# Diet and risk of hip fracture in adults using data linkage

**James Webster**

Submitted in accordance with the requirements for the degree of

Doctor of Philosophy

The University of Leeds

School of Food Science and Nutrition

September 2023

# Intellectual property and Publication Statements

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

**Chapter 2** incorporates the work of one jointly-authored publication:

> **Webster J**, Rycroft CE, Greenwood DC, and Cade JE. Dietary risk factors for hip fracture in adults: An umbrella review of meta-analyses of prospective cohort studies. PLoS One. 2021; 16(11): e0259144. https://doi.org/10.1371/journal.pone.0259144

The candidate was responsible for designing the study protocol and statistical analysis plan; conducting the literature search; screening; data extraction; quality assessment; interpreting the data; writing the initial draft; revising the paper critically for important intellectual content; and managing the publication process as the corresponding author. JC and DCG conceived and supervised the work, and all authors provided input on the study design, data analysis, and interpretation of results; revised the paper critically for important intellectual content; and approved the final version. CR also conducted literature searches, data extraction and quality assessment in duplicate.

**Chapter 3** incorporates the work of one jointly-authored publication:

> **Webster J**, Greenwood DC, Cade JE. Foods, nutrients and hip fracture risk: A prospective study of middle-aged women. Clinical Nutrition. 2022; 41(12): 2825-32. https://doi.org/10.1016/j.clnu.2022.11.008

This publication was a secondary analysis of the UK Women's Cohort Study (UKWCS) dataset. The candidate was responsible for designing the study protocol and statistical analysis plan; data cleaning and analysis; and drafting of the manuscript. JC and DCG were responsible for the conception of the UKWCS and supervised the secondary data analysis, and all authors provided input on the study design, data analysis, and interpretation of results; revised the paper critically for important intellectual content; and approved the final manuscript version.

**Chapter 4** incorporates the work of one jointly-authored publication:

> **Webster J**, Greenwood DC, Cade JE. Risk of hip fracture in meat-eaters, pescatarians, and vegetarians: results from the UK Women's Cohort Study. BMC medicine. 2022; 20(1): 1-10. https://doi.org/10.1186/s12916-022-02468-0

This publication includes a secondary analysis of the UKWCS dataset. The candidate was responsible for designing the study protocol and statistical analysis plan; data cleaning and analysis; and drafting of the manuscript. JC and DCG were responsible for the conception of the UKWCS and supervised the secondary data analysis, and all authors provided input on the study design, data analysis, and interpretation of results; revised the paper critically for important intellectual content; and approved the final version.

**Chapter 5** incorporates the work of one jointly-authored publication:

> **Webster J**, Greenwood DC, Cade JE. Risk of hip fracture in meat-eaters, pescatarians, and vegetarians: results from the UK Biobank. BMC Medicine. 2023; 21(278). https://doi.org/10.1186/s12916-023-02993-6

This publication was a secondary analysis of the UK Biobank dataset. The candidate was responsible for designing the study protocol and statistical analysis plan; data cleaning and analysis; and drafting of the manuscript. All authors provided input on the study design, data

analysis, and interpretation of results; revised the paper critically for important intellectual content; and approved the final version.



This thesis is submitted in accordance with the requirements of the “alternative route via publication” due to the volume of published material produced from the analyses conducted in this thesis.

# Acknowledgements

I thank my supervisors, Prof Janet Cade and Dr Darren Greenwood, for devoting time and expertise to my research and academic development. You encouraged me to conduct high-quality research, publish results, present at conferences, generate impact, and to be confident and take pride in my research, and have helped me create a strong foundation for my future career.

I thank my colleagues from the Nutritional Epidemiology Group for their academic and personal support and friendship. The research group was a great platform for me to share my research, receive feedback, and learn from others in a constructive community. In particular, I thank Dr Catherine Rycroft for her input in the umbrella review, and Dr Mark Hopkins and Dr Charlotte Evans for their feedback during the early stages of this work at transfer.

I thank all staff members, researchers, and clinicians who established and managed the UK Women's Cohort Study and UK Biobank cohorts, and the participants who made these studies possible. Thanks to Leeds Institute of Data Analytics – in particular Sean Tuck – who facilitated access to this data, and provided support and advice when needed. I am grateful to Rank Prize Funds and the School of Food Science and Nutrition who funded this work and supported me throughout my PhD, particularly with publications and some unforgettable conference trips. I especially thank Gita Winder for her support in managing my PhD activities.

I am grateful to have met many inspiring colleagues over the last three years – Dr Dena Zeraatkar, Dr Tammy Tong, Dr Keren Papier, and Dr Marc Sim in particular – who have supported areas of my research or development, and are role model researchers. I am also grateful to my teachers, mentors, and supervisors before my PhD, from sixth-form at The Dixie Grammar School to my Masters at the University of Leeds – thanks to Jon Dixon, Dr Laura McFarlane, and Dr Mark Hopkins for their academic guidance and confidence in me.

Finally, thanks to my friends, family, and my partner for their support. To my partner – Clem, and to my mum, Dave, my dad, and my brothers – you encouraged me to do my best, and have been instrumental in bringing me here today.

# Abstract

**Background:** Hip fractures commonly initiate hospitalisation and health decline in older adults, and are becoming increasingly prevalent in the global ageing population. Long-term dietary habits impact musculoskeletal health, but associations between diet and hip fracture risk are unclear due to limited and inconsistent evidence. Specifically, vegetarian diets are becoming increasingly popular in developed countries, but often lack nutrients related to musculoskeletal health. Therefore, this thesis aimed to better understand associations between dietary habits and hip fracture risk in adults.

**Methods:** Associations between food and nutrient intakes, as well as meat-free diets (regular meat-eater, occasional meat-eater, pescatarian, or vegetarian) with hip fracture risk were investigated using data from two large prospective cohort studies in the UK: the UK Women's Cohort Study (UKWCS, n=26,000 women) and the UK Biobank (n=410,000 men and women). In both datasets, dietary data were collected using a food frequency questionnaire at recruitment, and incident hip fractures were identified by linkage to national hospital records.

**Results:** In the UKWCS, a linear dose-response relationship was observed between dietary protein, as well as combined tea and coffee intake, with hip fracture risk. In both the UKWCS and UK Biobank, vegetarians but not occasional meat-eaters or pescatarians were at a greater risk of hip fracture than regular meat-eaters, regardless of sex. All associations remained after adjustment for confounders.

**Conclusion:** This thesis strengthens the evidence that British vegetarians are at a greater risk of hip fracture than meat-eaters, and shows for the first time in a British population that dietary protein and combined tea and coffee consumption are each associated with a lower risk of hip fracture. Further prospective cohort studies and randomised controlled trials are needed to confirm if these findings are causal before dietary recommendations for preventing hip fractures can be formed.

# Table of Contents

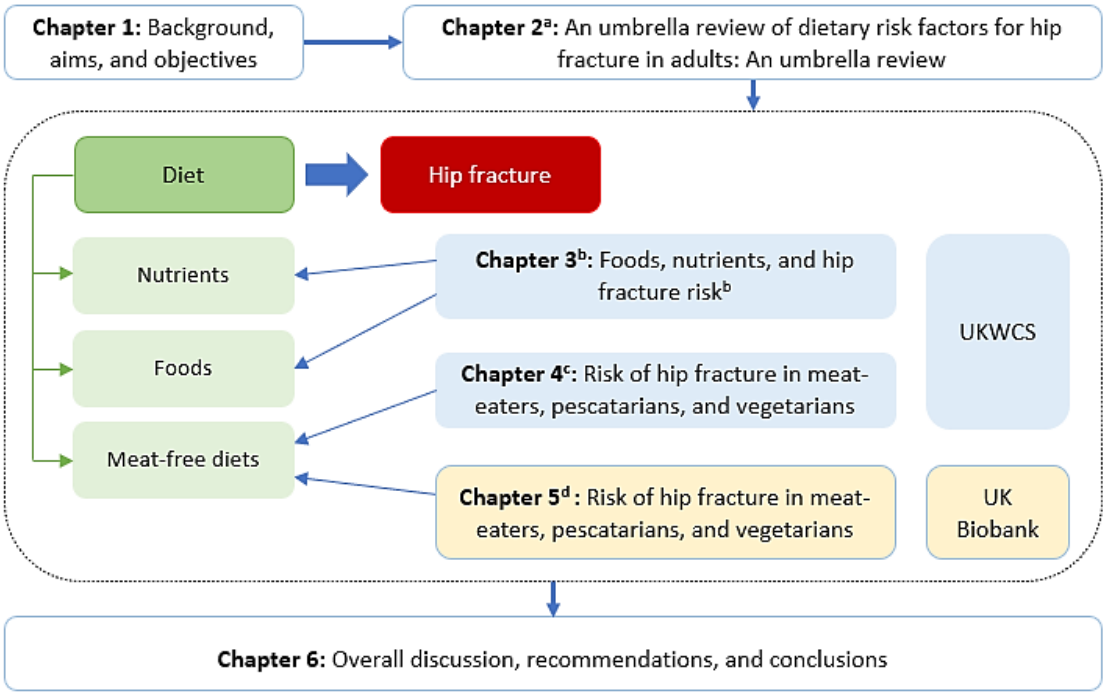
# List of Tables

# List of Figures

# List of Abbreviations

| | |
|---|---|
| AHS-2 | Adventist Healthy Study-2 |
| BMD | Bone mineral density |
| BMI | Body mass index |
| DAG | Directed acyclic graph |
| EAA | Essential amino acids |
| EIPC | European Investigation into Cancer |
| FFM | Fat-free mass |
| FFQ | Food frequency questionnaire |
| HR (95% CI) | Hazard ratio (95% confidence interval) |
| HRT | Hormone replacement therapy |
| ICD | International classification of diseases |
| IGF-1 | Insulin-like growth factor 1 |
| IORW | Inverse odds ratio weighting |
| MPS | Muscle protein synthesis |
| NDE | Natural direct effect |
| NDNS | National Diet and Nutrition Survey |
| NHS | Nurses Health Study |
| NIE | Natural indirect effect |
| PTH | Parathyroid hormone |
| PBAF | Plant based alternative food |
| RCT | Randomised controlled trial |
| SMC | Swedish Mammography Cohort |
| TE | Total effect |
| UKWCS | UK Women's Cohort Study |

# Thesis Outline




[a]Webster J, Rycroft CE, Greenwood DC, Cade JE. 2021. PLoS One. 16(11).
[b]Webster J, Greenwood DC, Cade JE. 2022. Clinical Nutrition. 41(12).
[c]Webster J, Greenwood DC, Cade JE. 2022. BMC Medicine. 20(1).
[d]Webster J, Greenwood DC, Cade JE. 2023. BMC Medicine. 21(278).

# Chapter 1 Background, aims, and objectives

## 1.1 Hip fracture epidemiology

### 1.1.1 Prevalence

The number of older adults worldwide is increasing due to global population growth and extended individual longevity. Almost a third of older adults (≥ 65 years) fall at least once a year, and fracture is a major consequence (1). Prevalence of frailty, sarcopenia, osteoporosis, and other chronic conditions are therefore increasing in the UK and internationally, resulting in more falls and fractures (2). Hip fractures are the most common fracture site resulting in hospitalisation (3). The annual incidence rate in the UK is estimated at 250 hip fractures per 100,000 people, equivalent to 105,000 hip fractures annually (4, 5). Globally, age-standardised hip fracture incidence rates in 2019 were estimated at 190 per 100,000 women, and 166 per 100,000 men, representing increases of 2.7% and 0.8% from 1990, respectively (6). Whilst age-adjusted hip fracture rates are relatively stable, population ageing has caused absolute counts to increase substantially, with estimates in 2019 of 8.1 million new hip fractures in women, and 6.1 million in men, representing increases of 107% and 76% since 1990, respectively (6). This trend is set to continue, with the number of new total fragility fractures expected to increase by 19.6% by 2030 if changes are not made to current practice (5).

### 1.1.2 Clinical cost to patients

Hip fracture reduces quality of life, mobility, and independence, and can cause social isolation, depression, comorbidity, and premature mortality (3, 7, 8). For example, around 40% of hip fracture patients are unable to walk independently 12 months after hip fracture, and permanent disability in hip fracture patients ranges from 32-80% globally (8). Moreover, 10% of cases die within a month of hip fracture, and a third die within 12 months (8).

### 1.1.3 Social cost to healthcare systems

The economic burden from hip fractures is substantial due to long hospitalisation and rehabilitation periods, as well as additional costs from resulting comorbidities (8). Hip fractures account for half a million hospital bed days each year (5). Estimated costs to the UK and US healthcare systems are £2–3 billion and $6 billion per year, respectively (9, 10), and the estimated international average cost 12 months after the first hip fracture is $44,000 per patient (11). Preventing hip fractures is therefore a public health priority, nationally and internationally.

## 1.2 Hip fracture pathophysiology

Hip fractures can result from high energy trauma, such as in motor vehicle accidents, but most hip fractures in older adults occur following a fall (12, 13). Risk factors for fall-related, fragility hip fractures include both those affecting risk of fracture following a fall, and those affecting risk of falling. Non-physiological factors such as the climate, surface properties, and landing biomechanics impact risk of falling and hip fracture (14, 15), but the single largest risk factor for hip fracture is age, with rates increasing 100 to 1000-fold over 60 years of ageing (16). The average age of hip fracture in men and women is 84 and 83 years, respectively (17), and is often the result of age-related physiological changes.

### 1.2.1 Bone

Peak bone mineral density (BMD) is achieved during late adolescence, and declines at all bone sites from age 35 years onwards in both sexes, but the rate of BMD loss accelerates following menopause in women (18). Mendelian Randomisation analyses have shown that low femoral neck BMD increases hip fracture risk (19). Experimental evidence also shows that small improvements in total hip BMD (2%) reduce hip fracture risk modestly (16% risk reduction) (20), demonstrating the value of maintaining or improving hip BMD to prevent hip fractures. The structural integrity of bone also affects hip fracture risk; cortical bone at the femoral neck thins and becomes less elastic with age, and therefore becomes more prone to fracture (16).

### 1.2.2 Muscle

Poor muscle health adds to hip fracture risk by increasing risk of falls (18). Inadequate muscle mass and function are also related to poorer bone health, since weaker local muscle contractions reduce the mechanical load on bone that stimulates remodelling (18). Similarly to bone, muscle mass and strength peak in early adulthood, and decline from age 50 years onwards (18). On average, muscle mass is lost at a rate of 1-2% per year, and strength at 1.5-3% per year (18). The cumulative loss of muscle mass and strength with age can lead to sarcopenia, characterised by the age-induced loss of muscle function (18). Sarcopenia also involves negative changes to muscle composition (e.g. fatty infiltration and fibrosis), aerobic capacity, insulin resistance, and neural activation (18); and is associated with an increased risk of falls and hip fracture (1, 21, 22). The Joint American and British Geriatric Society guidelines for the prevention of falls in older adults note muscle weakness as the single biggest intrinsic risk factor for falling (18, 23). Some observational studies have also demonstrated independent associations between measures of muscle mass and strength, such as hand grip, hip flexor, and spine extensor strength as well as lower limb peak muscle force with hip fracture risk in men and women (24-26). Additionally, observational evidence has shown that physical function (e.g., time for five chair stands, walking speed over 6 m distance, and ability to stand on one leg for 10 s) predicts hip fracture risk (27, 28). Whilst achieving a high peak muscle mass and strength in early life is important to lifelong musculoskeletal health, it is important for adults of all ages, but particularly older adults and those with osteoporosis or sarcopenia, to slow the rate of musculoskeletal decline to prevent hip fracture.

### 1.2.3 Body mass index

The relationship between body mass index (BMI) and hip fracture risk likely depends on age, sex, body composition, and musculoskeletal health (29). Some observational studies have shown a U-shaped relationship between BMI and risk of falls and hip fracture, where underweight (BMI < 18.5 kg/m$^2$) and obesity (BMI ≥ 30 kg/m$^2$) increase the risk, and overweight (BMI between 25-30 kg/m$^2$) is associated with the lowest risk (1, 30-32). In a cohort of 288,000 Korean adults aged 50-80 years, the lowest incidence of hip fracture was observed in men with a BMI of 27.5-29.9 kg/m$^2$, and in women with a BMI between 25-27.4 kg/m$^2$, respectively (31). In contrast, in

925,345 postmenopausal women followed for an average of 6.2 years in the UK, hip fracture risk increased with decreasing BMI, where women with obesity were at the lowest risk (33). Similarly, in an analysis of nine cohort studies, the 10-year probability of hip fracture was higher in individuals with a BMI of 20 kg/m$^2$ compared to those with a BMI of 40 kg/m$^2$, regardless of the number of clinical risk factors present (34). For example, the 10-year hip fracture probability in women (age 65 years) was 2.3% at a BMI of 20 kg/m$^2$, but was 0.6% at a BMI of 40 kg/m$^2$. In a cohort of around 60,000 Norwegian men and women, compared to adults with a BMI of 22-24.9 kg/m$^2$, the risk of hip fracture was higher in men and women with underweight (38% and 66% greater risk), but was lower in men and women with obesity (43% and 23% lower risk) (35). When stratified by age, there was only a further decrease in hip fracture risk beyond a BMI of 25 kg/m$^2$ in women aged 70-79 years, showing that associations between BMI and hip fracture risk are age and sex-specific.

Individuals with underweight may be at a greater risk of falls and hip fracture than individuals with a healthy weight due to poorer bone health (in particular lower bone mass and femoral neck BMD) (1, 18, 29, 36). One cohort study in 2199 women and 1351 men aged 60 years or older showed an inverse association between BMI and hip fracture risk that was mediated through femoral neck BMD (37). In women, 96% of the total effect of BMI on hip fracture risk was mediated by femoral neck BMD, whereas femoral neck BMD accounted for 44% of the association in men (37). In contrast, a Mendelian randomisation study of 336,000 adults showed that whilst BMI was causally and positively associated with lumbar and heel BMD, the association with femoral neck BMD was non-significant (36). Therefore, whilst femoral neck BMD contributes to some of the effect of BMI on hip fracture risk, other factors are also important, particularly in men.

Individuals with underweight are at an increased likelihood of sarcopenia; impaired mobility; walking instability; inadequate fat mass; and malnutrition, which each increase the risk of falls and hip fracture (1). For example, inadequate fat mass at a lower BMI may contribute to a higher risk of hip fracture by reducing cushioning from impact forces during a fall, as well as reducing mechanical loading on bone, which reduces bone strength (30). However, obesity may increase hip fracture risk due to postural instability; lower physical activity levels; systemic inflammation; vitamin D deficiency; calcium malabsorption; and comorbidity in individuals with obesity (30).

For example, adipose tissue secretes inflammatory cytokines which may stimulate osteoclastogenesis, which causes bone resorption (30). Obesity is also associated with many metabolic complications (e.g. type 2 diabetes), insulin resistance, and chronic inflammation that are associated with an increased risk of hip fracture (30). Obesity and sarcopenia can also coexist in older adults (i.e. sarcopenic obesity), since musculoskeletal health and function decline with age, whilst body fat and weight increase, leading to an increased risk of hip fracture (18). Therefore, BMI is an important risk factor in hip fracture aetiology through its age- and sex-specific interaction with musculoskeletal health, as well as with other health systems.

## 1.3 Risk factors for falls and hip fractures

Several factors contribute to the rate of bone and muscle loss with age and impact BMI, and therefore may influence risk of falls and hip fracture. These factors can act independently and/or synergistically, and include non-modifiable and modifiable risk factors.

### 1.3.1 Non-modifiable risk factors

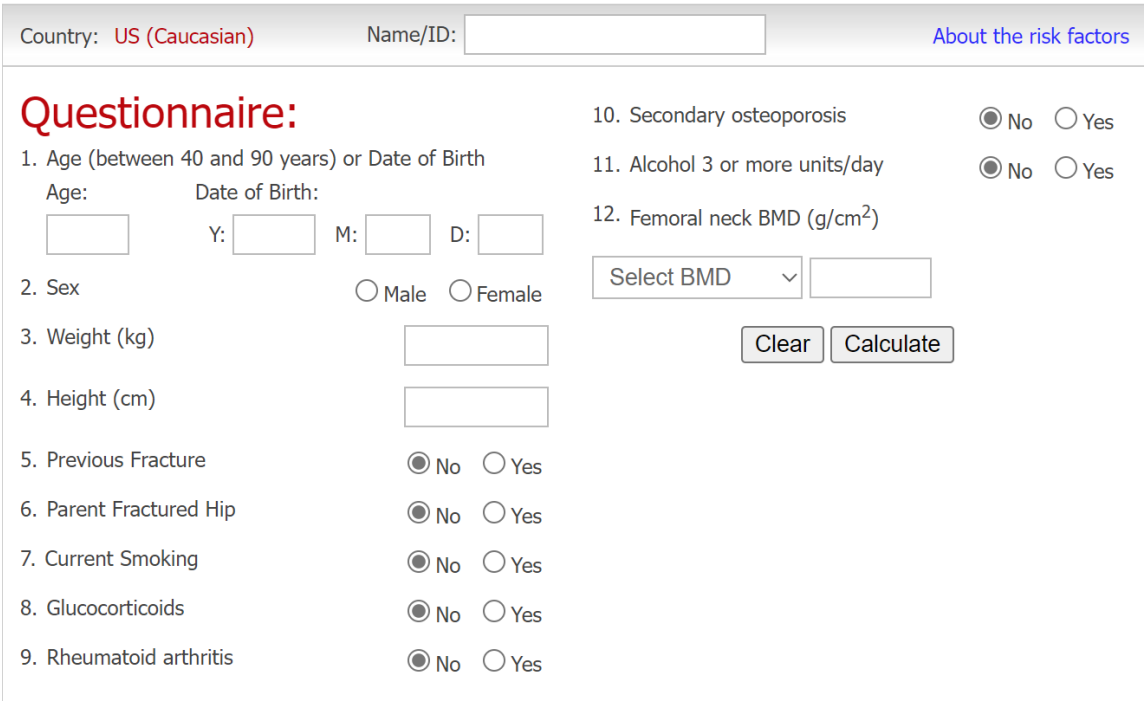



**Figure 1.1: Fracture Risk Assessment tool (FRAX) (34).**

**Figure 1.1** shows risk factors highlighted in the Fracture Risk Assessment Tool (FRAX) that is used to predict 10-year fracture risk (34). Besides age, non-modifiable risk factors for hip fracture include female sex, height, previous fracture at any site, and parental history of hip fracture. Women are at a greater risk of hip fractures than men; 18% of women and 6% of men globally sustain a hip fracture (38). However, mortality rates within six months of hip fracture in men are approximately double that in similarly aged women, therefore preventing hip fracture is important in both sexes (4).

### 1.3.2 Modifiable risk factors

The heritability of hip fractures is estimated at 48% according to twin studies (19, 39), implying that both genetic and environmental factors contribute to hip fracture risk. Risk factors that are modifiable represent targets for hip fracture prevention. Modifiable elements of the FRAX tool include body weight, smoking, alcohol, glucocorticoid use, femoral neck BMD, and comorbidities including rheumatoid arthritis, secondary osteoporosis, and diabetes (34). Some of these factors (body weight, femoral neck BMD, and prevalence of comorbidities) are in turn influenced by both genetic and environmental or lifestyle factors (18). For instance, a recent genome-wide association study with meta-analysis of five European biobanks identified five genetic signals associated with hip fractures, of which four associated with BMD, and one associated with falls (19).

Recommendations from the National Osteoporosis Guideline Group (NOGG) and the International Osteoporosis Foundation (IOF) suggest to reduce risk of osteoporosis, falls, and hip fracture through regular exercise (particularly resistance exercise), preventing calcium and vitamin D deficiencies through supplementation, and by eating a balanced diet (5, 40). There is strong evidence that regular exercise benefits bone strength and muscle function (41, 42), and reduces risk of falls and fragility fractures (43, 44). There is experimental evidence that daily combined calcium and vitamin D supplementation (but not independent) reduces hip fracture risk where a deficiency is present in older adults (45). There is some evidence that dietary modification can attenuate bone loss associated with weight reduction or reductions in BMI (29), but evidence linking a balanced diet with hip fracture risk is comparatively limited. Studies investigating diet and hip fracture risk are mostly observational, whereas the evidence

supporting the benefits of exercise and supplementation comes mostly from randomised controlled trials (RCTs), which circumvent issues with residual confounding observed in observational studies. However, the evidence-base for a role of diet in hip fracture prevention is continually increasing; the 2022 World Guidelines for Falls Prevention and Management for Older Adults concluded that malnutrition is a causal factor in pathological ageing, and recommended including a nutritional assessment within a multifactorial risk assessment for falls in older adults (1). Many aspects of diet, including intake of nutrients beyond calcium and vitamin D; consumption of foods in which relevant nutrients are obtained; and patterns of consumption over time have the potential to influence risk of hip fracture through their long-term effects on musculoskeletal health and BMI. This topic is introduced in Chapter 1: section 1.4, and is comprehensively reviewed in Chapter 2.

## 1.4 Diet and hip fracture risk

### 1.4.1 Nutrients

Calcium and vitamin D are essential to bone and muscle health. Calcium is essential in regulating muscle contraction and in the formation and mineralisation of bone. Insufficient calcium intake or absorption results in low serum calcium levels. To compensate, calcium is resorbed from bone, and over time, if bone formation cannot equal rates of resorption, calcium deficiency can reduce BMD and increase hip fracture risk. Vitamin D facilitates the intestinal absorption of calcium; therefore, low serum vitamin D levels may indirectly reduce BMD and increase hip fracture risk (46). Vitamin D deficiency can also result in disordered muscle repair and atrophy of type II (fast-twitch) muscle fibres (which are the first to be recruited to prevent a fall), as well as fatty infiltration and fibrosis of muscle tissue, leading to poorer physical function (47, 48).

Current guidelines for calcium and vitamin D intakes vary by country, but generally suggest that older adults should consume 700-1300 mg/day of calcium, and 10-20 µg/day of vitamin D (49, 50) (51). In the UK, National Diet and Nutrition Survey (NDNS) data in 2019 showed that mean calcium intakes from food sources only were above UK recommendations (700 mg/day) for men and women aged 16-64 years (885 mg/day and 740 mg/day) and aged 65 years and over (863 mg/day and 750 mg/day), but were below WHO recommendations of 1000 mg/day (49, 52).

Mean vitamin D intakes (including from supplements) were below the UK recommendations (10 µg/day) in all groups except women aged 65-74 years (mean intake 10.1 µg/day), and the proportion of men and women with serum vitamin D levels below the recommended 25 nmol/L was 18% and 15% in men and women aged 19-64 years, respectively; and 13% in both men and women aged 65 years and over (52).

Despite the importance of calcium and vitamin D to musculoskeletal health, effects of calcium and vitamin D intakes from dietary sources on hip fracture risk remain unclear. A 2015 systematic review reported that dietary calcium intake is not associated with risk of total or hip fractures (53). In contrast, a more recently published prospective cohort study in Sweden reported the lowest hip fracture rates among men and women with dietary calcium intakes above 800 mg/day and when adherence to the Mediterranean diet (a diet high in olive oil, fruit, vegetables, wholegrains, legumes, and oily fish; and low in red and processed meat and refined foods) was high (54). A recent Mendelian randomisation analysis found no support for a causal relationship between serum vitamin D levels and femoral neck BMD in 50,000 European adults (55). In contrast, a meta-analysis of 28 studies showed that compared to higher levels, lower serum vitamin D levels in older adults were associated with an increased hip fracture risk (52%) (56). However, heterogeneity between studies was high, and the role of vitamin D from dietary sources (as opposed to supplements or sun exposure) remains unclear. Therefore, previous meta-analyses on dietary calcium and vitamin D intakes and hip fracture risk were systematically reviewed in Chapter 2. The wider roles of calcium and vitamin D in musculoskeletal health were also reviewed elsewhere (57).

Protein is important to bone and muscle health. Protein feeding stimulates muscle protein synthesis (MPS); it is well-documented that if MPS rates outweigh muscle breakdown, this results in a net positive nitrogen balance that causes accrual of muscle mass, strength and function over time, especially when combined with exercise (58, 59). The relationship of protein with bone health is less clear. High protein intakes that induce a net positive nitrogen balance could negatively impact bone health by inducing chronic metabolic acidosis, leading to skeletal calcium loss to compensate (60). However, increases in urinary calcium excretion observed following a high protein diet are more likely a result of increased intestinal calcium absorption (61). Moreover, protein forms the structural matrix of bone and stimulates insulin-like growth factor-

1 (IGF-1) production whilst reducing parathyroid hormone (PTH) levels, leading to greater osteoblast formation and consequently higher whole-body BMD levels (62).

Current recommendations for adults of all ages are to consume 0.75 g/kg body weight/day of protein per day to maintain musculoskeletal health (63) (64). However, recent evidence suggests that higher protein intakes (around 1.2 g/kg body weight/day) in older adults may help attenuate age-related bone and muscle loss, since a decline in the anabolic response to protein consumption with age necessitates higher protein intakes to achieve the same skeletal and muscle acute and chronic response (58, 65-67). Two IOF-indorsed expert consensus reviews concluded that high dietary protein intakes above current recommendations (0.75 g/kg/day for the UK, and 0.8 g/kg/day for the US) are associated with a slower rate of bone loss, and are net beneficial for older adults, where insufficient intakes may cause greater health risks than protein excess (60, 68). It was concluded that higher dietary protein intakes may be associated with a lower risk of hip fractures, provided that dietary calcium intakes are adequate, but there are a limited number of studies on the topic. Specifically, no study has assessed this potential association in British adults. One cohort study in 2007 of around 35,000 British women and men found no clear association between protein intake and total fracture risk, but did not investigate protein intake in relation to hip fracture risk specifically (69). Further understanding of the role of protein in hip fracture risk is required before policy recommendations on protein intake in older adults can advance. Therefore, previously published meta-analyses summarising associations between dietary protein intake and hip fracture risk were systematically reviewed in Chapter 2, and the potential association was investigated in the UK Women's Cohort Study (UKWCS) in Chapter 3.

Several nutrients beyond calcium, vitamin D, and protein impact musculoskeletal health and BMI, and therefore could influence risk of hip fracture. For example, dietary intake of carbohydrates, saturated and unsaturated fats, B-vitamins, and several micronutrients have been associated with hip fracture risk in cross-sectional and case-control studies, but prospective evidence of these potential associations is limited (70-73). Therefore, all published prospective studies on dietary nutrient intakes (including protein, calcium, vitamin D, and several others) and hip fracture risk were systematically searched for and reviewed in Chapter 2, and these potential associations were investigated in the UKWCS in Chapter 3.

### 1.4.2 Foods and food groups

Foods that are abundant in nutrients important to musculoskeletal health may be associated with hip fracture risk. These foods represent readily-available targets for hip fracture prevention, and may be advantageous over single-nutrient approaches, as foods encompass the physiological effects of several nutrients acting independently and/or synergistically within a food matrix, which likely confers a greater benefit than the sum of individual nutrient effects (74, 75). Compared to pharmacological and supplement approaches to hip fracture prevention, food is a widely accessible and often affordable strategy for promoting nutritional status and musculoskeletal health.

Several foods may be related to hip fracture risk. Fruits and vegetables have the potential to reduce hip fracture risk by reducing oxidative stress and chronic inflammation, which can increase bone remodelling and attenuate bone loss (76). Similarly, tea and coffee are high in polyphenols and phytoestrogens which may reduce hip fracture risk through their positive effects on BMD, although caffeine within tea and coffee may inhibit bone formation, having the opposite effect on hip fracture risk (77). Animal-sourced foods including meat, fish, eggs, and dairy products may promote musculoskeletal health due to their high concentrations of protein, calcium, and vitamin D, alongside several other micronutrients with a role in bone and/or muscle health. In a recent two-year RCT in institutionalised older adults in Australia, consuming additional milk, yoghurt, and cheese to reach calcium intakes of 1100 mg/day, and protein intakes of 1.1 g/kg body weight/day, was associated with a 46% lower risk of hip fracture compared to the control group who consumed an average of ~700 mg/day calcium and ~0.9 g/kg body weight/day protein (78).

Despite the potential for many of these foods and food groups to influence hip fracture risk, for most foods, the number of published prospective studies investigating their relationship with hip fracture risk is small, and the certainty of evidence is very low. Studies are often limited by small sample sizes; risk of outcome misclassification due to subjective reporting of hip fractures; residual confounding; and study durations that are too short for a long-term effect of diet to be observed. Therefore, dietary guidelines for hip fracture prevention remain underdeveloped, and the potential links between many foods and hip fracture risk require further investigation. To

address this, in Chapter 2, all published meta-analyses of prospective cohort studies on food consumption and hip fracture risk were systematically reviewed. In Chapter 3, these potential associations were investigated in the UKWCS.

### 1.4.3 Dietary patterns: meat-free diets

Individual foods are consumed in different combinations over time as part of a dietary pattern. Just as foods may have effects beyond the sum of their individual nutrient components, dietary patterns may have physiological effects on health beyond the sum of their food components due to interactions between foods and their cumulative effects over time (75). Therefore, long-term habitual dietary patterns are important to health, and represent a modifiable target for hip fracture prevention that may be more clinically meaningful than targeting individual nutrients.

Plant-based diets are becoming more popular in developed countries due to perceived health benefits, concerns on the environmental effects of animal products, particularly red and processed meat, and for ethical or cultural reasons. An estimated 5% of the US population and 30% of India's population follow vegetarian or vegan diets (79, 80). NDNS data in 2012 showed that there are 1.7 million vegetarians (do not eat meat or fish) or vegans (do not eat meat, fish, eggs, or dairy products) in the UK (81). More recent NDNS data showed that the number of vegetarians and vegans in the UK has increased by 3% from 2008/09 to 2018/19 such that an estimated 5% of the UK population follow vegetarian or vegan diets (82).

Accumulating evidence suggests beneficial effects of vegetarian and vegan diets on the blood lipid profile, as well as a reduced risk of several non-communicable diseases, including obesity, diabetes, cancer, and cardiovascular disease (CVD) (83, 84). However, there are growing concerns over musculoskeletal health in individuals following meat-free diets. Previous studies have reported that vegetarians, on average, have a lower BMI than meat-eaters, and are less likely to be overweight or obese, and more likely to be underweight (85, 86). This may be beneficial for metabolic health, but may increase risk of falls and hip fracture (30). Observational studies show slightly lower total and site-specific BMD and measures of physical function and muscle strength in vegetarians compared to meat-eaters (85, 87, 88). It remains unclear if these differences are

clinically relevant, but as mentioned in Chapter 1: section 1.2.1, even small changes in BMD can have a clinically relevant impact on hip fracture risk (20).

Observational studies have also reported lower intakes of nutrients important to bone and muscle health in vegetarians, including protein, calcium, vitamin D, and several other micronutrients (89, 90). Meat and fish are abundant in nutrients related to bone and muscle health; omitting these foods from the diet without adequate replacement could adversely affect musculoskeletal health if nutrient requirements are not met. However, whether meat-free diets are associated with risk of hip fracture is unclear, and has only been studied in two previous prospective studies (91, 92). One prospective cohort study of British adults reported a higher risk of total fracture and hip fracture in vegetarians, vegans, and pescatarians over an average of 17.6 years of follow-up (91). Another prospective study in American seventh-day Adventists reported no clear difference in hip fracture risk between vegetarians and meat-eaters over an average of 8.4 years of follow-up (92). Additionally, once recent study in 126,000 UK Biobank participants reported no clear association between adherence to a healthy plant-based diet with hip fracture risk, though on average, even participants in the highest quartile of adherence to a healthy plant-based diet ate meat 5.6 times per week, therefore implications from that study cannot be applied to vegetarians (93).

## 1.5 Aims, hypotheses, and objectives

Many foods and nutrients impact musculoskeletal health, but prospective evidence associating their consumption with hip fracture risk is limited and inconsistent. More research is therefore needed to clarify the potential independent effects of several foods and nutrients on hip fracture risk. Additionally, further work is needed to determine if vegetarian diets in which consumption of these foods and nutrients often differs from diets including meat and fish are associated with hip fracture risk, and to determine factors responsible for any risk differences. This is particularly important as the global population ages, hip fracture prevalence rises, and the number of vegetarians increases.

### 1.5.1 Aim

This thesis had the following overarching aim:

*To better understand relationships between dietary habits and hip fracture risk in adults.*

The rationale for this work was to support the formulation of dietary recommendations for reducing hip fracture risk, providing important information on the adequacy of vegetarian diets in terms of hip fracture risk. This could result in fewer and delayed hip fractures.

### 1.5.2 Hypotheses

This thesis had two overall hypotheses:

1. Individual foods and nutrients are independently associated with hip fracture risk in British women.
2. Vegetarians are at a greater risk of hip fracture than regular meat-eaters in British men and women.

The null hypotheses were as follows:

1. Individual foods and nutrients are not independently associated with hip fracture risk in British women.
2. There is no difference in risk of hip fracture between vegetarians and regular meat-eaters in British men and women.

### 1.5.3 Objectives

These hypotheses motivated the following objectives per chapter:

**Chapter 2 Dietary risk factors for hip fracture in adults: An umbrella review of meta-analyses of prospective cohort studies**

1. To comprehensively summarise prospective evidence on diet and hip fracture risk, evaluating the quality of evidence.

**Chapter 3 Foods, nutrients, and hip fracture risk: a prospective study of middle-aged women**

1. To investigate associations between intake of foods, nutrients, and hip fracture risk in British women in the UK Women's Cohort Study.
2. To investigate the role of BMI as a potential effect modifier.

**Chapter 4 Risk of hip fracture in meat-eaters and vegetarians in the UK Women's Cohort Study**

1. To investigate hip fracture risk in occasional meat-eaters, pescatarians, and vegetarians compared to meat-eaters in the UK Women's Cohort Study.
2. To investigate the role of BMI as a potential effect modifier.

**Chapter 5 Risk of hip fracture in meat eaters, pescatarians, and vegetarians: A prospective cohort study of 413,914 UK Biobank participants**

1. To investigate hip fracture risk in occasional meat-eaters, pescatarians, and vegetarians compared to meat-eaters in British men and women in the UK Biobank cohort.
2. To investigate the role of anthropometric and biomarker factors as potential effect mediators of any observed risk differences.

## 1.6 References

1. Montero-Odasso M, van der Velde N, Martin FC, Petrovic M, Tan MP, Ryg J, et al. World guidelines for falls prevention and management for older adults: a global initiative. Age Ageing. 2022;51(9).

2. Prince MJ, Wu F, Guo Y, Gutierrez Robledo LM, O'Donnell M, Sullivan R, et al. The burden of disease in older people and implications for health policy and practice. Lancet. 2015;385(9967):549-62.

3. Dhanwal DK, Dennison EM, Harvey NC, Cooper C. Epidemiology of hip fracture: Worldwide geographic variation. Indian J Orthop. 2011;45(1):15-22.

4. Kanis JA, Odén A, McCloskey EV, Johansson H, Wahl DA, Cooper C. A systematic review of hip fracture incidence and probability of fracture worldwide. Osteoporos Int. 2012;23(9):2239-56.

5. National Osteoporosis Guideline Group. Section 2: Introduction to Osteoporosis and Fragility Fractures 2023 [Available from: https://www.nogg.org.uk/.

6. GBD 2019 Fracture Collaborators. Global, regional, and national burden of bone fractures in 204 countries and territories, 1990-2019: a systematic analysis from the Global Burden of Disease Study 2019. Lancet Healthy Longev. 2021;2(9):e580-e92.

7. Alexiou KI, Roushias A, Varitimidis SE, Malizos KN. Quality of life and psychological consequences in elderly patients after a hip fracture: a review. Clin Interv Aging. 2018;13:143-50.

8. Veronese N, Maggi S. Epidemiology and social costs of hip fracture. Injury. 2018;49(8):1458-60.

9. Manetti S, Turchetti G, Fusco F. Determining the cost-effectiveness requirements of an exoskeleton preventing second hip fractures using value of information. BMC Health Serv Res. 2020;20(1):955.

10. Adeyemi A, Delhougne G. Incidence and Economic Burden of Intertrochanteric Fracture: A Medicare Claims Database Analysis. JB JS Open Access. 2019;4(1):e0045.

11. Williamson S, Landeiro F, McConnell T, Fulford-Smith L, Javaid MK, Judge A, et al. Costs of fragility hip fractures globally: a systematic review and meta-regression analysis. Osteoporos Int. 2017;28(10):2791-800.

12. Healthcare Quality Improvement Partnership. National Hip Fracture Database Annual Report 2018. 2022.

13. Parkkari J, Kannus P, Palvanen M, Natri A, Vainio J, Aho H, et al. Majority of hip fractures occur as a result of a fall and impact on the greater trochanter of the femur: a prospective controlled hip fracture study with 206 consecutive patients. Calcif Tissue Int. 1999;65(3):183-7.

14. Hayes WC, Myers ER, Morris JN, Gerhart TN, Yett HS, Lipsitz LA. Impact near the hip dominates fracture risk in elderly nursing home residents who fall. Calcif Tissue Int. 1993;52(3):192-8.

15. Robinovitch SN, Inkster L, Maurer J, Warnick B. Strategies for avoiding hip impact during sideways falls. J Bone Miner Res. 2003;18(7):1267-73.

16. Mayhew PM, Thomas CD, Clement JG, Loveridge N, Beck TJ, Bonfield W, et al. Relation between age, femoral neck cortical stability, and hip fracture risk. Lancet. 2005;366(9480):129-35.

17. Swift CG. Prevention and management of hip fracture in older patients. Practitioner. 2011;255(1743):29-33, 3.

18. Curtis E, Litwic A, Cooper C, Dennison E. Determinants of Muscle and Bone Aging. J Cell Physiol. 2015;230(11):2618-25.

19. Nethander M, Coward E, Reimann E, Grahnemo L, Gabrielsen ME, Wibom C, et al. Assessment of the genetic and clinical determinants of hip fracture risk: Genome-wide association and Mendelian randomization study. Cell Rep Med. 2022;3(10):100776.

20. Bouxsein ML, Eastell R, Lui LY, Wu LA, de Papp AE, Grauer A, et al. Change in Bone Density and Reduction in Fracture Risk: A Meta-Regression of Published Trials. J Bone Miner Res. 2019;34(4):632-42.

21. Yeung SSY, Reijnierse EM, Pham VK, Trappenburg MC, Lim WK, Meskers CGM, et al. Sarcopenia and its association with falls and fractures in older adults: A systematic review and meta-analysis. J Cachexia Sarcopenia Muscle. 2019;10(3):485-500.

22. Martin FC, Ranhoff AH. Frailty and Sarcopenia. In: Falaschi P, Marsh D, editors. Orthogeriatrics: The Management of Older Patients with Fragility Fractures. Cham (CH): Springer Copyright 2021, The Author(s). 2021. p. 53-65.

23. Panel on Prevention of Falls in Older Persons AGSaBGS. Summary of the Updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons. J Am Geriatr Soc. 2011;59(1):148-57.

24. Denk K, Lennon S, Gordon S, Jaarsma RL. The association between decreased hand grip strength and hip fracture in older people: A systematic review. Exp Gerontol. 2018;111:1-9.

25. Kim KH, Lee JH, Lim EJ. Weak psoas and spine extensors potentially predispose to hip fracture. Hip Int. 2021;31(3):430-4.

26. Lang T, Cauley JA, Tylavsky F, Bauer D, Cummings S, Harris TB. Computed tomographic measurements of thigh muscle cross-sectional area and attenuation coefficient predict hip fracture: the health, aging, and body composition study. J Bone Miner Res. 2010;25(3):513-9.

27. Harvey NC, Odén A, Orwoll E, Lapidus J, Kwok T, Karlsson MK, et al. Measures of Physical Performance and Muscle Strength as Predictors of Fracture Risk Independent of FRAX, Falls, and

aBMD: A Meta-Analysis of the Osteoporotic Fractures in Men (MrOS) Study. J Bone Miner Res. 2018;33(12):2150-7.

28. Rikkonen T, Poole K, Sirola J, Sund R, Honkanen R, Kröger H. Long-term effects of functional impairment on fracture risk and mortality in postmenopausal women. Osteoporos Int. 2018;29(9):2111-20.

29. Shapses SA, Sukumar D. Bone metabolism in obesity and weight loss. Annu Rev Nutr. 2012;32:287-309.

30. Caffarelli C, Alessi C, Nuti R, Gonnelli S. Divergent effects of obesity on fragility fractures. Clin Interv Aging. 2014;9:1629-36.

31. Kim SH, Yi SW, Yi JJ, Kim YM, Won YJ. Association Between Body Mass Index and the Risk of Hip Fracture by Sex and Age: A Prospective Cohort Study. J Bone Miner Res. 2018;33(9):1603-11.

32. Trevisan C, Crippa A, Ek S, Welmer AK, Sergi G, Maggi S, et al. Nutritional Status, Body Mass Index, and the Risk of Falls in Community-Dwelling Older Adults: A Systematic Review and Meta-Analysis. J Am Med Dir Assoc. 2019;20(5):569-82.e7.

33. Armstrong ME, Spencer EA, Cairns BJ, Banks E, Pirie K, Green J, et al. Body mass index and physical activity in relation to the incidence of hip fracture in postmenopausal women. J Bone Miner Res. 2011;26(6):1330-8.

34. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX and the assessment of fracture probability in men and women from the UK. Osteoporos Int. 2008;19(4):385-97.

35. Søgaard AJ, Holvik K, Omsland TK, Tell GS, Dahl C, Schei B, et al. Age and Sex Differences in Body Mass Index as a Predictor of Hip Fracture: A NOREPOS Study. Am J Epidemiol. 2016;184(7):510-9.

36. Song J, Zhang R, Lv L, Liang J, Wang W, Liu R, et al. The Relationship Between Body Mass Index and Bone Mineral Density: A Mendelian Randomization Study. Calcif Tissue Int. 2020;107(5):440-5.

37. Chan MY, Frost SA, Center JR, Eisman JA, Nguyen TV. Relationship between body mass index and fracture risk is mediated by bone mineral density. J Bone Miner Res. 2014;29(11):2327-35.

38. Cooper C, Campion G, Melton LJ, 3rd. Hip fractures in the elderly: a world-wide projection. Osteoporos Int. 1992;2(6):285-9.

39. Michaëlsson K, Melhus H, Ferm H, Ahlbom A, Pedersen NL. Genetic liability to fractures in the elderly. Arch Intern Med. 2005;165(16):1825-30.

40. International Osteoporosis Foundation. Epidemiology of osteoporosis and fragility fractures 2023 [Available from: https://www.osteoporosis.foundation/.

41. Kemmler W, Shojaa M, Kohl M, von Stengel S. Effects of Different Types of Exercise on Bone Mineral Density in Postmenopausal Women: A Systematic Review and Meta-analysis. Calcif Tissue Int. 2020;107(5):409-39.

42. Lu L, Mao L, Feng Y, Ainsworth BE, Liu Y, Chen N. Effects of different exercise training modes on muscle strength and physical performance in older people with sarcopenia: a systematic review and meta-analysis. BMC Geriatr. 2021;21(1):708.

43. Sherrington C, Fairhall NJ, Wallbank GK, Tiedemann A, Michaleff ZA, Howard K, et al. Exercise for preventing falls in older people living in the community. Cochrane Database Syst Rev. 2019;1(1):Cd012424.

44. Hoffmann I, Kohl M, von Stengel S, Jakob F, Kerschan-Schindl K, Lange U, et al. Exercise and the prevention of major osteoporotic fractures in adults: a systematic review and meta-analysis with special emphasis on intensity progression and study duration. Osteoporos Int. 2023;34(1):15-28.

45. Yao P, Bennett D, Mafham M, Lin X, Chen Z, Armitage J, et al. Vitamin D and Calcium for the Prevention of Fracture: A Systematic Review and Meta-analysis. JAMA Netw Open. 2019;2(12):e1917789.

46. Feskanich D, Willett WC, Colditz GA. Calcium, vitamin D, milk consumption, and hip fractures: a prospective study among postmenopausal women. Am J Clin Nutr. 2003;77(2):504-11.

47. Ceglia L. Vitamin D and its role in skeletal muscle. Curr Opin Clin Nutr Metab Care. 2009;12(6):628-33.

48. Gunton JE, Girgis CM. Vitamin D and muscle. Bone reports. 2018;8:163-7.

49. Cormick G, Belizán JM. Calcium Intake and Health. Nutrients. 2019;11(7).

50. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(7):1911-30.

51. British Nutrition Foundation. Nutrition requirements. 2021. [Available from: https://www.nutrition.org.uk/media/nmmewdug/nutrition-requirements.pdf].

52. Public Health England. NDNS: results from years 9 to 11 (2016 to 2017 and 2018 to 2019). 2020.

53. Bolland MJ, Leung W, Tai V, Bastin S, Gamble GD, Grey A, et al. Calcium intake and risk of fracture: systematic review. Bmj. 2015;351:h4580.

54. Warensjö Lemming E, Byberg L, Höijer J, Larsson SC, Wolk A, Michaëlsson K. Combinations of dietary calcium intake and mediterranean-style diet on risk of hip fracture: A longitudinal cohort study of 82,000 women and men. Clin Nutr. 2021;40(6):4161-70.

55. Tang Y, Wei F, Yu M, Zhou H, Wang Y, Cui Z, et al. Absence of causal association between Vitamin D and bone mineral density across the lifespan: a Mendelian randomization study. Sci Rep. 2022;12(1):10408.

56. Habibi Ghahfarrokhi S, Mohammadian-Hafshejani A, Sherwin CMT, Heidari-Soureshjani S. Relationship between serum vitamin D and hip fracture in the elderly: a systematic review and meta-analysis. J Bone Miner Metab. 2022;40(4):541-53.

57. Webster J, Dalla Via J, Langley C, Smith C, Sale C, Sim M. Nutritional strategies to optimise musculoskeletal health for fall and fracture prevention: Looking beyond calcium, vitamin D and protein. Bone Reports. 2023:101684.

58. Deer RR, Volpi E. Protein intake and muscle function in older adults. Curr Opin Clin Nutr Metab Care. 2015;18(3):248-53.

59. Morton RW, Murphy KT, McKellar SR, Schoenfeld BJ, Henselmans M, Helms E, et al. A systematic review, meta-analysis and meta-regression of the effect of protein supplementation on resistance training-induced gains in muscle mass and strength in healthy adults. Br J Sports Med. 2018;52(6):376-84.

60. Shams-White MM, Chung M, Du M, Fu Z, Insogna KL, Karlsen MC, et al. Dietary protein and bone health: a systematic review and meta-analysis from the National Osteoporosis Foundation. Am J Clin Nutr. 2017;105(6):1528-43.

61. Calvez J, Poupin N, Chesneau C, Lassale C, Tomé D. Protein intake, calcium balance and health consequences. Eur J Clin Nutr. 2012;66(3):281-95.

62. Groenendijk I, Grootswagers P, Santoro A, Franceschi C, Bazzocchi A, Meunier N, et al. Protein intake and bone mineral density: Cross-sectional relationship and longitudinal effects in older adults. J Cachexia Sarcopenia Muscle. 2023;14(1):116-25.

63. Joint WHO/FAO/UNU Expert Consultation. Protein and amino acid requirements in human nutrition. World Health Organ Tech Rep Ser. 2007(935):1-265, back cover.

64. Jäger R, Kerksick CM, Campbell BI, Cribb PJ, Wells SD, Skwiat TM, et al. International Society of Sports Nutrition Position Stand: protein and exercise. J Int Soc Sports Nutr. 2017;14:20.

65. Deutz NE, Bauer JM, Barazzoni R, Biolo G, Boirie Y, Bosy-Westphal A, et al. Protein intake and exercise for optimal muscle function with aging: recommendations from the ESPEN Expert Group. Clin Nutr. 2014;33(6):929-36.

66. Kiesswetter E, Sieber CC, Volkert D. Protein intake in older people : Why, how much and how? Z Gerontol Geriatr. 2020;53(4):285-9.

67. Phillips SM, Chevalier S, Leidy HJ. Protein "requirements" beyond the RDA: implications for optimizing health. Appl Physiol Nutr Metab. 2016;41(5):565-72.

68. Rizzoli R, Biver E, Bonjour JP, Coxam V, Goltzman D, Kanis JA, et al. Benefits and safety of dietary protein for bone health-an expert consensus paper endorsed by the European Society for Clinical and Economical Aspects of Osteopororosis, Osteoarthritis, and Musculoskeletal Diseases and by the International Osteoporosis Foundation. Osteoporos Int. 2018;29(9):1933-48.

69. Key TJ, Appleby PN, Spencer EA, Roddam AW, Neale RE, Allen NE. Calcium, diet and fracture risk: a prospective study of 1898 incident fractures among 34 696 British women and men. Public Health Nutr. 2007;10(11):1314-20.

70. Mozaffari H, Daneshzad E, Azadbakht L. Dietary carbohydrate intake and risk of bone fracture: a systematic review and meta-analysis of observational studies. Public Health. 2020;181:102-9.

71. Mozaffari H, Djafarian K, Mofrad MD, Shab-Bidar S. Dietary fat, saturated fatty acid, and monounsaturated fatty acid intakes and risk of bone fracture: a systematic review and meta-analysis of observational studies. Osteoporos Int. 2018;29(9):1949-61.

72. Macêdo LLG, Carvalho C, Cavalcanti JC, Freitas B. Vitamin B12, bone mineral density and fracture risk in adults: A systematic review. Rev Assoc Med Bras (1992). 2017;63(9):801-9.

73. Farsinejad-Marj M, Saneei P, Esmaillzadeh A. Dietary magnesium intake, bone mineral density and risk of fracture: a systematic review and meta-analysis. Osteoporos Int. 2016;27(4):1389-99.

74. Benetos IS, Babis GC, Zoubos AB, Benetou V, Soucacos PN. Factors affecting the risk of hip fractures. Injury. 2007;38(7):735-44.

75. Warensjö Lemming E, Byberg L. Is a Healthy Diet Also Suitable for the Prevention of Fragility Fractures? Nutrients. 2020;12(9).

76. Brondani JE, Comim FV, Flores LM, Martini LA, Premaor MO. Fruit and vegetable intake and bones: A systematic review and meta-analysis. PLoS One. 2019;14(5):e0217223.

77. Sheng J, Qu X, Zhang X, Zhai Z, Li H, Liu X, et al. Coffee, tea, and the risk of hip fracture: a meta-analysis. Osteoporos Int. 2014;25(1):141-50.

78. Iuliano S, Poon S, Robbins J, Bui M, Wang X, De Groot L, et al. Effect of dietary sources of calcium and protein on hip fractures and falls in older adults in residential care: cluster randomised controlled trial. Bmj. 2021;375:n2364.

79. Le LT, Sabaté J. Beyond meatless, the health effects of vegan diets: findings from the Adventist cohorts. Nutrients. 2014;6(6):2131-47.

80. Shridhar K, Dhillon PK, Bowen L, Kinra S, Bharathi AV, Prabhakaran D, et al. Nutritional profile of Indian vegetarian diets--the Indian Migration Study (IMS). Nutr J. 2014;13:55.

81. Public Health England. NDNS: results from Years 1 to 4 (combined). 2014.

82. Stewart C, Piernas C, Cook B, Jebb SA. Trends in UK meat consumption: analysis of data from years 1-11 (2008-09 to 2018-19) of the National Diet and Nutrition Survey rolling programme. Lancet Planet Health. 2021;5(10):e699-e708.

83. Oussalah A, Levy J, Berthezène C, Alpers DH, Guéant JL. Health outcomes associated with vegetarian diets: An umbrella review of systematic reviews and meta-analyses. Clin Nutr. 2020;39(11):3283-307.

84. Selinger E, Neuenschwander M, Koller A, Gojda J, Kühn T, Schwingshackl L, et al. Evidence of a vegan diet for health benefits and risks – an umbrella review of meta-analyses of observational and clinical studies. Critical Reviews in Food Science and Nutrition. 2022:1-11.

85. Tong TY, Key TJ, Sobiecki JG, Bradbury KE. Anthropometric and physiologic characteristics in white and British Indian vegetarians and nonvegetarians in the UK Biobank. Am J Clin Nutr. 2018;107(6):909-20.

86. Barnard ND, Levin SM, Yokoyama Y. A systematic review and meta-analysis of changes in body weight in clinical trials of vegetarian diets. J Acad Nutr Diet. 2015;115(6):954-69.

87. Iguacel I, Miguel-Berges ML, Gómez-Bruton A, Moreno LA, Julián C. Veganism, vegetarianism, bone mineral density, and fracture risk: a systematic review and meta-analysis. Nutr Rev. 2019;77(1):1-18.

88. Chan H, Ribeiro RV, Haden S, Hirani V. Plant-Based Dietary Patterns, Body Composition, Muscle Strength and Function in Middle and Older Age: A Systematic Review. J Nutr Health Aging. 2021;25(8):1012-22.

89. Tucker KL. Vegetarian diets and bone status. Am J Clin Nutr. 2014;100 Suppl 1:329s-35s.

90. Davey GK, Spencer EA, Appleby PN, Allen NE, Knox KH, Key TJ. EPIC-Oxford: lifestyle characteristics and nutrient intakes in a cohort of 33 883 meat-eaters and 31 546 non meat-eaters in the UK. Public Health Nutr. 2003;6(3):259-69.

91. Tong TYN, Appleby PN, Armstrong MEG, Fensom GK, Knuppel A, Papier K, et al. Vegetarian and vegan diets and risks of total and site-specific fractures: results from the prospective EPIC-Oxford study. BMC Med. 2020;18(1):353.

92. Thorpe DL, Beeson WL, Knutsen R, Fraser GE, Knutsen SF. Dietary patterns and hip fracture in the Adventist Health Study 2: combined vitamin D and calcium supplementation mitigate increased hip fracture risk among vegans. Am J Clin Nutr. 2021;114(2):488-95.

93. Thompson AS, Tresserra-Rimbau A, Karavasiloglou N, Jennings A, Cantwell M, Hill C, et al. Association of Healthful Plant-based Diet Adherence With Risk of Mortality and Major Chronic Diseases Among Adults in the UK. JAMA Netw Open. 2023;6(3):e234714.

# Chapter 2 Dietary risk factors for hip fracture in adults: An umbrella review of meta-analyses of prospective cohort studies

**James Webster[1], Catherine E. Rycroft[1], Darren C. Greenwood[2], and Janet E. Cade[1]**

1 School of Food Science and Nutrition, University of Leeds, Leeds, LS2 9JT.

2 School of Medicine, University of Leeds, Leeds, LS2 9JT.

Published: PLoS One. 2021. 16(11): p.e0259144. https://doi.org/10.1371/journal.pone.0259144

**This chapter is an exact copy of the journal paper referred to above.**

## 2.1 Abstract

**Aim:** To summarise the totality of evidence regarding dietary risk factors for hip fracture in adults, evaluating the quality of evidence, to provide recommendations for practice and further research.

**Design:** Systematic review of meta-analyses of prospective cohort studies.

**Eligibility criteria:** Systematic reviews with meta-analyses reporting summary risk estimates for associations between hip fracture incidence and dietary exposures including oral intake of a food, food group, beverage, or nutrient, or adherence to dietary patterns.

**Information sources:** Medline, Embase, Web of Science, and the Cochrane Library from inception until November 2020.

**Data synthesis:** The methodological quality of systematic reviews and meta-analyses was assessed using AMSTAR-2, and the quality of evidence for each association was assessed using GRADE. Results were synthesised descriptively.

**Results:** Sixteen systematic reviews were identified, covering thirty-four exposures, including dietary patterns (n = 2 meta-analyses), foods, food groups, or beverages (n = 16), macronutrients (n = 3), and micronutrients (n = 13). Identified meta-analyses included 6,282 to 3,730,424 participants with between 322 and 26,168 hip fractures. The methodological quality (AMSTAR-2) of all systematic reviews was low or critically low. The quality of evidence (GRADE) was low for an inverse association between hip fracture incidence and intake of fruits and vegetables combined (adjusted summary relative risk for higher vs lower intakes: 0.92 [95% confidence interval: 0.87 to 0.98]), and very low for the remaining thirty-three exposures.

**Conclusion:** Dietary factors may play a role in the primary prevention of hip fracture, but the methodological quality of systematic reviews and meta-analyses was below international standards, and there was a lack of high-quality evidence. More long-term cohort studies reporting absolute risks and robust, well-conducted meta-analyses with dose-response information are needed before policy guidelines can be formed.

**Systematic review registration:** PROSPERO CRD42020226190

## 2.2 Introduction

Fragility fracture is a global health issue that predominantly occurs in elderly populations (1). Hip fracture in particular affects 18% of women and 6% of men globally; because the global population continues to age and grow, cases are projected to rise from 1.26 million in 1990 to 4.5 million by 2050 (2). Hip fracture patients are at increased risk for other health problems, such as a decreased quality of life due to impaired mobility, and increased morbidity and mortality (1, 3, 4). The economic burden is also high because of direct costs due to long hospitalisation and rehabilitation periods, and additional indirect costs associated with comorbidities (2). Preventing hip fracture is therefore imperative to global public health clinically and economically.

Both genetic and environmental components contribute to the risk of hip fracture, including the potential for risk reduction through diet modification (3). Associations between an array of dietary factors, including dietary patterns, foods, food groups, beverages, macronutrients, and micronutrients and hip fracture incidence have been the subject of previously published systematic reviews and meta-analyses. However, their methodological quality and the quality of evidence for most dietary factor-hip fracture associations are uncertain.

Umbrella reviews are one way of synthesising and critically appraising the quality of evidence from systematic reviews and meta-analyses to provide a comprehensive overview of a given topic with recommendations for practice or further research (5). One umbrella review published in 2007 has synthesised the generic risk factors for hip fracture, including dietary factors (3). Calcium combined with vitamin D supplementation and increasing dietary protein and tea intake decreased the risk of hip fracture, whilst alcohol, vitamin A, and caffeine intake increased the risk. However, their evaluation of the quality of evidence for these associations was based only on the consistency of results, and did not account for potential biases or imprecision. A recent scoping review also synthesised the evidence for non-pharmacological interventions in preventing hip fracture, but evidence for diet was restricted to nutritional supplementation in older adults, with little to no evidence on dietary patterns or dietary intake of foods or nutrients and hip fracture risk (4). Therefore, we aimed to summarise the totality of evidence regarding

dietary risk factors for hip fracture in adults, evaluating the quality of evidence, to provide recommendations for practice or further research.

## 2.3 Methods

The review protocol was registered in the International Prospective Register of Systematic Reviews (CRD42020226190). We followed the latest Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (**Appendix A: Tables A1** and **A2**), and adhered to the guidance suggested by Fusar-Poli and Radua (2018) for the conduct of umbrella reviews (6, 7).

### 2.3.1 Eligibility criteria

Articles were eligible if they were peer-reviewed and written in the English language. Eligible study designs were systematic reviews with meta-analysis of prospective cohort studies. Meta-analyses in any adult population (> 18 years) of any ethnicity, sex, or country were eligible. We included meta-analyses that pooled relative risks (RR), odds ratios (OR), or hazard ratios (HR) from studies assessing the relationship between a given dietary exposure and hip fracture incidence, where the dietary exposure was oral intake of a food, food group, beverage, or nutrient, or adherence to dietary patterns, such as the Mediterranean diet (MD).

Articles were excluded if they were duplicates, non-review articles, umbrella reviews, cohort pooling projects, or lacked a meta-analysis component (where no summary effect estimate was reported). Abstracts and conference proceedings were excluded. When a meta-analysis had one or more updates, the latest version was included and earlier versions were excluded, since the updated version usually contains more primary studies. Meta-analyses including case-control or cross-sectional studies were excluded unless a summary effect estimate was obtainable from cohort studies only. Cross-sectional and case-control studies are especially prone to selection and recall bias, thus were excluded to increase the quality of observational evidence. Meta-analyses where the population were non-adults, animal subjects, or were restricted to a specific patient population, such as diabetic or osteoarthritic patients, were excluded to enable wider generalisation of findings. We also excluded articles that assessed total fracture as the outcome

without reporting a summary effect estimate for hip fracture. Meta-analyses of non-dietary exposures including supplements or exposures measured using biomarkers rather than dietary intake were excluded, such as those associating serum vitamin D levels with hip fracture incidence. Meta-analyses assessing hip fracture treatment or aftercare rather than prevention or risk were excluded to keep in line with our objectives.

### 2.3.2 Information sources and search strategy

A systematic literature search of Medline, Embase, Web of Science, and the Cochrane Library of Systematic Reviews from inception until November 2020 was conducted. The search strategy comprised dietary exposure terms (foods, food groups, beverages, nutrients, and dietary patterns) combined with outcome (hip fracture) and review terms. The full search strategy is detailed in **Appendix A: Table A3**. Returned umbrella reviews and reference lists of eligible full texts were scanned for potentially relevant articles. We did not search the grey literature or trial registries for additional articles.

### 2.3.3 Screening and study selection

Two reviewers (JW and CR) independently screened the title and abstract of returned articles, and subsequently reviewed potentially relevant full-text articles for eligibility according to the pre-specified eligibility criteria. Discrepancies were resolved by consensus. Agreement between authors regarding eligible articles was assessed using Cohen's kappa statistic, and was interpreted using the Altman scale (8). In cases where multiple meta-analyses addressed the same association, we selected and included only the highest quality meta-analysis for each association identified based on our quality assessment to minimise risk of bias and to prevent double-counting primary studies. If multiple meta-analyses were judged to be of equal quality (had the same overall methodological quality and number of critical and non-critical flaws), the one with dose-response information was selected. If multiple meta-analyses still remained for one association, the meta-analysis with the greater number of total participants was selected for inclusion. The remaining eligible meta-analyses were excluded. The screening process was managed using EndNote (X9).

### 2.3.4 Data extraction

Outcome data was independently extracted from eligible articles by two reviewers (JW and CR), with 83% agreement, and disagreements resolved by consensus. Study characteristics were extracted by one reviewer (JW). The characteristics, design, and exposure and outcome details of eligible systematic reviews were extracted. Review characteristics included: first author name, date of publication, number of primary studies included and their design, population characteristics, number of total subjects, number of subjects in each exposure category if reported, and the range in follow-up durations. Information extracted concerning the review and meta-analytic design included: number of databases searched with date ranges, objectives, methods used for meta-analysis (fixed or random-effects models), and sources of funding. Exposure details extracted from each review included: dietary exposures studied, dietary assessment methods used across primary studies per exposure (such as validated or non-validated food frequency questionnaires; FFQs), and the type of comparisons made with cut-off points used for categorical comparisons (i.e., high vs low) and increments used for linear dose-response comparisons per exposure. If categorical and dose-response comparisons were reported, only the latter was extracted. Outcome details extracted were: hip fracture assessment methods used across primary studies (such as self-reported questionnaires or review of medical records), total number of incident hip fracture cases at the latest point of follow-up, maximally adjusted summary effect estimates (OR, HR, or RR) with 95% confidence intervals (95% CI), estimates of heterogeneity, risk of small study effects, and confounders included in multivariable models of primary studies. Full risk of bias assessments were also extracted from each review at the domain level, and review authors were contacted for this data if it was not reported.

### 2.3.5 Quality assessment

Two reviewers (JW and CR) independently assessed the methodological quality of eligible systematic reviews with meta-analyses using the validated AMSTAR-2 tool (a revised measurement tool to assess the methodological quality of systematic reviews) (9). Discrepancies were resolved by consensus. Overall quality scores per review were determined by the number of critical and non-critical weaknesses. Of the domains covered by AMSTAR-2, those considered critical were: establishment of an a priori protocol (item 2), adequacy of the literature search

(item 4), justification for excluding studies (item 7), adequate risk of bias assessment (item 9), appropriate meta-analytic methods (item 11), consideration of risk of bias when interpreting results (item 13), and risk of publication bias (item 15) (9). Item 9 was considered a critical flaw if risk of bias assessments were not presented in full. Item 11 was considered a critical flaw if meta-analyses lacked dose-response information despite being appropriate, or combined effect sizes inappropriately. The methodological quality of reviews was considered high (< 1 non-critical weakness), moderate (> 1 non-critical weakness), low (1 critical weakness with or without non-critical weaknesses), or critically low (> 1 critical weakness with or without non-critical weaknesses) (9).

The quality of evidence for each dietary exposure-hip fracture association was then evaluated by applying the Cochrane GRADE tool (Grading of Recommendations for Assessment, Developing and Evaluation) based on evidence from the included meta-analyses (one per association) using the GRADEpro software and adhering to the GRADE handbook (10, 11). Evidence was classified as high, moderate, low, or very low quality. If review authors did not present risk of bias assessments of primary studies in full, a serious risk was assumed. If no risk of bias assessment was reported, a very serious risk was assumed.

### 2.3.6 Data synthesis

The findings of included meta-analyses (one per association) were tabulated and synthesised descriptively. We present adjusted summary effect estimates (RR, OR, or HR) with 95% CIs as reported in each meta-analysis, with $I^2$ values for heterogeneity, and Egger's p values for risk of publication bias.

## 2.4 Results

### 2.4.1 Study selection

The systematic search retrieved 841 publications, and two additional studies were found manually (**Figure 2.1**) (12, 13). Of 601 unique articles, 138 full-texts were screened, and twenty-eight systematic reviews met the inclusion criteria, including sixty-two summary effect sizes. Agreement between authors regarding eligible articles was moderate (Cohen's k = 0.46). A list

of excluded articles with reasons for their exclusion is documented in **Appendix A: Table A4**. After selecting one meta-analysis per identified dietary exposure, sixteen systematic reviews with thirty-four summary effect estimates on dietary patterns (n=2), foods, food groups, or beverages (n=16), macronutrients (n=3), and micronutrients (n=13) remained and were included in the descriptive analysis regarding risk of hip fracture.

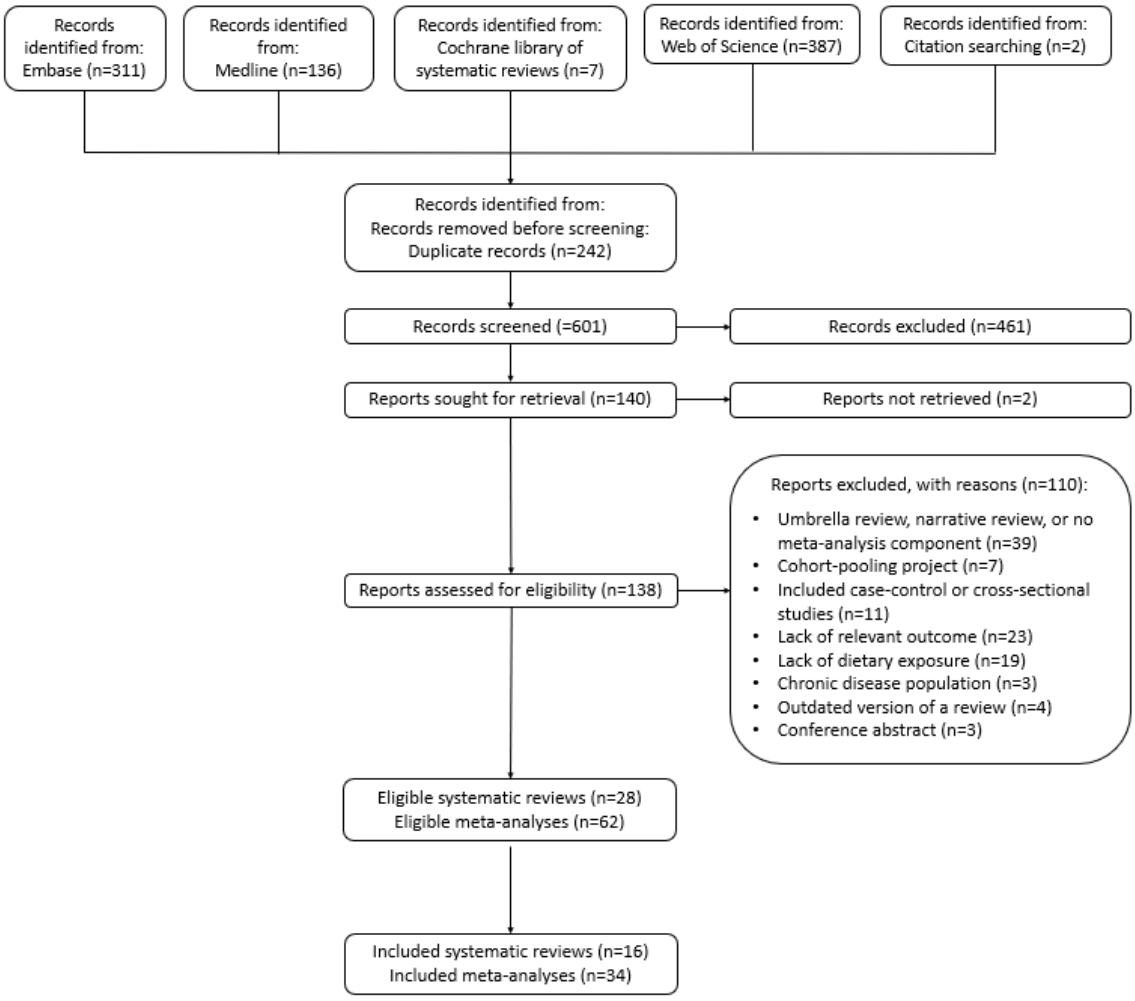



**Figure 2.1: PRISMA flow diagram of the study selection process.**

### 2.4.2 Characteristics of eligible studies

Characteristics and findings of the twenty-eight eligible reviews are shown in **Appendix A: Table A5**. Thirty-four unique exposures were identified, including: adherence to the alternative healthy eating index (AHEI) (14), adherence to the MD (15), dairy (16-18), milk (16-20), yogurt (16, 18, 20, 21), cheese (16, 18, 20, 21), fruits (22), vegetables (22), fruits and vegetables combined (22, 23), tea (24), coffee (13, 24, 25), alcohol (any, light, moderate, and heavy) (26), wine (26), beer (26), liquor (spirits) (26), total protein (27-29), animal protein (27, 29), vegetable protein (27, 29), dietary calcium (30-33), vitamin C (34, 35), vitamin A (36, 37), carotenoids (38), retinol (36, 37), a-carotene (38), b-carotene (36-38), b-cryptoxanthin (38), lycopene (38), lutein/zeaxanthin (38), alpha lipoic acid (ALA) (39), eicosapentaenoic acid with docosahexaenoic acid (EPA with DHA) (39), and antioxidant vitamin intake (40). Multiple meta-analyses were retrieved for fourteen exposures, with only the highest quality meta-analysis retained per exposure. Only one meta-analysis was retrieved for: AHEI adherence (14), MD adherence (15), fruits (22), vegetables (22), tea (24), all alcohol associations (26), carotenoids (38), a-carotene (38), b-cryptoxanthin (38), lycopene (38), lutein/zeaxanthin (38), ALA (39), EPA with DHA (39), and antioxidant vitamin intake (40). Most meta-analyses that investigated the same exposure included the same primary studies, with differences attributable to varying years of publication and eligibility criterion amongst meta-analyses. Nineteen systematic reviews reported their sources of funding, three declared no funding (21, 25), and six provided no information on funding (**Appendix A: Table A6**) (17, 22, 31, 33, 34, 39).

### 2.4.3 Characteristics of included studies

When restricting analyses to one meta-analysis per association, the number of primary studies ranged from 2 to 18, with follow-up durations of 3 to 32 years. The total sample size in each meta-analysis ranged from 6,282 to 3,730,424 participants with 322 to 26,168 cases. Twenty-nine meta-analyses compared categories of consumption (e.g., high vs low), and five provided linear dose-response information (13, 15, 18, 20, 30). The most common exposure measurement methods were validated or non-validated FFQs. Other techniques included 24-hour recalls and 7-day food records. Four meta-analyses provided no exposure measurement method information (27, 40). Hip fracture was ascertained mostly by self-report (questionnaires or

interviews) and review of medical records. Other techniques included radiologic or x-ray exams, or linkage to hospital registers (such as the National Danish Patient Registry). Seven meta-analyses did not report hip fracture ascertainment techniques used in primary studies (23, 27, 30, 40). Most meta-analyses included middle-aged to older adults of any sex or ethnicity. One meta-analysis regarding dairy intake was conducted in healthy non-Hispanic whites (18). Three meta-analyses regarding ALA, EPA with DHA, and antioxidant vitamin intake excluded participants with a history of fracture (39, 40). whilst the remaining studies did not report prior fracture as an exclusion criteria. Publication dates ranged from 2007 to 2020.

Each meta-analysis included cohort studies that adjusted for a variety of confounders (**Appendix A: Table A5**). Summary effect estimates were adjusted for confounders in either all primary cohort studies in a meta-analysis (fully adjusted), or in some of the included primary cohort studies (partly adjusted). Confounders that were fully adjusted for included: age (n=26 meta-analyses), smoking (n=14), Body mass Index (BMI; n=13), total energy intake (n=11), physical activity (n=10), calcium intake (n=5), calcium and vitamin D supplementation (n=3), alcohol intake (n=2), hormone replacement therapy (n=1), and height (n=1). All meta-analyses except one included studies adjusted for or stratified by sex, or included single-sex studies (23). Four meta-analyses presented summary effect estimates that were not fully adjusted for any potential confounders, corresponding to the following exposures: adherence to the AHEI (14), milk (20), protein (27), and dietary calcium (30). Summary effect estimates were often partly adjusted for weight, protein intake, caffeine intake, history of fracture or fall, and chronic disease.

### 2.4.4 Methodological quality

The overall and item-specific AMSTAR-2 ratings for each eligible systematic review and their meta-analyses are shown in **Appendix A: Table A7**. Of the sixteen included systematic reviews, the methodological quality was low in one (20), and critically low in the remaining fifteen reviews. Three summary effect estimates were extracted from the low-quality review regarding milk, yogurt, and cheese consumption based on cohort studies (20). Effect estimates for the remaining dietary exposures were reported from critically low-quality reviews. Common critical weaknesses in reviews were that methods were not established a priori; excluded studies were not listed with justification for their exclusion; risk of bias assessments were mostly inadequate;

and meta-analytic methods used were often inappropriate, such as when meta-analyses compared 'high vs low' dietary exposure categories using varying thresholds for these categories from each primary cohort study. All risk of bias assessments used the Newcastle-Ottawa scale, which does not assess the potential for bias due to selective reporting or changes in dietary exposure classifications throughout follow-up (41). Nine included reviews did not report domain-specific risk of bias assessments (14, 15, 22, 34, 37-40), and four reviews did not report any risk of bias assessment (13, 24, 26, 30).

### 2.4.5 Dietary exposures and hip fracture: associations and quality of evidence

Adjusted summary effect estimates and the quality of evidence for each exposure regarding risk of hip fracture are summarised in Tables 2.1-2.4. Of thirty-four potential diet-hip fracture associations, the quality of evidence for each was graded as low (n=1) (23) and very low (n=33), respectively. No association was considered as moderate or high-quality evidence. The quality of evidence for all associations except combined fruits and vegetables intake and hip fracture incidence was downgraded from low to very low due to a serious or very serious risk of bias amongst primary studies (23). For sixteen associations, a serious risk of bias was assumed because their meta-analyses did not report risk of bias assessments at the domain level (i.e., potential biases from specific sources). Twenty-two associations were further downgraded due to inconsistency (n=8), imprecision (n=8), or both (n=6). No association was upgraded in quality for any reason. Full quality of evidence assessments using GRADE are shown in **Appendix A: Table A8**.

