction only); and the association between monounsaturated fat and meningioma risk was no longer statistically significant (even before correction) but the statistical power for these stratified analyses was limited.

As for glioma, the generally null results based on the best current prospective evidence suggest that associations of meningioma risk with dietary intakes previously reported in case-control studies may potentially be spurious. The large number of meningioma included in these analyses suggest that diet is unlikely to be associated with observed RRs for meningioma of $\geq$1.34 (or $\leq$0.75) with 80% power at 95% significance level comparing extreme fourth intakes, corresponding to true RRs of about 1.62 to 2.06 (or 0.62 to 0.49) provided that regression coefficients were 0.6 to 0.4 between true and measured dietary intakes. These results also suggest

further investigation using baseline dietary data collected through conventional questionnaire is unlikely to find an association with meningioma risk of moderate to large magnitude (e.g. true RR $\geq$ 2.0 to 2.5), which is of public health importance. Any attempt to find an association with diet of small to moderate magnitude requires significant improvement in measurement of dietary data used for analysis and/or collaborative effort to combine large meningioma data (see section 9.3). Research into association of meningioma risk with serum metabolomics particularly those which are related to physical activity and/or BMI (associated with meningioma risk; see Chapter 2), may provide clue for further study on diet.

9.1.3 Diet and risk of pituitary tumours and vestibular schwannoma

In the literature, there was only 1 case-control study reporting risk of vestibular schwannoma in relation to diet (alcohol intake only), and there was only 1 case-control study (including children in the study population) reporting risk of pituitary tumours in relation to diet (intake of tea, wine and fat only). Both studies found no significant associations with diet. In the Million Women Study, I found little evidence for a significant association between diet and risk of pituitary tumours or risk of vestibular schwannoma. Initially, increasing consumption of processed meat was associated with increased risk of vestibular schwannoma but it was not statistically significant after correcting for multiple testing using the Bonferroni method. The results were not changed when other correction methods such the FDR method with Benjamini-Hochberg procedures[13] or a method correcting for the number of 'effective exposure'[14] was used. In analyses excluding the first 5 years of follow-up to reduce potential reverse causation, the association between processed meat and vestibular schwannoma risk remained statistically significant (before correction only), and there was also some weak evidence that increasing consumption of plant-based foods or nutrients (i.e. grains/cereal, fibre, and carotene) was associated with decreased risk of vestibular schwannoma (before correction only). For pituitary tumours, there was no evidence of an association with diet in

any analysis, even before correction for multiple testing. The few weak significant associations found with diet (before correction only) among the 32 dietary factors examined for vestibular schwannoma (based on a relatively small number of cases) may be due to chance and so should not be over-emphasised.

Because there was nearly no published evidence at all for diet and risk of pituitary tumours or acoustic neuroma, the current analyses were the first to explore comprehensively any potential association with diet. Despite being the largest dietary analyses for pituitary tumours (191 cases) and vestibular schwannoma (174 cases), the analyses had very limited statistical power to detect an association. In particular, the generally null results suggest diet is unlikely to be associated with observed RRs for pituitary tumours of $\geq$1.77 (or $\leq$0.56) and for vestibular schwannoma of $\geq$1.82 (or $\leq$0.55) with 80% power at 95% significance level comparing extreme fourth intakes, corresponding to true RRs of about 2.60 to 4.19 (or 0.38 to 0.24) for pituitary tumours and of about 2.72 to 4.49 (or 0.37 to 0.22) for vestibular schwannoma (provided that regression coefficients were 0.6 to 0.4 between true and measured dietary intakes). The exploratory analyses with generally null findings here suggest further investigation using dietary data collected through conventional questionnaires at baseline is unlikely to find associations with pituitary tumour or vestibular schwannoma risk of large magnitude (e.g. true RR $\geq$4.0 to 4.5). For extremely rare tumours like pituitary tumours and vestibular schwannoma, associations without RRs of large magnitude are not of major public health concern, so the need for further investigation is negligible.

9.2 Methodological issues and interpretation of the results

The analyses presented in this thesis provide an overview for the associations between diet and risk of CNS tumours. Interpretation of these results should take into account some methodological issues as well as chance findings, confounding, bias, and reverse causation, as described in the following sections.

9.2.1 Measurement errors and regression dilution

Self-reported dietary intakes that are collected through a single questionnaire at baseline are subject to random measurement error, which may appreciably attenuate any possible association examined in epidemiological analysis due to regression dilution.[18, 19] In the Million Women Study, I found that regression dilution ratios for the intakes of the vast majority of food groups and nutrients were lower than 0.5 over time (about 10 years apart). While all the analyses in the Million Women Study were also corrected for regression dilution using re-measured dietary intakes, analyses in the NIH-AARP Study and the PLCO Study were not because there is no information on re-measured dietary intakes. Additionally, to reduce measurement errors related to under-or-over-reporting of dietary intakes, all analyses in this thesis used energy-standardised dietary intakes as the primary exposures because these measurement errors were partly associated with dietary energy intake.[20] It is possible that small but genuine associations between diet and risk of CNS tumours were not detected due to measurement errors that were not accounted for, especially in the NIH-AARP Study and the PLCO Study.

9.2.2 Correlations between dietary intakes

In all three cohorts, there was some degree of correlation between intakes of different dietary items. Associations found for a particular dietary factor could be due to the effect of other correlated dietary factors and may be difficult to interpret. In my systematic review, I did not find strong evidence for an association between any particular dietary factor and risk of subtypes of CNS tumours. Therefore, in the analyses in Chapters 6–8 examining the associations between particular dietary factors and risk of CNS tumours, I did not simultaneously adjust for any other dietary variable.

Because food and beverages are consumed in combination, examining the risk of CNS tumours in relation to combinations of dietary intakes may be more practical

than individual dietary items. Therefore, I also investigated associations between three established healthy dietary patterns and risk of CNS tumours.

9.2.3 The role of chance and correction for multiple testing

Results from nutritional epidemiology studies are likely to be subject to selective reporting of significant findings as well as overstatement of significant associations that are based on weak evidence (small number of cases),[21] for which the play of chance is high. Therefore, a systematic investigation into diet and risk of subtypes of CNS tumours was performed and presented here, but the issue of multiple testing needs to be addressed. To reduce the number of tests, analyses were performed restricting to food groups, nutrients, and dietary patterns which were identified in the systematic review plus carbohydrate (a major macronutrient), monounsaturated and polyunsaturated fat (instead of non-saturated fat identified in the review), and two common dietary patterns (generally covering major components of diet), rather than all dietary variables available in the three cohorts. To control the risk of type I error, the main interpretations were based on results that have been corrected for multiple testing using the Bonferroni method.[22] There is no consensus in the field about which method should be used to account for multiple testing, although principal component analysis may be used to reduce the number of dietary exposures. Other methods used in correction for multiple testing that are less conservative than the Bonferroni method include the false discovery rate method which controls the proportion of falsely rejected null hypothesis (indirectly controlling the rate of type I error)[13], and a method correcting for multiplicity based on the number of 'effective exposures' (highly correlated variables not counted independently)[23] rather than the total number of tests performed. The Bonferroni method used in this thesis does not take account of correlations between dietary exposures, so true associations between diet and risk of CNS tumours may have been missed after applying a more stringent control of the type I error rate. Therefore, all associations that were statistically significant at the conventional significance level (uncorrected

p<0.05) were reported. Uncorrected nominal p values of all tested associations were also presented in the figures to allow an overview of the associations.

Interpretation should also take into consideration factors such as the consistency of the association (across the three cohorts and available existing evidence), strength of the association, and biological plausibility, rather than be solely based on the use of statistical testing and arbitrarily chosen thresholds for statistical significance. For example, although without strong statistical evidence, the play of chance is a less likely explanation for associations between increasing consumption of plant-based foods or nutrients and moderately increased glioma risk, which were consistently observed across the three cohorts presented in this thesis (analyses of all follow-up time) and in published reports with results from the combined analysis of Health Professionals Follow-Up Study and Nurses' Health Study I & II (although not statistically significant)[11]. Other consistent significant findings across the three cohorts include healthier dietary patterns (as measured by increasing dietary pattern scores) and moderately increased glioma risk (no evidence in the literature). The associations between plant-based foods or dietary patterns and risk of glioma, however, may need to consider the impact of confounding, bias, or reverse causation, as discussed next. While the consistency and strength of associations between diet and risk of glioma can be compared across the three cohorts, findings for meningioma, pituitary tumours, and vestibular schwannoma in relation to diet were only available in the Million Women Study.

9.2.4 The role of confounding

Dietary intakes of individuals in these studies varied considerably by many characteristics including smoking, physical activity, and level of educational attainment, which were themselves associated with incidence of subtypes of CNS tumours (see Chapters 4–5). Briefly, intakes of plant-based foods or nutrients and scores of all 3 common healthy dietary patterns (higher scores indicate better adherence) were higher in never smokers than current smokers, in individuals with higher

educational attainment than those with lower, and in individuals who did more strenuous exercise than those who did less. The relative risks of subtypes of CNS tumours in relation to these non-dietary factors were generally much greater than those in relation to diet, so the impact of confounding by these factors on the association between diet and risk of CNS tumours must not be overlooked. With the detailed information on diet, socio-demographic, anthropometric, and lifestyle factors collected by the three cohort studies, all analyses performed in this thesis were adjusted for many potential confounders, although there was often little difference between the minimally adjusted (age and sex) and the fully adjusted results. Nevertheless, the impact of residual confounding from these non-dietary factors due to imperfect measurement and/or crude categorisation of these factors, and from unmeasured confounding factors, cannot be ruled out. To remove residual confounding from smoking, by which dietary intakes varied the most, sensitivity analyses were conducted in never smokers; however the great majority of RRs were not materially changed.

9.2.5 The role of bias

According to the 'Route to diagnosis for cancer' report in England published in 2012, the proportion of CNS tumours that were diagnosed through emergency presentation was the highest of all specified cancers at 62%, compared to 24% in all cancers overall.[24] The high emergency presentation of CNS tumours, which indicates later diagnosis, could be attributable to a lack of awareness of early neurological symptoms which may be associated with some characteristics including dietary intakes. A study in the US found that higher level of educational attainment was associated with increased glioma incidence when compared to lower level (this was also found in the NIH-AARP Study, Table 5.14 in Chapter 5), and suggested that the association was related more to the diagnosis of the tumours than to their inception.[25] In this study, intakes of plant-based foods or nutrients and dietary pattern scores were generally higher in individuals with higher educational attainment than those with lower, and in more health conscious individuals (e.g. never smokers or those who do

strenuous exercise ≥2 times per week) than less health conscious ones (e.g. current smokers or those who never or rarely do strenuous exercise) in the three cohorts. So the consistent association between increasing intakes of plant-based foods or nutrients on healthier dietary patterns (higher scores) and increased risk of glioma may be subject to bias related to ascertainment of glioma rather than inception.

9.2.6 The role of reverse causation

The time from tumour inception to emergence of clinical symptoms and actual diagnosis of the tumours varies. The latent period may be long for CNS tumours, which are generally diagnosed late (discussed in the previous section), and means that potential reverse causation must be considered in epidemiological analysis. To account for possible reverse causation between diet and risk of CNS tumours, I performed analyses stratified by follow-up time at 5 years. For the potential associations (seen before correction for multiple testing) between increasing consumption of plant-based foods or nutrients, or healthier dietary patterns and increased risk of glioma found in analyses of all follow-up time, relative risks for glioma usually became larger in analyses including the first 5 years of follow-up only but attenuated towards null in analyses excluding the first 5 years of follow-up, indicating reverse causation. The same phenomena were observed for the vast majority of associations observed between diet and risk of subtypes of CNS tumours in the analyses performed in this thesis, although numbers were limited for the rarer subtypes. Possible explanations for the reverse causation between plant-based foods or nutrients, or dietary patterns and increased glioma risk include the emergence of disease symptoms which prompted an increase in consumption of plant-based foods that are healthy as well as eating a more healthy diet overall. Besides, I also found that about 14% of women in the Million Women Study reported making major changes to their diet due to illness in the last 5 years prior to baseline dietary assessment. While these women were excluded from all analyses in the Million Women Study to reduce the impact of reverse causation, information on dietary changes is not available in the NIH-AARP Study and the PLCO Study and may have

resulted in some biased estimates in the latter two studies, although all associations examined were mostly null in analyses excluding the first 5 years of follow-up.

9.3 Future research

9.3.1 Diet and risk of meningioma in other populations

Considering the null evidence for glioma risk in relation to diet as well as other modifiable factors (e.g. lifestyle factors), and the absence of an association of large magnitude associated with diet for the extremely rare pituitary tumours and vestibular schwannoma, further research into diet and risk of glioma, pituitary tumours, or vestibular schwannoma may be of limited value. It may be valuable to study the associations between diet and risk of meningioma in other populations with different dietary habits because there is some evidence for associations with physical activity and BMI, which are correlated with dietary intakes.

9.3.2 Measurement and collection of dietary data

Repeated measurement of dietary intakes is needed to reduce random measurement error. However, the cost of collecting large samples of repeated measures of dietary data using traditional questionnaires could be high and the response rate may be low, meaning that the re-measured data may not be representative of the baseline population. Future studies need to make use of advanced technology such as the imaging capabilities of mobile devices, which are common, to capture an objective measurement of diet from the general populations, which could be done repeatedly with low cost. Such data could be stored and analysed when necessary. A standardised algorithm that converts dietary intake to analysable dietary data can be built on a reasonable number of training set samples in which the intakes of foods, beverages, and others can actually be quantified. The algorithm can then be introduced to the rest of the samples collected.

9.3.3 Meningioma data

Studies need to be large to include a sufficient number of cases of meningioma for meaningful analyses. Therefore, it is very important to improve the registration of non-malignant CNS tumours (the vast majority of meningioma is benign) so that most if not all non-malignant tumours are recorded and can eventually be included in epidemiological studies. One way of doing it is to make the registration mandatory for non-biopsied tumours such as those found in imaging tests. Additionally, collaborative work is needed to pool as many cases as possible for the same analyses to increase statistical power to detect an association. However, knowing the heterogeneity between studies/populations in terms of dietary intakes and meningioma incidence, and performing a careful analysis of these data is important in order to limit potential bias.

9.4 Conclusion

The work presented in this thesis contributes substantially to the field of diet and risk of subtypes of CNS tumours. I have presented the first systematic review of the literature and the first comprehensive analyses in large prospective studies that have a systematic coverage of diet from dietary patterns, food groups, to nutrients. The prospective evidence provided here is particularly valuable for non-malignant CNS tumours, for which published evidence and research resources are scarce. This largest study thus far suggests that there is little evidence for an association between any particular diet and any particular CNS tumour subtype, at least in UK and US populations, after taking account of factors such as chance findings, bias, confounding, and reverse causation, which might distort the association. With the rarity of subtypes of CNS tumours and the statistical power of the analyses performed here, this systematic investigation is unlikely to have overlooked any association between diet and CNS tumours that is of public health concern. Future studies on diet and CNS tumours may be valuable for meningioma, but there

is a need for improvement in the measurement of diet and in the registration of non-malignant CNS tumours, including meningioma.

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Appendices

A

Study Questionnaires

A.1 The Million Women Study 3-year re-survey questionnaire

THE MILLION WOMEN STUDY

Confidential National Study of Women's Health

The Million Women Study is an important national study of women's health. A few years ago you received the first questionnaire with your invitation to the National Health Service Breast Screening Programme. Your help is needed again. Can you find time to complete this second questionnaire? Some of the questions may seem familiar and others are new, but all will provide vital up to date information for the study. Your answers are valuable and important - the enclosed leaflet explains how the study will benefit women and improve medical knowledge world-wide. We very much hope you are still willing to be one of the Million Women in the study.

We guarantee that all information provided will be treated with absolute confidentiality and used for medical research only.

To help us read your answers please write as clearly as possible and complete the questionnaire as shown:

Please put a cross in the appropriate box(es) ☒ ☐

OR put numbers in the appropriate places

eg 54 *(age)* 0 2 0 8 2 0 0 0 — *2nd August 2000*

Any questions? Ring us on Freephone 0800 262 872

QUESTIONS ABOUT YOU AND YOUR HEALTH

Please answer every question as best you can as all the information that you give us is very useful. If you are not sure about exact dates or ages an approximate answer is better than none. Please use a black pen, if possible.

1. In the last 5 years has a doctor told you that you have had any of the following conditions?

*If **YES** please cross the box ☒ and write your age when the condition was first diagnosed (eg. 57 (age))*

Yes			Yes			Yes	
☐ High blood pressure	____ (age)		☐ Asthma	____ (age)		☐ Gallstones/gall bladder problems	____ (age)
☐ High blood cholesterol	____ (age)		☐ Osteoporosis	____ (age)		☐ Blood clot in leg	____ (age)
☐ Diabetes	____ (age)		☐ Thyroid problem	____ (age)		☐ Blood clot elsewhere (please describe below)	____ (age)
☐ Heart problem (please describe below)	____ (age)		☐ Breast cancer	____ (age)		☐ Inflammatory bowel disease (please describe below)	____ (age)
☐ Stroke/TIA (please describe below)	____ (age)		☐ Other cancer (please describe below)	____ (age)		☐ Any other serious illness (please describe below)	____ (age)

Please give as many details as possible about any illness mentioned above

2. Are you NOW being treated for: *If YES please cross the box ☒ and write your age when the condition was first treated (eg. 60 (age))*

Yes			Yes			Yes	
☐ High blood pressure	____ (age)		☐ Asthma	____ (age)		☐ Osteoporosis	____ (age)
☐ Diabetes	____ (age)		☐ Rheumatoid arthritis	____ (age)		☐ Depression/anxiety	____ (age)
☐ Heart problem (please describe below)	____ (age)		☐ Osteoarthritis	____ (age)		☐ Other serious illness or disability (please describe below)	____ (age)

Please give further details of any serious illness or disability you are now being treated for

3. Have you had any broken/fractured bones in the last 5 years? *(please cross)* ☐ No ☐ Yes

If Yes, which bones were broken? ☐ wrist ☐ arm ☐ ankle ☐ hip ☐ spine ☐ other _____ *(please describe)*

If Yes, how did the fracture occur? ☐ after a fall ☐ in a car accident ☐ some other way _____ *(please describe)*

If Yes, when did it occur? month ☐☐ year ☐☐☐☐ *(give month/year of the most recent fracture, if you have had more than one)*

4. Have you had any major operations in the last 5 years? ☐ No ☐ Yes - ***If Yes***, when? month ☐☐ year ☐☐☐☐

*If **Yes**, please describe the operation and why it was done. (If you have had more than one operation please give the dates and details of each)*

5. When did you last go for breast screening? month ☐☐ year ☐☐☐☐

6. Have you ever had a cervical smear test? ☐ No ☐ Yes - ***If Yes***, when was your last test? month ☐☐ year ☐☐☐☐

About how many cervical smear tests have you had in the last 10 years? ☐ number of tests

Were you told that any of the cervical smear tests (in the last 10 years) were abnormal? ☐ No ☐ Yes

7. How would you describe your health now? ☐ excellent ☐ good ☐ fair ☐ poor

QUESTIONS ABOUT MEDICATIONS

8. **Have you ever used H R T (hormone replacement therapy)?** ☐ No - ***if No*** - *please go to question 13* ☐ Yes

9. **How old were you when you *first started* using HRT?** ☐☐ years old

10. **Are you *now* using HRT?** ☐ No - ***if No,*** when did you stop using HRT? ☐☐ month ☐☐☐☐ year ☐ Yes

11. **For about how many years *in total* have you used HRT?** ☐ years of use
(Add together all the years and months when you were using HRT. Please write "0" if you used HRT for less than a year in total)

12. **Which HRT did you use MOST RECENTLY?**

☐ Prempak C 0.625mg	☐ Premarin 0.625mg	
☐ Prempak C 1.25mg	☐ Premarin 1.25mg	
☐ Tridestra	☐ Evorel 25mcg/50mcg	
☐ Trisequens	☐ Evorel 75mcg/100mcg	
☐ Cycloprogynova 1mg	☐ Progynova 1mg	
☐ Cycloprogynova 2mg	☐ Progynova 2mg	
☐ Estrapak	☐ Estraderm 25mcg	
☐ Estracombi	☐ Estraderm 50mcg	
☐ Climaval 1mg	☐ Estraderm 100mcg	
☐ Climaval 2mg	☐ Zumenon 1mg	
☐ Premique Cycle	☐ Zumenon 2mg	
☐ Premique	☐ Ethinyloestradiol	
☐ Nuvelle	☐ Oestrogel	☐ Micronor
☐ Kliofem	☐ Implants	☐ Duphaston
☐ Livial	☐ Provera	☐ Do not know

Other (please write here)

13. **Have you taken any medications (other than HRT) for most of the last 4 weeks?** ☐ No ☐ Yes
If Yes, was it:

☐ thyroxine	☐ ibuprofen	☐ aspirin	
☐ tamoxifen	☐ bendrofluazide	☐ amlodipine *Istin*	☐ digoxin
☐ paracetamol	☐ propranolol	☐ atenolol	☐ warfarin
☐ prednisolone	☐ Losec/Zoton	☐ Prozac	☐ insulin
☐ co-proxamol *Distalgesic*	☐ amitriptyline *Tryptizol etc*	☐ sleeping pills	☐ lithium

Please give the name(s) of any other medication you have used for most of the last 4 weeks:

14. **Do you regularly take any vitamins, minerals or supplements?** ☐ No ☐ Yes - ***if Yes,*** do you take:

☐ multivitamins (with minerals)		☐ vitamin A
☐ multivitamins (without minerals)		☐ vitamin B (including B_6, B_{12})
☐ fish oil (including cod liver oil)		☐ vitamin C
☐ evening primrose oil	☐ garlic	☐ vitamin D
☐ iron ☐ zinc	☐ calcium	☐ vitamin E

☐ other *(please describe)*_____

QUESTIONS ABOUT YOUR DIET

We know it may be difficult for you to give exact answers to these questions about your diet. An approximate answer is very valuable for this study. So, please answer as best you can, thinking of a typical week.

15. **Which types of meat do you eat about once a week or more often?** *(you can cross more than one box)*

☐ beef	☐ bacon	☐ chicken/poultry
☐ lamb	☐ ham	☐ kidney
☐ pork	☐ sausages	☐ liver/pâté
☐ beefburger/hamburger		☐ never eat meat

16. **Which types of fish do you eat about once a week or more often?** *(you can cross more than one box)*

☐ tuna	☐ sardines	☐ trout	☐ "fish & chips"
☐ salmon	☐ kippers/herring		☐ other seafood *(prawns, scampi etc)*
☐ cod/haddock or other white fish	☐ mackerel		☐ never eat fish

17. **About how many times each week do you eat:**
(please count all meals and snacks. put '0' if never eaten or eaten less than once a week)

meat	☐	number of times eaten each week *(remember meat in sandwiches)*
fish/ seafood	☐	number of times eaten each week
chips	☐	number of times eaten each week
potatoes (except chips)	☐	number of times eaten each week
pasta/ spaghetti	☐	number of times eaten each week
rice	☐	number of times eaten each week
cheese	☐	number of times eaten each week *(remember cheese in pizzas, quiches, cheese sauce, etc)*

18. **About how many eggs do you eat each week?**
eggs ☐ number of eggs eaten each week *(remember eggs in omelettes, quiches, cakes etc. put '0' if less than one)*

19. **Which types of vegetables/salads (fresh, frozen or tinned) do you eat once a week or more often?**
(you can cross more than one box)

☐ green peas	☐ tomatoes	☐ green beans
☐ broccoli	☐ onions	☐ baked beans
☐ cabbage	☐ garlic	☐ soya meat/tofu
☐ carrots	☐ swede	☐ chick peas/lentils
☐ courgettes	☐ spinach	☐ cauliflower
☐ beetroot	☐ sweetcorn	☐ green/red peppers
☐ leeks	☐ avocado	☐ brussels sprouts
☐ parsnip	☐ aubergine	☐ mushrooms
☐ lettuce	☐ celery	☐ cucumber

20. **About how much do you eat each week of:**
(put "0" if less than one)
cooked vegetables (except potatoes) ☐ number of heaped tablespoons each week
salad items/ raw vegetables ☐ number of heaped tablespoons each week *(please count lettuce, tomato etc in sandwiches)*

21. **Which types of fruit do you eat once a week or more often, when in season?** *(you can cross more than one box)*

☐ apples	☐ bananas	☐ oranges, satsumas, etc
☐ grapefruit	☐ pears	☐ stone fruit *(peaches, plums, nectarines etc)*

22. **About how much fruit or fruit juice do you eat or drink each week?** *(count 10 grapes, berries or raisins as one piece; put "0" if less than one a week)*

☐ number of pieces of **fresh fruit** eaten each week	☐ number of pieces of **dried fruit** eaten each week
☐ number of glasses of **fruit juice** each week	☐ number of tablespoons of **stewed or tinned fruit** eaten each week

MORE ABOUT YOUR DIET

23. About how many of the following do you eat: *(put "0" if none or less than one)*

slices/pieces of white bread		slices each week
slices/pieces of brown/wholemeal bread *(also include granary, rye bread etc)*		slices each week
crackers, crispbread etc *(ryvita, water biscuits etc)*		number each week
sweet biscuits		number each week
dairy desserts (yoghurts etc)		number each week
cakes, puddings, pies, buns etc		number each week
chocolate (in any food or drink)		approx. number of pieces each week
nuts (including peanut butter)		tablespoons each week
soup		bowls/cups each week
gravy, cream/cheese sauces etc		tablespoons each week
breakfast type cereal		bowls each week

If you eat breakfast cereal is it usually: *(please cross)*

☐ bran cereal *(allbran, branflakes etc)* ☐ muesli
☐ biscuit cereal *(weetabix, shreddies etc)* ☐ other *(e.g. cornflakes, rice crispies etc)*
☐ oat cereal *(porridge, ready brek etc)*

24. Which type of spread do you use on bread, crispbreads etc, once a week or more often? *(you can cross more than one box)*

☐ butter ☐ margarine ☐ soft cheese
☐ low fat spread ☐ mayonnaise ☐ salad cream
☐ olive oil spread ☐ marmite etc ☐ rarely use spread

Do you spread it: ☐ thick? ☐ medium? ☐ thin? *(please cross)*

Do you add butter etc to: ☐ potatoes? ☐ other vegetables?

25. Which types of fats or oils do you use for cooking or salad dressing once a week or more often? *(you can cross more than one box)*

☐ butter ☐ soft (tub) margarine ☐ white flora
☐ olive oil ☐ hard (block) margarine ☐ lard/dripping
☐ corn oil ☐ sunflower oil ☐ mayonnaise
☐ soya oil ☐ other vegetable oil ☐ salad cream

Please put a cross in the box if you RARELY OR NEVER:

☐ use fats or oils for cooking ☐ use salad dressing/cream

26. Please put a cross in the box if you NEVER eat:

☐ beef ☐ pork/ham ☐ lamb ☐ dairy products
☐ kidney ☐ liver/pâté ☐ sugar ☐ wheat products
☐ salami ☐ sausages ☐ eggs ☐ beefburgers

27. Which type of milk or cream do you drink or use once a week or more often? *(you can cross more than one box)*

milk: ☐ full cream ☐ semi-skimmed ☐ skimmed ☐ soya
cream: ☐ single ☐ double ☐ other
other: ☐ dairy ice cream ☐ never have milk/cream

28. Do you:

	never	sometimes	usually	always
add milk to your tea?	☐	☐	☐	☐
add milk to your coffee?	☐	☐	☐	☐
add salt to your food?	☐	☐	☐	☐
remove fat from meat? *(cross "never" if vegetarian)*	☐	☐	☐	☐
eat organic food?	☐	☐	☐	☐

29. Have you made any major changes to your diet in the last 5 years? ☐ No ☐ Yes-because of illness ☐ Yes-for some other reason

30. About how much alcohol do you drink each week?

☐ number of drinks of alcohol each week
one drink = a glass of wine, half pint of lager, or tot of spirits
(put "0" if you do not drink, or have less than one drink each week)

If you have more than one drink of alcohol each week:

is it usually with meals? ☐ No ☐ Yes ☐ it varies

on how many days each week do you usually drink? ☐ days each week

31. About how much do you drink EACH DAY of:

tea? ☐ *cups daily* milk? *(include hot chocolate etc)* ☐ *cups daily* fizzy/soft drink? ☐ *glasses daily*
coffee? ☐ *cups daily* water? ☐ *glasses daily* fruit squash? ☐ *glasses daily*

32. How many teaspoons of sugar do you add to tea, coffee, cereal, fruit etc EACH DAY? ☐ teaspoons of sugar each day

33. What size clothes do you wear now? *(you can cross more than one box if the size varies)*

Clothes	☐ 10 or less	☐ 12	☐ 14	☐ 16	☐ 18	☐ 20+
Bra	☐ 32	☐ 34	☐ 36	☐ 38	☐ 40	☐ 42+
Cup	☐ A/AA	☐ B	☐ C	☐ D	☐ DD/E +	

34. What is your: *(please put "0" if you do not know)*

waist measurement? ☐☐ inches hip measurement? ☐☐ inches

35. About how much do you weigh now? ☐ stone ☐ lbs *(Put "0" if you do not know)*

36. About how many hours each week do you spend doing:

housework? *(include cooking, cleaning etc)* ☐ hours per week

	summer	winter	
gardening?	☐	☐	hours per week
walking?	☐	☐	hours per week
cycling?	☐	☐	hours per week
any work or exercise causing sweating or a fast heartbeat?	☐	☐	hours per week

WHEN YOU WERE YOUNG

37. About how much did you weigh when you were born? ☐ lbs ☐ ozs *(Put "0" if you do not know)*

38. Were you breastfed when you were a baby?

☐ No ☐ Yes ☐ do not know

39. Did your parents smoke:

at around the time that you were born?