**Table 2.1: Summary characteristics and findings of meta-analyses of cohort studies assessing associations between dietary patterns and hip fracture risk.**

| Exposure | Author (year) | n studies | Follow-up range (years) | Comparison | Summary effect estimate (95% CI) | $I^2$ (%) | Egger's p-value | AMSTAR | GRADE |
|---|---|---|---|---|---|---|---|---|---|
| Alternative healthy eating index | Panahande et al. (2018) | 4 | 10-32 | High vs low | RR: 0.83 (0.71, 0.97) | N/A | 0.19 | Critically low | ⊕◯◯◯ |
| Mediterranean diet | Malmir et al. (2018a) | 4 | 8-16 | Per 1 score increase in adherence | RR: 0.95 (0.92, 0.98) | 68* | 0.78 | Critically low | ⊕◯◯◯ |

N/A = not applicable or available; * = significant heterogeneity; RR = relative risk; 95% CI = 95% confidence interval; ⊕◯◯◯ = very low quality of evidence.

**Table 2.2: Summary characteristics and findings of meta-analyses of cohort studies assessing associations between dietary intake of foods, food groups, and beverages and hip fracture risk.**

| Exposure | Author (year) | n studies | Follow-up range (years) | Comparison | Summary effect estimate (95% CI) | $I^2$ (%) | Egger's p-value | AMSTAR | GRADE |
|---|---|---|---|---|---|---|---|---|---|
| Total dairy | Matia-Martin et al. (2019) | 4 | 8-22 | Per 'increment' increase | RR: 0.98 (0.95, 1.01) | 86* | 0.98 | Critically low | ⊕◯◯◯ |
| Milk | Hidayat et al. (2020) | 7 | 6-21 | Per 1 glass/day increase | RR: 0.97 (0.92, 1.03) | 60* | 0.21 | Low | ⊕◯◯◯ |
| Yogurt | Hidayat et al. (2020) | 4 | 12-21 | High vs low | RR: 0.78 (0.68, 0.90) | 14 | > 0.45 | Low | ⊕◯◯◯ |
| Cheese | Hidayat et al. (2020) | 4 | 6-21 | High vs low | RR: 0.85 (0.66, 1.08) | 77* | > 0.45 | Low | ⊕◯◯◯ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Fruits | Luo et al. (2016) | 5 | 8-14 | High vs low | HR: 0.91 (0.77, 1.07) | 73* | N/A | Critically low | ⊕◯◯◯ |
| Vegetables | Luo et al. (2016) | 5 | 8-14 | High vs low | HR: 0.81 (0.68, 0.96) | 71* | N/A | Critically low | ⊕◯◯◯ |
| Fruit and vegetables | Brondani et al. (2019) | 5 | 7-20 | High vs low | RR: 0.92 (0.87, 0.98) | 56 | 0.15 | Critically low | ⊕⊕◯◯ |
| Tea | Sheng et al. (2013) | 3 | 6-12 | High vs low | RR: 1.03 (0.54, 1.52) | 42 | 0.06 | Critically low | ⊕◯◯◯ |
| Coffee | Li and Xu (2013) | 4 | 6-30 | Per cup increase/day | OR: 1.00 (0.96, 1.03) | N/A | 0.89 | Critically low | ⊕◯◯◯ |
| Alcohol | Zhang et al. (2015) | 18 | 3-30 | Any vs none | RR: 1.03 (0.91, 1.15) | 72* | > 0.10 | Critically low | ⊕◯◯◯ |
| | Zhang et al. (2015) | 7 | 3-30 | Light vs none | RR: 0.88 (0.83, 0.92) | 20 | > 0.10 | Critically low | ⊕◯◯◯ |
| | Zhang et al. (2015) | 7 | 3-30 | Moderate vs none | RR: 1.00 (0.85, 1.14) | 56* | > 0.10 | Critically low | ⊕◯◯◯ |
| | Zhang et al. (2015) | 3 | 3-30 | Heavy vs none | RR: 1.71 (1.41, 2.01) | 0 | > 0.10 | Critically low | ⊕◯◯◯ |
| Wine | Zhang et al. (2015) | 4 | 3-14 | Any vs no alcohol | RR: 0.81 (0.71, 0.92) | 0 | > 0.10 | Critically low | ⊕◯◯◯ |
| Beer | Zhang et al. (2015) | 4 | 3-14 | Any vs no alcohol | RR: 1.13 (0.69, 1.56) | 79* | > 0.10 | Critically low | ⊕◯◯◯ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Liquor (spirits) | Zhang et al. (2015) | 4 | 3-14 | Any vs no alcohol | RR: 0.94 (0.75, 1.12) | 33 | > 0.10 | Critically low | ⊕◯◯◯ |

N/A = not applicable or available; * = significant heterogeneity; RR = relative risk; OR = odds ratio; HR = hazard ratio; 95% CI = 95% confidence interval; ⊕◯◯◯ = very low quality of evidence; ⊕⊕◯◯ = low quality of evidence. For milk and coffee consumption, $I^2$ and Egger's p-value were unobtainable from dose-response meta-analyses, thus values from high vs low comparisons are presented as an estimate where available.

**Table 2.3: Summary characteristics and findings of meta-analyses of cohort studies assessing associations between dietary intake of macronutrients and hip fracture risk.**

| Exposure | Author (year) | n studies | Follow-up range (years) | Comparison | Summary effect estimate (95% CI) | $I^2$ (%) | Egger's p-value | AMSTAR | GRADE |
|---|---|---|---|---|---|---|---|---|---|
| Dietary protein | Wu et al. (2015) | 3 | N/A | High vs low | RR: 0.89 (0.82, 0.97) | 0 | 0.05 | Critically low | ⊕◯◯◯ |
| Animal protein | Wu et al. (2015) | 4 | N/A | High vs low | RR: 1.04 (0.70, 1.54) | 52 | 0.90 | Critically low | ⊕◯◯◯ |
| Vegetable protein | Wu et al. (2015) | 3 | N/A | High vs low | RR: 1.00 (0.53, 1.91) | 57 | 0.91 | Critically low | ⊕◯◯◯ |

N/A = not applicable or available; RR = relative risk; 95% CI = 95% confidence interval; ⊕◯◯◯ = very low quality of evidence.

**Table 2.4: Summary characteristics and findings of meta-analyses of cohort studies assessing associations between dietary intake of micronutrients and hip fracture risk.**

| Exposure | Author (year) | n studies | Follow-up range (years) | Comparison | Summary effect estimate (95% CI) | $I^2$ (%) | Egger's p-value | AMSTAR | GRADE |
|---|---|---|---|---|---|---|---|---|---|
| Dietary calcium intake | Bischoff-Ferrari et al. (2007) | 4 | 3-18 | Per 300 mg increase/day | RR: 1.01 (0.96, 1.06) | N/A | N/A | Critically low | ⊕◯◯◯ |
| Dietary vitamin C | Malmir et al. (2018b) | 3 | 13-15 | High vs low | RR: 0.92 (0.59, 1.44) | 55 | 0.83 | Critically low | ⊕◯◯◯ |
| Dietary vitamin A | Zhang et al. (2017) | 3 | 12-18 | High vs low | RR: 1.29 (1.06, 1.57) | 0 | 0.85 | Critically low | ⊕◯◯◯ |
| Dietary carotenoids | Xu et al. (2017) | 2 | 10-17 | High vs low | OR: 0.72 (0.51, 1.01) | 59 | 0.16 | Critically low | ⊕◯◯◯ |
| Dietary retinol | Zhang et al. (2017) | 4 | 12-18 | High vs low | RR: 1.40 (1.02, 1.91) | 65* | 0.17 | Critically low | ⊕◯◯◯ |
| Dietary a-carotene | Xu et al. (2017) | 2 | 10-17 | High vs low | OR: 0.77 (0.55, 1.08) | 64* | 0.36 | Critically low | ⊕◯◯◯ |
| Dietary b-carotene | Zhang et al. (2017) | 2 | 17-18 | High vs low | RR: 0.91 (0.64, 1.31) | 82* | 0.80 | Critically low | ⊕◯◯◯ |
| Dietary b-cryptoxanthin | Xu et al. (2017) | 2 | 10-17 | High vs low | OR: 1.11 (0.97, 1.28) | 0 | 0.49 | Critically low | ⊕◯◯◯ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Dietary lycopene | Xu et al. (2017) | 2 | 10-17 | High vs low | OR: 0.84 (0.69, 1.01) | 8 | 0.14 | Critically low | ⊕◯◯◯ |
| Dietary lutein/zeaxanthin | Xu et al. (2017) | 2 | 10-17 | High vs low | OR: 0.94 (0.79, 1.11) | 8 | 0.60 | Critically low | ⊕◯◯◯ |
| Dietary ALA | Sadheghi et al. (2019) | 3 | 8-24 | High vs low | RR: 1.01 (0.90, 1.13) | 71* | N/A | Critically low | ⊕◯◯◯ |
| Dietary EPA + DHA | Sadheghi et al. (2019) | 3 | 8-24 | High vs low | RR: 0.91 (0.81, 1.03) | 0 | N/A | Critically low | ⊕◯◯◯ |
| Antioxidant vitamins | Zhou et al. (2020) | 9 | 4-19 | High vs low | RR: 0.87 (0.69, 1.08) | 89* | 0.45 | Critically low | ⊕◯◯◯ |

N/A = not applicable or available; * = significant heterogeneity; RR = relative risk; OR = odds ratio; 95% CI = 95% confidence interval; ⊕◯◯◯ = very low quality of evidence; For antioxidant vitamins intake, Egger's p-value was obtained for total fracture, since this value was not presented for just hip fracture and both outcomes included mostly the same primary studies.

#### 2.4.5.1 Dietary patterns

**Table 2.1** shows the findings and the quality of evidence for associations between adherence to dietary patterns and the incidence of hip fracture. An inverse linear association was observed between MD adherence and hip fracture incidence from very low-quality evidence (for an increment of one unit in MD score, adjusted summary HR: 0.95 (95% CI: 0.92, 0.98)) (15). AHEI adherence was also inversely associated with hip fracture incidence in a higher vs lower comparison based on very low-quality evidence (RR: 0.83 (0.71, 0.97)) (14). No other associations were identified regarding dietary patterns and hip fracture.

#### 2.4.5.2 Foods, food groups, and beverages

**Table 2.2** shows the findings and the quality of evidence for associations between intake of foods, food groups, and beverages and the incidence of hip fracture. Low-quality evidence was found for an inverse association between intake of fruits and vegetables combined and hip fracture when comparing higher vs lower intakes (HR: 0.92 (0.87, 0.98)) (23). An inverse association was also observed for higher vs lower vegetable and yogurt intakes and hip fracture incidence with very low-quality evidence, respectively (vegetables HR: 0.81 (0.68, 0.96); yogurt RR: 0.78 (0.68, 0.90)) (20, 22). For alcohol intake, multiple comparisons were made with very low-quality evidence: compared to abstainers, light alcohol intake (0.01-12.5 g/day) and wine intake were inversely associated with hip fracture (RR: 0.88 (0.83, 0.92); RR: 0.81 (0.71, 0.92)) (26). Conversely, heavy (> 50 g/day) vs no alcohol intake was positively associated with hip fracture (RR: 1.71 (1.41, 2.01)) (26). No significant association was observed for any or moderate alcohol intake (12.6-49.9 g/day), beer, and liquor vs no alcohol and hip fracture (26). Very low quality evidence also showed no clear association between hip fracture and total dairy (18), milk (20), fruits (22), cheese (20), tea (24), and coffee intakes (13).

#### 2.4.5.3 Macronutrients

**Table 2.3** shows the findings and the quality of evidence for associations between intake of macronutrients and the incidence of hip fracture. Very low-quality evidence showed an inverse association between total dietary protein intake and hip fracture incidence (higher vs lower RR:

0.89 (0.82, 0.97)) (27). No clear association was observed between animal or vegetable protein intake and hip fracture in a higher vs lower comparison of very low-quality evidence, respectively (27).

#### 2.4.5.4 Micronutrients

**Table 2.4** shows the findings and the quality of evidence for associations between the intake of micronutrients and the incidence of hip fracture. The quality of evidence was very low for all micronutrient exposures. Near-significant inverse associations were observed between dietary intake of carotenoids or lycopene and hip fracture (higher vs lower intakes; carotenoids OR: 0.72 (0.51, 1.01); lycopene OR: 0.84 (0.69, 1.01)) (38). Significant positive associations were observed between dietary vitamin A and retinol intake and hip fracture in meta-analyses of higher vs lower comparisons, respectively (vitamin A RR: 1.29 (1.06, 1.57); retinol RR: 1.40 (1.02, 1.91)) (37). In dose-response meta-analyses (per 300 mg increase per day), no clear association was observed between hip fracture and dietary calcium intake (30). In meta-analyses comparing higher vs lower intakes, no clear association was observed between hip fracture and dietary intake of vitamin C (34), a-carotene (38), b-carotene (37), b-cryptoxanthin (38), lutein/zeaxanthin (38), ALA (39), EPA with DHA (39), or antioxidant vitamins (40).

#### 2.4.5.5 Heterogeneity

Estimates of the proportion of heterogeneity attributable to between-study variation using the $I^2$ statistic were available in all but three meta-analyses (13, 14, 30). Nineteen meta-analyses had an $I^2$ value above 50%, and heterogeneity was significant for the following 14 exposures: MD adherence (15), total dairy (18), milk (20), cheese (20), fruits (22), vegetables (22), alcohol (any, moderate, beer) (26), retinol (37), a-carotene (38), b-carotene (37), ALA (39), and antioxidant vitamins (40). $I^2$ values were above 75% for total dairy (18), cheese (20), beer (26), b-carotene (37), and antioxidant vitamin intake (40). $I^2$ values were not available for AHEI adherence (14), coffee intake (13), and dietary calcium intake (30).

#### 2.4.5.6 Small study effects

All meta-analyses assessed the risk of small study effects (such as publication bias) except those regarding fruits (22), vegetables (22), animal protein (27), and vegetable protein intake (27). Methods used included: Egger's test (n=30 meta-analyses); Egger's and Begg's test (n=21); both tests with visual inspection of funnel plots (n=11); and Egger's test with visual inspection (n=7). No meta-analysis showed evidence of publication bias.

## 2.5 Discussion

### 2.5.1 Principal findings

The effects of several dietary factors on the incidence of hip fracture have been quantified in previously published meta-analyses. This umbrella review aimed to summarise the totality of evidence regarding diet and hip fracture risk in adults, evaluating the quality of evidence for each association. We included thirty-four meta-analyses of cohort studies relating different dietary factors to hip fracture incidence. The key findings of this umbrella review are four-fold. Firstly, low-quality evidence showed that high intake of fruits and vegetables combined may decrease the risk of hip fracture compared to low intakes (23). Secondly, there was no clear association between consumption of dairy, dairy products, or dietary calcium and hip fracture incidence based on very low-quality evidence (18, 20, 30). Thirdly, there was a lack of evidence regarding dietary patterns and hip fracture incidence. Finally, the methodological quality of most systematic reviews and their meta-analyses and the quality of evidence for most diet-hip fracture associations were very low.

### 2.5.2 Comparison with other studies

Few up-to-date, evidence-based guidelines exist for preventing hip fracture through diet (3, 42). Our umbrella review addresses the dietary risk factors for hip fracture identified in a previous umbrella review (excluding nutritional supplements) (3), and provides information for 31 additional dietary exposures.

The National Osteoporosis Foundation (NOF) and a previous umbrella review suggest increasing consumption of fruits and vegetables or vegetables alone to prevent hip fracture (3, 42, 43). Consistent with this, we found that higher intake of vegetables but not fruits was associated with a reduced risk of hip fracture, but with very low-quality evidence due to serious inconsistency and a serious risk of bias among primary studies (22). We also found low-quality evidence that a higher intake of fruits and vegetables combined was associated with a reduced risk of hip fracture (23). Further cohort studies with dose-response and absolute risk information would increase the certainty of evidence for this association. The potential for fruits or vegetables alone to reduce hip fracture incidence requires further research.

Contrary to existing recommendations (42), we found no clear association between hip fracture incidence and intake of dietary calcium, total dairy, and dairy products except yogurt, which was inversely associated with hip fracture. The quality of evidence for these associations was very low due to a serious risk of bias amongst primary cohort studies (stemming from inadequate follow-up data and unvalidated dietary assessment methods) and inconsistent results (18, 20). Meta-analyses excluded from our review largely support these findings (16, 17, 19, 21, 31-33), though in higher vs lower comparisons, one meta-analysis found a near-significant protective effect of total dairy intake, and a reduced risk of hip fracture with higher cheese consumption (16). This discrepancy may be due to differences in primary studies included and meta-analytic methods used between meta-analyses.

To our knowledge, no specific dietary pattern is recommended for the primary prevention of hip fracture. We found that higher adherence to the AHEI or the MD may decrease the risk of hip fracture, but the quality of evidence was very low for both associations due to a serious risk of bias amongst primary studies (14, 15). Our findings were consistent with other meta-analyses that included case-control studies (44, 45), such as a recent meta-analysis that showed that higher adherence to a diet high in fruits and vegetables, poultry, fish, and wholegrains (resembling the MD) was associated with a reduced risk of hip fracture, whilst higher adherence to a 'Western diet' (high red meat, processed meat, animal fat, eggs, and sweets) increased the risk (45). Future large prospective cohort studies are needed to explore the effects of various dietary patterns on the risk of hip fracture before preventative recommendations can be made. A recent European Prospective Investigation into Cancer (EPIC) cohort study published after our

last database search showed a greater risk of hip fracture among fish-eaters, vegetarians, and vegans compared to meat-eaters after adjustment for socio-economic factors, lifestyle confounders, and BMI in a UK population that consisted predominantly of middle-aged, white females (46). Equivalent studies would help elucidate the effect of other dietary patterns on hip fracture incidence. This is of particular importance given that dietary patterns encompass several individual dietary risk factors that could act synergistically to impact the risk of hip fracture (47).

NOF guidelines and previous umbrella reviews have suggested increasing consumption of tea and dietary protein, and limiting alcohol consumption to prevent hip fracture (3, 42, 48). We also found a protective effect of dietary protein (27), but the effect of tea was unclear (24), and the association between alcohol intake and hip fracture was dependent on the type and amount consumed (26). In line with previous evidence (24, 25), we also found no clear association between coffee consumption and hip fracture (13). In any case, the methodological quality of included systematic reviews and meta-analyses and the quality of evidence for these associations were very low. Many meta-analyses assessing diet-hip fracture associations included a small number of studies (< 5 studies), reducing statistical power and the precision of confidence intervals. Many showed a serious risk of bias within included studies, presented an inadequate quality assessment (for which we assumed a serious risk of bias), or did not present a quality assessment of included studies (for which we assumed a very serious risk of bias). Several associations also showed a high degree of inconsistency. Future large, well-conducted cohort studies are required to remedy these issues.

Epidemiological evidence has considered the role of other dietary factors in relation to risk of hip fracture, such as dietary intake of carbohydrates, fats, B-vitamins, magnesium, zinc, and isoflavones (49-55). These studies were not included in our review because they lacked a meta-analysis component, did not assess the effect of a dietary exposure on hip fracture risk, or met other aspects of our exclusion criteria. Nonetheless, their findings are relevant points for future research. For instance, one meta-analysis including case-control studies showed a strong, positive association between saturated fatty acid intake and hip fracture incidence (RR: 1.79 [1.05, 3.03]) (53). Well-conducted trials, cohort studies, and meta-analyses are needed to better understand the role of dietary factors in preventing hip fracture, including those not explored in our review.

### 2.5.3 Possible mechanisms

A possible explanation for the inverse association between intake of fruits and vegetables and hip fracture risk is the potential for fruits and vegetables to decrease bone loss through several potential pathways, which decreases fracture risk (23). Potential pathways include shifting the acid-base balance to a more alkaline state to increase calcium reabsorption, and improving bone remodelling by reducing oxidative stress (23). A third proposed mechanism is that fruits and vegetables may decrease chronic inflammation, which is associated with fracture incidence (23, 56).

Alternatively, those that consume more fruits and vegetables may have other healthy dietary and lifestyle habits, and may be less likely to have other health problems (such as diabetes or depression) that could increase the risk of hip fracture (43, 57). Indeed, adherence to dietary patterns with higher intakes of fruits and vegetables (AHEI and the MD) reduced the risk of hip fracture in our review. The association between intake of fruits and vegetables and hip fracture incidence remained after adjustment for relevant confounders, but physical activity was not accounted for (23). Since physical activity is positively associated with fruit and vegetable intake and inversely associated with hip fracture incidence, the apparent protective effect of fruits and vegetables against hip fracture could be exaggerated by residual confounding (58, 59).

Milk, yogurt, cheese, and therefore total dairy consumption could plausibly reduce the risk of hip fracture via their high content of nutrients associated with bone health acting synergistically, including protein, calcium, and vitamin D (18). Milk, however, is a major source of D-galactose, which could contribute to bone loss through oxidative stress and chronic inflammation, thus may have no net effect on hip fracture incidence (20). The potential benefit of yogurt but not cheese consumption may be explained by a lack of statistical power to detect an association for cheese and hip fracture, or the association between cheese consumption and hip fracture incidence may depend on the type of cheese (20). Indeed, a large degree of unexplained heterogeneity was observed for cheese but not yogurt consumption (20). Total dairy intake may therefore not be associated with hip fracture because of the large degree of heterogeneity between studies caused by combining effects of different dairy products into a single summary effect.

Associations between dairy, dairy products, dietary calcium intake, and hip fracture incidence may also depend on factors not considered in our review, further contributing to the heterogeneity observed for total dairy intake. The effect of dietary calcium intake could depend on sex, but the meta-analysis here was restricted to women (30). Findings for total dairy were limited to non-Hispanic whites (18), but could vary by ethnicity. In their sub-group analyses, Hidayat et al. (2020) showed a protective effect for milk that was attenuated by adjustment for BMI and physical activity (20). Moreover, milk had a protective effect in USA populations but not in Scandinavian populations, and was attributed to differences in vitamin D fortification policies for milk between the two regions (20). Therefore, obtaining higher quality evidence regarding dairy and calcium intake and hip fracture incidence to enable strong preventative recommendations to be made is challenging. Future high-quality cohort studies should aim to clarify the relationship between calcium intake and individual dairy products and hip fracture incidence.

### 2.5.4 Strengths and limitations

The main strength of this umbrella review was that it systematically synthesised the totality of evidence from all published meta-analyses of cohort studies considering the role of diet and dietary factors in preventing hip fracture. We used validated tools to assess the methodological quality of systematic reviews and meta-analyses and the overall quality of evidence for each association. Common methodological limitations of systematic reviews and meta-analyses and implications for further research were identified.

Given the broad scope of our umbrella review, we restricted our search to systematic reviews with meta-analyses. In doing so, cohort studies that were not included in a previously published meta-analysis may have been missed, such as the recently published EPIC-Oxford cohort study comparing dietary patterns and hip fracture risk (46). These studies may point towards understudied dietary risk factors for hip fracture.

We did not re-meta-analyse primary study data from eligible meta-analyses for each association because the principal objective of an umbrella review is to summarise existing relevant research syntheses (60). We relied on the information reported in included systematic reviews and meta-

analyses when assessing the quality of evidence for each association using the GRADE tool; therefore, our review inherited their limitations. Many included systematic reviews did not present a risk of bias assessment at the domain level for each primary cohort study. Evidence for these associations were assumed to contain a serious or very serious risk of bias, downgrading their quality. As observational research begins at low quality in GRADE (due to being non-randomised), the quality of evidence for all but one association in our umbrella review was very low. Therefore, our review could have underestimated the quality of evidence for associations assessed, but given the high degree of inconsistency and imprecision of results across cohort studies for many associations assessed, this is unlikely. This could limit the ability of our umbrella review to provide evidence for the formulation of preventative recommendations against hip fracture, but highlights the need for rigorous risk of bias assessments in future systematic reviews to facilitate more robust assessments of the quality of evidence.

Our umbrella review identified other limitations common to meta-analyses of diet and hip fracture that reduced the quality of evidence for many associations. Knowledge of the absolute risk of hip fracture for a given dietary exposure is required to put relative effects into context, and for robust evidence-based recommendations to be made (61). Since hip fracture is a rare event in cohort studies, large relative effects may not translate into large absolute effects. However, none of the included meta-analyses reported absolute effects for risk of hip fracture, and this could not be calculated due to insufficient data in meta-analyses (meta-analyses did not report baseline risks of hip fracture in their respective populations, and most did not report the number of participants in each exposure category).

Many meta-analyses lacked dose-response information and compared high vs low consumption of a dietary factor on hip fracture risk without defining thresholds for these categories. Since cohort studies often define exposure categories at different thresholds, pooling effect estimates from comparisons between different levels of an exposure masks the true comparison being made, and limits the utility of findings.

All included meta-analyses included observational studies. Excluding met-analyses of case-control or cross-sectional studies reduced the risk of recall and selection bias, and ensured that dietary assessments preceded hip fracture events. However, cohort studies remain prone to

residual confounding bias. Most meta-analyses included cohort studies with effect estimates that were unadjusted for prior fracture – a risk factor for subsequent fracture – and did not explicitly exclude participants with a history of fracture (3). Other key confounders that were often not adjusted for by cohort studies within meta-analyses include total energy intake, alcohol intake, and the presence of chronic disease. Therefore, summary effect estimates for most associations were not fully adjusted for key confounders, distorting true effect sizes.

### 2.5.5 Conclusions and future directions

The effects of dietary factors on the risk of hip fracture in adults have been quantified in previously published meta-analyses. It is clear from these that foods, nutrients, and dietary patterns could play a role in the primary prevention of hip fracture. Fruits and vegetables intake may decrease the risk of hip fracture, but the methodological quality of almost all systematic reviews and meta-analyses was critically low, and the effects of other dietary exposures such as dairy and calcium intakes on hip fracture risk was uncertain. This umbrella review highlights the potential dietary risk factors for hip fracture that warrant further research, and points towards the need for review authors to improve the conduct and reporting of their syntheses.

Given the very low quality of evidence for most associations, we recommend more well-conducted, long-term cohort studies and subsequently robust meta-analyses so that stronger policy recommendations can be made to prevent hip fracture through diet. To increase the quality of evidence, authors of systematic reviews should establish their protocol a priori, justify the exclusion of each study, and provide a rigorous assessment of the risk of bias of included primary studies. Authors of meta-analyses should additionally present dose-response information and absolute risks if possible, explore sources of heterogeneity, and consider if meta-analysis is appropriate with the data available. We recommend a particular focus on the effect of dietary patterns to account for interactive effects of foods and nutrients on the risk of hip fracture.

## 2.6 References


1. Dhanwal DK, Dennison EM, Harvey NC, Cooper C. Epidemiology of hip fracture: Worldwide geographic variation. Indian J Orthop. 2011;45(1):15-22.
2. Veronese N, Maggi S. Epidemiology and social costs of hip fracture. Injury. 2018;49(8):1458-60.
3. Benetos LS, Babis GC, Zoubos AB, Benetou V, Soucacos PN. Factors affecting the risk of hip fractures. Injury-Int J Care Inj. 2007;38(7):735-44.
4. Peraza-Delgado A, Sanchez-Gomez MB, Gomez-Salgado J, Romero-Martin M, Novo-Munoz M, Duarte-Climents G. Non-pharmacological interventions towards preventing the triad osteoporosis-falls risk-hip fracture, in population older than 65. Scoping review. Journal of Clinical Medicine. 2020;9(8):1-27.
5. Neuenschwander M, Ballon A, Weber KS, Norat T, Aune D, Schwingshackl L, et al. Role of diet in type 2 diabetes incidence: umbrella review of meta-analyses of prospective observational studies. BMJ (Clinical research ed). 2019;366:l2368-l.
6. Page M, McKenzie J, Bossuyt P, Boutron I, Hoffmann T, mulrow c, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews2020.
7. Fusar-Poli P, Radua J. Ten simple rules for conducting umbrella reviews. Evid Based Ment Health. 2018;21(3):95-100.
8. Wongpakaran N, Wongpakaran T, Wedding D, Gwet KL. A comparison of Cohen's Kappa and Gwet's AC1 when calculating inter-rater reliability coefficients: a study conducted with personality disorder samples. BMC Med Res Methodol. 2013;13:61-.
9. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. Bmj. 2017;358:j4008.
10. Schunemann H, Brozek J, Guyatt G, Oxman A. GRADE handbook for grading quality of evidence and strength of recommendations. Updated October 2013: The GRADE Working Group; 2013. Available from: guidelinedevelopment.org/handbook.
11. GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University, 2020 (developed by Evidence Prime, Inc.) [Available from: https://gradepro.org/.

12. Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. Lancet. 2007;370(9588):657-66.

13. Li XL, Xu JH. Coffee consumption and hip fracture risk: a meta-analysis. J Nutr Sci. 2013;2:e23.

14. Panahande B, Sadeghi A, Parohan M. Alternative healthy eating index and risk of hip fracture: a systematic review and dose-response meta-analysis. J Hum Nutr Diet. 2019;32(1):98-107.

15. Malmir H, Saneei P, Larijani B, Esmaillzadeh A. Adherence to Mediterranean diet in relation to bone mineral density and risk of fracture: a systematic review and meta-analysis of observational studies. Eur J Nutr. 2018;57(6):2147-60.

16. Bian SS, Hu JM, Zhang K, Wang YG, Yu MH, Ma J. Dairy product consumption and risk of hip fracture: a systematic review and meta-analysis. BMC Public Health. 2018;18:16.

17. Malmir H, Larijani B, Esmaillzadeh A. Consumption of milk and dairy products and risk of osteoporosis and hip fracture: a systematic review and Meta-analysis. Crit Rev Food Sci Nutr. 2020;60(10):1722-37.

18. Matia-Martin P, Torrego-Ellacuria M, Larrad-Sainz A, Fernandez-Perez C, Cuesta-Triana F, Rubio-Herrera MA. Effects of Milk and Dairy Products on the Prevention of Osteoporosis and Osteoporotic Fractures in Europeans and Non-Hispanic Whites from North America: A Systematic Review and Updated Meta-Analysis. Adv Nutr (Bethesda). 2019;10(suppl_2):S120-S43.

19. Bischoff-Ferrari HA, Dawson-Hughes B, Baron JA, Kanis JA, Orav EJ, Staehelin HB, et al. Milk Intake and Risk of Hip Fracture in Men and Women: A Meta-Analysis of Prospective Cohort Studies. J Bone Miner Res. 2011;26(4):833-9.

20. Hidayat K, Du X, Shi BM, Qin LQ. Systematic review and meta-analysis of the association between dairy consumption and the risk of hip fracture: critical interpretation of the currently available evidence. Osteoporos Int. 2020;31(8):1411-25.

21. Ong AM, Kang K, Weiler HA, Morin SN. Fermented Milk Products and Bone Health in Postmenopausal Women: A Systematic Review of Randomized Controlled Trials, Prospective Cohorts, and Case-Control Studies. Adv Nutr (Bethesda). 2020;11(2):251-65.

22. Luo SY, Li Y, Luo H, Yin XH, Lin DR, Zhao K, et al. Increased intake of vegetables, but not fruits, may be associated with reduced risk of hip fracture: A meta-analysis. Sci. 2016;6:8.

23. Brondani JE, Comim FV, Flores LM, Martini LA, Premaor MO. Fruit and vegetable intake and bones: A systematic review and meta-analysis. PLoS ONE. 2019;14(5).

24. Sheng J, Qu X, Zhang X, Zhai Z, Li H, Liu X, et al. Coffee, tea, and the risk of hip fracture: a meta-analysis. Osteoporos Int. 2014;25(1):141-50.

25. Li S, Dai ZP, Wu Q. Effect of coffee intake on hip fracture: a meta-analysis of prospective cohort studies. Nutr J. 2015;14:7.

26. Zhang X, Yu Z, Yu M, Qu X. Alcohol consumption and hip fracture risk. Osteoporos Int. 2015;26(2):531-42.

27. Wu AM, Sun XL, Lv QB, Zhou Y, Xia DD, Xu HZ, et al. The Relationship between Dietary Protein Consumption and Risk of Fracture: a subgroup and dose-response meta-analysis of prospective cohort studies. Sci. 2015;5:8.

28. Groenendijk I, den Boeft L, van Loon LJC, de Groot LCPGM. High Versus low Dietary Protein Intake and Bone Health in Older Adults: a Systematic Review and Meta-Analysis. Comp Struct Biotechnol J. 2019;17:1101-12.

29. Darling AL, Millward DJ, Torgerson DJ, Hewitt CE, Lanham-New SA. Dietary protein and bone health: A systematic review and meta-analysis. Am J Clin Nutr. 2009;90(6):1674-92.

30. Bischoff-Ferrari HA, Dawson-Hughes B, Baron JA, Burckhardt P, Li R, Spiegelman D, et al. Calcium intake and hip fracture risk in men and women: A meta-analysis of prospective cohort studies and randomized controlled trials. Am J Clin Nutr. 2007;86(6):1780-90.

31. Cumming RG, Nevitt MC. Calcium for prevention of osteoporotic fractures in postmenopausal women. J Bone Miner Res. 1997;12(9):1321-9.

32. Wang D, Chen XH, Fu G, Gu LQ, Zhu QT, Liu XL, et al. Calcium intake and hip fracture risk: A meta-analysis of prospective cohort studies. Int J Clin Exp Med. 2015;8(8):14424-31.

33. Xu LZ, McElduff P, D'Este C, Attia J. Does dietary calcium have a protective effect on bone fractures in women? A meta-analysis of observational studies. Br J Nutr. 2004;91(4):625-34.

34. Malmir H, Shab-Bidar S, Djafarian K. Vitamin C intake in relation to bone mineral density and risk of hip fracture and osteoporosis: A systematic review and meta-analysis of observational studies. Br J Nutr. 2018;119(8):847-58.

35. Zeng LF, Luo MH, Liang GH, Yang WY, Xiao X, Wei X, et al. Can Dietary Intake of Vitamin C-Oriented Foods Reduce the Risk of Osteoporosis, Fracture, and BMD Loss? Systematic Review With Meta-Analyses of Recent Studies. Front Endocrinol. 2020;10:12.

36. Wu AM, Huang CQ, Lin ZK, Tian NF, Ni WF, Wang XY, et al. The Relationship Between Vitamin A and Risk of Fracture: Meta-Analysis of Prospective Studies. J Bone Miner Res. 2014;29(9):2032-9.

37. Zhang XG, Zhang R, Moore JB, Wang YG, Yan HY, Wu YR, et al. The Effect of Vitamin A on Fracture Risk: A Meta-Analysis of Cohort Studies. Int J Environ Res Public Health. 2017;14(9):15.

38. Xu JH, Song CL, Song XC, Zhang X, Li XL. Carotenoids and risk of fracture: a meta-analysis of observational studies. Oncotarget. 2017;8(2):2391-9.

39. Sadeghi O, Djafarian K, Ghorabi S, Khodadost M, Nasiri M, Shab-Bidar S. Dietary intake of fish, n-3 polyunsaturated fatty acids and risk of hip fracture: A systematic review and meta-analysis on observational studies. Crit Rev Food Sci Nutr. 2019;59(8):1320-33.

40. Zhou PH, Shao RY, Wang H, Miao JQ, Wang XH. Dietary vitamin A, C, and E intake and subsequent fracture risk at various sites A meta-analysis of prospective cohort studies. Medicine (Baltimore). 2020;99(35):9.

41. Lo CK, Mertz D, Loeb M. Newcastle-Ottawa Scale: comparing reviewers' to authors' assessments. BMC Med Res Methodol. 2014;14:45.

42. National Osteoporosis Foundation. Preventing Fractures 2021 [Available from: https://www.nof.org/preventing-fractures/prevention/.

43. Angelino D, Godos J, Ghelfi F, Tieri M, Titta L, Lafranconi A, et al. Fruit and vegetable consumption and health outcomes: an umbrella review of observational studies. Int J Food Sci Nutr. 2019;70(6):652-67.

44. Kunutsor SK, Laukkanen JA, Whitehouse MR, Blom AW. Adherence to a Mediterranean-style diet and incident fractures: pooled analysis of observational evidence. Eur J Nutr. 2018;57(4):1687-700.

45. Fabiani R, Naldini G, Chiavarini M. Dietary Patterns in Relation to Low Bone Mineral Density and Fracture Risk: A Systematic Review and Meta-Analysis. Adv Nutr (Bethesda). 2019;10(2):219-36.

46. Tong TYN, Appleby PN, Armstrong MEG, Fensom GK, Knuppel A, Papier K, et al. Vegetarian and vegan diets and risks of total and site-specific fractures: results from the prospective EPIC-Oxford study. BMC Med. 2020;18(1):353.

47. Cespedes EM, Hu FB. Dietary patterns: from nutritional epidemiologic analysis to national guidelines. The American Journal of Clinical Nutrition. 2015;101(5):899-900.

48. Yi M, Wu X, Zhuang W, Xia L, Chen Y, Zhao R, et al. Tea Consumption and Health Outcomes: Umbrella Review of Meta-Analyses of Observational Studies in Humans. Mol Nutr Food Res. 2019;63(16):e1900389.

49. Bolanos R, Francia J. Isoflavones versus hormone therapy for reduction of vertebral fracture risk: Indirect comparison. Menopause. 2010;17(6):1201-5.

50. Ruan JW, Gong XK, Kong JS, Wang HB, Zheng X, Chen T. Effect of B Vitamin (Folate, B6, and B12) Supplementation on Osteoporotic Fracture and Bone Turnover Markers: A Meta-Analysis. Med Sci Monit. 2015;21:875-81.

51. Farsinejad-Marj M, Saneei P, Esmaillzadeh A. Dietary magnesium intake, bone mineral density and risk of fracture: a systematic review and meta-analysis. Osteoporos Int. 2016;27(4):1389-99.

52. de Macedo LLG, de Carvalho C, Cavalcanti JC, Freitas B. Vitamin B12, bone mineral density and fracture risk in adults: A systematic review. Rev Assoc Med Bras. 2017;63(9):801-9.

53. Mozaffari H, Djafarian K, Mofrad MD, Shab-Bidar S. Dietary fat, saturated fatty acid, and monounsaturated fatty acid intakes and risk of bone fracture: a systematic review and meta-analysis of observational studies. Osteoporos Int. 2018;29(9):1949-61.

54. Mozaffari H, Daneshzad E, Azadbakht L. Dietary carbohydrate intake and risk of bone fracture: a systematic review and meta-analysis of observational studies. Public Health. 2020;181:102-9.

55. Ceylan MN, Akdas S, Yazihan N. Is Zinc an Important Trace Element on Bone-Related Diseases and Complications? A Meta-analysis and Systematic Review from Serum Level, Dietary Intake, and Supplementation Aspects. Biol Trace Elem Res.15.

56. Briot K, Geusens P, Em Bultink I, Lems WF, Roux C. Inflammatory diseases and bone fragility. Osteoporos Int. 2017;28(12):3301-14.

57. Shi TT, Min M, Zhang Y, Sun CY, Liang MM, Sun YH. Depression and risk of hip fracture: a systematic review and meta-analysis of cohort studies. Osteoporos Int. 2019;30(6):1157-65.

58. van der Avoort CMT, Ten Haaf DSM, de Vries JHM, Verdijk LB, van Loon LJC, Eijsvogels TMH, et al. Higher Levels of Physical Activity Are Associated with Greater Fruit and Vegetable intake in Older Adults. J Nutr Health Aging. 2021;25(2):230-41.

59. Stattin K, Michaëlsson K, Larsson SC, Wolk A, Byberg L. Leisure-Time Physical Activity and Risk of Fracture: A Cohort Study of 66,940 Men and Women. J Bone Miner Res. 2017;32(8):1599-606.

60. Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P. Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. Int J Evid Based Healthc. 2015;13(3):132-40.

61. Tucker G, Metcalfe A, Pearce C, Need AG, Dick IM, Prince RL, et al. The importance of calculating absolute rather than relative fracture risk. Bone. 2007;41(6):937-41.

# Chapter 3 Foods, nutrients, and hip fracture risk: a prospective study of middle-aged women

**James Webster[1], Darren C. Greenwood[2], and Janet E. Cade[1]**

1 School of Food Science and Nutrition, University of Leeds, Leeds, LS2 9JT.

2 School of Medicine, University of Leeds, Leeds, LS2 9JT.

Published: Clinical Nutrition. 2022. 41(12): 2825-2832.

https://doi.org/10.1016/j.clnu.2022.11.008

**This Chapter is an exact copy of the journal paper referred to above.**

## 3.1 Abstract

**Background and aims:** Hip fracture affects 1.6 million people globally each year, and increases morbidity and mortality. There is potential for risk reduction through diet modification, but prospective evidence for associations between intake of several foods and nutrients and hip fracture risk is limited. This study aimed to investigate associations between food and nutrient intakes and hip fracture risk in the UK Women's Cohort Study, and to determine the role of body mass index (BMI) as a potential effect modifier.

**Methods:** Dietary, lifestyle, anthropometric, and socio-economic information of UK women, ages 35–69 years, were collected in a survey at recruitment (1995-1998), and included a validated 217-item food frequency questionnaire. Hip fracture cases were identified by linking participant data at recruitment with their Hospital Episode Statistics (HES) up to March 2019. Cox regression models were used to estimate associations between standard portions of food and nutrient intakes and hip fracture risk over a median follow-up time of 22.3 years.

**Results:** Among 26,318 women linked to HES data (556,331 person-years), 822 hip fracture cases were identified. After adjustment for confounders, every additional cup of tea or coffee per day was associated with a 4% lower risk of hip fracture (HR (95% CI): 0.96 (0.92, 1.00)). A 25 g/day increment of dietary protein intake was also associated with a 14% lower risk of hip fracture (0.86 (0.73, 1.00)). In subgroup analyses, BMI modified linear associations between dietary intakes of protein, calcium, total dairy, milk, and tea and hip fracture risk (pinteraction = 0.02, 0.002, 0.003, 0.001, and 0.003, respectively); these foods and nutrients were associated with a reduced risk of hip fracture in underweight but not healthy or overweight participants. In particular, risk of hip fracture in underweight participants (28 cases, 545 participants) was 45% lower for every 25g/day protein consumed (0.55 (0.38, 0.78)).

**Conclusions:** This is the first prospective cohort study internationally of multiple food and nutrient intakes in relation to hip fracture risk by BMI using linkage to hospital records. Results suggest that the potential roles of some foods and nutrients in hip fracture prevention, particularly protein, tea and coffee in underweight women, merit confirmation.

**Key words:** Diet, nutrition, hip fracture, cohort study, epidemiology, body mass index

**Protocol registration:** clinicaltrials.gov NCT05081466

## 3.2 Introduction

Hip fractures are the most common fractures resulting in hospitalisation, particularly among older women (1). Around 1.6 million cases occur globally each year and rates are increasing (2), particularly in Europe and Asia (3, 4). Mobility and independence decrease after hip fracture incidence whilst risk of comorbidities increases, resulting in a reduced health-related quality of life and increased mortality (1, 5, 6). Hip fractures also burden healthcare systems, costing the UK £2 -3 billion and the US healthcare system $6 billion per year, respectively (7, 8). There is potential for risk reduction through diet modification (9), but the extent to which dietary intake of specific foods and nutrients impact hip fracture risk remains unclear.

Adequate bone health and muscle function are important in preventing hip fracture (10, 11). The importance of protein, calcium, and vitamin D to bone health and muscle function are becoming increasingly recognised (12-15); experimental evidence suggests a reduced risk of hip fracture with concurrent supplementation of calcium and vitamin D (16), but the impact of dietary protein, calcium, and vitamin D intakes on hip fracture risk are less clear (9). Dietary intake of other nutrients including fat, vitamin A, and B-vitamins have also been associated with bone health and hip fracture risk in observational studies (17-19), but prospective evidence is limited for many nutrients in relation to hip fracture risk.

Consumption of foods in which nutrients important to bone health are abundant may also be associated with hip fracture risk. Higher intakes of fruits and vegetables have been inversely associated with hip fracture risk, possibly through reducing oxidative stress and consequently reducing bone loss (20, 21). Protective roles for meat, fish, and dairy products are also plausible due to their protein, calcium, and vitamin D contents, but inconclusive (9, 22-24). Our previous umbrella review of dietary risk factors for hip fracture showed potential associations between hip fracture risk and intake of several foods and nutrients, but with low or very low quality evidence for all exposures (9). There is a lack of prospective evidence investigating hip fracture

risk in relation to intake of many foods and nutrients. Previous studies are limited by small sample sizes, selective loss to follow-up due to identification of hip fracture cases through self-reported measures, or study durations too short for a long-term effect of diet to be observed. Associations between food and nutrient intakes and hip fracture risk require further investigation.

Many foods and nutrients are individually associated with BMI, which is inversely associated with hip fracture risk (25). Associations between foods, nutrients and hip fracture risk may depend on BMI, and may be more pronounced in underweight individuals where bone and muscle health are more likely to be inadequate (26), though this remains unclear. This study aimed to investigate associations between food and nutrient intakes and hip fracture risk in the UK Women's Cohort Study (UKWCS), and to determine if these associations are modified by BMI.

## 3.3 Methods

We followed the Strengthening the Reporting of Observational Studies in Epidemiology – Nutritional Epidemiology (STROBE-nut) guidelines for the reporting of cohort studies (**Appendix B: Table B1**) (27).

### 3.3.1 Study design

The UKWCS is a prospective cohort study of 35,372 middle-aged women (ages 35-69 years at recruitment) recruited via postal questionnaire across the UK between 1995-1998. The recruitment process has been detailed elsewhere (28). Dietary, lifestyle, demographic, and anthropometric data were collected through the questionnaire at recruitment. Participants were then excluded for the following reasons: lived outside of England (n=3821), had a hip fracture on or before the date of recruitment according to hospital episode statistics (n=2), had missing age data (n=341), or had outlier dietary or covariate data (daily energy intake < 500 kcal or > 5000 kcal, BMI < 10 or > 60 kg/m$^2$, or food intakes > 3 standard deviations from the mean; n=941), leaving 30,244 participants potentially eligible for inclusion in this study (**Appendix B: Figure B1**). Ethical approval was obtained at the cohort's inception in 1993 from the National Research Ethics Service Committee for Yorkshire & the Humber – Leeds East (reference 15/YH/0027). This has

now become the UK Women's Cohort Study – HES research database with ethical approval 17/YH/0144, in addition to an National Health Service Digital Data Sharing Agreement DARS-NIC-109867-M8S6B-v1.5.

### 3.3.2 Dietary assessment

At recruitment, dietary information of participants was collected via a self-administered 217-item food frequency questionnaire (FFQ) that was based on the Oxford branch of the European Prospective Investigation into Cancer and Nutrition (EPIC) study (29). The FFQ was validated against four-day weighed food diaries and a repeat FFQ on 283 women, both administered three years after recruitment (28).

Primary foods and nutrients of interest were identified based on potential dietary risk factors for hip fracture identified in previously published studies (9), and included: dietary intake of fruits and vegetables combined, fruit, vegetables, total meat, total fish, total dairy, milk, yoghurt, cheese, tea and coffee combined, tea, coffee, protein, calcium, and vitamin D. Secondary foods and nutrients considered in exploratory analyses included dietary intake of other foods or nutrients with a plausible relation to hip fracture risk but with very limited evidence, and are listed in **Appendix B: Supplementary methods**. Each food exposure was calculated by converting responses to each FFQ item to servings per day, multiplying by standard portion sizes to give grams per day (g/day), then summing relevant FFQ items (g/day) that constituted each food exposure. Exposure definitions and their derivations are documented in **Appendix B: Table B2**. Standard portion sizes for food exposures were derived by averaging standard portion sizes of all relevant FFQ items (based on the Foods Standards Agency) that constituted an exposure (30). Nutrient intakes were calculated by multiplying daily intake of each FFQ item (g/day) by each items' specific nutrient contents, and summing the products. Nutrient concentrations for each FFQ item were based on McCance and Widdowson's Food Composition database (5th edition) (31).

### 3.3.3 Outcome

First incidence of hip fracture was the primary outcome, and was identified by linking participants' diet and lifestyle characteristics with their Hospital Episode Statistics up to 31st March 2019 (International Classification of Diseases, ICD-9 code 820, ICD-10 codes S72.0-72.2). We also checked for hip fracture cases by searching for hip replacements (ICD-10 code Z96.64), but no cases were identified from this search. The timeframe was person-years until hip fracture incidence, end of study period, or death; whichever came first, with attained age as the timescale (32).

### 3.3.4 Statistical analysis

All statistical methods were pre-registered on clinicaltrials.gov (NCT05081466). Dietary, lifestyle, demographic, and anthropometric characteristics of cohort participants at recruitment with and without a hip fracture during the study period were summarised using descriptive statistics. Cox proportional hazard regression models were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) for associations between intake of foods and nutrients and hip fracture risk. All exposures were modelled as continuous variables to investigate associations between standard portion sizes of each food and nutrient intake and hip fracture risk. Non-meat-eaters were preferentially sampled into the UKWCS (28); to account for this and to increase the generalisability of our findings to the UK population, cox models used weights based on the inverse probability of being sampled (33).

We also investigated potential non-linear associations between dietary intake of fruits and vegetables, fruits, vegetables, tea and coffee, tea, coffee, and calcium and hip fracture risk using Cox regression with restricted cubic splines, since previously published studies have suggested potential non-linear relationships between these exposures and hip fracture risk (34-36). Four knots were placed at the 5th, 35th, 65th, and 95th percentiles of each exposure intake (37). Reference levels were set to five portions/day for fruits and vegetables combined, and 700 mg/day for dietary calcium, corresponding to UK recommended intakes (38, 39). The reference level was set at three portions/day for fruits and vegetables individually, and zero cups per day for tea and coffee to compare risks in consumers and non-consumers.

Unadjusted and multivariable-adjusted models were applied. Age was controlled for in both models using attained age as the timeframe (32). Additional potential confounders included in adjusted models for food intake – hip fracture risk associations, and nutrient intake – hip fracture risk associations, were informed by a Directed Acyclic Graph (DAG) for each. Confounders for models with food or nutrient exposures included (all measured at recruitment): ethnicity (white, Asian, black, other), socio-economic status (SES; professional/managerial, intermediate, routine/manual), marital status (married/living as married, separated/divorced, single/widowed), menopausal status (premenopausal, postmenopausal), number of children (continuous), prevalence of cardiovascular disease (CVD), cancer, or diabetes (yes, no), physical activity in hours per day (continuous), smoking status (current, former, never), alcohol intake (> 1/week, ≤ 1/week, never), height (continuous), body weight (continuous), and use of any nutritional supplements (yes, no). All adjusted models were adjusted for energy intake using the all-components method, where all other individual components of energy intake besides the exposure were adjusted for (40). For models with food exposures, this involved mutual adjustment for other food and beverage groups. Models with primary nutrient exposures (dietary protein, calcium, and vitamin D intakes) were adjusted for dietary carbohydrates (excluding sugar and fibre), fibre, sugar, saturated fat (SFA), monounsaturated fatty acids (MUFA), and polyunsaturated fatty acids (PUFA) intakes, and were mutually adjusted for one-another. Models for secondary nutrients were adjusted for protein, calcium and vitamin D intakes, and were also adjusted for: carbohydrates (excluding sugar and fibre), fibre, SFA, MUFA, PUFA, and sugar intakes except where the exposure of interest was one of these variables, in which case it was omitted from the adjustment set. Confounder variable definitions, DAGs, and informed adjustment sets for each potential association are detailed in **Appendix B: Supplementary methods, Figures B2** and **B3**, and **Tables B3** and **B4**. The proportional hazards assumption was tested on the basis of Schoenfeld residuals, and was not violated for all terms in adjusted models.

BMI (< 18.5, 18.5–24.9, ≥ 25 kg/m$^2$) was added to linear adjusted models independently as an interaction term to compare potential associations between standard portion size increments in daily intake of foods and nutrients and hip fracture risk in underweight, healthy weight, and overweight women. We also stratified models with restricted cubic splines by BMI (using the same cut-offs as in linear tests) to test for non-linear associations in each BMI subgroup. Further

exploratory analyses included testing for interaction effects with each exposure modelled linearly for: age (≤ 60, > 60), menopausal status (premenopausal, postmenopausal), SES (routine/manual, intermediate, professional/managerial), smoking status (current, former, never), physical activity (< 150 minutes per week, ≥ 150 minutes per week), and use of nutritional supplements (yes, no). In each case, the potential effect modifier was omitted from the relevant adjustment set.

As a sensitivity analysis, we applied models with and without adjustment for body weight to determine if weight management contributes to any observed associations. Additional sensitivity analyses were as follows: adjusting for BMI rather than height and weight individually; adjusting for energy intake using the energy-partition method to enhance comparison with other studies (see **Appendix B: Supplementary methods** for more detail); excluding participants on long-term treatment for illness at baseline who may be generally unhealthier and at a higher risk of hip fracture; excluding participants with short survival times (< 5 years) to check for reverse causation; further adjusting for hormone replacement therapy (HRT); and further adjusting for prevalence of fracture at sites other than the hip at recruitment identified in hospital episode statistics. Participants with missing data for a variable required in a given analysis were excluded from that analysis. Statistical analyses were performed in Stata (version 17).

## 3.4 Results

### 3.4.1 Participants

Of the 30,244 potentially eligible women at recruitment, 26,318 women were included in unadjusted and adjusted analyses after excluding participants with missing covariate data for body weight (n=596), height (n=649), ethnicity (n=811), physical activity (n=1561), marital status (n=460), SES (n=331), or menopausal status (n=309). The participant flow chart is detailed in **Appendix B: Figure B2**.

### 3.4.2 Descriptive data

Characteristics of the 26,318 cohort participants at recruitment with and without a hip fracture during the study period are summarised in **Table 3.1**. Over a median follow-up time of 22.3 years (556,331 person-years), we observed 822 hip fracture cases – an overall rate of 3.1%. On average, women with a hip fracture were older at recruitment (mean (SD): 62.1 (8.0) years for cases vs 51.8 (9.1) years for non-cases), more likely to be post-menopausal, less likely to have degree-level education, and less likely to be married. BMI and height at recruitment were similar in cases and non-cases. Prevalence of CVD, cancer, or diabetes at recruitment was higher in cases (126 (15.0%) than in non-cases (2262 (9.0%)). Dietary characteristics including energy intake and protein, calcium, and vitamin D intakes were similar in cases and non-cases, as was use of any nutritional supplements. Other food and nutrient intakes of the included participants at recruitment are summarised by hip fracture incidence in **Appendix B: Table B5**. Across BMI subgroups, hip fracture rates were higher in underweight women (28 cases/545 participants) than in healthy weight (514 cases/16,659 participants) or overweight women (280 cases/9114 participants). Characteristics of the cohort at recruitment were similar when including or restricting to the 3923 women with missing covariate data (**Appendix B: Table B6**).

**Table 3.1: Characteristics of UK Women's Cohort Study participants at recruitment by hip fracture incidence.**

| Characteristics, n (%) or M (SD) | Total | Cases | Non-cases |
|---|---|---|---|
| Participants (%) | 26318 | 822 (3.1) | 25496 (96.9) |
| **Socio-demographics** | | | |
| Age, years (SD) | 52.1 (9.2) | 62.1 (8.0) | 51.8 (9.1) |
| Degree-level education (%) | 6502 (26.8) | 155 (22.2) | 6347 (27.0) |
| Socio-economic status | | | |
| Professional or managerial (%) | 19057 (72.4) | 565 (68.7) | 18492 (72.5) |
| Intermediate (%) | 2440 (9.3) | 111 (13.5) | 2329 (9.1) |
| Routine or manual (%) | 4821 (18.3) | 146 (17.8) | 4675 (18.3) |
| Married (%) | 20268 (77.0) | 586 (71.3) | 19682 (77.2) |
| White ethnicity (%) | 25992 (98.8) | 815 (99.1) | 25177 (98.7) |

| | | | |
|---|---|---|---|
| **Lifestyle** | | | |
| Exercise, hours/day (SD) | 0.2 (0.5) | 0.2 (0.4) | 0.2 (0.5) |
| Smoking status | | | |
| Current (%) | 3513 (13.3) | 112 (13.6) | 3401 (13.3) |
| Former (%) | 7947 (30.2) | 255 (31.0) | 7692 (30.2) |
| Never (%) | 14858 (56.5) | 455 (55.4) | 14403 (56.5) |
| Alcohol consumption | | | |
| >1 serving/week (%) | 13918 (52.9) | 389 (47.3) | 13529 (53.1) |
| ≤ 1 serving/week (%) | 9290 (35.3) | 280 (34.1) | 9010 (35.3) |
| Never (%) | 3110 (11.8) | 153 (18.6) | 2957 (11.6) |
| Nutritional supplementation (%) | 14009 (53.2) | 425 (51.7) | 13584 (53.3) |
| **Anthropometrics** | | | |
| BMI, $kg/m^2$ (SD) | 24.4 (4.2) | 24.2 (4.3) | 24.4 (4.2) |
| < 18.5 (%) | 545 (2.1) | 28 (3.4) | 517 (2.0) |
| 18.5 – 24.9 (%) | 16659 (63.3) | 514 (62.5) | 16145 (63.3) |
| ≥ 25 (%) | 9114 (34.6) | 280 (34.1) | 8834 (34.6) |
| Height, m (SD) | 1.6 (0.1) | 1.6 (0.1) | 1.6 (0.1) |
| **Diet and nutritional intake** | | | |
| Dietary pattern | | | |
| Regular meat-eater (%) | 12221 (46.4) | 394 (47.9) | 11827 (46.4) |
| Occasional meat-eater (%) | 6902 (26.2) | 247 (30.0) | 6655 (26.1) |
| Pescatarian (%) | 3377 (12.8) | 80 (9.7) | 3297 (12.9) |
| Vegetarian (%) | 3818 (14.5) | 101 (12.3) | 3717 (14.6) |
| Energy, kcal/day (SD) | 2300 (654.8) | 2346 (696.6) | 2298 (653.4) |
| Fruits and vegetables, g/day (SD) | 648.7 (299.8) | 679.5 (313.0) | 647.7 (299.4) |
| Fruit, g/day (SD) | 377.4 (227.3) | 395.1 (231.9) | 376.9 (227.1) |
| Vegetables, g/day (SD) | 271.3 (139.0) | 284.4 (146.3) | 270.9 (138.7) |
| Total meat, g/day (SD) | 86.5 (81.2) | 87.5 (77.4) | 86.4 (81.3) |
| Total fish, g/day (SD) | 33.7 (29.6) | 36.1 (30.6) | 33.6 (29.6) |
| Total dairy, g/day (SD) | 412.8 (213.6) | 432.7 (218.5) | 412.1 (213.5) |
| Milk, ml/day (SD) | 304.1 (190.0) | 317.5 (198.0) | 303.6 (189.7) |
| Yogurt, g/day (SD) | 59.6 (68.2) | 61.0 (67.5) | 59.5 (68.2) |
| Cheese, g/day (SD) | 27.4 (27.6) | 26.7 (34.8) | 27.5 (27.4) |

| | | | |
|---|---|---|---|
| Tea and coffee, cups/day (SD) | 5.0 (2.2) | 4.8 (2.2) | 5.0 (2.2) |
| Tea, cups/day (SD) | 3.0 (2.0) | 3.0 (2.0) | 3.0 (2.0) |
| Coffee, cups/day (SD) | 2.0 (1.8) | 1.8 (1.7) | 2.0 (1.8) |
| | | | |
| Protein, g/day (SD) | 88.1 (26.3) | 89.7 (27.2) | 88.1 (26.2) |
| Calcium, mg/day (SD) | 1135 (365.4) | 1160 (377.1) | 1134 (365.0) |
| Vitamin D, µg/day (SD) | 3.1 (1.7) | 3.4 (1.8) | 3.1 (1.7) |
| **Other** | | | |
| Menopausal status | | | |
| Postmenopausal (%) | 14611 (55.5) | 734 (89.3) | 13877 (54.4) |
| Premenopausal (%) | 11707 (44.5) | 88 (10.7) | 11619 (45.6) |
| ≥ 1 children (%) | 20723 (78.7) | 667 (81.1) | 20056 (78.7) |
| Prevalence of CVD, cancer, or diabetes (%) | 2388 (9.1) | 126 (15.3) | 2262 (8.9) |

Nutritional intakes are from diet sources only and do not include supplementary sources. M (SD): mean (standard deviation); BMI: body mass index; CVD: cardiovascular disease.

### 3.4.3 Main results

Amongst primary foods and nutrients investigated, a 25 g/day increment in dietary protein intake was associated with a reduced risk of hip fracture in the adjusted model (0.86 (0.73, 1.00); **Figure 1**). One extra cup per day of tea or coffee was also inversely associated with hip fracture risk in the adjusted model (0.96 (0.92, 0.996)). There was no clear evidence of an association between hip fracture risk and dietary calcium (per 300 mg/day), vitamin D (per µg/day), or any other food intakes in adjusted models.

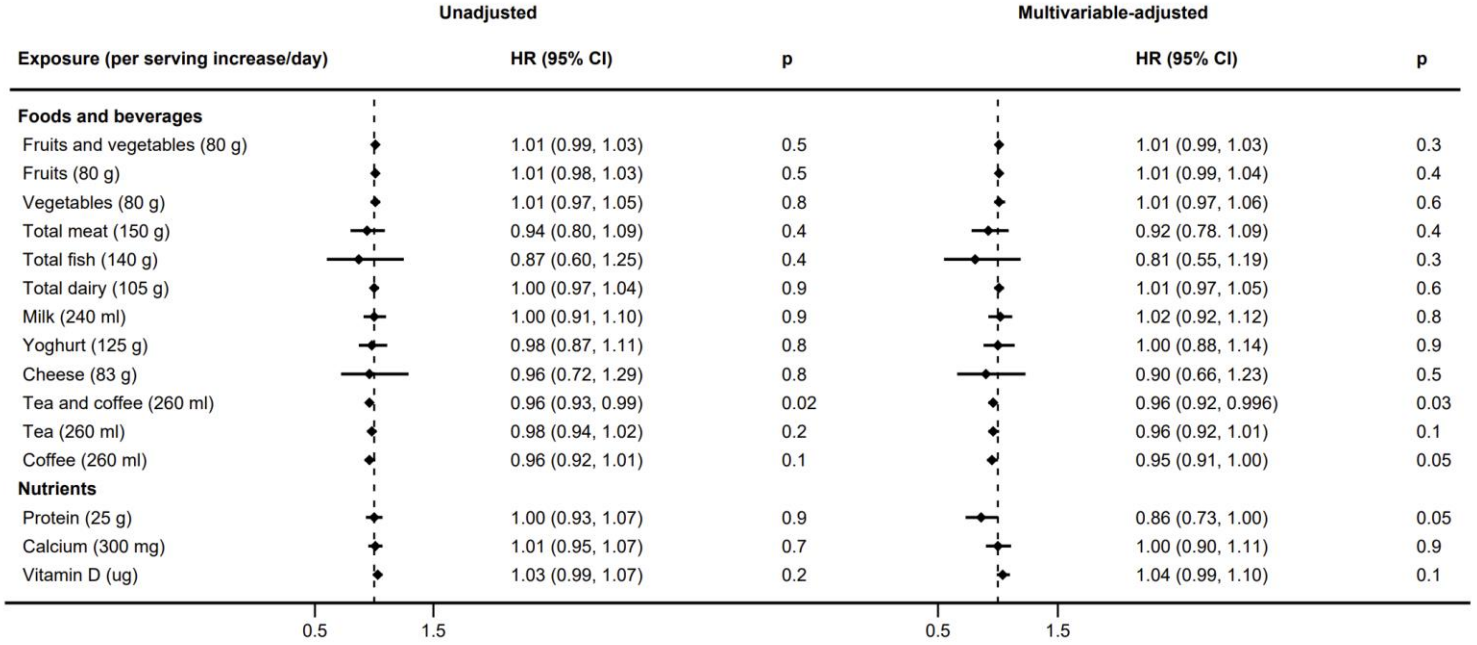



**Figure 3.1: Associations between dietary intake of foods, nutrients and risk of hip fracture in UK Women's Cohort Study participants.** Unadjusted and adjusted models were based on 26,318 women with 822 hip fracture cases (556,331 person-years), and both controlled for age. All adjusted models were also adjusted for (all at recruitment): ethnicity (white, Asian, black, other), socio-economic status (SES; professional/managerial, intermediate, routine/manual), marital status (married/living as married, separated/divorced, single/widowed), menopausal status (premenopausal, postmenopausal), number of children (continuous), prevalence of cardiovascular disease, cancer, or diabetes (yes, no), physical activity in hours per day (continuous), smoking status (current, former, never), alcohol intake (> 1/week, ≤ 1/week, never), height (continuous), weight (continuous), and use of any nutritional supplements (yes, no). Models with food exposures were mutually adjusted for other major foods and beverages. Models for protein, calcium, and vitamin D intakes were adjusted for carbohydrates (excluding sugar and fibre), fibre, sugar, saturated fat, monounsaturated fatty acids (MUFA), and polyunsaturated fatty acids (PUFA) intakes, and were mutually adjusted for one-another. HR (95% CI): hazard ratio (95% confidence interval).

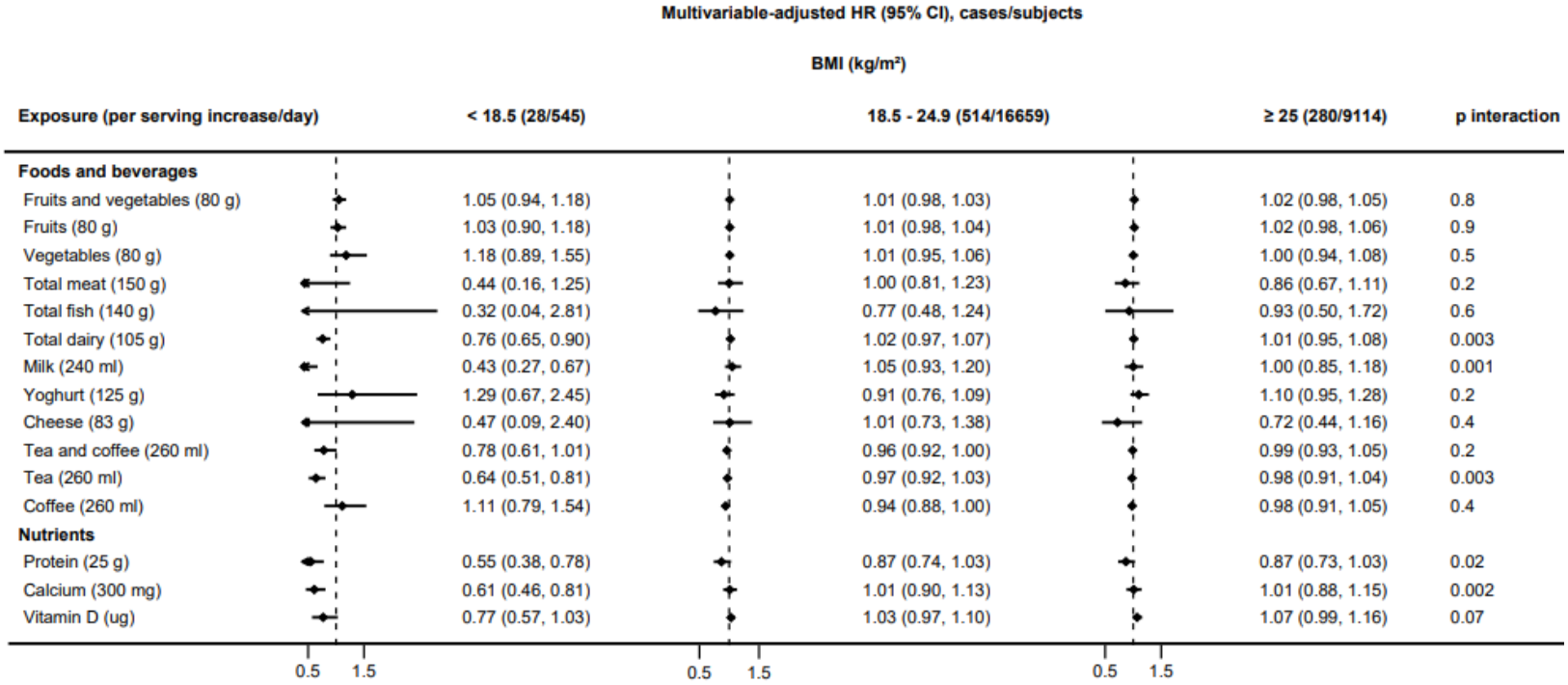



**Figure 3.2: Associations between dietary intake of foods, nutrients and risk of hip fracture in UK Women's Cohort Study participants by body mass index (BMI).** All models were adjusted for (all at recruitment): ethnicity (white, Asian, black, other), socio-economic status (SES; professional/managerial, intermediate, routine/manual), marital status (married/living as married, separated/divorced, single/widowed), menopausal status (premenopausal, postmenopausal), number of children (continuous), prevalence of cardiovascular disease, cancer, or diabetes (yes, no), physical activity in hours per day (continuous), smoking status (current, former, never), alcohol intake (> 1/week, ≤ 1/week, never), and use of any nutritional supplements (yes, no). Models with food exposures were mutually adjusted for other major foods and beverages. Models for protein, calcium, and vitamin D intakes were adjusted for carbohydrates (excluding sugar and fibre), fibre, sugar, saturated fat, monounsaturated fatty acids (MUFA), and polyunsaturated fatty acids (PUFA) intakes, and were mutually adjusted for one-another. HR (95% CI): hazard ratio (95% confidence interval).

Restricted cubic spline models showed no evidence of non-linear associations between dietary intake of calcium, fruits and vegetables combined, fruits, vegetables, tea and coffee combined, tea, and coffee and hip fracture risk (**Appendix B: Figures B4-B6**).

Among secondary foods and nutrients, after adjusting for confounders, a 10 g/day increment in fat intake was associated with an higher risk of hip fracture (1.04 (1.00, 1.08); **Appendix B: Table B7**). There was no clear evidence of associations of other secondary foods or nutrients with hip fracture risk.

### 3.4.4 Subgroup analyses

BMI modified linear associations between increments in dietary protein (25 g/day) and calcium (300 mg/day) intakes and hip fracture risk ($p_{interaction}$= 0.02 and $p_{interaction}$ = 0.002, respectively; **Figure 3.2**). A 25 g/day increment in protein intake was associated with a reduced risk of hip fracture in underweight women, but less so in healthy or overweight women. A 300 mg/day increment in dietary calcium intake was associated with a reduced risk of hip fracture in underweight women only. Whilst there was no evidence of an overall association between vitamin D intake and hip fracture risk, there was some evidence for a more potential protective association in underweight women ($p_{interaction}$= 0.07).

BMI also modified linear associations between hip fracture risk and dietary intake of total dairy, milk, and tea ($p_{interaction}$ = 0.003, $p_{interaction}$ = 0.001, and $p_{interaction}$ = 0.003, respectively). Increments of 105 g/day of total dairy, 240 ml/day of milk, and 260 ml/day of tea were associated with reduced risks of hip fracture in underweight women only. In analyses of secondary foods and nutrients, BMI modified linear associations between dietary intake of vitamin B2, vitamin B12, and zinc hip fracture risk ($p_{interaction}$ = 0.02, $p_{interaction}$= 0.03, and $p_{interaction}$= 0.02, respectively; **Appendix B: Table B8**). There was no clear evidence of a non-linear association between any food or nutrient intake and hip fracture risk in any BMI category (**Appendix B: Figures B7-B9**). Results of other subgroup analyses by age, menopausal status, SES, smoking status, physical activity, and use of nutritional supplements are presented and described in **Appendix B: Tables B9-14** and **Supplementary results**.

### 3.4.5 Sensitivity analyses

All adjusted estimates remained broadly unchanged across most sensitivity analyses, though excluding participants on long-term treatment for illness changed the association of total fish intake with hip fracture risk from 0.81 (0.55, 1.19) to 1.16 (0.74, 1.82) (**Appendix B: Table B15**).

## 3.5 Discussion

### 3.5.1 Principal findings

In this prospective cohort of middle-aged UK women, there was suggestive evidence of inverse associations between intake of dietary protein, tea and coffee, and hip fracture risk. There was no clear evidence of overall associations between hip fracture risk and dietary intake of calcium, vitamin D, or animal foods, including meat, fish, eggs, and dairy products. Subgroup analyses showed suggestive evidence of effect modification by BMI for dietary protein, calcium, total dairy, milk, and tea intakes, where inverse associations were stronger in underweight women.

### 3.5.2 Comparison with other studies

There is limited prospective evidence of associations between consumption of many foods and nutrients and hip fracture risk (9). This study provides further information on relationships of 37 foods, beverages, or nutrients with hip fracture risk.

The inverse association between dietary protein intake and hip fracture risk observed here is largely consistent with previous evidence (12, 41-43). A meta-analysis of observational studies reported a lower risk of hip fracture with higher protein intakes in adults (41). A more recent study of US adults showed an inverse association in men but not women, though an inverse association was observed when restricted to women < 65 years old at recruitment, which resembles the age range of the women in the UKWCS at recruitment (43). We found that the association for protein was more pronounced in underweight women. Similarly, a recent case-control study in Chinese adults showed an inverse association for protein intake with hip fracture risk that was more evident in those with a lower BMI (42).

We found a small reduction in hip fracture risk for each additional cup of tea or coffee consumed daily, where the association for tea was stronger in underweight participants. Similarly, a meta-analysis of Western studies found that individuals consuming 1-4 cups per day of tea were at a lower risk for hip fracture than non-consumers (44). In contrast, two meta-analyses found no clear association between coffee consumption and hip fracture risk (44, 45). The majority of studies included in those meta-analyses had insufficient power to detect small associations, and had follow-up durations that may have been too short for a long-term effect of regular tea and coffee consumption to be observed. In the more recently published Singapore-Chinese Health study, an higher risk of hip fracture was observed in men and women with intakes of coffee exceeding four cups per day compared to those that drank coffee less than once per week (34). An elevated risk of hip fracture at high coffee intakes was not observed here, possibly due to the lower mean coffee consumption in the UK Women's Cohort (2 cups per day).

In line with our previous umbrella review (9), we found no clear evidence of overall associations between hip fracture risk and dietary intake of calcium, vitamin D, or several animal foods. A systematic review also showed no association between dietary intake of calcium, milk, or total dairy and risk of hip fracture (46). In contrast to our results, meat consumption has been associated with a reduced risk of hip fracture in an American cohort (24). However, that study identified hip fracture cases through a self-administered questionnaire, which is more prone to selective drop-out than objective record linkage used here, or this could reflect differences in type of meat consumed between the cohorts.

### 3.5.3 Possible explanations and implications

The linear dose-response relationship between protein intake and hip fracture risk could be explained by the positive effects of protein on bone and muscle properties that decline with age. Protein has been positively associated with BMD directly (47), and stimulates insulin-like growth factor-1 (IGF-1) production which increases formation of osteoblasts, is positively associated with BMD, and is negatively associated with risk of fractures (43, 48, 49). Higher protein intakes also contribute to adequate muscle mass, which may reduce risk of fall-related hip fractures, which account for 90% of all hip fractures (11, 50, 51). The association between protein intake and hip fracture risk was stronger in underweight women. Given that BMD and muscle mass may

decrease with BMI (26, 52), protein may be particularly important in contributing to adequate bone and muscle health, mitigating the increased risk of hip fracture observed with particularly low BMD or muscle mass (10, 11). However, statistical power here was limited in underweight participants, and information on BMD and muscle mass was not available. Further research is needed to confirm if the association depends on body weight and body composition, in particular BMD.

Tea and coffee are high in biologically active compounds such as polyphenols and phytoestrogens, particularly catechins, which may enhance osteoblast activity and suppress osteoclastic activity by reducing oxidative stress, resulting in higher BMD and lower risk of hip fracture (44). A stronger association was observed for tea consumption in underweight women; tea could help to mitigate the low BMD-induced increase in hip fracture risk that may be more prominent at a lower BMI (26). Further research is needed to clarify associations between tea and coffee consumption and hip fracture risk, and should determine if associations depend on the type of tea or coffee consumed and the amount of milk or sugar added, since polyphenol and nutrient contents vary (53).

We observed inverse associations between hip fracture risk and dietary intake of calcium, vitamin D, milk, and total dairy in underweight women only. Calcium is the dominant mineral in bone and vitamin D aids its absorption (54). Total calcium intake and serum vitamin D levels may be independently associated with higher BMD (13, 55), and therefore could reduce risk of hip fracture when BMD levels are very low, as may be the case in underweight women (26, 56). The abundance of protein, calcium, and vitamin D in dairy products could also explain the inverse association of total dairy and milk intakes with hip fracture risk in underweight women. However, effects of dietary calcium and vitamin D on BMD are less clear, and when determining their associations with hip fracture risk, we could not account for non-dietary sources, including supplements and sunlight exposure, which may modify associations. We also had insufficient power to precisely estimate these associations in the underweight group. Further research is needed to confirm the role of dietary calcium, vitamin D, and foods such as dairy products in which these nutrients are abundant on hip fracture risk with non-dietary sources accounted for, particularly in underweight women who may have lower BMD.

### 3.5.4 Strengths and limitations

The large sample size facilitated good statistical power to precisely estimate associations between several foods, nutrients, and hip fracture risk. The large number of foods and nutrients considered increased the risk of a type-one error, but we pre-specified hypothesis-testing primary exposures and hypothesis-generating secondary exposures to reduce this risk. We identified hip fracture cases by linking participants' dietary and lifestyle data with their hospital records, which reduced reporting error and selective drop-out over a long follow-up duration.

We were unable to differentiate between fragility and traumatic hip fractures due to a lack of data on the cause of hip fractures. Whilst we excluded participants with a previous hip fracture at recruitment based on hospital records, this was likely an incomplete exclusion, since the questionnaire did not ask about history of fractures, and hospital data of records before 1997 was not available. Of other limitations, BMI was calculated based on self-reported height and weight, implying potential measurement error. Additionally, the low number of underweight women in this study limited statistical power to precisely estimate associations between foods, nutrients, and hip fracture risk in that group. We adjusted for all potential confounders, but residual confounding remains possible. For example, we could not adjust for calcium or vitamin D supplementation, which could mask true relationships between hip fracture risk and dietary calcium and vitamin D in particular. Whilst we adjusted for alcohol consumption, we were unable to differentiate between moderate and heavy drinkers, who may be at different risks of hip fracture (9). A validated FFQ was used to measure food and nutrient intake at recruitment only, meaning any changes in food and nutrient intake over time were not captured, potentially resulting in attenuated estimates. Our results may not apply to men or other ethnic groups, and UKWCS participants may be healthier on average than the UK population due to a healthy participant bias, reducing generalisability.

### 3.5.5 Conclusion

In this prospective cohort of middle-aged UK women, findings suggest that a higher protein intake and consumption of tea and coffee may each independently reduce risk of hip fracture in a linear dose-response manner. There was no clear evidence of overall associations between hip

fracture risk and dietary intake of calcium, vitamin D, or animal products, but there was some evidence of stronger inverse associations in underweight women for these foods and nutrients. The potential roles of some foods and nutrients in hip fracture prevention, particularly protein, tea and coffee in underweight women, merit confirmation in further cohort studies and randomised controlled trials to enable the formulation of dietary recommendations for reducing hip fracture risk.

## 3.6 References


1. Dhanwal DK, Dennison EM, Harvey NC, Cooper C. Epidemiology of hip fracture: Worldwide geographic variation. Indian J Orthop. 2011;45(1):15-22.
2. Murphy EA, Ehrhardt B, Gregson CL, von Arx OA, Hartley A, Whitehouse MR, et al. Machine learning outperforms clinical experts in classification of hip fractures. Sci Rep. 2022;12(1):2058.
3. Rosengren BE, Karlsson MK. The annual number of hip fractures in Sweden will double from year 2002 to 2050: projections based on local and nationwide data. Acta Orthop. 2014;85(3):234-7.
4. Cheung CL, Ang SB, Chadha M, Chow ES, Chung YS, Hew FL, et al. An updated hip fracture projection in Asia: The Asian Federation of Osteoporosis Societies study. Osteoporos Sarcopenia. 2018;4(1):16-21.
5. Alexiou KI, Roushias A, Varitimidis SE, Malizos KN. Quality of life and psychological consequences in elderly patients after a hip fracture: a review. Clin Interv Aging. 2018;13:143-50.
6. Peraza-Delgado A, Sánchez-Gómez MB, Gómez-Salgado J, Romero-Martín M, Novo-Muñoz M, Duarte-Clíments G. Non-Pharmacological Interventions towards Preventing the Triad Osteoporosis-Falls Risk-Hip Fracture, in Population Older than 65. Scoping Review. J Clin Med. 2020;9(8).
7. Manetti S, Turchetti G, Fusco F. Determining the cost-effectiveness requirements of an exoskeleton preventing second hip fractures using value of information. BMC Health Serv Res. 2020;20(1):955.

8. Adeyemi A, Delhougne G. Incidence and Economic Burden of Intertrochanteric Fracture: A Medicare Claims Database Analysis. JB JS Open Access. 2019;4(1):e0045.

9. Webster J, Rycroft CE, Greenwood DC, Cade JE. Dietary risk factors for hip fracture in adults: An umbrella review of meta-analyses of prospective cohort studies. PLoS One. 2021;16(11):e0259144.

10. Bouxsein ML, Eastell R, Lui LY, Wu LA, de Papp AE, Grauer A, et al. Change in Bone Density and Reduction in Fracture Risk: A Meta-Regression of Published Trials. J Bone Miner Res. 2019;34(4):632-42.

11. Lang T, Cauley JA, Tylavsky F, Bauer D, Cummings S, Harris TB. Computed tomographic measurements of thigh muscle cross-sectional area and attenuation coefficient predict hip fracture: the health, aging, and body composition study. J Bone Miner Res. 2010;25(3):513-9.

12. Groenendijk I, den Boeft L, van Loon LJC, de Groot LCPGM. High Versus low Dietary Protein Intake and Bone Health in Older Adults: a Systematic Review and Meta-Analysis. Computational and Structural Biotechnology Journal. 2019;17:1101-12.

13. Vannucci L, Fossi C, Quattrini S, Guasti L, Pampaloni B, Gronchi G, et al. Calcium Intake in Bone Health: A Focus on Calcium-Rich Mineral Waters. Nutrients. 2018;10(12).

14. Khazai N, Judd SE, Tangpricha V. Calcium and vitamin D: skeletal and extraskeletal health. Curr Rheumatol Rep. 2008;10(2):110-7.

15. Gunton JE, Girgis CM. Vitamin D and muscle. Bone Rep. 2018;8:163-7.

16. Yao P, Bennett D, Mafham M, Lin X, Chen Z, Armitage J, et al. Vitamin D and Calcium for the Prevention of Fracture: A Systematic Review and Meta-analysis. JAMA Netw Open. 2019;2(12):e1917789.

17. Mozaffari H, Djafarian K, Mofrad MD, Shab-Bidar S. Dietary fat, saturated fatty acid, and monounsaturated fatty acid intakes and risk of bone fracture: a systematic review and meta-analysis of observational studies. Osteoporos Int. 2018;29(9):1949-61.

18. Knapik JJ, Hoedebecke SS. Vitamin A and Bone Fractures: Systematic Review and Meta-Analysis. J Spec Oper Med. 2021;21(2):100-7.

19. Dai Z, Wang R, Ang LW, Yuan JM, Koh WP. Dietary B vitamin intake and risk of hip fracture: the Singapore Chinese Health Study. Osteoporos Int. 2013;24(7):2049-59.

20. Brondani JE, Comim FV, Flores LM, Martini LA, Premaor MO. Fruit and vegetable intake and bones: A systematic review and meta-analysis. PLoS One. 2019;14(5):e0217223.
21. Luo SY, Li Y, Luo H, Yin XH, Lin DR, Zhao K, et al. Increased intake of vegetables, but not fruits, may be associated with reduced risk of hip fracture: A meta-analysis. Sci Rep. 2016;6:8.
22. Hidayat K, Du X, Shi BM, Qin LQ. Systematic review and meta-analysis of the association between dairy consumption and the risk of hip fracture: critical interpretation of the currently available evidence. Osteoporosis Int. 2020;31(8):1411-25.
23. Sadeghi O, Djafarian K, Ghorabi S, Khodadost M, Nasiri M, Shab-Bidar S. Dietary intake of fish, n-3 polyunsaturated fatty acids and risk of hip fracture: A systematic review and meta-analysis on observational studies. Crit Rev Food Sci Nutr. 2019;59(8):1320-33.
24. Lousuebsakul-Matthews V, Thorpe DL, Knutsen R, Beeson WL, Fraser GE, Knutsen SF. Legumes and meat analogues consumption are associated with hip fracture risk independently of meat intake among Caucasian men and women: the Adventist Health Study-2. Public Health Nutr. 2014;17(10):2333-43.
25. Armstrong ME, Cairns BJ, Banks E, Green J, Reeves GK, Beral V. Different effects of age, adiposity and physical activity on the risk of ankle, wrist and hip fractures in postmenopausal women. Bone. 2012;50(6):1394-400.
26. Hariri AF, Almatrafi MN, Zamka AB, Babaker AS, Fallatah TM, Althouwaibi OH, et al. Relationship between Body Mass Index and T-Scores of Bone Mineral Density in the Hip and Spine Regions among Older Adults with Diabetes: A Retrospective Review. J Obes. 2019;2019:9827403.
27. Lachat C, Hawwash D, Ocké MC, Berg C, Forsum E, Hörnell A, et al. Strengthening the Reporting of Observational Studies in Epidemiology-Nutritional Epidemiology (STROBE-nut): An Extension of the STROBE Statement. PLoS Med. 2016;13(6):e1002036.
28. Cade JE, Burley VJ, Alwan NA, Hutchinson J, Hancock N, Morris MA, et al. Cohort Profile: The UK Women's Cohort Study (UKWCS). Int J Epidemiol. 2017;46(2):e11.
29. Riboli E, Kaaks R. The EPIC Project: rationale and study design. European Prospective Investigation into Cancer and Nutrition. Int J Epidemiol. 1997;26 Suppl 1:S6-14.
30. Foods Standards Agency. Food Portion Sizes. London: The Stationery Office. 2002.

31. Public Health England. McCance and Widdowson's composition of foods integrated dataset. 2019.

32. Korn EL, Graubard BI, Midthune D. Time-to-event analysis of longitudinal follow-up of a survey: choice of the time-scale. Am J Epidemiol. 1997;145(1):72-80.

33. Rada-Fernandez de Jauregui D, Evans CEL, Jones P, Greenwood DC, Hancock N, Cade JE. Common dietary patterns and risk of cancers of the colon and rectum: Analysis from the United Kingdom Women's Cohort Study (UKWCS). Int J Cancer. 2018;143(4):773-81.

34. Dai Z, Jin A, Soh AZ, Ang LW, Yuan JM, Koh WP. Coffee and tea drinking in relation to risk of hip fracture in the Singapore Chinese Health Study. Bone. 2018;112:51-7.

35. Byberg L, Bellavia A, Orsini N, Wolk A, Michaëlsson K. Fruit and vegetable intake and risk of hip fracture: a cohort study of Swedish men and women. J Bone Miner Res. 2015;30(6):976-84.

36. Warensjö E, Byberg L, Melhus H, Gedeborg R, Mallmin H, Wolk A, et al. Dietary calcium intake and risk of fracture and osteoporosis: prospective longitudinal cohort study. Bmj. 2011;342:d1473.

37. Harrell FE, Jr., Lee KL, Pollock BG. Regression models in clinical studies: determining relationships between predictors and response. J Natl Cancer Inst. 1988;80(15):1198-202.

38. NHS. The Eatwell Guide. 2019 [Available from: https://www.nhs.uk/live-well/eat-well/food-guidelines-and-food-labels/the-eatwell-guide/].

39. NHS. Vitamins and minerals: calcium. 2020 [Available from: https://www.nhs.uk/conditions/vitamins-and-minerals/calcium/].

40. Tomova GD, Arnold KF, Gilthorpe MS, Tennant PWG. Adjustment for energy intake in nutritional research: a causal inference perspective. Am J Clin Nutr. 2022;115(1):189-98.

41. Wu AM, Sun XL, Lv QB, Zhou Y, Xia DD, Xu HZ, et al. The Relationship between Dietary Protein Consumption and Risk of Fracture: a subgroup and dose-response meta-analysis of prospective cohort studies. Sci Rep. 2015;5:8.

42. Liu ZM, Huang Q, Li SY, Liu YP, Wu Y, Zhang SJ, et al. A 1:1 matched case-control study on dietary protein intakes and hip fracture risk in Chinese elderly men and women. Osteoporos Int. 2021;32(11):2205-16.

43. Fung TT, Meyer HE, Willett WC, Feskanich D. Protein intake and risk of hip fractures in postmenopausal women and men age 50 and older. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2017;28(4):1401-11.

44. Sheng J, Qu X, Zhang X, Zhai Z, Li H, Liu X, et al. Coffee, tea, and the risk of hip fracture: a meta-analysis. Osteoporos Int. 2014;25(1):141-50.

45. Li S, Dai Z, Wu Q. Effect of coffee intake on hip fracture: a meta-analysis of prospective cohort studies. Nutr J. 2015;14:38.

46. Bolland MJ, Leung W, Tai V, Bastin S, Gamble GD, Grey A, et al. Calcium intake and risk of fracture: systematic review. Bmj. 2015;351:h4580.

47. Shams-White MM, Chung M, Du M, Fu Z, Insogna KL, Karlsen MC, et al. Dietary protein and bone health: a systematic review and meta-analysis from the National Osteoporosis Foundation. Am J Clin Nutr. 2017;105(6):1528-43.

48. Bonjour JP. The dietary protein, IGF-I, skeletal health axis. Horm Mol Biol Clin Investig. 2016;28(1):39-53.

49. Yuan S, Wan Z-H, Cheng S-L, Michaëlsson K, Larsson SC. Insulin-like Growth Factor-1, Bone Mineral Density, and Fracture: A Mendelian Randomization Study. The Journal of clinical endocrinology and metabolism. 2021;106(4):e1552-e8.

50. Tagawa R, Watanabe D, Ito K, Ueda K, Nakayama K, Sanbongi C, et al. Dose-response relationship between protein intake and muscle mass increase: a systematic review and meta-analysis of randomized controlled trials. Nutr Rev. 2020;79(1):66-75.

51. Hayes WC, Myers ER, Morris JN, Gerhart TN, Yett HS, Lipsitz LA. Impact near the hip dominates fracture risk in elderly nursing home residents who fall. Calcif Tissue Int. 1993;52(3):192-8.

52. Song J, Zhang R, Lv L, Liang J, Wang W, Liu R, et al. The Relationship Between Body Mass Index and Bone Mineral Density: A Mendelian Randomization Study. Calcif Tissue Int. 2020;107(5):440-5.

53. Liczbiński P, Bukowska B. Tea and coffee polyphenols and their biological properties based on the latest in vitro investigations. Ind Crops Prod. 2022;175:114265.

54. Feskanich D, Willett WC, Colditz GA. Calcium, vitamin D, milk consumption, and hip fractures: a prospective study among postmenopausal women. Am J Clin Nutr. 2003;77(2):504-11.

55. Sadat-Ali M, Al Elq AH, Al-Turki HA, Al-Mulhim FA, Al-Ali AK. Influence of vitamin D levels on bone mineral density and osteoporosis. Ann Saudi Med. 2011;31(6):602-8.

56. Mendes MM, Hart KH, Lanham-New SA, Botelho PB. Association between 25-Hydroxyvitamin D, Parathyroid Hormone, Vitamin D and Calcium Intake, and Bone Density in Healthy Adult Women: A Cross-Sectional Analysis from the D-SOL Study. Nutrients. 2019;11(6):1267.

# Chapter 4 Risk of hip fracture in meat-eaters, pescatarians, and vegetarians: results from the UK Women's Cohort Study

**James Webster[1], Darren C. Greenwood[2,] and Janet E. Cade[1]**

1 Nutritional Epidemiology Group, School of Food Science and Nutrition, University of Leeds, Leeds, LS2 9JT.

2 School of Medicine, University of Leeds, Leeds, LS2 9JT.

Published: BMC Medicine. 2022. 20(1): 1-10. https://doi.org/10.1186/s12916-022-02468-0

**This chapter is an exact copy of the journal paper referred to above.**

11

## 4.1 Abstract

**Background:** Risk of hip fracture in women on plant-based diets is unclear. We aimed to investigate the risk of hip fracture in occasional meat-eaters, pescatarians, and vegetarians compared to regular meat-eaters in the UK Women's Cohort Study, and to determine if potential associations between each diet group and hip fracture risk are modified by body mass index (BMI).

**Methods:** UK women, ages 35–69 years, were classified as regular meat-eaters (≥ 5 servings/week), occasional meat-eaters (< 5 servings/week), pescatarian (ate fish but not meat), or vegetarian (ate neither meat or fish) based on a validated 217-item food frequency questionnaire completed in 1995-1998. Incident hip fractures were identified via linkage to Hospital Episode Statistics up to March 2019. Cox regression models were used to estimate associations between each diet group and hip fracture risk over a median follow-up time of 22.3 years.

**Results:** Among 26,318 women, 822 hip fracture cases were observed (443,277 person-years). After adjustment for confounders, vegetarians (HR (95% CI): 1.33 (1.03, 1.71)) but not occasional meat-eaters (1.00 (0.85, 1.18)) or pescatarians (0.97 (0.75, 1.26)) had a greater risk of hip fracture than regular meat-eaters. There was no clear evidence of effect modification by BMI in any diet group ($p_{interaction}$ = 0.3).

**Conclusions:** Vegetarian women were at a higher risk of hip fracture compared to regular meat-eaters. Further research is needed to confirm this in men and non-European populations, and to identify factors responsible for the observed risk difference. Further research exploring the role of BMI and nutrients abundant in animal-sourced foods is recommended.

**Keywords:** Diet, nutrition, vegetarian, hip fracture, cohort study

**Protocol registration:** Clinicaltrials.gov NCT05081466, registered retrospectively

## 4.2 Background

Hip fractures are most common in elderly women (1), and are becoming increasingly prevalent in the UK and globally due to growing ageing populations (2, 3). Health-related quality of life declines after hip fracture and mortality increases (1, 4). Social and economic costs from hip fractures are also substantial (2), with an international average cost 12 months after first hip fracture of $44,000 per patient (5). There are growing concerns regarding bone health and fracture risk in individuals on meat-free diets (6-9), but associations between these diet groups and hip fracture risk remain unclear. An estimated 5% of the US population (10), 3% of the UK population (11, 12), and 30% of India's population follow vegetarian diets (13). The number of vegetarians worldwide is increasing (7), possibly due to accumulating evidence of reduced risks of several chronic diseases, including diabetes (14), ischaemic heart disease, and cancer (15), and a lower environmental footprint of vegetarian diets compared to omnivorous diets (16, 17). Understanding hip fracture risk in vegetarians in particular is therefore becoming increasingly important to public health.

Whilst diet quality varies within vegetarians (16), vegetarian diets are often characterised by higher intake of fruits and vegetables including foods high in vegetable protein (8), which have been associated with a reduced hip fracture risk in adults in reviews of previous epidemiological studies (18-21). However, vegetarian diets have also been characterised by lower dietary intakes of nutrients that have been positively associated with bone mineral density (BMD) and are more abundant in animal products than in plants. Examples include total protein, calcium, vitamin D, vitamin B12, and ω-3 fatty acids (6, 22), though associations between these nutrients and hip fracture risk are unclear and complex (20). Studies have also reported a lower average body mass index (BMI) in vegetarians and pescatarians compared to omnivores (8, 23), which has been inversely associated with hip fracture risk (24). Risk differences for hip fracture between vegetarians, pescatarians, and meat-eaters are therefore plausible, but evidence is limited exploring these dietary patterns.

Cross-sectional studies show lower BMD in vegetarians compared to non-vegetarians (25, 26), but prospective studies comparing risk of hip fracture in these diet groups over time are scarce

and limited (8, 9). The recently published European Prospective Investigation into Cancer (EPIC)-Oxford cohort study of UK men and women showed a greater risk of hip fracture in pescatarians, vegetarians, and vegans compared to meat-eaters (8). The Adventist Health Study-2 (AHS-2) also showed greater risk of hip fracture in vegans but not vegetarians compared to meat-eaters in US women, but with outcome data based on self-administered questionnaires (9). To our knowledge, no other prospective study has compared risk of hip fracture in vegetarians and non-vegetarians, therefore associations between these diet groups and hip fracture risk require further investigation.

The United Kingdom Women's Cohort Study (UKWCS) has been enriched with vegetarians and pescatarians, so is well-suited to study risk of chronic diseases over time in these diet groups (27). Our objectives were therefore to investigate the risk of hip fracture in occasional meat-eaters, pescatarians, and vegetarians compared to regular meat-eaters in middle-aged UK women, and to determine if potential associations between each diet group and hip fracture risk are modified by BMI.

## 4.3 Methods

We followed the Strengthening the Reporting of Observational Studies in Epidemiology – Nutritional Epidemiology (STROBE-nut) guidelines for the reporting of cohort studies (**Appendix C: Table C1**) (28).

### 4.3.1 Study design and participants

The UKWCS has been described in detail elsewhere (27). In brief, 500,000 women from England, Scotland, and Wales responded to a direct mail questionnaire from the World Cancer Research Fund (WCRF) between 1995-1998. Of the 75% that agreed to participate in a more detailed survey, those who identified as vegetarian or non-red meat-eaters, and were aged 35–69 years when completing the WCRF questionnaire, were eligible for inclusion in the UKWCS. For each vegetarian, the next non-vegetarian or red meat-eater who was aged within 10 years of the vegetarian was selected to form a comparison group. In total, 35,372 women across the UK, aged 35–69 years, responded to a postal questionnaire that collected dietary, lifestyle, demographic,

and anthropometric data at recruitment (1995–1998). This approach was taken to maximise power in comparing risk of hip fracture across diet groups (29). Participants were then excluded if they lived outside of England (n=3821), had a hip fracture on or before the date of recruitment according to hospital episode statistics (n=2), had missing age data (n=364), or had outlier FFQ or covariate data (daily energy intake < 500 kcal or > 5000 kcal, BMI < 10 or > 60 kg/m2, or FFQ intakes > 3 standard deviations from the mean; n=941), leaving 30,244 participants potentially eligible for inclusion in this study (**Appendix C: Figure C1**). Ethical approval was granted from the National Research Ethics Service Committee for Yorkshire & the Humber – Leeds East (reference 15/YH/0027) at the cohort's inception in 1993, and was updated to include linkage outcomes, such as hip fracture incidence, in 2017 (reference 17/YH/0144).

### 4.3.2 Diet group

Dietary habits of cohort participants over 12 months were assessed at recruitment using a self-administered 217-item food frequency questionnaire (FFQ). The FFQ was validated by comparison with four-day weighed food diaries and a repeated FFQ on 283 women, both administered three years after baseline (27). Based on responses to questions on meat, fish, eggs, and dairy intakes, participants were classified as regular meat-eaters (ate meat ≥ 5 times/week), occasional meat-eaters (ate meat < 5 times/week), pescatarians (ate fish but not meat), vegetarians (ate eggs or dairy but not meat or fish), or vegans (did not eat meat, fish, eggs, or dairy). Vegans were combined with the vegetarian group due to the small number of vegan participants (n=130) and cases (n=5). Participants with intakes of a food item of less than once per month were considered non-consumers. Further details on the questionnaire and classification of diet groups are provided in **Appendix C: Supplementary methods** and **Table C2**.

### 4.3.3 Outcome

Participants' diet and lifestyle characteristics were linked with their hospital episode statistics up to 31st March 2019. The primary outcome was hip fracture incidence (International Classification of Diseases, ICD-9 code 820, ICD-10 codes S72.0-72.2). We also used hip replacements (ICD-10 code Z96.64) as an indicator of hip fracture, but no additional cases were identified using this

criteria. The timeframe was person-years until hip fracture incidence, or until end of study period or death in non-cases, using attained age as the timescale (30).

### 4.3.4 Statistical analysis

All statistical methods were registered in advance on clinicaltrials.gov (NCT05081466).

Socio-demographic, lifestyle, anthropometric, and nutritional characteristics of UKWCS participants at recruitment were summarised by diet group using descriptive statistics. Cox proportional hazard regression models were fitted to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) for associations between each diet group and hip fracture risk, with regular meat-eaters as the reference group. The target estimand was the relative causal effect of each diet group on hip fracture risk compared to regular meat-eaters. Cox models used weights based on the inverse probability of being sampled to account for the over-sampling of pescatarians and vegetarians at recruitment, increasing the representativeness of the cohort to the UK population (29).

We applied both unadjusted and multivariable-adjusted models. Both models controlled for age by using attained age as the timescale (30). Additional confounders included in the adjusted model were based on a Directed Acyclic Graph (DAG), following available guidelines on their creation and reporting (31), and included (all at recruitment): ethnicity (white, Asian, black, other), socio-economic status (SES, professional/managerial, intermediate, routine/manual), marital status (married/living as married, separated/divorced, single/widowed), menopausal status (premenopausal, postmenopausal), number of children (continuous), prevalence of cardiovascular disease, cancer, or diabetes at recruitment (yes, no), physical activity in hours per day (continuous), smoking status (current, former, never), alcohol consumption (> 1/week, ≤ 1/week, never), BMI (continuous), and any nutritional supplement use (yes, no). The DAG and definitions of confounders are given in **Appendix C: Supplementary methods**, **Table C3**, and **Figure C2**. The proportional hazards assumption was assessed based on Schoenfeld residuals and was not violated for all terms in the adjusted model.

To determine the role of BMI as a potential effect modifier, we added dichotomized BMI level (<23.5, ≥23.5 kg/$m^2$) to the adjusted model as an interaction term with each diet group, with these cut-off points defined to ensure a similar number of participants in each strata. We also added individual BMI (continuous per kg/$m^2$ increase) to the adjusted model as an interaction term with each diet group, and omitted BMI from the adjustment set for that analysis. Further exploratory analyses included testing for interaction effects with each diet group for: menopausal status (premenopausal, postmenopausal), physical activity level (< 150 minutes/week, ≥ 150 minutes/week), age (≤ 60, > 60 years), SES (routine/manual, intermediate, professional/managerial), smoking status (current, former, never), and use of any nutritional supplements (yes, no). In each exploratory subgroup analysis, the potential effect modifier was omitted from the relevant adjustment set.

We explored the effect of potential mediators by further adjusting the adjusted model for each mediator independently. Potential mediators were total energy intake, and intake of protein, calcium, vitamin D, vitamin B12, monounsaturated fatty acids (MUFA), polyunsaturated fatty acids (PUFA), and zinc from dietary sources only (not including supplemental sources). An adjusted model with BMI removed from the adjustment set is also presented to determine its influence on any associations.

As a sensitivity analysis, we explored the risk of hip fracture in vegans compared to meat-eaters by fitting the adjusted model with vegetarians and vegans separated. Additional sensitivity analyses were as follows: excluding participants with a survival time < 5 years to check for reverse causation; excluding participants on long-term treatment for illness; and further adjusting for hormone replacement therapy (HRT) and prevalence of fracture at sites other than the hip at recruitment (identified in hospital episode statistics), respectively, since these are known risk factors for hip fracture (32). Other fractures were identified using participants' Hospital Episode Statistics. Participants with missing data for a variable required in a given analysis were excluded from that analysis. We did not impute missing covariate data. All statistical analyses were performed using Stata (version 17).

## 4.4 Results

### 4.4.1 Participants

Of the 30,244 women potentially eligible at recruitment, those with missing covariate data for body weight (n=596), height (n=649), ethnicity (n=811), physical activity (n=1561), marital status (n=460), SES (n=331), or menopausal status (n=309) were excluded, leaving 26,318 women for unadjusted and adjusted analyses. The study flow chart is given in **Appendix C: Figure C1**.

### 4.4.2 Descriptive data

Characteristics of the 26,318 cohort participants at recruitment are summarised by diet group in **Table 4.1**. Over a median follow-up time of 22.3 years, 822 hip fracture cases were observed (443,277 person-years), corresponding to 3.1% of the cohort. On average, at recruitment, pescatarians and vegetarians were younger than regular meat-eaters, reported higher education levels, were more likely to have professional or managerial jobs and less likely to have routine or manual jobs, and were less likely to be married or have any children. BMI was lower in vegetarians (mean (standard deviation, SD): 23.3 (3.9 $kg/m^2$)) and pescatarians (23.3 (3.5 $kg/m^2$)) than in regular meat-eaters (25.2 (4.4 $kg/m^2$)). Prevalence of CVD, cancer, or diabetes at recruitment was highest in regular meat-eaters (n=1250 (10.2%)), and lowest in vegetarians (222 (5.8%)). Exercise and smoking habits were similar across diet groups, but a higher proportion of vegetarians reported never drinking alcohol than all other diet groups. Regular meat-eaters reported the highest absolute dietary intakes of protein, vitamin D, and vitamin B12, whilst vegetarians reported the lowest. Calcium intakes were similar across diet groups. Other food and nutrient intakes in each diet group are summarised in **Appendix C: Table C4**. Characteristics of the cohort at recruitment were similar when including or restricting to participants with missing covariate data (**Appendix C: Table C5**).

**Table 4.1: Characteristics of 26,318 UKWCS participants at recruitment by diet group.**

| | Total | Diet group | | | |
|---|---|---|---|---|---|
| **Characteristics, mean (SD) or n (%)** | | **Regular meat-eater** | **Occasional meat-eater** | **Pescatarian** | **Vegetarian** |
| Participants (%) | 26318 | 13984 (46.2) | 8000 (26.5) | 3867 (12.8) | 4393 (14.5) |
| Cases (%) | 822 (3.1) | 394 (3.2) | 247 (3.6) | 80 (2.4) | 101 (2.6) |
| **Socio-demographics** | | | | | |
| Age, years (SD) | 52.1 (9.2) | 53.3 (9.2) | 53.2 (9.4) | 49.7 (8.5) | 48.3 (8.2) |
| Degree-level education (%) | 6502 (26.8) | 2306 (20.7) | 1780 (28.2) | 1143 (35.9) | 1273 (35.1) |
| Socioeconomic status (%) | | | | | |
| Professional or managerial | 19057 (72.4) | 8518 (69.7) | 5120 (74.2) | 2576 (76.3) | 2843 (74.5) |
| Intermediate | 2440 (9.3) | 1117 (9.1) | 694 (10.1) | 270 (8.0) | 359 (9.4) |
| Routine or manual | 4821 (18.3) | 2586 (21.2) | 1088 (15.8) | 531 (15.7) | 616 (16.1) |
| Married (%) | 20268 (77.0) | 10103 (82.7) | 5007 (72.5) | 2432 (72.0) | 2726 (71.4) |
| White ethnicity (%) | 25992 (98.8) | 12139 (99.3) | 6820 (98.8) | 3331 (98.6) | 3702 (97.0) |
| **Lifestyle** | | | | | |
| Exercise (hours/day) | 0.2 (0.5) | 0.2 (0.5) | 0.2 (0.4) | 0.3 (0.5) | 0.3 (0.5) |
| Smoking status (%) | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| Current | 3513 (13.3) | 1678 (13.7) | 921 (13.3) | 448 (13.3) | 466 (12.2) |
| Former | 7947 (30.2) | 3519 (28.8) | 2078 (30.1) | 1161 (34.4) | 1189 (31.1) |
| Never | 3110 (11.8) | 7024 (57.5) | 3903 (56.5) | 1768 (52.4) | 2163 (56.7) |
| Alcohol consumption (%) | | | | | |
| > 1 serving/week | 13918 (52.9) | 6798 (55.6) | 3548 (51.4) | 1830 (54.2) | 1742 (45.6) |
| ≤ 1 serving/week | 9290 (35.3) | 4276 (35.0) | 2471 (35.8) | 1145 (33.9) | 1398 (36.6) |
| Never | 3110 (11.8) | 1147 (9.4) | 883 (12.8) | 402 (11.9) | 678 (17.8) |
| Nutritional supplementation (%) | 14009 (53.2) | 5902 (48.3) | 3881 (56.2) | 2070 (61.3) | 2156 (56.5) |
| **Anthropometrics** | | | | | |
| BMI, kg/m$^2$ (SD) | 24.4 (4.2) | 25.3 (4.5) | 24.1 (3.9) | 23.3 (3.5) | 23.3 (3.9) |
| Height, m (SD) | 1.6 (0.1) | 1.6 (0.1) | 1.6 (0.1) | 1.6 (0.1) | 1.6 (0.1) |
| **Dietary nutrient intakes** | | | | | |
| Energy intake, kcal/day (SD) | 2300 (654.8) | 2445 (640.3) | 2069 (605.9) | 2294 (656.3) | 2259 (658.2) |
| Protein intake, g/day (SD) | 88.1 (26.3) | 100.9 (24.8) | 77.5 (21.3) | 79.6 (23.1) | 74.0 (22.3) |
| ≥ 0.75 g protein/kg body weight/day (%) | 24837 (94.4) | 12067 (98.7) | 6262 (90.7) | 3116 (92.3) | 3392 (88.8) |
| Calcium intake, mg/day (SD) | 1135 (365.4) | 1163 (344.6) | 1060 (356.3) | 1183 (395.0) | 1138 (398.0) |
| Vitamin D intake, µg/day (SD) | 3.1 (1.7) | 3.6 (1.6) | 2.9 (1.6) | 3.1 (1.8) | 1.9 (1.1) |
| Vitamin B12 intake, µg/day (SD) | 2.5 (1.2) | 7.5 (2.9) | 5.1 (2.2) | 4.3 (2.0) | 2.5 (1.2) |

| | | | | | |
|---|---|---|---|---|---|
| **Other** | | | | | |
| Premenopausal (%) | 14611 (55.5) | 4700 (38.5) | 2788 (40.4) | 1846 (54.7) | 2373 (62.2) |
| Postmenopausal (%) | 11707 (44.5) | 7521 (61.5) | 4114 (59.6) | 1531 (45.3) | 1445 (37.8) |
| ≥ 1 children (%) | 20723 (78.7) | 10263 (84.0) | 5324 (77.1) | 2468 (73.1) | 2668 (69.9) |
| Prevalence of CVD, cancer, or diabetes (%) | 2388 (9.1) | 1250 (10.2) | 664 (9.6) | 252 (7.5) | 222 (5.8) |

SD: standard deviation; SES: social economic status; BMI: body mass index.

### 4.4.3 Diet groups

Compared with regular meat-eaters, vegetarians (HR: 1.40 (95% CI: 1.11, 1.78)) but not occasional meat-eaters (1.03 (0.88, 1.21)) or pescatarians (1.04 (0.81, 1.34)) had a greater risk of hip fracture in the unadjusted model (**Figure 4.1**). Adjustment for confounders slightly attenuated these associations in the adjusted model, but the higher risk in vegetarians remained and was statistically significant (vegetarians: 1.33 (1.03, 1.71); occasional meat-eaters: 1.00 (0.85, 1.18); pescatarians: 0.97 (0.75, 1.26)).

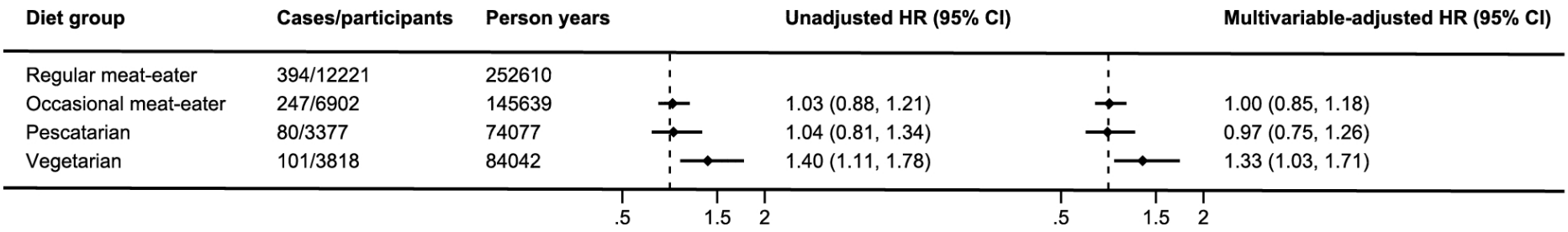



**Figure 4.1: Risk of hip fracture in occasional meat-eaters, pescatarians, and vegetarians compared to regular meat-eaters in the UKWCS.** The multivariable-adjusted model was adjusted for (all at recruitment): ethnicity (white, Asian, black, other), socio-economic status (professional/managerial, intermediate, routine/manual), marital status (married/living as married, separated/divorced, single/widowed), menopausal status (premenopausal, postmenopausal), number of children (continuous), prevalence of cardiovascular disease, cancer, or diabetes (yes, no), physical activity in hours per day (continuous), smoking status (current, former, never), alcohol consumption (> 1/week, ≤ 1/week, never), BMI (continuous), and any nutritional supplement use (yes, no). HR (95% CI): hazard ratio (95% confidence interval).

### 4.4.4 Subgroup analyses

Whilst risk of hip fracture was 46% higher in participants with BMI < 23.5 kg/m$^2$ compared to BMI ≥ 23.5 kg/m$^2$, there was no evidence of effect modification by BMI on hip fracture risk in each diet group when BMI was modelled categorically (p-interaction = 0.3) or linearly ($p_{interaction}$ = 0.6) (**Table 4.2**). There was also no evidence of effect modification in any diet group by age, physical activity, nutritional supplementation, SES, or smoking status (**Appendix C: Table C6**). There was some evidence of effect modification by menopausal status, where occasional meat-eaters were at a reduced risk of hip fracture in premenopausal women only (0.43 (0.21, 0.86), $p_{interaction}$ = 0.05).

**Table 4.2: Risk of hip fracture in occasional meat-eaters, pescatarians, and vegetarians compared to regular meat-eaters by BMI in the UKWCS.**

| Stratifying variable | n cases/participants, adjusted HR (95% CI) | | | | |
|---|---|---|---|---|---|
| **BMI** | | **< 23.5 kg/m$^2$** | | **≥ 23.5 kg/m$^2$** | ***p* interaction** |
| Regular meat-eaters (reference) | 161/4927 | 1.00 | 233/7294 | 1.00 | |
| Occasional meat-eaters | 123/3554 | 0.96 (0.75, 1.21) | 124/3348 | 1.05 (0.84, 1.31) | |
| Pescatarians | 50/2075 | 0.90 (0.65, 1.25) | 30/1302 | 1.06 (0.71, 1.60) | |
| Vegetarians | 72/2338 | 1.49 (1.10, 2.03) | 29/1480 | 1.02 (0.66, 1.58) | 0.3 |

Models were adjusted for (all at recruitment): ethnicity (white, Asian, black, other), socio-economic status (SES, professional/managerial, intermediate, routine/manual), marital status (married/living as married, separated/divorced, single/widowed), menopausal status (premenopausal, postmenopausal), number of children (continuous), prevalence of cardiovascular disease, cancer, or diabetes (yes, no), physical activity in hours per day (continuous), smoking status (current, former, never), alcohol consumption (> 1/week, ≤ 1/week, never), BMI (continuous), and any nutritional supplement use (yes, no). HR (95% CI): hazard ratio (95% confidence interval); BMI: body mass index.

### 4.4.5 Sensitivity analyses

Risk of hip fracture appeared higher without adjustment for BMI in vegetarians (1.43 (1.12, 1.83); **Table 4.3**). Further adjusting the adjusted model for dietary vitamin D intake in vegetarians increased the magnitude of the association with hip fracture risk (1.44 (1.10, 1.87)), whilst further adjustment for dietary MUFA intake increased the strength of associations for occasional meat-eaters (1.07, 0.90, 1.27)) and vegetarians (1.39 (1.08, 1.79)) (**Table 4.3**). Further adjustment for total energy intake and dietary intake of protein, calcium, vitamin B12, and PUFAs did not alter results substantially.

All adjusted results were robust to the addition or removal of other individual covariates from the model, with estimates remaining broadly unchanged across most sensitivity analyses (**Appendix C: Table C7**). Exclusion of participants on long-term treatment for illness slightly increased the magnitude of associations in all diet groups (occasional meat-eaters: 1.09 (0.88, 1.37); pescatarians: 1.08 (0.78, 1.50); vegetarians: 1.48 (1.07, 2.04)). Considering vegetarians (96 cases/3688 participants) and vegans (5 cases/130 participants) separately did not substantially alter estimates in vegetarians (vegetarians: 1.38 (1.07, 1.78) and vegans: 1.10 (0.42, 2.84)).

**Table 4.3: Risk of hip fracture in occasional meat-eaters, pescatarians, and vegetarians compared to regular meat-eaters in the UKWCS, with varying levels of adjustment.**

| Model ± further adjustments | HR (95% CI) per diet group | | | |
|---|---|---|---|---|
| | **Regular meat-eaters (reference)** | **Occasional meat-eaters** | **Pescatarians** | **Vegetarians** |
| Model 1[a] | 1.00 | 1.03 (0.88, 1.21) | 1.04 (0.81, 1.34) | 1.40 (1.11, 1.78) |
| Model 2[b] | 1.00 | 1.00 (0.85, 1.18) | 0.97 (0.75, 1.26) | 1.33 (1.03, 1.71) |
| Model 2 - BMI | 1.00 | 1.05 (0.89, 1.24) | 1.05 (0.81, 1.35) | 1.43 (1.12, 1.83) |
| **Potential mediators** | | | | |
| Model 2 + total energy | 1.00 | 1.05 (0.89, 1.24) | 0.99 (0.76, 1.28) | 1.36 (1.06, 1.75) |
| Model 2 + dietary protein | 1.00 | 1.03 (0.86, 1.23) | 0.99 (0.76, 1.29) | 1.36 (1.05, 1.78) |
| Model 2 + dietary calcium | 1.00 | 1.01 (0.86, 1.20) | 0.97 (0.75, 1.25) | 1.33 (1.04, 1.72) |
| Model 2 + dietary vitamin D | 1.00 | 1.03 (0.87, 1.22) | 0.99 (0.77, 1.29) | 1.44 (1.10, 1.87) |
| Model 2 + dietary vitamin B12 | 1.00 | 1.01 (0.85, 1.22) | 0.98 (0.75, 1.30) | 1.36 (1.01, 1.82) |
| Model 2 + dietary MUFA | 1.00 | 1.07 (0.90, 1.27) | 1.00 (0.77, 1.30) | 1.39 (1.08, 1.79) |
| Model 2 + dietary PUFA | 1.00 | 1.03 (0.87, 1.21) | 0.96 (0.74, 1.24) | 1.32 (1.02, 1.69) |
| Model 2 + dietary zinc | 1.00 | 1.01 (0.85, 1.21) | 0.97 (0.75, 1.27) | 1.34 (1.03, 1.73) |

[a] Model 1 included 26,318 participants and was unadjusted; [b] model 2 included 26,318 participants and was adjusted for ethnicity (white, Asian, black, other), socio-economic status (SES, professional/managerial, intermediate, routine/manual), marital status (married/living as married, separated/divorced, single/widowed), menopausal status (premenopausal, postmenopausal), number of children (continuous), chronic disease prevalence at baseline (yes, no - including stroke, cancer, or diabetes), physical activity in hours per day (continuous), smoking status (current, former, never), alcohol consumption (> 1/week, ≤ 1/week, never), body mass index (BMI, continuous), and any nutritional supplement use (yes, no). All other models were based on the 26,318 participants in model 2. HR (95% CI): hazard ratio (95% confidence interval); MUFA: monounsaturated fatty acids; PUFA: polyunsaturated fatty acids.

## 4.5 Discussion

### 4.5.1 Principal findings

Vegetarians but not occasional meat-eaters or pescatarians were at a higher risk of hip fracture than regular meat-eaters in this cohort of UK women. There was no clear evidence of effect modification by BMI across diet groups. Risk differences remained after accounting for confounders and were not explained by differences in key nutrient intakes related to bone health between vegetarians and regular meat-eaters, implying the potential importance of other unaccounted factors.

### 4.5.2 Comparison with previous studies

Prospective evidence of hip fracture risk in individuals on meat-free diets is limited. Our findings largely concur with the results of the only other two cohort studies on this topic (8, 9), strengthening the evidence of a higher risk of hip fracture in UK vegetarian women.

In the EPIC-Oxford cohort, there was evidence of a higher risk of hip fracture in vegetarian women of a similar magnitude (25%) (8). The slightly higher effect estimate in our study (33%) may be due to our reference group being regular meat-eaters, whereas the reference group in the EPIC-Oxford cohort was meat-eaters of any amount. The AHS-2 also found limited evidence of a 17% higher risk of hip fracture in US vegetarian women (9). Differences in estimates between the AHS-2 and our results may be due different adjustment strategies when accounting for confounders; in the AHS-2, attained age was used as the timeframe, and adjustment was made for age and energy, calcium, potassium, and vitamin D intakes at recruitment amongst other factors. This may have resulted in overadjustment and adjustment for factors potentially on the causal pathway, diluting risk estimates. The AHS-2 also relied on self-report for case ascertainment. We identified hip fracture cases using participants' hospital episode statistics, which incurs less reporting error and selective loss to follow-up. We found no clear evidence of a difference in hip fracture risk in pescatarians or occasional meat-eaters (ate meat < 5 times/week) compared to regular meat-eaters. Similarly, in the AHS-2, there was no clear

evidence of a difference in hip fracture risk in semi-vegetarian (ate meat or fish ≤ once/week) or pescatarian women compared to non-vegetarians (9). In contrast, the EPIC-Oxford cohort study found a 30% increased risk in pescatarian women, potentially due to population differences between EPIC-Oxford and the UKWCS, different intakes of fish or other dietary components, or other sources of residual confounding in either study (8). Both the EPIC-Oxford and AHS-2 cohort studies reported higher risks of hip fracture in vegans compared to meat-eaters (8, 9). Due to the low number of vegans in the UKWCS, we could not precisely estimate their risk of hip fracture separate from the vegetarian group. Since vegans may face greater challenges in achieving adequate intake of several nutrients, in particular protein and calcium (6), cohort studies with a high proportion of vegans are needed investigating their risk of hip fracture.

Other epidemiological studies have found that adherence to diets low in meat consumption, such as the Mediterranean diet and Alternative Healthy Eating Index, was protectively associated with hip fracture risk (33, 34), and adherence to Western diets in which meat consumption is high was positively associated with hip fracture risk (35). Conversely, total meat intake has been inversely associated with hip fracture risk (21). These results cannot be fairly compared with risks in vegetarians and non-vegetarians, which no other study has directly assessed.

### 4.5.3 Interpretation and implications

The observed higher risk of hip fracture in vegetarians compared to regular meat-eaters may be partly explained by differences in body anthropometrics between diet groups. Whilst there was no clear evidence of BMI modifying associations between diet groups and hip fracture risk, the lower mean BMI in vegetarians partly explained their higher risk. Previous studies have shown BMI and body weight to be lower in vegetarians (26, 36), and inversely associated with hip fracture risk (24, 37). Possible mechanisms include the protective roles of bone mass, fat mass, and muscle mass, which have each been inversely associated with hip fracture risk independently (38). Inadequate fat mass may reduce cushioning from impact force at the hip during falls, which account for 90% of hip fractures (39). Higher fat mass could also increase bone strength through increased mechanical loading and enhanced oestrogen production (38). Low muscle mass and strength of hip flexor muscles and spine extensors have also been associated with an increased risk of hip fracture (40), possibly due to reduced balance and mobility. Weight

management may therefore be an important consideration in reducing hip fracture risk in vegetarians, but further research is required exploring the roles of BMI and body composition in hip fracture risk in vegetarians and meat-eaters.

A second potential reason for the higher risk of hip fracture in vegetarians is their lower intake of nutrients important to bone health that are abundant in animal products. Previous studies have found lower dietary intakes of protein, calcium, vitamin D, and vitamin B12 in vegetarians (6, 22), and have suggested protective associations of these nutrients with hip fracture risk (6, 41, 42). In our study, vegetarians had lower dietary intakes of protein, vitamin D, and vitamin B12, but similar dietary calcium intakes to other diet groups. In particular, vegetarians were less likely to meet the UK recommendation for protein intake in adults of 0.75 g/kg body weight/day than regular meat-eaters (88.8% vs 98.3%) (43), but the higher risk of hip fracture in vegetarians was not explained by any dietary nutrient intake. It is likely that measurement error incurred by estimating nutrient intakes from an FFQ precluded accurate estimation of the importance of nutrients from dietary sources to hip fracture risk in vegetarians.

Since the higher risk of hip fracture in vegetarians remained after adjustment for BMI and several dietary nutrient intakes, other factors may be important. Supplemental sources of specific nutrients and circulating vitamin D concentrations could differ between vegetarians and non-vegetarians and may impact risk of hip fracture (9, 44), but could not be accounted for in this analysis due to a lack of data. Circulating levels of insulin-like growth factor-1 (IGF-1) may also be lower in vegetarians than in non-vegetarians (45), and has been positively associated with BMD and negatively associated with risk of total fracture and hip fracture (46), but could not be considered here. Future studies should investigate the roles of IGF-1 and nutrients abundant in animal products on hip fracture risk in vegetarians to better understand reasons for their observed higher risk.

### 4.5.4 Strengths and limitations

This study has three main strengths. Firstly, the large number of pescatarians and vegetarians included gave good statistical power to estimate their risk of hip fracture. Secondly, identification of hip fractures based on hospital records over a long follow-up period reduced reporting error

and loss to follow-up. Finally, we classified subjects into diet groups based on reported intakes of animal foods using a validated FFQ, which may more accurately allocate participants into diet groups than asking participants to identify their diet group.

On average, UKWCS participants were younger by end of follow-up than the average age at hip fracture in women (83 years) (47), limiting the number of hip fractures observed. Moreover, high-energy trauma may account for more hip fractures in younger adults, whereas fragility hip fractures are more common in older adults (48). We could not distinguish between traumatic and fragility fractures here since information on the cause of hip fractures was not available. We had insufficient power to detect effect modification by covariates in subgroup analyses. For BMI, the strong correlation with diet group meant that the number of vegetarians with a high BMI or regular meat-eaters with a low BMI was low, respectively. Moreover, BMI was derived from self-reported height and body weight, implying possible measurement error. Investigation of hip fracture risk in underweight participants by diet group was also not possible but merits further investigation.

Women with missing covariate data (n=3926) were excluded from analyses in this study, which introduced a risk of selection bias. However, the magnitude of any selection bias is unlikely to be clinically significant, given that characteristics of participants included or excluded in analyses here at recruitment were similar (**Appendix C: Table C5**). Although we adjusted for likely confounders, residual confounding was possible. For example, we could not adjust for use of medications that could impact associations between diet groups and hip fracture risk due to a lack of data. The risk of hip fracture could differ between moderate and heavy consumers of alcohol (20), but we were unable to differentiate between these groups when adjusting for alcohol consumption. In addition, the exclusion of participants with prior hip fractures was likely an incomplete exclusion, since hospital data of fracture incidences before 1997 was not available, and the questionnaire did not ask about fracture history. The single questionnaire administered at recruitment was the only method of assessing diet and lifestyle information; therefore, we could not account for changes in diet group or covariates over time. Additionally, food and nutrient intake in vegetarians in recent years could differ from when data were collected at recruitment due to changes over the last two decades in the availability of vegetarian food

products, such as increases in the number of available meat substitute products (49). Consequently, generalisability of our findings to modern-day vegetarians is reduced. Our findings were also predominantly in white UK women; previous studies have shown that total fracture risk could depend on ethnicity (50), therefore more research is needed investigating hip fracture risk in non-European vegetarians and non-vegetarians.

### 4.5.5 Conclusion

Overall, vegetarians but not occasional meat-eaters or pescatarians were at a higher risk of hip fracture compared to regular meat-eaters in this cohort of UK women. Further research is needed to confirm this in other populations, such as men and non-European populations, and to identify factors responsible for the observed risk difference. In particular, further research exploring the roles of BMI and nutrients abundant in animal-sourced foods is recommended so that public health interventions and policy guidelines aiming to reduce hip fracture risk in vegetarians through dietary change or weight management can be formed.

## 4.6 References


1. Dhanwal DK, Dennison EM, Harvey NC, Cooper C. Epidemiology of hip fracture: Worldwide geographic variation. Indian J Orthop. 2011;45(1):15-22.
2. Veronese N, Maggi S. Epidemiology and social costs of hip fracture. Injury. 2018;49(8):1458-60.
3. Jennison T, Brinsden M. Fracture admission trends in England over a ten-year period. Ann R Coll Surg Engl. 2019;101(3):208-14.
4. Peraza-Delgado A, Sánchez-Gómez MB, Gómez-Salgado J, Romero-Martín M, Novo-Muñoz M, Duarte-Clíments G. Non-Pharmacological Interventions towards Preventing the Triad Osteoporosis-Falls Risk-Hip Fracture, in Population Older than 65. Scoping Review. J Clin Med. 2020;9(8).
5. Williamson S, Landeiro F, McConnell T, Fulford-Smith L, Javaid MK, Judge A, et al. Costs of fragility hip fractures globally: a systematic review and meta-regression analysis. Osteoporos Int. 2017;28(10):2791-800.
6. Tucker KL. Vegetarian diets and bone status. Am J Clin Nutr. 2014;100 Suppl 1:329s-35s.

7. Iguacel I, Miguel-Berges ML, Gómez-Bruton A, Moreno LA, Julián C. Veganism, vegetarianism, bone mineral density, and fracture risk: a systematic review and meta-analysis. Nutr Rev. 2019;77(1):1-18.

8. Tong TYN, Appleby PN, Armstrong MEG, Fensom GK, Knuppel A, Papier K, et al. Vegetarian and vegan diets and risks of total and site-specific fractures: results from the prospective EPIC-Oxford study. BMC Med. 2020;18(1):353.

9. Thorpe DL, Beeson WL, Knutsen R, Fraser GE, Knutsen SF. Dietary patterns and hip fracture in the Adventist Health Study 2: combined vitamin D and calcium supplementation mitigate increased hip fracture risk among vegans. Am J Clin Nutr. 2021;114(2):488-95.

10. Le LT, Sabaté J. Beyond meatless, the health effects of vegan diets: findings from the Adventist cohorts. Nutrients. 2014;6(6):2131-47.

11. Foods Standards Agency. National Diet and Nutrition Survey: Headline results from Years 1 and 2 (combined) of the Rolling Programme (2009/2009 - 2009/10). 2012.

12. Benson A, Irdam D, Bulceag I, Barber T, Draper A. Food and you survey: Wave 5 secondary analysis: The current food landscape across England, Wales, and Northern Ireland. Foods Standards Agency; 2019.

13. Shridhar K, Dhillon PK, Bowen L, Kinra S, Bharathi AV, Prabhakaran D, et al. Nutritional profile of Indian vegetarian diets--the Indian Migration Study (IMS). Nutr J. 2014;13:55.

14. Lee Y, Park K. Adherence to a Vegetarian Diet and Diabetes Risk: A Systematic Review and Meta-Analysis of Observational Studies. Nutrients. 2017;9(6).

15. Dinu M, Abbate R, Gensini GF, Casini A, Sofi F. Vegetarian, vegan diets and multiple health outcomes: A systematic review with meta-analysis of observational studies. Crit Rev Food Sci Nutr. 2017;57(17):3640-9.

16. Rosi A, Mena P, Pellegrini N, Turroni S, Neviani E, Ferrocino I, et al. Environmental impact of omnivorous, ovo-lacto-vegetarian, and vegan diet. Sci Rep. 2017;7(1):6105.

17. Fresán U, Sabaté J. Vegetarian Diets: Planetary Health and Its Alignment with Human Health. Adv Nutr. 2019;10(Suppl_4):S380-s8.

18. Luo S, Li Y, Luo H, Yin X, Lin du R, Zhao K, et al. Increased intake of vegetables, but not fruits, may be associated with reduced risk of hip fracture: A meta-analysis. Sci Rep. 2016;6:19783.

19. Brondani JE, Comim FV, Flores LM, Martini LA, Premaor MO. Fruit and vegetable intake and bones: A systematic review and meta-analysis. PLoS One. 2019;14(5):e0217223.

20. Webster J, Rycroft CE, Greenwood DC, Cade JE. Dietary risk factors for hip fracture in adults: An umbrella review of meta-analyses of prospective cohort studies. PLoS One. 2021;16(11):e0259144.

21. Lousuebsakul-Matthews V, Thorpe DL, Knutsen R, Beeson WL, Fraser GE, Knutsen SF. Legumes and meat analogues consumption are associated with hip fracture risk independently of meat intake among Caucasian men and women: the Adventist Health Study-2. Public Health Nutr. 2014;17(10):2333-43.

22. Davey GK, Spencer EA, Appleby PN, Allen NE, Knox KH, Key TJ. EPIC-Oxford: lifestyle characteristics and nutrient intakes in a cohort of 33 883 meat-eaters and 31 546 non meat-eaters in the UK. Public Health Nutr. 2003;6(3):259-69.

23. Bradbury KE, Tong TYN, Key TJ. Dietary Intake of High-Protein Foods and Other Major Foods in Meat-Eaters, Poultry-Eaters, Fish-Eaters, Vegetarians, and Vegans in UK Biobank. Nutrients. 2017;9(12).

24. Armstrong ME, Cairns BJ, Banks E, Green J, Reeves GK, Beral V. Different effects of age, adiposity and physical activity on the risk of ankle, wrist and hip fractures in postmenopausal women. Bone. 2012;50(6):1394-400.

25. Ho-Pham LT, Nguyen ND, Nguyen TV. Effect of vegetarian diets on bone mineral density: a Bayesian meta-analysis. Am J Clin Nutr. 2009;90(4):943-50.

26. Tong TY, Key TJ, Sobiecki JG, Bradbury KE. Anthropometric and physiologic characteristics in white and British Indian vegetarians and nonvegetarians in the UK Biobank. Am J Clin Nutr. 2018;107(6):909-20.

27. Cade JE, Burley VJ, Alwan NA, Hutchinson J, Hancock N, Morris MA, et al. Cohort Profile: The UK Women's Cohort Study (UKWCS). Int J Epidemiol. 2017;46(2):e11.

28. Lachat C, Hawwash D, Ocké MC, Berg C, Forsum E, Hörnell A, et al. Strengthening the Reporting of Observational Studies in Epidemiology-Nutritional Epidemiology (STROBE-nut): An Extension of the STROBE Statement. PLoS Med. 2016;13(6):e1002036.

29. Rada-Fernandez de Jauregui D, Evans CEL, Jones P, Greenwood DC, Hancock N, Cade JE. Common dietary patterns and risk of cancers of the colon and rectum: Analysis from the United Kingdom Women's Cohort Study (UKWCS). Int J Cancer. 2018;143(4):773-81.

30. Korn EL, Graubard BI, Midthune D. Time-to-event analysis of longitudinal follow-up of a survey: choice of the time-scale. Am J Epidemiol. 1997;145(1):72-80.

31. Tennant PWG, Murray EJ, Arnold KF, Berrie L, Fox MP, Gadd SC, et al. Use of directed acyclic graphs (DAGs) to identify confounders in applied health research: review and recommendations. Int J Epidemiol. 2021;50(2):620-32.

32. Benetos IS, Babis GC, Zoubos AB, Benetou V, Soucacos PN. Factors affecting the risk of hip fractures. Injury. 2007;38(7):735-44.

33. Malmir H, Saneei P, Larijani B, Esmaillzadeh A. Adherence to Mediterranean diet in relation to bone mineral density and risk of fracture: a systematic review and meta-analysis of observational studies. Eur J Nutr. 2018;57(6):2147-60.

34. Panahande B, Sadeghi A, Parohan M. Alternative healthy eating index and risk of hip fracture: a systematic review and dose-response meta-analysis. J Hum Nutr Diet. 2019;32(1):98-107.

35. Fabiani R, Naldini G, Chiavarini M. Dietary Patterns in Relation to Low Bone Mineral Density and Fracture Risk: A Systematic Review and Meta-Analysis. Adv Nutr (Bethesda). 2019;10(2):219-36.

36. Barnard ND, Levin SM, Yokoyama Y. A systematic review and meta-analysis of changes in body weight in clinical trials of vegetarian diets. J Acad Nutr Diet. 2015;115(6):954-69.

37. Kim SH, Yi SW, Yi JJ, Kim YM, Won YJ. Association Between Body Mass Index and the Risk of Hip Fracture by Sex and Age: A Prospective Cohort Study. J Bone Miner Res. 2018;33(9):1603-11.

38. Gonnelli S, Caffarelli C, Nuti R. Obesity and fracture risk. Clin Cases Miner Bone Metab. 2014;11(1):9-14.

39. Hayes WC, Myers ER, Morris JN, Gerhart TN, Yett HS, Lipsitz LA. Impact near the hip dominates fracture risk in elderly nursing home residents who fall. Calcif Tissue Int. 1993;52(3):192-8.

40. Kim KH, Lee JH, Lim EJ. Weak psoas and spine extensors potentially predispose to hip fracture. Hip Int. 2021;31(3):430-4.

41. Wu AM, Sun XL, Lv QB, Zhou Y, Xia DD, Xu HZ, et al. The Relationship between Dietary Protein Consumption and Risk of Fracture: a subgroup and dose-response meta-analysis of prospective cohort studies. Sci Rep. 2015;5:8.

42. Bailey RL, van Wijngaarden JP. The Role of B-Vitamins in Bone Health and Disease in Older Adults. Curr. 2015;13(4):256-61.

43. British Nutrition Foundation. Nutrition requirements. 2021. [Available from: https://www.nutrition.org.uk/media/nmmewdug/nutrition-requirements.pdf].

44. Yao P, Bennett D, Mafham M, Lin X, Chen Z, Armitage J, et al. Vitamin D and Calcium for the Prevention of Fracture: A Systematic Review and Meta-analysis. JAMA Network Open. 2019.

45. Allen NE, Appleby PN, Davey GK, Kaaks R, Rinaldi S, Key TJ. The associations of diet with serum insulin-like growth factor I and its main binding proteins in 292 women meat-eaters, vegetarians, and vegans. Cancer Epidemiol Biomarkers Prev. 2002;11(11):1441-8.

46. Yuan S, Wan ZH, Cheng SL, Michaëlsson K, Larsson SC. Insulin-like Growth Factor-1, Bone Mineral Density, and Fracture: A Mendelian Randomization Study. J Clin Endocrinol Metab. 2021;106(4):e1552-e8.

47. Swift CG. Prevention and management of hip fracture in older patients. Practitioner. 2011;255(1743):29-33, 3.

48. Robinson CM, Court-Brown CM, McQueen MM, Christie J. Hip fractures in adults younger than 50 years of age. Epidemiology and results. Clin Orthop Relat Res. 1995(312):238-46.

49. Curtain F, Grafenauer S. Plant-Based Meat Substitutes in the Flexitarian Age: An Audit of Products on Supermarket Shelves. Nutrients. 2019;11(11).

50. Barrett-Connor E, Siris ES, Wehren LE, Miller PD, Abbott TA, Berger ML, et al. Osteoporosis and fracture risk in women of different ethnic groups. J Bone Miner Res. 2005;20(2):185-94.

# Chapter 5 Risk of hip fracture in meat eaters, pescatarians, and vegetarians: A prospective cohort study of 413,914 UK Biobank participants

**James Webster[1], Darren C. Greenwood[2], and Janet E. Cade[1]**

1 Nutritional Epidemiology Group, School of Food Science and Nutrition, University of Leeds, Leeds, LS2 9JT.

2 School of Medicine, University of Leeds, Leeds, LS2 9JT.

Published: BMC Medicine. 2023. 21(278). https://doi.org/10.1186/s12916-023-02993-6

**This Chapter is an exact copy of the journal paper referred to above.**

## 5.1 Abstract

**Background:** Meat-free diets may be associated with a higher risk of hip fracture, but prospective evidence is limited. We aimed to investigate the risk of hip fracture in occasional meat-eaters, pescatarians, and vegetarians compared to regular meat-eaters in the UK Biobank, and to explore the role of potential mediators of any observed risk differences.

**Methods:** Middle-aged UK adults were classified as regular meat-eaters (n=258,765), occasional meat-eaters (n=137,954), pescatarians (n=9557), or vegetarians (n=7638) based on dietary and lifestyle information at recruitment (2006-2010). Incident hip fractures were identified by record linkage to Hospital Episode Statistics up to September 2021. Multivariable Cox regression models were used to estimate associations between each diet group and hip fracture risk, with regular meat-eaters as the reference group, over a median follow-up time of 12.5 years.

**Results:** Among 413,914 women, 3503 hip fractures were observed. After adjustment for confounders, vegetarians (HR (95% CI): 1.50 (1.18, 1.91)) but not occasional meat-eaters (0.99 (0.93, 1.07)) or pescatarians (1.08 (0.86, 1.35)) had a greater risk of hip fracture than regular meat-eaters. This is equivalent to an adjusted absolute risk difference of 3.2 (1.2, 5.8) more hip fractures per 1000 people over 10 years in vegetarians. There was limited evidence of effect modification by BMI on hip fracture risk across diet groups ($p_{interaction}$ = 0.08), and no clear evidence of effect modification by age or sex ($p_{interaction}$ = 0.9 and 0.3, respectively). Mediation analyses suggest that BMI explained 28% of the observed risk difference between vegetarians and regular meat-eaters (95% CI: 1.1%, 69.8%).

**Discussion:** Vegetarian men and women had a higher risk of hip fracture than regular meat-eaters, and this was partly explained by their lower BMI. Ensuring adequate nutrient intakes and weight management are therefore particularly important in vegetarians in the context of hip fracture prevention.

**Protocol registration**: NCT05554549, registered retrospectively

**Key words:** Vegetarian; Plant-based; Cohort; fracture; dietary patterns; diet; nutrition; bone; osteoporosis

## 5.2 Background

Global population growth and longevity increase the number of older adults worldwide. Prevalence of chronic diseases, including frailty, osteoporosis, and sarcopenia are therefore rising, which increases the risk of falls and fractures (1). Hip fractures result in a significant loss of independence and quality of life, risk of refracture, other chronic illnesses, and premature mortality. Long hospitalisation periods after a hip fracture also accrue a significant economic burden to healthcare systems (£2-3 billion and $6 billion annually in the UK and US, respectively) (2). Reducing the risk of hip fracture is therefore a public health priority.

Meat-free diets are becoming more popular in developed countries due to perceived health benefits as well as environmental and ethical concerns (3). Evidence suggests that vegetarians may have a lower risk of some chronic diseases compared to meat-eaters, including cancer and cardiovascular disease, but a higher risk of fractures (4-6). However, data from large prospective studies on risk of hip fracture in vegetarians are limited, because few cohorts have recruited sufficient numbers of vegetarians (7). Two previously published cohort studies in the UK that included mostly women found a greater risk of hip fracture in vegetarians compared to meat-eaters (6, 8). In contrast, an American cohort of seventh-day Adventists found no clear difference in risk of hip fracture between vegetarians and meat-eaters, but identified cases by self-reported questionnaires (9). Similarly, one recent study in 126,000 UK Biobank participants reported no difference in hip fracture risk between highest and lowest quartiles of adherence to a healthful plant-based diet (PBD), where meat and fish intake were considered unhealthy (10). However, even participants in the highest quartile of adherence to the healthful PBD index ate meat 5.6 times per week, on average. More prospective evidence is required to understand if vegetarian diets, where meat and fish intake are avoided entirely, are associated with hip fracture risk, and more evidence is needed in men, for whom data is scarce.

Risk differences between vegetarians and meat-eaters are plausible due to differences in dietary, anthropometric, and hormonal factors, but remain underexplored. Previous studies report lower intakes of nutrients related to musculoskeletal health, including protein, vitamin D, and vitamin B12 (8, 11, 12). Studies also report lower body mass index (BMI) and poorer musculoskeletal

outcomes in vegetarians, including bone mineral density (BMD), fat-free mass (FFM), and muscle strength (13, 14), which each increase hip fracture risk (15-17). Additionally, observational studies have shown lower insulin-like growth factor-1 (IGF-1) levels in vegetarians than in meat-eaters (18), potentially due to lower protein intakes (19); IGF-1 has been positively associated with BMD and inversely associated with hip fracture risk (20). No study has assessed the role of these factors in explaining any risk differences between diet groups, which could help inform strategies for mitigating any observed risk differences.

We therefore aimed to investigate the risk of hip fracture in occasional meat-eaters, pescatarians, and vegetarians compared to regular meat-eaters in the UK Biobank. We also aimed to determine the roles of BMI, FFM, heel BMD, hand grip strength, IGF-1, and serum vitamin D levels as potential mediators of any observed risk differences.

## 5.3 Methods

We followed the Strengthening the Reporting of Observational Studies in Epidemiology – Nutritional Epidemiology (STROBE-nut) guidelines for the reporting of cohort studies (**Appendix D: Table D1**) (4, 7, 8, 21-31).

### 5.3.1 Study design and participants

The UK Biobank is a large prospective cohort of over 500,000 adults across England, Scotland, and Wales, aged 40-69 years at recruitment in 2006-2010. Participants were recruited via National Health Service patient registers, and attended one of 22 assessment centres across the UK, where participants completed a touchscreen questionnaire, verbal interview, physical measures, and a biosample collection. A full description of the UK Biobank study rationale and design is available elsewhere (32). Ethical approval was granted from the National Health Service North West Multicentre Research Ethics Committee (21/NW/0157), and participants provided informed consent for data linkage to health records.

Participants were excluded from this analysis if they had a previous hip fracture (n=1263) or osteoporosis (n=2826) on or before the date of recruitment, were lost to follow-up (n=1260), their genetic sex did not match their reported sex (n=372), their BMI was implausible (< 10 or ≥

60 kg/m2, n=3161), or they were unable to be classified into a diet group due to insufficient data on meat and fish intake (n=4257). This left a total of 489,703 participants potentially eligible for inclusion in this study (**Appendix D: Figure D1**).

### 5.3.2 Diet group

At recruitment, participants completed a touchscreen food frequency questionnaire (FFQ) that asked about their frequency of consumption of various meat, fish, eggs, and dairy products. Participants were invited to attend an assessment centre for a repeat visit to complete the same questionnaire again in 2012-2013, 2014, and in 2019. Similarly to our previous study on this topic in the UK Women's Cohort Study (UKWCS) (8), participants were then classified as regular meat-eaters (ate meat ≥ 5 times/week), occasional meat-eaters (ate meat < 5 times/week), pescatarians (ate fish but not meat), vegetarians (ate eggs or dairy but not meat or fish), or vegans (did not eat meat, fish, eggs, or dairy) at recruitment and at the latest point of available follow-up for each participant. Vegans were combined with the vegetarian group due to the small number of vegan participants (10 cases / 400 participants). Diet group classifications at recruitment were used to represent participants' diet group during follow-up. Further details on the questionnaire, diet group classification, and agreement of diet group at recruitment and follow-up are provided in **Appendix D: Supplementary methods** and **Table D2**.

### 5.3.3 Outcome ascertainment

First incidence of hip fracture was identified using hospital inpatient data for England, Scotland, and Wales (International Classification of Diseases, ICD-9 code 820, and ICD-10 codes S72.0 – S72.2). This included Hospital Episode Statistics for England from 1997 until September 2021, Scottish Morbidity Records for Scotland from 1981 until July 2021, and the Patient Episode Database for Wales from 1998 until February 2018. The timeframe was person-years until hip fracture incidence, or until end of study period or death in those without a hip fracture, calculated as age at time of event or censoring minus age at study entry (33).

### 5.3.4 Statistical analyses

#### 5.3.4.1 Main analyses

All statistical methods were pre-registered on ClinicalTrials.gov (NCT05554549).

Dietary, lifestyle, socio-demographic, anthropometric, and other relevant characteristics of UK Biobank participants at recruitment were summarised across diet groups for all participants, and separately for men and women. Cox proportional hazard regression models were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) for potential associations between diet groups and hip fracture risk, with regular meat-eaters as the reference group. The target estimand was the relative causal effect of each diet group on hip fracture risk compared with regular meat-eaters.

Unadjusted and multivariable-adjusted models were applied, with attained age as the timescale (33). Additional confounders included in the adjusted model were determined from a directed acyclic graph (DAG), and included (all at recruitment): region (England, Scotland, Wales), sex (male, female), ethnicity (white, black, Asian, mixed, other), Townsend Deprivation Index (continuous), live alone (yes, no), smoking status (current, former, never), any regular nutritional supplementation (yes, no), total metabolic equivalent task (MET)-minutes of physical activity per week (continuous), alcohol consumption in drinks per day (continuous), BMI (continuous), and history of diabetes (yes, no), cancer (yes, no), cardiovascular disease (CVD; yes, no), or fractures at sites other than the hip (yes, no). Female-specific confounders included: number of children (0, 1, 2, 3, ≥ 4 children), menopausal status (premenopausal, postmenopausal), and hormone replacement therapy (HRT) use (current, former, never). The DAG and further information on classification of covariates is available in **Appendix D: Figure D2** and **Supplementary Methods**. The proportional hazards assumption was checked graphically using the Schoenfeld residuals and log(-log) survival plot methods, and no violations were observed (**Appendix D: Figures D3** and **D4**).

To estimate the population impact of each diet group on hip fracture risk, absolute risk differences were generated between each diet group and regular meat-eaters (reference group).

Predicted incidences for each diet group were calculated using HRs and 95% CIs expressed as floating absolute risks (7, 25, 26). Absolute risk differences between each diet group and regular meat-eaters were then calculated as the crude difference between the predicted incidence in each diet group versus regular meat-eaters, and were expressed per 1000 people over 10 years. Further details of this method are described in **Appendix D: Supplementary Methods**; and elsewhere (7).

#### 5.3.4.2 Subgroup analyses

To determine the roles of age (continuous, and dichotomised at < 60, ≥ 60 years), sex (male, female), and BMI (continuous, and dichotomized at ≤ 22.5, > 22.5 kg/m$^2$) as potential effect modifiers, we used likelihood ratio tests comparing adjusted Cox regression models with and without an interaction term between diet groups and each subgroup variable. In each case, the potential effect modifier was omitted from the adjustment set.

#### 5.3.4.3 Mediation analyses

We explored the potential of selected anthropometric (BMI, heel BMD, FFM, and hand grip strength) and biomarker measures (serum vitamin D and IGF-1) (all continuous variables measured at recruitment) as effect mediators of any significant association(s) between diet group and hip fracture risk. These variables have each been associated with diet groups and hip fracture risk previously (13, 17, 18, 20, 34-37). Multiple linear regression models, adjusted for relevant confounders (**Appendix D: Supplementary Methods**) were applied to compare each potential mediator across diet groups.

The inverse odds-ratio weighting (IORW) method was used to test for causal mediation, which aims to decompose diet group – hip fracture associations (total effect, TE) into estimated associations that are mediated by the potential mediator of interest (natural indirect effect, NIE), or are not mediated by the potential mediator of interest (natural direct effect, NDI) (28). The proportion of any diet group – hip fracture association mediated by a given anthropometric or biomarker variable of interest (% mediation) was calculated as the natural log of the $HR^{NIE}$ divided by the natural log of the $HR^{TE}$. We did not test for mediation if there was no significant difference in hip fracture risk for a given diet group compared to regular meat-eaters, or if there was no

significant difference between diet groups in the anthropometric or biomarker mediator of interest. All mediation analyses are described in detail in **Appendix D: Table D3** and **Supplementary Methods**.

#### 5.3.4.4 Sensitivity analyses

To determine if any association in vegetarians could be affected by vegans in that group, we fitted an adjusted model with vegetarians and vegans separated. Additional sensitivity analyses were: excluding participants with a survival time < 3 years to check for reverse causation; excluding participants on long-term treatment for illness who may be generally less healthy than the UK population; adjusting for height and weight together rather than BMI; and accounting for death during follow-up as a potentially competing risk. Participants with missing data for a variable required in a given analysis were excluded from that analysis. We also repeated the primary analysis using multiple imputation via chained equations for missing covariate data using 100 imputations under the assumption of missing at random, and combined analytical results using Rubin's Rule. All statistical analyses were performed using Stata (version 17).

## 5.4 Results

### 5.4.1 Participants

Of 489,703 participants potentially eligible at recruitment, those with missing covariate data for ethnicity (n=2183), SES (n=600), live alone (n=3775), smoking status (n=1737), supplement use (n=1391), physical activity (n=56,753), number of children (n=248), menopausal status (n=1830), and HRT use (n=15,052) were excluded, leaving 413,914 participants for unadjusted and adjusted analyses. The study flow chart is given in **Appendix D: Figure D1**.

### 5.4.2 Descriptive data

Characteristics of the 413,914 UK Biobank participants at recruitment stratified by diet group are summarised in **Table 5.1**. Over a median follow-up time of 12.5 years, 3503 hip fractures were observed (5,034,336 person years total), corresponding to 0.8% of the cohort. On average, at recruitment, pescatarians and vegetarians were younger than meat-eaters, though time to hip

fracture and age at hip fracture were similar across diet groups (**Appendix D: Fig D5**). Pescatarians and vegetarians reported higher education levels, and were more likely to report living alone (**Table 5.1**). The proportion of vegetarians of Asian ethnicity (1184 (15.5%)) was higher than that of regular meat-eaters (3970 (1.5%)). BMI was lower in pescatarians and vegetarians (25.6 (4.6)) kg/$m^2$ than in regular meat-eaters (27.8 (4.8) kg/$m^2$). Physical activity levels were similar across diet groups. History of diabetes, CVD, and cancer at recruitment were lower in vegetarians than in regular meat-eaters, and there was no difference in history of other fractures at recruitment across diet groups. **Appendix D: Table D5** shows characteristics of participants at recruitment across diet groups stratified by sex; both male and female pescatarians and vegetarians had lower BMIs and were younger than regular meat-eaters at recruitment. Dietary characteristics of participants at recruitment, as well as characteristics when including or restricting to participants with missing covariate data, are presented in **Appendix D: Tables D6** and **D7**, and are summarised in **Appendix D: Supplementary results**.

**Table 5.1: Characteristics of regular meat-eaters, occasional meat-eaters, pescatarians, and vegetarians in the UK Biobank at recruitment.**

| Characteristics, mean (SD), or *n* (%) | Total | Diet group | | | |
|---|---|---|---|---|---|
| | | Regular meat-eater | Occasional meat-eater | Pescatarian | Vegetarian |
| Participants (%) | 413,914 | 258,765 (62.5) | 137,954 (33.3) | 9557 (2.3) | 7638 (1.8) |
| Cases (%) | 3503 (0.8) | 2045 (0.8) | 1310 (0.9) | 78 (0.8) | 70 (0.9) |
| **Socio-demographics** | | | | | |
| Age, years (SD) | 56.3 (8.1) | 56.1 (8.1) | 56.9 (8.0) | 53.9 (8.0) | 52.9 (7.9) |
| Sex (%) | | | | | |
| Male | 199,688 (48.2) | 139,354 (53.9) | 54,842 (39.8) | 2811 (29.4) | 2681 (35.1) |
| Female | 214,226 (51.8) | 119,411 (46.1) | 83,112 (60.2) | 6746 (70.6) | 4957 (64.9) |
| Region (%) | | | | | |
| England | 366,964 (88.7) | 228,925 (88.5) | 122,492 (88.8) | 8581 (89.8) | 6966 (91.2) |
| Scotland | 29,709 (7.2) | 19,130 (7.4) | 9616 (7.0) | 575 (6.0) | 388 (5.1) |
| Wales | 17,241 (4.2) | 10,710 (4.1) | 5846 (4.2) | 401 (4.2) | 284 (3.7) |
| Ethnicity (%) | | | | | |
| White | 393,251 (95.0) | 247,212 (95.5) | 130,780 (94.8) | 8977 (93.9) | 6282 (82.2) |
| Black | 6,113 (1.5) | 4,109 (1.6) | 1824 (1.3) | 138 (1.4) | 42 (0.5) |
| Asian | 8,692 (2.1) | 3,970 (1.5) | 3253 (2.4) | 285 (3.0) | 1184 (15.5) |
| Mixed | 2,402 (0.6) | 1,445 (0.6) | 814 (0.6) | 84 (0.9) | 59 (0.8) |

| | | | | | |
|---|---|---|---|---|---|
| Other | 3,456 (0.8) | 2,029 (0.8) | 1283 (0.9) | 73 (0.8) | 71 (0.9) |
| Degree-level education (%) | 141,274 (47.4) | 82,529 (44.6) | 49,546 (49.9) | 5274 (68.6) | 3925 (65.4) |
| Townsend deprivation index (SD) | -1.4 (3.0) | -1.4 (3.0) | -1.4 (3.0) | -1.0 (3.1) | -0.7 (3.1) |
| Live alone (%) | 75,245 (18.2) | 41,406 (16.0) | 29,930 (21.7) | 2287 (23.9) | 1622 (21.2) |
| **Lifestyle** | | | | | |
| Physical activity, MET.mins/week (SD) | 2951 (3879) | 2984 (3993) | 2885 (3689) | 3038 (3572) | 2895 (3690) |
| Smoking status (%) | | | | | |
| Current | 42,697 (10.3) | 28,316 (10.9) | 13,188 (9.6) | 676 (7.1) | 517 (6.8) |
| Former | 143,863 (34.8) | 90,750 (35.1) | 47,390 (34.4) | 3437 (36.0) | 2286 (29.9) |
| Never | 227,354 (54.9) | 139,699 (54.0) | 77,376 (56.1) | 5444 (57.0) | 4835 (63.3) |
| Alcohol consumption (drinks/day) | 1.2 (1.4) | 1.3 (1.5) | 1.0 (1.3) | 1.0 (1.2) | 0.7 (1.2) |
| Nutritional supplementation (%) | 206,442 (49.9) | 124,388 (48.1) | 72,604 (52.6) | 5372 (56.2) | 4078 (53.4) |
| **Anthropometrics** | | | | | |
| BMI, kg/m$^2$ (SD) | 27.3 (4.7) | 27.8 (4.8) | 26.7 (4.5) | 25.2 (4.2) | 25.6 (4.6) |
| < 18.5 (%) | 2070 (0.5) | 955 (0.4) | 846 (0.6) | 149 (1.6) | 120 (1.6) |
| 18.5 – 24.9 (%) | 136,230 (32.9) | 74,806 (28.9) | 52,611 (38.1) | 5038 (52.7) | 3775 (49.4) |
| ≥ 25 (%) | 275,614 (66.6) | 183,004 (70.7) | 84,497 (61.3) | 4370 (45.7) | 3743 (49.0) |
| Height, m (SD) | 169.0 (9.3) | 169.7 (9.3) | 167.8 (9.1) | 167.4 (8.7) | 167.1 (9.3) |
| **Comorbidities** | | | | | |
| History of diabetes (%) | 36,970 (8.9) | 25,162 (9.7) | 10,859 (7.9) | 395 (4.1) | 554 (7.3) |

| | | | | | |
|---|---|---|---|---|---|
| History of cancer (%) | 42,641 (10.3) | 25,788 (10.0) | 15,221 (11.0) | 1001 (10.5) | 631 (8.3) |
| History of CVD (%) | 46,095 (11.1) | 30,129 (11.6) | 14,853 (10.8) | 609 (6.4) | 504 (6.6) |
| History of other fracture (%) | 41,196 (10.0) | 25,800 (10.0) | 13,560 (9.8) | 1026 (10.7) | 810 (10.6) |
| **Female-specific covariates** | | | | | |
| Menopausal status (%) | | | | | |
| Premenopausal | 62,162 (29.0) | 36,214 (30.3) | 21,389 (25.7) | 2516 (37.3) | 2043 (41.2) |
| Postmenopausal | 152,064 (71.0) | 83,197 (69.7) | 61,723 (74.3) | 4230 (62.7) | 2914 (58.8) |
| HRT use (%) | | | | | |
| Current | 13,102 (6.1) | 7385 (6.2) | 5111 (6.1) | 394 (5.8) | 212 (4.3) |
| Former | 59,758 (27.9) | 33,525 (28.1) | 24,129 (29.0) | 1331 (19.7) | 773 (15.6) |
| Never | 141,366 (66.0) | 78,501 (65.7) | 53,872 (64.8) | 5021 (74.4) | 3972 (80.1) |
| ≥ 1 children (%) | 172,827 (80.7) | 99,652 (83.5) | 65,071 (78.3) | 4673 (69.3) | 3431 (69.2) |

Nutritional supplementation refers to regularly consuming any nutritional supplements. SD: standard deviation; METs: Metabolic equivalents; BMI: body mass index; CVD: cardiovascular disease; HRT: hormone replacement therapy.