Mother ☐ No ☐ Yes ☐ do not know
Father ☐ No ☐ Yes ☐ do not know

at around the time that you were 10 years old?

Mother ☐ No ☐ Yes ☐ do not know
Father ☐ No ☐ Yes ☐ do not know

40. When you were about 10 years old, compared to average, would you describe yourself as *(please cross)*:

☐ thinner? ☐ plumper? ☐ about average?

41. What size clothes did you wear when you were about 20 years old? *(you can cross more than one box)*

☐ 8 or less ☐ 10 ☐ 12 ☐ 14 ☐ 16 ☐ 18 +

QUESTIONS ABOUT YOUR FAMILY AND LIFESTYLE

42. Is your mother still alive?

- ☐ Yes-please give her age now ☐☐ years old
- ☐ No-please give her age when she died ☐☐ years old
- ☐ Do not know

43. If your mother has died, what did she die from?

- ☐ heart disease *heart attack etc*
- ☐ stroke
- ☐ chest infection *pneumonia*
- ☐ "old age"
- ☐ breast cancer
- ☐ cancer of the womb
- ☐ cancer of ovary
- ☐ other/unknown_____

44. Has your mother or father ever suffered from:

mother	father		mother	father	
☐	☐	heart disease	☐	☐	breast cancer
☐	☐	stroke	☐	☐	bowel cancer
☐	☐	high blood pressure	☐	☐	lung cancer
☐	☐	diabetes		☐	prostate cancer
☐	☐	Alzheimer's disease	☐	☐	osteoporosis
☐	☐	Parkinson's disease	☐	☐	hip fracture
☐	☐	severe depression	☐	☐	severe arthritis

other*(mother)*_____ other*(father)*_____

45. How tall is/was your mother? *(Put "0" if you do not know)* ☐ feet ☐ inches

How tall is/was your father? ☐ feet ☐ inches

46. Have you ever been a smoker?

- ☐ No - ***if No*** - *please go to question 50*
- ☐ Yes

47. How old were you when you started smoking regularly? ☐☐ years old

48. Are you a smoker now?

- ☐ No - ***if No*** - how old were you when you stopped smoking? ☐☐ years old
- ☐ Yes -***if Yes*** - please write the tar & nicotine content of your usual brand of cigarettes: *(this is written on each packet of cigarettes)* tar ☐ mg nicotine ☐ mg

49. About how many cigarettes do you/*did you* smoke on average *each day*? *(If you are an ex-smoker, how many did you smoke on average when you smoked?)*

☐☐ cigarettes per day

50. Have you had your menopause?

- ☐ No ☐ Not sure *(because periods irregular, taking HRT etc)*
- ☐ Yes- How old were you when you had your menopause? ☐☐ years old

51. Are you now in paid work?

- ☐ No ☐ Yes, full time ☐ Yes, part time
- ***If Yes***, does your work involve physical effort? ☐ No ☐ Yes
- ***At work***, do you mostly ☐ stand? ☐ sit? ☐ both

52. Are you currently married or living with a partner?

- ☐ No ☐ Yes- ***If Yes***- does your husband/partner smoke? ☐ No ☐ Yes

53. About how often do you use a mobile phone?

- ☐ Never ☐ less than once a day ☐ every day
- **For how long have you used one?** *(put "0" if never or less than 1 year)* ☐ years

54. Do you belong to or participate in any of the following?

☐ religious group	☐ art/craft group	☐ bingo
☐ voluntary work	☐ music/singing group	
☐ adult education	☐ sports club (swimming,golf etc)	
☐ dancing group	☐ yoga,etc	☐ other group activity

55. How often do you feel:

	rarely/ never	some-times	usually	most of the time
happy	☐	☐	☐	☐
relaxed	☐	☐	☐	☐
in control	☐	☐	☐	☐
stressed	☐	☐	☐	☐
tired	☐	☐	☐	☐

56. Do you have a nap during the day?

- ☐ rarely/never ☐ sometimes ☐ usually

57. About how many hours sleep do you get in every 24 hours? ☐ hours sleep *(please include naps)*

58. To which ethnic group do you consider you belong?

- ☐ White ☐ Black - Caribbean, African etc.
- ☐ Asian ☐ Other -*please specify*_____

59. What is your date of birth? day ☐☐ month ☐☐ year ☐☐☐☐

60. On what date did you fill in this form? ☐☐ ☐☐ ☐☐☐☐

61. In case we need to check on any details, it would be helpful if you would write your telephone number below.

☐☐☐☐☐☐☐☐☐☐☐☐

STD code Telephone number

THANK YOU VERY MUCH FOR YOUR HELP

Please put your completed questionnaire in the pre-paid envelope and post it back to us

If your name /address has changed or is incorrect could you please cross this box ☐ & give the correct details below.

Surname:

Given name(s):

House number and street:

District:

Town/County: Postcode:

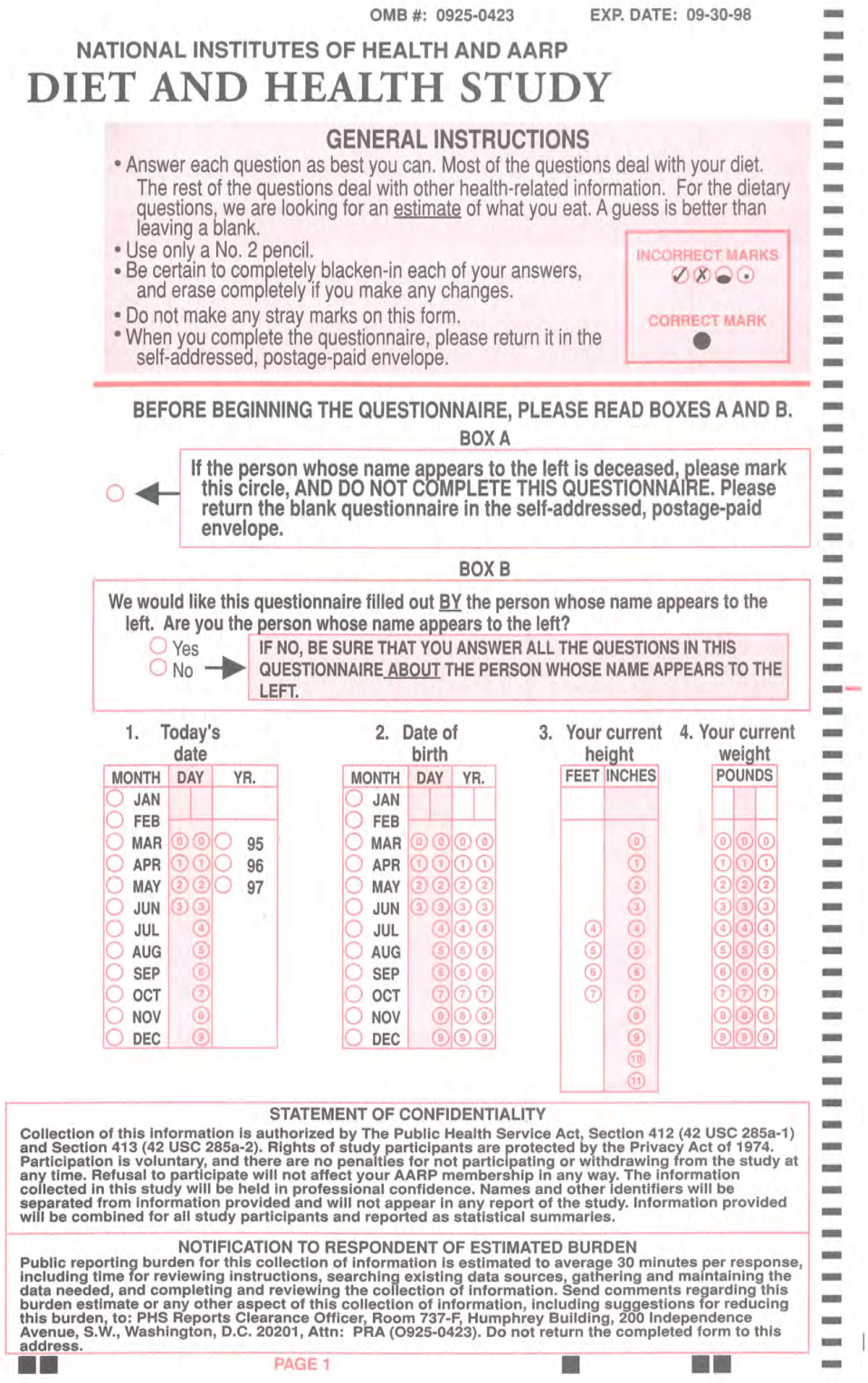
For office use only

MWS-PF/103
0012
05/01

PROFESSOR VALERIE BERAL, THE MILLION WOMEN STUDY, ICRF-CEU, GIBSON BUILDING, RADCLIFFE INFIRMARY, OXFORD OX2 6HE FREEPHONE: 0800 262 872 www.icnet.uk/research/studies/mws

The Million Women Study is supported by the Imperial Cancer Research Fund, the Medical Research Council and the National Health Service Breast Screening Programme.

A.2 The NIH-AARP Study Baseline Questionnaire



OMB #: 0925-0423 EXP. DATE: 09-30-98

NATIONAL INSTITUTES OF HEALTH AND AARP

DIET AND HEALTH STUDY

GENERAL INSTRUCTIONS

- Answer each question as best you can. Most of the questions deal with your diet. The rest of the questions deal with other health-related information. For the dietary questions, we are looking for an estimate of what you eat. A guess is better than leaving a blank.
- Use only a No. 2 pencil.
- Be certain to completely blacken-in each of your answers, and erase completely if you make any changes.
- Do not make any stray marks on this form.
- When you complete the questionnaire, please return it in the self-addressed, postage-paid envelope.

INCORRECT MARKS ✓ ✗ ◒ ⊙

CORRECT MARK ●

BEFORE BEGINNING THE QUESTIONNAIRE, PLEASE READ BOXES A AND B.

BOX A

○ ← If the person whose name appears to the left is deceased, please mark this circle, AND DO NOT COMPLETE THIS QUESTIONNAIRE. Please return the blank questionnaire in the self-addressed, postage-paid envelope.

BOX B

We would like this questionnaire filled out BY the person whose name appears to the left. Are you the person whose name appears to the left?

○ Yes
○ No → IF NO, BE SURE THAT YOU ANSWER ALL THE QUESTIONS IN THIS QUESTIONNAIRE ABOUT THE PERSON WHOSE NAME APPEARS TO THE LEFT.

1. Today's date

MONTH	DAY	YR.
○ JAN		
○ FEB		
○ MAR	0 0	○ 95
○ APR	1 1	○ 96
○ MAY	2 2	○ 97
○ JUN	3 3	
○ JUL	4	
○ AUG	5	
○ SEP	6	
○ OCT	7	
○ NOV	8	
○ DEC	9	

2. Date of birth

MONTH	DAY	YR.
○ JAN		
○ FEB		
○ MAR	0 0	0 0
○ APR	1 1	1 1
○ MAY	2 2	2 2
○ JUN	3 3	3 3
○ JUL	4	4 4
○ AUG	5	5 5
○ SEP	6	6 6
○ OCT	7	7 7
○ NOV	8	8 8
○ DEC	9	9 9

3. Your current height

FEET	INCHES
	0
	1
	2
	3
4	4
5	5
6	6
7	7
	8
	9
	10
	11

4. Your current weight

POUNDS	
0 0	0
1 1	1
2 2	2
3 3	3
4 4	4
5 5	5
6 6	6
7 7	7
8 8	8
9 9	9

STATEMENT OF CONFIDENTIALITY

Collection of this information is authorized by The Public Health Service Act, Section 412 (42 USC 285a-1) and Section 413 (42 USC 285a-2). Rights of study participants are protected by the Privacy Act of 1974. Participation is voluntary, and there are no penalties for not participating or withdrawing from the study at any time. Refusal to participate will not affect your AARP membership in any way. The information collected in this study will be held in professional confidence. Names and other identifiers will be separated from information provided and will not appear in any report of the study. Information provided will be combined for all study participants and reported as statistical summaries.

NOTIFICATION TO RESPONDENT OF ESTIMATED BURDEN

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to: PHS Reports Clearance Officer, Room 737-F, Humphrey Building, 200 Independence Avenue, S.W., Washington, D.C. 20201, Attn: PRA (0925-0423). Do not return the completed form to this address.

PAGE 1

5. The next section asks about your USUAL eating habits. Your answers should reflect your food intake over the past year. Please think about your food intake at home and in restaurants.

Step One: Mark the "HOW OFTEN" column to show how often you usually ate the food during the past year.
Step Two: Mark the "HOW MUCH" column to show your usual portion size for each food.

Sample: This person usually eats applesauce 5 times a week and usually eats between 1/2 and 3/4 cup each time.

TYPE OF FOOD	HOW OFTEN										HOW MUCH
EXAMPLE	Never	1-6 Times Per Year	7-11 Times Per Year	1 Time Per Month	2-3 Times Per Month	1-2 Times Per Week	3-4 Times Per Week	5-6 Times Per Week	1 Time Per Day	2+ Times Per Day	YOUR PORTION SIZE
Applesauce	○	○	○	○	○	○	○	●	○	○	○ Less than 1/2 cup ● 1/2 to 3/4 cup ○ More than 3/4 cup

ADDITIONAL COMMENTS:

- If you never eat a food, you may mark only "Never", leave the "How Much" column blank, and move on to the next food.
- Please do not skip any foods.
- Please be careful to put your answers in the correct columns and to fill out each food item completely.
- It is okay to estimate how often and how much you usually eat. We do not expect you to remember your intake exactly.
- The term "low-fat" includes low-fat, reduced-fat, and non-fat versions of foods.

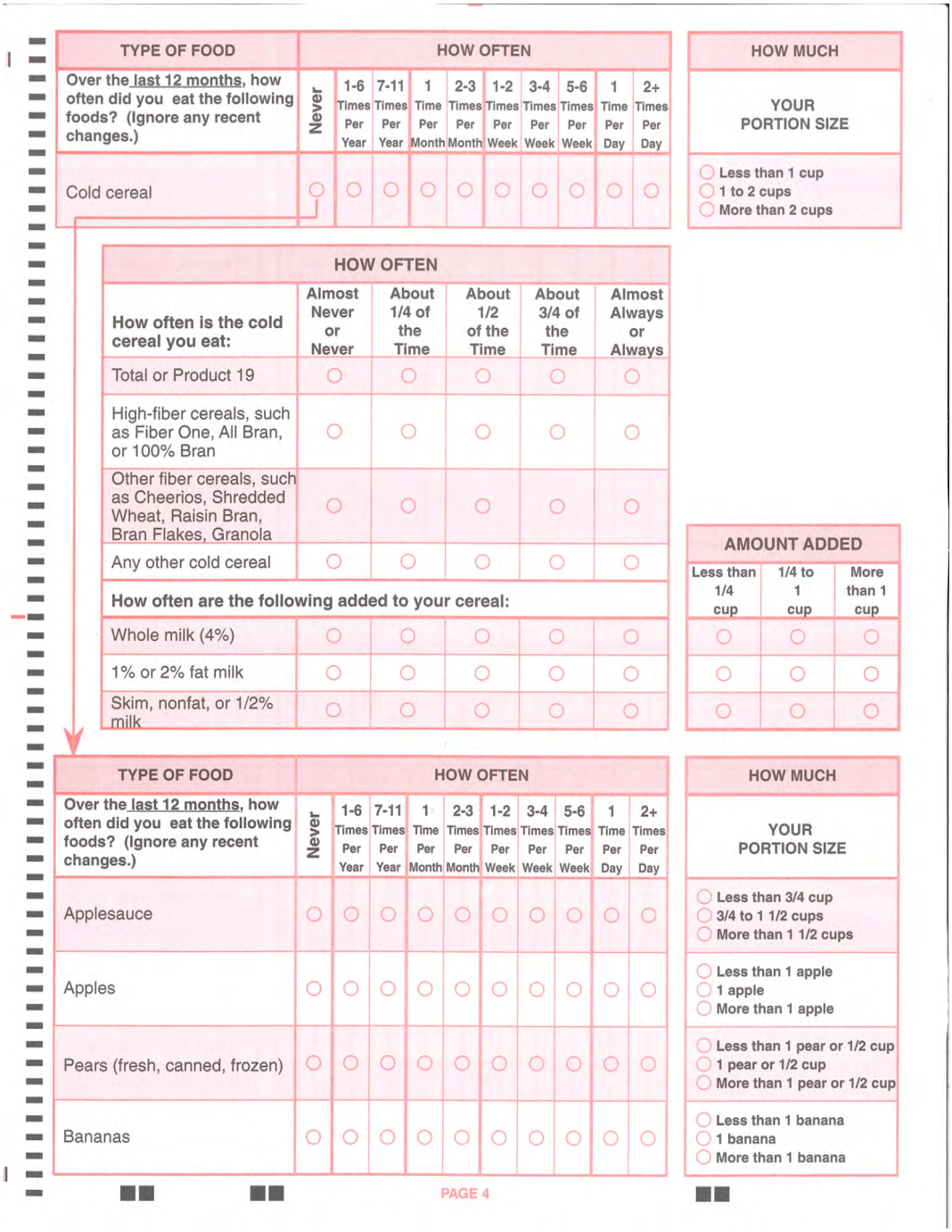
PLEASE BEGIN HERE

TYPE OF FOOD	HOW OFTEN										HOW MUCH
Over the last 12 months, how often did you eat the following foods? (Ignore any recent changes.)	Never	1 Time Per Month or Less	2-3 Times Per Month	1-2 Times Per Week	3-4 Times Per Week	5-6 Times Per Week	1 Time Per Day	2-3 Times Per Day	4-5 Times Per Day	6 + Times Per Day	YOUR PORTION SIZE
Tomato juice or vegetable juice	○	○	○	○	○	○	○	○	○	○	○ Less than 3/4 cup ○ 3/4 to 1 cup ○ More than 1 cup
Orange juice or grapefruit juice	○	○	○	○	○	○	○	○	○	○	○ Less than 3/4 cup ○ 3/4 to 1 cup ○ More than 1 cup
Other fruit juice or fruit juice mixture (such as apple, grape, pineapple, or others)	○	○	○	○	○	○	○	○	○	○	○ Less than 3/4 cup ○ 3/4 to 1 cup ○ More than 1 cup
Drinks, such as Hi-C, lemonade, Kool-Aid (diet or regular)	○	○	○	○	○	○	○	○	○	○	○ Less than 1 cup ○ 1 to 1 1/2 cups ○ More than 1 1/2 cups
Soft drinks, soda, pop (diet or regular)	○	○	○	○	○	○	○	○	○	○	○ Less than 10 oz or 1 can ○ 10 to 12 oz or 1 can ○ More than 12 oz or 1 can
Whole milk (4%) as a drink (NOT in coffee, NOT on cereal)	○	○	○	○	○	○	○	○	○	○	○ Less than 1/2 cup ○ 1/2 to 1 cup ○ More than 1 cup
1% or 2% fat milk as a drink (NOT in coffee, NOT on cereal)	○	○	○	○	○	○	○	○	○	○	○ Less than 1/2 cup ○ 1/2 to 1 cup ○ More than 1 cup

TYPE OF FOOD	HOW OFTEN										HOW MUCH
Over the last 12 months, how often did you eat the following foods? (Ignore any recent changes.)	Never	1 Time Per Month or Less	2-3 Times Per Month	1-2 Times Per Week	3-4 Times Per Week	5-6 Times Per Week	1 Time Per Day	2-3 Times Per Day	4-5 Times Per Day	6+ Times Per Day	YOUR PORTION SIZE
Skim, non-fat, or 1/2% milk as a drink (NOT in coffee, NOT on cereal)	○	○	○	○	○	○	○	○	○	○	○ Less than 1/2 cup ○ 1/2 to 1 cup ○ More than 1 cup
Beer (IN SUMMER)	○	○	○	○	○	○	○	○	○	○	○ Less than a 12-ounce can ○ 1 to 2 12-ounce cans ○ More than 2 12-ounce cans
Beer (REST OF THE YEAR)	○	○	○	○	○	○	○	○	○	○	○ Less than a 12-ounce can ○ 1 to 2 12-ounce cans ○ More than 2 12-ounce cans
Wine or wine coolers	○	○	○	○	○	○	○	○	○	○	○ Less than 4 ounces ○ 4 to 8 ounces ○ More than 8 ounces
Liquor or mixed drinks	○	○	○	○	○	○	○	○	○	○	○ Less than 1 shot of liquor ○ 1 to 2 shots of liquor ○ More than 2 shots of liquor

Please note that response categories change on the following questions.

TYPE OF FOOD	HOW OFTEN										HOW MUCH
Over the last 12 months, how often did you eat the following foods? (Ignore any recent changes.)	Never	1-6 Times Per Year	7-11 Times Per Year	1 Time Per Month	2-3 Times Per Month	1-2 Times Per Week	3-4 Times Per Week	5-6 Times Per Week	1 Time Per Day	2+ Times Per Day	YOUR PORTION SIZE
Cottage cheese (including low-fat)	○	○	○	○	○	○	○	○	○	○	○ Less than 1/4 cup ○ 1/4 to 3/4 cup ○ More than 3/4 cup
Yogurt (NOT including frozen yogurt)	○	○	○	○	○	○	○	○	○	○	○ Less than 1/2 cup ○ 1/2 to 1 cup ○ More than 1 cup
Pancakes, waffles, French toast, or crepes	○	○	○	○	○	○	○	○	○	○	○ Less than 2 pieces ○ 2 to 4 pieces ○ More than 4 pieces
Oatmeal, grits, or other cooked cereal (IN WINTER)	○	○	○	○	○	○	○	○	○	○	○ Less than 3/4 cup ○ 3/4 to 1 1/4 cups ○ More than 1 1/4 cups
Oatmeal, grits, or other cooked cereal (REST OF THE YEAR)	○	○	○	○	○	○	○	○	○	○	○ Less than 3/4 cup ○ 3/4 to 1 1/4 cups ○ More than 1 1/4 cups



TYPE OF FOOD	HOW OFTEN									HOW MUCH
Over the last 12 months, how often did you eat the following foods? (Ignore any recent changes.)	Never	1-6 Times Per Year	7-11 Times Per Year	1 Time Per Month	2-3 Times Per Month	1-2 Times Per Week	3-4 Times Per Week	5-6 Times Per Week	1 Time Per Day	2+ Times Per Day	YOUR PORTION SIZE
Cold cereal	○	○	○	○	○	○	○	○	○	○	○ Less than 1 cup ○ 1 to 2 cups ○ More than 2 cups

How often is the cold cereal you eat:	Almost Never or Never	About 1/4 of the Time	About 1/2 of the Time	About 3/4 of the Time	Almost Always or Always
Total or Product 19	○	○	○	○	○
High-fiber cereals, such as Fiber One, All Bran, or 100% Bran	○	○	○	○	○
Other fiber cereals, such as Cheerios, Shredded Wheat, Raisin Bran, Bran Flakes, Granola	○	○	○	○	○
Any other cold cereal	○	○	○	○	○
How often are the following added to your cereal:					
Whole milk (4%)	○	○	○	○	○
1% or 2% fat milk	○	○	○	○	○
Skim, nonfat, or 1/2% milk	○	○	○	○	○

AMOUNT ADDED		
Less than 1/4 cup	1/4 to 1 cup	More than 1 cup
○	○	○
○	○	○
○	○	○

TYPE OF FOOD	HOW OFTEN									HOW MUCH
Over the last 12 months, how often did you eat the following foods? (Ignore any recent changes.)	Never	1-6 Times Per Year	7-11 Times Per Year	1 Time Per Month	2-3 Times Per Month	1-2 Times Per Week	3-4 Times Per Week	5-6 Times Per Week	1 Time Per Day	2+ Times Per Day	YOUR PORTION SIZE
Applesauce	○	○	○	○	○	○	○	○	○	○	○ Less than 3/4 cup ○ 3/4 to 1 1/2 cups ○ More than 1 1/2 cups
Apples	○	○	○	○	○	○	○	○	○	○	○ Less than 1 apple ○ 1 apple ○ More than 1 apple
Pears (fresh, canned, frozen)	○	○	○	○	○	○	○	○	○	○	○ Less than 1 pear or 1/2 cup ○ 1 pear or 1/2 cup ○ More than 1 pear or 1/2 cup
Bananas	○	○	○	○	○	○	○	○	○	○	○ Less than 1 banana ○ 1 banana ○ More than 1 banana

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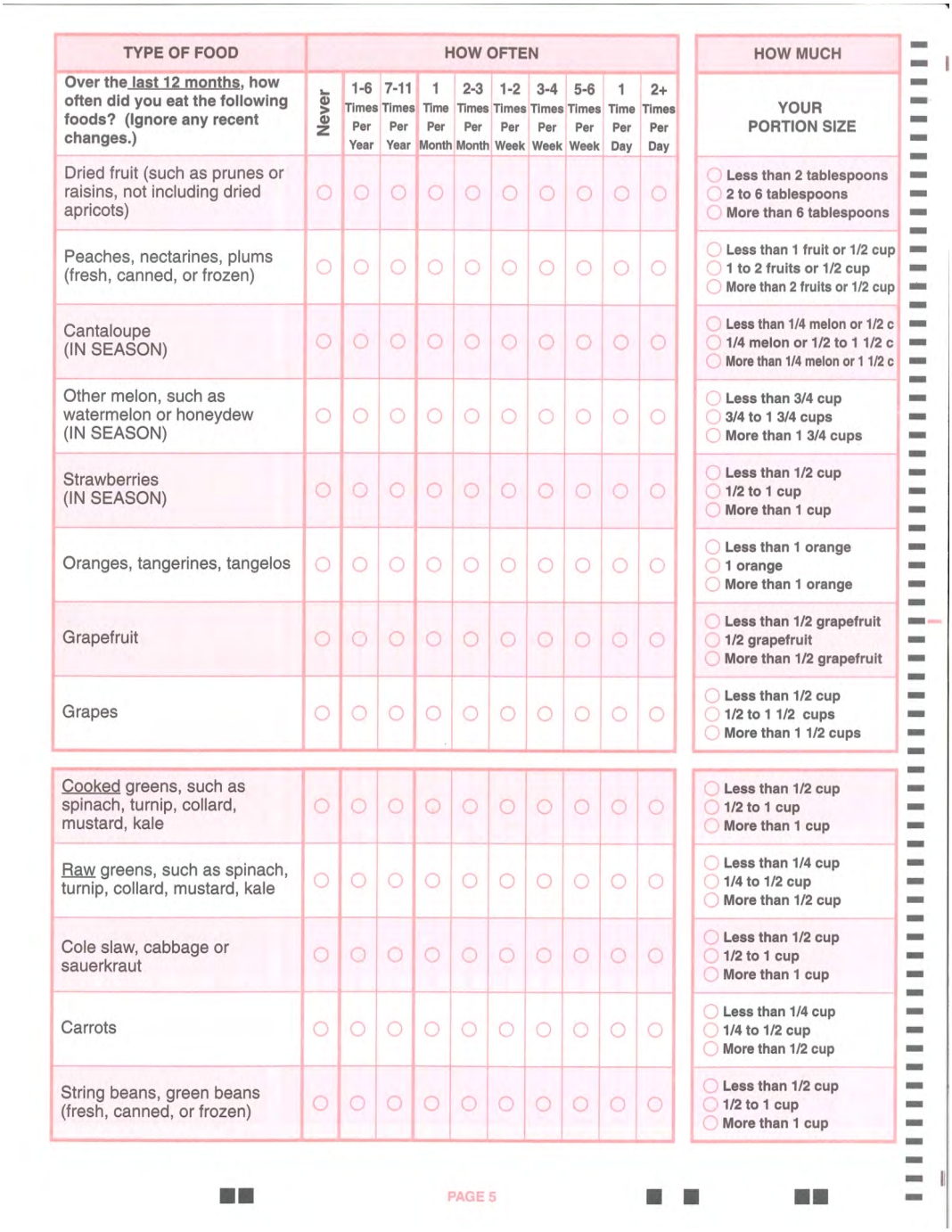