### 5.4.3 Diet groups

Compared with regular meat-eaters, vegetarians (HR 1.50 (95% CI 1.18, 1.91)) but not occasional meat-eaters (0.99 (0.93, 1.07)) or pescatarians (1.08 (0.86, 1.35)) had a greater risk of hip fracture after adjustment for confounders (**Figure 5.1**), equivalent to 3.2 (1.2, 5.8) more hip fractures in vegetarians for every 1000 people over 10 years (**Table 5.2**).

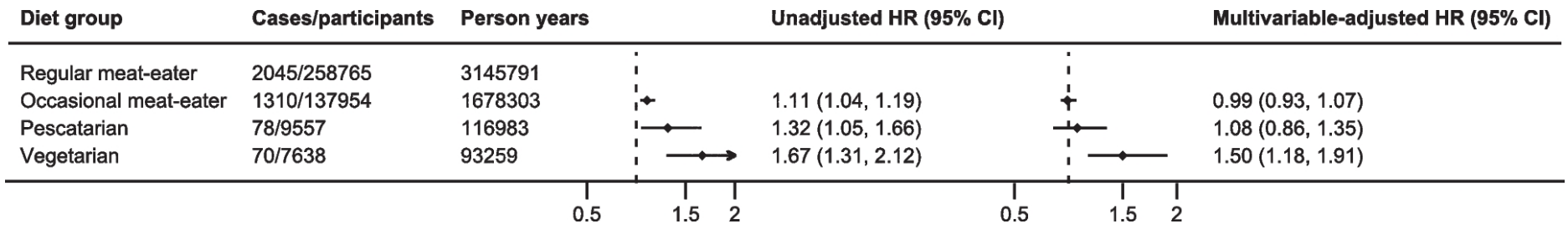



**Figure 5.1: Risk of hip fracture in occasional meat-eaters, pescatarians, and vegetarians compared to regular meat-eaters in the UK Biobank.** Both models controlled for age, and the multivariable-adjusted model was adjusted for the following (all at recruitment): region (England, Scotland, Wales), sex (male, female), ethnicity (white, black, Asian, mixed, other), Townsend deprivation index (continuous), live alone (yes, no), smoking (current, former, never), supplementation (yes, no), physical activity in MET-minutes per week (continuous), alcohol consumption in drinks per day (continuous), body mass index (continuous), number of children (0, 1, 2, ≥ 3), menopausal status (premenopausal, postmenopausal), hormone replacement therapy (current, former, never), diabetes (yes, no), cancer (yes, no), cardiovascular disease (yes, no), and other fracture (yes, no). HR (95% CI): hazard ratio (95% confidence interval).

**Table 5.2: Adjusted absolute rate differences for hip fracture in occasional meat-eaters, pescatarians, and vegetarians compared to regular meat-eaters in the UK Biobank.**

| Diet group | Predicted incidence per 1000 people over 10 years[a] | Absolute rate difference per 1000 people over 10 years[b] |
|---|---|---|
| **Regular meat-eater** | 6.5 (6.2, 6.8) | Reference |
| **Occasional meat-eater** | 6.5 (6.1, 6.8) | 0 (-0.4, 0.3) |
| **Pescatarian** | 7.0 (5.6, 8.7) | 0.5 (-0.9, 2.2) |
| **Vegetarian** | 9.7 (7.7, 12.3) | 3.2 (1.2, 5.8) |

[a] For regular meat-eaters, calculated as (1-Sr) x 1000, where Sr = (1-observed incidence in regular meat-eaters)$^{10}$, representing the predicted 10-year non-incidence or "survival" rate in regular meat-eaters. For other diet groups, calculated as (1-$Sr^{HR\ or\ 95\%\ CI}$) x 1000, where HR or CI are hazard ratios or 95% confidence intervals for hip fracture risk in that diet group, and $SR^{HR\ or\ 95\%\ CI}$ represents the predicted 10-year survival rate in each diet group.
[b] Calculated as the crude difference between the predicted incidence per 1000 people over 10 years for each diet group and regular meat-eaters.

### 5.4.4 Subgroup analyses

There was limited evidence of effect modification by BMI on hip fracture risk across diet groups when BMI was modelled categorically ($p_{interaction}$ = 0.08), but not when modelled continuously ($p_{interaction}$ = 0.5). There was no evidence of effect modification by age (< 60 years vs > 60 years: $p_{interaction}$ = 0.9; per 1-year increase: $p_{interaction}$ = 0.6) or sex ($p_{interaction}$ = 0.9) (**Table 5.3**).

**Table 5.3: Risk of hip fracture in occasional meat-eaters, pescatarians, and vegetarians compared to regular meat-eaters in UK Biobank participants, stratified by age, sex, and body mass index.**

| Stratifying variable | n cases, adjusted HR (95% CI) | | | | *p* interaction |
|---|---|---|---|---|---|
| **Age** | | **< 60 years** | | **≥ 60 years** | |
| Regular meat-eaters (reference) | 514 / 152,486 | 1.00 | 1531 / 106,279 | 1.00 | |
| Occasional meat-eaters | 317 / 75,670 | 1.03 (0.89, 1.18) | 993 / 62,284 | 0.98 (0.91, 1.07) | |
| Pescatarians | 31 / 6747 | 1.15 (0.80, 1.65) | 47 / 2810 | 1.04 (0.77, 1.39) | |
| Vegetarians | 32 / 5770 | 1.58 (1.10, 2.26) | 38 / 1868 | 1.45 (1.04, 2.00) | 0.9 |
| **Sex** | | **Male** | | **Female** | |
| Regular meat-eaters (reference) | 883 / 139,354 | 1.00 | 1162 / 199,411 | 1.00 | |
| Occasional meat-eaters | 381 / 54,842 | 0.98 (0.87, 1.10) | 929 / 83,112 | 1.00 (0.92, 1.09) | |
| Pescatarians | 19 / 2811 | 1.29 (0.82, 2.03) | 59 / 6746 | 1.02 (0.79, 1.33) | |
| Vegetarians | 24 / 2681 | 2.04 (1.36, 3.08) | 46 / 4957 | 1.32 (0.98, 1.78) | 0.3 |
| **BMI** | | **BMI ≤ 22.5 kg/m$^2$** | | **BMI > 22.5 kg/m$^2$** | |
| Regular meat-eaters (reference) | 343 / 25,794 | 1.00 | 1702 / 232,971 | 1.00 | |
| Occasional meat-eaters | 279 / 21,297 | 0.86 (0.74, 1.01) | 1031 / 116,657 | 1.06 (0.98, 1.15) | |
| Pescatarians | 27 / 2564 | 0.90 (0.61, 1.33) | 51 / 6993 | 1.22 (0.92, 1.61) | |
| Vegetarians | 31 / 1925 | 1.61 (1.12, 2.34) | 39 / 5713 | 1.42 (1.03, 1.96) | 0.08 |

All models controlled for age, and were adjusted for the following (all at recruitment): region (England, Scotland, Wales), sex (male, female), ethnicity (white, black, Asian, mixed, other), Townsend deprivation index (continuous), live alone (yes, no), smoking (current, former, never), supplementation (yes, no), physical activity in MET-minutes per week (continuous), alcohol consumption in drinks per day (continuous), body mass index

(continuous), number of children (0, 1, 2, ≥ 3), menopausal status (premenopausal, postmenopausal), hormone replacement therapy (current, former, never), diabetes (yes, no), cancer (yes, no), cardiovascular disease (yes, no), and other fracture (yes, no). Each potential effect modifier was omitted from their adjustment set. HR (95% CI): hazard ratio (95% confidence interval); BMI: body mass index.

### 5.4.5 Mediation analyses

Adjusted and relative means for BMI, heel BMD, FFM, hand grip strength, serum vitamin D, and IGF-1 at recruitment across diet groups are shown in **Appendix D: Table D8**. Potential mediation through each of these variables for the observed higher risk of hip fracture in vegetarians compared to regular meat-eaters is shown in **Table 5.4**. BMI, FFM, serum vitamin D, and IGF-1 were lower in vegetarians than in regular meat-eaters (**Appendix D: Table D8**). BMI was found to partly mediate the observed difference in hip fracture risk between vegetarians and regular meat-eaters, with a decomposed $HR^{NIE}$ of 1.17 (95% CI: 1.00, 1.35), implying that BMI may explain 27.8% (95% CI: 1.1%, 69.8%) of the risk difference (**Table 5.4**). There was no clear evidence of mediation through FFM, serum vitamin D, or IGF-1 for the observed risk difference between vegetarians and regular meat-eaters (**Table 5.4**). Heel BMD and hand grip strength did not differ significantly between these diet groups **(Appendix D: Table D8**), and were not considered in the causal mediation analyses.

**Table 5.4: Summary of the total, direct, and indirect effects of potential mediators for differences in hip fracture risk between vegetarians and regular meat-eaters in the UK Biobank.**

| Vegetarians vs regular meat-eaters | | Conditional effect, HR or % (95% CI) | | | |
|---|---|---|---|---|---|
| **Potential mediator** | **n / N** | **Total effect** | **Direct effect** | **Indirect effect** | **% mediation** |
| BMI | 2115/266,403 | 1.77 (1.34, 2.25) | 1.51 (1.11, 2.03) | 1.17 (1.00, 1.35) | 27.8 (1.1, 69.8) |
| FFM | 2056/262,679 | 1.68 (1.27, 2.13) | 1.78 (1.19, 2.44) | 0.95 (0.73, 1.21) | -10.5 (-77.4, 44.8) |
| Vitamin D | 1874/238,837 | 1.67 (1.26, 2.10) | 1.61 (1.18, 2.13) | 1.03 (0.86, 1.23) | 6.5 (-35.4, 45.6) |
| IGF-1 | 1949/248,163 | 1.63 (1.25, 2.06) | 1.64 (1.25, 2.08) | 1.00 (0.94, 1.06) | -0.8 (-16.7, 14.4) |

All models controlled for age, and were adjusted for the following (all at recruitment): region (England, Scotland, Wales), sex (male, female), ethnicity (white, black, Asian, mixed, other), Townsend deprivation index (continuous), live alone (yes, no), smoking (current, former, never), supplementation (yes, no), physical activity in MET-minutes per week (continuous), alcohol consumption in drinks per day (continuous), number of children (0, 1, 2, ≥ 3), menopausal status (premenopausal, postmenopausal), hormone replacement therapy (current, former, never), diabetes (yes, no), cancer (yes, no), cardiovascular disease (yes, no), and other fracture (yes, no). Models for vitamin D and IGF-1 were also adjusted for BMI, and the model for FFM was adjusted for height.
The natural indirect effect represents the estimated association of diet group and hip fracture risk through the potential mediator.
The natural direct effect represents the estimated association of diet group and hip fracture risk not through the potential mediator.
For each mediator, participants with missing values for that mediator or for relevant covariates were excluded from the analysis.
BMI: body mass index; FFM: fat-free mass; IGF-1: Insulin-like growth factor-1; HR (95% CI): hazard ratio (95% confidence intervals).

### 5.4.6 Sensitivity analyses

All sensitivity analyses are presented in **Appendix D: Figure D6** and **Table D9**. Excluding participants with short follow-up durations (< 3 years) and excluding those on long-term treatment for illness increased the magnitude of the association for vegetarians (1.64 (1.27, 2.11) and 1.91 (1.35, 2.70) respectively) but not for other diet groups, but confidence intervals also widened. Differentiating between vegetarians (60 cases / 7238 participants) and vegans (10 cases / 400 participants) slightly attenuated the estimate for vegetarians (vegetarians: 1.38 (1.06, 1.79); vegans: 3.26 (1.75, 6.08)). For all diet groups, estimates remained similar in the competing risks analysis (**Appendix D: Table D9**). Estimates were similar for occasional meat-eaters and vegetarians when missing covariate data were imputed, but the association strengthened for pescatarians (1.29 (1.05, 1.57); **Appendix D: Figure D6**).

## 5.5 Discussion

### 5.5.1 Principal findings

In this large prospective British cohort of men and women, there are three important findings: First, vegetarians but not pescatarians or occasional meat-eaters were at a higher risk of hip fracture than regular meat-eaters, but absolute risk differences were modest. These results remained after adjustment for key socio-demographic and lifestyle factors. Second, there was no clear evidence of effect modification by age or sex, and there was limited evidence of effect modification by BMI. Finally, the lower average BMI in vegetarians explained some of the observed risk difference compared to regular meat-eaters, but a large proportion remained unexplained.

### 5.5.2 Comparison with previous studies

Only three previously published prospective studies have assessed meat-free diets in relation to hip fracture risk (6, 8, 9). In the European Prospective Investigation into Cancer-Oxford (EPIC-Oxford) (6), UKWCS (8), and Adventist Health Study-2 (AHS-2) cohorts (9), compared to meat-eaters, vegetarians were at a greater risk in both UK cohorts but not in the AHS-2, whilst

pescatarians were at a greater risk in the EPIC-Oxford cohort only. Our findings are consistent with results from the two previous British cohorts on this topic for vegetarians, strengthening the evidence of an increased risk of hip fracture in British vegetarians. In the AHS-2, hip fractures were identified from self-reported questionnaires, which are prone to selective loss to follow-up compared to more deterministic linkage to hospital records used here and in the other UK cohorts, which may contribute to the difference in findings. Importantly, we provide evidence of a greater risk of hip fracture in vegetarian men, which has only been observed in the EPIC-Oxford study in which 77% of vegetarians were women. Similarly to the UKWCS and AHS-2 studies, there was no clear evidence of a risk difference for pescatarians in this study, whereas pescatarians were at a 26% greater risk in the EPIC-Oxford study. These differences may be attributable to differences in fish intake, population characteristics, and other sources of residual confounding across cohorts, although in the sensitivity analysis when we imputed for missing covariate data, the estimate was similar to that observed in the EPIC-Oxford study.

### 5.5.3 Interpretation and implications

Whilst the relative increase in hip fracture risk for vegetarians was high (50%), this represents an absolute difference of only 3.2 more cases per 1000 people over 10 years, which is consistent with estimates from the EPIC-Oxford study. This modest absolute risk difference should be weighed against the potential associated health benefits of vegetarian diets for more common conditions when formulating dietary guidelines, including 13 fewer cancers per 1000 people over 10 years and a 9% lower risk of CVD observed previously in the UK Biobank (4, 5). Evidence of associations for occasional meat-eaters and pescatarians were unclear, but absolute risk differences and their confidence intervals appeared to rule out a clinically relevant benefit or harm.

In this study, vegetarians had a lower BMI (adjusted means of 25.9 vs 27.7 kg/m2) and were less likely to be overweight (means of 49.0% vs 70.7%) than regular meat-eaters on average, which is consistent with previous studies (6, 8, 38). Low BMI is a known risk factor for hip fracture, and overweight (BMI between 25-29.9 kg/$m^2$) but not obesity (BMI ≥ 30 kg/$m^2$) may reduce hip fracture risk (36). In the subgroup analysis by BMI, the difference in p-interaction values when BMI was modelled continuously (p=0.5) compared to when dichotomised at 22.5 kg/$m^2$ (p=0.08)

may suggest a potential non-linear interaction of BMI with diet groups on hip fracture risk. However, further investigation of a potentially non-linear interaction of BMI with diet groups was not possible in this study due to the low number of vegetarians and pescatarians with obesity.

In the UKWCS and EPIC-Oxford cohorts (6, 8), adjustment for BMI slightly attenuated risk estimates. We extend these findings by showing through causal mediation analysis that differences in BMI explained approximately 28% of the higher risk in vegetarians. Lower BMI in vegetarians may reflect inadequate fat mass which reduces cushioning from impact forces during a fall. Alternatively, lower BMI may indicate poor musculoskeletal health. Previous studies have reported slightly lower whole-body and femoral neck BMD, FFM, and muscle strength in vegetarians than in meat-eaters (13, 14). These factors are more common at a lower BMI, and increase the risk of hip fracture (36). Small differences were observed for heel BMD, FFM, and hand grip strength between diet groups in this study, but their roles as potential mediators were unclear. Femoral neck BMD contributes to hip fracture risk more than heel BMD (17), but mediation analysis for femoral neck BMD was not possible since this data was only available in a subset of participants (around 10%). Weight management may therefore help to mitigate some of the increased risk of hip fracture in vegetarians and warrants exploration in future trials. Further studies are needed to understand musculoskeletal health across diet groups, and consequences on hip fracture risk. The generally protective role of BMI in hip fracture prevention should also be considered alongside the adverse health effects of overweight (39).

A large proportion of the higher risk of hip fracture in vegetarians was not explained by BMI, implying that other factors are important. Previously published studies have suggested lower circulating vitamin D and IGF-1 levels in vegetarians than in meat-eaters (18, 34), and inverse associations of these biomarkers with hip fracture risk through their effects on bone and muscle health (20, 35). Circulating vitamin D and IGF-1 were lower in vegetarians than in meat-eaters in this study, but there was no clear evidence of mediation through IGF-1 and vitamin D. Another possible explanation is that vegetarians, on average, have lower intakes of nutrients important to bone and muscle health, such as protein, vitamin D, and vitamin B12 (8, 11, 12). In this study, vegetarians consumed less dietary protein, iron, iodine, niacin, selenium, vitamin B12, and vitamin D than other diet groups. Specifically, vegetarians were less likely to meet daily

recommended protein intakes of 0.75 g/kg body weight/day for adults than regular meat-eaters (68.2% vs 85.2%) (31), and were less likely to achieve higher protein intakes of 1.2 g/kg body weight/day (15.8% vs 33.6%), which may help to attenuate age-related bone and muscle loss (40). We could not investigate mediation through dietary factors since nutrient data was only available in 50.1% of the cohort. Nevertheless, given that dietary protein has been inversely associated with hip fracture risk in previously published studies (41, 42), and high intakes have been reported to be safe (up to 2 g/kg body weight/day) (42), increasing protein intake may help to reduce hip fracture risk in vegetarians, and warrants exploration in further studies.

### 5.5.4 Strengths and limitations

This study has many strengths. The moderately long prospective follow-up and identification of hip fractures by linkage to hospital records minimised outcome misclassification and loss to follow-up. The wide array of lifestyle, hospital, and biomarker data available in the UK Biobank permitted adjustment for many likely confounders, and enabled exploration of the roles of anthropometric and biomarker factors as potential mediators of observed associations. In a sub-sample of participants with repeated measurements (n = 57,730), there was little evidence of changes in diet groups over time, which minimises risk of misclassification, and there was little evidence of reverse causality, as results were similar after excluding participants with < 3 years of follow-up. Finally, we provide evidence in men and women.

Our study has important limitations. Vegans (do not eat meat, fish, eggs, or dairy) are less likely to meet nutrient intake recommendations for protein and calcium and may be at a higher risk of hip fractures than meat-eaters (6, 11), but there were not enough vegans in this cohort to assess their risk independently. Further prospective studies into hip fracture risk with a large proportion of vegans are needed. Additionally, diet quality may vary within and between diet groups, and may influence hip fracture risk. Future studies should aim to determine if a well-planned vegetarian diet mitigates the observed risk difference. This study focused on risk of hip fracture across diet groups; further research should investigate if associations vary by fracture site. Participants were, on average, younger at hip fracture or by end of follow-up than the average age at hip fracture in men (84 years) and women (83 years) (43), which limited the number of cases observed. Moreover, relatively low numbers of older adults could explain why there was

no evidence of effect modification by age. We were unable to differentiate between fragility and traumatic hip fractures because data on the cause of hip fractures were not available. However, most hip fractures in middle-aged to older adults are fragility fractures (44), and since risk of traumatic hip fracture is unlikely to differ across diet groups, any outcome misclassification would only dilute risk estimates. As with all observational studies, residual confounding remains possible, and causality cannot be inferred. In mediation analyses, residual confounding is also possible at the exposure-outcome, exposure-mediator, and mediator-outcome levels. Additionally, we used measures of anthropometrics and biomarkers at recruitment for mediators, which may not represent measures during follow-up, though correlations with repeat measures show high agreement. Nevertheless, the mediation results should be interpreted with caution, particularly given the wide confidence intervals for all mediators. UK Biobank participants have a healthy risk profile compared to the British population (45), and are mostly Caucasian. These factors reduce generalisability to the UK population and to other ethnic groups, respectively.

### 5.5.5 Conclusion

Vegetarian men and women had a higher risk of hip fracture than regular meat-eaters, and was in part explained by their lower BMI, but absolute risk differences were small, and should be weighed against the potential health benefits of vegetarian diets. Further work is needed to fully understand mechanisms underpinning risk differences; diet planning and weight management could help to mitigate the risk difference, and warrant exploration in further studies so that policy recommendations can advance.

## 5.6 References

1. Prince MJ, Wu F, Guo Y, Gutierrez Robledo LM, O'Donnell M, Sullivan R, et al. The burden of disease in older people and implications for health policy and practice. Lancet. 2015;385(9967):549-62.

2. Manetti S, Turchetti G, Fusco F. Determining the cost-effectiveness requirements of an exoskeleton preventing second hip fractures using value of information. BMC Health Serv Res. 2020;20(1):955.

3. Leahy E, Lyons S, Tol R. An estimate of the number of vegetarians in the world. ESRI working paper 340. . 2010.

4. Watling CZ, Schmidt JA, Dunneram Y, Tong TYN, Kelly RK, Knuppel A, et al. Risk of cancer in regular and low meat-eaters, fish-eaters, and vegetarians: a prospective analysis of UK Biobank participants. BMC Med. 2022;20(1):73.

5. Petermann-Rocha F, Parra-Soto S, Gray S, Anderson J, Welsh P, Gill J, et al. Vegetarians, fish, poultry, and meat-eaters: who has higher risk of cardiovascular disease incidence and mortality? A prospective study from UK Biobank. Eur Heart J. 2021;42(12):1136-43.

6. Tong TYN, Appleby PN, Armstrong MEG, Fensom GK, Knuppel A, Papier K, et al. Vegetarian and vegan diets and risks of total and site-specific fractures: results from the prospective EPIC-Oxford study. BMC Med. 2020;18(1):353.

7. Tong TYN, Appleby PN, Bradbury KE, Perez-Cornago A, Travis RC, Clarke R, et al. Risks of ischaemic heart disease and stroke in meat eaters, fish eaters, and vegetarians over 18 years of follow-up: results from the prospective EPIC-Oxford study. Bmj. 2019;366:l4897.

8. Webster J, Greenwood DC, Cade JE. Risk of hip fracture in meat-eaters, pescatarians, and vegetarians: results from the UK Women's Cohort Study. BMC Med. 2022;20(1):275.

9. Thorpe DL, Beeson WL, Knutsen R, Fraser GE, Knutsen SF. Dietary patterns and hip fracture in the Adventist Health Study 2: combined vitamin D and calcium supplementation mitigate increased hip fracture risk among vegans. Am J Clin Nutr. 2021;114(2):488-95.

10. Thompson AS, Tresserra-Rimbau A, Karavasiloglou N, Jennings A, Cantwell M, Hill C, et al. Association of Healthful Plant-based Diet Adherence With Risk of Mortality and Major Chronic Diseases Among Adults in the UK. JAMA Netw Open. 2023;6(3):e234714.

11. Tucker KL. Vegetarian diets and bone status. Am J Clin Nutr. 2014;100 Suppl 1:329s-35s.

12. Davey GK, Spencer EA, Appleby PN, Allen NE, Knox KH, Key TJ. EPIC-Oxford: lifestyle characteristics and nutrient intakes in a cohort of 33 883 meat-eaters and 31 546 non meat-eaters in the UK. Public Health Nutr. 2003;6(3):259-69.

13. Tong TY, Key TJ, Sobiecki JG, Bradbury KE. Anthropometric and physiologic characteristics in white and British Indian vegetarians and nonvegetarians in the UK Biobank. Am J Clin Nutr. 2018;107(6):909-20.

14. Iguacel I, Miguel-Berges ML, Gómez-Bruton A, Moreno LA, Julián C. Veganism, vegetarianism, bone mineral density, and fracture risk: a systematic review and meta-analysis. Nutr Rev. 2019;77(1):1-18.

15. Gonnelli S, Caffarelli C, Nuti R. Obesity and fracture risk. Clin Cases Miner Bone Metab. 2014;11(1):9-14.

16. Kim KH, Lee JH, Lim EJ. Weak psoas and spine extensors potentially predispose to hip fracture. Hip Int. 2021;31(3):430-4.

17. Bouxsein ML, Eastell R, Lui LY, Wu LA, de Papp AE, Grauer A, et al. Change in Bone Density and Reduction in Fracture Risk: A Meta-Regression of Published Trials. J Bone Miner Res. 2019;34(4):632-42.

18. Allen NE, Appleby PN, Davey GK, Kaaks R, Rinaldi S, Key TJ. The associations of diet with serum insulin-like growth factor I and its main binding proteins in 292 women meat-eaters, vegetarians, and vegans. Cancer Epidemiol Biomarkers Prev. 2002;11(11):1441-8.

19. Bonjour JP. The dietary protein, IGF-I, skeletal health axis. Horm Mol Biol Clin Investig. 2016;28(1):39-53.

20. Yuan S, Wan ZH, Cheng SL, Michaëlsson K, Larsson SC. Insulin-like Growth Factor-1, Bone Mineral Density, and Fracture: A Mendelian Randomization Study. J Clin Endocrinol Metab. 2021;106(4):e1552-e8.

21. Lachat C, Hawwash D, Ocké MC, Berg C, Forsum E, Hörnell A, et al. Strengthening the Reporting of Observational Studies in Epidemiology-Nutritional Epidemiology (STROBE-nut): An Extension of the STROBE Statement. PLoS Med. 2016;13(6):e1002036.

22. Bradbury KE, Young HJ, Guo W, Key TJ. Dietary assessment in UK Biobank: an evaluation of the performance of the touchscreen dietary questionnaire. J Nutr Sci. 2018;7:e6.

23. Perez-Cornago A, Pollard Z, Young H, van Uden M, Andrews C, Piernas C, et al. Description of the updated nutrition calculation of the Oxford WebQ questionnaire and comparison with the previous version among 207,144 participants in UK Biobank. Eur J Nutr. 2021;60(7):4019-30.

24. Galante J, Adamska L, Young A, Young H, Littlejohns TJ, Gallacher J, et al. The acceptability of repeat Internet-based hybrid diet assessment of previous 24-h dietary intake: administration of the Oxford WebQ in UK Biobank. Br J Nutr. 2016;115(4):681-6.

25. Easton DF, Peto J, Babiker AG. Floating absolute risk: an alternative to relative risk in survival and case-control analysis avoiding an arbitrary reference group. Stat Med. 1991;10(7):1025-35.
26. Plummer M. Improved estimates of floating absolute risk. Stat Med. 2004;23(1):93-104.
27. Tchetgen Tchetgen EJ. Inverse odds ratio-weighted estimation for causal mediation analysis. Stat Med. 2013;32(26):4567-80.
28. Nguyen QC, Osypuk TL, Schmidt NM, Glymour MM, Tchetgen Tchetgen EJ. Practical guidance for conducting mediation analysis with multiple mediators using inverse odds ratio weighting. Am J Epidemiol. 2015;181(5):349-56.
29. Wang W, Nelson S, Albert JM. Estimation of causal mediation effects for a dichotomous outcome in multiple-mediator models using the mediation formula. Stat Med. 2013;32(24):4211-28.
30. Preacher KJ, Hayes AF. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. Behav Res Methods. 2008;40(3):879-91.
31. British Nutrition Foundation. Nutrition requirements. 2021. [Available from: https://www.nutrition.org.uk/media/nmmewdug/nutrition-requirements.pdf].
32. UK Biobank Coordinating Centre. UK Biobank: Protocol for a large-scale prospective epidemiological resource. Cheshire, UK: UK Biobank; 2007 [Available from: https://www.ukbiobank.ac.uk/media/gnkeyh2q/study-rationale.pdf.
33. Korn EL, Graubard BI, Midthune D. Time-to-event analysis of longitudinal follow-up of a survey: choice of the time-scale. Am J Epidemiol. 1997;145(1):72-80.
34. Tong TYN, Perez-Cornago A, Bradbury KE, Key TJ. Biomarker Concentrations in White and British Indian Vegetarians and Nonvegetarians in the UK Biobank. J Nutr. 2021;151(10):3168-79.
35. Habibi Ghahfarrokhi S, Mohammadian-Hafshejani A, Sherwin CMT, Heidari-Soureshjani S. Relationship between serum vitamin D and hip fracture in the elderly: a systematic review and meta-analysis. J Bone Miner Metab. 2022;40(4):541-53.
36. Gonnelli S, Caffarelli C, Nuti R. Obesity and fracture risk. Clin Cases Miner Bone Metab. 2014;11(1):9-14.
37. Denk K, Lennon S, Gordon S, Jaarsma RL. The association between decreased hand grip strength and hip fracture in older people: A systematic review. Exp Gerontol. 2018;111:1-9.

38. Barnard ND, Levin SM, Yokoyama Y. A systematic review and meta-analysis of changes in body weight in clinical trials of vegetarian diets. J Acad Nutr Diet. 2015;115(6):954-69.

39. Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, Lee A, et al. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. N Engl J Med. 2017;377(1):13-27.

40. Houston DK, Nicklas BJ, Ding J, Harris TB, Tylavsky FA, Newman AB, et al. Dietary protein intake is associated with lean mass change in older, community-dwelling adults: the Health, Aging, and Body Composition (Health ABC) Study. Am J Clin Nutr. 2008;87(1):150-5.

41. Webster J, Greenwood DC, Cade JE. Foods, nutrients and hip fracture risk: A prospective study of middle-aged women. Clin Nutr. 2022;41(12):2825-32.

42. Webster J, Dalla Via J, Langley C, Smith C, Sale C, Sim M. Nutritional strategies to optimise musculoskeletal health for fall and fracture prevention: Looking beyond calcium, vitamin D and protein. Bone Reports. 2023:101684.

43. Swift CG. Prevention and management of hip fracture in older patients. Practitioner. 2011;255(1743):29-33, 3.

44. Robinson CM, Court-Brown CM, McQueen MM, Christie J. Hip fractures in adults younger than 50 years of age. Epidemiology and results. Clin Orthop Relat Res. 1995(312):238-46.

45. Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, et al. Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants With Those of the General Population. Am J Epidemiol. 2017;186(9):1026-34.

# Chapter 6 Critical discussion

Hip fractures are the most common fracture site resulting in hospitalisation, and increase morbidity and mortality (1). In the ageing national and global population, absolute rates of hip fracture will increase if prevention measures do not improve. Diet is one of the major modifiable factors that could reduce hip fracture risk by attenuating age-related decline in musculoskeletal health, and improving body composition. Many aspects of diet, including nutrients beyond those traditionally considered in hip fracture aetiology (calcium and vitamin D); foods in which relevant nutrients are consumed; and patterns of consumption over time may influence risk of hip fracture. However, the potential roles of many individual foods and nutrients are unclear, preventing dietary guidelines from advancing. Additionally, vegetarian and pescatarian diets are increasing in popularity in developed countries, and recent evidence has suggested that these diets may be associated with poorer musculoskeletal health and a higher risk of fractures, but evidence on this topic is scarce in relation to hip fractures.

To address these research gaps, this thesis had the following aim:

*To better understand relationships between dietary habits and hip fracture risk in adults.*

The preceding chapters describe the approach taken to achieve this aim, and present the findings through four papers:

1. **Paper 1** *(Chapter 2) Dietary risk factors for hip fracture in adults: An umbrella review of meta-analyses of prospective cohort studies*
2. **Paper 2** *(Chapter 3) Foods, nutrients and hip fracture risk: A prospective study of middle-aged women*
3. **Paper 3** *(Chapter 4) Risk of hip fracture in meat-eaters, pescatarians, and vegetarians: results from the UK Women's Cohort Study*
4. **Paper 4** *(Chapter 5) Risk of Hip Fracture in Meat Eaters, Pescatarians, and Vegetarians: A Prospective Cohort Study of 413,914 UK Biobank Participants*

In this final Chapter, evidence generated from each paper (Chapter) is drawn together and summarised; novel findings are highlighted; results across chapters are critically evaluated in the wider research context; potential mechanisms are explored; strengths and limitations are discussed; public health implications and future recommendations are provided; and conclusions are drawn.

## 6.1 Summary of findings

Key findings from this thesis are highlighted in **Table 6.1**. First, the umbrella review (Chapter 2) showed that dietary patterns and several individual foods and nutrients may be independently associated with hip fracture risk, but the existing published evidence prior to this thesis was limited to a small number of studies for each dietary exposure, with inconsistent findings. Evidence was particularly limited for dietary patterns and British populations. Second, in Chapter 3, there was suggestive evidence of inverse associations between dietary protein intake, combined tea and coffee consumption, and hip fracture risk in the UKWCS. There was no clear evidence of overall associations between hip fracture risk and dietary intake of calcium or vitamin D; fruit and vegetables; or animal foods, including meat, fish, and dairy products. Finally, in Chapters 4 and 5, vegetarians but not pescatarians or occasional meat-eaters were at a greater risk of hip fracture than regular meat-eaters in both the UKWCS and UK Biobank cohorts of British adults. These results remained after adjustment for key socio-demographic and lifestyle factors, and were independent of sex. The risk difference was partly explained by the lower average BMI in vegetarians versus meat-eaters.

**Table 6.1: Summary of key findings, potential explanations, and novelty in this thesis.**

| Chapter | Key finding | Potential explanations | Novelty |
|---|---|---|---|
| 2 | Quality of previously published evidence was very low for most diet-hip fracture associations, particularly for dietary patterns and in British populations | • Low number of studies<br>• Small sample sizes<br>• Short follow-up durations<br>• Inconsistent results<br>• Dietary measurement error | First study in 13 years to comprehensively synthesise the available evidence on this topic |

| | | | |
|---|---|---|---|
| | | • Hip fractures captured from self-reported methods | |
| 3 | Protein intake was linearly inversely associated with hip fracture risk in British women | • ↑ IGF-1 and ↓ PTH levels<br>• ↑ BMD<br>• ↑ Muscle mass, strength, and function | First prospective study in the UK on this topic |
| 3 | Combined tea and coffee intake were linearly inversely associated with hip fracture risk in British women | • ↑ intake of caffeine & antioxidants<br>• ↓ oxidative stress<br>• ↑ BMD<br>• ↑ Cardiovascular and metabolic health | First prospective study in the UK on this topic |
| 4 & 5 | British vegetarian men and women were at a greater risk of hip fracture than regular meat-eaters | • ↓ BMI<br>• ↓ protein quantity (and potentially quality)<br>• ↓ serum vitamin D<br>• ↓ IGF-1<br>• ↑ PTH levels<br>• ↓ BMD<br>• ↓ Muscle mass, strength, and function | • Second and third studies on this topic internationally with hip fractures confirmed using hospital data<br>• First study to formally investigate mediating pathways |

Up arrows indicate increases and down arrows indicate decreases. IGF-1: insulin-like growth factor-1; PTH: parathyroid hormone; BMD: bone mineral density; BMI: body mass index.

## 6.2 Highlights of what is novel in this thesis

1. The first study in 13 years to comprehensively synthesise published prospective evidence around diet and hip fracture risk.
2. The first prospective study in British women to investigate associations between diet and hip fracture risk for many foods and nutrients, including: dietary protein intake and consumption of high-protein animal foods (i.e. meat and fish); dietary calcium and vitamin D intake and consumption of dairy products; and consumption of tea, coffee, fruit, and vegetables, respectively.

3. Only the second and third studies to compare hip fracture risk in vegetarians and meat-eaters in the UK, and the second and third to do so internationally with hip fractures accurately confirmed using hospital records.
4. The first study to formally investigate potential mediators of the difference in hip fracture risk between vegetarians and regular meat-eaters.
5. The first prospective study to investigate if associations of several food and nutrient intakes, as well as vegetarian diets, with hip fracture risk depend on BMI.

## 6.3 Comparison with previous literature

This section describes what was known prior to this thesis, and how each novel finding presented in Chapter 6: section 6.2 advances the evidence-base.

### 6.3.1 The umbrella review

One previous umbrella review published in 2007 synthesised general risk factors for hip fracture, including a limited number of dietary factors, and was discussed in Chapter 2: section 2.2 (2). The umbrella review presented in Chapter 2 provides an updated comprehensive synthesis of all published prospective observational evidence for associations between diet and hip fracture risk, including new evidence published since that review over a decade ago. This includes information for 31 additional dietary exposures, with a systematic evaluation of the quality of evidence for each diet-hip fracture association. Chapter 2 highlighted the need for more robust prospective studies reporting both relative and absolute risk estimates with long follow-up durations, adequate power, and appropriate adjustment for confounders for several food and nutrient exposures, but particularly for dietary patterns. Findings from the UKWCS and UK Biobank in papers 2, 3, and 4 (presented in Chapters 3, 4, and 5) directly address this need.

### 6.3.2 Protein, high-protein animal foods, and vegetarian diets

Results from Chapter 2 suggest that dietary protein intake may be inversely associated with hip fracture risk (3), but the quality of evidence was very low. Prospective cohort studies included in previous meta-analyses on this topic showed mixed results, with two studies showing an inverse

association with hip fracture risk (4, 5), and six showing no clear association, all with wide confidence intervals (6-11). Many previous studies were underpowered, with ≤ 100 cases in four of the cohorts (7-10), and ≤ 250 in another (6), resulting in unclear (but not null) associations. In Chapter 3, an extra 25 g of protein per day was associated with a 14% lower risk of hip fracture in the UKWCS, strengthening the evidence of a linear, dose-response inverse association of dietary protein intake with hip fracture risk in women. Data is provided for the first time on this topic from a British cohort of women, with more than 800 hip fracture cases accurately confirmed in hospital records.

Meat and fish are good protein sources, but in Chapter 2, no previously published meta-analyses of cohort studies investigating associations between meat, fish, or meat-free diets with hip fracture risk were identified. For meat, in the AHS-2 cohort, participants who consumed meat regularly (> 3 times/week) but not those who consumed meat occasionally (1-3 times/week) were at a lower risk of hip fracture than those consuming meat rarely (< 1 serving/week), suggesting a non-linear relationship between meat intake and hip fracture risk (12). However, that study was not able to confirm self-reported hip fractures using medical records. For fish, one meta-analysis that was not eligible for inclusion in the umbrella review, including four prospective and two case control studies, found an inverse association between total fish intake and risk of hip fracture (13). However, the association was not significant when restricted to studies with good follow-up length (≥ 10 years), or with hip fractures confirmed using medical records. In Chapter 3, there was no clear evidence of independent linear associations between meat or fish intake with hip fracture risk in the UKWCS, nor for red meat, processed meat, poultry, oily fish, or non-oily fish. In Chapters 4 and 5, vegetarians but not pescatarians or occasional meat-eaters were at a greater risk of hip fracture than regular meat-eaters in both British cohorts.

Only two large prospective cohort studies (EPIC-Oxford and AHS-2) have investigated if reducing or excluding meat and/or fish from the diet altogether is associated with hip fracture risk (12, 14). The EPIC-Oxford study showed a higher risk of hip fracture in pescatarians, vegetarians, and vegans compared to meat-eaters in a British population of middle-aged adults, with a gradient-like effect of a greater risk of hip fracture with more restrictive diets (14). There were no clear

differences between men and women, but that cohort consisted of 77% women, therefore was likely underpowered to detect a reliable estimate in men. In the AHS-2 study, there was no clear difference in hip fracture risk in vegetarians, semi-vegetarians (ate meat or fish ≤ once/week), or pescatarians compared to non-vegetarians in middle-aged Seventh-day Adventists, with no sex differences (12). Reasons for slight discrepancies in findings from the UKWCS, UK Biobank, EPIC-Oxford, and AHS-2 cohorts include differences in the reference group; adjustment strategies; population characteristics; hip fracture ascertainment methods; and length of follow-up, and were discussed in detail Chapters 4 and 5. Overall, results from Chapters 4 and 5 are largely consistent with the only other British study on the topic (the EPIC-Oxford study) for vegetarians, strengthening the evidence of an increased risk of hip fracture in British vegetarian men and women. Importantly, results from Chapters 4 and 5 are the first in the UK to show that eating meat occasionally (< 5 servings/week) was not associated with a greater risk of hip fracture compared to regularly eating meat (≥ 5 servings/week), with good precision, particularly in the UK Biobank.

### 6.3.3 Calcium, vitamin D, and dairy products

In Chapter 2, dietary calcium intake was not associated with hip fracture risk, based on very low quality evidence, and no meta-analyses were identified on dietary vitamin D intake in relation to hip fracture risk. In Chapter 3, there was no clear evidence for an overall association between dietary calcium or vitamin D intakes with hip fracture risk in the UKWCS.

A 2015 systematic review reported no association between dietary calcium intake and hip fracture risk in adults, in which 17/21 cohort studies reported null or unclear associations in adults age 50 years and over (15). The largest study included in that systematic review (the Swedish Mammography cohort, SMC, including 3871 hip fractures) found a non-linear relationship (16), where calcium intakes below the recommended 800 mg/day in Sweden were associated with a greater risk of hip fracture, and intakes above 800 mg/day did not confer any additional benefit. The only previous study on this topic in a British population found a higher risk of any fracture at lower versus higher calcium intakes (< 525 mg/day versus ≥ 1200 mg/day), but did not differentiate by fracture site (17). Reasons for differences in these findings might be due to variability in calcium intakes in each study population. In Chapter 3, the mean calcium

intake in UKWCS (1135 mg/day) was above recommended levels (700 mg/day) (18), and too few women in the UKWCS, despite its large size, had low enough dietary calcium intakes to observe any potentially greater risk of hip fracture, with only 11% of participants consuming less than 700 mg/day from dietary sources. Additionally, the SMC study calculated cumulative average dietary calcium intake using repeated FFQs, adjusted for supplemental calcium intake; in this thesis, data were only available for dietary calcium intake at recruitment and any supplement use (yes or no). Therefore, changes in dietary calcium intake over time, and specific use of calcium or vitamin D supplements were not accounted for.

Regarding vitamin D, in 2003, the Nurses Health Study (NHS), including over 70,000 US adults, found an inverse association between dietary and total vitamin D intakes with hip fracture risk, respectively (19). In contrast, the SMC of 61,000 women followed for 19 years found positive associations between both dietary and total vitamin D intakes with hip fracture risk (20). Findings from the Swedish cohort could indicate reverse causation, where participants increased their vitamin D intake after diagnosis of osteoporosis preceding hip fracture events. These discrepant findings may also be due to several differences in study design between the UKWCS, NHS, and SMC; the NHS ascertained hip fractures via self-reported questionnaires, whereas the UKWCS and SMC used hospital records, providing greater accuracy and less selective loss to follow-up. The NHS and SMC both had repeated dietary measurements and data on vitamin D supplementation, whereas in the UKWCS, dietary measures at recruitment were assumed to reflect dietary intake during follow-up, and data on use of calcium and vitamin D supplements specifically was not available. Additionally, sunlight exposure was not accounted for in the UKWCS, which may modify associations between both dietary vitamin D and calcium intakes with hip fracture risk. A recent meta-analysis showed that low serum vitamin D levels increase hip fracture risk in elderly adults (21), and the majority of serum vitamin D (~80–90 %) is generated via endogenous skin synthesis resulting from direct sun exposure (22).

Dairy products are high in calcium and vitamin D; although existing guidelines recommend dairy consumption for hip fracture prevention (23), the umbrella review in Chapter 2 indicated that higher consumption of yoghurt but not milk, cheese, or total dairy was inversely associated with hip fracture risk, with a high degree of heterogeneity amongst primary studies, and very low

quality evidence for all dairy products. In Chapter 3, there was no clear evidence of linear associations between total dairy intake with hip fracture risk in the UKWCS, nor for any subtypes. A recent RCT showed that supplementation with milk, yoghurt and cheese to achieve higher protein and calcium intakes above recommended levels (intervention: 1142 mg/day calcium and 1.1 g/kg/day protein vs control: 700 mg/day calcium and 0.9 g/kg/day protein) reduced hip fracture risk in aged care residents in Australia (aged 86 years) (24). In a subgroup of participants who provided blood samples, IGF-1 levels increased by 6% in the intervention group but not in the control group after 12 months, and IGF-1 has previously been associated with greater BMD at multiple sites, and a lower risk of hip fracture (25). There were also small (1-3%) differences between groups in BMD measures, including a non-significant 1.7% greater femoral neck BMD in the intervention group versus controls. A beneficial effect of dairy consumption on hip fracture risk was not observed in previous studies in Chapter 2 (26, 27), or in the UKWCS in Chapter 3, potentially because in those cohorts, protein and calcium intakes were mostly adequate. Additionally, participants were younger in the UKWCS (mean age 52.1 years), therefore were less likely to have low BMD and poor muscle function compared to the elderly subjects in the aforementioned RCT.

### 6.3.4 Tea and coffee

In Chapter 3, each additional cup of tea or coffee consumed daily was associated with a lower risk of hip fracture, where the association for tea was stronger in women with underweight. As indicated in Chapter 2, several meta-analyses of observational studies have investigated associations of tea and coffee consumption with hip fracture risk (28-31). Regarding coffee, three meta-analyses showed no clear overall association (28-30), and one showed a J-shaped relationship, where compared to non-consumers, consuming 2-3 cups of coffee per day resulted in an 11% lower risk of hip fracture, whilst no clear risk difference was observed for participants consuming more than four cups/day (31). However, the association was non-significant when restricted to studies with greater sample sizes, lower risk of bias, and to studies that adjusted for more potential confounders. One meta-analysis showed a similar non-linear relationship for tea consumption to that described for coffee (28). Many primary studies included in these meta-analyses were limited by small sample sizes, short follow-up durations, self-reported case

ascertainment, and/or inadequate adjustment for confounders, which could explain heterogeneity observed in those meta-analyses (see Chapter 2 for more detail). In the UKWCS, there was good statistical power to detect small associations for tea and coffee intake; the follow up duration was longer than in previous studies (22.3 years median), enabling a long-term association with regular consumption to be observed; hip fractures were confirmed by linkage to hospital records; and adjustment was made for several potential confounders. Therefore, findings from Chapter 3 strengthen the evidence of an inverse association between tea and coffee consumption with hip fracture risk, providing evidence in a UK population for the first time.

More recently, in the Singapore-Chinese Health Study (32), a J-shaped relationship was reported between coffee and caffeine intake and hip fracture risk in postmenopausal women, where the lowest risk was observed in those drinking 2-3 cups of coffee/day (200-300 mg/day caffeine), with the highest risk in those drinking ≥ 4 cups/day (400 mg/day caffeine) compared to non-consumers. These findings are similar to those in Chapter 3, but a greater risk of hip fracture at high coffee intakes was not observed in the UKWCS, potentially because UKWCS participants consumed less caffeine at higher coffee intakes than women in the Singapore-Chinese Health Study. Total coffee intake in the UKWCS included both caffeinated and decaffeinated coffee, whereas coffee intake was assumed to be caffeinated in the Singapore-Chinese Health Study, since decaffeinated hot beverages were rarely consumed in that study population at recruitment (32). Low to moderate caffeine intakes may support bone health, since caffeine binds to adenosine receptors that inhibit bone resorption and increase bone formation (32). However, higher doses of caffeine (e.g. 400 mg from four cups of coffee per day) can increase calcium excretion and reduce expression of vitamin D receptors, resulting in net reductions in BMD (32).

For tea consumption, three prospective studies not included in the aforementioned meta-analyses have investigated its relationship with hip fracture risk (33, 34). In the Singapore-Chinese Health Study, there was no clear association between tea drinking and risk of hip fracture overall and when stratified by sex and type of tea (any, black, or green) (32). Similarly, a small Australian cohort showed no clear association for tea consumption with hip fracture risk, but found an inverse association with risk of any fracture (34). In the Chinese-Kadoori Biobank,

those who self-reported consuming tea for ≥ 31 years were at a 32% lower risk of hip fracture than those who reported never consuming tea (33). Reasons for these discrepant findings may relate to differences in statistical power, study design, and population characteristics across the cohorts. For example, the small Australian cohort included only 129 hip fractures, therefore may have been underpowered to detect small associations. The Singapore-Chinese Health Study compared risk of hip fracture in participants who reported drinking tea weekly or daily versus less than weekly, whereas in the UKWCS in Chapter 3, the association between an additional cup of tea per day and hip fracture risk was investigated.

### 6.3.5 Fruit and vegetables

As summarised in Chapter 2, previous prospective studies investigating fruit and vegetable intake and hip fracture risk have produced inconsistent results. In studies that showed an inverse association between fruit and/or vegetable intake and hip fracture risk (35-37), inverse relationships were observed when comparing hip fracture risk at very low intakes (0-2 servings/day) compared to adequate intakes (3-5 servings/day). For example, in a pooled analysis of five cohorts of older European and US adults (35), individuals who consumed ≤ 1 serving/day of fruit and vegetables had a 39% higher risk of hip fracture compared with individuals consuming 3-5 servings/day. The association was mostly driven by vegetable intake. Similarly, in two Swedish cohorts including men and women, compared to the recommended 5 servings/day, low (3-5 servings/day) and very low intakes of fruit and vegetables combined (≤ 1 serving/day) were associated with a 38% and 54% greater risk of hip fracture, respectively (36). In both examples, consuming more than 5 servings of fruit and vegetables did not provide any additional benefit (35, 36). In the UKWCS (Chapter 3), restricted cubic spline analyses showed the same reverse J-shaped relationship between fruit and/or vegetable intake with hip fracture risk, but tests for linearity and non-linearity were non-significant. Mean fruit and vegetable intakes in the UKWCS were above recommended levels (around 8 servings/day), and there was likely insufficient power to detect a significant difference in hip fracture risk between adequate and low intakes. One small cohort study of French adults found that consuming more than 2 servings/day of fruit was associated with an increased risk of hip fracture (38), though that study was unable to confirm self-reported hip fractures using hospital records. Overall, findings from

this thesis support suggestions from previous studies that intakes beyond 3-5 servings of fruit and vegetables daily are not associated with a lower risk of hip fracture, providing evidence in British women for the first time.

### 6.3.6 Effect modification by BMI

For many foods and nutrients, prospective evidence is presented for the first time in Chapter 3 showing that their relationships with hip fracture risk may depend on BMI. The association between dietary protein intake with hip fracture risk was stronger in women with underweight (BMI < 18.5 kg/m$^2$), where an extra 25 g of protein per day was associated with a 45% lower risk of hip fracture. Similarly, there was suggestive evidence that dietary calcium, vitamin D, total dairy, and milk intake were each associated with a lower risk of hip fracture in women with underweight, but not healthy or overweight. One case-control study in Chinese adults showed an inverse association for protein intake with hip fracture risk that was more evident in those with a lower BMI, supporting these findings (39). However, there was insufficient power to precisely estimate these associations in the underweight group in the UKWCS, as described in Chapter 3: section 3.5.3.

## 6.4 Critique of potential mechanisms

### 6.4.1 Protein

As introduced in Chapter 1: section 1.4.2 and Chapter 3: section 3.5.3, protein has positive effects on musculoskeletal health, which may explain the observed inverse association with hip fracture risk. Regarding bone health, a systematic review from the IOF concluded that high protein intakes (typically up to 1.5 g/kg/day in the included studies) above UK-recommended levels (0.8 g/kg/day) is positively associated with BMD at multiple sites including the femoral neck, a slower rate of bone loss, and a lower risk of hip fracture in older adults, provided dietary calcium intakes are adequate (40). Dietary protein may support bone health by reducing PTH levels and increasing IGF-1 production (41, 42). A mendelian randomisation analysis showed that high PTH levels were causally associated with lower femoral neck BMD in adults aged 30-45, 45-60, and > 60 years (43). Another mendelian randomisation analysis showed that IGF-1 levels were inversely

associated with risk of any fracture, which was partly mediated by greater BMD observed at higher IGF-1 levels (44). IGF-1 may support bone health through several mechanisms, including stimulating osteoblast formation, reducing bone apoptosis, suppressing PTH levels, and increasing serum vitamin D levels (25). The latter increases calcium absorption, and previous studies have suggested that dietary protein intake is only associated with higher BMD if calcium intakes are adequate (9, 45, 46). In the UKWCS, mean calcium intakes were adequate in participants with and without an incident hip fracture (mean: 1134 vs 1160 mg/day), and results were unchanged after adjustment for dietary calcium intakes.

Dietary protein consists of essential amino acids (EAAs) that provide an acute anabolic stimulus for muscle protein synthesis (MPS) (47). If MPS rates outweigh muscle breakdown rates over time, muscle growth occurs (47). Dietary protein may therefore help to attenuate age-related declines in muscle mass, strength, and function (48). Improved muscle health may reduce hip fracture risk by reducing risk of falling, and providing a greater osteogenic stimulus for bone remodelling during muscle contraction (49). However, evidence supporting a role for protein intake in relation to risk of falling is limited and inconsistent (50, 51). Additionally, some EAAs are more important in maximally stimulating MPS than others (e.g. leucine via the mTOR pathway), and the EAA profile of dietary protein varies across foods (52). Associations between individual amino acids and hip fracture risk were not explored in this thesis, but could help to inform which high-protein foods support musculoskeletal health most and have the greatest potential to prevent hip fractures according to their EAA profiles.

### 6.4.2 Meat, fish, and meat-free diets

There was no evidence of linear relationships between meat or fish consumption with hip fracture risk in Chapter 3, despite their high protein content and the benefits of protein described in section 6.4.1. This may suggest that other components related to musculoskeletal health in meat and fish may contribute to a more complex relationship with hip fracture risk. Meat and fish are often high in saturated fat, which may increase hip fracture risk (53), attenuating the potentially beneficial effects of other nutrients, such as protein. Moreover, the nutritional content of meat and fish and their subtypes varies by cuts of meat and types of fish, as well as by processing and cooking methods (54). Alongside a lack of statistical power, these factors could

contribute to the wide confidence intervals observed for meat and fish consumption in relation to hip fracture risk.

In Chapters 4 and 5, compared to participants who regularly ate meat, participants who excluded meat and fish from the diet entirely (i.e. vegetarians) were at a greater risk of hip fracture, but there was no difference in hip fracture risk in participants who excluded meat but not fish from the diet (pescatarians), or in participants who ate meat occasionally (< 5/week). This suggests that relationships for meat and fish with hip fracture risk may be non-linear. Potential mechanisms explaining why vegetarians but not pescatarians or occasional meat-eaters were at a greater risk of hip fracture than regular meat-eaters were explored in Chapters 4 and 5; common mechanistic themes across findings from the UKWCS and UK Biobank are further discussed here.

#### 6.4.2.1 BMI and musculoskeletal differences

In the UKWCS, UK Biobank, and in other cohorts (12, 14), compared to meat-eaters, vegetarians had a lower BMI, were more likely to be underweight, and were less likely to be overweight. In the UKWCS, adjustment for BMI slightly attenuated the hip fracture risk estimate for vegetarians. In the UK Biobank, causal mediation analyses showed for the first time that the lower BMI in vegetarians (means 25.9 $kg/m^2$ vs 27.7 $kg/m^2$) explained approximately 28% of their greater hip fracture risk, though 95% confidence intervals were wide (1%, 70%). As discussed in Chapter 1: section 1.2.3, overweight but not obesity may be associated with a lower risk of hip fracture (55, 56), and may be partly attributable to higher femoral neck BMD with overweight (57, 58). Cross-sectional studies have shown lower BMD at several sites including the femoral neck in vegetarians compared to in meat-eaters (59), as well as poorer measures of muscle strength and physical function (e.g. hand grip strength) (60), though the clinical relevance of these potential differences remains unclear.

Data on muscle and bone health was not available in the UKWCS, and in the UK Biobank, only heel BMD, hand grip strength, and fat-free mass (FFM) were available in all participants. In the UK Biobank, vegetarians had slightly lower FFM compared to meat-eaters, but there was no clear mediating effect of FFM, with wide confidence intervals. Differences in hand grip strength and

heel BMD between diet groups were non-significant, therefore were unlikely to explain the risk difference. Further research is needed to fully understand differences in musculoskeletal health between vegetarians and non-vegetarians, and their clinical relevance. Future studies should compare femoral neck BMD across diet groups, given its strong causal association with hip fracture risk (61), and mediating effect in the relationship between BMI and hip fracture risk (58).

#### 6.4.2.2 Dietary differences

Vegetarians consumed more fruits and vegetables than regular meat-eaters in the UKWCS and UK Biobank, which may be related to a lower hip fracture risk, as outlined in Chapter 6: section 6.3.5. However, all diet groups consumed above 5 servings/day, and in Chapter 3, fruit and vegetable intakes beyond this threshold were not associated with a lower risk of hip fracture. Therefore, differences in fruit and vegetable intakes between diet groups are unlikely to contribute to differences in hip fracture risk. Vegetarians consumed marginally more fibre and less total and saturated fat than regular meat-eaters in both cohorts, which are generally healthy differences in nutrient profiles, particularly for CVD prevention (62, 63). However, vegetarians may face greater challenges in achieving adequate intakes of nutrients important to musculoskeletal health that are abundant in animal products, including protein, calcium, vitamin D, vitamin B12, iron, and others (64).

Compared to meat-eaters, vegetarians had lower protein intakes in the UKWCS (Chapter 4), UK Biobank (Chapter 5), and in other studies (12, 14). Vegetarians were also less likely to meet the current UK recommendation for protein (0.8 g/kg/day) than regular meat-eaters (UKWCS: 88.8% vs 98.3%; UK Biobank: 68.2% vs 85.2%), and were less likely to meet higher protein intakes (1.2 g/kg/day) that may optimise musculoskeletal health (UKWCS: 47.2% vs 77.4%; UK Biobank: 15.8% vs 33.6%). Further adjustment for protein intake did not alter effect estimates in the UKWCS, and it was not possible to formally assess the effect of differences in protein intake between diet groups as a mediator in the UK Biobank, since nutrient intake information was only available in 50% of participants.

Lower dietary protein intakes may reduce serum IGF-1 levels (42), which are inversely associated with hip fracture risk (25). In the UK Biobank, serum IGF-1 levels were lower in vegetarians than

in other diet groups (e.g. 6% lower than in regular meat-eaters). However, there was no clear evidence of a mediating effect of IGF-1 on the difference in hip fracture risk between diet groups, with wide confidence intervals. One small cross-sectional study (n=292 women) showed lower IGF-1 levels in vegans compared to meat-eaters that was mostly explained by lower intake of protein rich in EAAs. However, in that study, there were no significant differences in IGF-1 levels between vegetarians and meat-eaters (65).

Protein quality and bioavailability may also vary across animal and plant-based foods (52). Vegetarians in both the UKWCS and UK Biobank consumed less milk and roughly equal amounts of other dairy products and eggs as meat-eaters, therefore by excluding meat and fish, were more reliant on plant-derived proteins. Compared to animal proteins that contain all EAAs, many commonly consumed plant-based proteins contain some, but not all EAAs, and their digestion and absorption kinetics may be poorer (52). These factors could contribute to differential effects of animal and plant proteins on musculoskeletal health. However, evidence on this topic is scarce, and existing prospective studies mostly show no difference in BMD and bone turnover markers between animal and plant protein consumption when matched for total protein intake (66), and no clear difference in risk of hip fracture (3). A recently published study combining the result of four trials showed that total protein and animal protein intakes were associated with higher total body and spine BMD, whilst plant protein intake was associated with lower BMD at these sites, though that study did not consider BMD at the femoral neck which predicts hip fracture risk more than BMD at other sites (67). Further evidence is needed to determine if total daily protein intake mediates differences in hip fracture risk across diet groups.

In both the UKWCS and UK Biobank, mean calcium intakes were adequate across all diet groups (all diet groups ≥ 1000 mg/day in the UKWCS, and all ≥ 1000 mg/day in the UK Biobank except regular meat-eaters at 990 mg/day). However, vegetarians had lower dietary intakes of vitamin B12 and vitamin D than other diet groups in both cohorts, and vegetarians in the UK Biobank had lower serum vitamin D levels. These between-group differences are consistent with biomarker estimations in vegetarians and meat-eaters in other cohorts (68, 69), and may contribute to potential differences in musculoskeletal health and the observed higher risk of hip fracture in vegetarians (70, 71). However, there was no evidence of mediation through any

dietary nutrient intake in the UKWCS, and in the UK biobank, there was no clear mediating effect through differences in serum vitamin D levels. Overall diet quality may also vary across vegetarians and meat-eaters due to the aforementioned nutritional differences, and may contribute to hip fracture risk more than individual nutrients, as outlined in Chapter 1: section 1.4.3 (72).

### 6.4.3 Tea and coffee

Tea and coffee are abundant in polyphenols and phytoestrogens, particularly catechins including epigallocatechin gallate, epicatechin gallate, epicatechin, and epigallocatechin (28). These compounds may reduce oxidative stress, increasing osteoblast activity and decreasing osteoclast activity, increasing BMD, therefore potentially reducing hip fracture risk (28). In the aforementioned Australian cohort study on tea consumption (34), an inverse association was observed for total flavonoid intake with hip fracture risk, supporting this hypothesis. Tea, and polyphenols within tea, have also been positively associated with cardiovascular health, and CVD is a known risk factor for falls and hip fractures (34, 73). Results for tea in Chapter 3 remained after adjustment for self-reported CVD cases, but access to hospital records of prevalent CVD cases at recruitment was not available for this thesis before 1997 (roughly the time of recruitment), therefore prevalent CVD cases were likely underestimated.

Alternatively, associations between tea and coffee consumption with hip fracture risk could be due to residual confounding. Those who drink more tea and coffee may consume more milk and sugar, therefore may consume slightly more protein, calcium, and vitamin D. However, findings from the UKWCS in Chapter 3 were adjusted for intake of other major foods, including total dairy intake, so any residual confounding from these competing exposures is likely negligible. Associations could also depend on the type of tea and coffee consumed, since nutrient and polyphenol contents vary across subtypes. For instance, in the Chinese Kadoori Biobank, habitual consumers of green tea but not non-green tea were at a lower risk of hip fracture than non-consumers of each tea subtype (33). However, in the Singapore-Chinese Health Study, neither black or green tea was associated with hip fracture risk (32).

### 6.4.4 Fruit and vegetables

Fruit and vegetables are abundant in alkaline ions (e.g., calcium, potassium, and magnesium), nitrate, vitamin K, and antioxidants such as carotenoids, which have been related to musculoskeletal health and/or fracture risk previously (74, 75). These components may shift the acid-base balance to a more alkaline state to increase calcium reabsorption, and may reduce oxidative stress and inflammation, which contribute to the maintenance of bone and muscle health (36, 74). Higher intakes of fruit and vegetables have also been associated with a more diverse gut microbiome (76), which emerging evidence suggests may play a role in osteoporosis and hip fracture aetiology (77, 78).

Alternatively, inverse associations for fruit and vegetable intake with hip fracture risk observed in previous studies could be due to residual confounding. Higher fruit and vegetable intakes often indicate a healthier lifestyle, which is challenging to account for in cohort studies. Additionally, nutrient and antioxidant contents vary across types of fruits and vegetables, and are impacted by agricultural, preparation, and cultural cooking practices (79). For example, vegetable diversity (per increase in one different vegetable/day) was associated with a lower risk of falls and any fracture in a cohort of older Australian women (80). Investigating subtypes of fruits and vegetables was beyond the scope of this thesis, but differences in the types of fruits and vegetables consumed in the UKWCS and in other cohorts may explain why no significant association was observed here.

### 6.4.5 Effect modification by BMI

In Chapter 3, several foods and nutrients had more pronounced associations with hip fracture risk in women with underweight compared to other BMI groups, including protein, calcium, vitamin D, tea, and some dairy products. One explanation for these subgroup findings might be that as BMI decreases, bone and/or muscle health are likely to be poorer (81, 82), and malnutrition is more likely (83). Therefore, higher intakes of foods and nutrients that may support musculoskeletal health may be more important in hip fracture prevention in states of nutritional deficiencies and/or poor musculoskeletal health. This is in line with findings from experimental evidence that calcium and vitamin D supplements reduce hip fracture risk only in

deficient populations (71). However, information on BMD and muscle function was not available in the UKWCS.

## 6.5 Critique of study strengths and methods

### 6.5.1 Umbrella review design

First, by including systematic reviews of meta-analyses, the umbrella review in Chapter 2 provided an overview of the evidence for associations between diet and hip fracture risk, including several dietary factors. Second, risk of bias in included systematic reviews was rigorously assessed using the AMSTAR-2 tool, and highlighted common critical flaws. Many reviews did not establish protocols a priori, which increases the risk of selective reporting bias; did not justify excluding studies, which increases the risk of study selection bias during screening; and did not include a sufficiently detailed risk of bias assessment. Third, the quality of evidence for each diet-hip fracture association was systematically evaluated using the GRADE tool, and was low or very low for all potential associations. This approach highlighted factors that reduced the evidence certainty for many observed associations. These included a serious risk of bias across primary studies; imprecise estimates (indicated by wide confidence intervals); and inconsistent estimates (indicated by high $I^2$ values and/or minimal overlap in confidence intervals). Finally, by identifying gaps and limitations in previously published evidence, this umbrella review highlighted the need for further cohort studies on several aspects of diet in relation to hip fracture risk (such as those presented in Chapters 3-5), and provided specific recommendations for authors of future systematic reviews and meta-analyses (see Chapter 2, section 2.5.5).

### 6.5.2 UKWCS and UK Biobank designs

A major strength of this thesis is that data were used from two large prospective, population-based cohort studies, the UKWCS and UK Biobank, to address research gaps highlighted in Chapter 2. These cohorts are amongst the few cohort studies worldwide that include a large number of pescatarians and vegetarians, providing sufficient statistical power to estimate their risk of hip fracture. Their prospective designs ensured that dietary assessment occurred before

incident hip fractures, reducing the risk of reverse causation. In both cohorts, effect estimates were robust to sensitivity analyses where hip fractures that occurred within the first three years of follow-up were excluded, showing no evidence of reverse causation for all associations observed.

The UKWCS and UK Biobank have strengths and weaknesses that compliment each other. For example, dietary information collected at recruitment in all participants in the UK Biobank via the touchscreen questionnaire covered a limited number of food items; food and nutrient intakes were only calculable in participants who completed 24 hour recalls, which included around half of the study population. In contrast, the UKWCS collected detailed dietary information at recruitment through an FFQ in all participants, enabling derivation of food and nutrient intakes, and adjustment for energy intake for analyses on foods and nutrient intakes. The UKWCS provided a longer follow-up duration than the UK Biobank (median 22.3 years vs 12.5 years), allowing more time for diet-hip fracture associations to manifest. The UKWCS included only women, whereas the UK Biobank provided information in men and women, increasing generalisability of results. The UK Biobank also provided anthropometric and biomarker data that was not available in the UKWCS, which enabled comparison of these characteristics across diet groups, and investigation of non-dietary mediation pathways for observed associations.

### 6.5.3 Dietary assessment

In the UKWCS, dietary intakes of foods and nutrients were measured using an FFQ, and participants were classified into diet groups thereafter. The FFQ was validated against a 4-day weighed food diary in a subgroup of participants (n=283). In the UK Biobank, analysis of a sub-sample of participants (n=57,000) with repeated measurements showed little evidence of changes in diet groups over time, minimising risk of diet group misclassification.

### 6.5.4 Using hospital records to identify hip fractures

Chapter 2 showed that previous studies investigating associations between diet and hip fracture risk mostly identified hip fracture records through self-reported questionnaires. In this thesis,

hip fractures were identified in UKWCS and UK Biobank participants through linkage to national hospital records. This approach reduced selective loss to follow-up, permitting almost complete-case ascertainment; and provided the exact date of hip fractures, which enabled more accurate time-to-event analysis.

### 6.5.5 Statistical approaches to reduce bias

Estimates for all diet-hip fracture associations were adjusted for several potential confounders as informed by pre-defined DAGs. This enabled clear, transparent identification of potential confounders, moderators, mediators, competing exposures, and competing risks. Additionally, in Chapter 5, by using the floating absolute risks method described in **Appendix C: Supplementary methods**, absolute risk differences in hip fracture risk between diet groups were calculated and were adjusted for confounders, fully contextualising relative estimates.

Another advantage of using linked hospital records was that prevalent hip fractures and osteoporosis cases at recruitment were identified, and these participants were excluded from analytical samples, since hip fractures and osteoporosis increase the risk of subsequent hip fracture (2). Additionally, in the UK Biobank, linked information from Cancer Registries and National Death Registries was available. Combined with hospital data, this enabled adjustment for prevalent cases of comorbidities that increase hip fracture risk, such as diabetes, cancer, and CVD in Cox regression models comparing hip fracture risk across meat-free and meat-eater diets. It also enabled a sensitivity analysis to be conducted accounting for death as a potential competing risk, since death could have prevented hip fractures from occurring; associations remained unchanged.

In the UKWCS and UK Biobank, complete-case analyses were presented where participants with missing covariate data were excluded, potentially introducing selection bias. However, in the UKWCS, characteristics of included and excluded participants were similar. In the UK Biobank, multiple imputation for missing covariate data did not meaningfully alter effect estimates for occasional meat-eaters or vegetarians, though the association for pescatarians became significant (**Appendix D: Figure D6**). The amount of missing data per covariate was broadly similar across diet groups; differences in characteristics of pescatarians with and without

complete covariate data may explain the change in estimates for pescatarians after imputation. Pescatarians with missing covariate data also had higher hip fracture rates and more risk factors for hip fracture than pescatarians with complete covariate data, including a slightly older mean age, a greater proportion of females, and lower education levels. Unadjusted estimates for pescatarians were similar in complete-case versus imputed analyses; therefore, including participants who had missing covariate data could have altered the strength of confounding, though there were no differences in covariate means and standard deviations for all confounders in complete-case and imputed datasets.

### 6.5.6 Generalisability

This thesis used a population-based approach to investigate relationships between diet and hip fracture risk, identifying trends in British men and women, in many cases for the first time. As mentioned in Chapters 3 and 4, Cox regression models in the UKWCS used inverse probability weights to account for the preferential sampling of non-meat-eaters, increasing generalisability of findings to the UK population.

## 6.6 Critique of potential limitations

### 6.6.1 Umbrella review design

By including only meta-analyses in the umbrella review in Chapter 2, recently published cohort studies that have not yet been synthesised into a meta-analysis were not identified. Additionally, limitations of retrieved meta-analyses were inherited, such as biases in selection of articles and their risk of bias assessments. The GRADE tool was used in this work to robustly evaluate evidence quality. However, this approach may underestimate the evidence quality for potential associations, since all non-randomised research begins at low quality rather than moderate, even if concerns regarding residual confounding are insignificant. These limitations are discussed in full in Chapter 2 (section 2.5.4).

### 6.6.2 Dietary measurement error

Chapter 2 highlighted that measuring diet, including long-term dietary patterns and food and nutrient intakes, is a major challenge in observational research. The FFQs used to collect the data analysed in this thesis, like all FFQs, may be subject to several forms of bias. First, there is potential for recall bias, where participants' memory of past dietary habits contain inaccuracies. Second, energy intake and intake of several nutrients, including protein, are often under-reported in FFQs (84). Third, food and nutrient intakes in Chapter 3 were calculated in grams per day assuming standard portion sizes. In reality, portion sizes vary between individuals and within individuals across meals and over time. Fourth, nutrient concentrations within each food item were obtained from food composition tables, but these vary across brands of a given food item (e.g. yoghurt with/without sugar), by region of origin, and agricultural practises, alongside other factors. Finally, dietary habits may change over time, particularly as the food environment continually develops in terms of product reformulation and availability. Nevertheless, FFQs are better able to characterise long-term dietary habits than 24h recalls, and are less expensive and burdensome on participants than food diaries. Therefore, FFQs were a suitable dietary measurement method for tracking long-term dietary habits in the large cohort studies used in this thesis, with reasonable accuracy.

### 6.6.3 Using hospital records to identify hip fractures

In the UKWCS, hospital data was only available from 1997 onwards, which was around the time of recruitment (1995-1998). Therefore, prevalent cases of hip fractures, osteoporosis, and comorbidities at recruitment could not be fully captured, introducing potential residual confounding. Hospital data in the UK precludes differentiation of fragility from traumatic hip fractures, which have different aetiologies. However, as outlined in Chapter 5: section 5.5.4, traumatic hip fractures are unlikely to be affected by diet, so any outcome misclassification would only dilute risk estimates.

### 6.6.4 Residual confounding

In all observational studies, residual confounding remains possible, and causation cannot be inferred. Adjustment was made in all analyses for physical activity levels, but information on different types of activity, such as resistance training, weight-bearing exercise, and aerobic exercise, was not available. These exercise types have different effects on musculoskeletal health, and possibly hip fracture risk (85). Additionally, relationships between diet and chronic disease risk (including hip fracture) are highly individualised due to genetic and lifestyle factors. Therefore, findings in this thesis are applicable to British adults, but not to individuals per sae. The potential for residual confounding is higher in the mediation analyses in Chapter 5, since confounding is possible at the exposure-outcome, mediator-outcome, and exposure-mediator levels. Furthermore, covariate measurement error could exacerbate any residual confounding.

### 6.6.5 Generalisability

In the UKWCS and UK Biobank, most participants were Caucasian, meaning results cannot be generalised to other ethnic groups. Additionally, the UKWCS and UK Biobank may be prone to volunteer bias, since participants volunteering to take part in a research study are generally healthier than the population of interest.

The diet composition of vegetarians in recent years could differ from when data were collected at recruitment in 1995-1998 for the UKWCS, and 2006-2010 for the UK Biobank due to increases over the last two decades in the availability of plant-based alternative foods (PBAFs) (86, 87). An analysis of NDNS data showed that the proportion of individuals reporting consuming any PBAFs roughly doubled from 6.7% in 2008-2011 to 13.1% in 2017-2019, with younger adults (aged 24-39 years), women, and those with higher incomes more likely to report consuming PBAFs (87). Data from the UK Biobank in this thesis showed that vegetarians and pescatarians consumed more of these products than regular meat-eaters, therefore vegetarians may have been more likely to have changed their diet composition during follow-up. Consequently, generalisability of results regarding vegetarian diets to modern-day vegetarians is reduced. However, effect estimates were similar for vegetarians in the UKWCS (33% in women) and UK Biobank (32% in

women, 50% overall) despite the fact that the UK Biobank dietary data was collected 8-15 years after UKWCS data collection, during which time the availability of PBAFs increased in the UK (87).

## 6.7 Recommendations for further research

### 6.7.1 Establish causality and underpinning mechanisms

To better understand the possible short and long-term causal impacts of diet on hip fracture risk, more data is needed from both population and precision medicine approaches. Further studies are needed to replicate or refute findings in this thesis; to identify mechanisms underpinning observed associations; and to confirm causality. These include long-term cohort studies using linked health records to identify hip fracture outcomes, and tailored dietary interventions to account for individual genetic variation. This combination of evidence is essential to form general and personalised recommendations for preventing hip fractures. A focus on factors that were associated with hip fracture risk in this thesis, including dietary protein intake, adherence to a vegetarian diet, and tea and coffee consumption, is recommended.

For protein, it is recommended that future studies aim to determine how much protein is required to optimise musculoskeletal health and minimise hip fracture risk by investigating potential threshold effects to advance protein recommendations. Additionally, future studies should stratify by protein source to determine if the optimal daily protein intake for musculoskeletal health varies across animal and plant protein sources.

For tea and coffee, evidence is needed from further large prospective cohort studies and RCTs to determine if consuming tea and coffee improves bone health, or indicates healthy dietary or lifestyle habits (33). This is particularly important given that tea and coffee are among the most widely consumed hot beverages in the UK. Specific types that could have different effects on musculoskeletal health should be considered independently (e.g. green vs black tea).

For vegetarian diets, future large prospective studies should aim to estimate hip fracture risk in vegetarians and vegans independently, and should account for potential differences in diet quality within and between diet groups using previously established diet quality scores (e.g. MD score or the AHEI). This would help to determine if high-quality vegetarian diets mitigate any

increased risk of hip fracture. Long-term trials with hip fractures as the end-point may be unfeasible since effects of diet on hip fracture risk act over decades; musculoskeletal outcomes that impact risk of falls and/or hip fracture risk, such as femoral neck BMD and physical function (61, 88, 89), may provide a suitable proxy for such trials.

### 6.7.2 Improve dietary measurement accuracy and precision

Improving the accuracy of dietary measurement is essential to accurately quantifying diet-disease relationships. For example, given that consumption of PBAFs is accelerating in the UK (87), and their nutrient content continuously changes with product reformulation, more detailed dietary assessment of vegetarians and meat-eaters with repeated measures is needed in future studies to account for these changes. Novel technology-based approaches are promising solutions. For example, the web-based dietary record tool 'MyFood24' enables users to record food consumption, and calculates energy and nutrient intakes in real-time from a comprehensive food composition database, and is validated against biomarkers (90). Additionally, many country-specific versions are available to account for variation in food availability and composition between countries.

### 6.7.3 Investigate other fracture sites and outcomes

This thesis focused on associations between diet and hip fracture risk, since hip fractures are the most common serious fracture site resulting in hospitalisation (1). Previous studies have shown that relationships between diet and fracture risk are site-specific, including the aforementioned EPIC-Oxford study that found a higher risk of hip fracture but not ankle or leg fractures in vegetarians compared to meat-eaters (14). Therefore, further studies are needed with multiple fracture sites as endpoints to fully understand the potential utility of diet modification in preventing fractures.

### 6.7.4 More evidence in diverse populations

Further studies are required to confirm or refute findings from this thesis in men and in other ethnic groups besides Caucasians. For instance, the proportion of vegetarians in the Indian

population is higher than in the UK (30% vs 3%), and diet composition may differ between countries (91, 92).

## 6.8 Public health implications

This thesis has shown novel evidence that diet is a modifiable factor with the potential to reduce hip fracture risk. Since causality could not be inferred from these observational findings, recommendations for policymakers, nutritionists, and clinicians cannot be formed until the recommendations for further research outlined in the previous section are achieved. However, some potential considerations for practice are outlined in this section.

### 6.8.1 Dietary protein intake

Analyses for dietary protein in Chapter 3 were adjusted for energy intake from other foods rather than total energy intake to avoid over-adjustment. Therefore, findings from Chapter 3 of this thesis suggests that greater absolute protein intakes (in a non-isocaloric scenario) may be associated with a lower risk of hip fracture, but it remains unclear if a greater proportion of energy from dietary protein as opposed to other sources (in an isocaloric scenario) is associated with a lower risk of hip fracture. Additionally, the mean protein intake in the UKWCS (88 g/day) was higher than current recommendations (46 g/day) and estimates of current intakes for adult women from the NDNS (66.8 g/day), with only 3% of women consuming below 46 g/day, and 7.5% consuming below 0.8 g/kg/day in the UKWCS (93). Therefore, these findings suggest that whilst meeting protein recommendations may be associated with a lower risk of hip fracture, consuming additional protein beyond current recommendations may be beneficial for hip fracture prevention in middle-aged women. Importantly, results from this thesis, alongside previous work, collectively imply no negative effects of high protein intakes on bone health and hip fracture risk within the range of protein intake in the UKWCS and previous studies (up to 1.4 g/kg/day or 110 g/day) (40). These findings need to be considered alongside the benefits and risks of protein intake in other health contexts when making policy recommendations regarding protein intake. For example, a recent umbrella review of dietary protein and multiple health outcomes found highly suggestive evidence of a higher risk of type 2 diabetes with small

increases in energy intake from animal protein, but there was no convincing evidence for total or plant protein, or for other health conditions, including cancers and CVD (94).

### 6.8.2 Meet other nutrient requirements

Several nutrients beyond protein contribute to the maintenance of bone and muscle health, including calcium, vitamin D, vitamin B12, phosphorus, and many others (95, 96). Although their relationships with hip fracture risk were not clear in this thesis, achieving recommended nutrient intake levels for these nutrients is advisable to maintain general health, including musculoskeletal health. Current UK recommendations for calcium are 700 mg/day, and for vitamin D are 10 µg/day (18).

### 6.8.3 Tea and coffee

Although the inverse association between tea and coffee consumption with hip fracture risk could not be confirmed as causal, two previous umbrella reviews have indicated that tea and coffee consumption are generally safe within usual levels of intake, with the largest risk reductions for various health outcomes at 3-4 cups/day for coffee (except for pregnant women) (97), and 2-3 cups/day for tea (98). Therefore, consuming 3-4 cups/day of tea or coffee is more likely to benefit overall health than harm, and would likely be safe to test in interventions related to musculoskeletal and/or fracture outcomes in the general population, as long as high doses (> 4 cups/day) are avoided.

### 6.8.4 Fruit and vegetables

Whilst no association was observed between fruit and vegetable intake and hip fracture risk in this thesis, multiple outcome-wide umbrella reviews have shown that total fruit and vegetable intake is inversely associated with many non-communicable diseases, in particular CVD (99, 100). In one umbrella review, cruciferous vegetables and dark-green leafy vegetables had greater effects on chronic disease outcomes compared to other types (100). Similarly, two recent observational studies in elderly women in Australia showed that compared to women with low vegetable intakes, consuming ≥ 3 servings/day of cruciferous or allium vegetables was associated with a lower risk of falls, fractures, and hip fractures (88, 101). Moreover, cruciferous vegetables

are high in vitamin K, which may be associated with a lower risk of falls and fractures, including hip fractures (75, 102, 103). Therefore, meeting current UK recommendations of five servings per day of fruit and vegetables, with a focus on cruciferous or allium vegetables, may be advisable for both general and musculoskeletal health.

### 6.8.5 Vegetarian diets

In the UK Biobank, the 50% greater risk of hip fracture in vegetarians vs regular meat-eaters was equivalent to an absolute risk difference of 3.2 more cases per 1000 people over 10 years in vegetarians. This estimate is consistent with estimates from the EPIC-Oxford study (14), which alongside a similar relative risk in the UWKCS, collectively suggest a modest absolute risk difference. This risk difference may be clinically relevant, given that hip fractures incur a significant health burden with increased mortality rates, direct costs of rehabilitation, and indirect costs from the increased risk of associated comorbidities described in Chapter 1: sections 1.1.2 and 1.1.3. However, the risk difference should be weighed against the potential associated health benefits of vegetarian diets for more common conditions when policy makers formulate dietary guidelines, and when individuals choose to go vegetarian. Evidence of associations for occasional meat-eaters and pescatarians were less clear, but absolute risk differences and confidence intervals for occasional meat-eaters appeared to rule out a clinically relevant benefit or harm. Reducing but not eliminating meat intake may therefore have a limited, if at all clinically relevant effect on hip fracture risk. Moreover, reducing or eliminating animal products from the diet may confer some health and environmental benefits, including a lower risk of CVD and some cancers (104), as well as reductions in greenhouse gas emissions, water usage, land use, eutrophication risk, and biodiversity loss (105) (106).

To develop strategies to mitigate the greater risk of hip fracture observed in vegetarians in this thesis requires further understanding of factors driving risk differences between diet groups. However, vegetarians had a lower BMI and were less likely to meet dietary protein recommendations in both the UKWCS and UK Biobank, which may each be associated with a higher risk of hip fracture based on previously published evidence and evidence provided in this thesis (57). Therefore, maintaining a healthy BMI (preventing underweight or obesity), and increasing protein intakes beyond 0.8 g/kg/day may be especially important in vegetarians to

mitigate any greater risk of hip fracture. Importantly, nutrition and exercise interventions can partially attenuate bone loss associated with caloric restriction and weight loss (107). Therefore, vegetarian and vegan diets, as well as dietary interventions for reducing overweight and obesity, may not necessarily increase hip fracture risk if adequate intake of nutrients related to musculoskeletal health are achieved, particularly for protein, calcium, and vitamin D, even in a caloric deficit, and particularly when coupled with regular weight-bearing exercise (108).

## 6.9 Conclusions

### 6.9.1 What was already known

Hip fractures commonly initiate hospitalisation and health decline in older adults, and are becoming increasingly prevalent in the ageing global population. Diet modification may reduce hip fracture risk by attenuating age-related declines in musculoskeletal health, improving body composition, and regulating BMI. Many aspects of diet, including nutrients beyond calcium and vitamin D; foods in which relevant nutrients are consumed; and patterns of consumption over time may influence risk of hip fracture. However, the potential roles of many individual foods and nutrients are unclear due to limited prospective evidence with inconsistent findings, preventing dietary guidelines from advancing. Additionally, vegetarian and pescatarian diets are becoming increasingly adopted in developed countries, and recent evidence has suggested that these diets may be associated with poorer musculoskeletal health and a higher risk of fractures. However, evidence on this topic is scarce in relation to hip fractures.

### 6.9.2 What this thesis adds

Novel observational evidence was generated from two large British cohorts that supports a role of diet in hip fracture prevention. For the first time in British women, dietary protein intake, as well as combined tea and coffee consumption, were inversely associated with hip fracture risk. Associations for dietary calcium, vitamin D, and animal foods with hip fracture risk were only observed in women with underweight. This thesis also strengthens the evidence that in the UK, vegetarian men and women are at a greater risk of hip fracture than regular meat-eaters, which may be partly explained by the lower average BMI in vegetarians. This work highlights the need

for further research to confirm if these associations are causal, and to understand underlying mechanisms so that dietary guidelines for hip fracture prevention can advance.

## 6.10 References


1. Dhanwal DK, Dennison EM, Harvey NC, Cooper C. Epidemiology of hip fracture: Worldwide geographic variation. Indian J Orthop. 2011;45(1):15-22.

2. Benetos IS, Babis GC, Zoubos AB, Benetou V, Soucacos PN. Factors affecting the risk of hip fractures. Injury. 2007;38(7):735-44.

3. Wu AM, Sun XL, Lv QB, Zhou Y, Xia DD, Xu HZ, et al. The Relationship between Dietary Protein Consumption and Risk of Fracture: a subgroup and dose-response meta-analysis of prospective cohort studies. Scientific Reports. 2015;5:8.

4. Beasley JM, LaCroix AZ, Larson JC, Huang Y, Neuhouser ML, Tinker LF, et al. Biomarker-calibrated protein intake and bone health in the Women's Health Initiative clinical trials and observational study. Am J Clin Nutr. 2014;99(4):934-40.

5. Langsetmo L, Shikany JM, Cawthon PM, Cauley JA, Taylor BC, Vo TN, et al. The Association Between Protein Intake by Source and Osteoporotic Fracture in Older Men: A Prospective Cohort Study. J Bone Miner Res. 2017;32(3):592-600.

6. Feskanich D, Willett WC, Stampfer MJ, Colditz GA. Protein consumption and bone fractures in women. Am J Epidemiol. 1996;143(5):472-9.

7. Mussolino ME, Looker AC, Madans JH, Langlois JA, Orwoll ES. Risk factors for hip fracture in white men: the NHANES I Epidemiologic Follow-up Study. J Bone Miner Res. 1998;13(6):918-24.

8. Munger RG, Cerhan JR, Chiu BC. Prospective study of dietary protein intake and risk of hip fracture in postmenopausal women. Am J Clin Nutr. 1999;69(1):147-52.

9. Sahni S, Cupples LA, McLean RR, Tucker KL, Broe KE, Kiel DP, et al. Protective effect of high protein and calcium intake on the risk of hip fracture in the Framingham offspring cohort. J Bone Miner Res. 2010;25(12):2770-6.

10. Misra D, Berry S, Broe K, McLean R, Cupples L, Tucker K, et al. Does dietary protein reduce hip fracture risk in elders? The Framingham Osteoporosis Study. Osteoporosis international. 2011;22:345-9.

11. Fung TT, Meyer HE, Willett WC, Feskanich D. Protein intake and risk of hip fractures in postmenopausal women and men age 50 and older. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2017;28(4):1401-11.

12. Thorpe DL, Beeson WL, Knutsen R, Fraser GE, Knutsen SF. Dietary patterns and hip fracture in the Adventist Health Study 2: combined vitamin D and calcium supplementation mitigate increased hip fracture risk among vegans. Am J Clin Nutr. 2021;114(2):488-95.

13. Sadeghi O, Djafarian K, Ghorabi S, Khodadost M, Nasiri M, Shab-Bidar S. Dietary intake of fish, n-3 polyunsaturated fatty acids and risk of hip fracture: A systematic review and meta-analysis on observational studies. Critical Reviews in Food Science and Nutrition. 2019;59(8):1320-33.

14. Tong TYN, Appleby PN, Armstrong MEG, Fensom GK, Knuppel A, Papier K, et al. Vegetarian and vegan diets and risks of total and site-specific fractures: results from the prospective EPIC-Oxford study. BMC Med. 2020;18(1):353.

15. Bolland MJ, Leung W, Tai V, Bastin S, Gamble GD, Grey A, et al. Calcium intake and risk of fracture: systematic review. Bmj. 2015;351:h4580.

16. Warensjö E, Byberg L, Melhus H, Gedeborg R, Mallmin H, Wolk A, et al. Dietary calcium intake and risk of fracture and osteoporosis: prospective longitudinal cohort study. Bmj. 2011;342:d1473.

17. Key TJ, Appleby PN, Spencer EA, Roddam AW, Neale RE, Allen NE. Calcium, diet and fracture risk: a prospective study of 1898 incident fractures among 34 696 British women and men. Public Health Nutr. 2007;10(11):1314-20.

18. British Nutrition Foundation. Nutrition requirements. 2021. [Available from: https://www.nutrition.org.uk/media/nmmewdug/nutrition-requirements.pdf].

19. Feskanich D, Willett WC, Colditz GA. Calcium, vitamin D, milk consumption, and hip fractures: a prospective study among postmenopausal women. The American Journal of Clinical Nutrition. 2003;77(2):504-11.

20. Snellman G, Byberg L, Lemming EW, Melhus H, Gedeborg R, Mallmin H, et al. Long-Term Dietary Vitamin D Intake and Risk of Fracture and Osteoporosis: A Longitudinal Cohort Study of Swedish Middle-aged and Elderly Women. The Journal of Clinical Endocrinology & Metabolism. 2014;99(3):781-90.

21. Habibi Ghahfarrokhi S, Mohammadian-Hafshejani A, Sherwin CMT, Heidari-Soureshjani S. Relationship between serum vitamin D and hip fracture in the elderly: a systematic review and meta-analysis. J Bone Miner Metab. 2022;40(4):541-53.

22. Herrmann M, Farrell CL, Pusceddu I, Fabregat-Cabello N, Cavalier E. Assessment of vitamin D status - a changing landscape. Clin Chem Lab Med. 2017;55(1):3-26.

23. National Osteoporosis Foundation. Preventing Fractures 2021 [Available from: https://www.nof.org/preventing-fractures/prevention/.

24. Iuliano S, Poon S, Robbins J, Bui M, Wang X, De Groot L, et al. Effect of dietary sources of calcium and protein on hip fractures and falls in older adults in residential care: cluster randomised controlled trial. Bmj. 2021;375:n2364.

25. Yuan S, Wan ZH, Cheng SL, Michaëlsson K, Larsson SC. Insulin-like Growth Factor-1, Bone Mineral Density, and Fracture: A Mendelian Randomization Study. J Clin Endocrinol Metab. 2021;106(4):e1552-e8.

26. Hidayat K, Du X, Shi BM, Qin LQ. Systematic review and meta-analysis of the association between dairy consumption and the risk of hip fracture: critical interpretation of the currently available evidence. Osteoporosis International. 2020;31(8):1411-25.

27. Malmir H, Larijani B, Esmaillzadeh A. Consumption of milk and dairy products and risk of osteoporosis and hip fracture: a systematic review and Meta-analysis. Critical Reviews in Food Science and Nutrition. 2020;60(10):1722-37.

28. Sheng J, Qu X, Zhang X, Zhai Z, Li H, Liu X, et al. Coffee, tea, and the risk of hip fracture: a meta-analysis. Osteoporos Int. 2014;25(1):141-50.

29. Li S, Dai Z, Wu Q. Effect of coffee intake on hip fracture: a meta-analysis of prospective cohort studies. Nutr J. 2015;14:38.

30. Li XL, Xu JH. Coffee consumption and hip fracture risk: a meta-analysis. J Nutr Sci. 2013;2:e23.

31. Zeng X, Su Y, Tan A, Zou L, Zha W, Yi S, et al. The association of coffee consumption with the risk of osteoporosis and fractures: a systematic review and meta-analysis. Osteoporos Int. 2022;33(9):1871-93.

32. Dai Z, Jin A, Soh AZ, Ang LW, Yuan JM, Koh WP. Coffee and tea drinking in relation to risk of hip fracture in the Singapore Chinese Health Study. Bone. 2018;112:51-7.

33. Shen Q, Yu C, Guo Y, Bian Z, Zhu N, Yang L, et al. Habitual Tea Consumption and Risk of Fracture in 0.5 Million Chinese Adults: A Prospective Cohort Study. Nutrients. 2018;10(11).

34. Myers G, Prince RL, Kerr DA, Devine A, Woodman RJ, Lewis JR, et al. Tea and flavonoid intake predict osteoporotic fracture risk in elderly Australian women: a prospective study. Am J Clin Nutr. 2015;102(4):958-65.

35. Benetou V, Orfanos P, Feskanich D, Michaëlsson K, Pettersson-Kymmer U, Eriksson S, et al. Fruit and Vegetable Intake and Hip Fracture Incidence in Older Men and Women: The CHANCES Project. J Bone Miner Res. 2016;31(9):1743-52.

36. Byberg L, Bellavia A, Orsini N, Wolk A, Michaëlsson K. Fruit and vegetable intake and risk of hip fracture: a cohort study of Swedish men and women. J Bone Miner Res. 2015;30(6):976-84.

37. Benetou V, Orfanos P, Pettersson-Kymmer U, Bergström U, Svensson O, Johansson I, et al. Mediterranean diet and incidence of hip fractures in a European cohort. Osteoporos Int. 2013;24(5):1587-98.

38. Feart C, Lorrain S, Ginder Coupez V, Samieri C, Letenneur L, Paineau D, et al. Adherence to a Mediterranean diet and risk of fractures in French older persons. Osteoporos Int. 2013;24(12):3031-41.

39. Liu ZM, Huang Q, Li SY, Liu YP, Wu Y, Zhang SJ, et al. A 1:1 matched case-control study on dietary protein intakes and hip fracture risk in Chinese elderly men and women. Osteoporos Int. 2021;32(11):2205-16.

40. Rizzoli R, Biver E, Bonjour JP, Coxam V, Goltzman D, Kanis JA, et al. Benefits and safety of dietary protein for bone health-an expert consensus paper endorsed by the European Society for Clinical and Economical Aspects of Osteopororosis, Osteoarthritis, and Musculoskeletal Diseases and by the International Osteoporosis Foundation. Osteoporos Int. 2018;29(9):1933-48.

41. Kerstetter JE, O'Brien KO, Insogna KL. Dietary protein, calcium metabolism, and skeletal homeostasis revisited. The American Journal of Clinical Nutrition. 2003;78(3):584S-92S.

42. Bonjour JP. The dietary protein, IGF-I, skeletal health axis. Horm Mol Biol Clin Investig. 2016;28(1):39-53.

43. Qu Z, Yang F, Hong J, Wang W, Yan S. Parathyroid Hormone and Bone Mineral Density: A Mendelian Randomization Study. The Journal of Clinical Endocrinology & Metabolism. 2020;105(11):e4038-e45.

44. Yuan S, Wan Z-H, Cheng S-L, Michaëlsson K, Larsson SC. Insulin-like Growth Factor-1, Bone Mineral Density, and Fracture: A Mendelian Randomization Study. The Journal of clinical endocrinology and metabolism. 2021;106(4):e1552-e8.

45. Dargent-Molina P, Sabia S, Touvier M, Kesse E, Bréart G, Clavel-Chapelon F, et al. Proteins, dietary acid load, and calcium and risk of postmenopausal fractures in the E3N French women prospective study. J Bone Miner Res. 2008;23(12):1915-22.

46. Dawson-Hughes B, Harris SS. Calcium intake influences the association of protein intake with rates of bone loss in elderly men and women. Am J Clin Nutr. 2002;75(4):773-9.

47. Morton RW, Murphy KT, McKellar SR, Schoenfeld BJ, Henselmans M, Helms E, et al. A systematic review, meta-analysis and meta-regression of the effect of protein supplementation on resistance training-induced gains in muscle mass and strength in healthy adults. Br J Sports Med. 2018;52(6):376-84.

48. Deer RR, Volpi E. Protein intake and muscle function in older adults. Curr Opin Clin Nutr Metab Care. 2015;18(3):248-53.

49. Curtis E, Litwic A, Cooper C, Dennison E. Determinants of Muscle and Bone Aging. J Cell Physiol. 2015;230(11):2618-25.

50. Zoltick ES, Sahni S, McLean RR, Quach L, Casey VA, Hannan MT. Dietary protein intake and subsequent falls in older men and women: the Framingham Study. J Nutr Health Aging. 2011;15(2):147-52.

51. Larocque SC, Kerstetter JE, Cauley JA, Insogna KL, Ensrud K, Lui LY, et al. Dietary Protein and Vitamin D Intake and Risk of Falls: A Secondary Analysis of Postmenopausal Women from the Study of Osteoporotic Fractures. J Nutr Gerontol Geriatr. 2015;34(3):305-18.

52. van Vliet S, Burd NA, van Loon LJ. The Skeletal Muscle Anabolic Response to Plant- versus Animal-Based Protein Consumption. J Nutr. 2015;145(9):1981-91.

53. Mozaffari H, Djafarian K, Mofrad MD, Shab-Bidar S. Dietary fat, saturated fatty acid, and monounsaturated fatty acid intakes and risk of bone fracture: a systematic review and meta-analysis of observational studies. Osteoporos Int. 2018;29(9):1949-61.

54. Gómez I, Janardhanan R, Ibañez FC, Beriain MJ. The effects of processing and preservation technologies on meat quality: Sensory and nutritional aspects. Foods. 2020;9(10):1416.

55. Gonnelli S, Caffarelli C, Nuti R. Obesity and fracture risk. Clin Cases Miner Bone Metab. 2014;11(1):9-14.

56. Kim SH, Yi SW, Yi JJ, Kim YM, Won YJ. Association Between Body Mass Index and the Risk of Hip Fracture by Sex and Age: A Prospective Cohort Study. J Bone Miner Res. 2018;33(9):1603-11.

57. Caffarelli C, Alessi C, Nuti R, Gonnelli S. Divergent effects of obesity on fragility fractures. Clin Interv Aging. 2014;9:1629-36.

58. Chan MY, Frost SA, Center JR, Eisman JA, Nguyen TV. Relationship between body mass index and fracture risk is mediated by bone mineral density. J Bone Miner Res. 2014;29(11):2327-35.

59. Iguacel I, Miguel-Berges ML, Gómez-Bruton A, Moreno LA, Julián C. Veganism, vegetarianism, bone mineral density, and fracture risk: a systematic review and meta-analysis. Nutrition Reviews. 2018;77(1):1-18.

60. Chan H, Ribeiro RV, Haden S, Hirani V. Plant-Based Dietary Patterns, Body Composition, Muscle Strength and Function in Middle and Older Age: A Systematic Review. J Nutr Health Aging. 2021;25(8):1012-22.

61. Bouxsein ML, Eastell R, Lui LY, Wu LA, de Papp AE, Grauer A, et al. Change in Bone Density and Reduction in Fracture Risk: A Meta-Regression of Published Trials. J Bone Miner Res. 2019;34(4):632-42.

62. Evans CEL. Dietary fibre and cardiovascular health: a review of current evidence and policy. Proc Nutr Soc. 2020;79(1):61-7.

63. Forouhi NG, Krauss RM, Taubes G, Willett W. Dietary fat and cardiometabolic health: evidence, controversies, and consensus for guidance. Bmj. 2018;361:k2139.

64. Tucker KL. Vegetarian diets and bone status. Am J Clin Nutr. 2014;100 Suppl 1:329s-35s.

65. Allen NE, Appleby PN, Davey GK, Kaaks R, Rinaldi S, Key TJ. The associations of diet with serum insulin-like growth factor I and its main binding proteins in 292 women meat-eaters, vegetarians, and vegans. Cancer Epidemiol Biomarkers Prev. 2002;11(11):1441-8.

66. Shams-White MM, Chung M, Fu Z, Insogna KL, Karlsen MC, LeBoff MS, et al. Animal versus plant protein and adult bone health: A systematic review and meta-analysis from the National Osteoporosis Foundation. PLoS One. 2018;13(2):e0192459.

67. Groenendijk I, Grootswagers P, Santoro A, Franceschi C, Bazzocchi A, Meunier N, et al. Protein intake and bone mineral density: Cross-sectional relationship and longitudinal effects in older adults. J Cachexia Sarcopenia Muscle. 2023;14(1):116-25.

68. Gilsing AM, Crowe FL, Lloyd-Wright Z, Sanders TA, Appleby PN, Allen NE, et al. Serum concentrations of vitamin B12 and folate in British male omnivores, vegetarians and vegans: results from a cross-sectional analysis of the EPIC-Oxford cohort study. Eur J Clin Nutr. 2010;64(9):933-9.

69. Crowe FL, Steur M, Allen NE, Appleby PN, Travis RC, Key TJ. Plasma concentrations of 25-hydroxyvitamin D in meat eaters, fish eaters, vegetarians and vegans: results from the EPIC-Oxford study. Public Health Nutr. 2011;14(2):340-6.

70. Macêdo LLG, Carvalho C, Cavalcanti JC, Freitas B. Vitamin B12, bone mineral density and fracture risk in adults: A systematic review. Rev Assoc Med Bras (1992). 2017;63(9):801-9.

71. Yao P, Bennett D, Mafham M, Lin X, Chen Z, Armitage J, et al. Vitamin D and Calcium for the Prevention of Fracture: A Systematic Review and Meta-analysis. JAMA Netw Open. 2019;2(12):e1917789.

72. Warensjö Lemming E, Byberg L. Is a Healthy Diet Also Suitable for the Prevention of Fragility Fractures? Nutrients. 2020;12(9).

73. Sennerby U, Farahmand B, Ahlbom A, Ljunghall S, Michaëlsson K. Cardiovascular diseases and future risk of hip fracture in women. Osteoporos Int. 2007;18(10):1355-62.

74. Luo SY, Li Y, Luo H, Yin XH, Lin DR, Zhao K, et al. Increased intake of vegetables, but not fruits, may be associated with reduced risk of hip fracture: A meta-analysis. Scientific Reports. 2016;6:8.

75. Webster J, Dalla Via J, Langley C, Smith C, Sale C, Sim M. Nutritional strategies to optimise musculoskeletal health for fall and fracture prevention: Looking beyond calcium, vitamin D and protein. Bone Reports. 2023:101684.

76. Jeffery IB, O'Toole PW. Diet-microbiota interactions and their implications for healthy living. Nutrients. 2013;5(1):234-52.

77. Ozaki D, Kubota R, Maeno T, Abdelhakim M, Hitosugi N. Association between gut microbiota, bone metabolism, and fracture risk in postmenopausal Japanese women. Osteoporos Int. 2021;32(1):145-56.

78. Seely KD, Kotelko CA, Douglas H, Bealer B, Brooks AE. The Human Gut Microbiota: A Key Mediator of Osteoporosis and Osteogenesis. Int J Mol Sci. 2021;22(17).

79. Palermo M, Pellegrini N, Fogliano V. The effect of cooking on the phytochemical content of vegetables. J Sci Food Agric. 2014;94(6):1057-70.

80. Sim M, Blekkenhorst LC, Lewis JR, Bondonno CP, Devine A, Zhu K, et al. Vegetable Diversity, Injurious Falls, and Fracture Risk in Older Women: A Prospective Cohort Study. Nutrients. 2018;10(8).

81. Hariri AF, Almatrafi MN, Zamka AB, Babaker AS, Fallatah TM, Althouwaibi OH, et al. Relationship between Body Mass Index and T-Scores of Bone Mineral Density in the Hip and Spine Regions among Older Adults with Diabetes: A Retrospective Review. J Obes. 2019;2019:9827403.

82. Song J, Zhang R, Lv L, Liang J, Wang W, Liu R, et al. The Relationship Between Body Mass Index and Bone Mineral Density: A Mendelian Randomization Study. Calcif Tissue Int. 2020;107(5):440-5.

83. Coin A, Sergi G, Benincà P, Lupoli L, Cinti G, Ferrara L, et al. Bone mineral density and body composition in underweight and normal elderly subjects. Osteoporos Int. 2000;11(12):1043-50.

84. Park Y, Dodd KW, Kipnis V, Thompson FE, Potischman N, Schoeller DA, et al. Comparison of self-reported dietary intakes from the Automated Self-Administered 24-h recall, 4-d food records, and food-frequency questionnaires against recovery biomarkers. Am J Clin Nutr. 2018;107(1):80-93.

85. Senderovich H, Tang H, Belmont S. The Role of Exercises in Osteoporotic Fracture Prevention and Current Care Gaps. Where Are We Now? Recent Updates. Rambam Maimonides Med J. 2017;8(3).

86. Curtain F, Grafenauer S. Plant-Based Meat Substitutes in the Flexitarian Age: An Audit of Products on Supermarket Shelves. Nutrients. 2019;11(11).

87. Alae-Carew C, Green R, Stewart C, Cook B, Dangour AD, Scheelbeek PFD. The role of plant-based alternative foods in sustainable and healthy food systems: Consumption trends in the UK. Sci Total Environ. 2022;807(Pt 3):151041.

88. Sim M, Blekkenhorst LC, Lewis JR, Bondonno CP, Devine A, Zhu K, et al. Vegetable and fruit intake and injurious falls risk in older women: a prospective cohort study. Br J Nutr. 2018;120(8):925-34.

89. Montero-Odasso M, van der Velde N, Martin FC, Petrovic M, Tan MP, Ryg J, et al. World guidelines for falls prevention and management for older adults: a global initiative. Age Ageing. 2022;51(9).

90. Wark PA, Hardie LJ, Frost GS, Alwan NA, Carter M, Elliott P, et al. Validity of an online 24-h recall tool (myfood24) for dietary assessment in population studies: comparison with biomarkers and standard interviews. BMC Med. 2018;16(1):136.

91. Benson A, Irdam D, Bulceag I, Barber T, Draper A. Food and you survey: wave 5 secondary analysis: the current food landscape across England, Wales, and Northern Ireland. Foods Standards Agency. 2019.

92. Shridhar K, Dhillon PK, Bowen L, Kinra S, Bharathi AV, Prabhakaran D, et al. Nutritional profile of Indian vegetarian diets--the Indian Migration Study (IMS). Nutr J. 2014;13:55.

93. Public Health England. McCance and Widdowson's composition of foods integrated dataset. 2019.

94. Lv JL, Wu QJ, Li XY, Gao C, Xu MZ, Yang J, et al. Dietary protein and multiple health outcomes: An umbrella review of systematic reviews and meta-analyses of observational studies. Clin Nutr. 2022;41(8):1759-69.

95. Gaffney-Stomberg E. The Impact of Trace Minerals on Bone Metabolism. Biol Trace Elem Res. 2019;188(1):26-34.

96. Mendes MM, Botelho PB, Ribeiro H. Vitamin D and musculoskeletal health: outstanding aspects to be considered in the light of current evidence. Endocr Connect. 2022;11(10).

97. Poole R, Kennedy OJ, Roderick P, Fallowfield JA, Hayes PC, Parkes J. Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes. Bmj. 2017;359:j5024.

98. Yi M, Wu X, Zhuang W, Xia L, Chen Y, Zhao R, et al. Tea Consumption and Health Outcomes: Umbrella Review of Meta-Analyses of Observational Studies in Humans. Mol Nutr Food Res. 2019;63(16):e1900389.

99. Angelino D, Godos J, Ghelfi F, Tieri M, Titta L, Lafranconi A, et al. Fruit and vegetable consumption and health outcomes: an umbrella review of observational studies. Int J Food Sci Nutr. 2019;70(6):652-67.

100. Wallace TC, Bailey RL, Blumberg JB, Burton-Freeman B, Chen CO, Crowe-White KM, et al. Fruits, vegetables, and health: A comprehensive narrative, umbrella review of the science and recommendations for enhanced public policy to improve intake. Crit Rev Food Sci Nutr. 2020;60(13):2174-211.

101. Blekkenhorst LC, Hodgson JM, Lewis JR, Devine A, Woodman RJ, Lim WH, et al. Vegetable and Fruit Intake and Fracture-Related Hospitalisations: A Prospective Study of Older Women. Nutrients. 2017;9(5).

102. Sim M, Strydom A, Blekkenhorst LC, Bondonno NP, McCormick R, Lim WH, et al. Dietary Vitamin K1 intake is associated with lower long-term fracture-related hospitalization risk: the Perth longitudinal study of ageing women. Food Funct. 2022;13(20):10642-50.

103. Sim M, Smith C, Bondonno NP, Radavelli-Bagatini S, Blekkenhorst LC, Dalla Via J, et al. Higher Dietary Vitamin K Intake is Associated with Better Physical Function and Lower Long-Term Injurious Falls Risk in Community-Dwelling Older Women. J Nutr Health Aging. 2023;27(1):38-45.

104. Battaglia Richi E, Baumer B, Conrad B, Darioli R, Schmid A, Keller U. Health Risks Associated with Meat Consumption: A Review of Epidemiological Studies. Int J Vitam Nutr Res. 2015;85(1-2):70-8.

105. Godfray HCJ, Aveyard P, Garnett T, Hall JW, Key TJ, Lorimer J, et al. Meat consumption, health, and the environment. Science. 2018;361(6399).

106. Scarborough P, Clark M, Cobiac L, Papier K, Knuppel A, Lynch J, et al. Vegans, vegetarians, fish-eaters and meat-eaters in the UK show discrepant environmental impacts. Nat Food. 2023;4(7):565-74.

107. Shapses SA, Sukumar D. Bone metabolism in obesity and weight loss. Annu Rev Nutr. 2012;32:287-309.

108. Korpelainen R, Keinänen-Kiukaanniemi S, Heikkinen J, Väänänen K, Korpelainen J. Effect of exercise on extraskeletal risk factors for hip fractures in elderly women with low BMD: a population-based randomized controlled trial. J Bone Miner Res. 2006;21(5):772-9.

# Appendix A Chapter 2 Supplementary material

**Table A1: PRISMA 2020 checklist.**

| Section/Topic | Item no. | Checklist item | Page number reported | Line number reported |
|---|---|---|---|---|
| **TITLE** | | | | |
| Title | 1 | Identify the report as a systematic review | 1 | 1-2 |
| **ABSTRACT** | | | | |
| Abstract | 2 | See the PRISMA 2020 for Abstracts checklist (Supplementary Table 8) | 2 | 11-36 |
| **INTRODUCTION** | | | | |
| Rationale | 3 | Describe the rationale for the review in the context of existing knowledge | 4 | 37-62 |
| Objectives | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | 4 | 62-64 |
| **METHODS** | | | | |
| Eligibility criteria | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | 5-6 | 70-92 |
| Information sources | 6 | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | 6 | 93-99 |

| | | | | |
|---|---|---|---|---|
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | 6 | 93-99 (See Table S1) |
| Selection process | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | 6-7 | 100-112 |
| Data collection process | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | 7-8 | 113-133 |
| Data items | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | 7-8 | 113-133 |
| | 10b | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | 7-8 | 113-133 |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | 8-9 | 134-148 |
| Effect measures | 12 | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | 9 | 156-159 |
| Synthesis methods | 13a | Describe the processes used to decide which studies were eligible for each synthesis. | 6-7 | 100-113 |
| | 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | 9 | 156-159 |

| | | | | |
|---|---|---|---|---|
| | 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | 9 | 156-159 |
| | 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | 9 | 156-159 |
| | 13e | Describe any methods used to explore possible causes of heterogeneity among study results. | N/A | N/A |
| | 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | N/A | N/A |
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | 8 | 159 |
| Certainty assessment | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome | 8-9 | 149-155 |
| **RESULTS** | | | | |
| Study selection | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram (see Fig 1). | 9 | 161-170 (see Figure 1) |
| | 16b | Cite studies that met many but not all inclusion criteria ('near-misses') and explain why they were excluded | N/A | See S2 Table |
| Study characteristics | 17 | Cite each included study and present its characteristics. | 10-11 | 190-217 (see Table S3) |
| Risk of bias in studies | 18 | Present assessments of risk of bias for each included study | 11-12 | 218-232 (see Table S5) |
| Results of individual studies | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | 13-16 | See Tables 1-4 |

| | | | | |
|---|---|---|---|---|
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | N/A | N/A |
| | 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | N/A | N/A |
| | 20c | Present results of all investigations of possible causes of heterogeneity among study results. | N/A | N/A |
| | 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | N/A | N/A |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed | 19 | 289-294 |
| Certainty of evidence | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | 12 | 233-245 (see Tables 1-4 and Table S6) |
| **DISCUSSION** | | | | |
| Discussion | 23a | Provide a general interpretation of the results in the context of other evidence. | 19-22 | 295-369 |
| | 23b | Discuss any limitations of the evidence included in the review. | 24-26 | 409-458 |
| | 23c | Discuss any limitations of the review processes used. | 24-26 | 409-458 |
| | 23d | Discuss implications of the results for practice, policy, and future research. | 26-27 | 459-476 |
| **OTHER INFORMATION** | | | | |
| Registration and protocol | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | 5 | 65-69 |
| | 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | 5 | 65-69 |

| | | | | |
|---|---|---|---|---|
| | 24c | Describe and explain any amendments to information provided at registration or in the protocol. | See protocol updates | See protocol updates |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review | N/A | N/A |
| Competing interests | 26 | Declare any competing interests of review authors. | N/A | N/A |
| Availability of data, code, and other materials | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | N/A | N/A |

**Table A2: PRISMA 2020 checklist for abstracts.**

| Section/Topic | Item no. | Checklist item | Line number reported |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review. | 1-2 |
| **BACKGROUND** | | | |
| Objectives | 2 | Provide an explicit statement of the main objective(s) or question(s) the review addresses. | 12 13 |
| **METHODS** | | | |
| Eligibility criteria | 3 | Specify the inclusion and exclusion criteria for the review. | 15-17 |

| | | | |
|---|---|---|---|
| Information sources | 4 | Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched. | 18-19 |
| Risk of bias | 5 | Specify the methods used to assess risk of bias in the included studies. | 20-22 |
| Synthesis of results | 6 | Specify the methods used to present and synthesize results | 20-22 |
| **RESULTS** | | | |
| Included studies | 7 | Give the total number of included studies and participants and summarise relevant characteristics of studies. | 23-30 |
| Synthesis of results | 8 | Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured). | 23-30 |
| **DISCUSSION** | | | |
| Limitations of evidence | 9 | Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision). | 31-35 |
| Interpretation | 10 | Provide a general interpretation of the results and important implications. | 31-35 |
| **OTHER** | | | |
| Funding | 11 | Specify the primary source of funding for the review | N/A |
| Registration | 12 | Provide the register name and registration number. | 36 |

**Table A3: Search strategy.**

| **Ovid Embase (311 articles returned)** | |
|---|---|
| 1.Exposure terms | (Nutrient* OR micronutrient* OR macronutrient* OR phytonutrient* OR antioxidant*).tw. OR (exp nutrient/ OR trace element/ OR macronutrient intake/ OR macronutrient/ OR antioxidant/ OR phytonutrient/) OR (vitamin* OR vitamin D OR vitamin K OR vitamin C OR vitamin B* OR thiamine OR riboflavin OR pyridoxine OR cyanocobalamin OR dietary minerals OR iron intake OR zinc intake OR magnesium intake OR sodium intake OR potassium intake OR silicon intake OR boron intake OR calcium intake OR copper intake OR manganese intake OR iodine intake).tw. OR (vitamin B group/ OR vitamin D deficiency/ OR vitamin B deficiency/ OR vitamin deficiency/ OR vitamin K deficiency/ OR vitamin/ OR vitamin intake/ OR vitamin K group/ OR vitamin D/ OR thiamine/ OR riboflavin/ OR pyridoxine/ OR cyanocobalamin/ OR mineral intake/ OR iron intake/ OR zinc intake/ OR magnesium intake/ OR sodium intake/ OR potassium intake/ OR calcium intake/ OR copper intake/ OR iodine intake/) OR (protein intake OR protein consumption OR animal protein OR plant protein OR dietary protein OR dietary fat* OR saturated fat OR mono-unsaturated fatty acids OR poly-unsaturated fatty acids OR MUFAs OR PUFAs OR carbohydrate* OR sugar* OR dietary fibre OR dietary fiber OR energy intake OR calorie intake OR caloric intake).tw. OR (protein intake/ OR animal protein/ OR plant protein/ OR fat intake/ OR monounsaturated fatty acid/ OR unsaturated fatty acid/ OR saturated fatty acid/ OR polyunsaturated fatty acid/ OR carbohydrate intake/ OR sugar intake/ OR dietary fiber/ OR caloric intake/) OR (caffeinated intake OR caffeine intake OR caffeine OR decaffeinated OR decaffeinated intake OR dietary supplement* OR alcohol OR dairy OR milk OR cheese OR yogurt OR coffee OR meat OR fruit* OR vegetable* OR veg OR legumes OR nuts).tw. OR (caffeine intake/ OR diet supplementation/ OR dietary supplement/ OR alcohol consumption/ OR exp dairy product/ OR coffee consumption/ OR meat consumption/ OR processed meat/ OR red meat/ OR fruit consumption/ OR vegetable consumption/ OR food intake/) OR (dietary pattern OR diet OR omnivore OR omnivorous OR vegetarian OR vegan OR plant-based OR plant based OR lacto-vegetarian OR lactovegetarian OR Mediterranean diet OR MedDiet OR Western diet OR dietary approaches to stop hypertension OR DASH diet OR fasting OR dietary risk factor*).tw. OR (dietary pattern/ OR omnivore/ OR exp vegetarian/ OR exp vegetarian diet/ OR vegan diet/ OR vegan/ OR Mediterranean diet/ OR DASH diet/ OR intermittent fasting/ OR fasting/ OR Ramadan fasting/ OR dietary intake/) |
| 2.Primary outcome terms | (hip fracture* OR osteoporotic fracture OR bone fracture OR fragility fracture).tw. OR (hip fracture/ OR fragility fracture/) NOT treatment.tw. |
| 3.Review terms | *BMJ Embase pre-tested search filter for systematic reviews:*<br>1. exp review/<br>2. (literature adj3 review$).ti,ab.<br>3. exp meta analysis/<br>4. exp “Systematic Review”/ |

| | |
|---|---|
| | 5. or/1-4<br>6. (medline or medlars or embase or pubmed or cinahl or amed or psychlit or psyclit or psychinfo or psycinfo or scisearch or cochrane).ti,ab.<br>7. RETRACTED ARTICLE/<br>8. 6 or 7<br>9. 5 and 8<br>10. (systematic$ adj2 (review$ or overview)).ti,ab.<br>11. (meta?anal$ or meta anal$ or meta-anal$ or metaanal$ or metanal$).ti,ab.<br>12. 9 or 10 or 11 |
| 4. Boolean operators | 1 AND 2 AND 3 |
| 5. Limits | Limit 4 to humans<br><br>Limit 5 to English Language |
| **Ovid Medline (136 articles returned)** | |
| 1. Exposure terms | (Nutrient* OR micronutrient* OR macronutrient* OR phytonutrient* OR antioxidant*).tw. OR (nutrients/ OR micronutrients/ OR phytochemicals/ OR antioxidants/) OR (vitamin* OR vitamin D OR vitamin K OR vitamin C OR vitamin B* OR thiamine OR riboflavin OR pyridoxine OR cyanocobalamin OR dietary minerals OR iron intake OR zinc intake OR magnesium intake OR sodium intake OR potassium intake OR silicon intake OR boron intake OR calcium intake OR copper intake OR manganese intake OR iodine intake).tw. OR (vitamins/ OR vitamin D/ OR vitamin A deficiency/ OR vitamin B deficiency/ OR vitamin D deficiency/ OR vitamin E deficiency/ OR vitamin K deficiency/ OR thiamine/ OR riboflavin/ OR pyridoxine/ OR vitamin B12/ OR trace elements/ OR iron, dietary/ OR magnesium deficiency/ OR potassium deficiency/ OR sodium, dietary/ OR sodium chloride, dietary/ OR calcium, dietary/) OR (protein intake OR protein consumption OR animal protein OR plant protein OR dietary protein OR dietary fat* OR saturated fat OR mono-unsaturated fatty acids OR poly-unsaturated fatty acids OR MUFAs OR PUFAs OR carbohydrate* OR sugar* OR dietary fibre OR dietary fiber OR energy intake OR calorie intake OR caloric intake).tw. OR (Dietary proteins/ OR animal proteins, dietary/ OR fruit proteins/ OR grain proteins/ OR plant proteins, dietary/ OR dietary fats/ OR butter/ OR cholesterol, dietary/ OR dietary fats, unsaturated/ OR margarine/ OR fats, unsaturated/ OR dietary carbohydrates/ OR dietary fiber/ OR dietary sugars/ OR starch/ OR energy intake/ OR caloric restriction/ OR portion size/ OR serving size/) OR (caffeinated intake OR caffeine intake OR caffeine OR decaffeinated OR decaffeinated intake OR dietary supplement* OR alcohol OR dairy OR milk OR cheese OR yogurt OR coffee OR meat OR fruit* OR vegetable* OR veg OR legumes OR nuts).tw. OR (Caffeine/ OR dietary supplements/ OR alcohol abstinence/ OR alcohol drinking/ OR dairy products/ OR butter/ OR cultured milk products/ OR ice cream/ OR margarine/ OR milk/ OR coffee/ OR meat/ OR meat products/ OR poultry/ OR red meat/ OR seafood/ OR fruit/ OR nuts/ OR seeds/ OR vegetables/) OR (dietary pattern OR diet OR omnivore OR omnivorous OR vegetarian OR vegan OR plant-based OR plant based OR |

| | |
|---|---|
| | lacto-vegetarian OR lactovegetarian OR Mediterranean diet OR MedDiet OR Western diet OR dietary approaches to stop hypertension OR DASH diet OR fasting OR dietary risk factor*).tw. OR (diet/ OR diet, carbohydrate-restricted/ OR diet, fat-restricted/ OR diet, gluten-free/ OR diet, high-fat/ OR diet, high-protein/ OR diet, Mediterranean/ OR diet, vegetarian/ OR diet, western/ OR dietary approaches to stop hypertension/ OR fasting/ OR vegetarians/ OR vegans/) |
| 2. Primary outcome terms | (Hip fracture* OR osteoporotic fracture OR bone fracture OR fragility fracture).tw. OR (hip fractures/ OR femoral neck fractures/) NOT treatment.tw. |
| 3. Review terms | *BMJ Medline pre-tested search filter for systematic reviews:*<br>1. review.pt.<br>2. (medline or medlars or embase or pubmed or cochrane).tw,sh.<br>3. (scisearch or psychinfo or psycinfo).tw,sh.<br>4. (psychlit or psyclit).tw,sh.<br>5. cinahl.tw,sh.<br>6. ((hand adj2 search$) or (manual$ adj2 search$)).tw,sh.<br>7. (electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.<br>8. (pooling or pooled or mantel haenszel).tw,sh.<br>9. (peto or dersimonian or der simonian or fixed effect).tw,sh.<br>10. (retraction of publication or retracted publication).pt.<br>11. or/2-10<br>12. 1 and 11<br>13. meta-analysis.pt.<br>14. meta-analysis.sh.<br>15. (meta-analys$ or meta analys$ or metaanalys$).tw,sh.<br>16. (systematic$ adj5 review$).tw,sh.<br>17. (systematic$ adj5 overview$).tw,sh.<br>18. (quantitativ$ adj5 review$).tw,sh.<br>19. (quantitativ$ adj5 overview$).tw,sh.<br>20. (quantitativ$ adj5 synthesis$).tw,sh.<br>21. (methodologic$ adj5 review$).tw,sh.<br>22. (methodologic$ adj5 overview$).tw,sh.<br>23. (integrative research review$ or research integration).tw.<br>24. or/13-23<br>25. 12 or 24 |
| 4. Boolean operators | 1 AND 2 AND 3 |
| 5. Limits | Limit 4 to humans; Limit 5 to English language |
| **Cochrane Database of Systematic Reviews (7 articles returned)** | |
| 1. Exposure terms | (Nutrient* OR micronutrient* OR macronutrient* OR phytonutrient* OR antioxidant*) OR (vitamin* OR “vitamin D” OR “vitamin K” OR “vitamin C” OR “vitamin B*” OR thiamine OR riboflavin OR pyridoxine OR cyanocobalamin OR “dietary minerals” OR “iron intake” OR “zinc intake” OR “magnesium intake” OR “sodium intake” OR “potassium intake” OR “silicon intake” OR “boron intake” OR “calcium intake” OR “copper intake” OR “manganese intake” OR “iodine intake”) OR (“protein intake” |

| | |
|---|---|
| | OR “protein consumption” OR “animal protein” OR “plant protein” OR “dietary protein” OR “dietary fat*” OR “saturated fat” OR “mono-unsaturated fatty acids” OR “poly-unsaturated fatty acids” OR MUFAs OR PUFAs OR carbohydrate* OR sugar* OR “dietary fibre” OR “dietary fiber” OR “energy intake” OR “calorie intake” OR “caloric intake”) OR (“caffeinated intake” OR “caffeine intake” OR caffeine OR decaffeinated OR “decaffeinated intake” OR “dietary supplement*“ OR alcohol OR dairy OR milk OR cheese OR yogurt OR coffee OR meat OR fruit* OR vegetable* OR veg OR legumes OR nuts) OR (“dietary pattern” OR diet OR omnivore OR omnivorous OR vegetarian OR vegan OR plant-based OR “plant based” OR lacto-vegetarian OR lactovegetarian OR “Mediterranean diet” OR MedDiet OR “Western diet” OR “dietary approaches to stop hypertension” OR “DASH diet” OR fasting OR “dietary risk factor*”) OR [mh ^nutrients] OR [mh ^micronutrients] OR [mh ^phytochemicals] OR [mh ^antioxidants] OR [mh ^vitamins] OR [mh ^”vitamin D”] OR [mh ^”vitamin A deficiency”] OR [mh ^”vitamin B deficiency”] OR [mh ^”vitamin D deficiency”] OR [mh ^”vitamin E deficiency”] OR [mh ^”vitamin K deficiency”] OR [mh ^thiamine] OR [mh ^riboflavin] OR [mh ^pyridoxine] OR [mh ^”vitamin B12”] OR [mh ^”trace elements”] OR [mh ^”iron, dietary”] OR [mh ^”magnesium deficiency”] OR [mh ^”potassium deficiency”] OR [mh ^”sodium, dietary”] OR [mh ^”sodium chloride, dietary”] OR [mh ^”calcium, dietary”] OR [mh ^”Dietary proteins”] OR [mh ^”animal proteins, dietary”] OR [mh ^”fruit proteins”] OR [mh ^”grain proteins”] OR [mh ^”plant proteins, dietary”] OR [mh ^”dietary fats”] OR [mh ^butter] OR [mh ^”cholesterol, dietary”] OR [mh ^”dietary fats, unsaturated“] OR [mh ^margarine] OR [mh ^”fats, unsaturated”] OR [mh ^”dietary carbohydrates”] OR [mh ^”dietary fiber”] OR [mh ^”dietary sugars”] OR [mh ^starch] OR [mh ^”energy intake”] OR [mh ^”caloric restriction”] OR [mh ^”portion size”] OR [mh ^”serving size”] OR [mh ^Caffeine] OR [mh ^”dietary supplements”] OR [mh ^”alcohol abstinence”] OR [mh ^”alcohol drinking”] OR [mh ^”dairy products”] OR [mh ^butter] OR [mh ^”cultured milk products”] OR [mh ^”ice cream”] OR [mh ^margarine] OR [mh ^milk] OR [mh ^coffee] OR [mh ^meat] OR [mh ^”meat products”] OR [mh ^poultry] OR [mh ^”red meat”] OR [mh ^seafood] OR [mh ^fruit] OR [mh ^nuts] OR [mh ^seeds] OR [mh ^vegetables] OR [mh ^diet] OR [mh ^”diet, carbohydrate-restricted”] OR [mh ^”diet, fat-restricted“] OR [mh ^”diet, gluten-free”] OR [mh ^”diet, high-fat”] OR [mh ^”diet, high-protein”] OR [mh ^”diet, Mediterranean”] OR [mh ^”diet, vegetarian”] OR [mh ^”diet, western”] OR [mh ^”dietary approaches to stop hypertension”] OR [mh ^fasting] OR [mh ^vegetarians] OR [mh ^vegans] |
| 2. Primary outcome terms | (“Hip fracture” OR “osteoporotic fracture” OR “bone fracture” OR “fragility fracture”) OR [mh ^"hip fractures"] OR [mh ^"femoral neck fractures"] NOT treatment |
| 3. Boolean operators | 1 AND 2 |
| **Web of Science (387 articles returned)** | |
| 1. Exposure terms | TS=((Nutrient* OR micronutrient* OR macronutrient* OR phytonutrient* OR antioxidant*) OR (vitamin* OR “vitamin D” OR “vitamin K” OR |

| | |
|---|---|
| | "vitamin C" OR "vitamin B*" OR thiamine OR riboflavin OR pyridoxine OR cyanocobalamin OR "dietary minerals" OR "iron intake" OR "zinc intake" OR "magnesium intake" OR "sodium intake" OR "potassium intake" OR "silicon intake" OR "boron intake" OR "calcium intake" OR "copper intake" OR "manganese intake" OR "iodine intake") OR ("protein intake" OR "protein consumption" OR "animal protein" OR "plant protein" OR "dietary protein" OR "dietary fat*" OR "saturated fat" OR "mono-unsaturated fatty acids" OR "poly-unsaturated fatty acids" OR MUFAs OR PUFAs OR carbohydrate* OR sugar* OR "dietary fibre" OR "dietary fiber" OR "energy intake" OR "calorie intake" OR "caloric intake") OR ("caffeinated intake" OR "caffeine intake" OR caffeine OR decaffeinated OR "decaffeinated intake" OR "dietary supplement*" OR alcohol OR dairy OR milk OR cheese OR yogurt OR coffee OR meat OR fruit* OR vegetable* OR veg OR legumes OR nuts) OR ("dietary pattern" OR diet OR omnivore OR omnivorous OR vegetarian OR vegan OR plant-based OR "plant based" OR lacto-vegetarian OR lactovegetarian OR "Mediterranean diet" OR MedDiet OR "Western diet" OR "dietary approaches to stop hypertension" OR "DASH diet" OR fasting OR "dietary risk factor*")) |
| 2. Primary outcome terms | TS=("Hip fracture" OR "osteoporotic fracture" OR "bone fracture" OR "fragility fracture") NOT TS=treatment |
| 3. Review terms | TS=("systematic review" OR meta-analysis OR metaanalysis OR "meta analysis") |
| 4. Boolean operators | (1 AND 2 AND 3) AND LANGUAGE: (English) |

Each search is comprised of: 1) Dietary exposure terms AND 2) Outcome (hip fracture) terms AND 3) Review filter terms. Dietary exposure terms are either foods, nutrients, beverages, or dietary patterns. Black text = keywords; blue text = subject headings.

**Table A4: Excluded articles with justifications for their exclusion.**

| | |
|---|---|
| Angelino et al. (2019) | Umbrella review |
| Avenell et al. (2014) | Supplements |
| Avenell et al. (2009) | Old version of a review |
| Avenell et al. (2005) | Old version of a review |
| Bailey et al. (2015) | No meta-analysis |
| Benetos et al. (2007) | No meta-analysis |
| Benetou et al. (2018) | Cohort pooling project |
| Benetou et al. (2016) | Cohort pooling project |
| Berg et al. (2008) | Included case-control studies |
| Bergholdt et al. (2018) | Cohort pooling project |
| Bischoff-Ferrari et al. (2005) | Supplements |
| Bischoff-Ferrari (2010) | No meta-analysis |

| | |
|---|---|
| Bjelakovic et al. (2014) | No relevant outcome |
| Bolanos and Francia (2010) | No relevant outcome |
| Bolland et al. (2014a) | Review of meta-analyses |
| Bolland et al. (2015) | Supplements |
| Bolland et al. (2018) | Supplements |
| Bolland et al. (2014b) | Full text not found |
| Bonjour et al. (2013) | No meta-analysis |
| Brown (2008) | Umbrella review |
| Cawood et al. (2012) | No relevant outcome |
| Ceylan et al. (2020) | No relevant outcome |
| Chakhtoura et al. (2020) | Umbrella review |
| Chen et al. (2014) | Included case-control studies. Subgroup analysis restricting to cohort studies was on fracture generally, not specified to hip. |
| Chung et al. (2011) | No relevant outcome |
| Darling et al. (2016) | Conference abstract |
| Darling et al. (2019) | No relevant outcome |
| Darling et al. (2017) | Old version of a review |
| de Macedo et al. (2017) | No meta-analysis |
| Dennehy and Tsourounis (2010) | Umbrella review |
| Dong et al. (2014) | HIV/hepatitis C virus coinfection patients |
| Drake et al. (2012) | Included case-control studies |
| Eleni and Panagiotis (2020) | Supplements |
| Fabiani et al. (2019) | Included case-control studies |
| Fang et al. (2020) | Included cross-sectional and case-control studies |
| Farsinejad-Marj et al. (2016) | Included case-control studies |
| Frost et al. (2013) | Conference abstract |
| Frost et al. (2016) | Conference abstract |
| Gaugris et al. (2005) | No meta-analysis |
| Gillespie et al. (2009) | No relevant outcome |
| Gillespie et al. (2000) | Old version of a review |
| Guo et al. (2017) | No relevant outcome |
| Hamishehkar et al. (2016) | No meta-analysis |
| Handoll et al. (2009) | No meta-analysis |

| | |
|---|---|
| Hao et al. (2017) | No relevant outcome |
| Hiligsmann et al. (2017) | No meta-analysis |
| Hill et al. (2018) | No relevant outcome |
| Ho-Pham et al. (2009) | No relevant outcome |
| Hoidrup et al. (2000) | Lack of dietary exposure (considered tobacco smoking as exposure) |
| Holvik et al. (2019) | Cohort pooling project |
| Huang et al. (2006) | No meta-analysis |
| Iwamoto et al. (2009) | No meta-analysis |
| Izaks (2007) | No relevant outcome |
| Jackson et al. (2007) | No relevant outcome |
| Jackson and Sheehan (2005) | No meta-analysis |
| Kahwati et al. (2018) | Supplements |
| Kanis et al. (2005a) | Cohort pooling project |
| Kanis et al. (2005b) | Cohort pooling project |
| Kanis et al. (2008) | No meta-analysis |
| Kunutsor et al. (2017) | Included case-control studies |
| Lai et al. (2010) | Supplements |
| Lee et al. (2014) | Included case-control studies |
| Li et al. (2020) | Supplements |
| Liu et al. (2012) | No relevant outcome |
| Lv et al. (2017) | Lack of dietary exposure (considered serum vitamin D levels) |
| MacLean et al. (2008) | Umbrella review |
| Man et al. (2016) | No relevant outcome |
| Mosekilde et al. (2007) | No meta-analysis |
| Mott et al. (2019) | No relevant outcome |
| Mozaffari et al. (2020) | No relevant outcome |
| Mozaffari et al. (2018) | Included case-control studies |
| Murad et al. (2012) | Included only trials whose populations had or were at risk of osteoporosis, had previous fractures, or other chronic diseases (patient population) |
| Nakamura and Masayuki (2006) | Umbrella review |
| Oliver et al. (2007) | Umbrella review |

| | |
|---|---|
| Orchard et al. (2012) | No relevant outcome |
| Ong et al. (2018) | No meta-analysis |
| Papadimitriou et al. (2017) | Cohort pooling project |
| Pedersen and Cederholm (2014) | No meta-analysis |
| Peraza-Delgado et al. (2020) | Umbrella review |
| Plawecki and Chapman-Novakofski (2010) | No meta-analysis |
| Pripp and Dahl (2015) | Umbrella review |
| Ruan et al. (2015) | No relevant outcome |
| Sawka et al. (2010) | No meta-analysis |
| Scragg (2012) | Umbrella review |
| Shams-White et al. (2017) | No relevant outcome |
| Shams-White et al. (2018) | No relevant outcome |
| Shen et al. (2015) | Lack of dietary exposure (considered cigarette smoking) |
| Shi et al. (2019) | Lack of dietary exposure (considered depression) |
| Solbakken et al. (2014) | Not a systematic review |
| Sun et al. (2018) | Included case-control studies |
| Tang et al. (2007) | Supplements |
| Theodoratou et al. (2014) | Umbrella review |
| Thorning et al. (2016) | Umbrella review |
| Trakanoska et al. (2018) | Not a systematic review |
| van den Heuvel and Steijns (2018) | Narrative review |
| van der Velde et al. (2014) | Umbrella review |
| Veronese et al. (2015) | Lack of dietary exposure (considered vitamin K antagonists use) |
| Vestergaard et al. (2003) | Lack of dietary exposure (considered smoking) |
| Wallace et al. (2020) | No meta-analysis |
| Wang et al. (2020) | Lack of dietary exposure (considered serum vitamin D levels) |
| Weatherall (2000) | Lack of dietary exposure (considered serum vitamin D levels) |
| Weaver et al. (2016) | Supplements |
| Wikoff et al. (2017) | No relevant outcome |
| Wu et al. (2019) | Population was restricted to knee osteoarthritis patients (too narrow) |
| Wu et al. (2016) | Lack of dietary exposure (considered cigarette smoking) |

| | |
|---|---|
| Xiang et al. (2019) | No meta-analysis of cohort studies for risk of hip fracture (included CCs and other sites, inseparable) |
| Xu et al. (2017) | Not a systematic review |
| Yan et al. (2015) | Included case-control studies, and subgroup analysis restricting to just cohort studies was only available for total fracture, not hip fracture |
| Yang et al. (2012) | Lack of dietary exposure (considered serum homocysteine levels) |
| Yao et al (2019) | Supplements |

Reasons stated for exclusion are the primary reasons; studies may have multiple reasons for exclusion.

**Table A5: Characteristics of eligible meta-analyses assessing the association between risk of hip fracture and dietary exposures.**

| Exposure | Author (year) | Population | n cohorts | Follow-up range (years) | n subjects | n events | Exposure ascertainment | Outcome ascertainment | Comparison | Summary effect estimate (95% CI) | $I^2$ (%) | Egger's p-value | Fully adjusted confounders |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Dietary patterns** | | | | | | | | | | | | | |
| Alternative healthy eating index | Panahande et al. (2018) | Adults (30 - 79 y) | 4 | 10 - 32 | 264319 | 6212 | FFQ | Self-reported questionnaires, medical records | High vs low | RR: 0.83 (0.71, 0.97) | N/A | 0.189 | Sex |
| Mediterranean diet | Malmir et al. (2018a) | Adults (> 35 y) | 4 | 8-16 | 351625 | 6253 | FFQ, diet history questionnaire, 24 h recall | N/A | Per 1 unit increase in MD score | RR: 0.95 (0.92, 0.98) | 68 | 0.78 | Age, sex, BMI, smoking |
| **Food groups** | | | | | | | | | | | | | |
| Dairy | Bian et al. (2018) | Adults (> 30 y) | 10 | 3-22 | 363557 | 8613 | FFQ (validated, non-validated), or N/A | Self-reported, hospital registers, medical records, radiographic reports | High vs low | RR: 0.87 (0.76, 1.00) | 81* | N/A | None |
| Dairy | Malmir et al. (2019) | Adults (> 18 y) | 5 | 4-21 | 189501 | 9091 | FFQ | Self-reported, hospital registers | Per 200 g increase/day | RR: 0.98 (0.95, 1.01) | N/A | 0.223 | None |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dairy | Matia-martin et al. (2019) | Healthy non-Hispanic whites (> 26 y) | 4 | 8-22 | 231442 | 8629 | FFQ (self-reported, reviewed with clinic staff) | Self-reported, small validation study, medical records, hospital registers, radiographic reports | Per 'increment' increase | RR: 0.98 (0.95, 1.01) | 86* | 0.982 | Age, sex, smoking, calcium and vitamin D supplementation, total energy intake |
| Milk | Bian et al. (2018) | Adults (> 30 y) | 7 | 7-22 | 301590 | 7868 | FFQ (validated, non-validated), or N/A | Self-reported, hospital registers, medical records, radiographic reports | Per 200 g increase/day | RR: 1.00 (0.94, 1.07) | 87* | 0.81 | Age |
| Milk | Bischoff-Ferrari et al. (2011) | Middle-aged or older men | 3 | 8-14 | 75149 | 195 | FFQ | N/A | Per 300 mg increase/day | RR: 0.91 (0.81, 1.01) | N/A | N/A | Age, sex |
| | | Middle-aged or older women | 6 | 3-26 | 195102 | 3574 | FFQ | N/A | Per 300 mg increase/day | RR: 0.99 (0.96, 1.02) | N/A | N/A | Age, sex |
| Milk | Hidayat et al. (2020) | Adults (mean age > 50 y) | 7 | 6-22 | 383122 | 15020 | FFQ | Self-reported, medical records, radiographic reports, hospital registers | Per 1 glass increase/day | RR: 0.97 (0.92, 1.03) | N/A | 0.21 | Age, sex |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Milk | Malmir et al. (2019) | Adults (> 18 y) | 8 | 4-50 | 348181 | 33446 | FFQ | Self-reported, hospital records, x-ray exam | Per 200 g increase/day | RR: 1.09 (1.07, 1.11) | N/A | 0.015 | None |
| Milk | Matia-martin et al. (2019) | Adults (> 26 y) | 5 | 8-22 | 236136 | 8454 | FFQ (self-reported, reviewed with clinic staff) | Self-reported, small validation study, medical records, hospital registers, radiographic reports | Per 'increment' increase | RR: 1.01 (0.96, 1.06) | 84 | N/A | Age, sex, smoking, calcium and vitamin D supplementation, total energy intake |
| Yogurt | Bian et al. (2018) | Adults (> 30 y) | 3 | 8-20 | 109018 | 5579 | FFQ (validated, non-validated), or N/A | Self-reported, hospital registers, medical records, radiographic reports | High vs low | RR: 0.75 (0.66, 0.86) | 0 | N/A | Age, sex, calcium and vitamin D supplement use |
| Yogurt | Hidayat et al. (2020) | Adults (mean > 50 y) | 4 | 12-21 | 234654 | 8217 | FFQ | Self-reported, medical records, radiographic reports, hospital registers | High vs low | RR: 0.78 (0.68, 0.90) | 14 | >0.45 | Age, sex, height, smoking, calcium and vitamin D supplementation, total energy intake |
| Yogurt | Matia-martin et al. (2019) | Adults (> 26 y) | 5 | 8-22 | 236136 | 8454 | FFQ (self-reported, | Self-reported, small validation study, medical | Per 'increment' increase | RR: 0.96 (0.91, 1.01) | 72* | N/A | Age, sex, smoking, calcium and vitamin D supplementation |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | reviewed with clinic staff) | records, hospital registers, radiographic reports | | | | | , total energy intake |
| Yogurt | Ong et al. (2020) | Postmenopausal women (age > 55 y) | 3 | 12-22 | 108219 | 6991 | FFQ | N/A | High vs low | RR: 0.76 (0.63, 0.92) | 29 | N/A | Age, sex, BMI, height, smoking |
| Cheese | Bian et al. (2018) | Adults (> 30 y) | 3 | 7-20 | 117240 | 5648 | FFQ (validated, non-validated), or N/A | Self-reported, registers, medical records, radiographic and operative reports | High vs low | RR: 0.68 (0.61, 0.77) | 0 | N/A | Age, sex, calcium and vitamin D supplement use |
| Cheese | Hidayat et al. (2020) | Adults (mean> 50 y) | 4 | 6-21 | 305157 | 8860 | FFQ | Self-reported, medical records, radiographic reports, hospital registers | High vs low | RR: 0.85 (0.66, 1.08) | 77* | p>0.45 | Age, sex, smoking |
| Cheese | Matia-martin et al. (2019) | Adults (> 26 y) | 4 | 8-21 | 232924 | 8411 | FFQ (self-reported, reviewed with clinic staff) | Self-reported, small validation study, medical records, hospital registers, | Per 'increment' increase | RR: 0.96 (0.88, 1.04) | 91* | N/A | Age, sex, smoking, calcium and vitamin D supplementation , total energy intake |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | radiographic reports | | | | | |
| Cheese | Ong et al. (2020) | Postmenopausal women (age > 55 y) | 2 | 12-22 | 81069 | 2214 | FFQ (self-reported, reviewed with clinic staff) | Self-reported, small validation study, medical records, hospital registers, radiographic reports | High vs low | RR: 0.89 (0.73, 1.10) | 0 | N/A | Age, sex, BMI, height, smoking |
| Fruits | Luo et al. (2016) | Middle-aged to older adults (37 - 95 y) | 5 | 8-14 | 329125 | 6133 | FFQ | Telephone interviews, self-reported questionnaire, hospital registers | High vs low | HR: 0.91 (0.77, 1.07) | 73* | N/A | Age, sex, alcohol intake, total energy intake physical activity, smoking. |
| Vegetables | Luo et al. (2016) | Middle-aged to older adults (37 - 95 y) | 5 | 8-14 | 329125 | 6133 | FFQ | Telephone interviews, self-reported questionnaire, hospital registers | High vs low | HR: 0.81 (0.68, 0.96) | 71* | N/A | Age, sex, alcohol intake, total energy intake physical activity, smoking. |
| Fruits and vegetables | Luo et al. (2016) | Middle-aged to older adults (37 - 95 y) | 7 | 8-14 | 329125 | 6133 | FFQ | Telephone interviews, self-reported questionnaire, hospital registers | High vs low | HR: 0.88 (0.78, 1.01) | 74* | N/A | Age, sex, alcohol intake, total energy intake physical activity, smoking. |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Fruits and vegetables | Brondani et al. (2019) | Adults (age > 50 y) | 5 | 7-20 | 218926 | N/A | Validated FFQ | N/A | High vs low | RR: 0.92 (0.87, 0.98) | 56 | 0.147 | BMI, calcium and vitamin D supplementation |
| Tea | Sheng et al. (2013) | Adults | 3 | 6-12 | 136413 | 5171 | FFQ | Medical records, self-reported, hospital registers | High vs low | RR: 1.03 (0.54, 1.52) | 42 | 0.06 | Age, sex, alcohol intake, HRT |
| Coffee | Li et al. (2015) | Adults (> 30 y) | 9 | 4-30 | 205930 | 5408 | FFQ | Radiographic reports, hospital registers, self-reported, medical records | High vs low | RR: 1.13 (0.86, 1.48) | 79* | 0.181 | Sex |
| Coffee | Li and Xu (2013) | Adults (> 34 y) | 4 | 6-30 | 138009 | 857 | FFQ | Hospital registers, medical records, telephone, self-report | Per cup increase/day | OR: 1.00 (0.96, 1.03) | N/A | 0.891 | Age, sex |
| Coffee | Sheng et al. (2013) | Adults | 6 | 6-30 | 184947 | 5888 | FFQ | Medical records, self-reported, hospital registers | High vs low | RR: 1.09 (0.60, 1.58) | 68* | < 0.01 | Sex |
| Total alcohol | Zhang et al. (2014) | Adults (> 20 y) | 18 | 3-30 | 3730424 | 26168 | Self-administered FFQ | Self-reported, radiographic report, | Any vs none | RR: 1.03 (0.91, 1.15) | 72* | > 0.1 | Age, sex |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 7 | | 3363045 | 22072 | | medical records | Light (0.01 - 12.5 g/d) vs none | RR: 0.88 (0.83, 0.92) | 20 | > 0.1 | Age, sex |
| | | | 7 | | 3337647 | 21704 | | | Moderate (12.6 - 49.9 g/d) vs none | RR: 1.00 (0.85, 1.14) | 56* | > 0.1 | Age, sex |
| | | | 3 | | 3363253 | 21637 | | | Heavy (> 50 g/d) vs none | RR: 1.71 (1.41, 2.01) | 0 | > 0.1 | Age, sex, smoking, BMI |
| Wine | Zhang et al. (2014) | Adults (> 20 y) | 4 | 3-14 | 237789 | 2574 | | | Any vs no alcohol | RR: 0.81 (0.71, 0.92) | 0 | > 0.1 | Age, sex |
| Beer | Zhang et al. (2014) | Adults (> 20 y) | 4 | 3-14 | 237789 | 2574 | | | Any vs no alcohol | RR: 1.13 (0.69, 1.56) | 79* | > 0.1 | Age, sex |
| Liquor | Zhang et al. (2014) | Adults (> 20 y) | 4 | 3-14 | 237789 | 2574 | | | Any vs no alcohol | RR: 0.94 (0.75, 1.12) | 33 | > 0.1 | Age, sex |
| **Macronutrients** | | | | | | | | | | | | | |
| Protein | Darling et al. (2009) | Adults (35 – 74 y) | 3 | 1-22 | 120829 | N/A | FFQ, National survey data | Self-reported, medical records | High vs low | RR: 0.75 (0.47, 1.20) | 20 | N/A | Age, sex, weight, BMI, physical activity, menopausal status, smoking, HRT, alcohol, calcium intake |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Protein | Groenendijk et al. (2019) | Older men and women (> 65 y) | 4 | 6-32 | 152779 | N/A | FFQ, biomarkers | N/A | High vs low | RR: 0.89 (0.84, 0.94) | 0 | N/A | Sex |
| Protein | Wu et al. (2015) | Adults (> 18 y) | 6 | N/A | 270011 | 3787 | N/A | N/A | High vs low | RR: 0.89 (0.82, 0.97) | 0 | 0.054 | Sex |
| Animal protein | Wu et al. (2015) | Adults (> 18 y) | 4 | N/A | 161393 | 535 | N/A | N/A | High vs low | RR: 1.04 (0.70, 1.54) | 52 | N/A | Age, sex, smoking, physical activity |
| Animal protein | Darling et al. (2009) | Middle-aged or older adults | 3 | 1-22 | 157737 | N/A | FFQ | Self-reported, medical records | High vs low | RR: 0.83 (0.64, 1.30) | 48 | N/A | Age, sex, weight, BMI, physical activity, menopausal status, smoking, HRT use, alcohol, calcium intake |
| Vegetable protein | Wu et al. (2015) | Adults (> 18 y) | 3 | N/A | 121606 | 322 | N/A | N/A | High vs low | RR: 1.00 (0.53, 1.91) | 57 | N/A | Age, sex, smoking, physical activity |
| Vegetable protein | Darling et al. (2009) | Women (35 – 69 y) | 2 | 1-12 | 117950 | N/A | FFQ | Self-reported, medical records | High vs low | RR: 1.21 (0.82, 1.79) | 2 | N/A | Age, sex, weight, BMI, physical activity, menopausal status, smoking, HRT, alcohol, calcium intake |
| **Micronutrient** | | | | | | | | | | | | | |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dietary calcium | Bischoff-Ferrari et al. (2007) | Middle-aged or older women | 4 | 3-18 | 83198 | 854 | 24 h recall, FFQ | N/A | Per 300 mg increase/day | RR: 1.01 (0.96, 1.06) | N/A | N/A | Sex |
| Dietary calcium | Cumming and Nevitt (1997) | Postmenopausal women (> 50 y) | 5 | 4-15 | 28511 | 915 | 24 h recall, FFQ | N/A | Per 300 mg increase/day | OR: 0.96 (0.91, 1.02) | N/A | N/A | Sex, measurement error |
| Dietary calcium | Wang et al. (2015) | Adults (> 34 y) | 8 | 7-18 | 267762 | 2435 | 24 h recall, FFQ | Postcard or telephone interview, medical record | High vs low | RR: 0.97 (0.88, 1.06) | 0 | 0.06 | Age, sex |
| Dietary calcium | Xu et al. (2007) | Women (> 35 y) | 5 | 5-15 | 41645 | 941 | 24 h recall, FFQ | N/A | High vs low | RR: 0.96 (0.89, 1.04) | N/A | 0.54 | Age, sex |
| Dietary vitamin C | Malmir et al. (2018b) | Adults (39-80 y) | 3 | 13-15 | 6282 | 584 | 24 h recall, FFQ, 7-day food record | Interview, hospital record, medical report, or N/A | High vs low | RR: 0.92 (0.59, 1.44) | 55 | 0.83 | Age, sex |
| Dietary vitamin C | Zeng et al. (2020) | Adults (39-80 y) | 2 | 13-15 | N/A | N/A | 7-day food record or FFQ | N/A | High vs low | RR: 0.92 (0.59, 1.44) | 55 | N/A | Age, sex, total energy intake, HRT, BMI |
| Dietary vitamin A | Wu et al. (2014) | Adults (20-95 y) | 3 | N/A | 182787 | 1716 | N/A | N/A | High vs low | RR: 1.29 (1.07, 1.57) | 0 | 0.312 | Age, sex, total energy intake, alcohol, BMI |
| Dietary vitamin A | Zhang et al. (2017) | Adults (> 34 y) | 3 | 12-18 | 200716 | 1716 | FFQ | Self-reported, medical records | High vs low | RR: 1.29 (1.06, 1.57) | 0 | 0.85 | Age, sex, BMI, alcohol |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dietary carotenoids | Xu et al. (2017) | Adults | 2 | 10-17 | 62470 | 1730 | FFQ | Medical records, radiographic reports | High vs low | OR: 0.72 (0.51, 1.01) | 59 | 0.16 | Age, sex, BMI, total energy intake, smoking, physical activity, calcium intake |
| Dietary retinol | Wu et al. (2014) | Adults (20-95 y) | 4 | N/A | 183907 | 1963 | N/A | N/A | High vs low | RR: 1.40 (1.03, 1.91) | 64* | 0.338 | Total energy intake, sex, BMI |
| Dietary retinol | Zhang et al. (2017) | Adults (> 34 y) | 4 | 3-18 | 201836 | 1963 | FFQ | Self-reported, medical records | High vs low | RR: 1.40 (1.02, 1.91) | 65* | 0.17 | Sex, BMI, medicine use |
| Dietary a-carotene | Xu et al. (2017) | Adults (> 56 y) | 2 | 10-17 | 62470 | 1730 | FFQ | Medical records, radiographic reports | High vs low | OR: 0.77 (0.55, 1.08) | 64* | 0.36 | Age, sex, BMI, total energy intake, smoking, physical activity, calcium |
| Dietary b-carotene | Wu et al. (2014) | Adults (20-95 y) | 3 | N/A | 136523 | 2333 | N/A | N/A | High vs low | RR: 0.82 (0.59, 1.14) | 78* | 0.406 | Age, sex, BMI, smoking, physical activity, calcium, HRT |
| Dietary b-carotene | Xu et al. (2017) | Adults (mean > 56 y) | 3 | 10-17 | 134807 | 2333 | FFQ | Medical records, radiographic reports | High vs low | OR: 0.84 (0.62, 1.14) | N/A | 0.1 | Age, sex, BMI, smoking, physical activity, calcium |
| Dietary b-carotene | Zhang et al. (2017) | Adults (> 34 y) | 2 | 17-18 | 135594 | 2233 | FFQ | Self-reported, medical records | High vs low | RR: 0.91 (0.64, 1.31) | 82* | 0.8 | Age, sex, BMI, calcium intake, smoking, physical activity, HRT |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dietary b-cryptoxanthin | Xu et al. (2017) | Adults (mean > 56 y) | 2 | 10-17 | 62470 | 1730 | FFQ | Medical records, radiographic reports | High vs low | OR: 1.11 (0.97, 1.28) | 0 | 0.49 | Age, sex, BMI, total energy intake, smoking, physical activity, calcium |
| Dietary lycopene | Xu et al. (2017) | Adults (mean > 56 y) | 2 | 10-17 | 62470 | 1730 | FFQ | Medical records, radiographic reports | High vs low | OR: 0.84 (0.69, 1.01) | 8 | 0.14 | Age, sex, BMI, total energy intake, smoking, physical activity, calcium |
| Dietary lutein/zeaxanthin | Xu et al. (2017) | Adults (mean > 56 y) | 2 | 10-17 | 62470 | 1730 | FFQ | Medical records, radiographic reports | High vs low | OR: 0.94 (0.79, 1.11) | 8 | 0.6 | Age, sex, BMI, total energy intake, smoking, physical activity, calcium |
| Dietary ALA | Sadheghi et al. (2019) | Adults (> 30 y) | 3 | 8-24 | 260106 | 3316 | FFQ (self-reported or interview) | Blinded clinician using medical records, self-reported, interview | High vs low | RR: 1.01 (0.90, 1.13) | 71* | N/A | Sex, total energy intake, BMI |
| Dietary EPA + DHA | Sadheghi et al. (2019) | Adults (> 30 y) | 4 | 8-24 | 265151 | 3821 | FFQ (self-reported or interview) | Blinded clinician using medical records, self-reported, interview | High vs low | RR: 0.91 (0.81, 1.03) | 0 | N/A | Sex, total energy intake, BMI |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Antioxidant vitamin intake | Zhou et al. (2020) | Adults (28-95 y) | 9 | 4-19 | 329531 | 9052 | N/A | N/A | High vs low | RR: 0.87 (0.69, 1.08) | 89* | 0.447 | Age, sex, BMI |

N/A = not applicable or available; * = significant heterogeneity; RR = relative risk; OR = odds ratio; HR = hazard ratio; 95% CI = 95% confidence interval. For milk and coffee consumption, $I^2$ and Egger's p-value were unobtainable from dose-response meta-analyses, thus values from high vs low comparisons are presented as an estimate where available. For antioxidant vitamin intake, Egger's p value was only available for total fracture. Adjustment for confounders includes only those factors that were adjusted for in all of a meta-analyses' included cohort studies. Where meta-analyses included only single-sex studies or studies that adjusted for sex and single-sex studies, sex was considered fully adjusted for. BMI = body mass index; HRT = hormone replacement therapy, including oestrogen use. y = years.