TYPE OF FOOD	HOW OFTEN										HOW MUCH
Over the last 12 months, how often did you eat the following foods? (Ignore any recent changes.)	Never	1-6 Times Per Year	7-11 Times Per Year	1 Time Per Month	2-3 Times Per Month	1-2 Times Per Week	3-4 Times Per Week	5-6 Times Per Week	1 Time Per Day	2+ Times Per Day	YOUR PORTION SIZE
Dried fruit (such as prunes or raisins, not including dried apricots)	○	○	○	○	○	○	○	○	○	○	○ Less than 2 tablespoons ○ 2 to 6 tablespoons ○ More than 6 tablespoons
Peaches, nectarines, plums (fresh, canned, or frozen)	○	○	○	○	○	○	○	○	○	○	○ Less than 1 fruit or 1/2 cup ○ 1 to 2 fruits or 1/2 cup ○ More than 2 fruits or 1/2 cup
Cantaloupe (IN SEASON)	○	○	○	○	○	○	○	○	○	○	○ Less than 1/4 melon or 1/2 c ○ 1/4 melon or 1/2 to 1 1/2 c ○ More than 1/4 melon or 1 1/2 c
Other melon, such as watermelon or honeydew (IN SEASON)	○	○	○	○	○	○	○	○	○	○	○ Less than 3/4 cup ○ 3/4 to 1 3/4 cups ○ More than 1 3/4 cups
Strawberries (IN SEASON)	○	○	○	○	○	○	○	○	○	○	○ Less than 1/2 cup ○ 1/2 to 1 cup ○ More than 1 cup
Oranges, tangerines, tangelos	○	○	○	○	○	○	○	○	○	○	○ Less than 1 orange ○ 1 orange ○ More than 1 orange
Grapefruit	○	○	○	○	○	○	○	○	○	○	○ Less than 1/2 grapefruit ○ 1/2 grapefruit ○ More than 1/2 grapefruit
Grapes	○	○	○	○	○	○	○	○	○	○	○ Less than 1/2 cup ○ 1/2 to 1 1/2 cups ○ More than 1 1/2 cups
Cooked greens, such as spinach, turnip, collard, mustard, kale	○	○	○	○	○	○	○	○	○	○	○ Less than 1/2 cup ○ 1/2 to 1 cup ○ More than 1 cup
Raw greens, such as spinach, turnip, collard, mustard, kale	○	○	○	○	○	○	○	○	○	○	○ Less than 1/4 cup ○ 1/4 to 1/2 cup ○ More than 1/2 cup
Cole slaw, cabbage or sauerkraut	○	○	○	○	○	○	○	○	○	○	○ Less than 1/2 cup ○ 1/2 to 1 cup ○ More than 1 cup
Carrots	○	○	○	○	○	○	○	○	○	○	○ Less than 1/4 cup ○ 1/4 to 1/2 cup ○ More than 1/2 cup
String beans, green beans (fresh, canned, or frozen)	○	○	○	○	○	○	○	○	○	○	○ Less than 1/2 cup ○ 1/2 to 1 cup ○ More than 1 cup

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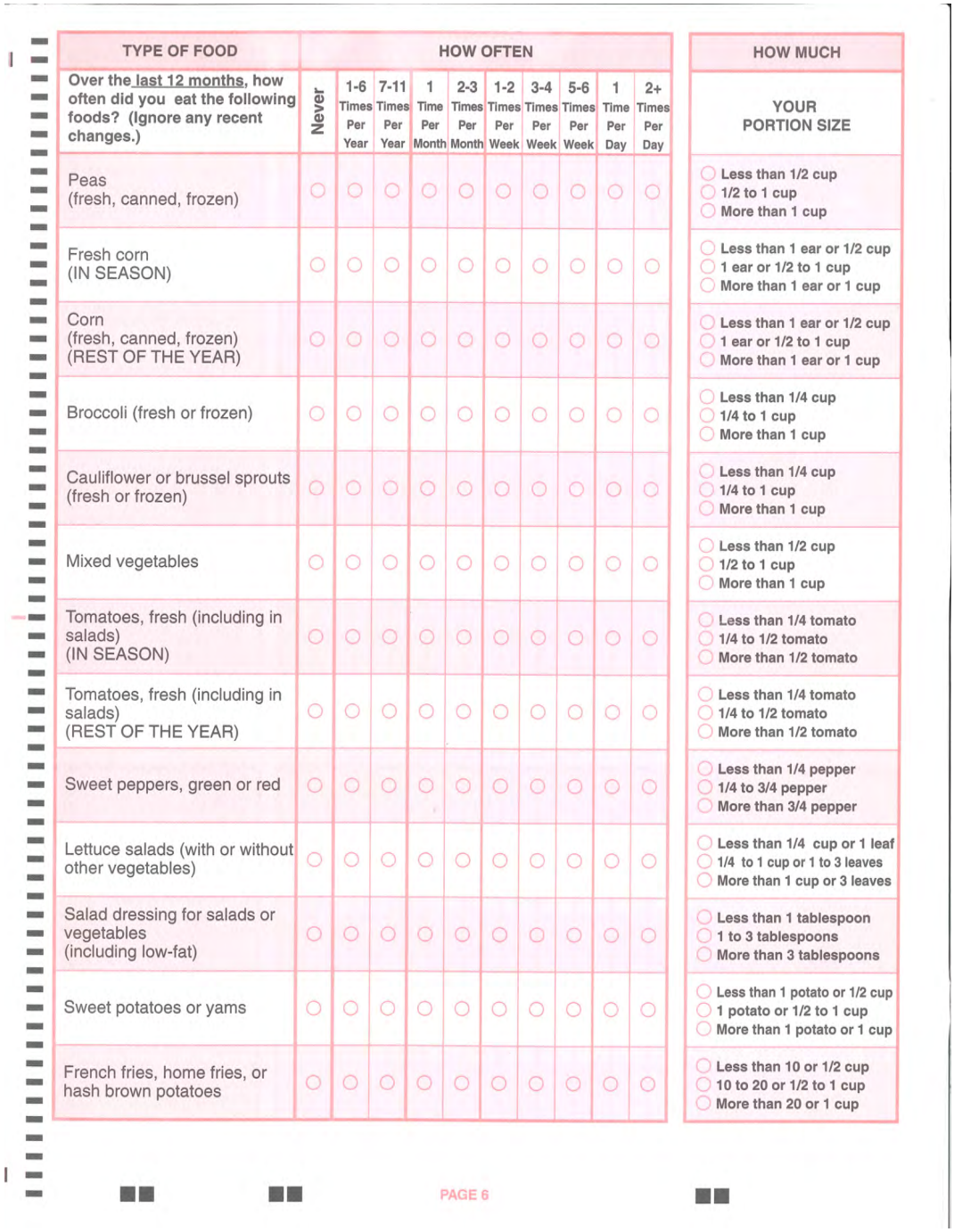

TYPE OF FOOD	HOW OFTEN										HOW MUCH
Over the last 12 months, how often did you eat the following foods? (Ignore any recent changes.)	Never	1-6 Times Per Year	7-11 Times Per Year	1 Time Per Month	2-3 Times Per Month	1-2 Times Per Week	3-4 Times Per Week	5-6 Times Per Week	1 Time Per Day	2+ Times Per Day	YOUR PORTION SIZE
Peas (fresh, canned, frozen)	○	○	○	○	○	○	○	○	○	○	○ Less than 1/2 cup ○ 1/2 to 1 cup ○ More than 1 cup
Fresh corn (IN SEASON)	○	○	○	○	○	○	○	○	○	○	○ Less than 1 ear or 1/2 cup ○ 1 ear or 1/2 to 1 cup ○ More than 1 ear or 1 cup
Corn (fresh, canned, frozen) (REST OF THE YEAR)	○	○	○	○	○	○	○	○	○	○	○ Less than 1 ear or 1/2 cup ○ 1 ear or 1/2 to 1 cup ○ More than 1 ear or 1 cup
Broccoli (fresh or frozen)	○	○	○	○	○	○	○	○	○	○	○ Less than 1/4 cup ○ 1/4 to 1 cup ○ More than 1 cup
Cauliflower or brussel sprouts (fresh or frozen)	○	○	○	○	○	○	○	○	○	○	○ Less than 1/4 cup ○ 1/4 to 1 cup ○ More than 1 cup
Mixed vegetables	○	○	○	○	○	○	○	○	○	○	○ Less than 1/2 cup ○ 1/2 to 1 cup ○ More than 1 cup
Tomatoes, fresh (including in salads) (IN SEASON)	○	○	○	○	○	○	○	○	○	○	○ Less than 1/4 tomato ○ 1/4 to 1/2 tomato ○ More than 1/2 tomato
Tomatoes, fresh (including in salads) (REST OF THE YEAR)	○	○	○	○	○	○	○	○	○	○	○ Less than 1/4 tomato ○ 1/4 to 1/2 tomato ○ More than 1/2 tomato
Sweet peppers, green or red	○	○	○	○	○	○	○	○	○	○	○ Less than 1/4 pepper ○ 1/4 to 3/4 pepper ○ More than 3/4 pepper
Lettuce salads (with or without other vegetables)	○	○	○	○	○	○	○	○	○	○	○ Less than 1/4 cup or 1 leaf ○ 1/4 to 1 cup or 1 to 3 leaves ○ More than 1 cup or 3 leaves
Salad dressing for salads or vegetables (including low-fat)	○	○	○	○	○	○	○	○	○	○	○ Less than 1 tablespoon ○ 1 to 3 tablespoons ○ More than 3 tablespoons
Sweet potatoes or yams	○	○	○	○	○	○	○	○	○	○	○ Less than 1 potato or 1/2 cup ○ 1 potato or 1/2 to 1 cup ○ More than 1 potato or 1 cup
French fries, home fries, or hash brown potatoes	○	○	○	○	○	○	○	○	○	○	○ Less than 10 or 1/2 cup ○ 10 to 20 or 1/2 to 1 cup ○ More than 20 or 1 cup

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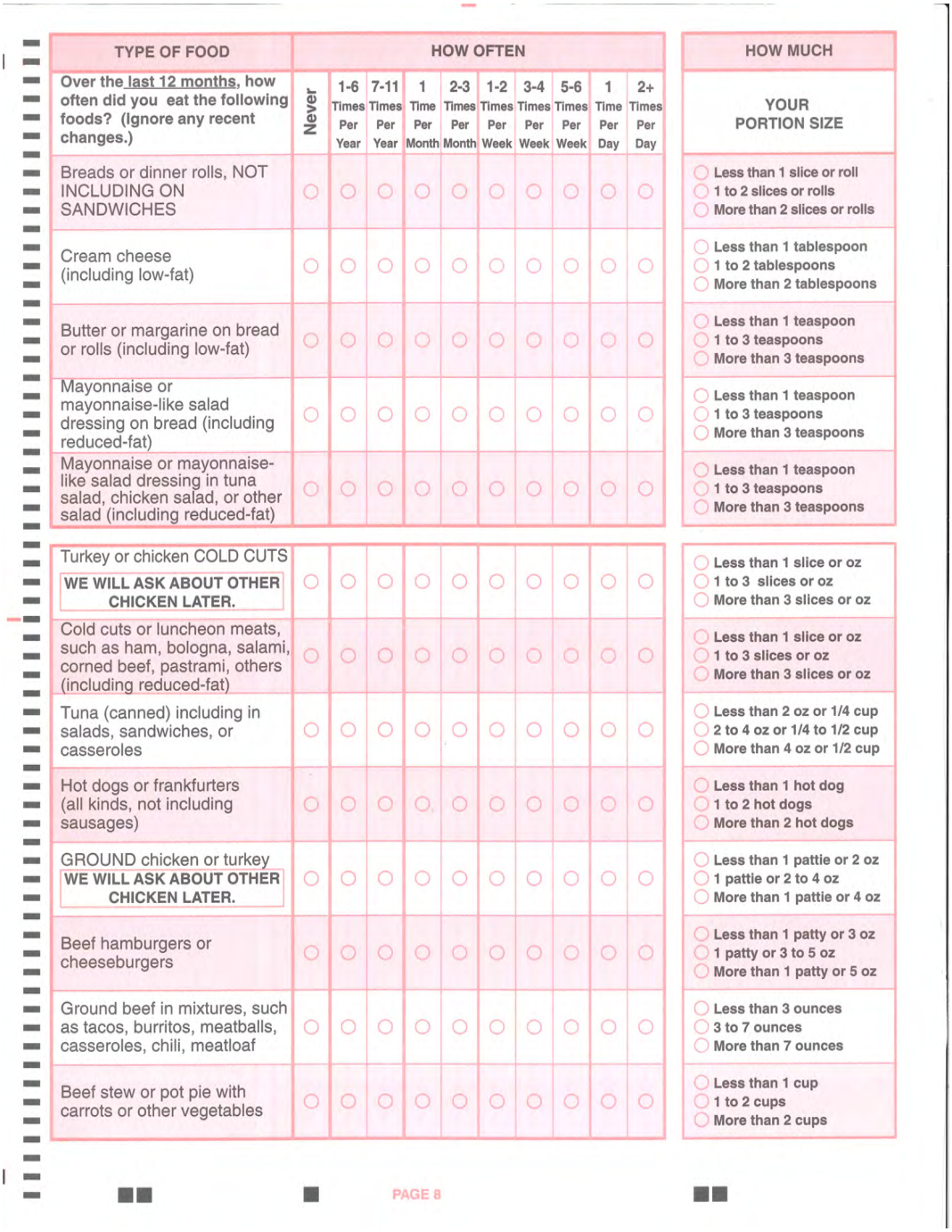
TYPE OF FOOD	HOW OFTEN										HOW MUCH
Over the last 12 months, how often did you eat the following foods? (Ignore any recent changes.)	Never	1-6 Times Per Year	7-11 Times Per Year	1 Time Per Month	2-3 Times Per Month	1-2 Times Per Week	3-4 Times Per Week	5-6 Times Per Week	1 Time Per Day	2+ Times Per Day	YOUR PORTION SIZE
Potato salad	○	○	○	○	○	○	○	○	○	○	○ Less than 3/4 cup ○ 3/4 to 1 1/2 cups ○ More than 1 1/2 cups
Baked, boiled, mashed (including instant) potatoes	○	○	○	○	○	○	○	○	○	○	○ Less than 1 potato or 1/2 cup ○ 1 to 2 potatoes or 1/2 to 1 cup ○ More than 1 potato or 1 cup
Salsa	○	○	○	○	○	○	○	○	○	○	○ Less than 1 tablespoon ○ 1 to 6 tablespoons ○ More than 6 tablespoons
Chili	○	○	○	○	○	○	○	○	○	○	○ Less than 1 cup ○ 1 to 2 cups ○ More than 2 cups
Beans, such as baked beans, refried beans, pintos, kidney, lima, lentils, or soybeans (NOT INCLUDING bean soup)	○	○	○	○	○	○	○	○	○	○	○ Less than 1/2 cup ○ 1/2 to 1 cup ○ More than 1 cup
Rice (all types), or other cooked grains	○	○	○	○	○	○	○	○	○	○	○ Less than 1/2 cup ○ 1/2 to 1 1/2 cups ○ More than 1 1/2 cups
Lasagna, stuffed shells, stuffed manicotti, ravioli, tortellini (NOT COUNTING SPAGHETTI)	○	○	○	○	○	○	○	○	○	○	○ Less than 1 cup ○ 1 to 2 cups ○ More than 2 cups
Macaroni and cheese	○	○	○	○	○	○	○	○	○	○	○ Less than 1 cup ○ 1 to 2 cups ○ More than 2 cups
Pasta, spaghetti, or other noodles	○	○	○	○	○	○	○	○	○	○	○ Less than 1 cup ○ 1 to 2 cups ○ More than 2 cups
Tomato sauce or spaghetti sauce made WITH meat	○	○	○	○	○	○	○	○	○	○	○ Less than 1/2 cup ○ 1/2 to 1 cup ○ More than 1 cup
Tomato sauce or spaghetti sauce made WITHOUT meat	○	○	○	○	○	○	○	○	○	○	○ Less than 1/2 cup ○ 1/2 to 1 cup ○ More than 1 cup
Bagels, English muffins	○	○	○	○	○	○	○	○	○	○	○ Less than 1 bagel or muffin ○ 1 bagel or muffin ○ More than 1 bagel or muffin
Breads or rolls FOR SANDWICHES (including burger or hot dog rolls)	○	○	○	○	○	○	○	○	○	○	○ Less than 1 slice or bun ○ 1 to 2 slices or 1 bun ○ More than 2 slices or 1 bun



TYPE OF FOOD	HOW OFTEN									HOW MUCH
Over the last 12 months, how often did you eat the following foods? (Ignore any recent changes.)	Never	1-6 Times Per Year	7-11 Times Per Year	1 Time Per Month	2-3 Times Per Month	1-2 Times Per Week	3-4 Times Per Week	5-6 Times Per Week	1 Time Per Day	2+ Times Per Day	YOUR PORTION SIZE
Breads or dinner rolls, NOT INCLUDING ON SANDWICHES	○	○	○	○	○	○	○	○	○	○	○ Less than 1 slice or roll ○ 1 to 2 slices or rolls ○ More than 2 slices or rolls
Cream cheese (including low-fat)	○	○	○	○	○	○	○	○	○	○	○ Less than 1 tablespoon ○ 1 to 2 tablespoons ○ More than 2 tablespoons
Butter or margarine on bread or rolls (including low-fat)	○	○	○	○	○	○	○	○	○	○	○ Less than 1 teaspoon ○ 1 to 3 teaspoons ○ More than 3 teaspoons
Mayonnaise or mayonnaise-like salad dressing on bread (including reduced-fat)	○	○	○	○	○	○	○	○	○	○	○ Less than 1 teaspoon ○ 1 to 3 teaspoons ○ More than 3 teaspoons
Mayonnaise or mayonnaise-like salad dressing in tuna salad, chicken salad, or other salad (including reduced-fat)	○	○	○	○	○	○	○	○	○	○	○ Less than 1 teaspoon ○ 1 to 3 teaspoons ○ More than 3 teaspoons
Turkey or chicken COLD CUTS **WE WILL ASK ABOUT OTHER CHICKEN LATER.**	○	○	○	○	○	○	○	○	○	○	○ Less than 1 slice or oz ○ 1 to 3 slices or oz ○ More than 3 slices or oz
Cold cuts or luncheon meats, such as ham, bologna, salami, corned beef, pastrami, others (including reduced-fat)	○	○	○	○	○	○	○	○	○	○	○ Less than 1 slice or oz ○ 1 to 3 slices or oz ○ More than 3 slices or oz
Tuna (canned) including in salads, sandwiches, or casseroles	○	○	○	○	○	○	○	○	○	○	○ Less than 2 oz or 1/4 cup ○ 2 to 4 oz or 1/4 to 1/2 cup ○ More than 4 oz or 1/2 cup
Hot dogs or frankfurters (all kinds, not including sausages)	○	○	○	○	○	○	○	○	○	○	○ Less than 1 hot dog ○ 1 to 2 hot dogs ○ More than 2 hot dogs
GROUND chicken or turkey **WE WILL ASK ABOUT OTHER CHICKEN LATER.**	○	○	○	○	○	○	○	○	○	○	○ Less than 1 pattie or 2 oz ○ 1 pattie or 2 to 4 oz ○ More than 1 pattie or 4 oz
Beef hamburgers or cheeseburgers	○	○	○	○	○	○	○	○	○	○	○ Less than 1 patty or 3 oz ○ 1 patty or 3 to 5 oz ○ More than 1 patty or 5 oz
Ground beef in mixtures, such as tacos, burritos, meatballs, casseroles, chili, meatloaf	○	○	○	○	○	○	○	○	○	○	○ Less than 3 ounces ○ 3 to 7 ounces ○ More than 7 ounces
Beef stew or pot pie with carrots or other vegetables	○	○	○	○	○	○	○	○	○	○	○ Less than 1 cup ○ 1 to 2 cups ○ More than 2 cups

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TYPE OF FOOD	HOW OFTEN										HOW MUCH
Over the last 12 months, how often did you eat the following foods? (Ignore any recent changes.)	Never	1-6 Times Per Year	7-11 Times Per Year	1 Time Per Month	2-3 Times Per Month	1-2 Times Per Week	3-4 Times Per Week	5-6 Times Per Week	1 Time Per Day	2+ Times Per Day	YOUR PORTION SIZE
Roast beef or steak IN SANDWICHES	○	○	○	○	○	○	○	○	○	○	○ Less than 1 ounce ○ 1 to 3 ounces ○ More than 3 ounces
Roast beef, including in mixtures (NOT in sandwiches)	○	○	○	○	○	○	○	○	○	○	○ Less than 2 ounces ○ 2 to 5 ounces ○ More than 5 ounces
Steak (beef)	○	○	○	○	○	○	○	○	○	○	○ Less than 3 ounces ○ 3 to 7 ounces ○ More than 7 ounces
Roast turkey, turkey cutlets, or nuggets (including in sandwiches)	○	○	○	○	○	○	○	○	○	○	○ Less than 2 ounces ○ 2 to 4 ounces ○ More than 4 ounces
Fried chicken or chicken nuggets* (*4 to 8 nuggets = 3 oz)	○	○	○	○	○	○	○	○	○	○	○ Less than 2 oz or 1 piece ○ 2 to 5 oz or 1 to 2 pieces ○ More than 5 oz or 2 pieces
Baked, broiled, roasted, or stewed chicken	○	○	○	○	○	○	○	○	○	○	○ Less than 2 oz or 1 piece ○ 2 to 5 oz or 1 to 2 pieces ○ More than 5 oz or 2 pieces
Chicken as part of salads, sandwiches, casseroles, stews, or other mixtures	○	○	○	○	○	○	○	○	○	○	○ Less than 1/2 cup ○ 1/2 to 1 cup ○ More than 1 cup
Roast ham or ham steak	○	○	○	○	○	○	○	○	○	○	○ Less than 2 ounces ○ 2 to 3 ounces ○ More than 3 ounces
Pork including chops, roasts, and in mixed dishes	○	○	○	○	○	○	○	○	○	○	○ Less than 3 ounces ○ 3 to 6 ounces ○ More than 6 ounces
Meat gravy on meat, chicken, potatoes, rice, etc.	○	○	○	○	○	○	○	○	○	○	○ Less than 2 tablespoons ○ 2 to 8 tablespoons ○ More than 8 tablespoons
Liver (all kinds) or liverwurst	○	○	○	○	○	○	○	○	○	○	○ Less than 2 ounces ○ 2 to 5 ounces ○ More than 5 ounces
Bacon (including reduced-fat)	○	○	○	○	○	○	○	○	○	○	○ Less than 3 slices ○ 3 to 4 slices ○ More than 4 slices
Sausage (including reduced-fat)	○	○	○	○	○	○	○	○	○	○	○ Less than 1 pattie or link ○ 1 to 4 patties or links ○ More than 4 patties or links

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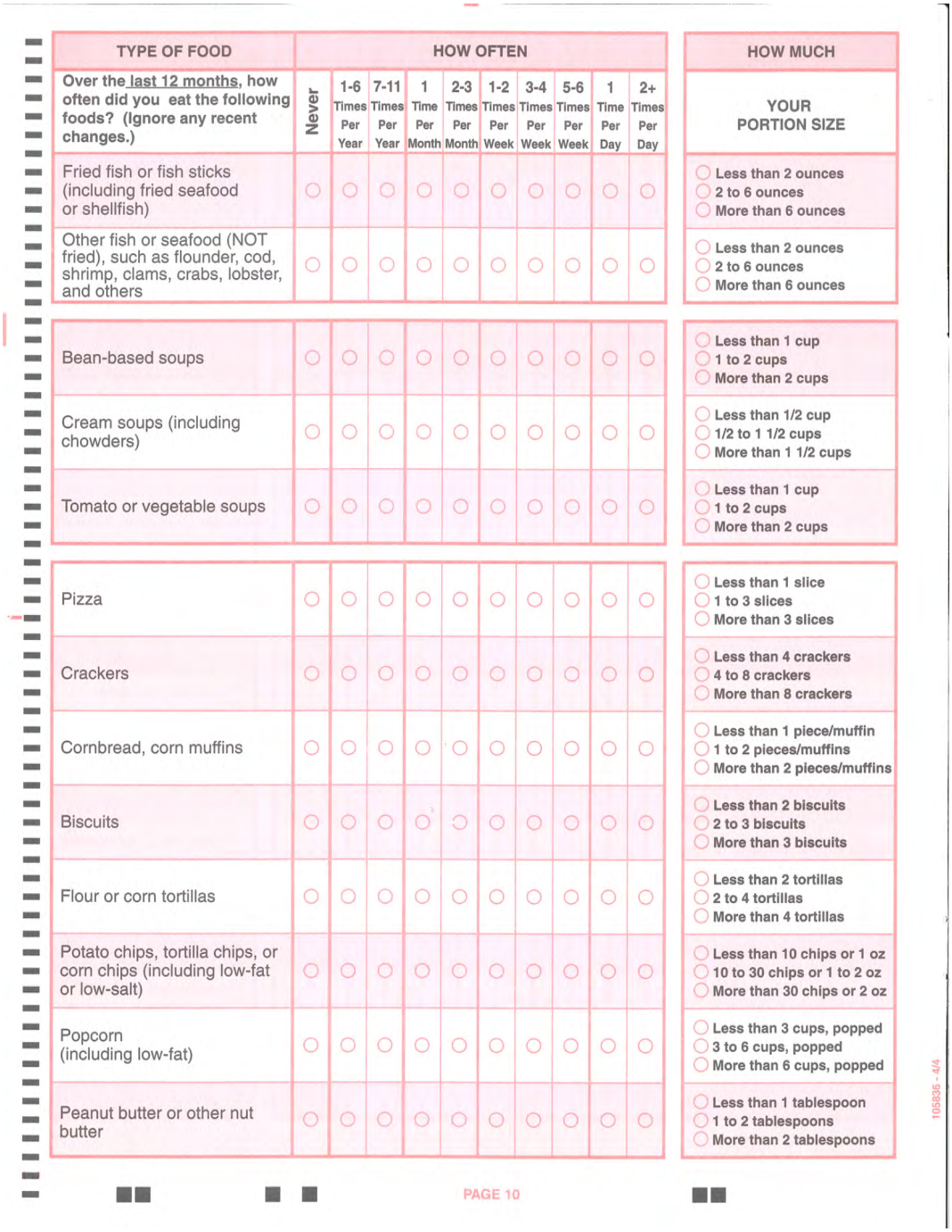

TYPE OF FOOD	HOW OFTEN										HOW MUCH
Over the last 12 months, how often did you eat the following foods? (Ignore any recent changes.)	Never	1-6 Times Per Year	7-11 Times Per Year	1 Time Per Month	2-3 Times Per Month	1-2 Times Per Week	3-4 Times Per Week	5-6 Times Per Week	1 Time Per Day	2+ Times Per Day	YOUR PORTION SIZE
Fried fish or fish sticks (including fried seafood or shellfish)	○	○	○	○	○	○	○	○	○	○	○ Less than 2 ounces ○ 2 to 6 ounces ○ More than 6 ounces
Other fish or seafood (NOT fried), such as flounder, cod, shrimp, clams, crabs, lobster, and others	○	○	○	○	○	○	○	○	○	○	○ Less than 2 ounces ○ 2 to 6 ounces ○ More than 6 ounces
Bean-based soups	○	○	○	○	○	○	○	○	○	○	○ Less than 1 cup ○ 1 to 2 cups ○ More than 2 cups
Cream soups (including chowders)	○	○	○	○	○	○	○	○	○	○	○ Less than 1/2 cup ○ 1/2 to 1 1/2 cups ○ More than 1 1/2 cups
Tomato or vegetable soups	○	○	○	○	○	○	○	○	○	○	○ Less than 1 cup ○ 1 to 2 cups ○ More than 2 cups
Pizza	○	○	○	○	○	○	○	○	○	○	○ Less than 1 slice ○ 1 to 3 slices ○ More than 3 slices
Crackers	○	○	○	○	○	○	○	○	○	○	○ Less than 4 crackers ○ 4 to 8 crackers ○ More than 8 crackers
Cornbread, corn muffins	○	○	○	○	○	○	○	○	○	○	○ Less than 1 piece/muffin ○ 1 to 2 pieces/muffins ○ More than 2 pieces/muffins
Biscuits	○	○	○	○	○	○	○	○	○	○	○ Less than 2 biscuits ○ 2 to 3 biscuits ○ More than 3 biscuits
Flour or corn tortillas	○	○	○	○	○	○	○	○	○	○	○ Less than 2 tortillas ○ 2 to 4 tortillas ○ More than 4 tortillas
Potato chips, tortilla chips, or corn chips (including low-fat or low-salt)	○	○	○	○	○	○	○	○	○	○	○ Less than 10 chips or 1 oz ○ 10 to 30 chips or 1 to 2 oz ○ More than 30 chips or 2 oz
Popcorn (including low-fat)	○	○	○	○	○	○	○	○	○	○	○ Less than 3 cups, popped ○ 3 to 6 cups, popped ○ More than 6 cups, popped
Peanut butter or other nut butter	○	○	○	○	○	○	○	○	○	○	○ Less than 1 tablespoon ○ 1 to 2 tablespoons ○ More than 2 tablespoons

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TYPE OF FOOD	HOW OFTEN										HOW MUCH
Over the last 12 months, how often did you eat the following foods? (Ignore any recent changes.)	Never	1-6 Times Per Year	7-11 Times Per Year	1 Time Per Month	2-3 Times Per Month	1-2 Times Per Week	3-4 Times Per Week	5-6 Times Per Week	1 Time Per Day	2+ Times Per Day	YOUR PORTION SIZE
Peanuts, walnuts, seeds, or other nuts	○	○	○	○	○	○	○	○	○	○	○ Less than 1/4 cup ○ 1/4 to 1/2 cup ○ More than 1/2 cup
Sour cream (including low-fat)	○	○	○	○	○	○	○	○	○	○	○ Less than 1 tablespoon ○ 1 to 3 tablespoons ○ More than 3 tablespoons
Cheese or cheese spreads (including low-fat but NOT including cream cheese or cheese on pizza)	○	○	○	○	○	○	○	○	○	○	○ Less than 3/4 ounce ○ 3/4 to 1 1/2 ounces ○ More than 1 1/2 ounces
Frozen yogurt, low-fat ice cream, ice milk, or sherbet	○	○	○	○	○	○	○	○	○	○	○ Less than 1/2 cup ○ 1/2 to 1 1/2 cups ○ More than 1 1/2 cups
Regular-fat ice cream or ice-cream bars	○	○	○	○	○	○	○	○	○	○	○ Less than 1/2 cup ○ 1/2 to 1 cup ○ More than 1 cup
Cake (including low-fat)	○	○	○	○	○	○	○	○	○	○	○ Less than 1 medium piece ○ 1 medium piece ○ More than 1 medium piece
Cookies or brownies (including low-fat)	○	○	○	○	○	○	○	○	○	○	○ Less than 1 piece ○ 1 to 3 pieces ○ More than 3 pieces
Doughnuts, sweet rolls, danish, sweet muffins or dessert breads	○	○	○	○	○	○	○	○	○	○	○ Less than 1 piece ○ 1 to 2 pieces ○ More than 2 pieces
Fruit pie, such as apple, blueberry, others	○	○	○	○	○	○	○	○	○	○	○ Less than 1/8 pie ○ About 1/8 to 1/6 pie ○ More than 1/6 pie
Cream, custard, or meringue pie	○	○	○	○	○	○	○	○	○	○	○ Less than 1/8 pie ○ About 1/8 to 1/6 pie ○ More than 1/6 pie
Pumpkin or sweet potato pie	○	○	○	○	○	○	○	○	○	○	○ Less than 1/8 pie ○ About 1/8 to 1/6 pie ○ More than 1/6 pie
Chocolate candy	○	○	○	○	○	○	○	○	○	○	○ Less than 1 bar or 1 oz ○ 1 bar or 1 to 2 oz ○ More than 1 bar or 2 oz
Other candy	○	○	○	○	○	○	○	○	○	○	○ Less than 2 pieces ○ 2 to 5 pieces ○ More than 5 pieces

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Please note that the response categories change in the following questions.