**Table A6: Source of funding for eligible systematic reviews.**

| **Author (year)** | **Source of Funding** |
|---|---|
| Bian et al. (2018) | National Natural Science Foundation of China |
| Bischoff-Ferrari et al. (2007) | Medical Foundation (Charles H Farnsworth Trust; US Trust Company; Trustee and the Charles A King Trust; Fleet National Bank) and the International Foundation for the Promotion of Nutrition Research and Nutrition Education (ISFE); the Swiss Foundation for Nutrition Research (SFEFS), and the Swiss National Foundation (SNF Professorship grant) |
| Bischoff-Ferrari et al. (2011) | Vontobel Foundation, The Baugarten Foundation, a Swiss National Foundations Professorship Grant (PP00B-114864), and the Velux Foundation. |
| Brondani et al. (2019) | The Coordination of Higher-Level Personnel (CAPES), Brazil; The Federal University of Santa Maria (UFSM) |
| Cumming and Nevitt (1997) | N/A |
| Darling et al. (2009) | None |
| Groenendijk et al. (2019) | Jaap Schouten Foundation |
| Hidayat et al. (2020) | National Key R&D Program of China (No. 2017YFC1310700, No. 2017YFC1310701) and the Suzhou Science and Technology Bureau (No. SYS201741). |

| | |
|---|---|
| Li and Xu (2013) | National Natural Science Foundation of China and the Universities Natural Science Foundation of Jiangsu Province |
| Li et al. (2015) | None |
| Luo et al. (2016) | N/A |
| Malmir et al. (2018a) | Joint collaboration of Endocrinology and Metabolism Molecular-Cellular Sciences Institute, Tehran University of Medical Sciences, and School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran, and the Iran National Science Foundation (INSF) |
| Malmir et al. (2018b) | N/A |
| Malmir et al. (2019) | N/A |
| Matia-Martin et al. (2019) | Interprofessional Dairy Organization (INLAC), Spain, GenObIA-CM with reference (S2017/BMD-3773), the Comunidad de Madrid and cofinanced with Structural Funds of the European Union; from Instituto de Salud Carlos III supported with funds from the Spanish Ministry of Health and FEDER (PI17/1732); and from Fundación de Investigación en Nutrición y Metabolismo (FINUMET). |
| Ong et al. (2020) | None |
| Panahande et al. (2018) | Students' Scientific Research Center, Tehran University of Medical Sciences, Tehran, Iran |
| Sadeghi et al. (2019) | Not reported |
| Sheng et al. (2013) | Fund for Key National Basic Research Program of China (grant 2012CB619101), Major Basic Research of Science and Technology Commission of Shanghai Municipality (grant no. 11DJ1400303), Key Disciplines of Shanghai Municipal Education Commission (grant no. J50206), Scientific Research from the National Natural Science Foundation for the Youth of China (grant no. 81201364), and Innovative Research from Shanghai Municipal Education Commission (grant no. 13YZ031) |
| Wang et al. (2015) | National Natural Science Foundation of China |
| Wu et al. (2014) | National Natural Science Foundation of China (81372014, 81371988); Department of Health of Zhejiang Province, Backbone of Talent Project (2012RCB037); and Department of Science and Technology of Wenzhou, Wenzhou Science and Technology Project (Y20120073) |
| Wu et al. (2015) | National Natural Science Foundation of China (81372014, 81371988); and Xinmiao talent plan of Zhejiang Province (2014R413053) |

| | |
|---|---|
| Xu et al. (2017) | National Natural Science Foundation of China [No_81372980, 81673150, 81001185] and the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD) |
| Xu et al. (2007) | N/A |
| Zeng et al. (2020) | China Postdoctoral Science Foundation (No. 2018M633036), the Medical Science Research Foundation of Guangdong Province (No. B2019091), the National Natural Science Foundation of China (No. 81873314), the Project of Guangdong Provincial Department of Finance (Nos. [2014]157, [2018]8), Key scientific research platforms and research projects of universities in Guangdong Province (No. 2018KQNCX041), and the Science and Technology Research Project of Guangdong Provincial Hospital of Chinese Medicine (Nos. YN2019ML08, YK2013B2N19, and YN2015MS15) |
| Zhang et al. (2014) | Fund for Key National Basic Research Program of China (grant no. 2012CB619101 and 81401852), Natural Science Foundation of Science and Technology Commission of Shanghai Municipality (14ZR1424000), Major Basic Research of Science and Technology Commission of Shanghai Municipality (grant no. 11DJ1400303) |
| Zhang et al. (2017) | National Natural Science Foundation of China (Grant No. 81402668) |
| Zhou et al. (2020) | Jiangsu University Clinical Medicine Science and Technology Development Fund Project |

N/A = not applicable or available.

**Table A7: Methodological quality assessments of eligible systematic reviews using the AMSTAR-2 tool.**

| | **Domain** | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study** | **1** | **2[c]** | **3** | **4[c]** | **5** | **6** | **7[c]** | **8** | **9[c]** | **10** | **11[c]** | **12** | **13[c]** | **14** | **15[c]** | **16** | **Score** |
| Bian et al. (2018) | 0 | 0 | 0 | 0.5 | 1 | 1 | 0 | 1 | 0.5 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | Critically low |
| Bischoff-Ferrari et al. (2007) | 0 | 0 | 1 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | Critically low |
| Bischoff-Ferrari et al. (2010) | 0 | 0 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 1 | Critically low |
| Brondani et al. (2019) | 1 | 1 | 1 | 0.5 | 1 | 1 | 0 | 0.5 | 0.5 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | Critically low |

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cumming and Nevitt (1997) | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | Critically low |
| Darling et al. (2009) | 0 | 0 | 0 | 0.5 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 1 | Critically low |
| Groenendijk et al. (2019) | 1 | 0 | 0 | 0.5 | 1 | 1 | 0 | 0 | 0.5 | 0 | 0 | 0 | 1 | 1 | 0 | 1 | Critically low |
| Hidayat et al. (2020) | 1 | 0 | 1 | 0.5 | 1 | 1 | 1 | 1 | 0.5 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | Low |
| Li et al. (2015) | 0 | 0 | 1 | 0 | 1 | 1 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 1 | Critically low |
| Li and Xu (2013) | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 1 | 1 | 1 | 1 | Critically low |
| Luo et al. (2016) | 0 | 0 | 0 | 0.5 | 1 | 1 | 1 | 0.5 | 0.5[b] | 0 | 0 | 0 | 1 | 1 | 0 | 1 | Critically low |
| Malmir et al. (2020) | 1 | 0 | 0 | 0.5 | 1 | 0 | 0 | 1 | 0.5 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | Critically low |
| Malmir et al. (2018a) | 1 | 0 | 0 | 0.5 | 1 | 0 | 1 | 1 | 0.5[a] | 0 | 1 | 0 | 1 | 1 | 1 | 1 | Critically low |
| Malmir et al. (2018b) | 0 | 1 | 0 | 0.5 | 1 | 0 | 1 | 1 | 0.5[a] | 0 | 0 | 0 | 1 | 1 | 1 | 1 | Critically low |
| Matia-Martin et al. (2019) | 0 | 1 | 0 | 0.5 | 1 | 1 | 0 | 1 | 0.5 | 0 | 1 | 0 | 0 | 0 | 1 | 1 | Critically low |
| Ong et al. (2019) | 1 | 1 | 0 | 0.5 | 1 | 1 | 0 | 1 | 0.5 | 0 | 0 | 0 | 1 | 1 | 0 | 1 | Critically low |
| Panahande et al. (2018) | 1 | 0 | 0 | 0.5 | 1 | 1 | 0 | 1 | 0.5[a] | 0 | 1 | 0 | 1 | 0 | 1 | 1 | Critically low |
| Sadeghi et al. (2019) | 0 | 0 | 0 | 0.5 | 1 | 1 | 0 | 1 | 0.5[a] | 0 | 0 | 0 | 1 | 1 | 1 | 1 | Critically low |
| Sheng et al. (2013) | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | Critically low |
| Wang et al. (2015) | 0 | 0 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | Critically low |
| Wu et al. (2014) | 0 | 0 | 0 | 0.5 | 1 | 1 | 0 | 0 | 0.5 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | Critically low |
| Wu et al. (2015) | 0 | 0 | 0 | 0.5 | 1 | 1 | 0 | 0 | 0.5 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | Critically low |
| Xu et al. (2017) | 0 | 0 | 0 | 0.5 | 0 | 1 | 0 | 1 | 0.5[a] | 0 | 0 | 0 | 1 | 0 | 1 | 1 | Critically low |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Xu et al. (2007) | 1 | 0 | 1 | 0 | 1 | 1 | 0 | 0 | 0.5 | 0 | 1 | 1 | 1 | 0 | 1 | 0 | Critically low |
| Zeng et al. (2020) | 0 | 0 | 0 | 0.5 | 1 | 1 | 0 | 0 | 0.5[a] | 0 | 0 | 0 | 1 | 1 | 1 | 1 | Critically low |
| Zhang et al. (2015) | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 1 | 1 | 1 | 1 | Critically low |
| Zhang et al. (2017) | 0 | 0 | 0 | 0.5 | 1 | 1 | 0 | 1 | 0.5[a] | 0 | 0 | 0 | 1 | 0 | 1 | 1 | Critically low |
| Zhou et al. (2020) | 0 | 0 | 1 | 0.5 | 1 | 1 | 0 | 0 | 0.5[a] | 0 | 0 | 0 | 1 | 0 | 1 | 1 | Critically low |

[a] = 0.5 was considered a critical flaw because risk of bias assessments per domain were not presented in the review. [c] = Critical domains. For item 11, dose-response meta-analyses or categorical comparisons using consistent thresholds were awarded a score of 1, whereas categorical comparisons without consistent thresholds (or with unclear threshold definitions) for defining exposure categories scored 0.

**Table A8: Quality of evidence assessments per association from the highest quality meta-analysis per exposure using the GRADE tool.**

| Exposure | Author (year) | Comparison | Number of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Overall quality |
|---|---|---|---|---|---|---|---|---|---|---|
| **Dietary patterns** | | | | | | | | | | |
| MD | Malmir et al. (2018a) | Increase of 1 in adherence score | 4 | Prospective cohort | Serious[c] | Not serious | Not serious | Not serious | None | ⊕◯◯◯ |
| AHEI | Panahande et al. (2018) | High vs low | 4 | Prospective cohort | Serious[c] | Not serious | Not serious | Not serious | None | ⊕◯◯◯ |
| **Food groups** | | | | | | | | | | |
| Dairy | Matia-martin et al. (2019) | Per 'increment' increase | 5 | Prospective cohort | Serious[ag] | Very serious[d] | Not serious | Not serious | None | ⊕◯◯◯ |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Milk | Hidayat et al. (2020) | Increase of 1 glass/day | 7 | Prospective cohort | Serious[g] | Serious[b] | Not serious | Not serious | None | ⊕◯◯◯ |
| Yogurt | Hidayat et al. (2020) | High vs low | 4 | Prospective cohort | Serious[g] | Not serious | Not serious | Not serious | None | ⊕◯◯◯ |
| Cheese | Hidayat et al. (2020) | High vs low | 4 | Prospective cohort | Serious[g] | Very serious[d] | Not serious | Serious[e] | None | ⊕◯◯◯ |
| Fruits | Luo et al. (2016) | High vs low | 5 | Prospective cohort | Serious[c] | Serious[b] | Not serious | Serious[e] | None | ⊕◯◯◯ |
| Vegetables | Luo et al. (2016) | High vs low | 5 | Prospective cohort | Serious[c] | Serious[b] | Not serious | Not serious | None | ⊕◯◯◯ |
| Fruits and vegetables | Brondani et al. (2019) | High vs low | 5 | Prospective cohort | Not serious | Not serious* | Not serious | Not serious | None | ⊕⊕◯◯ |
| Tea | Sheng et al. (2013) | High vs low | 3 | Prospective cohort | Very serious[f] | Not serious | Not serious | Serious[e] | None | ⊕◯◯◯ |
| Coffee | Li and Xu (2013) | Per cup increase/day | 4 | Prospective cohort | Very serious[f] | Serious[b] | Not serious | Not serious | None | ⊕◯◯◯ |
| Alcohol | Zhang et al. (2014) | Any vs none | 18 | Prospective cohort | Very serious[f] | Very serious[d] | Not serious | Not serious | None | ⊕◯◯◯ |
| | | Light vs none | 7 | Prospective cohort | Very serious[f] | Not serious | Not serious | Not serious | None | ⊕◯◯◯ |
| | | Moderate vs none | 7 | Prospective cohort | Very serious[f] | Serious[b] | Not serious | Not serious | None | ⊕◯◯◯ |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Heavy vs none | 3 | Prospective cohort | Very serious[f] | Not serious | Not serious | Not serious | None | ⊕◯◯◯ |
| Wine | Zhang et al. (2014) | Any vs no alcohol | 4 | Prospective cohort | Very serious[f] | Not serious | Not serious | Not serious | None | ⊕◯◯◯ |
| Beer | Zhang et al. (2014) | Any vs no alcohol | 4 | Prospective cohort | Very serious[f] | Serious[b] | Not serious | Serious[e] | None | ⊕◯◯◯ |
| Liquor | Zhang et al. (2014) | Any vs no alcohol | 4 | Prospective cohort | Very serious[f] | Not serious | Not serious | Serious[e] | None | ⊕◯◯◯ |
| **Macronutrients** | | | | | | | | | | |
| Dietary protein | Wu et al. (2015) | High vs low | 6 | Prospective cohort | Serious[a] | Not serious | Not serious | Not serious | None | ⊕◯◯◯ |
| Animal protien | Wu et al. (2015) | High vs low | 4 | Prospective cohort | Serious[a] | Not serious* | Not serious | Serious[e] | None | ⊕◯◯◯ |
| Vegetable protein | Wu et al. (2015) | High vs low | 3 | Prospective cohort | Serious[a] | Not serious* | Not serious | Serious[e] | None | ⊕◯◯◯ |
| **Micronutrients** | | | | | | | | | | |
| Dietary vitamin C | Malmir et al. (2018b) | High vs low | 3 | Prospective cohort | Serious[c] | Not serious | Not serious | Serious[e] | None | ⊕◯◯◯ |
| Dietary vitamin A | Zhang et al. (2017) | High vs low | 3 | Prospective cohort | Serious[c] | Not serious | Not serious | Not serious | None | ⊕◯◯◯ |
| Dietary carotenoids | Xu et al. (2017) | High vs low | 2 | Prospective cohort | Serious[c] | Not serious | Not serious | Serious[e] | None | ⊕◯◯◯ |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Dietary ALA | Sadeghi et al. (2019) | High vs low | 3 | Prospective cohort | Serious[c] | Serious[b] | Not serious | Not serious | None | ⊕◯◯◯ |
| Dietary EPA + DHA | Sadeghi et al. (2019) | High vs low | 4 | Prospective cohort | Serious[c] | Not serious | Not serious | Not serious | None | ⊕◯◯◯ |
| Dietary calcium | Bischoff-Ferrari et al. (2007) | Increase of 300 mg/d | 4 | Prospective cohort | Very serious[f] | Not serious | Not serious | Not serious | None | ⊕◯◯◯ |
| Dietary retinol | Zhang et al. (2017) | High vs low | 4 | Prospective cohort | Serious[c] | Serious[b] | Not serious | Not serious | None | ⊕◯◯◯ |
| Dietary a-carotene | Xu et al. (2017) | High vs low | 2 | Prospective cohort | Serious[c] | Serious[b] | Not serious | Serious[e] | None | ⊕◯◯◯ |
| Dietary b-carotene | Zhang et al. (2017) | High vs low | 2 | Prospective cohort | Serious[c] | Serious[b] | Not serious | Serious[e] | None | ⊕◯◯◯ |
| Dietary b-cryptoxanthin | Xu et al. (2017) | High vs low | 2 | Prospective cohort | Serious[c] | Not serious | Not serious | Serious[e] | None | ⊕◯◯◯ |
| Dietary lycopene | Xu et al. (2017) | High vs low | 2 | Prospective cohort | Serious[c] | Not serious | Not serious | Serious[e] | None | ⊕◯◯◯ |
| Dietary lutein/zeaxanthin | Xu et al. (2017) | High vs low | 2 | Prospective cohort | Serious[c] | Not serious | Not serious | Not serious | None | ⊕◯◯◯ |
| Antioxidant vitamins | Zhou et al. (2020) | High vs low | 9 | Prospective cohort | Serious[c] | Serious[b] | Not serious | Serious[e] | None | ⊕◯◯◯ |

a: rated down by one level due to possible bias from the method of ascertainment of exposure and outcome data in primary studies.
b: rated down by one level due to high, significant unexplained heterogeneity ($I^2$>50%, $p < 0.05$) or different direction of effects in different studies, with minimal or no overlap of confidence intervals.
c: rated down by one level because the risk of bias for each domain was not reported, thus remains unclear.

d: rated down by two levels due to high significant heterogeneity and minimal overlap of confidence intervals between studies, with different directions of effect.
e: rated down by one level because the confidence intervals of the meta-analytic effect overlapped 1 and failed to exclude the possibility of an appreciable benefit or harm (relative risk reduction or increase of 25% was used as a threshold as recommended in the GRADE handbook).
f: rated down by two levels because no risk of bias assessment was reported.
g: rated down by one level due to possible bias from inadequate follow-up.
*: near-significant p value for heterogeneity ($p < 0.1$).

# Appendix B Chapter 3 supplementary material

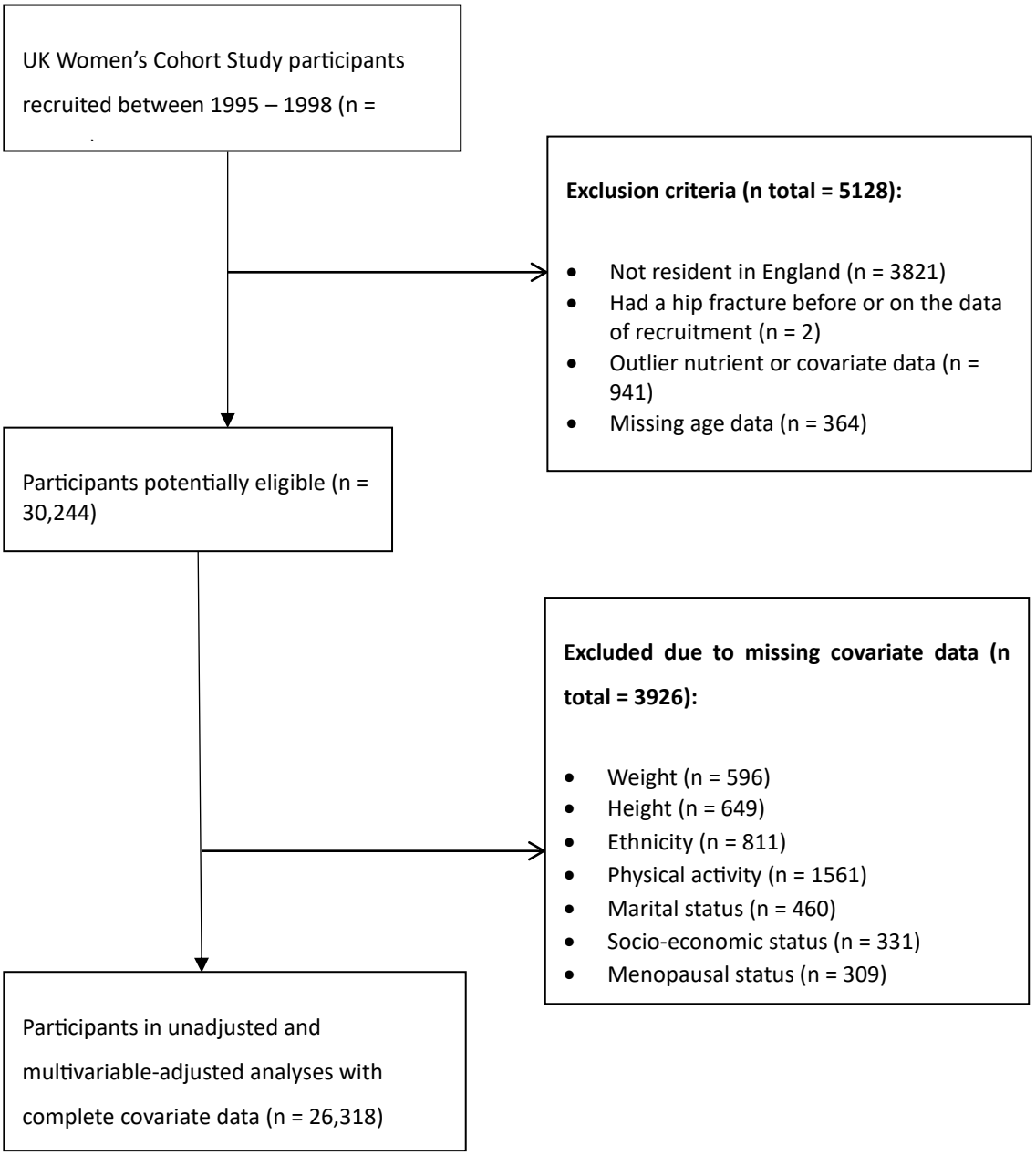



**Figure B1: Flow chart of UK Women's Cohort Study participants.**

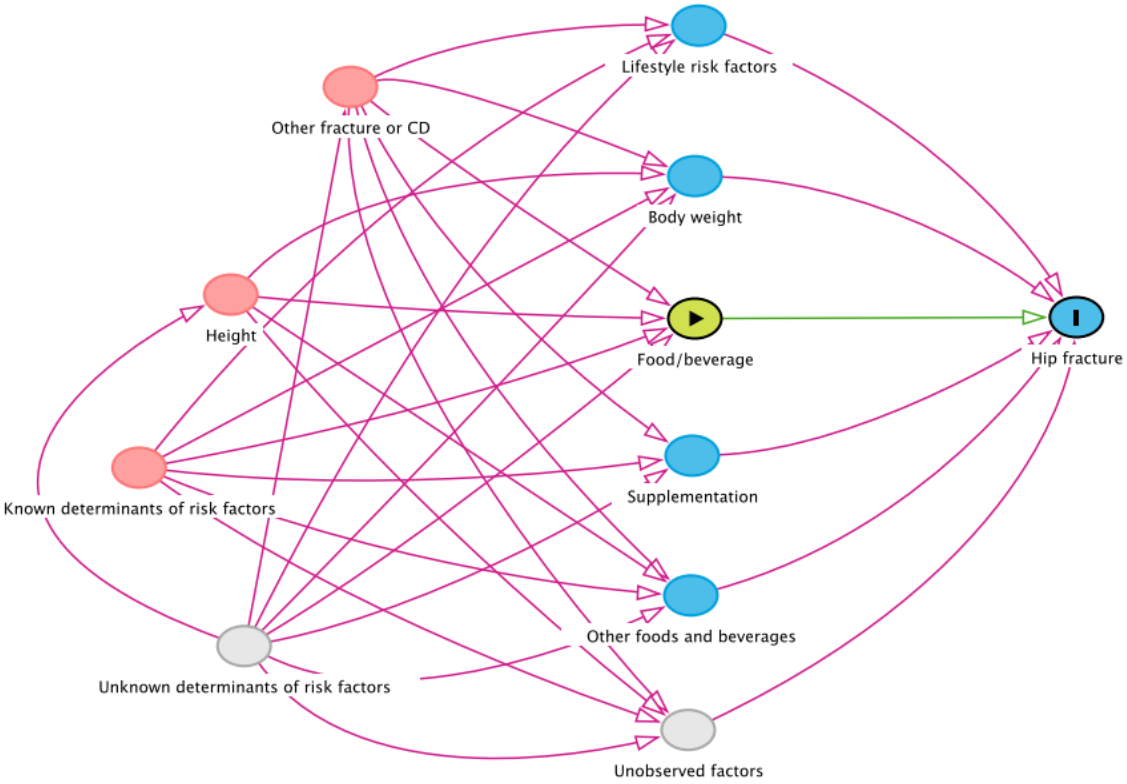



**Figure B2: Directed Acyclic Graph showing the relationship between intake of foods and beverages, hip fracture incidence, and related factors.** The exposure is depicted by the green oval and the outcome (hip fracture incidence) is depicted by the blue node with a black vertical line. Variables represented as pink nodes are ancestors of the exposure and outcome; variables represented as blue nodes are ancestors of the outcome only (competing exposures); and variables represented as grey nodes are unknown or unmeasured. The green line represents the causal link of interest. Pink lines are biasing paths. Known determinants of risk factors include age, ethnicity, education, socioeconomic status, marital status, menopausal status, and number of children. Lifestyle risk factors include physical activity, smoking, and alcohol intake. Supplementation refers to use of any nutritional supplements. CD: chronic disease, defined as prevalence of cardiovascular disease, cancer, diabetes.

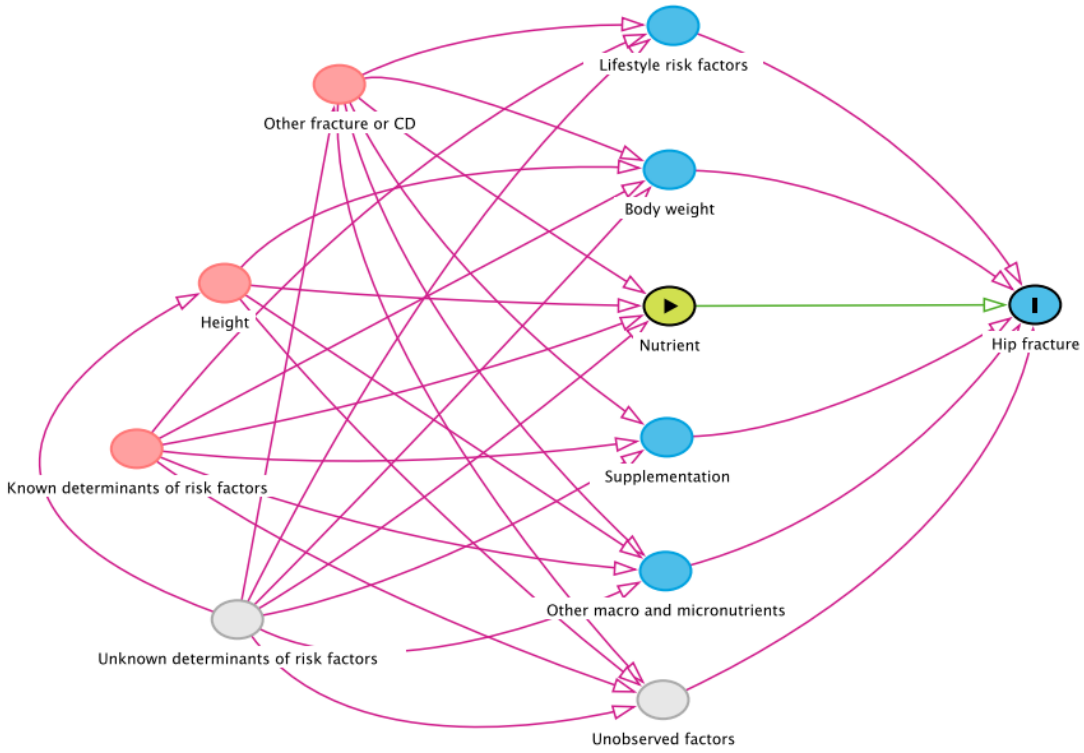



**Figure B3: Directed Acyclic Graph showing the relationship between intake of nutrients, hip fracture incidence, and related factors.** The exposure is depicted by the green oval and the outcome (hip fracture incidence) is depicted by the blue node with a black vertical line. Variables represented as pink nodes are ancestors of the exposure and outcome; variables represented as blue nodes are ancestors of the outcome only (competing exposures); and variables represented as grey nodes are unknown or unmeasured. The green line represents the causal link of interest. Pink lines are biasing paths. Known determinants of risk factors include age, ethnicity, education, socioeconomic status, marital status, menopausal status, and number of children. Lifestyle risk factors include physical activity, smoking, and alcohol intake. Supplementation refers to use of any nutritional supplements. CD: chronic disease, defined as prevalence of cardiovascular disease, cancer, diabetes.

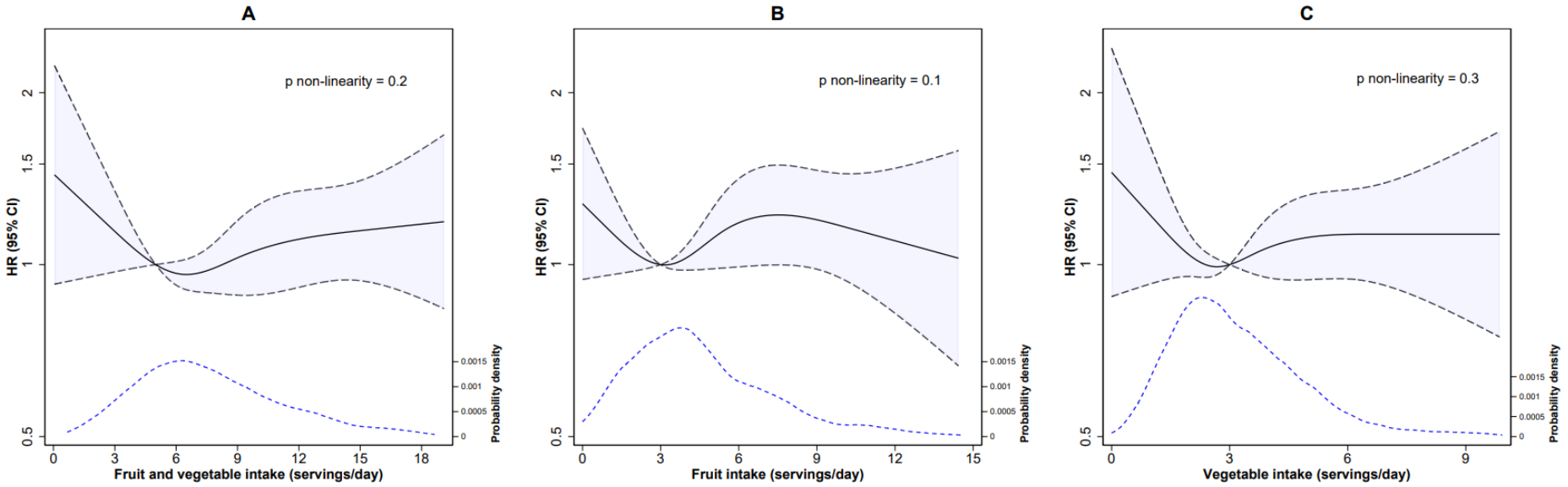



**Figure B4: Risk of hip fracture as a function of fruit and vegetable intake (A), fruit intake (B), or vegetable intake (C).** Dashed lines represent 95% CI's. Blue lines represent kernel density plots showing the distribution of daily fruit and vegetable intake in the cohort. Cox models were controlled for age, and were adjusted for ethnicity, socio-economic status, marital status, menopausal status, number of children, prevalence of cardiovascular disease, cancer, or diabetes, physical activity, smoking status, alcohol intake, height, body weight, use of any nutritional supplements, and intake of other major foods and beverages, and were mutually adjusted for fruit or vegetable intake as appropriate. HR (95% CI): adjusted hazard ratio, 95% confidence intervals.

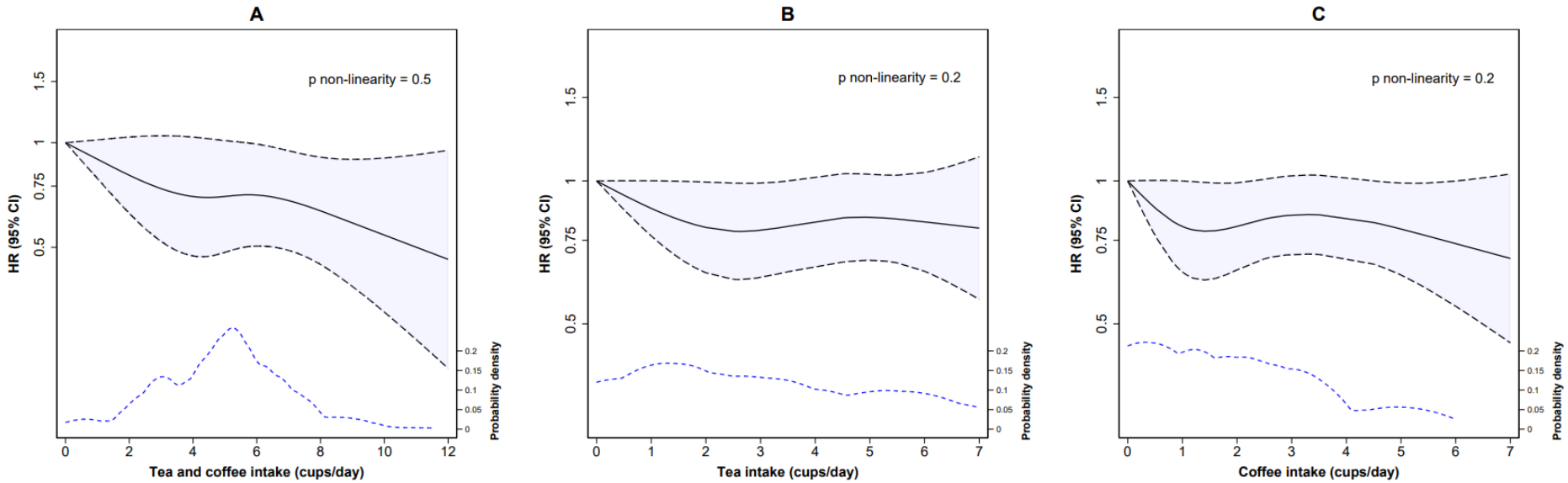



**Figure B5: Risk of hip fracture as a function of tea and coffee intake (A), tea intake (B), or coffee intake (C).** Dashed lines represent 95% CI's. Blue lines represent kernel density plots showing the distribution of daily tea and coffee intake in the cohort. Cox models were adjusted for ethnicity, socio-economic status, marital status, menopausal status, number of children, prevalence of cardiovascular disease, cancer, or diabetes, physical activity, smoking status, alcohol intake, height, body weight, use of any nutritional supplements, and intake of other major foods and beverages, and were mutually adjusted for tea or coffee intake as appropriate. HR (95% CI): adjusted hazard ratio, 95% confidence intervals.

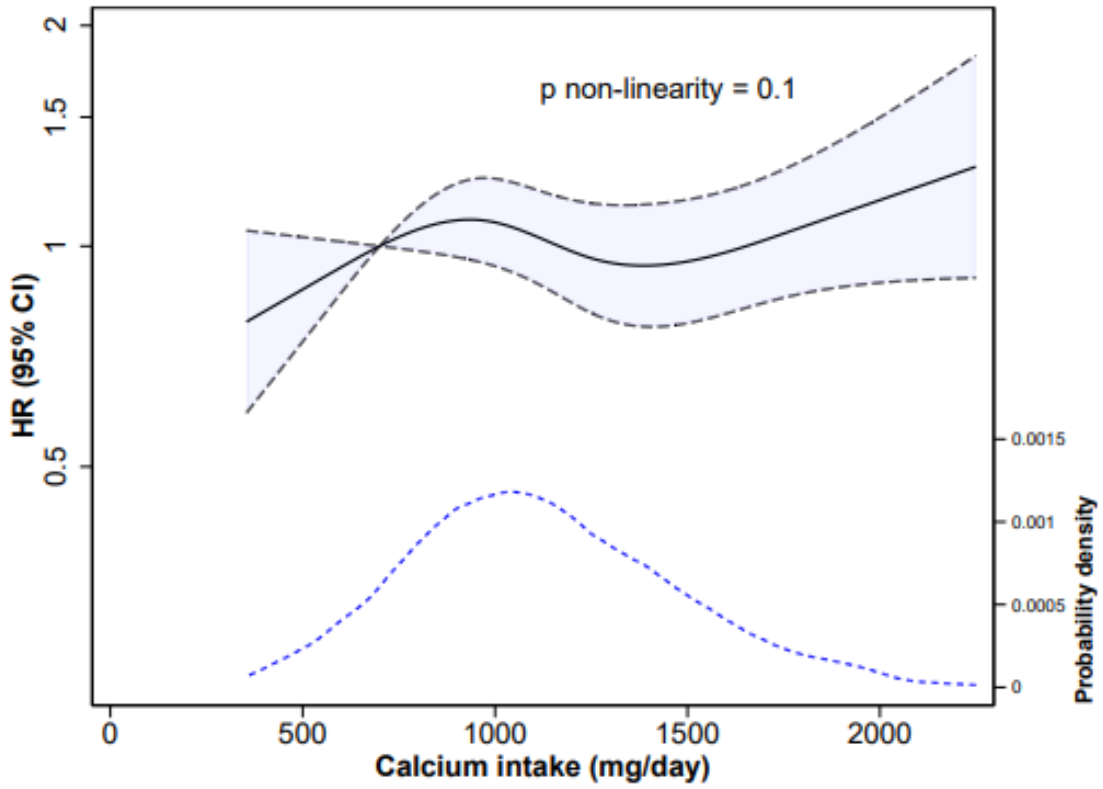



**Figure B6: Risk of hip fracture as a function of calcium intake.** Dashed lines represent 95% CI's. The blue line represents a kernel density plot showing the distribution of daily calcium intake in the cohort. Cox models were adjusted for ethnicity, socio-economic status, marital status, menopausal status, number of children, prevalence of cardiovascular disease, cancer, or diabetes, physical activity, smoking status, alcohol intake, height, body weight, use of any nutritional supplements, and dietary intake of protein, complex carbohydrates, fibre, sugar, saturated fat, monounsaturated fatty acids, polyunsaturated fatty acids, and vitamin D. HR (95% CI): adjusted hazard ratio, 95% confidence intervals.

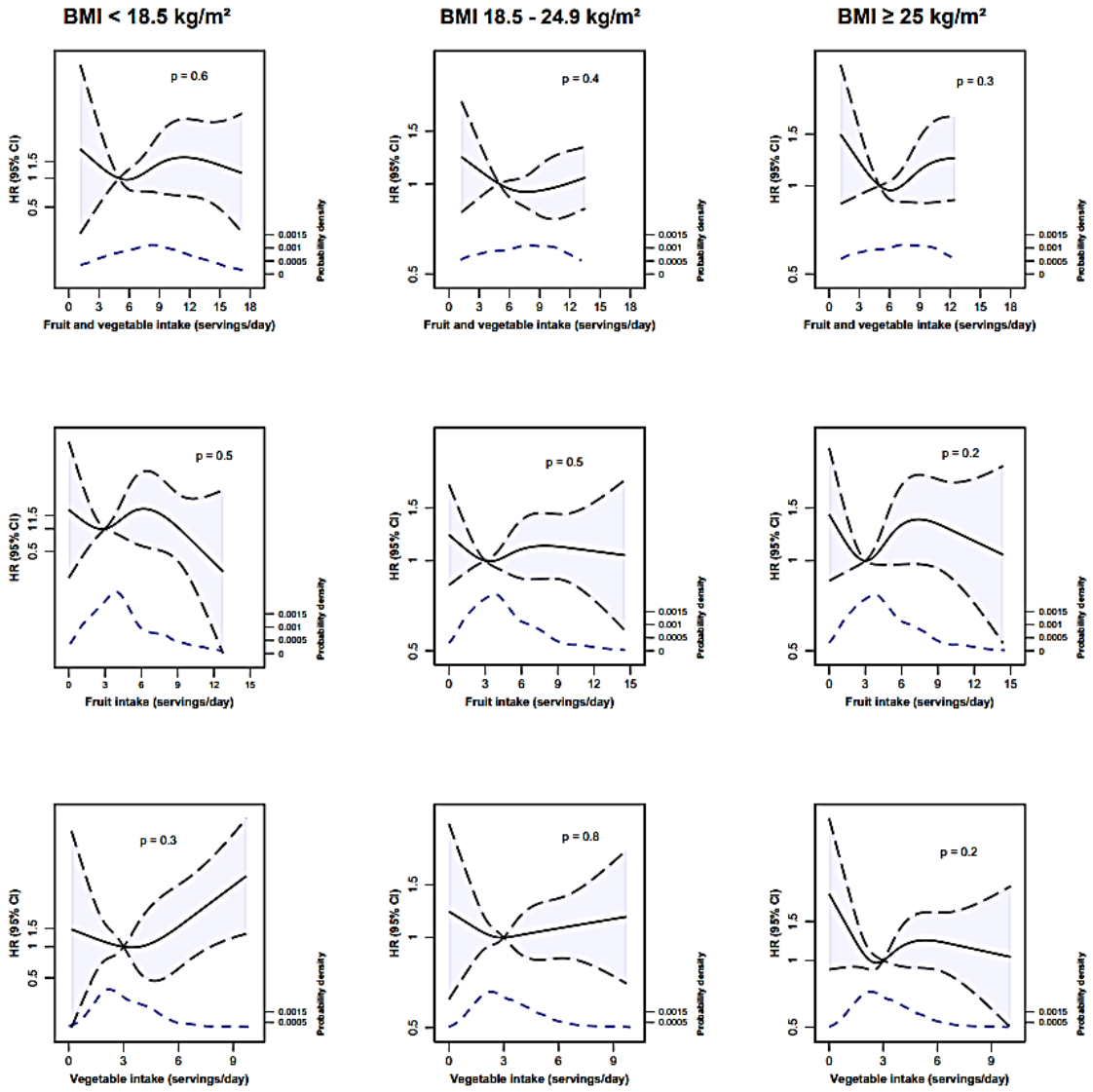



**Figure B7: Risk of hip fracture as a function of fruit, vegetable, or fruit and vegetable intake stratified by body mass index (BMI).** Dashed lines represent 95% CI's. Blue lines represent kernel density plots showing the distribution of daily fruit or vegetable intake in the cohort. Cox models were adjusted for ethnicity, socio-economic status, marital status, menopausal status, number of children, prevalence of cardiovascular disease, cancer, or diabetes, physical activity, smoking status, alcohol intake, use of any nutritional supplements, and intake of other major foods and beverages, and were mutually adjusted for fruit or vegetable intake as appropriate. HR (95% CI): adjusted hazard ratio, 95% confidence intervals; p refers to p non-linearity.

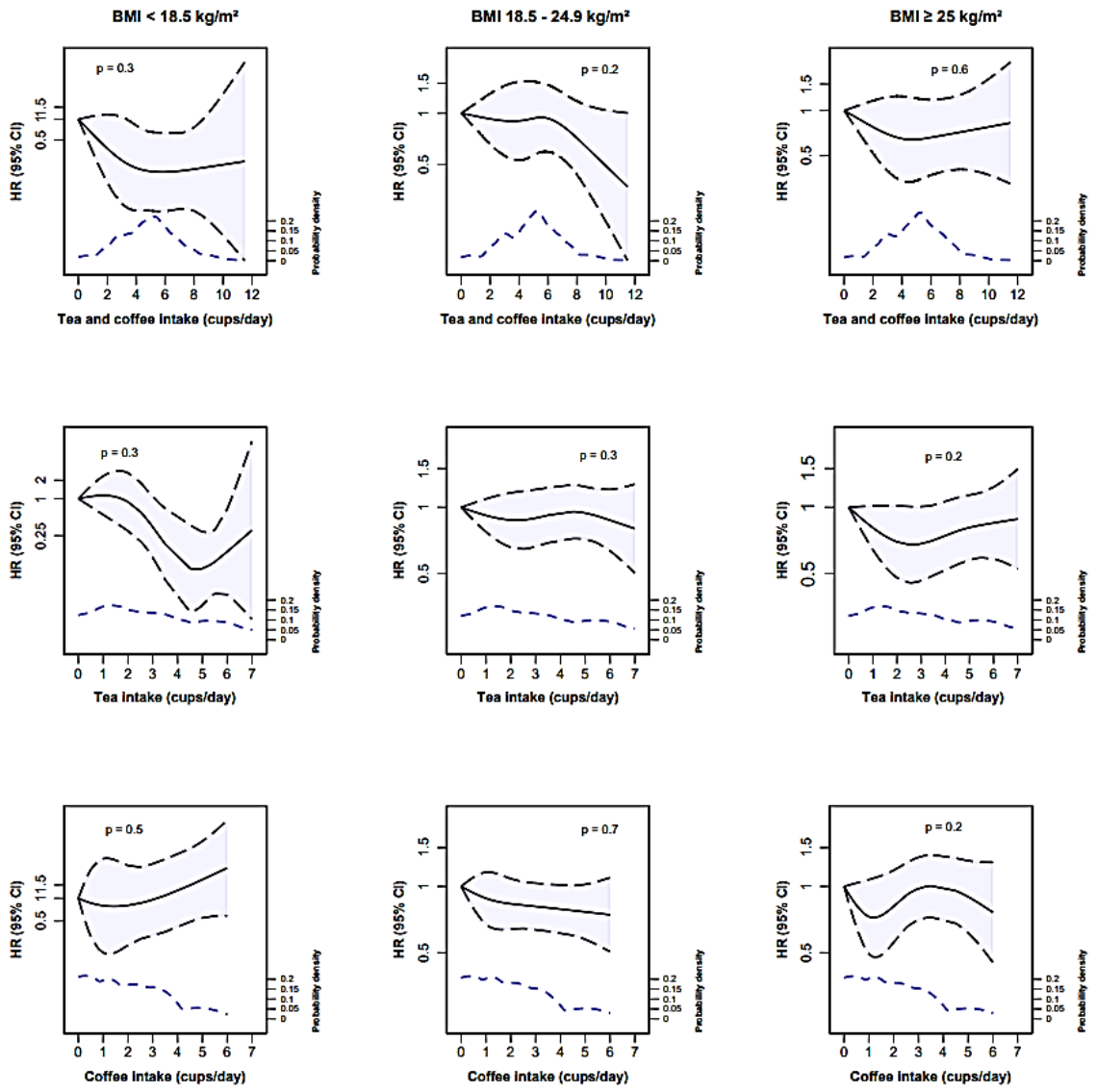



**Figure B8: Risk of hip fracture as a function of tea, coffee, or tea and coffee intake stratified by body mass index (BMI).** Dashed lines represent 95% CI's. Blue lines represent kernel density plots showing the distribution of daily tea or coffee intake in the cohort. Cox models were adjusted for ethnicity, socio-economic status, marital status, menopausal status, number of children, prevalence of cardiovascular disease, cancer, or diabetes, physical activity, smoking status, alcohol intake, use of any nutritional supplements, and intake of other major foods and beverages, and were mutually adjusted for tea or coffee intake as appropriate. HR (95% CI): adjusted hazard ratio, 95% confidence intervals.; p refers to p non-linearity.

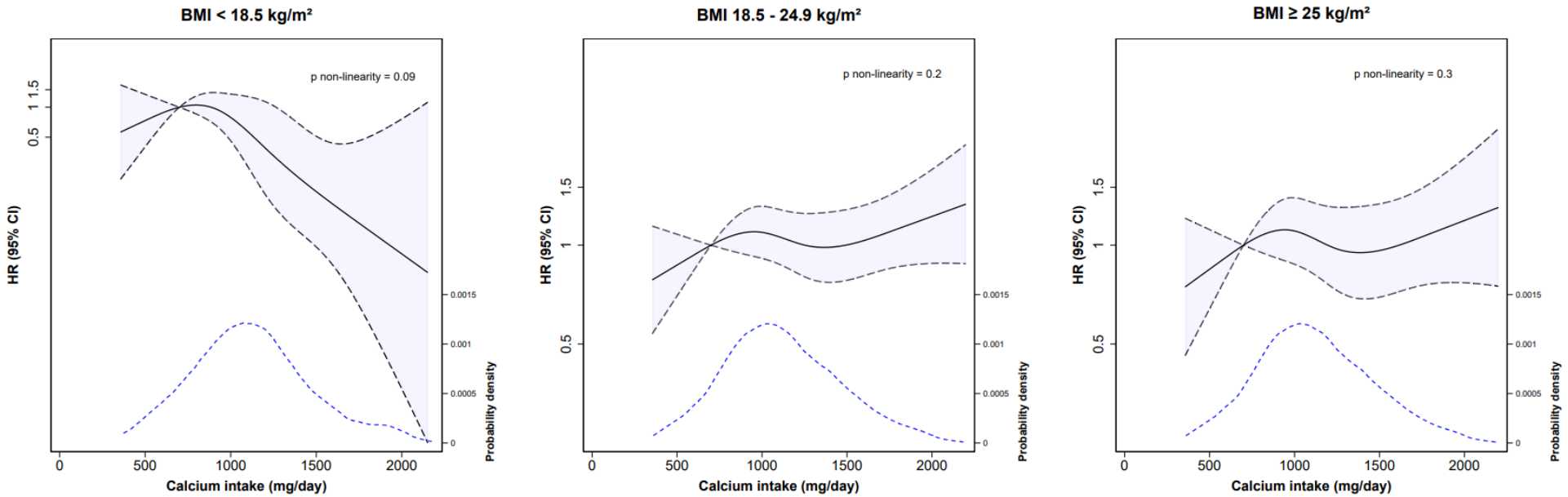



**Figure B9: Risk of hip fracture as a function of calcium intake stratified by BMI (A = underweight: < 18.5 kg/m$^2$; B = healthy weight: 18.5 – 24.9 kg/m$^2$; or C = overweight: ≥ 25 kg/m$^2$).** Dashed lines represent 95% CI's. Blue lines represent kernel density plots showing the distribution of daily calcium intake in the cohort. Cox models were adjusted for ethnicity, socio-economic status, marital status, menopausal status, number of children, prevalence of cardiovascular disease, cancer, or diabetes, physical activity, smoking status, alcohol intake, use of any nutritional supplements, and dietary intake of protein, complex carbohydrates, fibre, sugar, saturated fat, monounsaturated fatty acids, polyunsaturated fatty acids, and vitamin D. HR (95% CI): adjusted hazard ratio, 95% confidence intervals.

**Table B1: Strengthening the reporting of observational studies in nutritional epidemiology (STROBE-Nut) checklist.**

| Section/topic | Item number | Recommendation | Page (line number) |
|---|---|---|---|
| Title and abstract | 1 | Indicate the study's design with a commonly used term in the title or the abstract | 1 (1-3); 2 (11-13) |
| | | Provide in the abstract an informative and balanced summary of what was done and what was found | 2 (1-55); 3 (1-21) |
| Introduction | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 4 (1-57); 5 (1-20) |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 5 (19-24) |
| Methods | | | |
| Study design | 4 | Present key elements of study design early in the manuscript | 6 (11-43) |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 6 (11-43) |
| Participants | 6 | Cohort study - give the eligibility criteria, and the sources and methods of selection of participants; describe methods of follow-up | 6 (11-43); Additional file 1: Fig S1 |
| | | Cohort study - for matched studies, give matching criteria and number of exposed and unexposed Case-control study - for matched studies, give matching criteria and the number of controls per case | N/A |

| | | | |
|---|---|---|---|
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers; give diagnostic criteria, if applicable | 6 (46-54); 7 (1-57); 8 (1-57); 9 (1-57); 10 (1-10); Additional file 1: Figs S2 and S3, and Tables S2 and S3 |
| Data sources/measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement); describe comparability of assessment methods if there is more than one group | 6 (46-54); 7 (1-57); 8 (1-57); 9 (1-57); 10 (1-10); Additional file 1: Tables S2 and S3 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 8 (18-25; 49-57); 9 (1-45); 10 (12-36); Additional file 1: Figs S2 and S3 |
| Study size | 10 | Explain how the study size was arrived at | 6 (11-34); 10 (46-55); Additional file 1: Fig S1 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses; if applicable, describe which groupings were chosen and why | 9 (48-59); 10 (1-9) |
| Statistical methods | 12 | Describe all statistical methods, including those used to control for confounding | 8 (1-57); 9 (1-57); 10 (1-36) |
| | | Describe any methods used to examine subgroups and interactions | 9 (48-59); 10 (1-9) |
| | | Explain how missing data were addressed | 10 (31-34) |
| | | Cohort study - if applicable, explain how loss to follow-up was addressed | N/A |
| | | Describe any sensitivity analyses | 10 (12-36) |
| Results | | | |
| Participants | 13* | Report numbers of individuals at each stage of study - e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 10 (46-55); Additional file 1: Fig S1 |
| | | Give reasons for nonparticipation at each stage Consider use of a flow diagram | 10 (46-55); Additional file 1: Fig S1 |

| | | | |
|---|---|---|---|
| Descriptive data | 14* | Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders | 11 (1-37); Table 1; Additional file 1: Table S5 |
| | | Indicate number of participants with missing data for each variable of interest Cohort study - summarize follow-up time (e.g., average and total amount) | 10 (46-55); 11 (1-9) Additional file 1: Fig S1 |
| Outcome data | 15* | Cohort study - report numbers of outcome events or summary measures over time | 11 (6-8) |
| Main results | 16 | Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval); make clear which confounders were adjusted for and why they were included Report category boundaries when continuous variables were categorized | 11 (40-55); 12 (1-13); Fig 1 |
| | | If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | N/A |
| Other analyses | 17 | Report other analyses done - e.g., analyses of subgroups and interactions, and sensitivity analyses | 12 (15-57); 13 (1-8); Fig 2; Additional file 1: Figs S4-S9, Tables S7-S15, and Supplementary results |
| Discussion | | | |
| Key results | 18 | Summarize key results with reference to study objectives | 20 (1-19) |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision; discuss both direction and magnitude of any potential bias | 23 (15-57); 24 (1-7) |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 21 (44-57); 22 (1-56);-23 (1-9) |
| Generalizability | 21 | Discuss the generalizability (external validity) of the study results | 24 (2-7) |
| Other information | | | |

| | | | |
|---|---|---|---|
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 24 (42-48) |

**Table B2: Derivation of food intakes at recruitment.**

| Food | Subtypes of foods included |
|---|---|
| **Food exposures** | |
| Fruit | Apples, avocado, bananas, grapes, kiwi, mangoes, oranges, satsumas, grapefruit, papaya, pears, pineapple, apricots, melon, nectarines, peaches, plums, raspberries, redcurrants/blackcurrants, rhubarb, strawberries, dates, figs, prunes, mixed dried fruit, currants, raisins, sultanas, fruit bars, fresh orange juice, other fruit juice |
| Vegetables | Bean sprouts, butter beans/broad beans, beetroot, broccoli, spring greens, kale, brussels, cabbage, carrots, cauliflower, celery, coleslaw, low calorie coleslaw, courgettes, marrow, squash, cucumber, garlic, green beans, runner beans, leeks, lettuce, mushrooms, aubergine, olives, parsnips, peas, peppers, swedes, sweetcorn, tomatoes, turnip, mustard and cress, watercress |
| Fruits and vegetables | Fruits, vegetables |
| Processed meat | Chicken nuggets/kievs, bacon, ham, luncheon meat, sausages, pies, pasties, sausage rolls, meat lasagne, meat pizza |
| Unprocessed red meat | Beef steak, beef stew, casserole, mince, or curry, beefburger, roast pork, pork stew, lamb roast, lamb stew/casserole |
| Unprocessed poultry | Roast chicken/turkey |
| Offal | Liver, kidney |
| Total meat | Processed meat, unprocessed red meat, unprocessed poultry, or offal |
| Oily fish | Mackerel, sardines, tuna |
| Nonoily fish | Fishfingers, fishcakes, fried fish in batter, white fish, shellfish fish roe, taramasalata, fish pie/lasagne |
| Total fish | Oily or non-oily fish |
| Eggs | Boiled, poached, omelette, scrambled, fried, quiche |
| Milk | Whole milk, half fat milk, fat free milk, channel island milk, dried milk, sterilised milk |
| Yoghurt | Thick and creamy yoghurt, low fat yoghurt, diet yoghurt, Greek yoghurt, fromage frais/crème frais |
| Cheese | Low fat cheese, cheddar, brie, edam type cheese, cottage cheese, cheese and onion pastie |
| Cream | Sour cream, double/clotted cream |
| Dairy desserts | Ice cream, milk puddings, other |
| Total dairy | Milk, yoghurt, cheese, cream, or dairy desserts |
| Tea | Any tea |
| Coffee | Coffee caffeinated, decaffeinated, ground or instant |

| | |
|---|---|
| Tea and coffee | Any tea or coffee |
| Caffeinated coffee | Caffeinated coffee, ground or instant |
| Decaffeinated coffee | Decaffeinated coffee, ground or instant |
| **Energy-contributing food covariates** | **Foods included** |
| Grains | White bread, brown bread, wholemeal bread, chapati, papadum, tortilla, pitta bread, crispbread, cream crackers, barley, oats, bulgar wheat, wheatgerm, couscous |
| Cereals | Porridge, sugar coated cereals, non-sugar coated cereal, muesli, allbran, bran flakes, Weetabix, shredded wheat |
| Potatoes, rice, and pasta | Boiled, mashed, chips, jacket, roast, salad, white pasta, wholemeal pasta, white rice, brown rice, wild rice, macaroni cheese |
| Soya alternatives | Soya cheese, soya yoghurt, soya milk |
| Spreads | Butter, block margarine, low or very low fat spread, marmite, Bovril, vegemite, peanut butter, chocolate nut spread, jam, marmalade, honey, vegetable pate, nut pate |
| Sauces and soups | Salad cream, mayonnaise, French type dressing, curry sauce, tomato ketchup, pickles, chutney, pesto sauce, packet soup, vegetable soup, meat soup |
| Nuts and seeds | Pistachios, peanuts, cashew nuts, almonds, pecan nuts, walnuts, sunflower/sesame seeds |
| Beans and pulses | Lentils, dals, chick peas, hummus, baked beans, mung beans, red kidney beans, black eyed beans |
| Sweets and confectionery | Cereal bars, flapjack, chocolate bars, boiled sweets, toffees, mints, biscuits, cake, buns, pastries, croissants, scones, pancakes, muffins, crumpets, tarts, crumbles, sponge puddings |
| Savoury snacks | Crisps, fried snacks, Bombay mix |
| Textured vegetable protein | Quorn, sosmix, soy protein |
| Other hot beverages | Coffee substitute, coffee whitener, hot chocolate, cocoa, Horlick, Ovaltine |
| Other beverages | Squash, soft drinks |

**Table B3: Covariates at recruitment and their derivation.**

| **Covariate** | **How the variable was derived** |
|---|---|
| **Socio-demographic variables** | |
| Age | Calculated as year differences between date of birth and date of recruitment and was considered a continuous variable in adjustment sets. |

| | |
|---|---|
| Ethnicity | Participants were asked to select which ethnic group they belong to of 'white, 'Bangladeshi', 'Indian', 'Chinese', 'Pakistani', 'Black-Caribbean', 'Black – other', 'other'. We regrouped ethnicity into 'White', 'Asian', 'Black', and 'Other'. |
| Socio-economic status | Participants were asked about their occupation. Options were 'never had paid job', 'managers and administrators', 'professional', 'technical and associate professional', 'clerical and secretarial', 'craft and skilled', 'personal and protective', 'sales', 'plant and machine operatives', or 'other'. We condensed these options into 'routine/manual', 'intermediate', or 'managerial/professional'. |
| Education | Participants were asked what their highest educational qualification was. Options were 'no qualifications', 'O level', 'A level', 'degree', or 'missing'. |
| Marriage | Participants were asked 'what is your marital status?' with options of 'married or living as married', 'divorced', 'widowed', 'single', or 'separated'. We combined 'divorced' and 'separated' together, and 'widowed' and 'single' together. |
| **Lifestyle and other variables** | |
| Physical activity | Participants were asked how long they perform exercises that makes them sweat per week (in hours and minutes per week). This was computed as hours per day. |
| Smoking | Participants were asked to describe their smoking habit as 'smoke daily', 'smoke occasionally', 'ex-smoker', or 'never'. We combined daily and occasional smokers into 'smokers', and kept 'ex-smoker' and 'never smoked' the same. |
| Alcohol | Participants were asked how often they drink alcohol. Options were "more than once per week"; "once per week", "less than once per week", "never drink alcohol" |
| Body weight | Self-reported continuous variable |
| Height | Self-reported continuous variable |
| Body mass index | Calculated as self-reported weight divided by the square of self-reported height, considered as a continuous variable |
| Number of children | Self-reported continuous variable |
| Menopausal status | Categorised participants as pre-menopausal or post-menopausal. Criteria for postmenopausal was: age > 55 years, both ovaries removed, currently on hormone replacement therapy, or no periods in the last 12 months. |
| Hormone replacement therapy use | Participants were asked 'have you ever used hormone replacement therapy?' and 'are you using HRT now?' – based on these yes or no answers, we categorised hormone replacement therapy use as 'current', 'ex-user', and 'never'. |

**Table B4: Adjustment sets for each multivariable-adjusted model of associations between intake of primary foods and nutrients and hip fracture risk in the UK Women's Cohort Study.**

| | **Variables adjusted for** |
|---|---|
| **Common adjustment set** | Ethnicity (white, Asian, black, other), socio-economic status (SES; professional/managerial, intermediate, routine/manual), marital status (married/living as married, separated/divorced, single/widowed), menopausal status (premenopausal, postmenopausal), number of children (continuous), prevalence of cardiovascular disease, cancer, or diabetes (yes, no), physical activity in hours per day (continuous), smoking status (current, former, never), alcohol intake (> 1/week, ≤ 1/week, never), height (continuous), body weight (continuous), and use of any nutritional supplements (yes, no). |
| **Primary foods** | |
| Fruit and vegetables | Common adjustment set + total meat, total fish, eggs, total dairy, tea and coffee, grains, cereals, potatoes, soya alternative products, spreads, sauces, nuts and seeds, pulses, textured vegetable protein, confectionery, savoury snacks, other hot beverages, other beverages |
| Fruit | Common adjustment set + total meat, total fish, eggs, total dairy, tea and coffee, grains, total cereals, potatoes, soya alternative products, spreads, sauces, nuts and seeds, pulses, textured vegetable protein, confectionery, savoury snacks, other hot beverages, other beverages, vegetables |
| Vegetables | Common adjustment set + total meat, total fish, eggs, total dairy, tea and coffee, grains, total cereals, potatoes, soya alternative products, spreads, sauces, nuts and seeds, pulses, textured vegetable protein, confectionery, savoury snacks, other hot beverages, other beverages, fruit |
| Total meat | Common adjustment set + fruit and vegetables, total fish, eggs, total dairy, tea and coffee, grains, total cereals, potatoes, soya alternative products, spreads, sauces, nuts and seeds, pulses, textured vegetable protein, confectionery, savoury snacks, other hot beverages, other beverages |
| Total fish | Common adjustment set + fruit and vegetables, total meat, eggs, total dairy, tea and coffee, grains, total cereals, potatoes, soya alternative products, spreads, sauces, nuts and seeds, pulses, textured vegetable protein, confectionery, savoury snacks, other hot beverages, other beverages |
| Total dairy | Common adjustment set + fruit and vegetables, total meat, total fish, eggs, tea and coffee, grains, total cereals, potatoes, soya alternative products, spreads, sauces, nuts and seeds, pulses, textured vegetable protein, confectionery, savoury snacks, other hot beverages, other beverages |

| | |
|---|---|
| Milk | Common adjustment set + fruit and vegetables, total meat, total fish, eggs, yoghurt, cheese, cream, dairy desserts, tea and coffee, grains, total cereals, potatoes, soya alternative products, spreads, sauces, nuts and seeds, pulses, textured vegetable protein, confectionery, savoury snacks, other hot beverages, other beverages |
| Yoghurt | Common adjustment set + fruit and vegetables, total meat, total fish, eggs, milk, cheese, cream, dairy desserts, tea and coffee, grains, total cereals, potatoes, soya alternative products, spreads, sauces, nuts and seeds, pulses, textured vegetable protein, confectionery, savoury snacks, other hot beverages, other beverages |
| Cheese | Common adjustment set + fruit and vegetables, total meat, total fish, eggs, milk, yoghurt, cream, dairy desserts, tea and coffee, grains, total cereals, potatoes, soya alternative products, spreads, sauces, nuts and seeds, pulses, textured vegetable protein, confectionery, savoury snacks, other hot beverages, other beverages |
| Tea and coffee | Common adjustment set + fruit and vegetables, total meat, total fish, eggs, total dairy, grains, total cereals, potatoes, soya alternative products, spreads, sauces, nuts and seeds, pulses, textured vegetable protein, confectionery, savoury snacks, other hot beverages, other beverages |
| Tea | Common adjustment set + fruit and vegetables, total meat, total fish, eggs, total dairy, grains, total cereals, potatoes, soya alternative products, spreads, sauces, nuts and seeds, pulses, textured vegetable protein, confectionery, savoury snacks, coffee, other hot beverages, other beverages |
| Coffee | Common adjustment set + fruit and vegetables, total meat, total fish, eggs, total dairy, grains, total cereals, potatoes, soya alternative products, spreads, sauces, nuts and seeds, pulses, textured vegetable protein, confectionery, savoury snacks, tea, other hot beverages, other beverages |
| **Primary nutrients** | |
| Protein | Common adjustment set + carbohydrates, fibre, sugar, SFA, MUFA, PUFA, vitamin D, calcium |
| Calcium | Common adjustment set + protein, carbohydrates, fibre, sugar, SFA, MUFA, PUFA, vitamin D |
| Vitamin D | Common adjustment set + protein, carbohydrates, fibre, sugar, SFA, MUFA, PUFA, calcium |

All foods and beverages in adjustment sets were continuous variables measured in g/day or ml/day as appropriate. SFA: saturated fat; MUFA: monounsaturated fatty acids; PUFA: polyunsaturated fatty acids.

**Table B5: Further dietary characteristics of UK Women's Cohort Study participants at recruitment by hip fracture incidence.**

| Dietary intake, M (SD) | Total | Cases | Non-cases |
|---|---|---|---|
| Participants (%) | 26,318 | 822 (3.1) | 25496 (96.9) |
| **Foods and beverages** | | | |
| Red meat (g/day) | 39.4 (47.0) | 43.8 (48.5) | 39.3 (46.9) |
| Poultry (g/day) | 16.8 (20.0) | 15.7 (17.5) | 16.8 (20.1) |
| Processed meat (g/day) | 28.3 (30.9) | 25.8 (28.3) | 28.4 (31.0) |
| Offal (g/day) | 1.9 (3.6) | 2.3 (3.9) | 1.9 (3.6) |
| Oily fish (g/day) | 9.0 (12.0) | 9.5 (13.9) | 9.0 (11.9) |
| Non-oily fish (g/day) | 24.7 (22.9) | 26.7 (23.4) | 24.7 (22.8) |
| Cream (g/day) | 1.7 (3.4) | 2.0 (4.4) | 1.7 (3.4) |
| Dairy desserts (g/day) | 20.0 (25.9) | 25.5 (31.2) | 19.8 (25.7) |
| Eggs (number/day) | 0.3 (0.2) | 0.3 (0.3) | 0.3 (0.2) |
| Caffeinated coffee (cups/day) | 1.5 (1.7) | 1.4 (1.5) | 1.5 (1.7) |
| Decaffeinated coffee (cups/day) | 0.5 (1.1) | 0.4 (1.0) | 0.5 (1.1) |
| **Nutrients** | | | |
| Protein (% energy) | 15.5 (2.6) | 15.5 (2.6) | 15.5 (2.6) |
| Protein (g/kg-BW/day) | 1.4 (0.4) | 1.4 (0.5) | 1.4 (0.4) |
| Carbohydrate (g/day) | 304.2 (93.7) | 311.3 (98.8) | 304.0 (93.6) |
| Carbohydrate (% energy) | 53.0 (6.7) | 53.2 (6.9) | 52.9 (6.7) |
| Fibre intake (g/day) | 24.8 (9.1) | 25.5 (9.7) | 24.7 (9.1) |
| Fibre (% energy) | 2.2 (0.6) | 2.2 (0.6) | 2.2 (0.6) |
| Fat (g/day) | 83.2 (30.4) | 85.7 (33.1) | 83.2 (30.3) |
| Fat (% energy) | 32.2 (5.6) | 32.5 (5.8) | 32.2 (5.6) |
| SFA (g/day) | 28.9 (12.7) | 30.2 (14.2) | 28.9 (12.7) |
| SFA (% energy) | 11.1 (3.1) | 11.4 (3.3) | 11.1 (3.1) |
| MUFA (g/day) | 27.3 (10.5) | 28.0 (11.5) | 27.3 (10.4) |
| MUFA (% energy) | 10.6 (2.2) | 10.6 (2.4) | 10.6 (2.2) |
| PUFA (g/day) | 15.9 (6.4) | 15.9 (6.8) | 15.9 (6.4) |
| PUFA (% energy) | 6.2 (1.6) | 6.1 (1.8) | 6.2 (1.6) |
| Vitamin B12 (µg/day) | 5.7 (3.0) | 6.1 (3.2) | 5.7 (3.0) |
| Vitamin C (mg/day) | 165.2 (70.6) | 171.9 (71.5) | 165.0 (70.6) |

BW: body weight; SFA: saturated fat, MUFA: monounsaturated fatty acids; PUFA: polyunsaturated fatty acids. M (SD): mean (standard deviation).

**Table B6: Characteristics of UK Women's Cohort Study participants at recruitment that were included or excluded from adjusted analyses.**

| | 26,318 participants included in adjusted analyses | | | 3,923 participants excluded from adjusted analyses | | |
|---|---|---|---|---|---|---|
| **Characteristics, n (%) or M (SD)** | **Total** | **Cases** | **Non-cases** | **Total** | **Cases** | **Non-cases** |
| Participants (%) | 26318 | 822 (3.1) | 25496 (96.9) | 3926 | 171 (4.4) | 3755 (95.6) |
| **Socio-demographics** | | | | | | |
| Age, years (SD) | 52.1 (9.2) | 62.1 (8.0) | 51.8 (9.1) | 54.0 (10.0) | 62.3 (7.8) | 53.6 (9.9) |
| Degree-level education (%) | 6502 (26.8) | 155 (22.2) | 6347 (27.0) | 882 (22.5) | 34 (19.9) | 848 (22.6) |
| SES | | | | | | |
| Professional or managerial (%) | 19057 (72.4) | 565 (68.7) | 18492 (72.5) | 2387 (60.8) | 93 (54.4) | 2294 (61.1) |
| Intermediate (%) | 2440 (9.3) | 111 (13.5) | 2329 (9.1) | 484 (12.3) | 26 (15.2) | 458 (12.2) |
| Routine or manual (%) | 4821 (18.3) | 146 (17.8) | 4675 (18.3) | 724 (18.4) | 34 (19.9) | 690 (18.4) |
| Married (%) | 20268 (77.0) | 586 (71.3) | 19682 (77.2) | 2146 (54.7) | 69 (40.4) | 2077 (55.3) |
| White ethnicity (%) | 25992 (98.8) | 815 (99.1) | 25177 (98.7) | 3053 (77.8) | 128 (74.9) | 2925 (77.9) |
| **Lifestyle** | | | | | | |
| Exercise, hours/day (SD) | 0.2 (0.5) | 0.2 (0.4) | 0.2 (0.5) | 0.2 (0.4) | 0.2 (0.6) | 0.2 (0.4) |
| Smoking status | | | | | | |
| Current (%) | 3513 (13.3) | 112 (13.6) | 3401 (13.3) | 677 (17.2) | 35 (20.5) | 642 (17.1) |
| Former (%) | 7947 (30.2) | 255 (31.0) | 7692 (30.2) | 1193 (30.4) | 47 (27.5) | 1146 (30.5) |
| Never (%) | 14858 (56.5) | 455 (55.4) | 14403 (56.5) | 2056 (52.4) | 89 (52.0) | 1967 (52.4) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Alcohol consumption | | | | | | |
| >1/week (%) | 13918 (52.9) | 389 (47.3) | 13529 (53.1) | 1743 (44.4) | 64 (37.4) | 1679 (44.7) |
| ≤ 1/week (%) | 9290 (35.3) | 280 (34.1) | 9010 (35.3) | 1449 (36.9) | 60 (35.1) | 1389 (37.0) |
| Never (%) | 3110 (11.8) | 153 (18.6) | 2957 (11.6) | 734 (18.7) | 47 (27.5) | 687 (18.3) |
| Nutritional supplementation (%) | 14009 (53.2) | 425 (51.7) | 13584 (53.3) | 1984 (50.5) | 94 (55.0) | 1890 (50.3) |
| **Anthropometrics** | | | | | | |
| BMI, kg/m$^2$ (SD) | 24.4 (4.2) | 24.2 (4.3) | 24.4 (4.2) | 24.7 (4.5) | 24.7 (4.6) | 24.7 (4.5) |
| < 18.5 (%) | 545 (2.1) | 28 (3.4) | 517 (2.0) | 78 (2.0) | 5 (2.9) | 73 (1.9) |
| 18.5 – 24.9 (%) | 16659 (63.3) | 514 (62.5) | 16145 (63.3) | 1664 (42.4) | 74 (43.3) | 1590 (42.3) |
| ≥ 25 (%) | 9114 (34.6) | 280 (34.1) | 8834 (34.6) | 2184 (55.6) | 92 (53.8) | 2092 (55.7) |
| Height, m (SD) | 1.6 (0.1) | 1.6 (0.1) | 1.6 (0.1) | 1.6 (0.1) | 1.6 (0.1) | 1.6 (0.1) |
| **Diet** | | | | | | |
| Dietary pattern | | | | | | |
| Regular meat-eater (%) | 12221 (46.4) | 394 (47.9) | 11827 (46.4) | 1763 (44.9) | 77 (45.0) | 1686 (44.9) |
| Occasional meat-eater (%) | 6902 (26.2) | 247 (30.0) | 6655 (26.1) | 1098 (28.0) | 49 (28.7) | 1049 (27.9) |
| Pescatarian (%) | 3377 (12.8) | 80 (9.7) | 3297 (12.9) | 490 (12.5) | 18 (10.5) | 472 (12.6) |
| Vegetarian (%) | 3818 (14.5) | 101 (12.3) | 3717 (14.6) | 575 (14.6) | 27 (15.8) | 548 (14.6) |
| Energy intake (kcal/day) | 2300 (654.8) | 2346 (696.6) | 2298 (653.4) | 2251 (680.5) | 2224 (727.4) | 2252 (678.3) |
| Protein, g/day (SD) | 88.1 (26.3) | 89.7 (27.2) | 88.1 (26.2) | 86.2 (27.4) | 86.6 (28.2) | 86.1 (27.3) |
| Calcium, mg/day (SD) | 1135 (365.4) | 1160 (377.1) | 1134 (365.0) | 1109 (382.2) | 1106 (365.3) | 1110 (382.9) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Vitamin D intake (μg/day) | 3.1 (1.7) | 3.4 (1.8) | 3.1 (1.7) | 3.0 (1.7) | 3.1 (1.7) | 3.0 (1.7) |
| **Other** | | | | | | |
| Menopausal status | | | | | | |
| Postmenopausal (%) | 14611 (55.5) | 734 (89.3) | 13877 (54.4) | 2338 (59.6) | 149 (87.1) | 2189 (58.3) |
| Premenopausal (%) | 11707 (44.5) | 88 (10.7) | 11619 (45.6) | 1279 (32.6) | 18 (10.5) | 1261 (33.6) |
| ≥ 1 children (%) | 20723 (78.7) | 667 (81.1) | 20056 (78.7) | 2789 (71.0) | 119 (69.6) | 2670 (71.1) |
| Prevalence of CVD, cancer, or diabetes (%) | 2388 (9.1) | 126 (15.3) | 2262 (8.9) | 407 (10.4) | 23 (13.5) | 384 (10.2) |

SD: standard deviation; SES: social economic status; BMI: body mass index; CVD: cardiovascular disease.

**Table B7: Associations between dietary intake of secondary foods and nutrients and hip fracture risk in UK Women's Cohort Study participants.**

| | Unadjusted | | Multivariable-adjusted | |
|---|---|---|---|---|
| **Exposure (per serving increment/day)** | **HR (95% CI)** | **p** | **HR (95% CI)** | **P** |
| **Foods** | | | | |
| Red meat (189 g) | 1.02 (0.78, 1.35) | 0.9 | 1.14 (0.82, 1.59) | 0.4 |
| Processed meat (74 g) | 0.89 (0.71, 1.12) | 0.3 | 0.86 (0.66, 1.14) | 0.3 |
| Poultry (143 g) | 0.56 (0.32, 0.99) | 0.05 | 0.65 (0.36, 1.17) | 0.1 |
| Oily fish (90 g) | 0.95 (0.49, 1.83) | 0.9 | 1.03 (0.51, 2.09) | 0.9 |
| Non-oily fish (127 g) | 0.83 (0.55, 1.25) | 0.4 | 0.75 (0.47, 1.20) | 0.2 |
| Cream (25 g) | 1.17 (0.77, 1.77) | 0.5 | 1.10 (0.70, 1.72) | 0.7 |
| Dairy desserts (148 g) | 1.36 (0.98, 1.89) | 0.07 | 1.31 (0.93, 1.89) | 0.1 |
| Eggs (88 g) | 1.19 (0.87, 1.64) | 0.3 | 1.18 (0.84, 1.65) | 0.3 |
| Caffeinated coffee (260 ml) | 0.98 (0.94, 1.03) | 0.5 | 0.96 (0.91, 1.02) | 0.2 |
| Decaffeinated coffee (260 ml) | 0.94 (0.88, 1.02) | 0.1 | 0.93 (0.86, 1.00) | 0.07 |
| **Nutrients** | | | | |
| Carbohydrates (50 g) | 1.03 (0.99, 1.07) | 0.1 | 1.02 (0.92, 1.14) | 0.7 |
| Fibre (5 g) | 1.00 (0.96, 1.07) | 0.8 | 0.99 (0.92, 1.06) | 0.7 |
| Fat (10 g) | 1.03 (1.00, 1.05) | 0.03 | 1.04 (1.00, 1.08) | 0.06 |
| SFA (10 g) | 1.06 (1.00, 1.12) | 0.04 | 1.00 (0.84, 1.19) | 1 |
| MUFA (10 g) | 1.08 (1.01, 1.16) | 0.03 | 1.12 (0.81, 1.54) | 0.5 |
| PUFA (10 g) | 1.10 (0.98, 1.24) | 0.09 | 0.97 (0.71, 1.32) | 0.9 |
| Vitamin B1 (mg) | 1.01 (0.97, 1.04) | 0.7 | 1.01 (0.97, 1.05) | 0.6 |
| Vitamin B2 (mg) | 0.99 (0.91, 1.08) | 0.9 | 0.95 (0.80, 1.12) | 0.5 |
| Vitamin B6 (mg) | 1.02 (0.93, 1.12) | 0.7 | 1.04 (0.88, 1.23) | 0.6 |
| Vitamin B12 (µg) | 0.99 (0.97, 1.02) | 0.7 | 0.99 (0.95, 1.03) | 0.6 |
| Vitamin C (10 mg) | 1.01 (1.00, 1.02) | 0.3 | 1.01 (0.997, 1.03) | 0.1 |
| Iron (5 mg) | 0.98 (0.93, 1.04) | 0.6 | 0.92 (0.82, 1.02) | 0.1 |
| Folate (100 µg) | 1.03 (0.97, 1.09) | 0.4 | 1.09 (0.98, 1.22) | 0.1 |
| Sodium (1 g) | 1.05 (0.97, 1.13) | 0.2 | 1.14 (0.97, 1.34) | 0.1 |
| Zinc (5 mg) | 0.99 (0.89, 1.10) | 0.8 | 0.89 (0.63, 1.28) | 0.5 |
| Sugar (20 g) | 1.03 (1.00, 1.05) | 0.06 | 1.02 (0.96, 1.08) | 0.5 |
| Phosphorus (225 mg) | 1.00 (0.97, 1.02) | 0.8 | 1.00 (0.97, 1.02) | 0.7 |

| | | | | |
|---|---|---|---|---|
| Magnesium (135 mg) | 1.00 (0.93, 1.02) | 0.9 | 0.98 (0.90, 1.07) | 0.7 |
| Potassium (1750 mg) | 1.00 (0.92, 1.09) | 0.5 | 1.01 (0.91, 1.11) | 0.9 |
| Selenium (30 µg) | 1.00 (0.98, 1.01) | 0.9 | 0.96 (0.85, 1.09) | 0.5 |

Unadjusted and adjusted models were based on 26,318 women with 822 hip fracture cases (556,331 person-years), and both controlled for age (continuous). All adjusted models were also adjusted for (all at recruitment): ethnicity (white, Asian, black, other), socio-economic status (SES; professional/managerial, intermediate, routine/manual), marital status (married/living as married, separated/divorced, single/widowed), menopausal status (premenopausal, postmenopausal), number of children (continuous), prevalence of cardiovascular disease, cancer, or diabetes (yes, no), physical activity in hours per day (continuous), smoking status (current, former, never), alcohol intake (> 1/week, ≤ 1/week, never), height (continuous), body weight (continuous), and use of any nutritional supplements (yes, no). Models with food exposures were mutually adjusted for other major foods and beverages. Models for nutrient exposures were also adjusted for protein, complex carbohydrates, fibre, sugar, saturated fat (SFA), monounsaturated fatty acid (MUFA), polyunsaturated fatty acid (PUFA), calcium, and vitamin D intakes from dietary sources. HR (95% CI): hazard ratio 95% confidence interval.