TYPE OF FOOD	HOW MANY									
Over the last 12 months:	None	1 - 6 Eggs Per Year	7 - 11 Eggs Per Year	1 Egg Per Month	2 - 3 Eggs Per Month	1 - 2 Eggs Per Week	3 - 4 Eggs Per Week	5 - 6 Eggs Per Week	1 Egg Per Day	2 + Eggs Per Day
How many eggs, egg whites, or egg substitutes (NOT counting eggs in baked goods and desserts) did you eat?	○	○	○	○	○	○	○	○	○	○

Over the last 12 months:	None	Less than 1 Cup per Month	1 - 3 Cups Per Month	1 - 2 Cups Per Week	3 - 4 Cups Per Week	5 - 6 Cups Per Week	1 Cup Per Day	2 - 3 Cups Per Day	4 - 5 Cups Per Day	6 + Cups Per Day
How many cups of coffee, caffeinated or decaffeinated, did you drink?	○	○	○	○	○	○	○	○	○	○
How many cups of HOT tea, caffeinated or decaffeinated, did you drink?	○	○	○	○	○	○	○	○	○	○
How many glasses or cups of ICED tea, caffeinated or decaffeinated did you drink? (IN SUMMER)	○	○	○	○	○	○	○	○	○	○

We would like to ask you a few more questions about your usual eating patterns over the last 12 months. The term "usually" refers to MORE THAN HALF THE TIME.

6. When you drank the following beverages, please mark whether you usually (more than half the time) drank sugar-free (diet) or regular-calorie types. Please answer for all beverages.

	Didn't drink this beverage	More than half the time I drank: Sugar-free	Regular
Soft drinks, soda, or pop	○	○	○
Drinks such as Hi-C, lemonade, or Kool-aid	○	○	○
Sweetened iced tea	○	○	○

7. When you drank the following beverages, please mark whether you usually drank caffeine-free or caffeine-containing types.

	Didn't drink this beverage	More than half the time I drank: Caffeine - free	Caffeine - containing
Soft drinks, soda, or pop	○	○	○
Coffee	○	○	○
Hot tea	○	○	○
Iced tea	○	○	○

8. Please record the number of servings of vegetables and fruits you usually ate per week or per day.	HOW MANY SERVINGS								
	Less than One Per Week	1-2 Per Week	3-4 Per Week	5-6 Per Week	1 Per Day	1 1/2 Per Day	2 Per Day	3 Per Day	4+ Per Day
Number of servings of vegetables (not including salad or potatoes)	○	○	○	○	○	○	○	○	○
Number of servings of fruit (not including juices)	○	○	○	○	○	○	○	○	○

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9. Please mark whether you usually ate regular fat, low-fat or non-fat versions of the following foods:

	Didn't eat this food	More than half the time I ate : Regular fat	Low-fat	Non-fat
Sour cream	○	○	○	○
Cream cheese	○	○	○	○
Cottage cheese	○	○	○	○
Other cheese	○	○	○	○
Crackers	○	○	○	○
Potato chips, corn chips, or other chips	○	○	○	○
Cookies or brownies	○	○	○	○
Cake	○	○	○	○
Mayonnaise or mayonnaise-type dressing	○	○	○	○
Salad dressing	○	○	○	○

10. Please mark whether you usually ate regular-fat or low-fat versions of the following foods:

	Didn't eat this food	More than half the time I ate : Regular fat	Low-fat
Hot dogs	○	○	○
Cold cuts or luncheon meats, such as ham, bologna, salami, corned beef, pastrami, others (NOT including chicken or turkey cold cuts)	○	○	○
Bacon	○	○	○
Sausage	○	○	○

11. Over the last 12 months, when you ate ground beef (including hamburgers and cheeseburgers) which kind did you usually eat?

- ○ Didn't eat ground beef
- ○ Regular ground beef
- ○ Lean ground beef
- ○ Lean and regular about the same amount of time

12. When you ate beef steaks, roasts, or chops, which kind did you usually (more than half the time) eat?

- ○ Didn't eat steaks, roasts, or chops
- ○ Regular fat cuts
- ○ Lean cuts
- ○ Lean and regular about the same amount of time

13. Over the last 12 months, when you ate chicken, how did you usually (more than half the time) eat it?

- ○ Didn't eat chicken (**GO TO QUESTION 15**)
- ○ With skin
- ○ Without skin
- ○ With and without skin about the same amount of time

14. When you ate chicken, which kind did you usually eat?

- ○ Light meat
- ○ Dark meat
- ○ Dark and light meat about the same amount of time

15. When you ate canned tuna, which kind did you usually eat?

- ○ Didn't eat canned tuna
- ○ Water-packed tuna
- ○ Oil-packed tuna
- ○ Oil- and water- packed tuna about the same amount of time

16. Over the last 12 months, when you ate eggs (not including in baked goods and desserts), which kind of eggs did you usually eat?

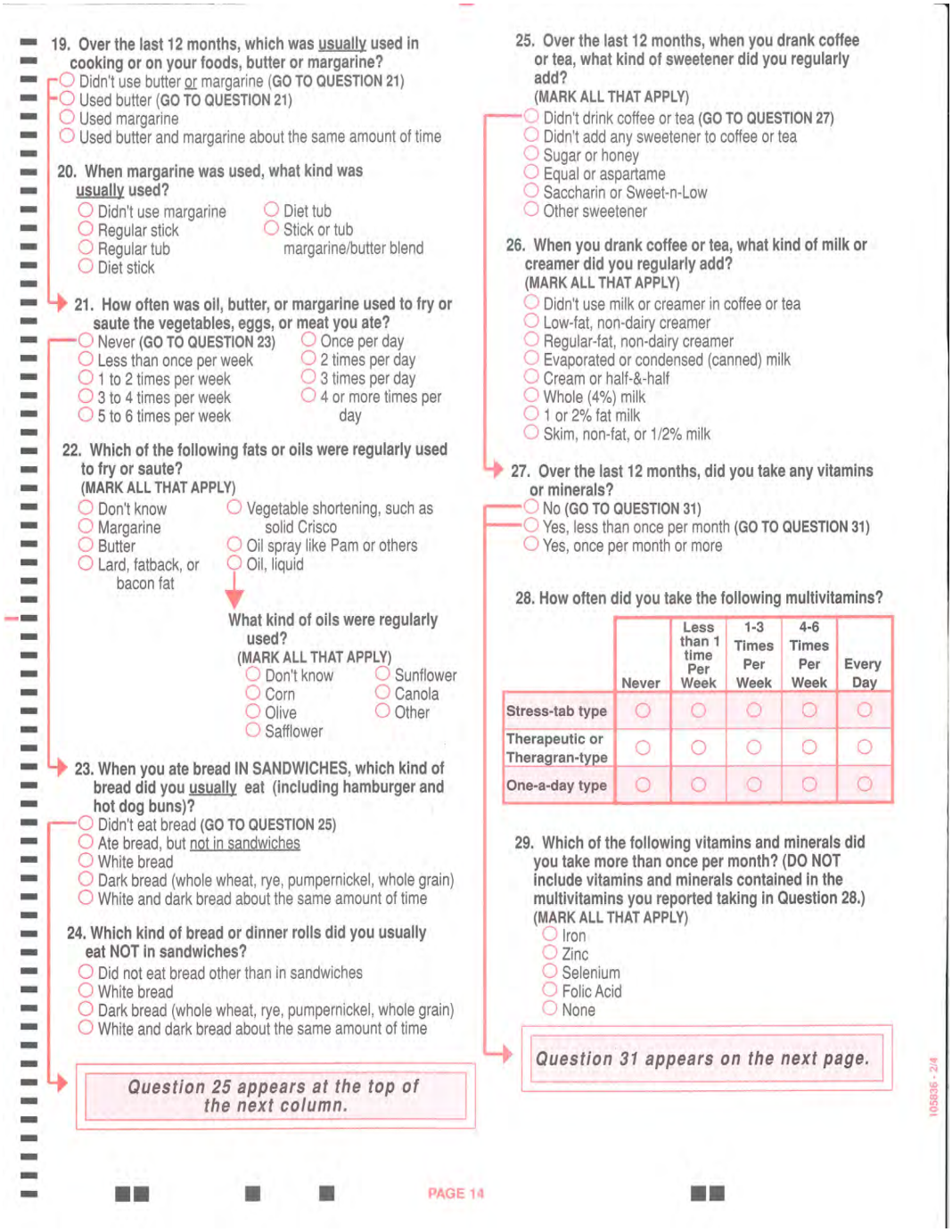
- ○ Didn't eat eggs (**GO TO QUESTION 18**)
- ○ Whole eggs
- ○ Egg whites
- ○ Egg substitutes

17. How were your eggs usually cooked?

- ○ In oil
- ○ In oil spray
- ○ In butter
- ○ In margarine
- ○ Poached or boiled
- ○ In non-stick pan with no oil, butter, or margarine

18. When you ate each of the foods listed in this table, how often was butter or margarine added AFTER COOKING OR AT THE TABLE?

	Didn't eat this food	Added margarine or butter after cooking: MORE than half the time	Half the time or LESS	Almost Never or Never
Oatmeal, grits, or other cooked cereals	○	○	○	○
Pancakes, waffles, or French toast	○	○	○	○
Baked, boiled, or mashed potatoes	○	○	○	○
Rice	○	○	○	○
Pasta	○	○	○	○
Cooked vegetables	○	○	○	○



19. Over the last 12 months, which was usually used in cooking or on your foods, butter or margarine?
- ○ Didn't use butter or margarine (GO TO QUESTION 21)
- ○ Used butter (GO TO QUESTION 21)
- ○ Used margarine
- ○ Used butter and margarine about the same amount of time

20. When margarine was used, what kind was usually used?
- ○ Didn't use margarine
- ○ Regular stick
- ○ Regular tub
- ○ Diet stick
- ○ Diet tub
- ○ Stick or tub margarine/butter blend

21. How often was oil, butter, or margarine used to fry or saute the vegetables, eggs, or meat you ate?
- ○ Never (GO TO QUESTION 23)
- ○ Less than once per week
- ○ 1 to 2 times per week
- ○ 3 to 4 times per week
- ○ 5 to 6 times per week
- ○ Once per day
- ○ 2 times per day
- ○ 3 times per day
- ○ 4 or more times per day

22. Which of the following fats or oils were regularly used to fry or saute?
(MARK ALL THAT APPLY)
- ○ Don't know
- ○ Margarine
- ○ Butter
- ○ Lard, fatback, or bacon fat
- ○ Vegetable shortening, such as solid Crisco
- ○ Oil spray like Pam or others
- ○ Oil, liquid

What kind of oils were regularly used?
(MARK ALL THAT APPLY)
- ○ Don't know
- ○ Corn
- ○ Olive
- ○ Safflower
- ○ Sunflower
- ○ Canola
- ○ Other

23. When you ate bread IN SANDWICHES, which kind of bread did you usually eat (including hamburger and hot dog buns)?
- ○ Didn't eat bread (GO TO QUESTION 25)
- ○ Ate bread, but not in sandwiches
- ○ White bread
- ○ Dark bread (whole wheat, rye, pumpernickel, whole grain)
- ○ White and dark bread about the same amount of time

24. Which kind of bread or dinner rolls did you usually eat NOT in sandwiches?
- ○ Did not eat bread other than in sandwiches
- ○ White bread
- ○ Dark bread (whole wheat, rye, pumpernickel, whole grain)
- ○ White and dark bread about the same amount of time

Question 25 appears at the top of the next column.

25. Over the last 12 months, when you drank coffee or tea, what kind of sweetener did you regularly add?
(MARK ALL THAT APPLY)
- ○ Didn't drink coffee or tea (GO TO QUESTION 27)
- ○ Didn't add any sweetener to coffee or tea
- ○ Sugar or honey
- ○ Equal or aspartame
- ○ Saccharin or Sweet-n-Low
- ○ Other sweetener

26. When you drank coffee or tea, what kind of milk or creamer did you regularly add?
(MARK ALL THAT APPLY)
- ○ Didn't use milk or creamer in coffee or tea
- ○ Low-fat, non-dairy creamer
- ○ Regular-fat, non-dairy creamer
- ○ Evaporated or condensed (canned) milk
- ○ Cream or half-&-half
- ○ Whole (4%) milk
- ○ 1 or 2% fat milk
- ○ Skim, non-fat, or 1/2% milk

27. Over the last 12 months, did you take any vitamins or minerals?
- ○ No (GO TO QUESTION 31)
- ○ Yes, less than once per month (GO TO QUESTION 31)
- ○ Yes, once per month or more

28. How often did you take the following multivitamins?

	Never	Less than 1 time Per Week	1-3 Times Per Week	4-6 Times Per Week	Every Day
Stress-tab type	○	○	○	○	○
Therapeutic or Theragran-type	○	○	○	○	○
One-a-day type	○	○	○	○	○

29. Which of the following vitamins and minerals did you take more than once per month? (DO NOT include vitamins and minerals contained in the multivitamins you reported taking in Question 28.)
(MARK ALL THAT APPLY)
- ○ Iron
- ○ Zinc
- ○ Selenium
- ○ Folic Acid
- ○ None

Question 31 appears on the next page.

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30. How often did you take the following single supplements, and what was the total amount of each single supplement you usually took in one day?

	Never	Less than 1 Time Per Week	1-3 Times Per Week	4-6 Times Per Week	Every Day	Total Amount You Usually Took in One Day				
Vitamin A	○	○	○	○	○	Less than 8,000 IU ○	8,000 to 12,000 IU ○	13,000 to 22,000 IU ○	23,000 IU or more ○	Don't know ○
Beta-carotene	○	○	○	○	○	Less than 8,000 IU ○	8,000 to 12,000 IU ○	13,000 to 22,000 IU ○	23,000 IU or more ○	Don't know ○
Vitamin C	○	○	○	○	○	Less than 400 mg ○	400 to 699 mg ○	700 to 1,250 mg ○	1300 mg or more ○	Don't know ○
Vitamin E	○	○	○	○	○	Less than 100 IU ○	100 to 250 IU ○	300 to 500 IU ○	600 IU or more ○	Don't know ○
Calcium (include Tums)	○	○	○	○	○	Less than 400 mg ○	400 to 900 mg ○	901 to 1300 mg ○	1301 mg or more ○	Don't know ○

The final group of questions asks about you, your family history, medical history, and smoking history.

31. Currently, which of the following best describes your daily routine at work? If you do not work at a job, select the response that best describes your routine throughout the day. Do not include the time you spend exercising or playing sports.
- ○ You sit during the day and do not walk around very much.
- ○ You sit much of the day, but also walk around a fair amount.
- ○ You stand or walk around a lot during the day, but do not have to carry or lift things very often.
- ○ You lift or carry light loads, or have to climb stairs or hills often.
- ○ You do heavy work or carry heavy loads.

32. During a typical month in the past 12 months, how often did you participate in physical activities at work or home, including exercise, sports, and activities such as carrying heavy loads? Only include periods of physical activities that lasted at least 20 minutes and caused increases in breathing or heart rate, or caused you to work up a sweat.
- ○ Never
- ○ Rarely
- ○ 1 to 3 times per month
- ○ 1 to 2 times per week
- ○ 3 to 4 times per week
- ○ 5 or more times per week

33. Think back in time to when you were around the ages of 15 to 18 years old. Back then, about how often did you participate in physical activities or sports during a typical month?
- ○ Never
- ○ Rarely
- ○ 1-3 times per month
- ○ 1-2 times per week
- ○ 3-4 times per week
- ○ 5 or more times per week

34. What is your current marital status?
- ○ Married or living as married
- ○ Widowed
- ○ Divorced
- ○ Separated
- ○ Never married

35. What is your sex?
- ○ Male
- ○ Female

36. Which of these best describes your race?
- ○ White, Not Hispanic
- ○ Black, Not Hispanic
- ○ Hispanic
- ○ Asian
- ○ Pacific Islander
- ○ American Indian or Alaskan Native

37. What is the highest grade or level of schooling you completed? (MARK ONLY ONE RESPONSE)
- ○ Less than 8 years
- ○ 8 through 11 years
- ○ 12 years or completed high school
- ○ Post-high school training other than college (for example, vocational or technical training)
- ○ Some college
- ○ College graduate
- ○ Postgraduate

38. We would like to have your Social Security Number. It will be used only to check against vital and health statistics records. This will have no effect on your benefits. This information is voluntary and is collected under the authority of the Public Health Service Act Section 412 (42 USC 285a-1) and Section 413 (42 USC 285a-2).

SOCIAL SECURITY NUMBER

39. Would you say your health in general is:
- ○ Excellent?
- ○ Very good?
- ○ Good?
- ○ Fair?
- ○ Poor?

40. Have you ever been told by a doctor that you had any of the following conditions? (MARK ALL THAT APPLY)
- ○ Gallbladder stone or disease
- ○ Diabetes
- ○ Heart disease
- ○ Emphysema
- ○ Osteoporosis
- ○ Bone fracture after age 45
- ○ Polyps of colon or rectum
- ○ End-stage renal disease
- ○ Stroke
- ○ No

41. Have you or any blood relatives in your immediate family (that includes your parents, full or half-brothers or sisters, and children) ever been diagnosed as having any type of cancer, except for basal-cell skin cancer?
- ○ No (GO TO QUESTION 42)
- ○ Yes → Please specify the types of cancer in the table below.

Family Member	Prostate Cancer	Breast Cancer	Colon Cancer	Other Cancer(s)
You	○	○	○	○
Father	○		○	○
Brother(s)	○		○	○
Son(s)	○		○	○
Mother		○	○	○
Sister(s)		○	○	○
Daughter(s)		○	○	○

42. Have you smoked 100 or more cigarettes during your entire life?
- ○ Yes
- ○ No (GO TO QUESTION 45)

43. Do you currently smoke cigarettes or have you stopped?
- ○ Currently smoke
- ○ Stopped within last year
- ○ Stopped 1 to 4 years ago
- ○ Stopped 5 to 9 years ago
- ○ Stopped 10 or more years ago

44. How many cigarettes per day do or did you usually smoke?
- ○ 1 to 10
- ○ 11 to 20
- ○ 21 to 30
- ○ 31 to 40
- ○ 41 to 60
- ○ 61 or more

45. Did you ever smoke pipes or cigars regularly for a year or longer?
- ○ No
- ○ Yes, pipes and cigars
- ○ Yes, pipes only
- ○ Yes, cigars only

IF YOU ARE MALE, STOP HERE.
Thank you very much for completing this questionnaire. Please return it in the self-addressed, postage-paid envelope.

46. How old were you when you had your first menstrual period?
- ○ 10 or younger
- ○ 11 to 12
- ○ 13 to 14
- ○ 15 or older

47. How many years did you take oral contraceptives (birth control pills)?
- ○ Never (or less than 1 year)
- ○ 1 to 4 years
- ○ 5 to 9 years
- ○ 10 or more years

48. How many live-born children have you had?
- ○ None
- ○ 1
- ○ 2
- ○ 3 to 4
- ○ 5 to 9
- ○ 10 or more

49. How old were you when you gave birth to your first child?
- ○ Never gave birth
- ○ Less than 16
- ○ 16 to 19
- ○ 20 to 24
- ○ 25 to 29
- ○ 30 to 34
- ○ 35 to 39
- ○ 40 or older

50. How old were you when you had your last menstrual period?
- ○ Less than 40
- ○ 40 to 44
- ○ 45 to 49
- ○ 50 to 54
- ○ 55 or older
- ○ Still menstruating

51. Did your periods stop because of natural menopause, surgery, radiation, or chemotherapy?
- ○ Periods did not stop
- ○ Natural menopause
- ○ Surgery
- ○ Radiation or chemotherapy

52. Have you had a hysterectomy (to remove your uterus)?
- ○ No
- ○ Yes

53. Have you had surgery to your ovaries?
- ○ No
- ○ Yes, both ovaries removed
- ○ Yes, other surgery to ovaries

54. How many times have you had a biopsy of the breast?
- ○ None
- ○ 1
- ○ 2
- ○ 3 or more

55. Are you currently taking replacement hormones?
- ○ No
- ○ Yes

56. How many years have you taken replacement hormones?
- ○ Never
- ○ Less than 5 years
- ○ 5 to 9 years
- ○ 10 or more years

Thank you very much for completing this questionnaire. Please return it in the self-addressed, postage-paid envelope.

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B

Supplementary Tables & Figures

B.1 Detailed dietary intakes by selected characteristics in the Million Women Study

Daily dietary intakes (mean)	Height (cm)		BMI		Strenuous exercise (times)		Social deprivation		Smoking		Alcohol		Parity		Use of oral contraceptive		Menopausal hormone use		Education	
	<160	170+	<25	30+	Never /rarely	3+/ week	Lower third	Upper third	Never	Current	Non-drinker	1+ drinks /day	Nulli-parous	Parous	Never	Ever	Never	Current	<13 years	Tertiary
Total fruit, g	201.4	211.1	211.6	198.8	187.3	226.6	195.7	214.4	214.7	146.0	212.2	195.7	213.4	206.0	204.7	208.2	205.0	204.9	194.7	232.7
Citrus fruit, g	43.7	45.1	45.8	42.1	39.9	49.0	42.5	45.9	45.5	32.9	43.3	43.7	45.3	44.2	43.1	45.2	44.2	43.9	41.2	51.8
Fruit juice, g	107.4	105.6	106.8	102.3	102.4	110.4	106.4	107.0	108.8	95.8	104.3	102.4	106.2	106.5	107.1	105.9	104.4	107.2	106.6	109.9
Total vegetables, g	118.0	125.3	123.5	120.5	112.9	130.8	114.8	126.3	122.0	107.2	117.8	130.2	126.5	121.5	117.6	124.9	119.1	125.1	113.6	138.4
Nuts, g	5.2	5.7	6.1	4.3	4.6	6.2	5.3	5.5	5.3	5.0	4.7	5.9	5.6	5.4	5.1	5.6	5.1	5.4	4.8	6.8
Grains/cereal, g	66.0	68.7	70.5	63.0	62.4	72.6	65.3	69.4	70.2	52.0	67.7	65.3	72.3	67.0	68.9	66.8	67.6	66.8	64.6	75.1
Red meat, g	30.6	29.9	28.9	32.5	31.1	29.3	29.5	30.8	30.0	32.1	28.6	32.5	29.7	30.4	29.3	31.0	30.1	30.9	29.7	30.6
Processed meat, g	11.6	11.3	10.5	12.8	12.1	10.5	11.8	10.9	11.2	12.6	11.8	10.9	10.5	11.5	11.4	11.3	11.8	11.0	11.8	10.1
White meat, g	22.1	21.4	21.8	21.9	21.7	22.0	21.3	22.4	22.0	19.8	21.7	22.1	21.9	21.9	20.5	22.8	21.1	23.1	20.9	23.5
Fish, g	34.3	33.4	33.9	34.2	32.4	35.6	33.5	34.7	33.9	31.9	32.4	35.1	35.0	33.9	34.1	34.0	33.8	34.0	32.8	36.5
Eggs, g	17.8	18.3	16.9	19.6	18.1	17.7	18.5	17.3	17.3	19.5	17.2	17.8	17.3	17.9	17.6	18.0	17.6	18.0	18.0	17.6
Dairy products, g	340.8	327.5	328.2	337.8	341.6	328.3	342.4	329.6	325.3	342.1	359.6	288.6	324.6	335.8	344.2	328.1	336.8	328.1	350.0	306.0
Cheese, g	18.8	20.1	20.2	18.0	18.9	19.6	19.1	19.4	19.3	19.7	18.4	20.1	20.2	19.2	19.1	19.5	19.4	19.5	18.3	22.1
Alcohol, g	5.0	5.7	6.2	4.0	4.8	6.1	4.7	6.0	4.5	6.1	0.0	16.1	6.4	5.3	4.2	6.2	4.9	6.2	4.3	7.6
Coffee, g	457.5	457.6	451.1	505.0	498.8	448.0	494.9	459.1	418.4	685.0	467.7	461.1	467.5	472.9	455.2	482.4	476.6	470.6	491.7	440.6
Tea, g	795.3	698.7	726.5	757.4	801.9	695.1	832.3	692.5	719.8	907.3	841.6	699.5	712.3	749.4	787.4	715.9	750.2	724.7	898.8	611.9
Carbohydrate, %E	47.7	46.9	47.0	47.7	47.6	47.2	47.9	46.9	47.8	46.0	49.9	43.1	47.0	47.3	48.1	46.8	47.5	47.0	48.3	45.2
Protein, %E	16.3	16.2	16.1	16.5	16.2	16.4	16.1	16.4	16.3	16.0	16.3	16.0	16.2	16.3	16.2	16.4	16.2	16.3	16.1	16.5
Total fat, %E	34.0	34.6	34.4	34.2	34.4	34.0	34.2	34.2	34.1	35.5	34.0	34.0	34.3	34.3	34.2	34.3	34.4	34.1	33.9	35.1
Saturated fat, %E	11.9	12.2	12.1	11.9	12.2	11.8	12.1	11.9	11.9	13.2	12.1	11.8	12.2	12.0	12.1	12.0	12.1	11.9	11.9	12.3
Monounsaturated fat, %E	12.4	12.6	12.6	12.4	12.4	12.5	12.3	12.6	12.5	12.6	12.2	12.7	12.6	12.5	12.4	12.6	12.4	12.5	12.2	13.1
Polyunsaturated fat, %E	6.4	6.4	6.3	6.6	6.5	6.4	6.5	6.3	6.4	6.6	6.4	6.3	6.2	6.4	6.4	6.4	6.4	6.4	6.4	6.3
Fibre, g	13.3	13.6	13.7	13.1	12.9	14.1	13.0	13.8	13.9	11.4	13.7	13.0	13.8	13.5	13.6	13.5	13.5	13.5	13.2	14.2
Carotene, ug	1276.9	1350.1	1350.9	1273.7	1233.0	1398.2	1239.7	1373.1	1396.4	1138.7	1281.9	1383.0	1388.1	1300.8	1283.8	1341.1	1301.4	1324.1	1216.5	1532.9
Vitamin C, ug	92.6	95.3	95.9	91.1	87.5	101.0	89.9	97.5	96.8	77.4	92.4	94.2	95.3	94.1	92.4	95.4	93.1	94.7	89.4	104.8
Vitamin E, mg	9.1	9.0	8.8	9.4	9.1	9.0	9.2	8.9	8.9	9.4	9.1	8.8	8.8	9.1	8.9	9.1	9.1	9.0	9.1	8.9
Folate, ug	247.9	246.2	246.9	246.5	244.0	251.1	245.4	248.5	249.1	233.6	251.5	239.6	249.0	247.2	249.4	246.0	246.6	247.2	247.8	246.8
Calcium, mg	825.9	820.9	821.0	821.6	824.1	823.5	827.4	820.5	828.3	817.0	853.3	764.9	818.6	824.1	836.4	815.0	828.5	812.8	833.0	810.4
Cholesterol, mg	214.0	218.0	210.8	223.6	216.8	213.6	216.1	214.8	212.5	228.6	210.4	217.5	214.0	215.6	212.8	217.1	215.2	215.0	212.4	222.2
DASH score	22.4	23.1	23.3	22.1	21.8	23.8	22.1	23.3	23.3	20.6	22.8	23.2	23.2	22.8	22.7	22.9	22.8	22.8	22.1	24.3
aMED score	3.8	4.0	4.1	3.7	3.6	4.3	3.7	4.2	4.1	3.2	3.5	4.4	4.1	4.0	3.8	4.0	3.9	4.0	3.7	4.6
AHEI	46.7	48.4	48.7	45.9	45.2	49.9	45.9	48.9	48.3	43.0	45.0	51.0	48.4	47.5	46.8	48.2	47.3	47.8	45.5	51.5
Total energy intake, kcal	1554.1	1680.3	1627.8	1611.6	1575.3	1641.9	1567.5	1639.6	1638.2	1550.2	1585.2	1690.5	1616.5	1611.4	1614.9	1611.6	1623.3	1600.0	1565.8	1683.9