**Table B8: Associations between dietary intake of secondary foods and nutrients and hip fracture risk in UK Women's Cohort Study participants, stratified by BMI.**

| | **Multivariable-adjusted HR (95% CI), cases/subjects** | | | |
|---|---|---|---|---|
| | | **BMI** | | |
| **Exposure (per serving increment/day)** | **< 18.5 (28/545)** | **18.5 – 24.9 (514/16659)** | **≥ 25 (280/9114)** | ***p* interaction** |
| **Secondary foods and beverages** | | | | |
| Red meat (189 g) | 0.16 (0.02, 1.43) | 1.18 (0.79, 1.77) | 1.13 (0.72, 1.77) | 0.2 |
| Processed meat (74 g) | 0.45 (0.13, 1.58) | 1.05 (0.76, 1.45) | 0.68 (0.46, 1.00) | 0.1 |
| Poultry (143 g) | | 0.81 (0.42, 1.59) | 0.42 (0.15, 1.17) | 0.6 |
| Oily fish (90 g) | | 0.93 (0.39, 1.08) | 1.51 (0.53, 4.27) | 0.5 |
| Non-oily fish (127 g) | 0.37 (0.04, 3.47) | 0.73 (0.41, 1.29) | 0.82 (0.41, 1.64) | 0.8 |
| Cream (25 g) | 0.82 (0.30, 2.21) | 1.09 (0.65, 1.81) | 1.24 (0.57, 2.72) | 0.8 |
| Dairy desserts (148 g) | 0.60 (0.06, 5.99) | 1.40 (0.93, 2.11) | 1.25 (0.69, 2.24) | 0.7 |
| Eggs (88 g) | 1.27 (0.25, 6.43) | 1.31 (0.89, 1.93) | 0.93 (0.53, 1.63) | 0.6 |
| Caffeinated coffee (260 ml) | 0.90 (0.55, 1.49) | 0.94 (0.87, 1.00) | 1.01 (0.94, 1.09) | 0.3 |
| Decaffeinated coffee (260 ml) | 1.33 (0.97, 1.83) | 0.95 (0.86, 1.04) | 0.90 (0.79, 1.02) | 0.07 |
| **Secondary nutrients** | | | | |
| Carbohydrates (50 g) | 0.90 (0.71, 1.14) | 1.02 (0.92, 1.14) | 1.04 (0.93, 1.16) | 0.4 |
| Fibre (5 g) | 0.92 (0.73, 1.16) | 0.98 (0.90, 1.06) | 1.00 (0.91, 1.10) | 0.7 |
| Fat (10 g) | 0.96 (0.85, 1.10) | 1.04 (1.00, 1.08) | 1.04 (0.99, 1.09) | 0.5 |
| SFA (10 g) | 0.82 (0.59, 1.14) | 1.00 (0.98, 1.02) | 1.02 (0.85, 1.22) | 0.4 |
| MUFA (10 g) | 0.96 (0.57, 1.62) | 1.11 (0.81, 1.53) | 1.11 (0.80, 1.56) | 0.8 |
| PUFA (10 g) | 0.98 (0.45, 2.12) | 1.01 (0.73, 1.40) | 0.94 (0.67, 1.33) | 0.8 |

| | | | | |
|---|---|---|---|---|
| Vitamin B1 (mg) | 1.14 (0.91, 1.43) | 1.00 (0.95, 1.05) | 1.02 (0.97, 1.07) | 0.5 |
| Vitamin B2 (mg) | 0.54 (0.35, 0.84) | 0.94 (0.79, 1.12) | 1.04 (0.84, 1.27) | 0.02 |
| Vitamin B6 (mg) | 0.80 (0.49, 1.31) | 1.04 (0.87, 1.24) | 1.10 (0.88, 1.36) | 0.4 |
| Vitamin B12 (µg) | 0.83 (0.71, 0.97) | 0.98 (0.94, 1.02) | 1.01 (0.96, 1.07) | 0.03 |
| Vitamin C (10 mg) | 0.98 (0.90, 1.05) | 1.01 (0.99, 1.03) | 1.01 (0.99, 1.03) | 0.6 |
| Iron (5 mg) | 0.74 (0.57, 0.96) | 0.91 (0.80, 1.02) | 0.96 (0.85, 1.08) | 0.1 |
| Folate (100 µg) | 0.82 (0.59, 1.13) | 1.08 (0.96, 1.21) | 1.12 (0.98, 1.29) | 0.2 |
| Sodium (1 g) | 0.82 (0.60, 1.13) | 1.15 (0.96, 1.37) | 1.14 (0.94, 1.38) | 0.09 |
| Zinc (5 mg) | 0.46 (0.26, 0.83) | 0.89 (0.62, 1.27) | 0.94 (0.64, 1.37) | 0.02 |
| Sugar (20 g) | 0.96 (0.80, 1.16) | 1.02 (0.96, 1.08) | 1.02 (0.96, 1.09) | 0.8 |
| Phosphorus (225 mg) | 0.95 (0.80, 1.12) | 0.99 (0.96, 1.02) | 1.01 (0.96, 1.05) | 0.7 |
| Magnesium (135 mg) | 1.02 (0.67, 1.55) | 0.96 (0.87, 1.06) | 1.01 (0.89, 1.16) | 0.7 |
| Potassium (1750 mg) | 0.97 (0.57, 1.65) | 0.98 (0.87, 1.10) | 1.05 (0.90, 1.22) | 0.7 |
| Selenium (30 µg) | 0.81 (0.50, 1.30) | 0.95 (0.82, 1.10) | 0.98 (0.82, 1.17) | 0.8 |

All models controlled for age (continuous), and were adjusted for (all at recruitment): ethnicity (white, Asian, black, other), socio-economic status (SES; professional/managerial, intermediate, routine/manual), marital status (married/living as married, separated/divorced, single/widowed), menopausal status (premenopausal, postmenopausal), number of children (continuous), prevalence of cardiovascular disease, cancer, or diabetes (yes, no), physical activity in hours per day (continuous), smoking status (current, former, never), alcohol intake (> 1/week, ≤ 1/week, never), and use of any nutritional supplements (yes, no). Models with food exposures were mutually adjusted for other major foods and beverages. Models for nutrient exposures were also adjusted for protein, complex carbohydrates, fibre, sugar, saturated fat (SFA), monounsaturated fatty acid (MUFA), polyunsaturated fatty acid (PUFA), calcium, and vitamin D intakes from dietary sources. Associations between poultry and oily fish intakes and hip fracture risk could not be estimated in the underweight group due to low heterogeneity in consumption among cases. HR (95% CI): hazard ratio 95% confidence interval.

**Table B9: Associations between dietary intake of foods, nutrients, and hip fracture risk in UK Women's Cohort Study participants, stratified by age.**

| | **Multivariable-adjusted HR (95% CI), cases/subjects** | | |
|---|---|---|---|
| | **Age (years)** | | |
| **Exposure (per serving increment/day)** | **≤ 60 (262/20384)** | **> 60 (560/5934)** | ***p* interaction** |
| **Primary foods and beverages** | | | |
| Fruits and vegetables (80 g) | 1.02 (0.98, 1.06) | 1.01 (0.98, 1.03) | 0.6 |
| Fruits (80 g) | 1.02 (0.98, 1.06) | 1.01 (0.98, 1.04) | 0.7 |
| Vegetables (80 g) | 1.03 (0.95, 1.10) | 1.00 (0.95, 1.06) | 0.6 |
| Total meat (150 g) | 0.93 (0.71, 1.23) | 0.92 (0.75, 1.12) | 0.9 |
| Total fish (140 g) | 0.87 (0.45 1.70) | 0.78 (0.49, 1.23) | 0.8 |
| Total dairy (105 g) | 1.01 (0.95, 1.08) | 1.01 (0.96, 1.05) | 0.9 |
| Milk (240 ml) | 1.02 (0.87, 1.21) | 1.01 (0.90, 1.14) | 0.9 |

| | | | |
|---|---|---|---|
| Yoghurt (125 g) | 0.97 (0.77, 1.21) | 1.01 (0.87, 1.18) | 0.7 |
| Cheese (83 g) | 0.94 (0.61, 1.45) | 0.89 (0.60, 1.31) | 0.9 |
| Tea and coffee (260 ml) | 0.91 (0.86, 0.97) | 0.98 (0.94, 1.03) | 0.04 |
| Tea (260 ml) | 0.93 (0.86, 1.00) | 0.98 (0.93, 1.03) | 0.2 |
| Coffee (260 ml) | 0.93 (0.86, 1.00) | 0.97 (0.91, 1.03) | 0.4 |
| **Primary nutrients** | | | |
| Protein (25 g) | 0.85 (0.70, 1.03) | 0.85 (0.73, 1.01) | 0.9 |
| Calcium (300 mg) | 1.01 (0.89, 1.15) | 1.00 (0.89, 1.12) | 0.9 |
| Vitamin D (ug) | 1.00 (0.92, 1.09) | 1.06 (0.99, 1.12) | 0.3 |
| **Secondary foods and beverages** | | | |
| Red meat (189 g) | 1.25 (0.75, 2.09) | 1.09 (0.75, 1.60) | 0.6 |
| Processed meat (74 g) | 0.92 (0.62, 1.37) | 0.83 (0.60, 1.15) | 0.7 |
| Poultry (143 g) | 0.50 (0.18, 1.38) | 0.73 (0.37, 1.45) | 0.5 |
| Oily fish (90 g) | 0.47 (0.13, 1.67) | 1.38 (0.67, 2.83) | 0.1 |
| Non-oily fish (127 g) | 1.11 (0.51, 2.41) | 0.64 (0.38, 1.08) | 0.2 |
| Cream (25 g) | 1.22 (0.33, 4.58) | 1.07 (0.70, 1.64) | 0.8 |
| Dairy desserts (148 g) | 1.86 (1.20, 2.90) | 1.10 (0.72, 1.70) | 0.1 |
| Eggs (88 g) | 1.32 (0.81, 2.17) | 1.12 (0.74, 1.70) | 0.6 |
| Caffeinated coffee (260 ml) | 0.93 (0.86, 1.01) | 0.98 (0.92, 1.05) | 0.3 |
| Decaffeinated coffee (260 ml) | 0.93 (0.82, 1.06) | 0.93 (0.85, 1.02) | 0.9 |
| **Secondary nutrients** | | | |
| Carbohydrates (50 g) | 1.03 (0.92, 1.16) | 1.02 (0.92, 1.13) | 0.8 |
| Fibre (5 g) | 0.97 (0.88, 1.06) | 0.99 (0.92, 1.08) | 0.5 |
| Fat (10 g) | 1.04 (0.99, 1.10) | 1.03 (0.99, 1.08) | 0.8 |
| SFA (10 g) | 1.00 (0.82, 1.22) | 1.01 (0.85, 1.20) | 0.9 |
| MUFA (10 g) | 1.15 (0.82, 1.60) | 1.10 (0.80, 1.52) | 0.6 |
| PUFA (10 g) | 1.04 (0.73, 1.48) | 0.95 (0.69, 1.30) | 0.4 |
| Vitamin B1 (mg) | 1.01 (0.96, 1.07) | 1.01 (0.96, 1.06) | 0.9 |
| Vitamin B2 (mg) | 0.93 (0.76, 1.14) | 0.96 (0.80, 1.14) | 0.7 |
| Vitamin B6 (mg) | 1.12 (0.90, 1.40) | 1.01 (0.85, 1.21) | 0.3 |
| Vitamin B12 (µg) | 0.98 (0.92, 1.03) | 0.99 (0.95, 1.04) | 0.6 |
| Vitamin C (10 mg) | 1.01 (0.99, 1.03) | 1.01 (0.99, 2.03) | 0.9 |
| Iron (5 mg) | 0.86 (0.74, 0.98) | 0.93 (0.83, 1.05) | 0.2 |
| Folate (100 µg) | 1.12 (0.97, 1.29) | 1.08 (0.96, 1.21) | 0.5 |
| Sodium (1 g) | 1.12 (0.92, 1.38) | 1.14 (0.96, 1.36) | 0.8 |

| | | | |
|---|---|---|---|
| Zinc (5 mg) | 0.85 (0.57, 1.26) | 0.91 (0.63, 1.30) | 0.6 |
| Sugar (20 g) | 1.03 (0.96, 1.10) | 1.02 (0.96, 1.08) | 0.6 |
| Phosphorus (225 mg) | 0.99 (0.94, 1.04) | 1.00 (0.97, 1.03) | 0.8 |
| Magnesium (135 mg) | 0.97 (0.84, 1.12) | 0.99 (0.90, 1.09) | 0.8 |
| Potassium (1750 mg) | 1.05 (0.88, 1.24) | 1.00 (0.90, 1.11) | 0.6 |
| Selenium (30 µg) | 0.91 (0.75, 1.09) | 0.98 (0.85, 1.12) | 0.5 |

All models controlled for age (continuous), and were adjusted for (all at recruitment): ethnicity (white, Asian, black, other), socio-economic status (SES; professional/managerial, intermediate, routine/manual), marital status (married/living as married, separated/divorced, single/widowed), menopausal status (premenopausal, postmenopausal), number of children (continuous), prevalence of cardiovascular disease, cancer, or diabetes (yes, no), physical activity in hours per day (continuous), smoking status (current, former, never), alcohol intake (> 1/week, ≤ 1/week, never), height (continuous), body weight (continuous), and use of any nutritional supplements (yes, no). Models with food exposures were mutually adjusted for other major foods and beverages. Models for nutrient exposures were also adjusted for protein, complex carbohydrates, fibre, sugar, saturated fat (SFA), monounsaturated fatty acid (MUFA), polyunsaturated fatty acid (PUFA), calcium, and vitamin D intakes from dietary sources. HR (95% CI): hazard ratio 95% confidence interval.

**Table B10: Associations between dietary intake of foods, nutrients, and hip fracture risk in UK Women's Cohort Study participants, stratified by menopausal status.**

| | **Multivariable-adjusted HR (95% CI), cases/subjects** | | |
|---|---|---|---|
| | **Menopausal status** | | |
| **Exposure (per serving increment/day)** | **Pre-menopausal (88/11707)** | **Post-menopausal (734/14611)** | ***p* interaction** |
| **Primary foods and beverages** | | | |
| Fruits and vegetables (80 g) | 1.01 (0.96, 1.07) | 1.01 (0.99, 1.03) | 0.7 |
| Fruits (80 g) | 1.01 (0.94, 1.09) | 1.01 (0.98, 1.03) | 0.6 |
| Vegetables (80 g) | 1.02 (0.90, 1.15) | 1.02 (0.98, 1.07) | 0.9 |
| Total meat (150 g) | 0.98 (0.66, 1.45) | 0.91 (0.77, 1.08) | 0.3 |
| Total fish (140 g) | 0.40 (0.13, 1.29) | 0.81 (0.57, 1.16) | 0.5 |
| Total dairy (105 g) | 0.98 (0.88, 1.08) | 1.01 (0.97, 1.05) | 0.7 |
| Milk (240 ml) | 0.98 (0.75, 1.28) | 1.02 (0.92, 1.12) | 0.9 |
| Yoghurt (125 g) | 0.81 (0.51, 1.28) | 1.00 (0.88, 1.14) | 0.4 |
| Cheese (83 g) | 0.34 (0.14, 0.83) | 1.02 (0.82, 1.26) | 0.04 |
| Tea and coffee (260 ml) | 0.88 (0.80, 0.97) | 0.99 (0.95, 1.02) | 0.08 |
| Tea (260 ml) | 0.87 (0.78, 0.97) | 1.00 (0.96, 1.04) | 0.05 |
| Coffee (260 ml) | 0.96 (0.86, 1.08) | 0.97 (0.92, 1.01) | 0.7 |
| **Primary nutrients** | | | |
| Protein (25 g) | 0.81 (0.63, 1.03) | 0.85 (0.73, 0.98) | 0.7 |
| Calcium (300 mg) | 0.98 (0.81, 1.19) | 1.02 (0.93, 1.13) | 0.9 |
| Vitamin D (ug) | 0.97 (0.84, 1.11) | 1.04 (0.98, 1.09) | 0.9 |

| | | | |
|---|---|---|---|
| **Secondary foods and beverages** | | | |
| Red meat (189 g) | 1.40 (0.57, 3.45) | 1.13 (0.81, 1.59) | 0.3 |
| Processed meat (74 g) | 0.89 (0.53, 1.50) | 0.86 (0.66, 1.12) | 0.6 |
| Poultry (143 g) | 1.55 (0.34, 7.16) | 0.58 (0.31, 1.09) | 0.04 |
| Oily fish (90 g) | 0.13 (0.01, 2.05) | 1.18 (0.95, 2.35) | 0.1 |
| Non-oily fish (127 g) | 0.58 (0.16, 2.17) | 0.73 (0.47, 1.14) | 1.0 |
| Cream (25 g) | 3.50 (1.61, 7.60) | 0.90 (0.57, 1.44) | 0.005 |
| Dairy desserts (148 g) | 2.12 (0.80, 5.59) | 1.29 (0.91, 1.83) | 0.07 |
| Eggs (88 g) | 0.98 (0.34, 2.85) | 1.12 (0.81, 1.56) | 0.4 |
| Caffeinated coffee (260 ml) | 0.99 (0.88, 1.12) | 0.97 (0.92, 1.02) | 0.5 |
| Decaffeinated coffee (260 ml) | 0.88 (0.71, 1.09) | 0.95 (0.88, 1.03) | 0.5 |
| **Secondary nutrients** | | | |
| Carbohydrates (50 g) | 1.02 (0.92, 1.13) | 1.09 (0.94, 1.27) | 0.3 |
| Fibre (5 g) | 0.99 (0.92, 1.07) | 0.95 (0.81. 1.11) | 0.6 |
| Fat (10 g) | 1.03 (0.99, 1.07) | 1.11 (1.03. 1.21) | 0.05 |
| SFA (10 g) | 0.99 (0.83, 1.18) | 1.18 (0.93. 1.50) | 0.06 |
| MUFA (10 g) | 1.09 (0.79, 1.50) | 1.36 (0.95. 1.95) | 0.05 |
| PUFA (10 g) | 0.93 (0.68, 1.27) | 1.34 (0.89. 2.03) | 0.03 |
| Vitamin B1 (mg) | 1.01 (0.97, 1.05) | 1.01 (0.92. 1.10) | 1.0 |
| Vitamin B2 (mg) | 0.95 (0.80, 1.13) | 0.90 (0.67. 1.22) | 0.7 |
| Vitamin B6 (mg) | 1.03 (0.87, 1.22) | 1.19 (0.84. 1.67) | 0.4 |
| Vitamin B12 (µg) | 0.99 (0.95, 1.03) | 0.98 (0.87. 1.09) | 0.8 |
| Vitamin C (10 mg) | 1.01 (1.00, 1.03) | 1.01 (0.97. 1.04) | 0.7 |
| Iron (5 mg) | 0.91 (0.82, 1.02) | 0.94 (0.76. 1.16) | 0.8 |
| Folate (100 µg) | 1.09 (0.97, 1.22) | 1.11 (0.89. 1.37) | 0.9 |
| Sodium (1 g) | 1.13 (0.96, 1.34) | 1.25 (0.92. 1.71) | 0.5 |
| Zinc (5 mg) | 0.89 (0.62, 1.27) | 0.96 (0.56. 1.66) | 0.7 |
| Sugar (20 g) | 1.01 (0.96, 1.07) | 1.07 (0.98. 1.17) | 0.2 |
| Phosphorus (225 mg) | 0.99 (0.97, 1.02) | 1.00 (0.92. 1.09) | 0.9 |
| Magnesium (135 mg) | 0.98 (0.90, 1.07) | 1.01 (0.81. 1.26) | 0.8 |
| Potassium (1750 mg) | 1.00 (0.91, 1.11) | 1.09 (0.83. 1.45) | 0.6 |
| Selenium (30 µg) | 0.96 (0.84, 1.09) | 0.96 (0.68. 1.36) | 0.9 |

All models controlled for age (continuous), and were adjusted for (all at recruitment): ethnicity (white, Asian, black, other), socio-economic status (SES; professional/managerial, intermediate, routine/manual), marital status (married/living as married, separated/divorced, single/widowed), number of children (continuous), prevalence of cardiovascular disease, cancer, or diabetes (yes, no), physical activity in hours per day (continuous), smoking status (current, former, never), alcohol intake (> 1/week, ≤ 1/week, never), height (continuous), body weight (continuous), and use of any nutritional supplements (yes, no). Models with food exposures were mutually adjusted for other major foods and beverages. Models for nutrient exposures were also adjusted for protein, complex

carbohydrates, fibre, sugar, saturated fat (SFA), monounsaturated fatty acid (MUFA), polyunsaturated fatty acid (PUFA), calcium, and vitamin D intakes from dietary sources. HR (95% CI): hazard ratio 95% confidence interval.

**Table B11: Associations between dietary intake of foods, nutrients, and hip fracture risk in UK Women's Cohort Study participants, stratified by use of nutritional supplements.**

| | Multivariable-adjusted HR (95% CI), cases/subjects | | |
|---|---|---|---|
| | Use of nutritional supplements | | |
| **Exposure (per serving increment/day)** | **Yes (425/14009)** | **No (397/12309)** | ***p* interaction** |
| **Primary foods and beverages** | | | |
| Fruits and vegetables (80 g) | 1.00 (0.97, 1.03) | 1.03 (1.00, 1.05) | 0.1 |
| Fruits (80 g) | 0.99 (0.96, 1.03) | 1.03 (1.00, 1.06) | 0.1 |
| Vegetables (80 g) | 0.99 (0.93, 1.05) | 1.03 (0.97, 1.10) | 0.4 |
| Total meat (150 g) | 0.87 (0.69, 1.10) | 0.97 (0.78, 1.21) | 0.5 |
| Total fish (140 g) | 0.76 (0.44, 1.30) | 0.85 (0.51, 1.44) | 0.8 |
| Total dairy (105 g) | 1.00 (0.95, 1.05) | 1.02 (0.97, 1.07) | 0.6 |
| Milk (240 ml) | 0.99 (0.87, 1.14) | 1.04 (0.91, 1.20) | 0.6 |
| Yoghurt (125 g) | 1.03 (0.86, 1.22) | 0.97 (0.81, 1.17) | 0.7 |
| Cheese (83 g) | 0.80 (0.53, 1.19) | 0.98 (0.68, 1.41) | 0.4 |
| Tea and coffee (260 ml) | 0.92 (0.88, 0.97) | 1.00 (0.95, 1.05) | 0.03 |
| Tea (260 ml) | 0.95 (0.90, 1.01) | 0.98 (0.92, 1.04) | 0.5 |
| Coffee (260 ml) | 0.90 (0.84, 0.97) | 1.00 (0.94, 1.06) | 0.04 |
| **Primary nutrients** | | | |
| Protein (25 g) | 0.83 (0.70, 0.99) | 0.88 (0.74, 1.05) | 0.4 |
| Calcium (300 mg) | 1.00 (0.88, 1.13) | 1.01 (0.89, 1.13) | 0.9 |
| Vitamin D (ug) | 1.04 (0.97, 1.11) | 1.04 (0.97, 1.12) | 0.9 |
| **Secondary foods and beverages** | | | |
| Red meat (189 g) | 1.04 (0.67, 1.63) | 1.22 (0.81, 1.85) | 0.6 |
| Processed meat (74 g) | 0.82 (0.57, 1.19) | 0.90 (0.64, 1.27) | 0.7 |
| Poultry (143 g) | 0.67 (0.33, 1.39) | 0.62 (0.25, 1.53) | 0.9 |
| Oily fish (90 g) | 0.81 (0.34, 1.96) | 1.32 (0.55, 3.17) | 0.4 |
| Non-oily fish (127 g) | 0.76 (0.40, 1.41) | 0.75 (0.41, 1.38) | 0.9 |
| Cream (25 g) | 1.12 (0.66, 1.90) | 1.07 (0.52, 2.20) | 0.9 |
| Dairy desserts (148 g) | 1.18 (0.74, 1.88) | 1.49 (0.90, 2.46) | 0.5 |
| Eggs (88 g) | 1.01 (0.61, 1.69) | 1.32 (0.88, 1.98) | 0.4 |
| Caffeinated coffee (260 ml) | 0.91 (0.84, 0.99) | 1.00 (0.94, 1.07) | 0.08 |

| | | | |
|---|---|---|---|
| Decaffeinated coffee (260 ml) | 0.91 (0.81, 1.01) | 0.95 (0.86, 1.06) | 0.5 |
| **Secondary nutrients** | | | |
| Carbohydrates (50 g) | 1.03 (0.93, 1.15) | 1.01 (0.91, 1.13) | 0.6 |
| Fibre (5 g) | 0.98 (0.89, 1.06) | 0.95 (0.81, 1.11) | 0.6 |
| Fat (10 g) | 1.05 (1.00, 1.10) | 1.02 (0.98, 1.07) | 0.3 |
| SFA (10 g) | 1.05 (0.87, 1.25) | 0.96 (0.80, 1.16) | 0.1 |
| MUFA (10 g) | 1.15 (0.83, 1.60) | 1.09 (0.78, 1.51) | 0.4 |
| PUFA (10 g) | 0.99 (0.72, 1.36) | 0.95 (0.67, 1.34) | 0.7 |
| Vitamin B1 (mg) | 1.02 (0.97, 1.07) | 0.99 (0.94, 1.05) | 0.4 |
| Vitamin B2 (mg) | 0.94 (0.78, 1.13) | 0.96 (0.80, 1.15) | 0.8 |
| Vitamin B6 (mg) | 1.02 (0.84, 1.25) | 1.06 (0.88, 1.27) | 0.7 |
| Vitamin B12 (µg) | 0.97 (0.92, 1.02) | 1.01 (0.96, 1.05) | 0.1 |
| Vitamin C (10 mg) | 1.01 (0.99, 1.02) | 1.02 (1.00, 1.03) | 0.3 |
| Iron (5 mg) | 0.92 (0.81, 1.04) | 0.92 (0.81, 1.03) | 0.9 |
| Folate (100 µg) | 1.08 (0.95, 1.22) | 1.10 (0.98, 1.24) | 0.7 |
| Sodium (1 g) | 1.14 (0.95, 1.36) | 1.14 (0.95, 1.38) | 0.9 |
| Zinc (5 mg) | 0.86 (0.60, 1.25) | 0.92 (0.64, 1.33) | 0.5 |
| Sugar (20 g) | 1.03 (0.97, 1.09) | 1.01 (0.95, 1.07) | 0.5 |
| Phosphorus (225 mg) | 1.01 (0.97, 1.04) | 0.98 (0.95, 1.02) | 0.4 |
| Magnesium (135 mg) | 1.00 (0.89, 1.12) | 0.97 (0.87, 1.08) | 0.7 |
| Potassium (1750 mg) | 1.03 (0.90, 1.18) | 0.99 (0.88, 1.12) | 0.7 |
| Selenium (30 µg) | 0.95 (0.81, 1.10) | 0.97 (0.83, 1.13) | 0.8 |

All models controlled for age (continuous), and were adjusted for (all at recruitment): ethnicity (white, Asian, black, other), socio-economic status (SES; professional/managerial, intermediate, routine/manual), marital status (married/living as married, separated/divorced, single/widowed), menopausal status (premenopausal, postmenopausal), number of children (continuous), prevalence of cardiovascular disease, cancer, or diabetes (yes, no), physical activity in hours per day (continuous), smoking status (current, former, never), alcohol intake (> 1/week, ≤ 1/week, never), height (continuous), and body weight (continuous). Models with food exposures were mutually adjusted for other major foods and beverages. Models for nutrient exposures were also adjusted for protein, complex carbohydrates, fibre, sugar, saturated fat (SFA), monounsaturated fatty acid (MUFA), polyunsaturated fatty acid (PUFA), calcium, and vitamin D intakes from dietary sources. HR (95% CI): hazard ratio 95% confidence interval.

**Table B12: Associations between dietary intake of foods, nutrients, and hip fracture risk in UK Women's Cohort Study participants, stratified by physical activity level.**

| | Multivariable-adjusted HR (95% CI), cases/subjects | | |
|---|---|---|---|
| | Physical activity (minutes/week) | | |
| **Exposure (per serving increment/day)** | **< 150 (665/20494)** | **≥ 150 (157/5824)** | ***p* interaction** |
| **Primary foods and beverages** | | | |
| Fruits and vegetables (80 g) | 1.01 (0.99, 1.04) | 1.01 (0.96, 1.05) | 0.8 |
| Fruits (80 g) | 1.01 (0.98, 1.04) | 1.01 (0.95, 1.07) | 0.9 |
| Vegetables (80 g) | 1.01 (0.96, 1.07) | 1.00 (0.92, 1.09) | 0.8 |
| Total meat (150 g) | 0.92 (0.77, 1.11) | 0.93 (0.65, 1.34) | 0.9 |
| Total fish (140 g) | 0.78 (0.51, 1.20) | 0.92 (0.38, 2.20) | 0.8 |
| Total dairy (105 g) | 1.01 (0.97, 1.06) | 0.99 (0.92, 1.07) | 0.6 |
| Milk (240 ml) | 1.03 (0.92, 1.16) | 0.95 (0.78, 1.15) | 0.5 |
| Yoghurt (125 g) | 0.99 (0.86, 1.14) | 1.04 (0.79, 1.37) | 0.8 |
| Cheese (83 g) | 0.92 (0.64, 1.30) | 0.85 (0.50, 1.45) | 0.8 |
| Tea and coffee (260 ml) | 0.97 (0.93, 1.01) | 0.93 (0.86, 1.01) | 0.5 |
| Tea (260 ml) | 0.97 (0.93, 1.02) | 0.93 (0.85, 1.02) | 0.4 |
| Coffee (260 ml) | 0.95 (0.90, 1.01) | 0.95 (0.86, 1.06) | 0.9 |
| **Primary nutrients** | | | |
| Protein (25 g) | 0.86 (0.73, 1.01) | 0.84 (0.69, 1.03) | 0.8 |
| Calcium (300 mg) | 1.00 (0.90, 1.12) | 0.99 (0.85, 1.16) | 0.9 |
| Vitamin D (ug) | 1.04 (0.98, 1.10) | 1.07 (0.97, 1.18) | 0.5 |
| **Secondary foods and beverages** | | | |
| Red meat (189 g) | 1.11 (0.76, 1.61) | 1.33 (0.77, 2.29) | 0.5 |
| Processed meat (74 g) | 0.87 (0.66, 1.13) | 0.86 (0.43, 1.70) | 0.9 |
| Poultry (143 g) | 0.76 (0.41, 1.38) | 0.31 (0.07, 1.42) | 0.3 |
| Oily fish (90 g) | 1.01 (0.45, 2.25) | 1.12 (0.29, 4.31) | 0.9 |
| Non-oily fish (127 g) | 0.73 (0.44, 1.21) | 0.86 (0.32, 2.34) | 0.8 |
| Cream (25 g) | 1.12 (0.69, 1.80) | 0.98 (0.31, 3.09) | 0.8 |
| Dairy desserts (148 g) | 1.22 (0.84, 1.77) | 1.95 (0.85, 4.44) | 0.3 |
| Eggs (88 g) | 1.15 (0.80, 1.66) | 1.32 (0.61, 2.86) | 0.8 |
| Caffeinated coffee (260 ml) | 0.97 (0.91, 1.03) | 0.94 (0.83, 1.06) | 0.6 |

| | | | |
|---|---|---|---|
| Decaffeinated coffee (260 ml) | 0.92 (0.84, 1.00) | 0.98 (0.84, 1.14) | 0.5 |
| **Secondary nutrients** | | | |
| Carbohydrates (50 g) | 1.03 (0.93, 1.14) | 1.01 (0.89, 1.15) | 0.7 |
| Fibre (5 g) | 0.99 (0.92, 1.07) | 0.95 (0.81, 1.11) | 0.5 |
| Fat (10 g) | 1.03 (0.99, 1.07) | 1.05 (0.99, 1.12) | 0.5 |
| SFA (10 g) | 1.00 (0.84, 1.19) | 1.03 (0.84, 1.26) | 0.7 |
| MUFA (10 g) | 1.09 (0.80, 1.51) | 1.18 (0.84, 1.66) | 0.4 |
| PUFA (10 g) | 0.95 (0.69, 1.30) | 1.06 (0.74, 1.52) | 0.4 |
| Vitamin B1 (mg) | 1.02 (0.98, 1.06) | 0.99 (0.91, 1.07) | 0.5 |
| Vitamin B2 (mg) | 0.95 (0.80, 1.13) | 0.94 (0.75, 1.18) | 0.9 |
| Vitamin B6 (mg) | 1.05 (0.88, 1.26) | 1.00 (0.80, 1.26) | 0.7 |
| Vitamin B12 (µg) | 0.99 (0.94, 1.03) | 0.98 (0.93, 1.05) | 0.9 |
| Vitamin C (10 mg) | 1.01 (1.00, 1.03) | 1.00 (0.97, 1.02) | 0.2 |
| Iron (5 mg) | 0.92 (0.83, 1.03) | 0.87 (0.75, 1.02) | 0.4 |
| Folate (100 µg) | 1.09 (0.98, 1.22) | 1.08 (0.92, 1.26) | 0.8 |
| Sodium (1 g) | 1.15 (0.97, 1.36) | 1.11 (0.89, 1.39) | 0.8 |
| Zinc (5 mg) | 0.89 (0.63, 1.28) | 0.86 (0.57, 1.30) | 0.9 |
| Sugar (20 g) | 1.02 (0.96, 1.08) | 1.01 (0.94, 1.09) | 0.8 |
| Phosphorus (225 mg) | 1.00 (0.97, 1.03) | 0.97 (0.92, 1.03) | 0.3 |
| Magnesium (135 mg) | 1.00 (0.91, 1.10) | 0.92 (0.79, 1.08) | 0.4 |
| Potassium (1750 mg) | 1.03 (0.92, 1.15) | 0.92 (0.76, 1.11) | 0.3 |
| Selenium (30 µg) | 0.97 (0.85, 1.11) | 0.90 (0.72, 1.14) | 0.6 |

All models controlled for age (continuous), and were adjusted for (all at recruitment): ethnicity (white, Asian, black, other), socio-economic status (SES; professional/managerial, intermediate, routine/manual), marital status (married/living as married, separated/divorced, single/widowed), menopausal status (premenopausal, postmenopausal), number of children (continuous), prevalence of cardiovascular disease, cancer, or diabetes (yes, no), smoking status (current, former, never), alcohol intake (> 1/week, ≤ 1/week, never), height (continuous), body weight (continuous), and use of any nutritional supplements (yes, no). Models with food exposures were mutually adjusted for other major foods and beverages. Models for nutrient exposures were also adjusted for protein, complex carbohydrates, fibre, sugar, saturated fat (SFA), monounsaturated fatty acid (MUFA), polyunsaturated fatty acid (PUFA), calcium, and vitamin D intakes from dietary sources. HR (95% CI): hazard ratio 95% confidence interval.

**Table B13: Associations between dietary intake of foods, nutrients, and hip fracture risk in UK Women's Cohort Study participants, stratified by socio-economic status.**

| | Multivariable-adjusted HR (95% CI), cases/subjects | | | |
|---|---|---|---|---|
| | Socio-economic status | | | |
| **Exposure (per serving increment/day)** | **Professional/managerial (565/19057)** | **Intermediate (111/2440)** | **Routine/manual (146/4821)** | ***p* interaction** |
| **Primary foods and beverages** | | | | |
| Fruits and vegetables (80 g) | 1.01 (0.99, 1.04) | 1.01 (0.96, 1.07) | 1.00 (0.96, 1.06) | 0.9 |
| Fruits (80 g) | 1.01 (0.98, 1.04) | 1.02 (0.95, 1.10) | 1.01 (0.95, 1.07) | 0.9 |
| Vegetables (80 g) | 1.02 (0.97, 1.08) | 0.98 (0.88, 1.10) | 0.98 (0.88, 1.09) | 0.6 |
| Total meat (150 g) | 0.85 (0.70, 1.03) | 0.87 (0.56, 1.34) | 1.28 (0.91, 1.80) | 0.1 |
| Total fish (140 g) | 0.73 (0.46, 1.18) | 0.94 (0.32, 2.80) | 1.04 (0.51, 2.14) | 0.7 |
| Total dairy (105 g) | 0.98 (0.94, 1.03) | 1.08 (0.99, 1.18) | 1.05 (0.97, 1.14) | 0.09 |
| Milk (240 ml) | 0.96 (0.85, 1.08) | 1.13 (0.87, 1.46) | 1.15 (0.93, 1.42) | 0.2 |
| Yoghurt (125 g) | 1.00 (0.87, 1.16) | 1.24 (0.95, 1.61) | 0.77 (0.53, 1.14) | 0.1 |
| Cheese (83 g) | 0.79 (0.57, 1.10) | 1.10 (0.51, 2.38) | 1.09 (0.74, 1.61) | 0.4 |
| Tea and coffee (260 ml) | 0.97 (0.93, 1.01) | 0.96 (0.88, 1.04) | 0.93 (0.85, 1.00) | 0.6 |
| Tea (260 ml) | 0.98 (0.93, 1.03) | 0.92 (0.82, 1.03) | 0.94 (0.86, 1.03) | 0.4 |
| Coffee (260 ml) | 0.95 (0.89, 1.00) | 1.01 (0.90, 1.14) | 0.93 (0.83, 1.04) | 0.5 |
| **Primary nutrients** | | | | |
| Protein (25 g) | 0.82 (0.69, 0.97) | 0.90 (0.72, 1.13) | 0.96 (0.78, 1.17) | 0.2 |
| Calcium (300 mg) | 0.97 (0.86, 1.08) | 1.09 (0.91, 1.30) | 1.06 (0.90, 1.25) | 0.2 |
| Vitamin D (ug) | 1.01 (0.95, 1.09) | 1.11 (0.99, 1.23) | 1.09 (0.99, 1.19) | 0.2 |
| **Secondary foods and beverages** | | | | |
| Red meat (189 g) | 1.05 (0.71, 1.56) | 0.82 (0.34, 1.97) | 1.72 (0.99, 2.97) | 0.2 |
| Processed meat (74 g) | 0.75 (0.56, 1.01) | 1.01 (0.57, 1.79) | 1.19 (0.64, 2.24) | 0.3 |
| Poultry (143 g) | 0.47 (0.22, 1.01) | 0.64 (0.11, 3.79) | 1.34 (0.65, 2.73) | 0.1 |
| Oily fish (90 g) | 1.14 (0.50, 2.60) | 0.87 (0.18, 4.12) | 0.76 (0.20, 2.94) | 0.9 |
| Non-oily fish (127 g) | 0.62 (0.35, 1.11) | 1.00 (0.32, 3.10) | 1.18 (0.56, 2.45) | 0.4 |
| Cream (25 g) | 1.03 (0.63, 1.67) | 0.65 (0.24, 1.77) | 2.70 (0.77, 9.52) | 0.2 |
| Dairy desserts (148 g) | 0.97 (0.60, 1.56) | 1.94 (0.85, 4.42) | 2.08 (1.22, 3.56) | 0.07 |
| Eggs (88 g) | 1.02 (0.67, 1.56) | 1.28 (0.49, 3.34) | 1.72 (0.97, 3.05) | 0.4 |
| Caffeinated coffee (260 ml) | 0.96 (0.90, 1.02) | 1.01 (0.89, 1.15) | 0.93 (0.81, 1.06) | 0.6 |

| | | | | |
|---|---|---|---|---|
| Decaffeinated coffee (260 ml) | 0.92 (0.83, 1.01) | 0.97 (0.81, 1.16) | 0.95 (0.80, 1.12) | 0.8 |
| **Secondary nutrients** | | | | |
| Carbohydrates (50 g) | 0.99 (0.89, 1.11) | 1.10 (0.96, 1.25) | 1.07 (0.95, 1.20) | 0.1 |
| Fibre (5 g) | 0.98 (0.91, 1.06) | 1.03 (0.91, 1.17) | 0.98 (0.87, 1.10) | 0.7 |
| Fat (10 g) | 1.02 (0.98, 1.06) | 1.05 (0.98, 1.13) | 1.02 (1.15, 1.08) | 0.1 |
| SFA (10 g) | 0.96 (0.81, 1.15) | 1.02 (0.83, 1.26) | 1.12 (0.92, 1.36) | 0.09 |
| MUFA (10 g) | 1.08 (0.78, 1.49) | 1.19 (0.82, 1.73) | 1.28 (0.91, 1.81) | 0.1 |
| PUFA (10 g) | 0.89 (0.65, 1.23) | 1.11 (0.75, 1.66) | 1.08 (0.73, 1.59) | 0.2 |
| Vitamin B1 (mg) | 1.01 (0.96, 1.06) | 1.05 (0.98, 1.13) | 0.98 (0.91, 1.05) | 0.3 |
| Vitamin B2 (mg) | 0.91 (0.76, 1.08) | 1.13 (0.87, 1.47) | 0.98 (0.78, 1.23) | 0.2 |
| Vitamin B6 (mg) | 0.98 (0.81, 1.18) | 1.23 (0.94, 1.60) | 1.13 (0.89, 1.42) | 0.1 |
| Vitamin B12 (μg) | 0.98 (0.93, 1.03) | 1.01 (0.94, 1.08) | 1.00 (0.94, 1.06) | 0.7 |
| Vitamin C (10 mg) | 1.01 (1.00, 1.03) | 1.01 (0.98, 1.04) | 1.01 (0.99, 1.04) | 0.9 |
| Iron (5 mg) | 0.90 (0.79, 1.01) | 1.00 (0.87, 1.16) | 0.90 (0.77, 1.06) | 0.3 |
| Folate (100 μg) | 1.08 (0.96, 1.21) | 1.18 (0.98, 1.41) | 1.07 (0.91, 1.27) | 0.6 |
| Sodium (1 g) | 1.11 (0.93, 1.32) | 1.25 (0.95, 1.65) | 1.17 (0.94, 1.46) | 0.5 |
| Zinc (5 mg) | 0.84 (0.58, 1.21) | 0.96 (0.63, 1.46) | 1.05 (0.69, 1.60) | 0.3 |
| Sugar (20 g) | 1.00 (0.94, 1.06) | 1.06 (0.99, 1.15) | 1.06 (0.98, 1.14) | 0.06 |
| Phosphorus (225 mg) | 0.98 (0.95, 1.01) | 1.01 (0.95, 1.07) | 1.02 (0.96, 1.09) | 0.4 |
| Magnesium (135 mg) | 0.96 (0.88, 1.06) | 1.03 (0.86, 1.23) | 1.01 (0.84, 1.23) | 0.7 |
| Potassium (1750 mg) | 0.98 (0.88, 1.09) | 1.06 (0.86, 1.31) | 1.06 (0.85, 1.32) | 0.7 |
| Selenium (30 μg) | 0.93 (0.81, 1.06) | 0.98 (0.75, 1.28) | 1.05 (0.83, 1.32) | 0.7 |

All models controlled for age (continuous), and were adjusted for (all at recruitment): ethnicity (white, Asian, black, other), marital status (married/living as married, separated/divorced, single/widowed), menopausal status (premenopausal, postmenopausal), number of children (continuous), prevalence of cardiovascular disease, cancer, or diabetes (yes, no), physical activity in hours per day (continuous), smoking status (current, former, never), alcohol intake (> 1/week, ≤ 1/week, never), height (continuous), body weight (continuous), and use of any nutritional supplements (yes, no). Models with food exposures were mutually adjusted for other major foods and beverages. Models for nutrient exposures were also adjusted for protein, complex carbohydrates, fibre, sugar, saturated fat (SFA), monounsaturated fatty acid (MUFA), polyunsaturated fatty acid (PUFA), calcium, and vitamin D intakes from dietary sources. HR (95% CI): hazard ratio 95% confidence interval.

**Table B14: Associations between dietary intake of foods, nutrients, and hip fracture risk in UK Women's Cohort Study participants, stratified by smoking status.**

| | Multivariable-adjusted HR (95% CI), cases/subjects | | | |
|---|---|---|---|---|
| | Smoking status | | | |
| **Exposure (per serving increment/day)** | **Current (112/3513)** | **Former (255/7947)** | **Never (455/14858)** | ***p* interaction** |
| **Primary foods and beverages** | | | | |
| Fruits and vegetables (80 g) | 1.03 (0.97, 1.08) | 0.99 (0.95 1.02) | 1.03 (0.99, 1.06) | 0.2 |
| Fruits (80 g) | 1.02 (0.96, 1.09) | 0.98 (0.95, 1.03) | 1.02 (0.96, 1.08) | 0.3 |
| Vegetables (80 g) | 1.07 (0.95, 1.20) | 0.98 (0.90, 1.06) | 0.86 (0.69, 1.07) | 0.4 |
| Total meat (150 g) | 1.03 (0.66, 1.60) | 0.99 (0.76, 1.28) | 0.69 (0.49, 0.97) | 0.6 |
| Total fish (140 g) | 0.73 (0.27, 1.97) | 0.90 (0.46, 1.77) | 1.10 (0.45, 2.72) | 0.9 |
| Total dairy (105 g) | 0.98 (0.89, 1.08) | 1.03 (0.97, 1.10) | 1.00 (0.87, 1.14) | 0.7 |
| Milk (240 ml) | 0.97 (0.76, 1.25) | 1.07 (0.90, 1.27) | 1.03 (0.89, 1.20) | 0.7 |
| Yoghurt (125 g) | 0.83 (0.54, 1.26) | 0.99 (0.78, 1.27) | 0.81 (0.55, 1.19) | 0.6 |
| Cheese (83 g) | 1.16 (0.89, 1.51) | 0.78 (0.48, 1.27) | 1.11 (0.65, 1.90) | 0.2 |
| Tea and coffee (260 ml) | 1.00 (0.92, 1.09) | 0.92 (0.86, 0.98) | 0.94 (0.89, 0.99) | 0.2 |
| Tea (260 ml) | 1.07 (0.96, 1.19) | 0.96 (0.89, 1.03) | 1.01 (0.95, 1.07) | 0.1 |
| Coffee (260 ml) | 0.89 (0.79, 1.02) | 0.89 (0.82, 0.97) | 1.00 (0.94, 1.08) | 0.03 |
| **Primary nutrients** | | | | |
| Protein (25 g) | 0.87 (0.68, 1.10) | 0.90 (0.75, 1.07) | 1.00 (0.88, 1.12) | 0.6 |
| Calcium (300 mg) | 0.97 (0.82, 1.16) | 1.03 (0.90, 1.18) | 1.04 (0.97, 1.12) | 0.8 |
| Vitamin D (ug) | 1.04 (0.93, 1.18) | 1.04 (0.96, 1.12) | 0.97 (0.70, 1.34) | 0.9 |
| **Secondary foods and beverages** | | | | |
| Red meat (189 g) | 0.87 (0.42, 1.84) | 1.31 (0.82, 2.10) | 0.54 (0.23, 1.26) | 0.6 |
| Processed meat (74 g) | 1.35 (0.70, 2.60) | 0.98 (0.68, 1.42) | 1.11 (0.71, 1.74) | 0.1 |
| Poultry (143 g) | | 0.52 (0.22, 1.24) | 0.78 (0.47, 1.29) | 0.08 |
| Oily fish (90 g) | | 0.78 (0.26, 2.32) | 1.10 (0.45, 2.72) | 0.8 |
| Non-oily fish (127 g) | 0.59 (0.21, 1.71) | 0.97 (0.44, 2.14) | 1.05 (0.64, 1.72) | 0.7 |
| Cream (25 g) | 0.46 (0.08, 2.59) | 1.38 (0.65, 2.92) | 1.28 (0.82, 2.00) | 0.5 |
| Dairy desserts (148 g) | 0.62 (0.18, 2.13) | 1.70 (1.01, 2.86) | 0.97 (0.93, 1.02) | 0.3 |
| Eggs (88 g) | 1.55 (0.93, 2.58) | 1.15 (0.64, 2.08) | 1.01 (0.96, 1.06) | 0.5 |
| Caffeinated coffee (260 ml) | 0.93 (0.82, 1.07) | 0.91 (0.83, 1.00) | 0.98 (0.90, 1.08) | 0.2 |

| | | | | |
|---|---|---|---|---|
| Decaffeinated coffee (260 ml) | 0.78 (0.62, 0.99) | 0.88 (0.75, 1.03) | 0.83 (0.70, 0.98) | 0.1 |
| **Secondary nutrients** | | | | |
| Carbohydrates (50 g) | 1.00 (0.88, 1.13) | 1.06 (0.94, 1.19) | 0.98 (0.91, 1.07) | 0.4 |
| Fibre (5 g) | 1.03 (0.90, 1.18) | 0.97 (0.89, 1.07) | 0.98 (1.07, 1.02) | 0.7 |
| Fat (10 g) | 1.02 (0.96, 1.10) | 1.06 (1.01, 1.11) | 0.97 (0.81, 1.16) | 0.4 |
| SFA (10 g) | 0.97 (0.78, 1.21) | 1.08 (0.90, 1.29) | 1.08 (0.78, 1.50) | 0.2 |
| MUFA (10 g) | 1.09 (0.76, 1.56) | 1.19 (0.86, 1.64) | 1.08 (0.78, 1.50) | 0.5 |
| PUFA (10 g) | 1.00 (0.88, 1.13) | 1.06 (0.94, 1.19) | 0.98 (0.91, 1.07) | 0.4 |
| Vitamin B1 (mg) | 1.02 (0.95, 1.10) | 1.00 (0.94, 1.06) | 0.94 (0.78, 1.13) | 0.9 |
| Vitamin B2 (mg) | 1.00 (0.74, 1.35) | 0.95 (0.78, 1.14) | 1.03 (0.84, 1.25) | 0.9 |
| Vitamin B6 (mg) | 1.11 (0.85, 1.44) | 1.03 (0.84, 1.27) | 0.99 (0.95, 1.04) | 0.8 |
| Vitamin B12 (μg) | 0.97 (0.89, 1.05) | 0.99 (0.93, 1.04) | 1.01 (1.00, 1.03) | 0.8 |
| Vitamin C (10 mg) | 1.02 (0.99, 1.05) | 1.00 (0.98, 1.02) | 0.90 (0.81, 1.01) | 0.4 |
| Iron (5 mg) | 0.99 (0.78, 1.26) | 0.91 (0.80, 1.04) | 1.09 (0.96, 1.24) | 0.7 |
| Folate (100 μg) | 1.15 (0.97, 1.37) | 1.06 (0.93, 1.20) | 1.12 (0.94, 1.35) | 0.6 |
| Sodium (1 g) | 1.13 (0.88, 1.45) | 1.17 (0.97, 1.42) | 0.86 (0.60, 1.25) | 0.9 |
| Zinc (5 mg) | 0.86 (0.55, 1.35) | 0.97 (0.66, 1.42) | 1.01 (0.95, 1.07) | 0.6 |
| Sugar (20 g) | 1.01 (0.92, 1.10) | 1.04 (0.98, 1.11) | 1.00 (0.97, 1.03) | 0.5 |
| Phosphorus (225 mg) | 0.99 (0.93, 1.06) | 0.99 (0.94, 1.04) | 1.00 (0.91, 1.11) | 0.9 |
| Magnesium (135 mg) | 1.01 (0.84, 1.22) | 0.94 (0.82, 1.09) | 0.98 (0.85, 1.13) | 0.7 |
| Potassium (1750 mg) | 1.02 (0.83, 1.26) | 0.96 (0.81, 1.13) | 1.01 (0.91, 1.13) | 0.7 |
| Selenium (30 μg) | 0.94 (0.73, 1.22) | 0.93 (0.77, 1.13) | 1.04 (0.92, 1.17) | 0.9 |

All models controlled for age (continuous), and were adjusted for (all at recruitment): ethnicity (white, Asian, black, other), socio-economic status (SES; professional/managerial, intermediate, routine/manual), marital status (married/living as married, separated/divorced, single/widowed), menopausal status (premenopausal, postmenopausal), number of children (continuous), prevalence of cardiovascular disease, cancer, or diabetes (yes, no), physical activity in hours per day (continuous), alcohol intake (> 1/week, ≤ 1/week, never), height (continuous), body weight (continuous), and use of any nutritional supplements (yes, no). Models with food exposures were mutually adjusted for other major foods and beverages. Models for nutrient exposures were also adjusted for protein, complex carbohydrates, fibre, sugar, saturated fat (SFA), monounsaturated fatty acid (MUFA), polyunsaturated fatty acid (PUFA), calcium, and vitamin D intakes from dietary sources. HR (95% CI): hazard ratio 95% confidence interval.

**Table B15: Associations between dietary intake of foods, nutrients, and hip fracture risk in UK Women's Cohort Study participants, with varying restrictions.**

| Exposure (per serving increment/day) | HR (95% CI) | p |
|---|---|---|
| **Adjusted models (822 cases / 26,318 participants)[a]** | | |
| Fruits and vegetables (80 g) | 1.01 (0.99, 1.03) | 0.3 |
| Fruits (80 g) | 1.01 (0.99, 1.04) | 0.4 |
| Vegetables (80 g) | 1.01 (0.97, 1.06) | 0.6 |
| Total meat (150 g) | 0.92 (0.78. 1.09) | 0.4 |
| Total fish (140 g) | 0.81 (0.55, 1.19) | 0.3 |
| Total dairy (105 g) | 1.01 (0.97, 1.05) | 0.6 |
| Milk (240 ml) | 1.02 (0.92, 1.12) | 0.8 |
| Yoghurt (125 g) | 1.00 (0.88, 1.14) | 0.9 |
| Cheese (83 g) | 0.90 (0.66, 1.23) | 0.5 |
| Tea and coffee (260 ml) | 0.96 (0.92, 1.00) | 0.03 |
| Tea (260 ml) | 0.96 (0.92, 1.01) | 0.1 |
| Coffee (260 ml) | 0.95 (0.91, 1.00) | 0.05 |
| Protein (25 g) | 0.86 (0.73, 1.00) | 0.05 |
| Calcium (300 mg) | 1.00 (0.90, 1.11) | 0.9 |
| Vitamin D (µg) | 1.04 (0.99, 1.10) | 0.1 |
| **Adjusting for energy intake using the energy-partition method (822 cases / 26,318 participants)[b]** | | |
| Fruits and vegetables (80 g) | 1.01 (0.99, 1.03) | 0.4 |
| Fruits (80 g) | 1.01 (0.99, 1.04) | 0.4 |
| Vegetables (80 g) | 1.00 (0.96, 1.05) | 0.9 |
| Total meat (150 g) | 0.94 (0.80, 1.10) | 0.4 |
| Total fish (140 g) | 0.81 (0.56, 1.19) | 0.3 |
| Total dairy (105 g) | 1.00 (0.96, 1.04) | 0.9 |
| Milk (240 ml) | 0.99 (0.90, 1.09) | 0.9 |
| Yoghurt (125 g) | 0.99 (0.88, 1.12) | 0.9 |
| Cheese (83 g) | 0.92 (0.68, 1.24) | 0.5 |
| Tea and coffee (260 ml) | 0.96 (0.92, 0.99) | 0.02 |
| Tea (260 ml) | 0.97 (0.94, 1.01) | 0.2 |
| Coffee (260 ml) | 0.92 (0.92, 1.01) | 0.1 |
| Protein (25 g) | 0.85 (0.73, 0.98) | 0.02 |
| Calcium (300 mg) | 0.95 (0.87, 1.04) | 0.3 |
| Vitamin D (µg) | 1.02 (0.97, 1.07) | 0.5 |
| **Without adjustment for body weight (822 cases / 26,318 participants)** | | |

| | | |
|---|---|---|
| Fruits and vegetables (80 g) | 1.01 (0.99, 1.03) | 0.3 |
| Fruits (80 g) | 1.01 (0.99, 1.04) | 0.4 |
| Vegetables (80 g) | 1.01 (0.96, 1.06) | 0.7 |
| Total meat (150 g) | 0.89 (0.75, 1.05) | 0.2 |
| Total fish (140 g) | 0.82 (0.56, 1.21) | 0.3 |
| Total dairy (105 g) | 1.01 (0.97, 1.05) | 0.7 |
| Milk (240 ml) | 1.01 (0.92, 1.12) | 0.8 |
| Yoghurt (125 g) | 1.00 (0.88, 1.13) | 0.9 |
| Cheese (83 g) | 0.91 (0.67, 1.25) | 0.6 |
| Tea and coffee (260 ml) | 0.96 (0.92, 0.99) | 0.02 |
| Tea (260 ml) | 0.96 (0.92, 1.01) | 0.09 |
| Coffee (260 ml) | 0.95 (0.90, 1.00) | 0.04 |
| Protein (25 g) | 0.83 (0.71, 0.97) | 0.02 |
| Calcium (300 mg) | 1.01 (0.91, 1.12) | 0.9 |
| Vitamin D (μg) | 1.04 (0.99, 1.10) | 0.1 |
| **Adjusting for BMI rather than height and weight (822 cases / 26,318 participants)** | | |
| Fruits and vegetables (80 g) | 1.01 (0.99, 1.03) | 0.3 |
| Fruits (80 g) | 1.01 (0.99, 1.04) | 0.3 |
| Vegetables (80 g) | 1.01 (0.96, 1.06) | 0.7 |
| Total meat (150 g) | 0.93 (0.78, 1.12) | 0.5 |
| Total fish (140 g) | 0.81 (0.55, 1.19) | 0.3 |
| Total dairy (105 g) | 1.01 (0.97, 1.05) | 0.6 |
| Milk (240 ml) | 1.02 (0.92, 1.13) | 0.7 |
| Yoghurt (125 g) | 1.01 (0.88, 1.14) | 0.9 |
| Cheese (83 g) | 0.90 (0.67, 1.22) | 0.5 |
| Tea and coffee (260 ml) | 0.96 (0.92, 0.99) | 0.03 |
| Tea (260 ml) | 0.96 (0.92, 1.01) | 0.09 |
| Coffee (260 ml) | 0.95 (0.91, 1.00) | 0.05 |
| Protein (25 g) | 0.87 (0.74, 1.02) | 0.08 |
| Calcium (300 mg) | 1.00 (0.90, 1.11) | 0.9 |
| Vitamin D (μg) | 1.04 (0.98, 1.10) | 0.2 |
| **Excluding those with survival times < 5 years (782 cases / 25,987 participants)** | | |
| Fruits and vegetables (80 g) | 1.01 (0.99, 1.04) | 0.2 |
| Fruits (80 g) | 1.02 (0.99, 1.04) | 0.3 |
| Vegetables (80 g) | 1.01 (0.97, 1.06) | 0.6 |
| Total meat (150 g) | 0.90 (0.75, 1.07) | 0.2 |
| Total fish (140 g) | 0.82 (0.55, 1.22) | 0.3 |
| Total dairy (105 g) | 1.01 (0.97, 1.05) | 0.6 |

| | | |
|---|---|---|
| Milk (240 ml) | 1.02 (0.92, 1.13) | 0.7 |
| Yoghurt (125 g) | 1.00 (0.88, 1.14) | 0.9 |
| Cheese (83 g) | 0.92 (0.67, 1.26) | 0.6 |
| Tea and coffee (260 ml) | 0.97 (0.93, 1.01) | 0.1 |
| Tea (260 ml) | 0.97 (0.93, 1.02) | 0.2 |
| Coffee (260 ml) | 0.96 (0.92, 1.01) | 0.2 |
| Protein (25 g) | 0.83 (0.71, 0.98) | 0.0 |
| Calcium (300 mg) | 1.03 (0.92, 1.15) | 0.6 |
| Vitamin D (μg) | 1.05 (1.00, 1.11) | 0.07 |
| **Excluding participants on long-term treatment for illness (468 cases / 18,435 participants)** | | |
| Fruits and vegetables (80 g) | 1.01 (0.98, 1.04) | 0.5 |
| Fruits (80 g) | 1.01 (0.97, 1.04) | 0.8 |
| Vegetables (80 g) | 1.02 (0.96, 1.08) | 0.5 |
| Total meat (150 g) | 0.88 (0.70, 1.10) | 0.3 |
| Total fish (140 g) | 1.16 (0.74, 1.82) | 0.5 |
| Total dairy (105 g) | 1.02 (0.97, 1.08) | 0.3 |
| Milk (240 ml) | 1.03 (0.90, 1.18) | 0.6 |
| Yoghurt (125 g) | 1.05 (0.91, 1.21) | 0.5 |
| Cheese (83 g) | 0.81 (0.55, 1.20) | 0.3 |
| Tea and coffee (260 ml) | 0.94 (0.90, 0.99) | 0.02 |
| Tea (260 ml) | 0.94 (0.88, 0.99) | 0.03 |
| Coffee (260 ml) | 0.95 (0.89, 1.01) | 0.1 |
| Protein (25 g) | 0.83 (0.67, 1.02) | 0.07 |
| Calcium (300 mg) | 1.05 (0.91, 1.21) | 0.5 |
| Vitamin D (μg) | 1.07 (1.00, 1.15) | 0.04 |
| **Further adjusting for HRT use (822 cases / 26,318 participants)** | | |
| Fruits and vegetables (80 g) | 1.01 (0.99, 1.03) | 0.3 |
| Fruits (80 g) | 1.01 (0.98, 1.04) | 0.5 |
| Vegetables (80 g) | 1.02 (0.97, 1.06) | 0.5 |
| Total meat (150 g) | 0.97 (0.81, 1.15) | 0.7 |
| Total fish (140 g) | 0.70 (0.47, 1.05) | 0.09 |
| Total dairy (105 g) | 1.00 (0.96, 1.05) | 0.8 |
| Milk (240 ml) | 1.01 (0.91, 1.12) | 0.9 |
| Yoghurt (125 g) | 0.97 (0.84, 1.13) | 0.7 |
| Cheese (83 g) | 0.90 (0.65, 1.24) | 0.5 |
| Tea and coffee (260 ml) | 0.95 (0.92, 0.99) | 0.01 |
| Tea (260 ml) | 0.96 (0.92, 1.00) | 0.07 |
| Coffee (260 ml) | 0.94 (0.89, 0.99) | 0.02 |

| | | |
|---|---|---|
| Protein (25 g) | 0.86 (0.73, 1.02) | 0.07 |
| Calcium (300 mg) | 1.00 (0.89, 1.11) | 0.9 |
| Vitamin D (μg) | 1.03 (0.97, 1.09) | 0.4 |
| **Further adjusting for other fracture prevalence (822 cases / 26,318 participants)** | | |
| Fruits and vegetables (80 g) | 1.01 (0.99, 1.03) | 0.3 |
| Fruits (80 g) | 1.01 (0.99, 1.04) | 0.4 |
| Vegetables (80 g) | 1.01 (0.97, 1.06) | 0.7 |
| Total meat (150 g) | 0.93 (0.78, 1.10) | 0.4 |
| Total fish (140 g) | 0.81 (0.55, 1.19) | 0.3 |
| Total dairy (105 g) | 1.01 (0.97, 1.05) | 0.6 |
| Milk (240 ml) | 1.01 (0.92, 1.12) | 0.8 |
| Yoghurt (125 g) | 1.00 (0.88, 1.14) | 0.9 |
| Cheese (83 g) | 0.90 (0.66, 1.23) | 0.5 |
| Tea and coffee (260 ml) | 0.96 (0.92, 1.00) | 0.03 |
| Tea (260 ml) | 0.96 (0.92, 1.01) | 0.10 |
| Coffee (260 ml) | 0.95 (0.91, 1.00) | 0.05 |
| Protein (25 g) | 0.86 (0.73, 1.01) | 0.06 |
| Calcium (300 mg) | 1.00 (0.90, 1.11) | 0.9 |
| Vitamin D (μg) | 1.04 (0.99, 1.10) | 0.1 |

[a]All adjusted models controlled for age (continuous), and were adjusted for (all at recruitment): ethnicity (white, Asian, black, other), socio-economic status (SES; professional/managerial, intermediate, routine/manual), marital status (married/living as married, separated/divorced, single/widowed), menopausal status (premenopausal, postmenopausal), number of children (continuous), prevalence of cardiovascular disease, cancer, or diabetes (yes, no), physical activity in hours per day (continuous), smoking status (current, former, never), alcohol intake (> 1/week, ≤ 1/week, never), height (continuous), body weight (continuous), and use of any nutritional supplements (yes, no). Models with food exposures were mutually adjusted for other major foods and beverages. Models for nutrient exposures were also adjusted for protein, complex carbohydrates, fibre, sugar, saturated fat (SFA), monounsaturated fatty acid (MUFA), polyunsaturated fatty acid (PUFA), calcium, and vitamin D intakes from dietary sources.
[b]Based on the adjusted models, but adjusted for energy intake from all sources except the exposure of interest combined rather than adjusting for each energy-contributing food or nutrient individually.
All other sensitivity analyses were based on the adjusted models. HR (95% CI): hazard ratio (95% confidence interval).

## Supplementary methods

**Secondary exposures**

Secondary exposures of interest included dietary intake of the following nutrients: carbohydrates, sugar, fibre, fat, saturated fat, monounsaturated fatty acids (MUFAs), polyunsaturated fatty acids (PUFAs), vitamins B1, B2, B6, B12, and C, iron, folate, sodium zinc, phosphorus, magnesium, potassium, and selenium.

**Sensitivity analysis adjusting for energy intake using the energy-partition method**

As a sensitivity analysis, we repeated the adjusted Cox proportional hazard regression models for primary foods and nutrients with adjustment for energy intake using the energy-partition method. This method targets the same estimand as the all-components method used in the main analyses (the total causal effect), and involves adjusting for total energy intake minus energy intake from the exposure.

## Supplementary results

In exploratory subgroup analyses, age (≤ 60 years, > 60 years) modified linear associations between tea and coffee consumption and hip fracture risk, where the association was more protective in younger adults ($p_{interaction}$= 0.04; **Table S9**). Menopausal status modified associations between hip fracture risk and dietary intake of tea ($p_{interaction}$= 0.05), poultry ($p_{interaction}$= 0.04), cream ($p_{interaction}$= 0.005), fat ($p_{interaction}$= 0.06), saturated fat ($p_{interaction}$= 0.06, monounsaturated fat ($p_{interaction}$= 0.05), and polyunsaturated fat ($p_{interaction}$= 0.03; **Table S10**). Linear associations of consumption of coffee individually and tea and coffee combined with hip fracture risk were modified by nutritional supplementation status, and were more protective in those who reported using nutritional supplements compared to those that did not ($p_{interaction}$= 0.04 and 0.03, respectively; **Table S11**). There was some evidence that the association between coffee consumption (per cup/day) and hip fracture risk depended on smoking status ($p_{interaction}$= 0.03; **Table S14**). There was no evidence of effect modification for any food or nutrient by physical activity level or socio-economic status (**Tables S12** and **S13**).

# Appendix C Chapter 4 supplementary material

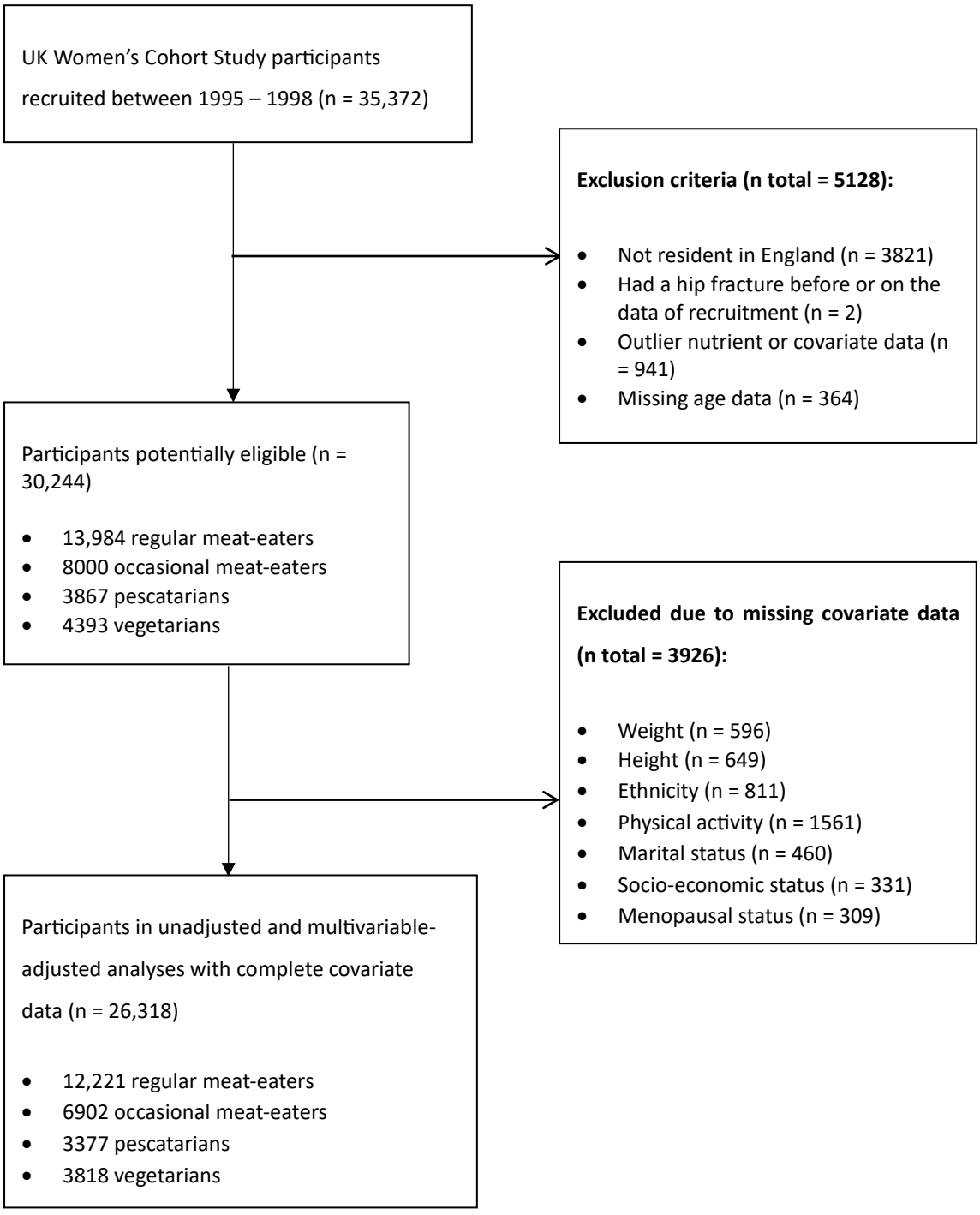



**Figure C1: Flow chart of UKWCS participants.** **Figure C1: Flow chart of UKWCS participants.**

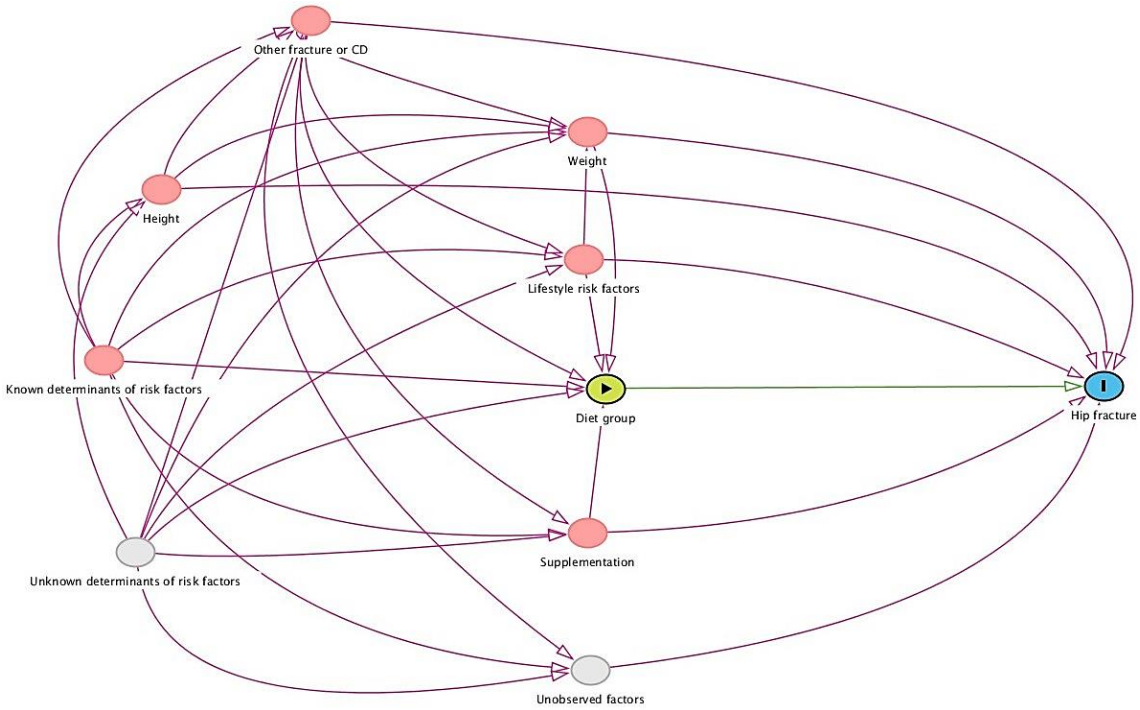



**Figure C2: Directed Acyclic Graph showing the relationship between diet group, hip fracture incidence, and related factors.** The exposure (diet group) is depicted by the green oval and the outcome (hip fracture incidence) is depicted by the blue node with a black vertical line. Variables represented as pink nodes are ancestors of the exposure and outcome, whilst variables represented as grey nodes are unknown or unmeasured. The green line represents the causal link of interest, whilst pink lines are biasing paths. Known determinants of risk factors include age, ethnicity, education, socioeconomic status, marital status, menopausal status, and number of children. Lifestyle risk factors include physical activity, smoking, and alcohol intake. Supplementation refers to use of any nutritional supplements. CD: chronic disease, defined as prevalence of cardiovascular disease, cancer, diabetes, or osteoporosis.