%E percentage energy intake

B.2 Dietary intakes of all women and responders of the Oxford WebQ, and regression dilution ratios in the Million Women Study

		All women		Oxford WebQ responders			
	Category of intake at baseline (fourth)	No. of women	Intake at baseline, mean (SD)	No. of women	Intake at baseline, mean (SD)	Intake at Oxford WebQ, mean (SD)	Regression dilution ratio
Total fruit (g)	1	166414	60.0 (30.8)	7152	65.1 (28.5)	135.8 (117.9)	
	2	166414	136.3 (20.0)	9546	137.9 (19.9)	173.8 (111.8)	
	3	166413	219.2 (29.3)	11903	220.3 (29.3)	210.2 (119.7)	
	4	166413	411.7 (140.1)	13046	412.6 (137.8)	269.2 (150.9)	
	Overall	665654	206.8 (150.4)	41647	235.0 (153.3)	206.9 (137.6)	0.4
Citrus fruit (g)	1	201413	0.0 (0.0)	10140	0.0 (0.0)	16.9 (35.8)	
	2	115453	24.1 (7.3)	6439	25.0 (7.1)	22.8 (36.8)	
	3	158433	49.7 (9.0)	11305	50.2 (9.0)	31.8 (43.2)	
	4	158433	110.2 (50.1)	12315	109.9 (48.5)	44.2 (53.5)	
	Overall	633732	44.4 (49.5)	40199	51.8 (50.8)	30.0 (45.3)	0.2
Fruit juice (g)	1	142053	3.4 (8.4)	9308	4.6 (9.3)	33.7 (70.7)	
	2	142053	66.1 (19.6)	9884	64.7 (19.8)	54.4 (83.5)	
	3	142053	129.8 (16.1)	9844	130.2 (15.9)	86.8 (95.7)	
	4	142052	226.5 (87.5)	8799	220.1 (73.2)	109.3 (114.5)	
	Overall	568211	106.5 (94.3)	37835	103.1 (87.1)	67.0 (94.9)	0.3
Total vegetables (g)	1	167554	45.9 (15.1)	6235	49.8 (13.0)	157.3 (117.1)	
	2	167553	84.2 (10.1)	9673	84.8 (10.0)	184.1 (116.6)	
	3	167553	125.0 (14.5)	11807	125.9 (14.6)	213.1 (133.9)	
	4	167553	233.0 (90.9)	13896	237.4 (95.0)	260.3 (181.7)	
	Overall	670213	122.0 (84.2)	41611	142.2 (91.0)	213.9 (150.8)	0.6
Nuts (g)	1	263975	0.0 (0.0)	14965	0.0 (0.0)	3.5 (8.1)	
	2	87793	4.5 (1.2)	8726	4.5 (1.1)	5.6 (9.3)	
	3	69893	9.9 (2.0)	6490	9.9 (2.0)	7.1 (10.7)	
	4	61590	24.9 (12.6)	5468	24.8 (12.5)	10.0 (13.0)	
	Overall	483251	5.4 (9.4)	35649	6.7 (9.9)	5.3 (9.8)	0.3
Grains/cereal (g)	1	170855	16.0 (10.4)	6759	18.4 (10.1)	35.9 (30.9)	
	2	170855	48.7 (8.5)	11130	49.3 (8.5)	42.6 (31.1)	
	3	170855	78.2 (9.0)	12469	78.4 (9.0)	49.5 (32.1)	
	4	170855	127.6 (31.3)	11671	124.2 (27.5)	58.9 (36.4)	
	Overall	683420	67.6 (44.6)	42029	73.8 (40.4)	48.1 (33.9)	0.2
Red meat (g)	1	161581	1.1 (2.9)	10489	0.6 (2.3)	22.0 (32.4)	
	2	161580	20.4 (4.8)	7936	20.7 (4.8)	27.7 (34.1)	
	3	161580	36.1 (4.8)	9546	36.4 (4.8)	32.7 (36.2)	
	4	161580	63.6 (18.7)	10805	63.9 (19.0)	38.0 (38.3)	
	Overall	646321	30.3 (25.0)	38776	31.2 (26.3)	28.4 (35.6)	0.3

B.2 Dietary intakes of all women and responders of the Oxford WebQ, and regression dilution ratios in the Million Women Study (continued)

		All women		Oxford WebQ responders			
	Category of intake at baseline (fourth)	No. of women	Intake at baseline, mean (SD)	No. of women	Intake at baseline, mean (SD)	Intake at Oxford WebQ, mean (SD)	Regression dilution ratio
Processed meat (g)	1	212493	0.0 (0.0)	14501	0.0 (0.0)	8.8 (16.3)	
	2	110668	6.3 (1.7)	5749	6.4 (1.6)	10.4 (16.8)	
	3	161580	12.6 (2.5)	9453	12.6 (2.4)	12.1 (18.0)	
	4	161580	28.5 (11.0)	9073	28.5 (11.2)	14.0 (19.8)	
	Overall	646321	11.4 (12.4)	38776	10.7 (12.3)	10.4 (17.5)	0.2
White meat (g)	1	161581	6.1 (4.4)	6770	6.4 (4.5)	20.4 (31.8)	
	2	161580	14.9 (1.8)	9451	15.0 (1.8)	23.9 (34.0)	
	3	161580	22.2 (2.6)	10708	22.3 (2.6)	26.3 (35.4)	
	4	161580	44.4 (20.4)	11847	43.9 (19.7)	30.4 (39.4)	
	Overall	646321	21.9 (17.7)	38776	24.4 (17.9)	24.5 (35.5)	0.3
Fish (g)	1	163006	11.5 (6.4)	9866	11.1 (6.5)	17.3 (29.7)	
	2	163006	24.1 (3.2)	9218	24.3 (3.2)	22.5 (32.8)	
	3	163006	36.2 (4.1)	10492	36.3 (4.1)	25.7 (33.7)	
	4	163005	64.4 (22.2)	11699	64.9 (21.6)	32.1 (37.7)	
	Overall	652023	34.0 (22.9)	41275	35.7 (23.8)	24.6 (34.2)	0.3
Eggs (g)	1	169065	3.3 (3.6)	11083	3.8 (3.6)	12.1 (23.0)	
	2	169065	12.7 (1.9)	10832	12.7 (1.9)	15.1 (24.3)	
	3	169065	19.4 (2.2)	10174	19.3 (2.2)	16.9 (25.4)	
	4	169065	36.0 (15.2)	9574	35.4 (14.2)	23.3 (30.9)	
	Overall	676260	17.9 (14.3)	41663	17.2 (13.5)	16.6 (26.3)	0.3
Dairy products (g)	1	173044	157.6 (62.8)	13061	155.6 (62.5)	166.6 (107.8)	
	2	173044	281.2 (25.3)	11164	280.6 (25.3)	224.7 (109.1)	
	3	173044	369.5 (27.6)	10220	368.0 (27.3)	253.7 (115.0)	
	4	173044	530.0 (110.6)	7676	509.9 (86.2)	286.3 (129.8)	
	Overall	692176	334.6 (151.0)	42121	304.8 (136.4)	224.9 (122.4)	0.3
Cheese (g)	1	158260	4.7 (3.5)	9463	4.6 (3.5)	11.0 (13.8)	
	2	158260	13.2 (2.2)	8742	13.3 (2.2)	13.2 (13.6)	
	3	158260	21.5 (2.7)	9972	21.6 (2.7)	15.2 (14.3)	
	4	158260	38.0 (11.3)	12453	38.8 (11.4)	20.1 (17.1)	
	Overall	633040	19.3 (13.8)	40630	21.2 (14.8)	15.1 (15.4)	0.3
Coffee (g)	1	145732	88.6 (80.0)	10590	82.9 (80.4)	150.2 (160.2)	
	2	145732	271.2 (54.6)	9186	274.3 (54.9)	254.4 (176.6)	
	3	145732	489.7 (78.6)	10121	490.9 (78.4)	382.0 (3,330.1)	
	4	145732	1040.0 (441.6)	8303	980.6 (366.2)	518.6 (286.2)	
	Overall	582928	472.4 (424.5)	38200	432.1 (373.4)	298.7 (1,648.1)	0.4

B.2 Dietary intakes of all women and responders of the Oxford WebQ, and regression dilution ratios in the Million Women Study (continued)

		All women		Oxford WebQ responders			
	Category of intake at baseline (fourth)	No. of women	Intake at baseline, mean (SD)	No. of women	Intake at baseline, mean (SD)	Intake at Oxford WebQ, mean (SD)	Regression dilution ratio
Tea (g)	1	155760	199.4 (137.6)	13546	185.1 (139.3)	278.1 (248.4)	
	2	155759	524.9 (75.0)	10349	520.4 (75.3)	482.8 (236.6)	
	3	155759	807.2 (94.0)	8726	802.7 (93.4)	599.3 (261.1)	
	4	155759	1450.8 (559.6)	6399	1350.4 (435.3)	733.1 (317.6)	
	Overall	623037	745.6 (546.5)	39020	603.3 (451.9)	456.0 (316.6)	0.4
Alcohol (g)	1	300162	0.0 (0.0)	9863	0.0 (0.0)	3.3 (7.7)	
	2	106756	2.4 (0.9)	7118	2.4 (0.9)	3.6 (5.7)	
	3	145199	6.7 (1.7)	11499	6.8 (1.7)	8.0 (8.3)	
	4	140059	17.9 (7.8)	13641	18.1 (7.6)	17.5 (13.5)	
	Overall	692176	5.4 (7.7)	42121	8.1 (8.6)	9.2 (11.6)	0.8
Carbo-hydrate (% energy)	1	173044	38.4 (4.4)	14950	38.0 (4.9)	41.3 (6.8)	
	2	173044	45.3 (1.3)	11367	45.2 (1.3)	44.4 (6.3)	
	3	173045	49.5 (1.3)	8940	49.4 (1.3)	45.8 (6.3)	
	4	173043	56.0 (3.6)	6864	55.6 (3.3)	47.6 (6.8)	
	Overall	692176	47.3 (7.0)	42121	45.2 (7.2)	44.1 (7.0)	0.4
Protein (% energy)	1	173045	13.1 (1.2)	8650	13.3 (1.1)	14.8 (3.0)	
	2	173043	15.4 (0.5)	10540	15.4 (0.5)	15.7 (2.9)	
	3	173044	17.0 (0.5)	11585	17.0 (0.5)	16.3 (3.0)	
	4	173044	19.7 (1.7)	11346	19.6 (1.7)	17.2 (3.3)	
	Overall	692176	16.3 (2.6)	42121	16.5 (2.5)	16.1 (3.2)	0.4
Total fat (% energy)	1	173044	26.6 (3.1)	9300	26.7 (3.1)	32.9 (6.4)	
	2	173045	32.4 (1.1)	10148	32.4 (1.1)	34.4 (6.0)	
	3	173043	36.1 (1.1)	10799	36.2 (1.1)	35.6 (6.0)	
	4	173044	41.9 (3.5)	11874	42.2 (3.9)	37.4 (6.1)	
	Overall	692176	34.3 (6.1)	42121	34.9 (6.2)	35.2 (6.4)	0.3
Saturated fat (% energy)	1	173044	7.8 (1.3)	10684	7.8 (1.2)	12.4 (3.2)	
	2	173044	10.5 (0.6)	10228	10.5 (0.6)	13.3 (3.1)	
	3	173044	12.8 (0.7)	10565	12.8 (0.8)	14.0 (3.0)	
	4	173044	17.0 (2.4)	10644	17.0 (2.4)	15.0 (3.2)	
	Overall	692176	12.0 (3.7)	42121	12.0 (3.7)	13.7 (3.3)	0.3
Mono-unsaturated fat (% energy)	1	173044	9.1 (1.3)	7991	9.2 (1.3)	10.7 (2.7)	
	2	173044	11.6 (0.5)	9232	11.6 (0.5)	11.2 (2.6)	
	3	173044	13.2 (0.5)	10954	13.2 (0.5)	11.6 (2.6)	
	4	173044	16.0 (1.9)	13944	16.3 (2.1)	12.1 (2.8)	
	Overall	692176	12.5 (2.8)	42121	13.1 (2.9)	11.5 (2.7)	0.2

B.2 Dietary intakes of all women and responders of the Oxford WebQ, and regression dilution ratios in the Million Women Study (continued)

		All women		Oxford WebQ responders			
	Category of intake at baseline (fourth)	No. of women	Intake at baseline, mean (SD)	No. of women	Intake at baseline, mean (SD)	Intake at Oxford WebQ, mean (SD)	Regression dilution ratio
Poly-unsaturated fat (% energy)	1	173044	4.2 (0.6)	10800	4.2 (0.6)	6.0 (2.1)	
	2	173044	5.6 (0.3)	10515	5.6 (0.3)	6.2 (2.0)	
	3	173044	6.8 (0.4)	10707	6.8 (0.4)	6.4 (2.1)	
	4	173044	9.0 (1.3)	10099	9.0 (1.3)	6.7 (2.2)	
	Overall	692176	6.4 (1.9)	42121	6.4 (1.9)	6.3 (2.1)	0.1
Fibre (g)	1	173044	8.8 (1.4)	6787	9.0 (1.3)	11.8 (3.8)	
	2	173044	11.9 (0.7)	10246	11.9 (0.7)	13.0 (3.7)	
	3	173044	14.4 (0.8)	12095	14.4 (0.8)	14.1 (4.1)	
	4	173044	18.9 (2.8)	12993	18.9 (2.7)	15.8 (4.8)	
	Overall	692176	13.5 (4.1)	42121	14.3 (3.9)	14.0 (4.4)	0.4
Carotene (µg)	1	173044	604.8 (176.1)	5896	645.5 (158.4)	2421.7 (1901.1)	
	2	173044	1010.7 (95.8)	9106	1016.9 (94.9)	2673.7 (1915.0)	
	3	173044	1379.3 (126.2)	11820	1387.9 (126.5)	3010.4 (2078.6)	
	4	173044	2275.9 (750.8)	15299	2336.9 (798.1)	3539.2 (2572.8)	
	Overall	692176	1317.7 (732.2)	42121	1548.5 (805.9)	3047.3 (2255.7)	0.7
Vitamin C (µg)	1	173044	43.1 (12.2)	6485	45.7 (11.3)	99.2 (63.0)	
	2	173044	74.3 (7.6)	9747	74.9 (7.7)	118.2 (67.9)	
	3	173044	102.1 (9.0)	12127	102.6 (8.9)	134.6 (71.8)	
	4	173044	157.3 (39.5)	13762	157.8 (38.6)	159.0 (88.8)	
	Overall	692176	94.2 (47.1)	42121	105.4 (47.0)	133.3 (78.6)	0.5
Vitamin E (mg)	1	173044	5.5 (0.9)	9790	5.7 (0.8)	7.5 (2.4)	
	2	173044	7.6 (0.5)	11159	7.6 (0.5)	7.9 (2.4)	
	3	173044	9.5 (0.6)	11507	9.5 (0.6)	8.0 (2.5)	
	4	173044	13.5 (2.7)	9665	13.2 (2.5)	8.1 (2.7)	
	Overall	692176	9.0 (3.3)	42121	9.0 (3.0)	7.8 (2.5)	0.1
Folate (µg)	1	173044	179.8 (20.0)	9989	181.6 (18.3)	218.3 (66.0)	
	2	173044	222.9 (10.0)	10943	222.9 (10.0)	240.3 (71.9)	
	3	173044	259.4 (11.8)	10957	259.3 (11.8)	254.5 (78.2)	
	4	173044	327.5 (44.1)	10232	326.2 (42.5)	278.0 (91.5)	
	Overall	692176	247.4 (59.8)	42121	247.7 (57.5)	247.9 (80.3)	0.4
Calcium (mg)	1	173045	580.0 (87.4)	11497	579.1 (87.4)	717.1 (187.0)	
	2	173043	747.5 (34.9)	10947	746.9 (34.9)	778.9 (180.8)	
	3	173044	870.4 (38.3)	10558	869.6 (38.4)	818.3 (188.2)	
	4	173044	1096.1 (157.1)	9119	1075.5 (129.8)	878.4 (220.2)	
	Overall	692176	823.5 (210.1)	42121	803.0 (195.2)	793.4 (201.9)	0.3
Cholesterol (mg)	1	173044	135.3 (27.9)	9858	136.6 (27.4)	200.1 (110.2)	
	2	173044	189.3 (11.2)	10573	189.5 (11.2)	218.3 (118.1)	
	3	173044	228.7 (12.4)	10991	228.5 (12.5)	230.1 (113.5)	
	4	173044	308.5 (64.6)	10699	307.0 (66.2)	260.1 (224.2)	
	Overall	692176	215.4 (72.7)	42121	217.1 (71.8)	227.7 (151.5)	0.3

B.3 Detailed dietary intakes by selected characteristics for men in the NIH-AARP Study

Daily dietary intakes (mean)	Height		BMI		Strenuous exercise		Smoking		Alcohol		Ethnicity		Marital status		Education	
	<175	185+	<25	30+	Never /rarely	3+/week	Never	Current	Non-drinkers	1+ drinks/day	Non-White	White	Married*	No partner	<12 years	Tertiary
Total fruit, g	256.2	236.6	257.2	229.2	265.7	272.7	275.4	153.8	277.5	191.0	314.2	239.5	252.9	242.9	244.9	253.0
Citrus fruit, g	49.9	44.5	48.3	44.8	37.8	53.4	51.1	26.6	49.1	40.1	57.4	46.1	46.3	46.9	45.9	49.6
Fruit juice, g	146.3	149.8	149.6	142.1	134.4	155.8	167.5	110.1	139.7	139.4	184.1	145.3	158.8	145.9	128.6	161.0
Total vegetables, g	258.6	253.6	260.0	250.6	222.4	274.6	262.2	210.3	259.7	240.8	266.4	254.3	257.1	254.8	233.2	269.6
Nuts, g	6.2	7.0	6.9	6.4	6.3	6.8	6.5	6.9	7.3	6.2	5.8	6.7	6.7	6.6	6.2	6.8
Grains/cereal, g	44.9	43.0	51.5	37.3	37.6	49.0	50.1	27.7	55.0	32.6	54.0	43.3	45.9	43.6	44.6	45.5
Red meat, g	73.8	77.9	65.9	89.0	85.0	69.6	71.7	91.3	75.8	74.3	65.9	76.7	73.2	76.5	79.1	71.5
Processed meat, g	23.7	24.1	21.8	27.1	26.8	22.4	22.2	27.9	25.1	22.2	21.6	24.1	23.1	24.1	26.9	21.8
White meat, g	64.5	64.1	62.2	65.9	58.4	67.0	67.0	51.8	62.4	60.6	67.7	64.0	62.4	64.5	55.6	69.1
Fish, g	21.9	22.0	21.6	22.3	19.8	22.9	22.6	18.7	19.9	22.1	23.9	21.8	22.2	21.9	18.3	24.2
Eggs, g	12.3	12.9	11.0	15.2	14.9	11.4	11.4	16.2	13.2	11.7	14.1	12.4	14.1	12.2	15.0	11.3
Dairy products, g	293.7	312.5	303.9	303.9	293.4	312.0	330.1	286.5	342.5	244.1	245.1	307.2	314.1	301.6	303.0	304.3
Cheese, g	4.0	4.6	3.9	4.9	4.4	4.2	4.0	4.6	3.9	4.7	2.7	4.4	4.3	4.3	3.6	4.7
Alcohol, g	13.1	14.7	14.8	12.3	14.0	14.0	9.8	19.0	0.0	41.0	10.3	14.5	16.8	13.7	10.5	15.6
Coffee, g	912.3	885.2	873.0	913.5	952.2	871.3	692.2	1,247.7	864.5	897.8	645.8	926.7	890.2	912.6	935.9	877.7
Tea, g	284.4	255.2	267.0	266.6	267.4	262.2	279.8	229.3	288.4	196.9	264.1	265.3	253.4	267.4	260.0	268.0
Carbohydrate, %E	49.0	47.4	49.7	46.2	46.5	49.3	49.9	44.2	51.2	42.5	51.4	47.9	47.7	48.1	48.6	48.2
Protein, %E	15.3	15.5	14.9	16.0	15.2	15.4	15.5	14.9	15.8	14.2	14.6	15.4	15.2	15.4	14.9	15.6
Total fat, %E	30.0	30.9	29.1	32.2	32.1	29.4	30.0	33.0	31.8	28.0	29.1	30.5	30.1	30.5	31.5	29.6
Saturated fat, %E	9.3	9.7	9.0	10.2	10.3	9.0	9.3	10.8	9.9	8.7	8.8	9.6	9.6	9.5	10.0	9.2
Monounsaturated fat, %E	11.4	11.8	11.1	12.3	12.3	11.1	11.4	12.7	12.1	10.7	11.1	11.6	11.4	11.6	12.1	11.2
Polyunsaturated fat, %E	6.8	7.0	6.7	7.1	7.0	6.8	6.8	7.0	7.2	6.4	6.8	6.9	6.7	6.9	6.9	6.8
Fibre, g	13.8	13.5	14.3	13.0	12.1	14.7	14.4	10.8	14.5	12.3	14.2	13.6	13.6	13.7	13.1	14.2
Carotene, ug	919.3	885.7	949.5	848.7	748.8	990.2	969.5	673.3	955.9	797.4	1,035.5	888.0	920.6	893.8	810.9	965.6
Vitamin C, ug	174.7	168.9	174.8	166.3	151.0	181.7	183.7	127.9	174.6	151.5	197.5	167.6	174.7	168.6	159.4	178.4
Vitamin E, mg	9.7	9.7	9.7	9.6	9.3	9.8	9.9	9.0	10.1	8.8	9.7	9.6	9.5	9.7	9.7	9.7
Folate, ug	576.0	556.5	586.2	539.9	525.8	589.0	593.1	475.5	585.5	510.9	605.8	562.5	554.4	566.9	539.2	587.1
Calcium, mg	817.4	895.6	837.4	829.5	798.2	846.5	852.3	771.0	888.7	723.3	765.3	830.1	834.7	824.8	815.8	837.5
Cholesterol, mg	219.6	229.4	205.5	251.1	243.4	212.0	217.2	255.6	228.6	210.7	221.5	224.1	229.9	223.0	236.3	215.8
DASH score	24.2	24.3	24.8	23.6	22.8	25.2	24.9	21.8	24.5	23.9	24.0	24.3	24.4	24.3	23.2	25.0
aMED score	4.2	4.2	4.4	3.9	3.6	4.5	4.4	3.3	4.0	4.2	4.3	4.2	4.1	4.2	3.7	4.5
AHEI	52.4	52.8	53.7	51.1	49.1	54.5	53.1	48.5	50.0	54.8	53.2	52.5	52.5	52.6	50.0	54.3
Total energy intake, kcal	1,906.4	2,062.7	1,944.9	2,039.1	1,977.6	1,987.5	1,943.7	2,148.3	1,923.2	2,167.9	1,945.3	1,976.7	1,976.8	1,974.3	2,068.8	1,938.4

*Married or living with a partner; %E percentage energy intake

B.4 Detailed dietary intakes by selected characteristics for women in the NIH-AARP Study

Daily dietary intakes (mean)	Height		BMI		Strenuous exercise		Smoking		Alcohol		Ethnicity		Marital status		Education	
	≤160	170+	<25	30+	Never /rarely	3+/week	Never	Current	Non-drinkers	1+ drinks /day	Non-White	White	Married*	No partner	≤13 years	Tertiary
Total fruit, g	263.4	253.3	266.1	239.4	216.6	290.5	278.3	185.2	280.4	188.0	332.7	248.8	261.4	251.1	250.7	268.9
Citrus fruit, g	53.8	49.3	53.4	46.8	40.5	60.6	54.7	33.1	52.1	41.8	62.3	49.9	51.2	51.0	46.2	56.7
Fruit juice, g	116.4	121.0	123.1	109.2	111.6	122.6	127.3	103.5	115.6	114.3	154.6	113.7	122.7	111.4	117.8	121.2
Total vegetables, g	256.4	254.7	260.4	243.8	218.6	281.5	252.7	223.0	253.7	243.8	253.4	254.1	251.8	257.2	227.4	275.2
Nuts, g	3.7	4.1	4.1	3.7	3.8	4.0	3.9	4.0	4.2	3.5	3.9	3.9	4.0	3.8	3.5	4.2
Grains/cereal, g	39.5	39.4	41.1	36.2	35.3	43.2	42.8	28.7	47.5	25.1	48.8	38.1	41.1	36.7	42.9	39.6
Red meat, g	47.1	47.1	42.4	54.5	53.5	41.6	45.8	56.2	46.4	47.7	41.6	47.7	44.6	50.2	52.0	42.1
Processed meat, g	13.3	13.1	11.6	15.7	15.3	11.8	12.6	15.4	13.8	12.6	13.4	13.2	12.9	13.6	15.7	11.5
White meat, g	57.2	57.4	55.5	60.1	53.1	60.2	56.5	50.4	55.2	56.4	63.6	56.9	56.9	58.2	50.2	62.1
Fish, g	17.9	17.9	17.7	18.3	16.7	18.9	17.4	17.1	16.4	18.9	20.2	17.7	17.6	18.4	15.5	19.7
Eggs, g	9.3	9.7	8.7	11.2	10.5	8.8	9.1	11.2	9.4	9.6	8.9	9.6	9.7	9.2	10.0	9.3
Dairy products, g	274.6	280.6	280.7	269.5	257.8	293.7	292.0	246.2	292.3	220.3	212.3	285.2	285.8	269.4	270.9	287.1
Cheese, g	3.3	3.9	3.5	3.9	3.7	3.5	3.4	3.8	3.1	4.7	2.2	3.8	3.7	3.5	2.7	4.2
Alcohol, g	5.0	6.7	7.5	3.3	5.5	6.1	3.7	9.2	0.0	31.1	3.3	6.1	5.8	5.9	3.4	7.0
Coffee, g	808.6	807.4	862.2	703.9	824.2	791.0	655.4	1,200.5	696.7	853.2	597.0	841.7	830.4	790.8	827.8	769.4
Tea, g	366.5	330.4	347.2	306.3	340.6	346.0	363.2	313.4	342.6	251.4	279.2	352.9	350.6	341.4	319.0	351.1
Carbohydrate, %E	51.6	50.6	51.7	49.8	49.4	52.5	52.3	47.5	53.1	43.4	53.7	50.8	51.4	50.7	51.1	51.5
Protein, %E	15.5	15.5	15.2	15.9	15.2	15.7	15.5	15.0	15.5	14.4	14.6	15.6	15.4	15.7	15.0	15.8
Total fat, %E	29.8	30.1	28.9	31.8	31.9	28.4	29.6	32.4	30.4	27.9	29.3	30.0	29.8	30.1	31.5	28.7
Saturated fat, %E	9.2	9.4	8.9	9.9	10.0	8.6	9.1	10.4	9.3	8.7	8.7	9.3	9.3	9.2	9.7	8.8
Monounsaturated fat, %E	11.1	11.1	10.7	11.9	11.9	10.5	11.0	12.0	11.3	10.3	11.0	11.1	11.0	11.2	11.8	10.6
Polyunsaturated fat, %E	7.1	7.2	7.0	7.5	7.5	6.9	7.1	7.5	7.3	6.7	7.3	7.2	7.1	7.3	7.4	6.9
Fibre, g	12.1	12.0	12.3	11.5	10.7	13.1	12.4	10.0	12.5	10.2	12.3	12.0	12.0	12.0	11.3	12.6
Carotene, ug	1,041.5	1,028.1	1,083.1	950.1	834.8	1,186.4	1,062.3	809.0	1,054.1	903.2	1,124.2	1,020.2	1,037.9	1,022.0	886.8	1,156.4
Vitamin C, ug	164.6	162.9	166.4	155.8	144.8	177.1	169.6	135.7	166.2	144.4	191.4	159.6	165.2	159.6	155.8	170.9
Vitamin E, mg	8.4	8.2	8.3	8.2	8.1	8.5	8.4	8.0	8.5	7.6	8.6	8.3	8.3	8.3	8.4	8.3
Folate, ug	478.8	467.5	482.0	455.0	442.1	495.9	482.7	448.2	479.7	420.5	484.8	470.9	472.2	472.3	450.8	493.5
Calcium, mg	731.5	738.2	739.7	723.9	694.9	766.5	750.9	677.6	756.4	637.9	665.1	742.9	747.0	721.8	714.4	760.1
Cholesterol, mg	168.4	172.3	160.1	188.3	181.7	160.3	166.6	187.8	168.1	165.8	165.4	170.8	169.9	170.7	175.9	166.0
DASH score	24.3	24.6	25.0	23.7	23.0	25.7	24.8	22.5	24.5	23.8	24.1	24.5	24.7	24.2	23.2	25.5
aMED score	4.1	4.2	4.3	3.9	3.6	4.5	4.2	3.5	4.0	3.8	4.3	4.1	4.1	4.2	3.7	4.5
AHEI	52.7	53.4	54.3	51.2	50.1	55.3	52.8	50.5	51.5	55.7	53.3	53.1	53.0	53.2	50.1	55.2
Total energy intake, kcal	1,506.1	1,588.9	1,508.3	1,607.7	1,547.3	1,545.9	1,541.6	1,586.5	1,541.0	1,670.2	1,625.4	1,532.8	1,527.4	1,557.6	1,612.6	1,523.7

*Married or living with a partner; %E percentage energy intake

B.4 Detailed dietary intakes by selected characteristics for women in the NIH-AARP Study (continued)

Daily dietary intakes (mean)	Parity		Oral contraceptive use		Menopausal hormone use	
	Nulliparous	Parous	Never	Ever	Never	Current
Total fruit, g	256.2	257.0	264.0	245.9	259.2	254.2
Citrus fruit, g	52.5	50.8	53.9	47.0	52.5	50.0
Fruit juice, g	118.9	117.4	121.2	112.3	122.7	113.3
Total vegetables, g	253.8	254.3	255.3	252.7	252.4	256.4
Nuts, g	4.1	3.8	3.9	3.9	3.8	3.9
Grains/cereal, g	38.5	39.2	40.6	36.9	38.4	39.8
Red meat, g	45.5	47.4	46.6	47.9	48.0	46.4
Processed meat, g	13.3	13.2	13.4	12.9	13.9	12.5
White meat, g	57.9	57.4	56.6	58.7	56.7	58.4
Fish, g	18.4	17.9	17.8	18.2	18.0	18.0
Eggs, g	9.6	9.5	9.4	9.7	9.5	9.5
Dairy products, g	282.2	277.8	284.9	268.9	272.9	284.1
Cheese, g	4.0	3.5	3.5	3.8	3.5	3.8
Alcohol, g	7.2	5.6	5.3	6.8	5.4	6.3
Coffee, g	773.3	820.2	813.0	813.2	818.2	805.6
Tea, g	336.3	347.9	348.5	342.6	358.7	334.5
Carbohydrate, %E	51.0	51.1	51.4	50.6	51.1	51.0
Protein, %E	15.5	15.5	15.5	15.5	15.4	15.6
Total fat, %E	29.5	30.1	29.9	30.0	30.2	29.7
Saturated fat, %E	9.1	9.3	9.2	9.3	9.4	9.1
Monounsaturated fat, %E	10.9	11.2	11.1	11.1	11.2	11.0
Polyunsaturated fat, %E	7.0	7.2	7.2	7.2	7.2	7.2
Fibre, g	12.1	12.0	12.1	11.8	11.8	12.2
Carotene, ug	1,045.2	1,028.5	1,044.4	1,010.5	1,021.5	1,038.9
Vitamin C, ug	162.5	162.7	166.0	157.7	165.4	160.4
Vitamin E, mg	8.2	8.3	8.4	8.2	8.3	8.3
Folate, ug	477.3	471.3	475.1	468.0	467.9	477.4
Calcium, mg	745.1	734.1	743.7	723.9	728.1	743.7
Cholesterol, mg	169.3	170.5	169.0	172.2	172.3	168.6
DASH score	24.7	24.5	24.6	24.3	24.2	24.8
aMED score	4.1	4.1	4.1	4.1	4.0	4.2
AHEI	53.3	53.1	52.9	53.3	52.3	53.9
Total energy intake, kcal	1,537.3	1,541.4	1,542.8	1,538.1	1,563.3	1,513.9

%E percentage energy intake

B.5 Detailed dietary intakes by selected characteristics for men in the PLCO Study

Daily dietary intakes (mean)	Height		BMI		Smoking		Alcohol		Ethnicity		Marital status		Education	
	<175	185+	<25	30+	Never	Current	Non-drinkers	1+ drinks /day	Non-White	White	Married*	No partner	<12 years	Tertiary
Total fruit, g	184.9	171.9	185.6	170.6	195.5	108.6	203.1	139.5	196.0	175.1	173.5	177.5	179.5	184.7
Citrus fruit, g	29.8	27.5	30.2	27.3	31.4	16.6	31.3	24.4	28.5	28.6	27.5	28.8	29.6	29.9
Fruit juice, g	104.0	111.3	113.3	100.5	121.3	79.1	107.8	100.9	117.1	107.4	117.8	106.6	92.4	122.2
Total vegetables, g	243.0	236.9	241.8	237.3	243.1	200.1	249.0	223.6	254.3	236.4	239.3	237.7	224.8	250.8
Nuts, g	11.2	11.6	12.1	10.7	11.7	10.3	11.7	11.4	11.4	11.4	11.1	11.5	8.9	12.5
Grains/cereal, g	51.2	49.7	57.5	42.5	55.9	31.5	62.8	35.2	58.5	48.6	49.5	49.5	51.9	51.6
Red meat, g	74.9	79.1	66.3	90.2	73.4	90.1	74.5	76.8	64.8	78.9	76.7	77.8	83.4	71.4
Processed meat, g	21.7	22.9	20.4	25.4	21.3	25.6	22.8	20.9	19.9	22.8	22.7	22.5	25.1	20.8
White meat, g	53.4	52.4	50.9	54.5	54.3	44.5	51.5	50.9	61.4	51.9	53.8	52.6	44.2	58.0
Fish, g	17.9	16.7	16.7	17.3	17.1	15.2	15.9	17.3	23.2	16.4	18.5	16.7	14.9	18.5
Eggs, g	15.6	15.6	13.8	18.8	14.4	18.6	16.1	14.7	16.4	15.5	17.9	15.2	17.8	14.2
Dairy products, g	269.7	300.6	288.2	282.3	311.4	269.0	322.7	231.4	176.2	299.6	275.5	290.7	274.4	293.1
Cheese, g	8.0	10.1	8.4	10.6	9.1	9.2	8.8	10.0	4.3	9.8	8.8	9.4	7.7	10.1
Alcohol, g	12.0	12.4	13.0	11.5	9.0	16.1	0.0	36.8	10.4	12.8	14.4	12.3	10.3	13.9
Coffee, g	1,114.8	1,032.8	1,079.3	1,083.7	819.8	1,648.5	921.8	1,160.9	808.9	1,130.1	1,125.1	1,097.0	1,208.5	1,025.1
Tea, g	298.5	271.4	288.1	267.7	285.4	245.3	286.7	212.4	325.0	270.7	277.6	275.5	223.7	304.5
Carbohydrate, %E	48.0	46.7	48.9	45.2	48.8	43.9	50.4	41.9	49.7	46.9	46.7	47.2	47.5	47.5
Protein, %E	15.2	15.4	14.8	16.0	15.4	15.0	15.6	14.3	14.6	15.4	15.2	15.4	14.9	15.5
Total fat, %E	31.7	32.7	31.0	33.9	31.9	34.3	33.1	30.1	30.8	32.4	32.1	32.3	33.0	31.5
Saturated fat, %E	10.0	10.6	9.8	11.0	10.2	11.5	10.7	9.6	9.1	10.5	10.4	10.3	10.9	9.9
Monounsaturated fat, %E	12.1	12.5	11.8	13.0	12.1	13.1	12.6	11.6	11.9	12.4	12.2	12.3	12.6	12.0
Polyunsaturated fat, %E	7.0	7.1	6.9	7.3	7.0	7.0	7.2	6.6	7.4	7.0	6.9	7.1	6.9	7.1
Fibre, g	13.3	13.0	13.7	12.4	13.7	10.6	13.9	12.0	13.4	13.0	12.8	13.1	12.4	13.7
Carotene, ug	769.8	737.2	796.7	708.0	807.3	568.3	801.8	665.8	879.9	735.1	733.2	750.5	649.7	823.9
Vitamin C, ug	145.3	146.0	149.1	141.8	156.0	112.6	153.8	129.8	154.8	144.7	150.2	144.7	136.4	155.3
Vitamin E, mg	8.5	8.5	8.7	8.4	8.7	7.7	8.8	7.9	8.7	8.5	8.4	8.5	7.9	8.9
Folate, ug	551.1	527.5	562.4	506.7	555.3	461.7	557.0	488.6	611.1	527.3	525.2	536.3	499.2	562.4
Calcium, mg	815.5	857.7	839.3	838.9	869.2	798.9	897.4	743.3	700.8	854.5	827.2	842.9	815.5	856.0
Cholesterol, mg	243.0	250.6	224.6	278.5	239.4	277.5	249.6	233.8	238.4	248.6	258.5	245.9	264.9	234.2
DASH score	23.9	24.1	24.7	23.2	24.7	21.6	24.5	23.6	23.4	24.1	23.7	24.1	22.7	25.0
aMED score	4.2	4.2	4.4	3.9	4.3	3.3	4.1	4.2	4.4	4.1	4.1	4.2	3.6	4.5
AHEI	57.2	57.4	58.3	55.9	57.1	54.9	54.6	60.7	59.3	57.0	57.0	57.2	54.4	58.9
Total energy intake, kcal	1,885.1	2,056.0	1,930.8	2,030.6	1,956.8	2,085.2	1,905.0	2,155.0	1,870.6	1,980.0	1,985.4	1,968.1	2,006.5	1,955.0

*Married or living with a partner; %E percentage energy intake

B.6 Detailed dietary intakes by selected characteristics for women in the PLCO Study

Daily dietary intakes (mean)	Height		BMI		Smoking		Alcohol		Ethnicity		Marital status		Education	
	<160	170+	<25	30+	Never	Current	Non-drinkers	1+ drinks /day	Non-White	White	Married*	No partner	<12 years	Tertiary
Total fruit, g	217.5	204.4	217.7	199.3	221.8	148.4	227.3	157.5	245.8	206.8	215.7	208.0	210.4	214.2
Citrus fruit, g	34.6	31.7	34.7	31.1	35.1	21.9	33.5	28.2	38.9	32.6	33.7	33.0	31.5	34.8
Fruit juice, g	99.4	104.2	108.4	91.4	107.1	83.7	100.9	99.3	119.7	99.7	107.4	99.1	92.3	108.3
Total vegetables, g	258.5	252.3	259.4	249.4	254.7	226.1	260.2	246.7	272.8	253.0	253.2	255.3	238.8	269.5
Nuts, g	7.8	8.5	8.8	7.2	8.1	6.9	8.1	8.0	8.4	8.0	8.2	8.0	6.7	9.0
Grains/cereal, g	48.2	45.1	48.9	43.2	49.7	33.5	55.3	29.6	61.9	44.9	51.2	44.5	50.9	45.8
Red meat, g	46.6	46.9	42.0	54.4	46.3	55.2	45.0	46.7	38.5	48.1	44.9	49.3	52.1	42.4
Processed meat, g	12.2	12.4	10.9	14.4	12.1	14.4	12.4	11.4	12.0	12.4	11.8	12.7	14.3	11.1
White meat, g	53.5	52.8	51.9	55.6	51.7	49.6	50.5	54.5	60.5	52.7	53.7	53.3	45.0	58.5
Fish, g	15.9	15.2	15.5	16.0	15.0	15.1	14.0	17.3	19.5	15.2	15.4	15.6	13.7	17.2
Eggs, g	10.7	11.1	9.5	13.2	10.5	12.1	10.6	10.9	9.3	11.1	11.6	10.7	11.2	10.9
Dairy products, g	241.4	265.7	264.6	242.5	270.4	219.1	270.9	202.9	151.1	265.5	259.2	254.0	220.5	270.8
Cheese, g	6.7	8.3	7.4	7.9	7.1	7.8	6.4	10.0	3.4	8.0	7.8	7.5	5.4	8.8
Alcohol, g	4.8	6.0	7.1	3.2	3.7	8.0	0.0	29.3	2.8	5.7	5.3	5.6	3.1	6.8
Coffee, g	837.3	824.4	885.5	745.1	694.2	1,395.5	621.0	970.8	555.0	872.1	869.5	834.5	1,004.9	763.6
Tea, g	325.7	298.3	323.9	300.2	318.0	298.0	307.8	240.3	301.3	316.9	324.2	312.2	284.0	333.8
Carbohydrate, %E	50.9	49.9	51.0	49.1	51.4	47.2	52.6	42.8	53.4	50.0	50.9	50.0	50.7	50.3
Protein, %E	15.4	15.5	15.2	15.9	15.5	15.1	15.5	14.6	14.6	15.6	15.3	15.6	14.9	15.8
Total fat, %E	31.0	31.5	30.2	32.9	31.0	33.3	31.4	29.4	30.2	31.4	31.0	31.4	32.4	30.4
Saturated fat, %E	9.6	9.9	9.3	10.5	9.7	10.9	9.8	9.1	8.6	9.9	9.8	9.8	10.3	9.4
Monounsaturated fat, %E	11.5	11.7	11.2	12.2	11.5	12.3	11.6	10.9	11.3	11.6	11.4	11.7	12.0	11.3
Polyunsaturated fat, %E	7.5	7.4	7.3	7.6	7.4	7.6	7.5	7.1	7.8	7.4	7.4	7.5	7.6	7.4
Fibre, g	12.2	11.9	12.4	11.5	12.4	10.1	12.6	10.4	12.6	12.0	12.1	12.0	11.6	12.5
Carotene, ug	913.5	882.1	939.2	823.4	917.3	702.0	910.9	797.8	1,019.0	878.8	899.2	887.8	754.0	987.9
Vitamin C, ug	151.8	150.1	155.3	144.8	155.9	125.5	155.0	135.9	168.4	149.2	155.4	149.2	144.9	157.6
Vitamin E, mg	7.8	7.8	7.9	7.6	7.8	7.3	7.9	7.3	8.0	7.8	7.9	7.8	7.4	8.1
Folate, ug	469.2	450.5	470.8	439.5	466.1	409.2	470.0	411.3	509.7	453.0	462.0	456.4	435.8	476.0
Calcium, mg	717.3	747.6	744.1	730.1	748.9	685.8	755.1	652.7	615.0	746.0	749.5	738.7	687.7	763.0
Cholesterol, mg	179.2	184.3	167.1	205.2	178.5	199.9	177.9	176.7	165.9	184.1	182.4	182.6	189.5	177.9
DASH score	24.0	24.3	24.9	23.1	24.4	21.8	24.3	23.7	23.9	24.1	24.5	24.0	22.7	25.1
aMED score	4.1	4.1	4.3	3.8	4.2	3.4	4.0	3.8	4.5	4.1	4.1	4.1	3.7	4.5
AHEI	58.3	58.7	59.7	56.8	57.9	57.0	57.0	62.6	59.9	58.3	58.7	58.3	55.8	60.2
Total energy intake, kcal	1,448.3	1,556.3	1,465.8	1,544.8	1,483.8	1,531.8	1,470.2	1,638.8	1,488.8	1,493.3	1,479.7	1,498.1	1,502.3	1,505.8

* Married or living with a partner; %E percentage energy intake

B.6 Detailed dietary intakes by selected characteristics for women in the PLCO Study (continued)

Daily dietary intakes (mean)	Parity		Oral contraceptive use		Menopausal hormone use	
	Nulliparous	Parous	Never	Ever	Never	Current
Total fruit, g	212.8	209.9	222.8	200.0	214.2	207.1
Citrus fruit, g	35.5	33.0	36.2	30.8	35.2	31.7
Fruit juice, g	101.4	101.4	105.5	98.1	104.7	100.1
Total vegetables, g	260.1	254.3	259.4	251.0	252.8	255.1
Nuts, g	8.4	8.0	7.9	8.2	7.5	8.4
Grains/cereal, g	47.8	46.3	49.5	43.8	47.1	45.5
Red meat, g	43.8	47.5	45.7	48.5	48.0	47.1
Processed meat, g	12.1	12.4	12.4	12.4	12.9	12.0
White meat, g	53.5	53.4	51.0	55.4	51.3	54.6
Fish, g	15.7	15.5	15.2	15.8	15.3	15.7
Eggs, g	10.9	11.0	10.5	11.3	10.7	11.2
Dairy products, g	261.5	255.0	263.4	249.2	257.1	256.0
Cheese, g	8.0	7.5	7.1	8.0	7.2	7.9
Alcohol, g	6.5	5.4	4.7	6.1	5.0	5.8
Coffee, g	827.0	845.8	838.8	849.2	898.0	809.5
Tea, g	317.6	315.5	312.8	317.8	305.9	318.5
Carbohydrate, %E	50.8	50.2	51.2	49.5	50.7	49.9
Protein, %E	15.5	15.5	15.4	15.6	15.4	15.6
Total fat, %E	30.4	31.4	30.9	31.7	31.2	31.4
Saturated fat, %E	9.5	9.8	9.6	9.9	9.8	9.8
Monounsaturated fat, %E	11.3	11.6	11.4	11.8	11.5	11.7
Polyunsaturated fat, %E	7.3	7.5	7.4	7.5	7.3	7.5
Fibre, g	12.4	12.0	12.3	11.8	11.9	12.1
Carotene, ug	927.9	888.0	911.5	874.3	876.2	897.9
Vitamin C, ug	152.5	150.8	155.4	147.3	152.8	149.6
Vitamin E, mg	7.9	7.8	7.8	7.8	7.6	7.9
Folate, ug	472.2	456.8	464.9	452.3	452.6	461.2
Calcium, mg	747.4	733.5	742.3	728.3	732.5	737.2
Cholesterol, mg	176.9	183.0	177.5	186.5	182.1	183.2
DASH score	24.6	24.1	24.4	23.9	23.8	24.3
aMED score	4.2	4.1	4.2	4.1	4.0	4.2
AHEI	59.1	58.4	58.1	58.7	57.5	59.0
Total energy intake, kcal	1,488.4	1,493.2	1,478.8	1,504.5	1,491.6	1,493.7

%E percentage energy intake

B.7 Mean dietary intakes for men in the NIH-AARP Study and the PLCO Study

Daily dietary intakes (mean)	NIH-AARP Study	PLCO Study
Number of men	277906	47196
Total fruit, g	244.5 (214.3)	177.0 (146.1)
Citrus fruit, g	46.8 (74.0)	28.6 (43.5)
Fruit juice, g	147.7 (195.3)	108.3 (148.2)
Total vegetables, g	255.2 (162.9)	238.0 (159.2)
Nuts, g	6.6 (10.6)	11.4 (15.3)
Grains/cereal, g	44.0 (59.2)	49.5 (63.7)
Red meat, g	76.0 (44.4)	77.6 (43.2)
Processed meat, g	24.0 (21.4)	22.5 (18.9)
White meat, g	64.2 (47.4)	52.8 (42.7)
Fish, g	21.9 (21.6)	17.0 (18.5)
Eggs, g	12.5 (15.4)	15.6 (18.8)
Dairy products, g	303.4 (298.1)	288.5 (283.7)
Cheese, g	4.3 (7.3)	9.3 (12.8)
Alcohol, g	14.2 (23.3)	12.6 (20.4)
Coffee, g	909.2 (792.5)	1,101.2 (1,052.2)
Tea, g	265.7 (410.8)	275.6 (552.5)
Carbohydrate, %E	48.1 (9.1)	47.1 (8.7)
Protein, %E	15.4 (3.1)	15.3 (2.9)
Total fat, %E	30.4 (7.6)	32.3 (7.4)
Saturated fat, %E	9.5 (2.9)	10.4 (3.0)
Monounsaturated fat, %E	11.6 (3.1)	12.3 (3.1)
Polyunsaturated fat, %E	6.9 (2.1)	7.1 (2.0)
Fibre, g	13.7 (5.2)	13.1 (4.6)
Carotene, ug	897.9 (808.2)	748.1 (622.5)
Vitamin C, ug	169.5 (103.0)	145.6 (83.0)
Vitamin E, mg	9.7 (4.0)	8.5 (3.1)
Folate, ug	565.2 (178.5)	534.8 (176.5)
Calcium, mg	826.2 (345.0)	840.7 (329.6)
Cholesterol, mg	224.0 (93.7)	247.7 (109.0)
DASH score	24.3 (4.7)	24.0 (4.7)
aMED score	4.2 (1.8)	4.2 (1.8)
AHEI	52.6 (10.2)	57.2 (9.0)
Total energy intake, kcal	1974.0 (694.7)	1970.2 (694.4)

%E percentage energy intake

B.8 Mean dietary intakes for women in the Million Women Study, the NIH-AARP Study, and the PLCO Study

Daily dietary intakes (mean)	Million Women Study	NIH-AARP Study	PLCO Study
Number of women	692176	192874	51952
Total fruit, g	206.8 (150.4)	257.1 (201.0)	210.2 (151.9)
Citrus fruit, g	44.4 (49.5)	51.1 (74.8)	33.2 (45.1)
Fruit juice, g	106.5 (94.3)	117.7 (163.7)	101.4 (132.3)
Total vegetables, g	122.0 (84.2)	254.3 (163.0)	254.7 (158.3)
Nuts, g	5.4 (9.4)	3.9 (7.0)	8.1 (12.1)
Grains/cereal, g	67.6 (44.6)	39.2 (52.4)	46.4 (56.2)
Red meat, g	30.3 (25.0)	47.1 (30.9)	47.3 (28.8)
Processed meat, g	11.4 (12.4)	13.2 (14.0)	12.4 (12.2)
White meat, g	21.9 (17.7)	57.5 (43.4)	53.4 (42.6)
Fish, g	34.0 (22.9)	18.0 (19.0)	15.6 (16.6)
Eggs, g	17.9 (14.3)	9.5 (12.4)	11.0 (14.6)
Dairy products, g	334.6 (151.0)	278.5 (265.8)	255.5 (247.5)
Cheese, g	19.3 (13.8)	3.6 (6.5)	7.6 (11.0)
Alcohol, g	5.4 (7.7)	5.9 (12.7)	5.5 (11.0)
Coffee, g	472.4 (424.5)	812.2 (797.3)	844.5 (893.6)
Tea, g	745.6 (546.5)	346.5 (502.1)	315.6 (548.5)
Carbohydrate, %E	47.3 (7.0)	51.1 (8.9)	50.2 (8.6)
Protein, %E	16.3 (2.6)	15.5 (3.2)	15.5 (2.9)
Total fat, %E	34.3 (6.1)	30.0 (7.7)	31.3 (7.6)
Saturated fat, %E	12.0 (3.7)	9.3 (2.9)	9.8 (2.9)
Monounsaturated fat, %E	12.5 (2.8)	11.1 (3.1)	11.6 (3.1)
Polyunsaturated fat, %E	6.4 (1.9)	7.2 (2.4)	7.4 (2.3)
Fibre, g	13.5 (4.1)	12.0 (4.4)	12.1 (4.0)
Carotene, ug	1,317.7 (732.2)	1,031.2 (931.2)	891.0 (698.3)
Vitamin C, ug	94.2 (47.1)	162.8 (92.6)	150.9 (76.9)
Vitamin E, mg	9.0 (3.3)	8.3 (3.1)	7.8 (2.9)
Folate, ug	247.4 (59.8)	472.3 (140.7)	457.9 (138.3)
Calcium, mg	823.5 (210.1)	735.8 (304.0)	734.6 (281.3)
Cholesterol, mg	215.4 (72.7)	170.3 (73.3)	182.5 (83.6)
DASH score	22.8 (5.2)	24.5 (4.7)	24.1 (4.7)
aMED score	4.0 (1.8)	4.1 (1.7)	4.1 (1.7)
AHEI	47.6 (12.1)	53.1 (9.6)	58.4 (8.6)
Total energy intake, kcal	1611.7 (430.0)	1540.6 (575.6)	1492.9 (541.0)

%E percentage energy intake

B.9 Risk of glioma in relation to total fruit and vegetable intake in the Million Women Study, the NIH-AARP Study, and the PLCO Study

Total fruit and vegetable intake	Mean intake (g/day)	Number of glioma	RR (95% CI)	Number of glioma	RR (95% CI)
		All follow-up time		Exclude first 5 years of follow up	
Million Women Study					
Lowest fourth	120.5	267	1.00 (reference)	190	1.00 (reference)
Second fourth	231.4	288	1.07 (0.90–1.26)	197	1.04 (0.85–1.27)
Third fourth	341.5	312	1.16 (0.98–1.37)	209	1.11 (0.91–1.36)
Highest fourth	582.5	302	1.13 (0.95–1.34)	210	1.12 (0.91–1.38)
			p for linear trend = 0.107		p for linear trend = 0.219
NIH-AARP Study (men)					
Lowest fourth	202.0	134	1.00 (reference)	97	1.00 (reference)
Second fourth	364.3	171	1.20 (0.96–1.51)	112	1.09 (0.82–1.43)
Third fourth	527.8	192	1.33 (1.06–1.67)	133	1.28 (0.98–1.67)
Highest fourth	904.8	193	1.35 (1.07–1.71)	115	1.13 (0.85–1.50)
			p for linear trend = 1.008		p for linear trend = 0.249
NIH-AARP Study (women)					
Lowest fourth	215.2	72	1.00 (reference)	51	1.00 (reference)
Second fourth	384.8	83	1.15 (0.84–1.58)	57	1.09 (0.74–1.60)
Third fourth	547.9	79	1.11 (0.80–1.54)	47	0.90 (0.60–1.35)
Highest fourth	897.7	81	1.19 (0.85–1.66)	55	1.10 (0.74–1.64)
			p for linear trend = 0.375		p for linear trend = 0.880
PLCO Study (men)					
Lowest fourth	169.9	18	1.00 (reference)	7	1.00 (reference)
Second fourth	302.6	21	1.08 (0.57–2.03)	9	1.16 (0.43–3.14)
Third fourth	437.2	19	0.92 (0.48–1.78)	5	0.61 (0.19–1.96)
Highest fourth	750.4	24	1.18 (0.62–2.22)	9	1.05 (0.38–2.93)
			p for linear trend = 0.729		p for linear trend = 0.816
PLCO Study (women)					
Lowest fourth	206.9	13	1.00 (reference)	4	1.00 (reference)
Second fourth	352.9	10	0.74 (0.32–1.69)	5	1.11 (0.30–4.18)
Third fourth	495.1	18	1.26 (0.61–2.61)	11	2.26 (0.71–7.19)
Highest fourth	804.6	12	0.84 (0.38–1.88)	5	1.01 (0.27–3.84)
			p for linear trend = 0.959		p for linear trend = 0.684
ALL STUDIES combined*			1.19 (1.05–1.35)		1.12 (0.96–1.30)

* Meta-analysis combining RRs comparing highest fourth versus lowest fourth in each study

B.10 Risk of glioma in relation to total coffee and tea intake in the Million Women Study, the NIH-AARP Study, and the PLCO Study

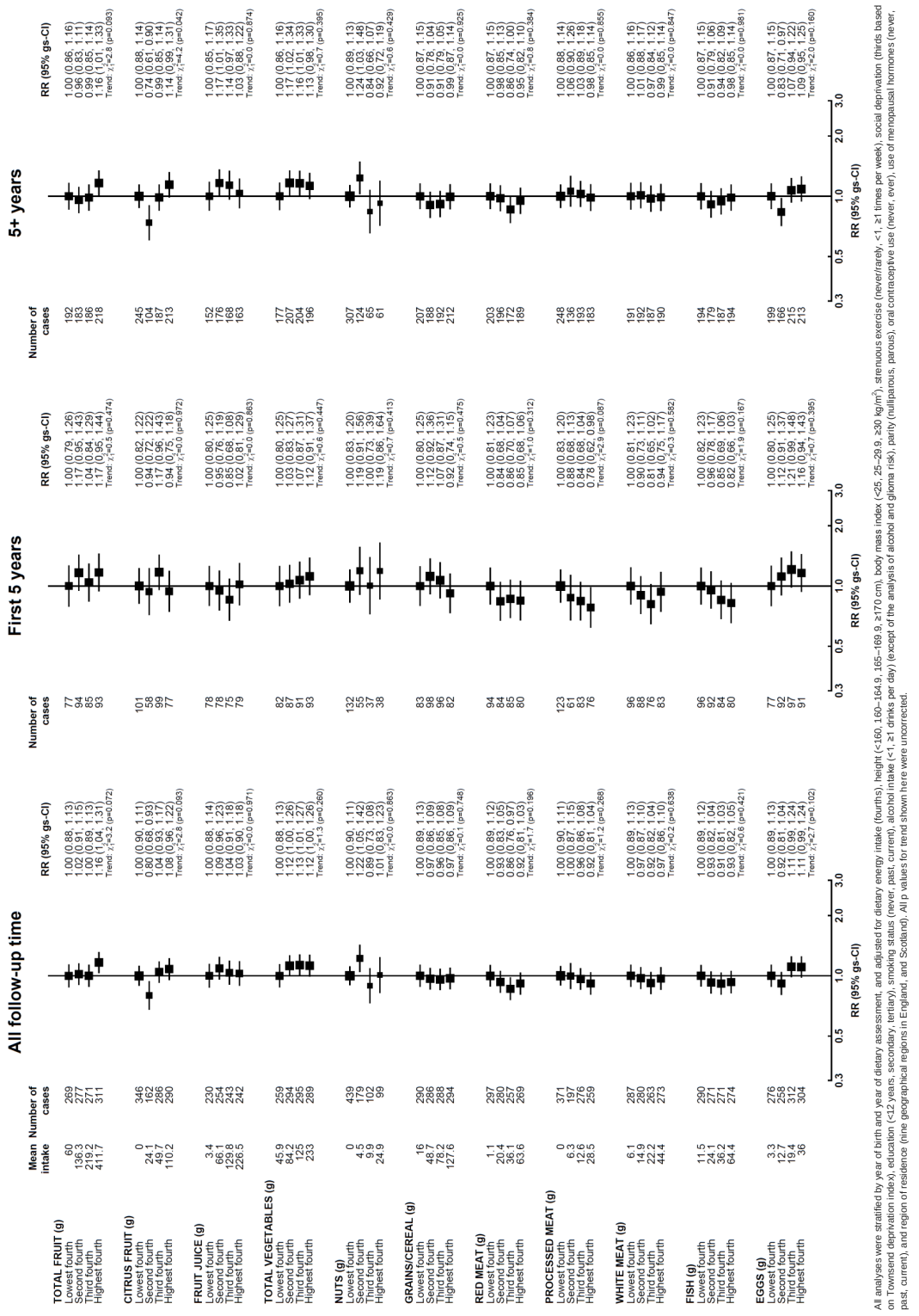
Total coffee and tea in fourth	Mean intake (mg/day)	Number of glioma	RR (95% CI)	Number of glioma	RR (95% CI)
		All follow-up time		Exclude first 5 years of follow up	
Million Women Study					
Lowest fourth	511.0	262	1.00 (reference)	171	1.00 (reference)
Second fourth	858.4	302	1.13 (0.96–1.34)	200	1.14 (0.93–1.39)
Third fourth	1,146.6	304	1.15 (0.97–1.36)	229	1.29 (1.05–1.58)
Highest fourth	1,827.3	281	1.09 (0.90–1.31)	200	1.11 (0.89–1.39)
			p for linear trend = 0.347		p for linear trend = 0.194
NIH-AARP Study (men)					
Lowest fourth	254.6	163	1.00 (reference)	110	1.00 (reference)
Second fourth	801.0	164	1.01 (0.81–1.26)	104	0.93 (0.71–1.22)
Third fourth	1,294.7	182	1.11 (0.89–1.37)	117	1.07 (0.82–1.40)
Highest fourth	2,349.2	181	1.13 (0.90–1.41)	126	1.24 (0.94–1.62)
			p for linear trend = 0.223		p for linear trend = 0.091
NIH-AARP Study (women)					
Lowest fourth	234.0	71	1.00 (reference)	47	1.00 (reference)
Second fourth	761.6	76	1.03 (0.74–1.43)	49	1.00 (0.67–1.49)
Third fourth	1,266.9	83	1.09 (0.79–1.51)	54	1.08 (0.73–1.62)
Highest fourth	2,372.3	85	1.19 (0.85–1.67)	60	1.27 (0.84–1.91)
			p for linear trend = 0.289		p for linear trend = 0.227
PLCO Study (men)					
Lowest fourth	173.4	24	1.00 (reference)	9	1.00 (reference)
Second fourth	864.9	21	0.92 (0.50–1.70)	8	0.86 (0.32–2.33)
Third fourth	1,527.7	21	0.95 (0.51–1.76)	7	0.74 (0.26–2.10)
Highest fourth	2,941.1	16	0.77 (0.39–1.54)	6	0.64 (0.21–1.96)
			p for linear trend = 0.519		p for linear trend = 0.411
PLCO Study (women)					
Lowest fourth	136.9	11	1.00 (reference)	6	1.00 (reference)
Second fourth	710.8	16	1.44 (0.64–3.21)	7	1.16 (0.37–3.62)
Third fourth	1,287.1	13	1.24 (0.53–2.90)	9	1.42 (0.47–4.32)
Highest fourth	2,505.7	13	1.24 (0.51–2.98)	3	0.48 (0.11–2.08)
			p for linear trend = 0.768		p for linear trend = 0.499
ALL STUDIES*			1.10 (0.97–1.25)		1.15 (0.98–1.34)

* Meta-analysis combining RRs comparing highest fourth versus lowest fourth in each study

B.11 Risk of glioma in relation to dietary nitrite intake for men the NIH-AARP Study

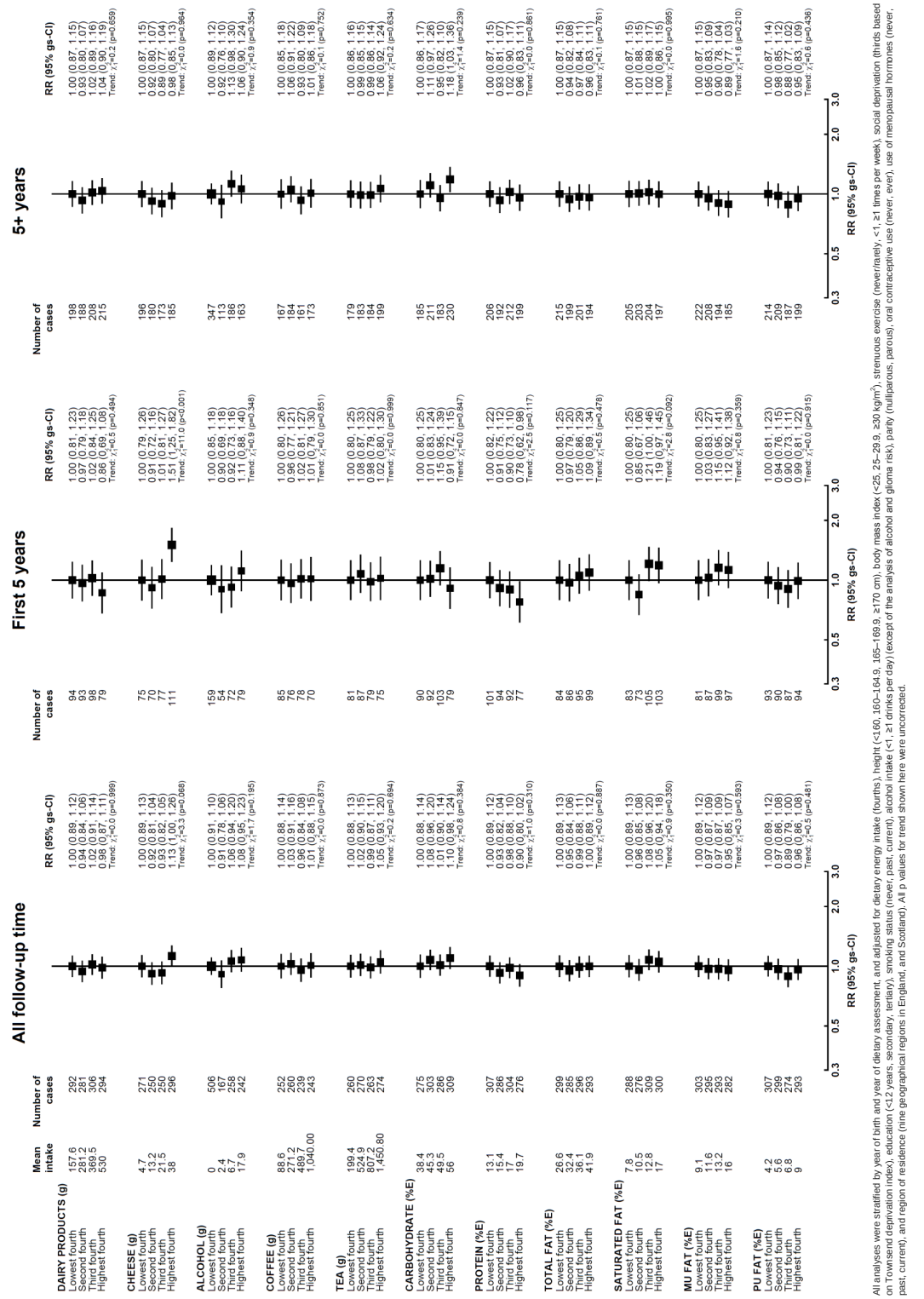
Dietary nitrite in fifth	Mean intake (mg/day)	Number of glioma	RR (95% CI)	Number of glioma	RR (95% CI)
		All follow-up time		Exclude first 5 years of follow up	
Lowest fifth	0.5	102	1.00 (reference)	78	1.00 (reference)
Second fifth	0.7	134	1.23 (0.95–1.60)	85	1.01 (0.74–1.38)
Third fifth	0.8	161	1.45 (1.12–1.87)	105	1.22 (0.91–1.65)
Fourth fifth	1.0	144	1.30 (1.00–1.69)	91	1.07 (0.78–1.46)
Highest fifth	1.4	149	1.37 (1.05–1.79)	98	1.19 (0.87–1.63)
			p for linear trend across fifth= 0.036		p for linear trend across fifth = 0.273

B.12 Diet and risk of glioma in the Million Women Study



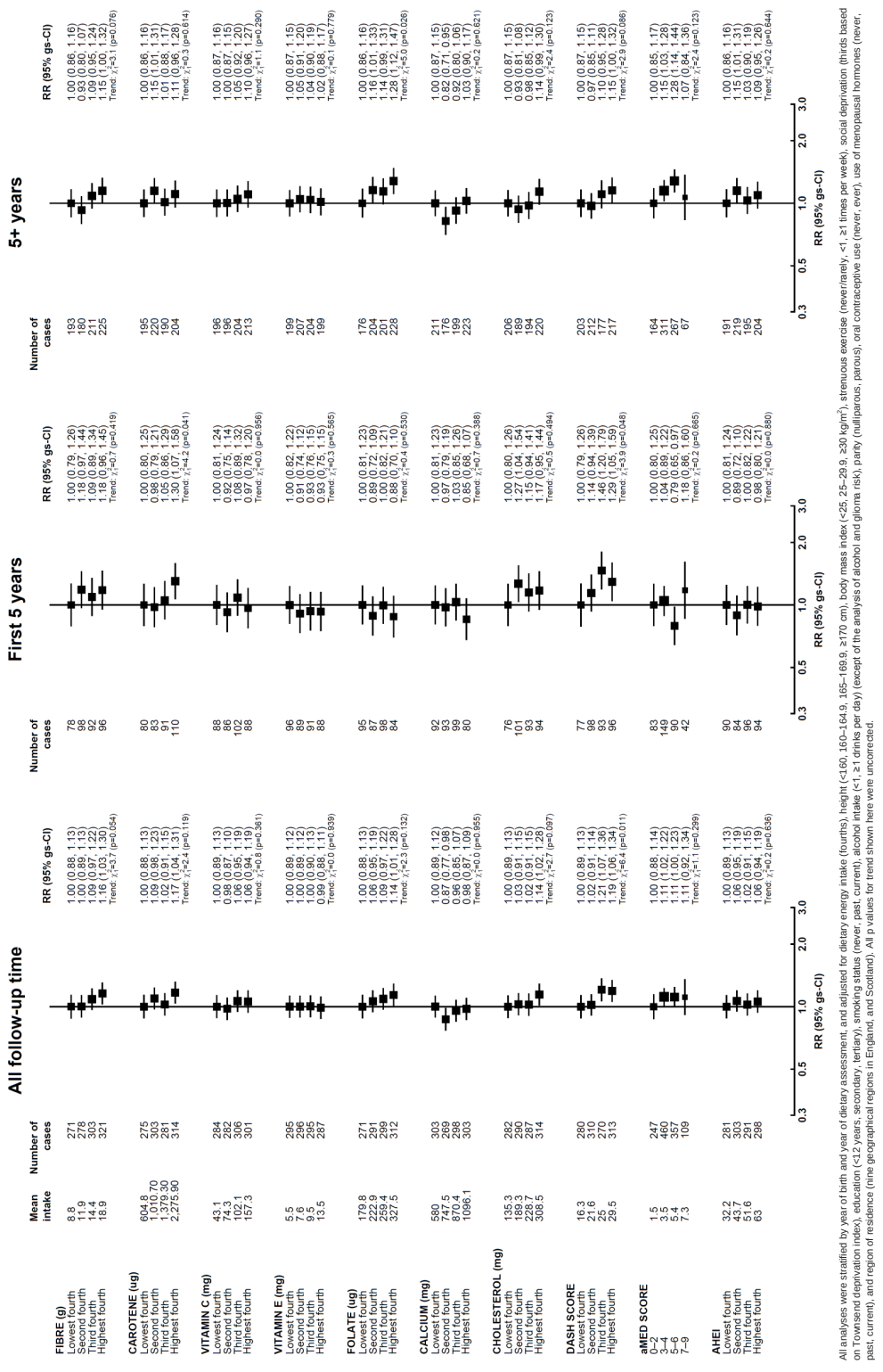
All analyses were stratified by year of birth and year of dietary assessment, and adjusted for dietary energy intake (fourths), height (<160, 160–164.9, 165–169.9, ≥170 cm), body mass index (<25, 25–29.9, ≥30 kg/m^2), strenuous exercise (never/rarely, <1, ≥1 times per week), social deprivation (thirds based on Townsend deprivation index), education (<12 years, secondary, tertiary), smoking status (never, past, current), alcohol intake (<1, ≥1 drinks per day) (except of the analysis of alcohol and glioma risk), parity (nulliparous, parous), oral contraceptive use (never, ever), use of menopausal hormones (never, past, current), and region of residence (nine geographical regions in England, and Scotland). All p values for trend shown here were uncorrected.

B.12 Diet and risk of glioma in the Million Women Study (continued)



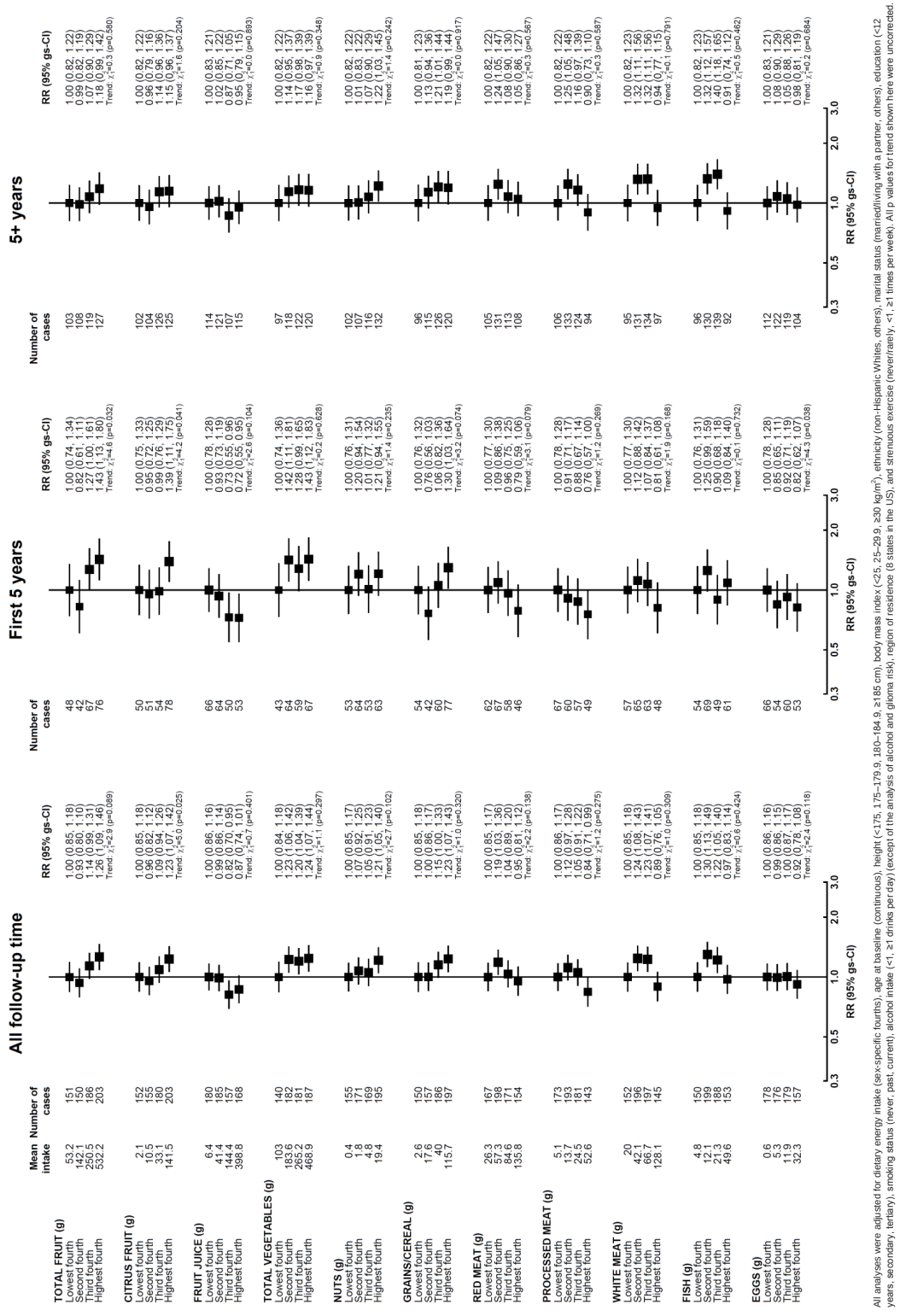
All analyses were stratified by year of birth and year of dietary assessment, and adjusted for dietary energy intake (fourths), height (<160, 160–164.9, 165–169.9, ≥170 cm), body mass index (<25, 25–29.9, ≥30 kg/m^2), strenuous exercise (never/rarely, <1, ≥1 times per week), social deprivation (thirds based on Townsend deprivation index), education (<12 years, secondary, tertiary), smoking status (never, past, current), alcohol intake (<1, ≥1 drinks per day) (except of the analysis of alcohol and glioma risk), parity (nulliparous, parous), oral contraceptive use (never, ever), use of menopausal hormones (never, past, current), and region of residence (nine geographical regions in England, and Scotland). All p values for trend shown here were uncorrected.

B.12 Diet and risk of glioma in the Million Women Study (continued)



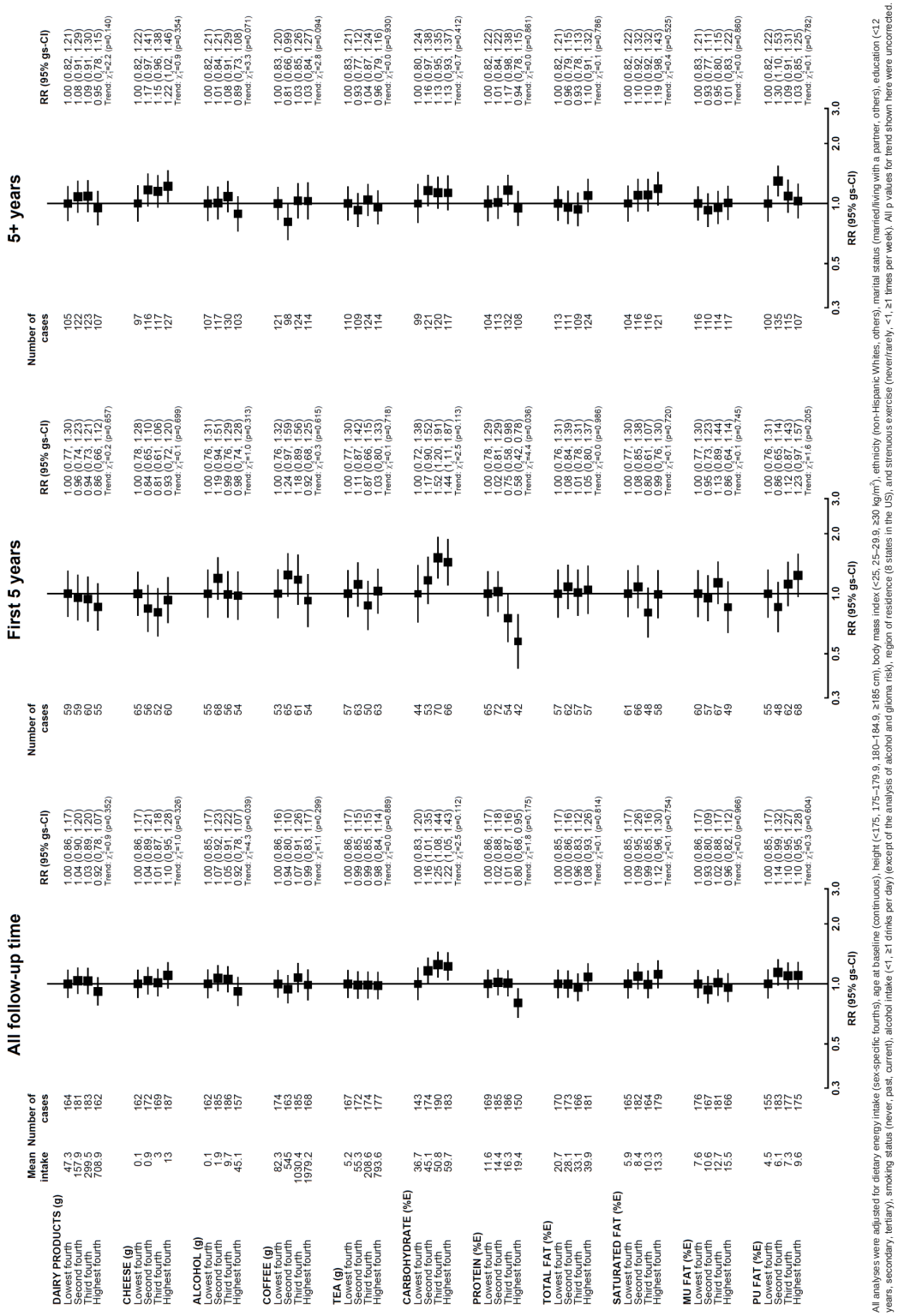
All analyses were stratified by year of birth and year of dietary assessment, and adjusted for dietary energy intake (fourths), height (<160, 160–164.9, 165–169.9, ≥170 cm), body mass index (<25, 25–29.9, ≥30 kg/m^2), strenuous exercise (never/rarely, <1, ≥1 times per week), social deprivation (thirds based on Townsend deprivation index), education (<12 years, secondary, tertiary), smoking status (never, past, current), alcohol intake (<1, ≥1 drinks per day) (except of the analysis of alcohol and glioma risk), parity (nulliparous, parous), oral contraceptive use (never, ever), use of menopausal hormones (never, past, current), and region of residence (nine geographical regions in England, and Scotland). All p values for trend shown here were uncorrected.

B.13 Diet and risk of glioma for men in the NIH-AARP Study



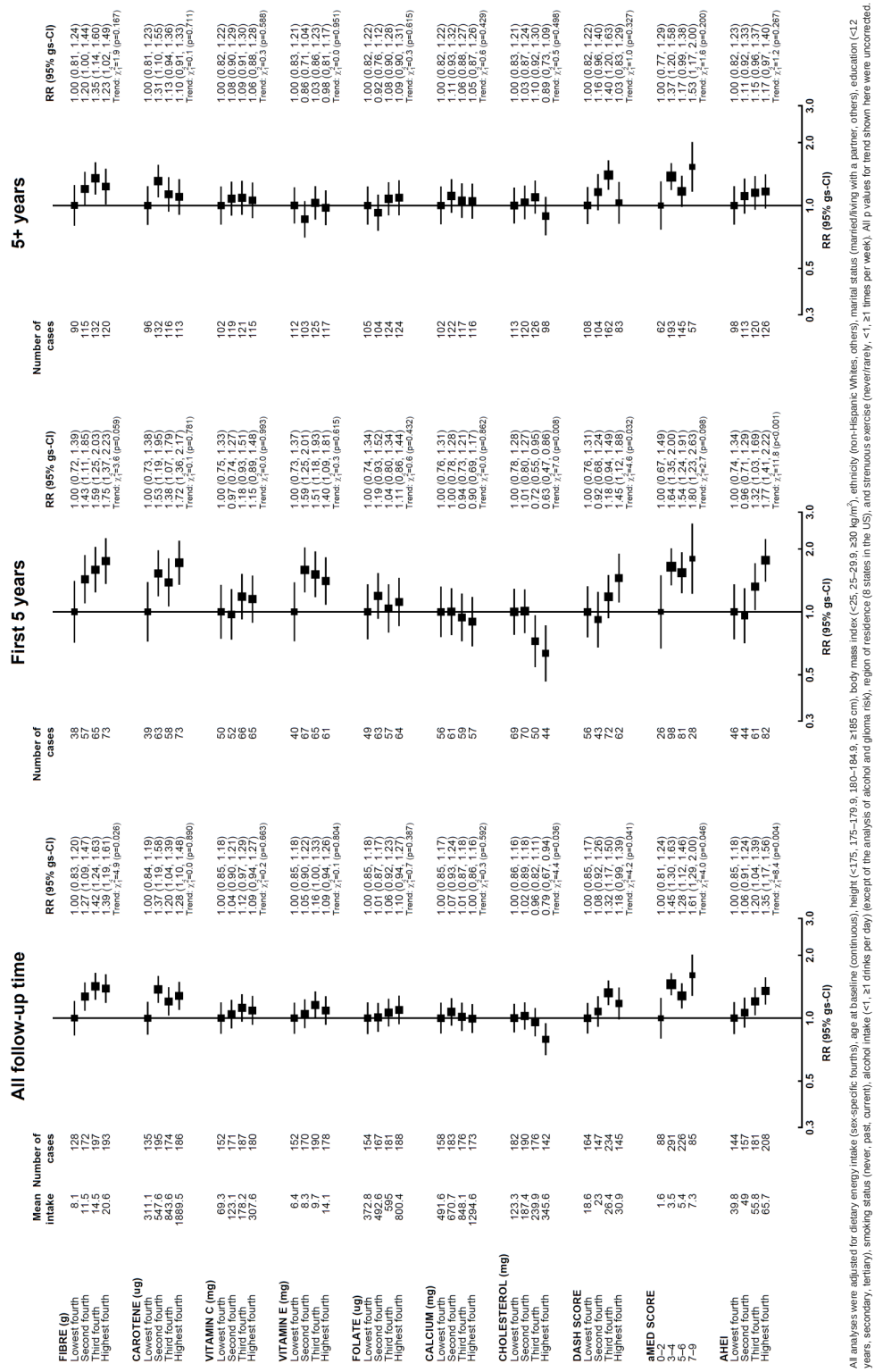
All analyses were adjusted for dietary energy intake (sex-specific fourths), age at baseline (continuous), height (<175, 175–179.9, 180–184.9, ≥185 cm), body mass index (<25, 25–29.9, ≥30 kg/m^2), ethnicity (non-Hispanic Whites, others), marital status (married/living with a partner, others), education (<12 years, secondary, tertiary), smoking status (never, past, current), alcohol intake (<1, ≥1 drinks per day) (except of the analysis of alcohol and glioma risk), region of residence (8 states in the US), and strenuous exercise (never/rarely, <1, ≥1 times per week). All p values for trend shown here were uncorrected.

B.13 Diet and risk of glioma for men in the NIH-AARP Study (continued)



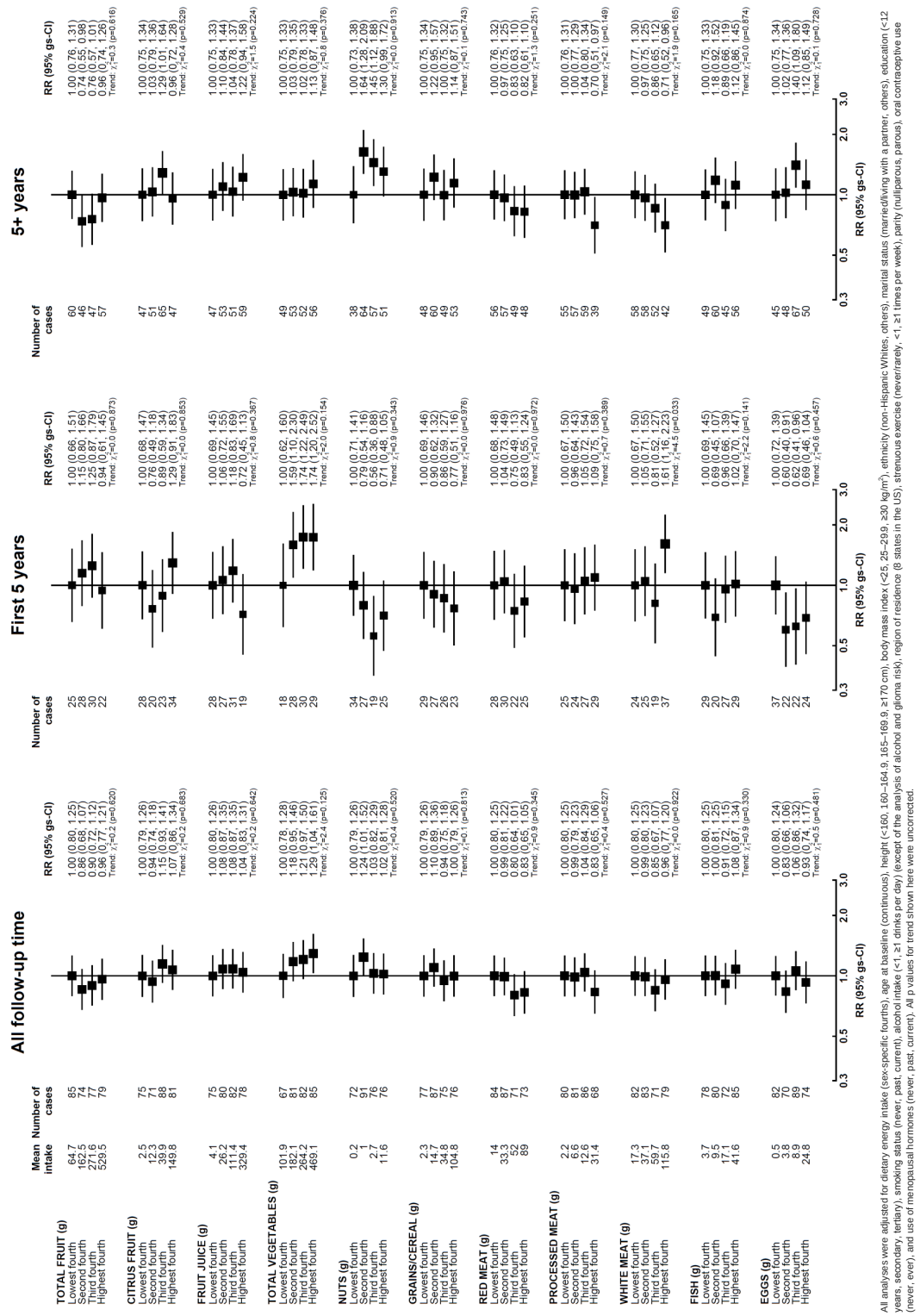
All analyses were adjusted for dietary energy intake (sex-specific fourths), age at baseline (continuous), height (<175, 175–179.9, 180–184.9, ≥185 cm), body mass index (<25, 25–29.9, ≥30 kg/m^2), ethnicity (non-Hispanic Whites, others), marital status (married/living with a partner, others), education (<12 years, secondary, tertiary), smoking status (never, past, current), alcohol intake (<1, ≥1 drinks per day) (except of the analysis of alcohol and glioma risk), region of residence (8 states in the US), and strenuous exercise (never/rarely, <1, ≥1 times per week). All p values for trend shown here were uncorrected.

B.13 Diet and risk of glioma for men in the NIH-AARP Study (continued)



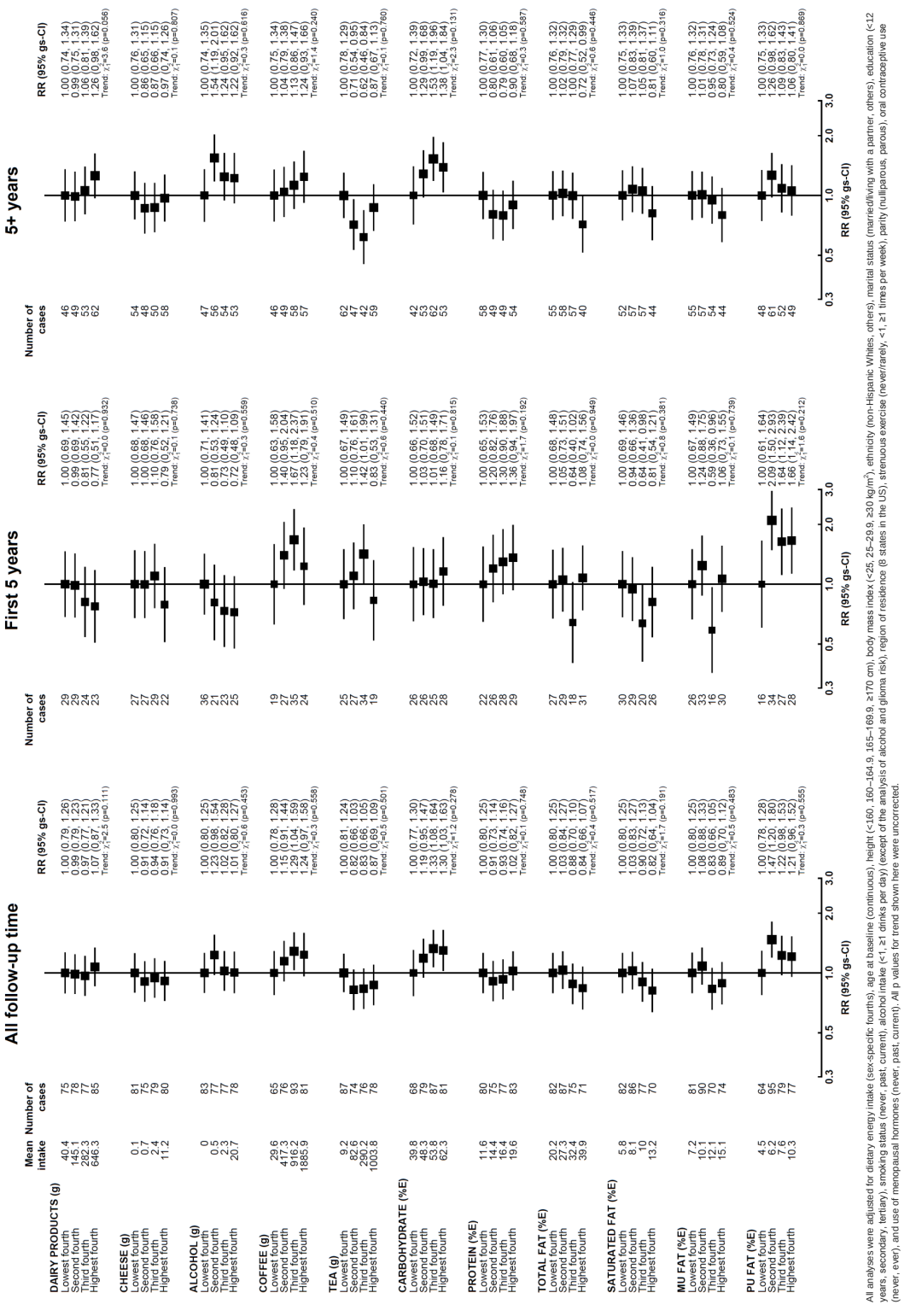
All analyses were adjusted for dietary energy intake (sex-specific fourths), age at baseline (continuous), height (<175, 175–179.9, 180–184.9, ≥185 cm), body mass index (<25, 25–29.9, ≥30 kg/m^2), ethnicity (non-Hispanic Whites, others), marital status (married/living with a partner, others), education (<12 years, secondary, tertiary), smoking status (never, past, current), alcohol intake (<1, ≥1 drinks per day) (except of the analysis of alcohol and glioma risk), region of residence (8 states in the US), and strenuous exercise (never/rarely, <1, ≥1 times per week). All p values for trend shown here were uncorrected.

B.14 Diet and risk of glioma for women in the NIH-AARP Study



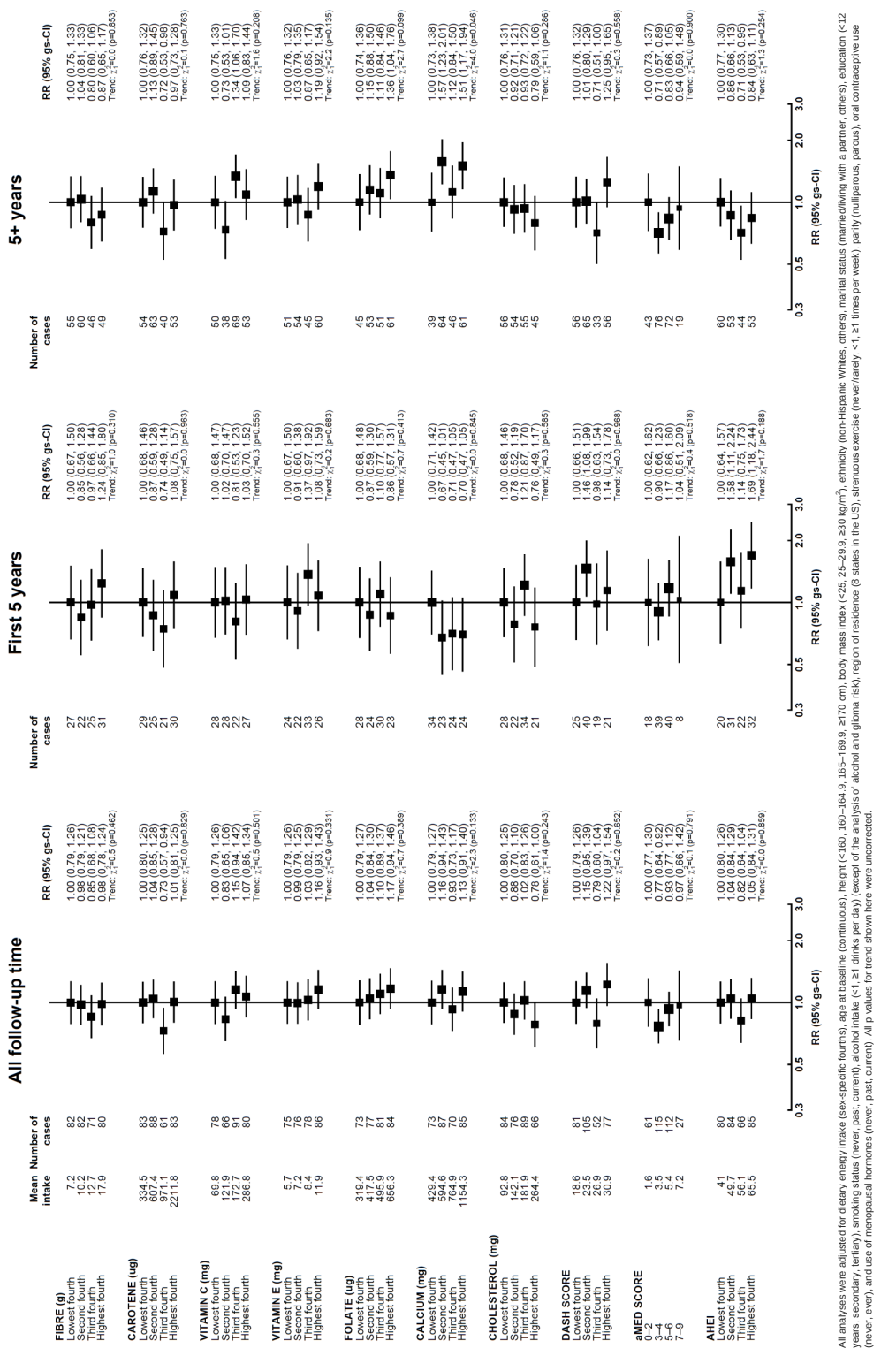
All analyses were adjusted for dietary energy intake (sex-specific fourths), age at baseline (continuous), height (<160, 160–164.9, 165–169.9, ≥170 cm), body mass index (<25, 25–29.9, ≥30 kg/m^2), ethnicity (non-Hispanic Whites, others), marital status (married/living with a partner, others), education (<12 years, secondary, tertiary), smoking status (never, past, current), alcohol intake (<1, ≥1 drinks per day) (except of the analysis of alcohol and glioma risk), region of residence (8 states in the US), strenuous exercise (never/rarely, <1, ≥1 times per week), parity (nulliparous, parous), oral contraceptive use (never, ever), and use of menopausal hormones (never, past, current). All p values for trend shown here were uncorrected.

B.14 Diet and risk of glioma for women in the NIH-AARP Study (continued)



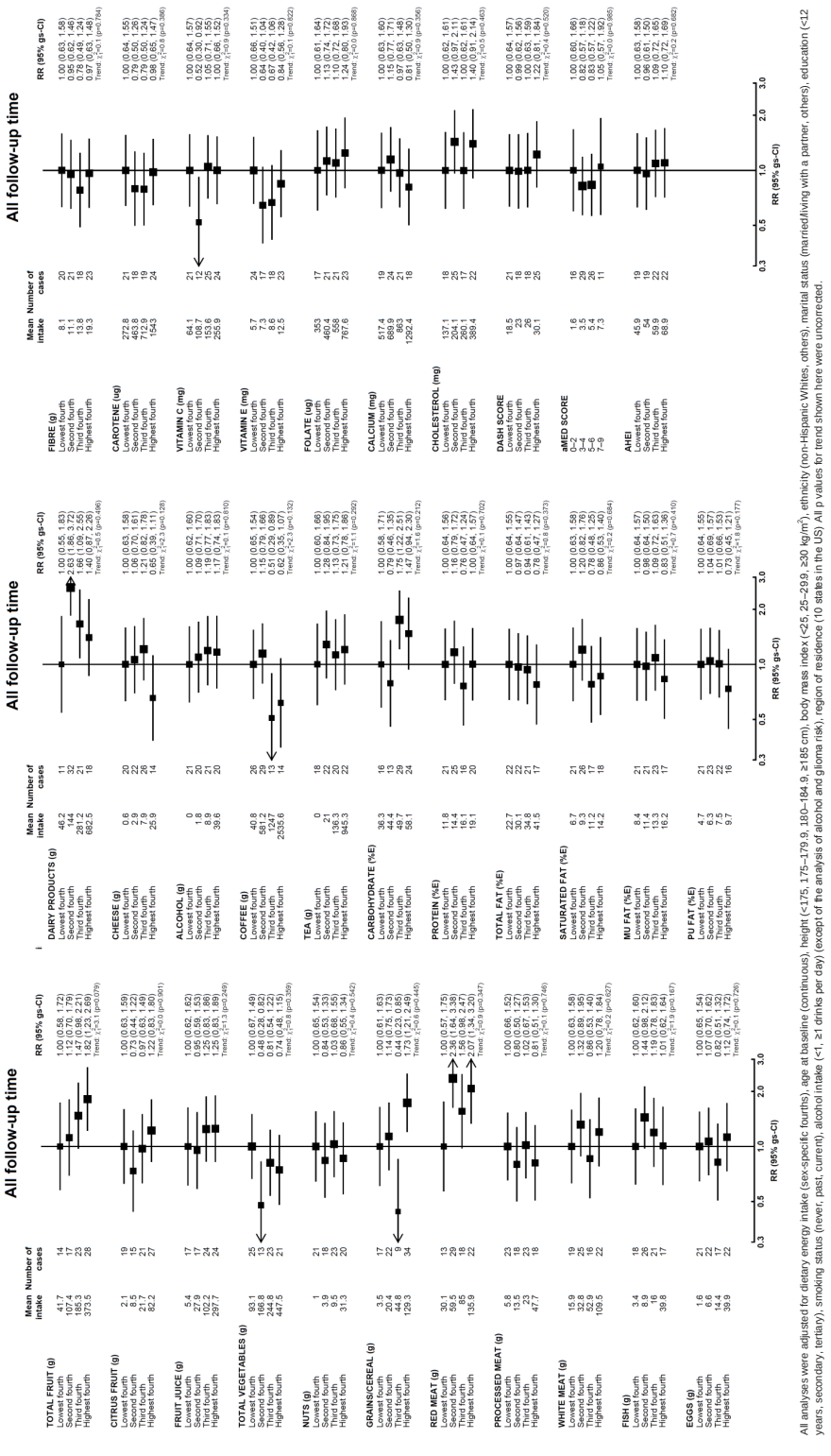
All analyses were adjusted for dietary energy intake (sex-specific fourths), age at baseline (continuous), height (<160, 160–164.9, 165–169.9, ≥170 cm), body mass index (<25, 25–29.9, ≥30 kg/m^2), ethnicity (non-Hispanic Whites, others), marital status (married/living with a partner, others), education (<12 years, secondary, tertiary), smoking status (never, past, current), alcohol intake (<1, ≥1 drinks per day) (except of the analysis of alcohol and glioma risk), region of residence (8 states in the US), strenuous exercise (never/rarely, <1, ≥1 times per week), parity (nulliparous, parous), oral contraceptive use (never, ever), and use of menopausal hormones (never, past, current). All p values for trend shown here were uncorrected.

B.14 Diet and risk of glioma for women in the NIH-AARP Study (continued)



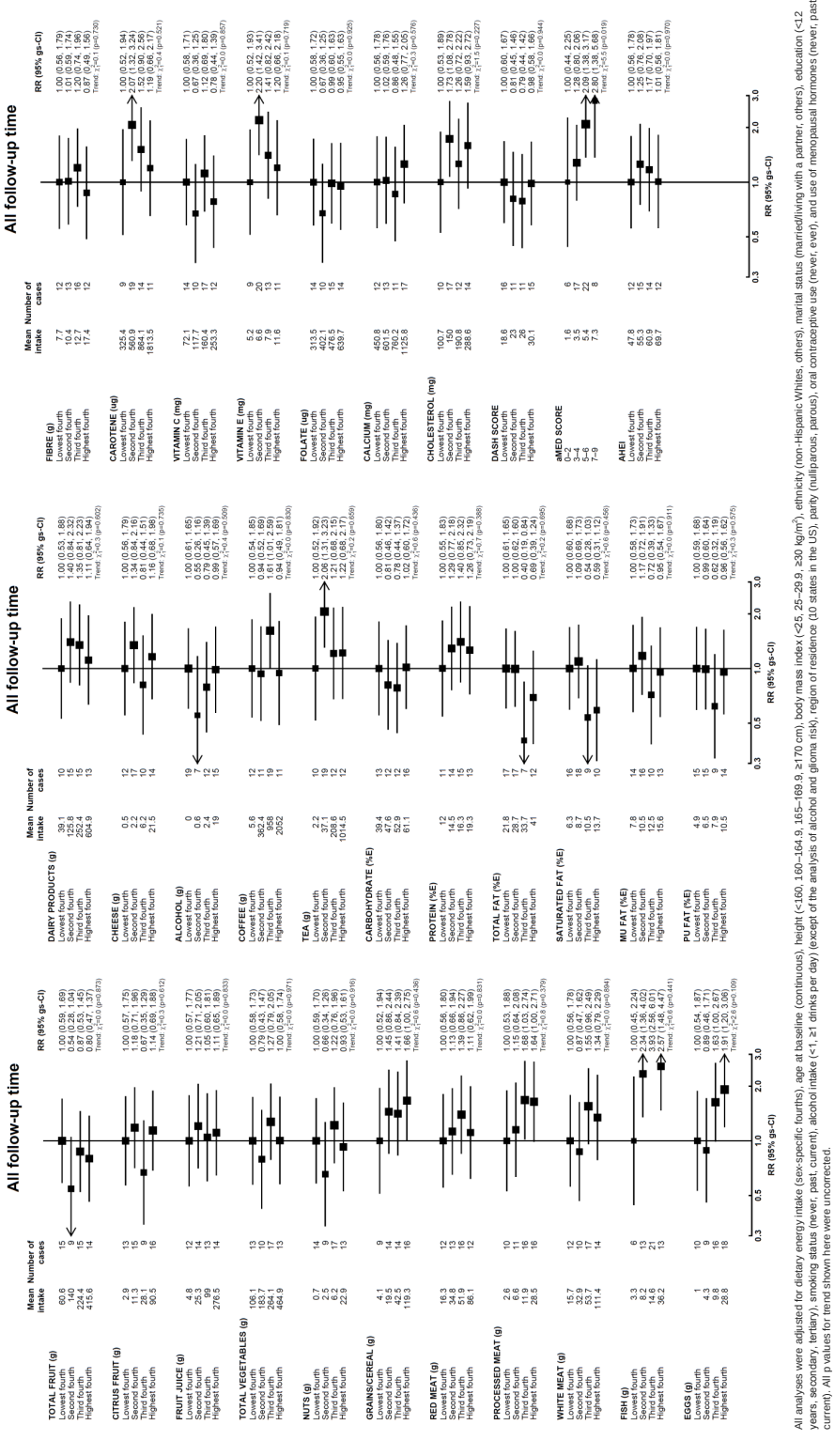
All analyses were adjusted for dietary energy intake (sex-specific fourths), age at baseline (continuous), height (<160, 160–164.9, ≥170 cm), body mass index (<25, 25–29.9, ≥30 kg/m^2), ethnicity (non-Hispanic Whites, others), marital status (married/living with a partner, others), education (<12 years, secondary, tertiary), smoking status (never, past, current), alcohol intake (<1, ≥1 drinks per day) (except of the analysis of alcohol and glioma risk), region of residence (8 states in the US), strenuous exercise (never/rarely, <1, ≥1 times per week), parity (nulliparous, parous), oral contraceptive use (never, ever), and use of menopausal hormones (never, past, current). All p values for trend shown here were uncorrected.

B.15 Diet and risk of glioma for men in the PLCO Study



All analyses were adjusted for dietary energy intake (sex-specific fourths), age at baseline (continuous), height (<175, 175–179.9, 180–184.9, ≥185 cm), body mass index (<25, 25–29.9, ≥30 kg/m^2), ethnicity (non-Hispanic Whites, others), marital status (married/living with a partner, others), education (<12 years, secondary, tertiary), smoking status (never, past, current), alcohol intake (<1, ≥1 drinks per day) (except of the analysis of alcohol and glioma risk), region of residence (10 states in the US) All p values for trend shown here were uncorrected.

B.16 Diet and risk of glioma for women in the PLCO Study



All analyses were adjusted for dietary energy intake (sex-specific fourths), age at baseline (continuous), height (<160, 160–164.9, 165–169.9, ≥170 cm), body mass index (<25, 25–29.9, ≥30 kg/m^2), ethnicity (non-Hispanic Whites, others), marital status (married/living with a partner, others), education (<12 years, secondary, tertiary), smoking status (never, past, current), alcohol intake (<1, ≥1 drinks per day) (except of the analysis of alcohol and glioma risk), region of residence (10 states in the US), parity (nulliparous, parous), oral contraceptive use (never, ever), and use of menopausal hormones (never, past, current). All p values for trend shown here were uncorrected.

C
Supplementary Methods

C.1 Supplementary methods for risk of subtypes of CNS tumours in relation to sociodemographic, anthropometric, and lifestyle factors in the Million Women Study

C.1.1 The Million Women Study

The methods of recruitment, data collection, and follow-up have been described in detail in Chapter 4. In contrast to the analyses of dietary factors, the analyses of sociodemographic, anthropometric and lifestyle factors were carried out using data from the recruitment questionnaire, which included a larger number of women with longer follow-up time.

C.1.2 Exposure variables

Information on height, body mass index, strenuous exercise, social deprivation (based on Townsend deprivation index), smoking status, alcohol intake, parity, oral contraceptive use, menopausal hormone use, and level of educational attainment was collected through the recruitment questionnaire.

C.1.3 Outcome

Incident central nervous system tumours were ascertained using International Classification of Diseases 10th Revision (ICD-10) codes (C70–C72, C75.1–C75.3, D32–D33, D35.2–35.4, D42–D43, D44.3–D44.5) and were further classified into subtypes using International Classification of Diseases for Oncology 3rd edition (ICD-O-3) codes for glioma (9380.3–9460.3), meningioma (9530.0–9539.1), and vestibular schwannoma (9560.0). Pituitary tumours were tumours of the pituitary gland (ICD-10 codes C75.1, D35.2, or D44.3) excluding glioma or meningioma (ICD-O-3 codes 9380.3–9460.3 and 9530.0–9539.1, respectively).

C.1.4 Statistical analysis

Women were excluded under standard rules if they had no corresponding follow-up information (n=44), or had missing information on date of birth (n=50), or date of follow-up (n=25). Women were also excluded if, prior to recruitment, they had any cancer (except non-melanoma skin cancer) or any benign CNS tumours (n=44,714), or any diagnosis of neurofibromatosis (n=284) or tuberous sclerosis (n=24). The remaining 1,319,283 women contributed person-years from the date of recruitment until the earliest of the date of registration of any CNS tumour or any cancer (except non-melanoma skin cancer), date of death, date of loss to follow-up, or the last date of follow-up (31 December 2015).

Relative risks (RRs) and 95% confidence intervals (CIs) of glioma, meningioma, pituitary tumours, and vestibular schwannoma in relation to the various exposure variables were estimated using Cox regression models with time in the study as the underlying time variable, stratified by year of birth and year of recruitment. All analyses were adjusted for region of residence (nine geographical regions in England, plus Scotland), and mutually adjusted for all factors under investigation in Table 4.13: height (<160, 160–164.9, 165–169.9, ≥170 cm), body mass index (<25, 25–29.9, ≥30 kg/m^2), strenuous exercise (never/rarely, <1, 1, ≥2 times per week), social deprivation (thirds based on Townsend deprivation index), smoking status (never, past, current), alcohol intake (non-drinkers, <1, ≥1 drinks per day), parity (nulliparous, parous), oral contraceptive use (never, ever), use of menopausal hormones (never, past, current – oestrogen, oestrogen-progestogen, or unspecified type), and level of educational attainment (<12 years, secondary, tertiary – had a university degree).

C.2 Supplementary methods for risk of glioma in relation to sociodemographic, anthropometric, and lifestyle factors in the NIH-AARP Study and PLCO Study

C.2.1 The NIH-AARP Study and the PLCO Study

The methods of recruitment, data collection, and follow-up have been described in detail in Chapter 5.

C.2.2 Exposure variables

Information on height, body mass index, strenuous exercise (in the NIH-AARP Study only as physical activity information was not available in the PLCO Study), smoking status, alcohol intake, ethnicity, marital status, and level of educational attainment, and additionally on parity, oral contraceptive use, menopausal hormone use for women, was collected from recruitment using the study questionnaires.

C.2.3 Outcome

Incident glioma was ascertained using ICD-10 codes (C70–C72, C75.1–C75.3,) and (ICD-O-3) codes in the NIH-AARP Study or International Classification of Diseases for Oncology 2nd edition (ICD-O-2) in PLCO for glioma (9380.3–9460.3)

C.2.4 Statistical analysis

In the NIH-AARP Study, participants were excluded under standard rules if the information of participants was provided by proxy respondents (n=15,760), or if they had missing information on follow-up (n=56), or had conflicted information on sex (n=162), or on cancer diagnosis (had a cancer diagnosis from death records but not cancer registries) (n=4,255). In the PLCO Study, participants were excluded under standard rules if they had missing information on follow-up time

(n=55). Participants in the two studies were also excluded from analyses if they had any prior cancer (except non-melanoma skin cancer). In the PLCO Study, to be in line with the main analysis in Chapter 6, the current analysis was restricted to participants who also provided dietary data only. The remaining 470,780 participants (277,906 men and 192,874 women) in the NIH-AARP Study, and 99,148 participants (47,196 men and 51,952 women) in the PLCO Study contributed person-years from the date of data provision until the earliest of the date of registration of glioma or any cancer (except non-melanoma skin cancer), date of death, date of loss to follow-up, or the last date of follow-up (31 December 2011 in the NIH-AARP Study and 31 December 2009 in the PLCO Study).

RRs and 95% CIs of glioma in relation to the exposure variables were estimated using Cox regression models with time in the study as the underlying time variable. All analyses in both studies were stratified by sex, and adjusted for age (continuous), region of residence (8 states in the NIH-AARP Study; 10 states in the PLCO Study), and mutually adjusted for all factors listed in Table 5.9: height (in men: <175, 175–179.9, 180–184.9, ≥185 cm; in women: <160, 160–164.9, 165–169.9, ≥170 cm), body mass index (<25, 25–29.9, ≥30 kg/m^2), strenuous exercise (never/rarely, <1, ≥1 times per week in the NIH-AARP Study only), smoking status (never, past, current), alcohol intake (<1, ≥1 drinks per day), ethnicity (non-Hispanic Whites, others), marital status (married/living with a partner, others), level of educational attainment (<12 years, secondary, tertiary), and additionally adjusted for parity (nulliparous, parous), oral contraceptive use (never, ever), and use of menopausal hormones (never, past, current) in women.