**Table C1: Strengthening the reporting of observational studies in nutritional epidemiology (STROBE-Nut) checklist.**

| Section/topic | Item number | Recommendation | Page (line number) |
|---|---|---|---|
| Title and abstract | 1 | Indicate the study's design with a commonly used term in the title or the abstract | 1-2 (2-3, 16) |
| | | Provide in the abstract an informative and balanced summary of what was done and what was found | 2-3 (12-35) |
| Introduction | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 4-5 (39-71) |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 5 (72-76) |
| Methods | | | |
| Study design | 4 | Present key elements of study design early in the manuscript | 5-6 (81-88) |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 5-6 (81-88) |
| Participants | 6 | Cohort study - give the eligibility criteria, and the sources and methods of selection of participants; describe methods of follow-up | 6 (91-98), Additional file 1: Fig S1 |
| | | Cohort study - for matched studies, give matching criteria and number of exposed and unexposed Case-control study - for matched studies, give matching criteria and the number of controls per case | N/A |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers; give diagnostic criteria, if applicable | 6-7 (99-110), 7 (111-117), 7-8 (129-138); 8 (140-149); Additional file 1: Tables S2 and S3 |

| | | | |
|---|---|---|---|
| Data sources/measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement); describe comparability of assessment methods if there is more than one group | 6-7 (99-110), 7 (111-117), 7-8 (129-138); 8 (140-149); Additional file 1: Tables S2 and S3 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 7-8 (125-139), 8-9 (155-165) |
| Study size | 10 | Explain how the study size was arrived at | 6 (91-95); 9 (166-171); Additional file 1: Fig S1 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses; if applicable, describe which groupings were chosen and why | 8 (140-149), Additional file 1: Supplementary methods, Table S2, and Table S3 |
| Statistical methods | 12 | Describe all statistical methods, including those used to control for confounding | 7-9 (118-165); Additional file 1: Supplementary methods and Fig S2 |
| | | Describe any methods used to examine subgroups and interactions | 8 (140-149) |
| | | Explain how missing data were addressed | 9 (163-165) |
| | | Cohort study - if applicable, explain how loss to follow-up was addressed | N/A |
| | | Describe any sensitivity analyses | 8-9 (154-164) |
| Results | | | |
| Participants | 13* | Report numbers of individuals at each stage of study - e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 9 (166-171), Additional file 1: Fig S1 |
| | | Give reasons for nonparticipation at each stage Consider use of a flow diagram | 9 (166-171), Additional file 1: Fig S1 |
| Descriptive data | 14* | Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders | 9-10 (172-187); Table 1 |

| | | | |
|---|---|---|---|
| | | Indicate number of participants with missing data for each variable of interest Cohort study - summarize follow-up time (e.g., average and total amount) | 9 (168-175); Additional file 1: Fig S1 |
| Outcome data | 15* | Cohort study - report numbers of outcome events or summary measures over time | 9 (173-175) |
| Main results | 16 | Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval); make clear which confounders were adjusted for and why they were included Report category boundaries when continuous variables were categorized | 10 (189-195); Fig 1; Additional file 1: Table S3 |
| | | If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | N/A |
| Other analyses | 17 | Report other analyses done - e.g., analyses of subgroups and interactions, and sensitivity analyses | 12-14 (196-217); Tables 2-3, Additional file 1: Tables S6 and S7. |
| Discussion | | | |
| Key results | 18 | Summarize key results with reference to study objectives | 16 (218-224) |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision; discuss both direction and magnitude of any potential bias | 19-20 (293-328) |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 17-19 (258-292) |
| Generalizability | 21 | Discuss the generalizability (external validity) of the study results | 20 (322-328) |
| Other information | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 21 (354-356) |

**Table C2: Diet group categorisation and definitions.**

| Diet group | Definition |
|---|---|
| Regular meat-eater | Total meat intake ≥ 5 servings/week |
| Occasional meat-eater | Total meat intake < 5 servings/week & ≥ 1 serving/month |
| Pescatarian | Total meat intake < 1 serving/month & total fish intake ≥ 1 serving/month |
| Vegetarian | Total meat and fish intakes < 1 serving/month, intake of dairy products or eggs ≥ 1 serving/month |
| Vegan | Total meat, total fish, dairy products, and eggs intake < 1 serving/month |

**Table C3: Covariates at recruitment and their derivation.**

| Covariate | How the variable was derived |
|---|---|
| **Socio-demographic variables** | |
| Age | Calculated as year differences between date of birth and date of recruitment and was considered a continuous variable in adjustment sets. |
| Ethnicity | Participants were asked to select which ethnic group they belong to of 'white, 'Bangladeshi', 'Indian', 'Chinese', 'Pakistani', 'Black-Caribbean', 'Black – other', 'other'. We regrouped ethnicity into 'White', 'Asian', 'Black', and 'Other'. |
| Socio-economic status | Participants were asked about their occupation. Options were 'never had paid job', 'managers and administrators', 'professional', 'technical and associate professional', 'clerical and secretarial', 'craft and skilled', 'personal and protective', 'sales', 'plant and machine operatives', or 'other'. We condensed these options into 'routine/manual', 'intermediate', or 'managerial/professional'. |
| Education | Participants were asked what their highest educational qualification was. Options were 'no qualifications', 'O level', 'A level', 'degree', or 'missing'. |
| Marriage | Participants were asked 'what is your marital status?' with options of 'married or living as married', 'divorced', 'widowed', 'single', or 'separated'. We combined 'divorced' and 'separated' together, and 'widowed' and 'single' together. |
| **Lifestyle and other variables** | |
| Physical activity | Participants were asked how long they perform exercises that makes them sweat per week (in hours and minutes per week). This was computed as hours per day. |
| Smoking | Participants were asked to describe their smoking habit as 'smoke daily', 'smoke occasionally', 'ex-smoker', or 'never'. We combined daily and occasional smokers into 'smokers', and kept 'ex-smoker' and 'never smoked' the same. |
| Alcohol | Participants were asked how often they drink alcohol. Options were '> 1/week', '1/week', '< 1/week', or 'never'. This was regrouped as '≥ 1/week', '< 1/week', or 'never'. |

| | |
|---|---|
| Body weight | Self-reported continuous variable |
| Height | Self-reported continuous variable |
| Body mass index | Calculated as self-reported weight divided by the square of self-reported height, considered as a continuous variable |
| Number of children | Self-reported continuous variable |
| Menopausal status | Categorised participants as pre-menopausal or post-menopausal. Criteria for postmenopausal was: age > 55 years, both ovaries removed, currently on hormone replacement therapy, or no periods in the last 12 months. |
| Hormone replacement therapy use | Participants were asked 'have you ever used hormone replacement therapy?' and 'are you using HRT now?' – based on these yes or no answers, we categorised hormone replacement therapy use as 'current', 'ex-user', and 'never'. |

**Table C4: Further dietary characteristics of the UKWCS by diet group at recruitment.**

| Characteristics | Total | Regular meat-eater | Occasional meat-eater | Pescatarian | Vegetarian |
|---|---|---|---|---|---|
| Participants | 30244 | 13984 | 8000 | 3867 | 4393 |
| **Foods and beverages intake** | | | | | |
| Total fruit and vegetable (g/day) | 647.7 (301.4) | 626.1 (290.7) | 630.8 (306.8) | 707.4 (309.2) | 694.9 (305.9) |
| Fruit (g/day) | 376.6 (228.4) | 358.3 (220.0) | 376.4 (232.4) | 411.8 (236.1) | 403.9 (234.0) |
| Vegetable (g/day) | 271.1 (140.2) | 267.7 (135.3) | 254.4 (141.2) | 295.6 (145.2) | 291.0 (144.0) |
| Total meat (g/day) | 86.1 (81.2) | 155.5 (63.2) | 53.7 (29.1) | 0.1 (0.5) | 0.0 (0.2) |
| Red meat (g/day) | 39.4 (47.1) | 73.3 (48.2) | 20.9 (19.7) | 0.0 (0.1) | 0.0 (0.1) |
| Poultry (g/day) | 16.6 (20.1) | 27.9 (22.1) | 14.0 (12.5) | 0.1 (0.5) | 0.0 (0.1) |
| Processed meat (g/day) | 28.2 (30.9) | 51.0 (30.0) | 17.4 (14.1) | 0.0 (0.2) | 0.0 (0.1) |
| Offal (g/day) | 1.9 (3.6) | 3.4 (4.5) | 1.3 (2.5) | 0.0 (0.1) | 0.0 (0.0) |
| Fish (g/day) | 33.7 (29.7) | 40.0 (26.0) | 37.9 (29.7) | 40.1 (33.9) | 0.1 (0.5) |
| Oily fish (g/day) | 8.9 (12.0) | 9.8 (10.9) | 10.6 (13.1) | 12.2 (15.3) | 0.1 (0.3) |
| Non-oily fish (g/day) | 24.7 (23.1) | 30.2 (20.9) | 27.2 (23.0) | 27.9 (25.9) | 0.1 (0.5) |
| Total dairy (g/day) | 411.2 (215.4) | 438.4 (202.8) | 402.5 (213.7) | 391.1 (225.7) | 358.5 (234.6) |
| Milk (g/day) | 302.8 (191.5) | 329.9 (182.2) | 299.0 (190.8) | 273.8 (196.5) | 248.6 (201.5) |
| Yoghurt (g/day) | 59.4 (68.9) | 58.8 (65.9) | 60.4 (70.7) | 64.0 (72.7) | 55.4 (71.1) |
| Cheese (g/day) | 27.3 (27.5) | 23.5 (23.3) | 24.7 (26.1) | 35.2 (29.6) | 37.3 (35.2) |
| Cream (g/day) | 1.7 (3.4) | 2.2 (3.9) | 1.4 (3.2) | 1.3 (2.4) | 1.2 (2.6) |
| Dairy desserts (g/day) | 20.1 (26.1) | 23.9 (27.8) | 17.0 (23.6) | 16.9 (24.2) | 16.1 (24.4) |

| | | | | | |
|---|---|---|---|---|---|
| Eggs (number/day) | 0.3 (0.2) | 0.3 (0.3) | 0.2 (0.2) | 0.3 (0.2) | 0.2 (0.3) |
| Tea (cups/day) | 3.0 (2.0) | 3.0 (2.0) | 2.9 (2.0) | 3.1 (2.1) | 3.0 (2.1) |
| Caffeinated coffee (cups/day) | 1.5 (1.7) | 1.6 (1.7) | 1.4 (1.6) | 1.3 (1.6) | 1.3 (1.6) |
| Decaffeinated coffee (cups/day) | 0.5 (1.1) | 0.5 (1.1) | 0.5 (1.1) | 0.5 (1.1) | 0.5 (1.1) |
| Tea and coffee (cups/day) | 5.0 (2.2) | 5.2 (2.1) | 4.8 (2.2) | 4.9 (2.2) | 4.8 (2.3) |
| **Nutrients** | | | | | |
| Protein (g/kg BW/day) | 1.37 (0.45) | 1.53 (0.45) | 1.23 (0.40) | 1.29 (0.42) | 1.21 (0.41) |
| Carbohydrate (g/day) | 303.6 (94.2) | 309.6 (92.3) | 283.0 (92.1) | 313.3 (95.2) | 313.5 (97.0) |
| Carbohydrate (% energy) | 53.0 (6.7) | 50.6 (6.0) | 54.7 (6.6) | 54.8 (6.5) | 55.9 (6.8) |
| Fibre intake (g/day) | 24.7 (9.1) | 23.7 (8.5) | 23.5 (9.2) | 27.6 (9.5) | 27.6 (9.5) |
| Fibre (% energy) | 2.2 (0.6) | 2.0 (0.5) | 2.3 (0.6) | 2.4 (0.6) | 2.5 (0.6) |
| Fat (g/day) | 83.0 (30.5) | 90.4 (29.8) | 71.4 (27.2) | 82.4 (30.9) | 81.3 (31.2) |
| Fat (% energy) | 32.3 (5.6) | 33.2 (5.0) | 30.8 (5.8) | 32.0 (6.0) | 32.2 (6.2) |
| Saturated fat (g/day) | 28.8 (12.8) | 32.5 (12.7) | 24.5 (11.1) | 27.1 (12.5) | 26.4 (12.6) |
| Saturated fat (% energy) | 11.2 (3.1) | 11.9 (2.9) | 10.6 (3.2) | 10.5 (3.1) | 10.4 (3.4) |
| MUFA (g/day) | 27.2 (10.5) | 30.1 (10.1) | 23.3 (9.4) | 26.7 (10.7) | 26.0 (10.9) |
| MUFA (% energy) | 10.6 (2.2) | 11.0 (1.9) | 10.1 (2.3) | 10.4 (2.4) | 10.3 (2.5) |
| PUFA (g/day) | 15.9 (6.4) | 16.2 (5.9) | 14.0 (6.1) | 17.3 (6.9) | 17.3 (7.4) |
| PUFA (% energy) | 6.2 (1.6) | 6.0 (1.4) | 6.0 (1.7) | 6.8 (1.8) | 6.9 (2.0) |
| Vitamin c (mg/day) | 165.1 (71.0) | 166.4 (69.9) | 157.2 (70.9) | 172.5 (73.1) | 169.0 (71.4) |
| Zinc (mg/day) | 11.2 (3.6) | 12.7 (3.5) | 9.8 (2.9) | 10.2 (3.2) | 10.0 (3.2) |
| Phosphorus (mg/day) | 1672 (623) | 1753 (620) | 1540 (621) | 1697 (597) | 1629 (616) |
| Magnesium (mg/day) | 399 (144) | 390 (135) | 375 (144) | 438 (146) | 439 (154) |
| Selenium (µg/day) | 57.7 (23.5) | 66.3 (23.8) | 53.0 (21.4) | 55.3 (20.8) | 41.2 (15.4) |

BW: body weight.

**Table C5: Characteristics of UKWCS participants at recruitment that were included or excluded from adjusted analyses.**

| **Characteristics, mean (SD) or n (%)** | **30,244 potentially eligible participants** | | | | **3,926 participants excluded from adjusted analyses** | | | |
|---|---|---|---|---|---|---|---|---|
| Diet group | **Regular meat-eater** | **Occasional meat-eater** | **Pescatarian** | **Vegetarian** | **Regular meat-eater** | **Occasional meat-eater** | **Pescatarian** | **Vegetarian** |
| Participants (%) | 13984 (46.2) | 8000 (26.5) | 3867 (12.8) | 4393 (14.5) | 1763 (44.9) | 1098 (30.0) | 490 (12.5) | 575 (14.6) |
| Cases (%) | 471 (3.4) | 296 (3.7) | 98 (2.5) | 128 (2.9) | 77 (4.4) | 49 (4.5) | 18 (3.7) | 27 (4.7) |
| **Socio-demographics** | | | | | | | | |
| Age, years (SD) | 53.6 (9.3) | 53.5 (9.5) | 49.8 (8.6) | 48.4 (8.3) | 55.6 (9.9) | 55.2 (9.9) | 50.6 (9.0) | 49.4 (9.1) |
| Degree-level education (%) | 2575 (18.4) | 2022 (25.3) | 1327 (34.3) | 1460 (33.2) | 269 (15.3) | 242 (22.0) | 184 (37.6) | 187 (32.5) |
| SES | | | | | | | | |
| Professional or managerial (%) | 9529 (68.1) | 5802 (72.5) | 2905 (75.1) | 3208 (73.0) | 1011 (57.3) | 682 (62.1) | 329 (67.1) | 365 (63.5) |
| Intermediate (%) | 1342 (9.6) | 840 (10.5) | 321 (8.3) | 421 (9.6) | 225 (12.8) | 146 (13.3) | 51 (10.4) | 62 (10.8) |
| Routine or manual (%) | 2978 (21.3) | 1265 (15.8) | 607 (15.7) | 695 (15.8) | 392 (22.2) | 177 (16.1) | 76 (15.5) | 79 (13.7) |
| Married (%) | 11183 (80.0) | 5566 (69.6) | 2663 (68.9) | 3002 (68.3) | 1080 (61.3) | 559 (50.9) | 231 (47.%) | 276 (48.0) |
| White ethnicity (%) | 13577 (97.1) | 7652 (95.7) | 3690 (95.4) | 4126 (93.9) | 1438 (81.6) | 832 (75.8) | 359 (73.3) | 424 (73.7) |
| **Lifestyle** | | | | | | | | |
| Exercise (hours/day) | 0.2 (0.5) | 0.2 (0.5) | 0.3 (0.5) | 0.3 (0.5) | 0.2 (0.4) | 0.2 (0.5) | 0.2 (0.4) | 0.3 (0.4) |
| Smoking status | | | | | | | | |
| Current | 1998 (14.3) | 1121 (14.0) | 516 (13.3) | 555 (12.6) | 320 (18.2) | 200 (18.2) | 68 (13.9) | 89 (15.5) |
| Former | 4037 (28.9) | 2409 (30.1) | 1328 (34.3) | 1366 (31.1) | 518 (29.4) | 331 (30.1) | 167 (34.1) | 177 (30.8) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Never | 7949 (56.8) | 4470 (55.9) | 2023 (52.3) | 2472 (56.3) | 925 (52.5) | 567 (51.6) | 255 (52.0) | 309 (53.7) |
| Alcohol consumption | | | | | | | | |
| > 1/week (%) | 7646 (54.7) | 4020 (50.2) | 2051 (53.0) | 1944 (44.3) | 848 (48.1) | 472 (43.0) | 221 (45.1) | 202 (35.1) |
| ≤ 1/week (%) | 4924 (35.2) | 2893 (36.2) | 1317 (34.1) | 1605 (36.5) | 648 (36.8) | 422 (38.4) | 172 (35.1) | 207 (36.0) |
| Never (%) | 1414 (10.1) | 1087 (13.6) | 499 (12.9) | 844 (19.2) | 267 (15.1) | 204 (18.6) | 97 (19.8) | 166 (28.9) |
| Nutritional supplementation (%) | 6701 (47.9) | 4475 (55.9) | 2347 (60.7) | 2470 (56.2) | 799 (45.3) | 594 (54.1) | 277 (56.5) | 314 (54.6) |
| **Anthropometrics** | | | | | | | | |
| BMI, kg/m$^2$ | 25.3 (4.5) | 24.1 (3.9) | 23.3 (3.5) | 23.3 (3.9) | 25.8 (4.8) | 24.2 (4.0) | 23.6 (3.6) | 23.2 (4.0) |
| Height (m) | 1.6 (0.1) | 1.6 (0.1) | 1.6 (0.1) | 1.6 (0.1) | 1.6 (0.1) | 1.6 (0.1) | 1.6 (0.1) | 1.6 (0.1) |
| **Diet** | | | | | | | | |
| Energy intake (kcal/day) | 2439 (643) | 2065 (613) | 2290 (659) | 2250 (663) | 2397 (657.4) | 2043 (652.3) | 2262 (679.4) | 2189 (693.6) |
| Protein intake (% energy) | 100.8 (25.0) | 77.3 (21.5) | 79.3 (23.2) | 73.6 (22.5) | 16.9 (2.6) | 15.2 (2.3) | 13.8 (2.3) | 13.1 (1.9) |
| Protein intake (g/day) | 100.9 (24.8) | 77.5 (21.3) | 79.6 (23.1) | 74.0 (22.3) | 99.6 (26.0) | 76.3 (22.7) | 77.5 (24.0) | 71.2 (23.4) |
| Protein intake (g/kg-BW/day) | 1.5 (0.4) | 1.2 (0.4) | 1.3 (0.4) | 1.2 (0.4) | 1.5 (0.5) | 1.2 (0.4) | 1.2 (0.4) | 1.2 (0.4) |
| Calcium intake (mg/day) | 1160 (346) | 1059 (360) | 1177.4 (398) | 1131 (400) | 1142 (357.8) | 1053 (385.0) | 1143 (413.9) | 1089 (407.1) |
| Vitamin D intake (µg/day) | 3.6 (1.6) | 2.9 (1.6) | 3.1 (1.8) | 1.9 (1.1) | 3.6 (1.7) | 2.9 (1.6) | 2.9 (1.7) | 1.8 (1.2) |
| Vitamin B12 intake (µg/day) | 7.5 (2.9) | 5.1 (2.2) | 4.2 (2.0) | 2.5 (1.2) | 7.4 (3.1) | 5.0 (2.1) | 4.0 (2.0) | 2.4 (1.2) |
| **Other** | | | | | | | | |
| Postmenopausal (%) | 5154 (36.9) | 3103 (38.8) | 2062 (53.3) | 2667 (60.7) | 1194 (67.7) | 689 (62.8) | 218 (44.5) | 237 (41.2) |
| Premenopausal (%) | 8715 (62.3) | 4803 (60.0) | 1749 (45.2) | 1682 (38.3) | 454 (25.8) | 315 (28.7) | 216 (44.1) | 294 (51.1) |
| ≥ 1 children (%) | 11607 (83.0) | 6087 (76.1) | 2785 (72.0) | 3033 (69.0) | 1344 (76.2) | 763 (69.5) | 317 (64.7) | 365 (63.5) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Chronic disease prevalence (%) | 1459 (10.4) | 773 (9.7) | 300 (7.8) | 263 (6.0) | 209 (11.9) | 109 (9.9) | 48 (9.8) | 41 (7.1) |

Chronic disease prevalence includes stroke, diabetes or cancer at baseline. SD: standard deviation; SES: social economic status; BMI: body mass index.

**Table C6: Risk of hip fracture in occasional meat-eaters, pescatarians, and vegetarians compared to regular meat-eaters stratified by potential effect modifiers in the UKWCS.**

| **Stratifying variable** | | **n cases, adjusted HR (95% CI)** | | | ***p* interaction** |
|---|---|---|---|---|---|
| **Age** | | **≤ 60 years** | | **> 60 years** | |
| Regular meat-eaters (reference) | 119 | 1 | 275 | 1 | |
| Occasional meat-eaters | 62 | 0.89 (0.65, 1.22) | 185 | 1.07 (0.88, 1.29) | |
| Pescatarians | 33 | 0.97 (0.64, 1.47) | 47 | 1.00 (0.72, 1.38) | |
| Vegetarians | 48 | 1.31 (0.92, 1.87) | 53 | 1.39 (0.99, 1.96) | 0.8 |
| **Menopausal status** | | **Pre-menopausal** | | **Post-menopausal** | |
| Regular meat-eaters (reference) | 38 | 1 | 356 | 1 | |
| Occasional meat-eaters | 11 | 0.43 (0.21, 0.86) | 236 | 1.08 (0.91, 1.27) | |
| Pescatarians | 17 | 1.17 (0.64, 2.13) | 63 | 0.93 (0.70, 1.24) | |
| Vegetarians | 22 | 1.16 (0.68, 1.97) | 79 | 1.37 (1.04, 1.82) | 0.05 |
| **Physical activity** | | **< 150 minutes/week** | | **≥ 150 minutes/week** | |
| Regular meat-eaters (reference) | 324 | 1 | 70 | 1 | |
| Occasional meat-eaters | 198 | 1.01 (0.84, 1.21) | 49 | 1.03 (0.71, 1.49) | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Pescatarians | 62 | 1.00 (0.74, 1.34) | 18 | 0.96 (0.56, 1.63) | | | |
| Vegetarians | 81 | 1.44 (1.09, 1.91) | 20 | 1.08 (0.66, 1.80) | | | 0.8 |
| **Supplementation** | | **Yes** | | **No** | | | |
| Regular meat-eaters (reference) | 180 | 1 | 214 | 1 | | | |
| Occasional meat-eaters | 139 | 1.11 (0.88, 1.39) | 108 | 0.92 (0.73, 1.17) | | | |
| Pescatarians | 49 | 1.03 (0.74, 1.44) | 31 | 0.95 (0.63, 1.42) | | | |
| Vegetarians | 57 | 1.41 (1.02, 1.96) | 44 | 1.32 (0.91, 1.91) | | | 0.8 |
| **SES** | | **Professional/managerial** | | **Intermediate** | | **Routine/manual** | |
| Regular meat-eaters (reference) | 256 | 1 | 51 | 1 | 87 | 1 | |
| Occasional meat-eaters | 178 | 1.05 (0.86, 1.28) | 38 | 1.13 (0.74, 1.72) | 31 | 0.80 (0.53, 1.21) | |
| Pescatarians | 59 | 1.02 (0.75, 1.38) | 8 | 0.98 (0.46, 2.01) | 13 | 0.90 (0.49, 1.67) | |
| Vegetarians | 72 | 1.41 (1.05, 1.91) | 14 | 1.31 (0.71, 2.39) | 15 | 1.23 (0.69, 2.16) | 0.9 |
| **Smoking status** | | **Current** | | **Former** | | **Never** | |
| Regular meat-eaters (reference) | 58 | 1 | 118 | 1 | 218 | 1 | |
| Occasional meat-eaters | 31 | 0.90 (0.57, 1.41) | 77 | 1.00 (0.74, 1.34) | 139 | 1.05 (0.85, 1.31) | |
| Pescatarians | 12 | 0.83 (0.43, 1.61) | 27 | 0.91 (0.59, 1.40) | 41 | 1.09 (0.76, 1.56) | |
| Vegetarians | 11 | 1.22 (0.59, 2.54) | 33 | 1.23 (0.83, 1.83) | 57 | 1.48 (1.06, 2.06) | 0.9 |

Models were adjusted for ethnicity (white, Asian, black, other), socio-economic status (SES, professional/managerial, intermediate, routine/manual), marital status (married/living as married, separated/divorced, single/widowed), menopausal status (premenopausal, postmenopausal), number of children (continuous), chronic disease prevalence at baseline (yes, no - including stroke, cancer, or diabetes), physical activity in hours per day (continuous), smoking status (current, former, never), alcohol consumption (> 1/week, ≤ 1/week, never), height (continuous), body weight (continuous), and any nutritional supplement use (yes, no). Each stratifying variable was omitted from their adjustment set. HR (95% CI): hazard ratio (95% confidence interval). SES: social economic status.

**Table C7: Risk of hip fracture by diet group with varying restrictions in the UKWCS.**

| Diet group | Cases/subjects | Person-years | HR (95% CI) | p |
|---|---|---|---|---|
| **Adjusted model** | | | | |
| Regular meat-eater (reference) | 394/12221 | 252610 | 1.00 | |
| Occasional meat-eater | 247/6902 | 145639 | 1.00 (0.85, 1.18) | 0.962 |
| Pescatarian | 80/3377 | 74077 | 0.97 (0.75, 1.26) | 0.818 |
| Vegetarian | 101/3818 | 84042 | 1.33 (1.03, 1.71) | 0.026 |
| **Further adjusted for HRT use** | | | | |
| Regular meat-eater (reference) | 365/11599 | 240994 | 1.00 | |
| Occasional meat-eater | 228/6530 | 138549 | 0.99 (0.84, 1.18) | 0.949 |
| Pescatarian | 74/3234 | 71156 | 0.96 (0.73, 1.24) | 0.734 |
| Vegetarian | 98/3671 | 80995 | 1.34 (1.06, 1.70) | 0.016 |
| **Excluding subjects with < 5 years of follow-up** | | | | |
| Regular meat-eater (reference) | 372/12029 | 252025 | 1.00 | |
| Occasional meat-eater | 235/6809 | 145359 | 1.02 (0.86, 1.20) | 0.857 |
| Pescatarian | 78/3353 | 73999 | 1.02 (0.78, 1.33) | 0.872 |
| Vegetarian | 97/3796 | 83966 | 1.40 (1.08, 1.81) | 0.011 |
| **Excluding subjects on long-term treatment for illness** | | | | |
| Regular meat-eater (reference) | 198/8206 | 173067 | 1.00 | |
| Occasional meat-eater | 148/4739 | 101953 | 1.09 (0.88, 1.37) | 0.424 |
| Pescatarian | 53/2531 | 56141 | 1.08 (0.78, 1.50) | 0.637 |
| Vegetarian | 69/2959 | 65603 | 1.48 (1.07, 2.04) | 0.016 |
| **Further adjusted for baseline fracture prevalence at other sites** | | | | |
| Regular meat-eater (reference) | 394/12221 | 252610 | 1.00 | |
| Occasional meat-eater | 247/6902 | 145639 | 1.01 (0.86, 1.19) | 0.971 |
| Pescatarian | 80/3377 | 74077 | 0.97 (0.75, 1.26) | 0.811 |
| Vegetarian | 101/3818 | 84042 | 1.33 (1.03, 1.71) | 0.027 |
| **Vegetarians and vegans separated** | | | | |
| Regular meat-eater (reference) | 394/12221 | 252610 | 1.00 | |
| Occasional meat-eater | 247/6902 | 145639 | 1.00 (0.85, 1.18) | 0.963 |
| Pescatarian | 80/3377 | 74077 | 0.97 (0.75, 1.26) | 0.817 |
| Vegetarian | 96/3688 | 81250 | 1.35 (1.04, 1.74) | 0.023 |
| Vegan | 5/130 | 2793 | 1.05 (0.40, 2.71) | 0.927 |

The adjusted model was adjusted for ethnicity (white, Asian, black, other), socio-economic status (professional/managerial, intermediate, routine/manual), marital status (married/living as married, separated/divorced, single/widowed), menopausal status (premenopausal, postmenopausal), number of children (continuous), chronic disease prevalence at baseline (yes, no - including stroke, cancer, or diabetes), physical activity in hours per day (continuous), smoking status (current, former, never), alcohol consumption (> 1/week, ≤ 1/week, never), height (continuous), body weight (continuous), and any nutritional supplement use (yes, no). All other models were based on the adjusted model. HR (95% CI): hazard ratio (95% confidence interval). HRT: hormone replacement therapy use at recruitment.

# Supplementary Methods

## Diet group classification

The food frequency questionnaire administered at recruitment included questions about consumption of foods and beverages in the form of 'how often do you eat [specific food or beverage]?' or similar. Ten responses were possible: 0 'never', 1 '< once per month', 2 '1-3 per month', 3 'once per week', 4 '2-4 per week', 5 '5-6 per week', 6 'once per day', 7 '2-3 per day', 8 '4-5 per day', or 9 '6+ per day'. We converted the responses to these questions into daily-based consumption frequencies as follows: 0, 0.02, 0.07, 0.14, 0.4, 0.8, 1, 2.5, 4.5, 6 times per day. Total meat, total fish, total eggs, and total dairy intakes were then calculated in servings per day by summing daily consumptions of relevant items. For example, we summed daily consumptions of beef, pork, lamb, chicken, turkey, bacon, ham, sausages, pies, and offal to derive total meat intake. Similarly, questions on fish intake were summed to calculate total fish intake; and questions on intake of milk, yogurt, cheese, cream, and dairy desserts were summed to calculate total dairy intake in servings per day. Meat, fish, eggs and dairy intakes were then used to classify subjects as regular meat-eaters, occasional meat-eaters, pescatarians, vegetarians, or vegans (**Table S2**).

## Determining the minimally sufficient adjustment set

**Figure C1** shows the Directed Acyclic Graph (DAG) used to inform the multivariable adjustment set for tests of associations between diet group and hip fracture risk. We did not adjust for age at recruitment as this was accounted for by using attained age as the survival time in Cox models. We did not adjust for education due to the high correlation between education and socio-economic status, which was included in the adjustment set. Hormone replacement therapy use was not adjusted for in multivariable adjusted models since it was considered in the definition of menopausal status. Osteoporosis prevalence at recruitment was not adjusted for since there

were no confirmed cases at recruitment. Similarly, prevalence of other fracture at baseline was not adjusted for since there were only 10 cases at recruitment.

# Appendix D Chapter 5 supplementary material

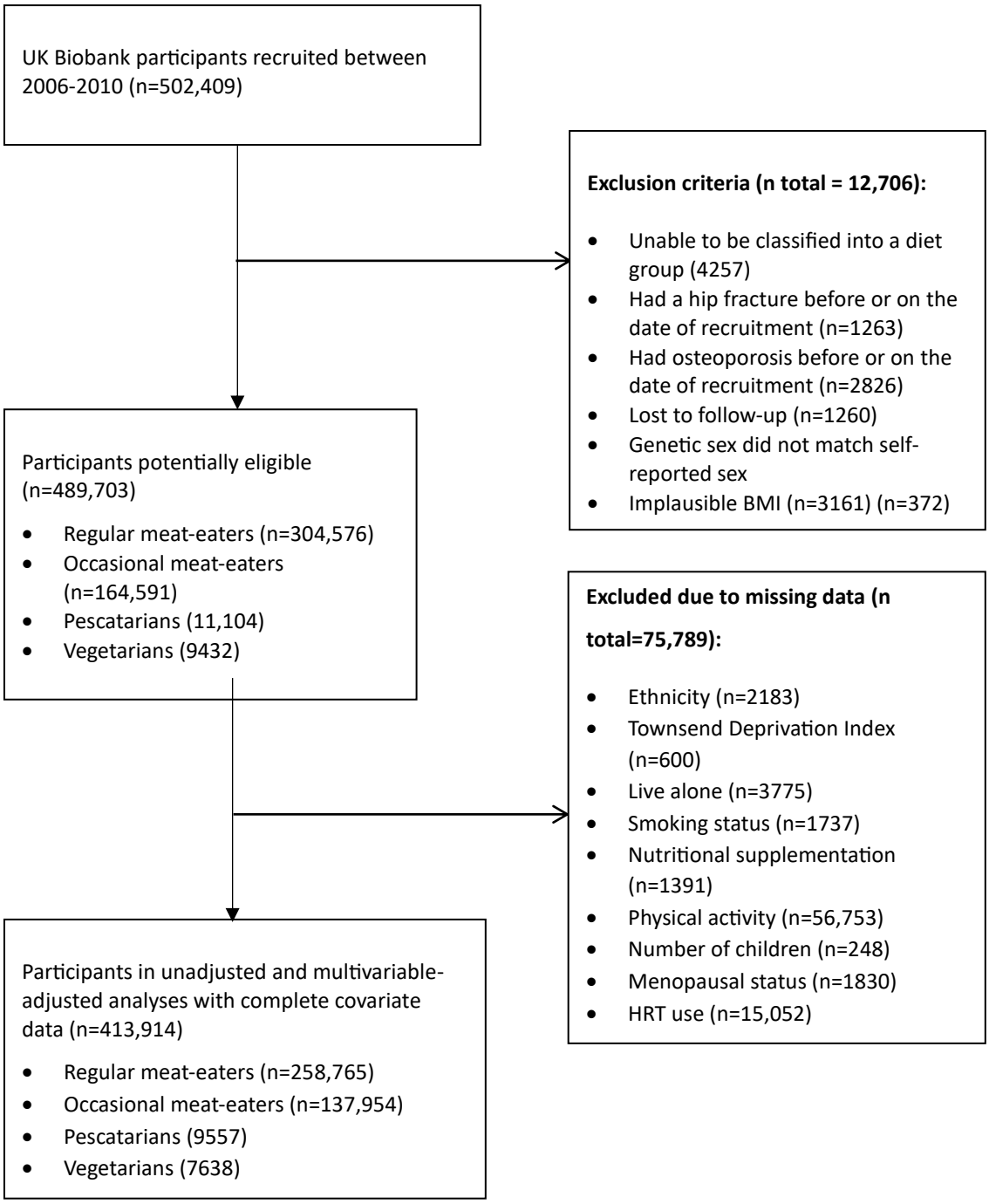



**Figure D1: Flow chart of UK Biobank participants for this study.**

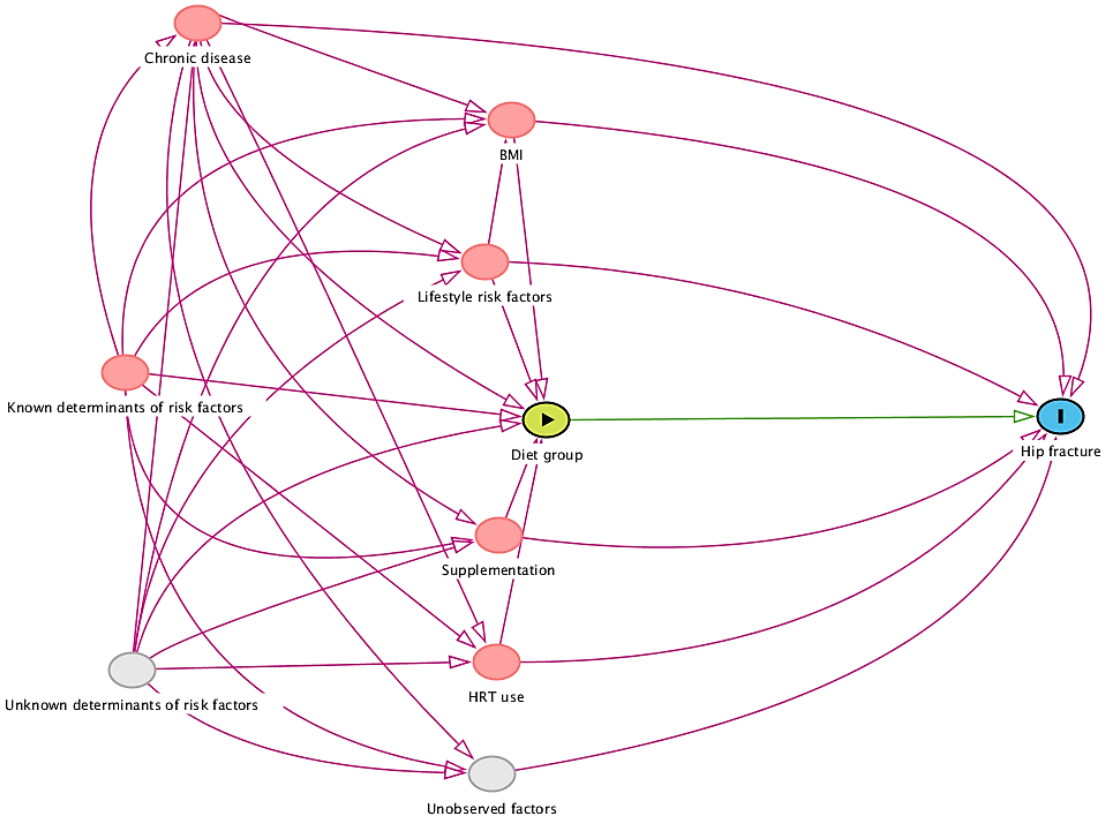



**Figure D2: Directed Acyclic Graph showing the relationship between diet group, hip fracture incidence, and related factors.** Adapted from Webster et al. (2022) (8). The green oval represents diet group (exposure), and the blue oval represents hip fracture incidence (outcome). Pink nodes are ancestors of the exposure and outcome (confounders), whilst grey nodes are unknown or unmeasured confounders. The green line represents the causal link of interest, whilst pink lines are biasing paths. Known determinants of risk factors include age, region, ethnicity, socio-economic status, living alone/marital status, menopausal status, and number of children. Lifestyle risk factors include physical activity, smoking, and alcohol intake. Supplementation refers to use of any nutritional supplements. CD: chronic disease, defined as prevalence of cardiovascular disease, cancer, diabetes, osteoporosis, and prior fracture (at any site).

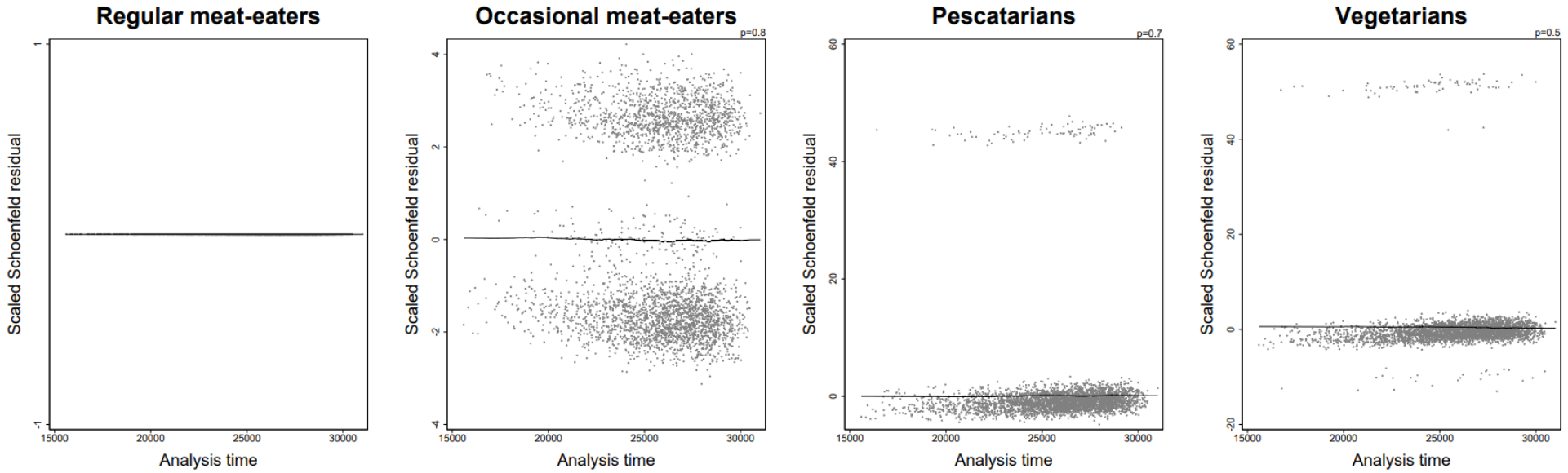



**Figure D3: Scaled Schoenfeld residuals over analysis time in regular meat-eaters, occasional meat-eaters, pescatarians, and vegetarians in the UK Biobank.**

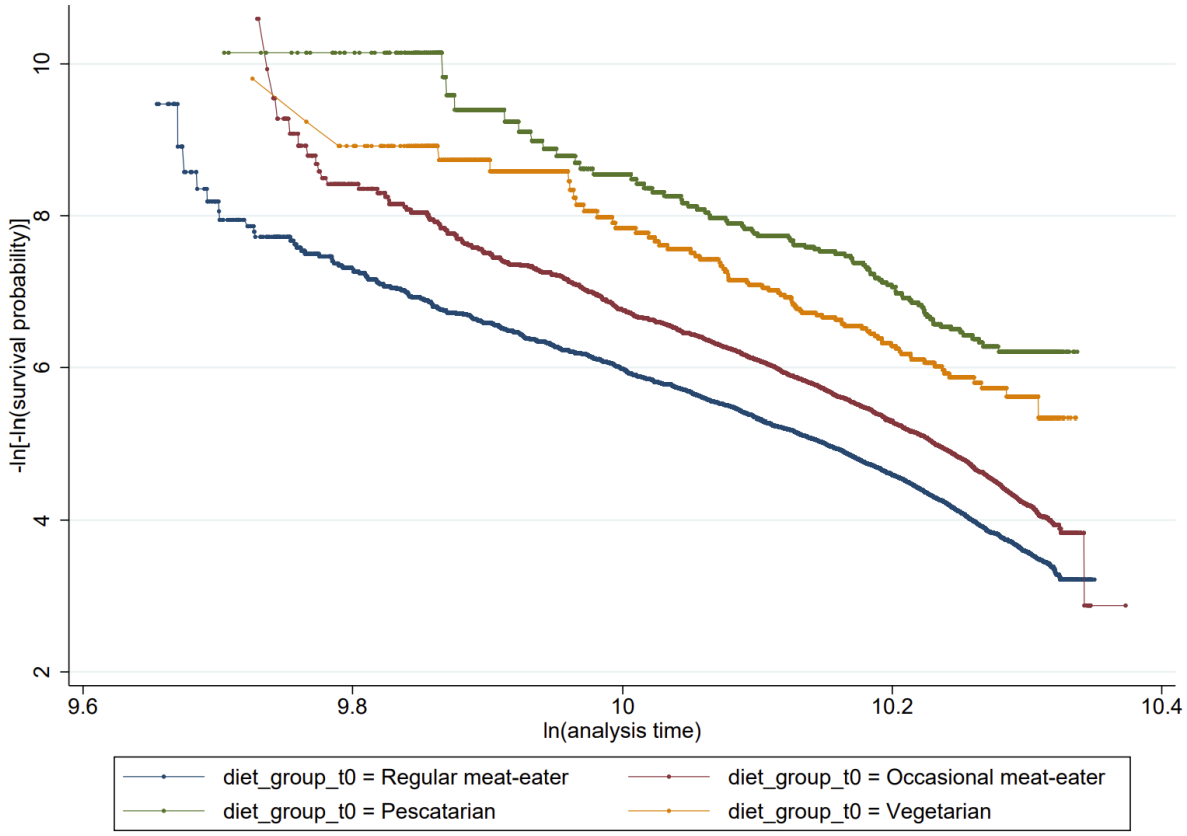



**Figure D4: Log(-log) survival plot for regular meat-eaters, occasional meat-eaters, pescatarians, and vegetarians in the UK Biobank.**

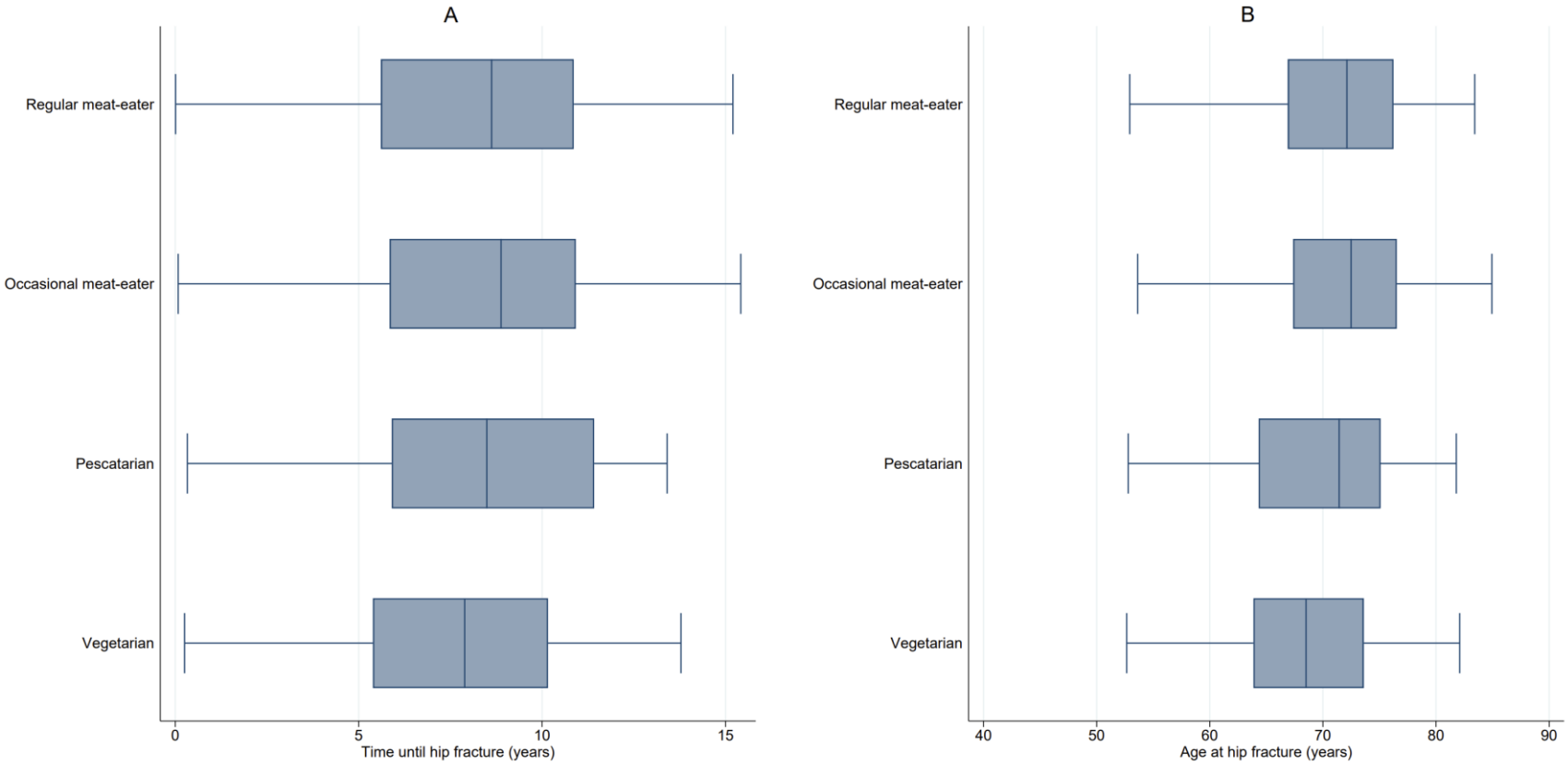



**Figure D5: A) Time until hip fracture and B) Age at hip fracture in regular meat-eaters, occasional meat-eaters, pescatarians, and vegetarians in the UK Biobank.**
The solid line within each box represents the median, and the outer box lines represent the interquartile range.

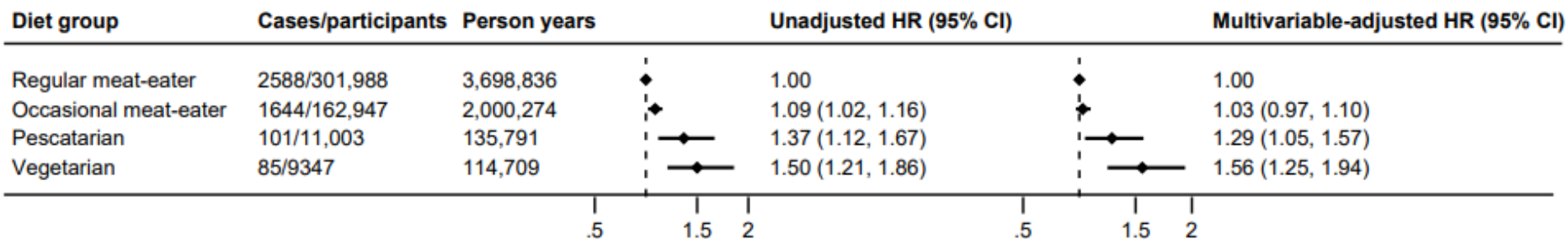



**Figure D6: Risk of hip fracture in occasional meat-eaters, pescatarians, and vegetarians compared to regular meat-eaters in the UK Biobank with multiple imputation via chained equations for missing covariate data.** Both models controlled for age, and the multivariable-adjusted model was adjusted for the following (all at recruitment): region (England, Scotland, Wales), sex (male, female), ethnicity (white, black, Asian, mixed, other), Townsend deprivation index (continuous), live alone (yes, no), smoking (current, former, never), supplementation (yes, no), physical activity in MET-minutes per week (continuous), alcohol consumption in drinks per day (continuous), body mass index (continuous), number of children (0, 1, 2, ≥ 3), menopausal status (premenopausal, postmenopausal), hormone replacement therapy (current, former, never), diabetes (yes, no), cancer (yes, no), cardiovascular disease (yes, no), and other fracture (yes, no). HR (95% CI): hazard ratio (95% confidence interval).

**Table D1: Strengthening the Reporting of Observational studies in Nutritional Epidemiology (STROBE-Nut) checklist.**

| Section/topic | Item number | Recommendation | Page (line number) |
|---|---|---|---|
| Title and abstract | 1 | Indicate the study's design with a commonly used term in the title or the abstract | 1 (2) |
| | | Provide in the abstract an informative and balanced summary of what was done and what was found | 2-3 (10-38) |
| Introduction | | | |

| | | | |
|---|---|---|---|
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 4-5 (39-77) |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 5 (74-77) |
| Methods | | | |
| Study design | 4 | Present key elements of study design early in the manuscript | 5-6 (82-96) |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 5-6 (82-96) |
| Participants | 6 | Cohort study - give the eligibility criteria, and the sources and methods of selection of participants; describe methods of follow-up | 5-6 (82-96); Additional file 1: Fig S1 |
| | | Cohort study - for matched studies, give matching criteria and number of exposed and unexposed Case-control study - for matched studies, give matching criteria and the number of controls per case | N/A |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers; give diagnostic criteria, if applicable | 6-7 (97-118); 7-9 (129-173); Additional file 1: Supplementary methods |
| Data sources/measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement); describe comparability of assessment methods if there is more than one group | 6-7 (97-118); 7-9 (129-173); Additional file 1: Supplementary methods |
| Bias | 9 | Describe any efforts to address potential sources of bias | 7-8 (129-142) |
| Study size | 10 | Explain how the study size was arrived at | 5-6 (91-96); 10 (186-191); Additional file 1: Fig S1 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses; if applicable, describe which groupings were chosen and why | 8 (151-155) |
| Statistical methods | 12 | Describe all statistical methods, including those used to control for confounding | 7-9 (119-184) |

| | | | |
|---|---|---|---|
| | | Describe any methods used to examine subgroups and interactions | 8 (150-155) |
| | | Explain how missing data were addressed | 9 (180-184) |
| | | Cohort study - if applicable, explain how loss to follow-up was addressed | N/A |
| | | Describe any sensitivity analyses | 9 (174-184); Additional file 1: Supplementary methods |
| Results | | | |
| Participants | 13* | Report numbers of individuals at each stage of study - e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 10 (186-191); Additional file 1: Fig S1 |
| | | Give reasons for nonparticipation at each stage Consider use of a flow diagram | 10 (186-191); Additional file 1: Fig S1 |
| Descriptive data | 14* | Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders | 10 (192-209); Table 1 |
| | | Indicate number of participants with missing data for each variable of interest Cohort study - summarize follow-up time (e.g., average and total amount) | 10 (186-191; 194-195); Additional file 1; Fig S1 |
| Outcome data | 15* | Cohort study - report numbers of outcome events or summary measures over time | 10 (194-195); Fig 1; Table 2 |
| Main results | 16 | Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval); make clear which confounders were adjusted for and why they were included Report category boundaries when continuous variables were categorized | 12 (212-216); Fig 1; Additional file 1: Supplementary methods |
| | | If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | 12 (215-216); Table 2 |
| Other analyses | 17 | Report other analyses done - e.g., analyses of subgroups and interactions, and sensitivity analyses | 15-19 (260-305); Tables 3, 4, S9, and Fig S6 |

| | | | |
|---|---|---|---|
| Discussion | | | |
| Key results | 18 | Summarize key results with reference to study objectives | 19 (307-314) |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision; discuss both direction and magnitude of any potential bias | 22-23 (385-418) |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 20-22 (333-384) |
| Generalizability | 21 | Discuss the generalizability (external validity) of the study results | 23 (416-418) |
| Other information | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 25 (437-439) |

**Table D2: Diet group categorisation and definitions.**

| Diet group | Definition |
|---|---|
| Regular meat-eater | Total meat intake ≥ 5 servings/week |
| Occasional meat-eater | Total meat intake < 5 servings/week & ≥ 1 serving/month |
| Pescatarian | Total meat intake < 1 serving/month & total fish intake ≥ 1 serving/month |
| Vegetarian | Total meat and fish intakes < 1 serving/month, intake of dairy products or eggs ≥ 1 serving/month |
| Vegan | Total meat, total fish, dairy products, and eggs intake < 1 serving/month |

Diet groups were defined as in Webster et al. (2022) (8).

**Table D3: Summary of mediation analyses using the inverse odds ratio weighting method in the UK Biobank.**

| | |
|---|---|
| **Step 1**<br>Determine if mediators differ between diet groups | Apply multiple linear regression models adjusted for confounders for each potential mediator (IV = diet group; DV = potential mediator) |
| **Step 2**<br>Create inverse odds ratio weights | Apply a logistic regression model adjusted for confounders for each mediator (IV = mediator; DV = diet group (binary))<br>For each mediator, create inverse odds ratio weights for each participant by taking the inverse of the predicted odds ratio for the binary diet groups. Regular meat-eaters (reference group) were assigned a weight of 1, and vegetarians were assigned the inverse odds ratio weights |
| **Step 3**<br>Calculate total effects | The total effect of the exposure (diet group, binary) on the outcome (hip fracture), conditioning on potential confounders, was estimated using adjusted Cox regression, with age as the underlying time-variable. This is the main Cox model in Fig 1 |
| **Step 4**<br>Calculate direct effects | The direct effect (i.e. the effect of the exposure on the outcome through pathways besides the mediator of interest) was estimated using adjusted Cox regression as in Step 3, but with the inverse odds ratio weights calculated in Step 2 applied |
| **Step 5**<br>Calculate indirect effects | The indirect effect (i.e. the effect of the exposure on the outcome through the mediator of interest only) was calculated as the HR or 95% CI for the total effect divided by the HR or 95% CI for the direct effect |
| **Step 6**<br>Calculate % mediation | % mediation (i.e. the proportion of an association explained by the mediator of interest) was calculated as: [[ln(HR total) – ln(HR direct)] divided by ln(HR total)], multiplied by 100 |

| | |
|---|---|
| **Step 7**<br>Estimate confidence intervals | HRs for total, direct, and indirect effects, as well as % mediation estimates, were bootstrapped to estimate confidence intervals. 300 replications were applied |

HR: hazard ratio. CI: 95% confidence intervals. IV: independent variable. DV: dependent variable.

**Table D4: Diet group classifications at recruitment and at the latest point of available follow-up in UK Biobank participants.**

| | | Diet group at recruitment | | | | |
|---|---|---|---|---|---|---|
| | **Total** | **Regular meat-eater** | **Occasional meat-eater** | **Pescatarian** | **Vegetarian** | **Vegan** |
| n participants (%) | 57,730 | 35801 (62.0) | 19009 (32.9) | 1621 (2.8) | 1223 (2.1) | 76 (0.1) |
| **Diet group at latest point of available follow-up** | | | | | | |
| Regular meat-eater (%) | 34,284 (59.4) | 27,277 (76.2) | 6,966 (36.6) | 32 (2.0) | 9 (0.7) | 0 (0.0) |
| Occasional meat-eater (%) | 19,713 (34.1) | 8,043 (22.5) | 11,487 (60.4) | 157 (9.7) | 25 (2.0) | 1 (1.3) |
| Pescatarian (%) | 1,896 (3.3) | 171 (0.5) | 336 (1.8) | 1,306 (80.6) | 81 (6.6) | 2 (2.6) |
| Vegetarian (%) | 1,673 (2.9) | 292 (0.8) | 199 (1.0) | 105 (6.5) | 1,058 (86.5) | 19 (25.0) |
| Vegan (%) | 164 (0.3) | 18 (0.1) | 21 (0.1) | 21 (1.3) | 50 (4.1) | 54 (71.1) |

**Table D5: Characteristics of UK Biobank participants by diet group at recruitment, stratified by sex.**

| Characteristics, mean (SD), or n (%) | Male | | | | Female | | | |
|---|---|---|---|---|---|---|---|---|
| | Regular meat-eater | Occasional meat-eater | Pescatarian | Vegetarian | Regular meat-eater | Occasional meat-eater | Pescatarian | Vegetarian |
| Participants (%) | 139,354 (69.8) | 54,842 (27.5) | 2811 (1.4) | 2,681 (1.3) | 119,411 (55.7) | 83,112 (38.8) | 6746 (3.1) | 4957 (2.3) |
| Cases (%) | 883 (0.6) | 381 (0.7) | 19 (0.7) | 24 (0.9) | 1162 (1.0) | 929 (1.1) | 59 (0.9) | 46 (0.9) |
| **Socio-demographics** | | | | | | | | |
| Age, years (SD) | 56.4 (8.2) | 57.6 (8.0) | 54.3 (8.0) | 53.1 (8.0) | 55.7 (8.1) | 56.5 (7.9) | 53.7 (8.0) | 52.8 (7.9) |
| Sex (%) | | | | | | | | |
| Male | 123,616 (88.7) | 48,870 (89.1) | 2524 (89.8) | 2454 (91.5) | 105,309 (88.2) | 73,622 (88.6) | 6057 (89.8) | 4512 (91.0) |
| Female | 9998 (7.2) | 3595 (6.6) | 172 (6.1) | 137 (5.1) | 9132 (7.6) | 6021 (7.2) | 403 (6.0) | 251 (5.1) |
| Region (%) | 5740 (4.1) | 2377 (4.3) | 115 (4.1) | 90 (3.4) | 4970 (4.2) | 3469 (4.2) | 286 (4.2) | 194 (3.9) |
| England | | | | | | | | |
| Scotland | 133,264 (95.6) | 51,817 (94.5) | 2620 (93.2) | 2176 (81.2) | 113,948 (95.4) | 78,963 (95.0) | 6357 (94.2) | 4106 (82.8) |
| Wales | 2002 (1.4) | 603 (1.1) | 43 (1.5) | 11 (0.4) | 2107 (1.8) | 1221 (1.5) | 95 (1.4) | 31 (0.6) |
| Ethnicity (%) | 2362 (1.7) | 1722 (3.1) | 100 (3.6) | 457 (17.0) | 1608 (1.3) | 1531 (1.8) | 185 (2.7) | 727 (14.7) |
| White | 677 (0.5) | 224 (0.4) | 21 (0.7) | 13 (0.5) | 768 (0.6) | 590 (0.7) | 63 (0.9) | 46 (0.9) |
| Black | 1049 (0.8) | 476 (0.9) | 27 (1.0) | 24 (0.9) | 980 (0.8) | 807 (1.0) | 46 (0.7) | 47 (0.9) |
| Asian | 46,611 (46.3) | 20,310 (51.4) | 1663 (72.6) | 1469 (68.8) | 35918 (42.5) | 29236 (48.9) | 3611 (66.9) | 2456 (63.4) |
| Mixed | -1.4 (3.1) | -1.4 (3.1) | -0.8 (3.2) | -0.6 (3.2) | -1.5 (3.0) | -1.3 (3.0) | -1.1 (3.0) | -0.8 (3.0) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Other | 22,319 (16.0) | 10,124 (18.5) | 629 (22.4) | 551 (20.6) | 19,087 (16.0) | 19,806 (23.8) | 1658 (24.6) | 1071 (21.6) |
| Degree-level education (%) | | | | | | | | |
| Townsend deprivation index (SD) | 3253 (4502) | 3102 (4170) | 3201 (4007) | 2940 (3731) | 2671 (3274) | 2741 (3325) | 2970 (3372) | 2872 (3668) |
| Live alone (%) | | | | | | | | |
| **Lifestyle** | 17,835 (12.8) | 5848 (10.7) | 233 (8.3) | 240 (9.0) | 10,481 (8.8) | 7340 (8.8) | 443 (6.6) | 277 (5.6) |
| Physical activity, METs.mins/week (SD) | 53,722 (38.6) | 21,134 (38.5) | 1031 (36.7) | 897 (33.5) | 37,028 (31.0) | 26256 (31.6) | 2406 (35.7) | 1389 (28.0) |
| Smoking status (%) | 67,797 (48.7) | 27,860 (50.8) | 1547 (55.0) | 1544 (57.6) | 71,902 (60.2) | 49,516 (59.6) | 3897 (57.8) | 3291 (66.4) |
| Current | 1.7 (1.8) | 1.4 (1.5) | 1.3 (1.4) | 1.0 (1.5) | 0.9 (1.1) | 0.8 (1.0) | 0.8 (1.0) | 0.6 (1.0) |
| Former | 60,761 (43.6) | 25,513 (46.5) | 1387 (49.3) | 1235 (46.1) | 63,627 (53.3) | 47,091 (56.7) | 3985 (59.1) | 2843 (57.4) |
| Never | | | | | | | | |
| Alcohol consumption (drinks/day) | 28.1 (4.3) | 27.3 (4.0) | 25.8 (3.6) | 25.8 (3.9) | 27.5 (5.2) | 26.4 (4.8) | 25.0 (4.5) | 25.5 (4.9) |
| Nutritional supplementation (%) | 295 (0.2) | 115 (0.2) | 14 (0.5) | 18 (0.7) | 660 (0.6) | 731 (0.9) | 135 (2.0) | 102 (2.1) |
| **Anthropometrics** | 32,023 (23.0) | 15,805 (28.8) | 1273 (45.3) | 1207 (45.0) | 42,783 (35.8) | 36,806 (44.3) | 3765 (55.8) | 2568 (51.8) |
| BMI, kg/m2 (SD) | 107,036 (76.8) | 38,922 (71.0) | 1524 (54.2) | 1456 (54.3) | 75,968 (63.6) | 45,575 (54.8) | 2846 (42.2) | 2287 (46.1) |
| Height, m (SD) | 175.8 (6.8) | 175.6 (6.8) | 176.4 (6.8) | 175.6 (7.2) | 162.6 (6.2) | 162.7 (6.3) | 163.7 (6.3) | 162.5 (6.8) |
| **Comorbidities** | | | | | | | | |
| Prevalence of diabetes (%) | 16,660 (12.0) | 5996 (10.9) | 158 (5.6) | 253 (9.4) | 8502 (7.1) | 4863 (5.9) | 237 (3.5) | 301 (6.1) |
| Prevalence of cancer (%) | 10,971 (7.9) | 4555 (8.3) | 187 (6.7) | 119 (4.4) | 14,817 (12.4) | 10,666 (12.8) | 814 (12.1) | 512 (10.3) |
| Prevalence of CVD (%) | 19,693 (14.1) | 8129 (14.8) | 244 (8.7) | 232 (8.7) | 10,436 (8.7) | 6724 (8.1) | 365 (5.4) | 272 (5.5) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Prevalence of other fracture (%) | 13,577 (9.7) | 4733 (8.6) | 314 (11.2) | 256 (9.5) | 12,223 (10.2) | 8827 (10.6) | 712 (10.6) | 554 (11.2) |
| **Female-specific covariates** | N/A | N/A | N/A | N/A | | | | |
| Menopausal status (%) | N/A | N/A | N/A | N/A | | | | |
| Premenopausal | N/A | N/A | N/A | N/A | 36,214 (30.3) | 21,389 (25.7) | 2516 (37.3) | 2043 (41.2) |
| Postmenopausal | N/A | N/A | N/A | N/A | 83,197 (69.7) | 61,723 (74.3) | 4230 (62.7) | 2914 (58.8) |
| HRT use (%) | N/A | N/A | N/A | N/A | | | | |
| Current | N/A | N/A | N/A | N/A | 7385 (6.2) | 5111 (6.1) | 394 (5.8) | 212 (4.3) |
| Former | N/A | N/A | N/A | N/A | 33,525 (28.1) | 24,129 (29.0) | 1331 (19.7) | 773 (15.6) |
| Never | N/A | N/A | N/A | N/A | 78,501 (65.7) | 53,872 (64.8) | 5021 (74.4) | 3972 (80.1) |
| ≥ 1 children (%) | N/A | N/A | N/A | N/A | 99,652 (83.5) | 65,071 (78.3) | 4673 (69.3) | 3431 (69.2) |

SD: standard deviation; METs: Metabolic equivalents; BMI: body mass index; CVD: cardiovascular disease; HRT: hormone replacement therapy.

**Table D6: Dietary characteristics of UK Biobank participants by diet group at recruitment.**

| Dietary food or nutrient intake | Total | Regular meat-eater | Occasional meat-eater | Pescatarian | Vegetarian |
|---|---|---|---|---|---|
| **From FFQ, n participants** | 403,968 | 252,126 | 134,940 | 9,435 | 7,467 |
| Poultry (servings/day) | 1.9 (1.2) | 2.5 (1.1) | 1.2 (0.8) | 0.0 (0.1) | 0.0 (0.1) |
| Beef (servings/day) | 0.9 (0.8) | 1.1 (0.9) | 0.6 (0.4) | 0.0 (0.1) | 0.0 (0.0) |
| Lamb (servings/day) | 0.6 (0.5) | 0.7 (0.6) | 0.5 (0.3) | 0.0 (0.0) | 0.0 (0.0) |
| Pork (servings/day) | 0.6 (0.6) | 0.7 (0.6) | 0.5 (0.3) | 0.0 (0.0) | 0.0 (0.0) |
| Processed meat (servings/day) | 1.5 (1.4) | 2.0 (1.4) | 0.7 (0.5) | 0.0 (0.1) | 0.0 (0.1) |
| Oily fish (servings/day) | 1.1 (1.0) | 1.1 (1.0) | 1.2 (1.1) | 1.7 (1.4) | 0.0 (0.1) |
| Non-oily fish (servings/day) | 1.2 (0.9) | 1.2 (0.9) | 1.1 (0.9) | 1.5 (1.2) | 0.0 (0.1) |
| Tea (servings/day) | 3.4 (2.8) | 3.4 (2.8) | 3.3 (2.7) | 3.3 (2.8) | 3.1 (2.9) |
| Coffee (servings/day) | 2.0 (2.0) | 2.1 (2.1) | 1.9 (2.0) | 1.8 (1.9) | 1.7 (2.0) |
| Fruit (servings/day) | 2.7 (1.9) | 2.5 (1.9) | 2.8 (2.0) | 3.3 (2.1) | 3.3 (2.5) |
| Vegetables (servings/day) | 2.5 (1.6) | 2.4 (1.6) | 2.5 (1.7) | 3.1 (2.2) | 3.2 (2.2) |
| **From 24h recall, n participants** | 181,142 | 110,875 | 60,910 | 5,224 | 4,133 |
| Wholegrains (g/day) | 97.0 (90.9) | 92.2 (88.8) | 102.4 (92.4) | 120.1 (98.7) | 117.0 (100.7) |
| Nuts and legumes (servings/day) | 0.4 (0.6) | 0.4 (0.6) | 0.4 (0.6) | 0.6 (0.7) | 0.7 (0.8) |
| SSB's (ml/day) | 4.1 (20.4) | 1.5 (12.0) | 3.6 (17.8) | 29.8 (50.0) | 47.0 (60.6) |
| Fruit juice (ml/day) | 162.8 (277.2) | 178.9 (290.9) | 137.4 (251.2) | 130.9 (251.3) | 145.9 (264.1) |
| Meat substitutes (g/day) | 106.7 (145.4) | 105.6 (145.0) | 106.9 (144.3) | 118.4 (152.8) | 120.9 (160.7) |
| Milk (ml/day) | 154.9 (141.4) | 161.7 (142.7) | 148.3 (138.9) | 122.5 (135.8) | 108.9 (130.2) |
| Cream (g/day) | 1.2 (4.6) | 1.2 (4.7) | 1.2 (4.5) | 1.0 (4.3) | 0.8 (3.7) |
| Dairy desserts (g/day) | 23.7 (46.2) | 24.9 (47.4) | 22.6 (44.9) | 17.6 (38.2) | 18.8 (39.8) |
| Cheese (g/day) | 17.4 (21.0) | 16.6 (20.7) | 17.5 (20.8) | 24.6 (23.6) | 26.8 (25.7) |
| Yoghurt (g/day) | 43.0 (59.1) | 40.9 (58.3) | 46.2 (60.2) | 48.4 (61.6) | 44.7 (60.6) |
| Eggs (g/day) | 21.4 (40.3) | 22.0 (40.9) | 20.3 (39.3) | 23.4 (41.4) | 19.2 (38.2) |
| Protein (g/day) | 81.2 (25.1) | 84.8 (25.5) | 76.9 (23.3) | 68.8 (21.2) | 63.1 (21.2) |

| | | | | | |
|---|---|---|---|---|---|
| Protein (g/kg BW/d) | 1.1 (0.4) | 1.1 (0.4) | 1.1 (0.4) | 1.0 (0.3) | 0.9 (0.3) |
| Protein | | | | | |
| < 0.75 g/kg BW/d | 29,571 (16.3) | 16,377 (14.8) | 10,768 (17.7) | 1,113 (21.3) | 1,313 (31.8) |
| ≥ 0.75 g/kg BW/d | 151,571 (83.7) | 94,498 (85.2) | 50,142 (82.3) | 4,111 (78.7) | 2,820 (68.2) |
| Protein | | | | | |
| < 1.2 g/kg BW/d | 123,877 (68.4) | 73,566 (66.4) | 42,778 (70.2) | 4,052 (77.6) | 3,481 (84.2) |
| ≥ 1.2 g/kg BW/d | 57,265 (31.6) | 37,309 (33.6) | 18,132 (29.8) | 1,172 (22.4) | 652 (15.8) |
| Animal protein (g/day) | 52.8 (21.7) | 56.8 (21.6) | 49.2 (19.7) | 33.6 (16.5) | 23.1 (13.4) |
| Vegetable protein (g/day) | 28.4 (10.6) | 28.0 (10.0) | 27.7 (10.3) | 35.2 (13.5) | 40.0 (16.1) |
| Total carotenoids (µg/day) | 2983 (2823) | 2916 (2748) | 3022 (2874) | 3486 (3244) | 3596 (3279) |
| Alpha carotene (µg/day) | 518.7 (645.2) | 517.6 (643.2) | 516.6 (645.9) | 537.4 (664.2) | 555.2 (661.6) |
| Beta carotene (µg/day) | 2637 (2444) | 2575 (2375) | 2672 (2492) | 3097 (2822) | 3192 (2865) |
| Beta cryptoxanthin (µg/day) | 174.6 (380.6) | 163.7 (359.1) | 183.2 (398.0) | 240.5 (480.1) | 253.3 (497.0) |
| Calcium (mg/day) | 987.8 (348.7) | 990.9 (349.9) | 970.2 (340.3) | 1054 (365.8) | 1081 (387.5) |
| Carbohydrates (g/day) | 255.5 (81.0) | 258.7 (82.4) | 248.1 (77.8) | 259.9 (76.5) | 272.6 (86.3) |
| Starch (g/day) | 129.7 (49.9) | 132.4 (50.4) | 123.8 (47.9) | 132.5 (50.0) | 142.6 (56.3) |
| Fibre (g/day) | 17.9 (6.8) | 17.6 (6.6) | 18.0 (6.8) | 21.2 (7.4) | 22.6 (8.7) |
| Sugar (g/day) | 61.2 (36.8) | 63.6 (38.3) | 57.5 (34.1) | 55.1 (31.4) | 58.0 (34.1) |
| Energy (kcal/day) | 8695 (2537) | 8924 (2593) | 8318 (2384) | 8408 (2370) | 8485 (2674) |
| Fat (g/day) | 73.6 (29.2) | 75.8 (29.9) | 69.9 (27.6) | 72.1 (28.5) | 73.4 (31.1) |
| Animal fat (g/day) | 41.3 (20.2) | 43.5 (20.6) | 38.6 (18.8) | 33.4 (18.4) | 30.6 (19.4) |
| MUFA (g/day) | 26.7 (11.3) | 27.6 (11.5) | 25.2 (10.6) | 25.8 (11.0) | 26.3 (12.1) |
| PUFA (g/day) | 874.2 (393.4) | 859.3 (373.6) | 894.4 (424.3) | 1012.4 (470.7) | 804.1 (257.3) |
| SFA (g/day) | 27.2 (12.3) | 28.1 (12.5) | 25.9 (11.6) | 25.4 (11.7) | 25.8 (12.5) |
| Omega-3 fatty acids (mg/day) | 2000 (1014) | 2018 (1002) | 1959 (1029) | 2237 (1143.5) | 1823 (838.5) |
| Omega-6 fatty acids (g/day) | 11.0 (5.2) | 11.2 (5.2) | 10.5 (5.1) | 12.1 (5.7) | 13.1 (6.5) |
| Trans fats (g/day) | 1.2 (0.7) | 1.2 (0.7) | 1.1 (0.6) | 1.1 (0.7) | 1.2 (0.7) |
| Iron (mg/day) | 12.4 (3.9) | 12.6 (3.9) | 12.1 (3.8) | 12.9 (4.1) | 13.3 (4.7) |

| | | | | | |
|---|---|---|---|---|---|
| Haem iron (mg/day) | 0.6 (0.5) | 0.7 (0.5) | 0.5 (0.5) | 0.2 (0.2) | 0.0 (0.1) |
| Iodine (µg/day) | 211.3 (102.9) | 215.2 (103.9) | 207.9 (101.7) | 208.2 (107.4) | 161.0 (68.7) |
| Magnesium (mg/day) | 334.7 (97.4) | 335.5 (96.6) | 328.8 (95.9) | 361.7 (103.8) | 366.3 (119.7) |
| Manganese (mg/day) | 4.2 (1.5) | 4.2 (1.5) | 4.3 (1.5) | 5.1 (1.7) | 5.4 (2.0) |
| Niacin (mg/day) | 38.3 (12.1) | 40.0 (12.2) | 36.3 (11.3) | 32.3 (10.0) | 29.3 (9.7) |
| Phosphorus (mg/day) | 1433 (401.8) | 1461 (405.3) | 1389 (389.4) | 1403 (395.7) | 1376 (427.5) |
| Potassium (mg/day) | 3682 (1094) | 3721 (1095) | 3609 (1079) | 3709 (1084) | 3663 (1214) |
| Retinol (µg/day) | 474.3 (925.2) | 498.1 (979.5) | 451.2 (887.0) | 345.8 (251.3) | 338.9 (202.7) |
| Riboflavin (mg/day) | 1.9 (0.6) | 1.9 (0.6) | 1.9 (0.6) | 1.9 (0.7) | 2.0 (0.9) |
| Selenium (µg/day) | 52.5 (24.6) | 54.0 (24.6) | 51.2 (24.5) | 52.2 (26.1) | 34.8 (14.5) |
| Sodium (mg/day) | 1971 (792.5) | 2038 (819.6) | 1851 (730.9) | 1950 (733.4) | 1962 (785.7) |
| Thiamine (mg/day) | 1.9 (0.7) | 1.9 (0.7) | 1.8 (0.7) | 2.1 (1.1) | 2.3 (1.2) |
| Nitrogen (g/day) | 12.7 (3.9) | 13.2 (4.0) | 12.0 (3.6) | 11.2 (3.5) | 10.4 (3.5) |
| Folate (µg/day) | 313.9 (109.9) | 314.4 (108.9) | 307.6 (108.0) | 341.3 (118.9) | 358.1 (134.5) |
| Vitamin B12 (µg/day) | 6.2 (3.4) | 6.4 (3.4) | 6.1 (3.3) | 5.6 (3.1) | 3.7 (2.0) |
| Vitamin B6 (mg/day) | 2.1 (0.7) | 2.1 (0.7) | 2.0 (0.7) | 1.9 (0.6) | 1.8 (0.7) |
| Vitamin C (mg/day) | 128.4 (78.9) | 126.0 (77.7) | 130.3 (79.6) | 144.0 (82.1) | 147.4 (90.4) |
| Vitamin D (µg/day) | 3.6 (2.9) | 3.7 (2.8) | 3.6 (3.0) | 3.8 (3.4) | 2.1 (1.6) |
| Zinc (mg/day) | 9.8 (3.4) | 10.1 (3.5) | 9.3 (3.2) | 8.6 (2.8) | 9.0 (3.3) |

Participants with missing dietary data were excluded. FFQ: food frequency questionnaire. SSB: sugar-sweetened beverages; BW: body weight; MUFA: mono-unsaturated fatty acids; PUFA: polyunsaturated fatty acids; SFA: saturated fatty acids.

**Table D7: Characteristics of UK Biobank participants at recruitment that were included or excluded from analyses.**

| Characteristics, mean (SD) or n (%) | 489,703 potentially eligible participants | | | | 75,789 participants excluded due to missing covariate data | | | |
|---|---|---|---|---|---|---|---|---|
| | Regular meat-eater | Occasional meat-eater | Pescatarian | Vegetarian | Regular meat-eater | Occasional meat-eater | Pescatarian | Vegetarian |
| Participants (%) | 304,576 (62.2) | 164,591 (33.6) | 11,104 (2.3) | 9,432 (1.9) | 45,811 (60.4) | 26,637 (35.1) | 1,547 (2.0) | 1,794 (2.4) |
| Cases (%) | 2588 (0.8) | 1644 (1.0) | 101 (0.9) | 85 (0.9) | 543 (1.2) | 334 (1.3) | 23 (1.5) | 15 (0.8) |
| **Socio-demographics** | | | | | | | | |
| Age, years (SD) | 56.3 (8.1) | 57.2 (7.9) | 54.1 (8.0) | 53.3 (8.0) | 57.7 (7.9) | 58.5 (7.6) | 55.6 (7.9) | 55.0 (8.1) |
| Sex (%) | | | | | | | | |
| Male | 155,610 (51.1) | 61,532 (37.4) | 3086 (27.8) | 3193 (33.9) | 16,256 (35.5) | 6690 (25.1) | 275 (17.8) | 512 (28.5) |
| Female | 148,966 (48.9) | 103,059 (62.6) | 8018 (72.2) | 6239 (66.1) | 29,555 (64.5) | 19,947 (74.9) | 1272 (82.2) | 1282 (71.5) |
| Region (%) | | | | | | | | |
| England | 269,451 (88.5) | 146,172 (88.8) | 9978 (89.9) | 8631 (91.5) | 40,526 (88.5) | 23,680 (88.9) | 1397 (90.3) | 1665 (92.8) |
| Scotland | 22,586 (7.4) | 11,401 (6.9) | 657 (5.9) | 464 (4.9) | 3456 (7.5) | 1785 (6.7) | 82 (5.3) | 76 (4.2) |
| Wales | 12,539 (4.1) | 7,018 (4.3) | 469 (4.2) | 337 (3.6) | 1829 (4.0) | 1172 (4.4) | 68 (4.4) | 53 (3.0) |
| Ethnicity (%) | | | | | | | | |
| White | 289,386 (95.3) | 155,336 (94.7) | 10,344 (93.7) | 7147 (80.7) | 42,174 (94.2) | 24,556 (94.0) | 1367 (92.2) | 865 (71.1) |
| Black | 5028 (1.7) | 2302 (1.4) | 168 (1.5) | 46 (0.5) | 919 (2.1) | 478 (1.8) | 30 (2.0) | 4 (0.3) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Asian | 4877 (1.6) | 3916 (2.4) | 342 (3.1) | 1508 (17.0) | 907 (2.0) | 663 (2.5) | 57 (3.8) | 324 (26.6) |
| Mixed | 1729 (0.6) | 964 (0.6) | 96 (0.9) | 67 (0.8) | 284 (0.6) | 150 (0.6) | 12 (0.8) | 8 (0.7) |
| Other | 2538 (0.8) | 1550 (0.9) | 89 (0.8) | 87 (1.0) | 509 (1.1) | 267 (1.0) | 16 (1.1) | 16 (1.3) |
| Degree-level education (%) | 92,012 (43.1) | 55,807 (48.3) | 5938 (67.1) | 4401 (63.9) | 9483 (33.7) | 6261 (38.4) | 664 (57.4) | 476 (54.2) |
| Townsend deprivation index (SD) | -1.4 (3.1) | -1.3 (3.1) | -1.0 (3.1) | -0.6 (3.2) | -1.0 (3.2) | -1.0 (3.2) | -0.8 (3.2) | 0.3 (3.5) |
| Live alone (%) | 49,083 (16.2) | 35,966 (22.0) | 2686 (24.4) | 1904 (21.6) | 7677 (17.5) | 6036 (23.7) | 399 (27.6) | 282 (23.7) |
| **Lifestyle** | | | | | | | | |
| Physical activity, METs.mins/week (SD) | 2975 (3988) | 2880 (3683) | 3039 (3579) | 2912 (3892) | 2738 (3864) | 2794 (3581) | 3044 (3722) | 3227 (6611) |
| Smoking status (%) | | | | | | | | |
| Current | 33,746 (11.1) | 16,026 (9.8) | 800 (7.2) | 611 (6.5) | 5430 (12.1) | 2838 (10.9) | 124 (8.2) | 94 (5.4) |
| Former | 106,287 (35.0) | 56,172 (34.3) | 3963 (35.8) | 2601 (27.7) | 15,537 (34.7) | 8782 (33.8) | 526 (34.8) | 315 (17.9) |
| Never | 163,514 (53.9) | 91,761 (56.0) | 6304 (57.0) | 6181 (65.8) | 23,815 (53.2) | 14,385 (55.3) | 860 (57.0) | 1346 (76.7) |
| Alcohol consumption (drinks/day) | 1.3 (1.5) | 1.0 (1.2) | 0.9 (1.2) | 0.7 (1.2) | 1.0 (1.4) | 0.8 (1.1) | 0.8 (1.1) | 0.4 (0.8) |
| Nutritional supplementation (%) | 147,359 (48.5) | 87,077 (53.0) | 6298 (56.8) | 4789 (50.9) | 22,971 (51.2) | 14,473 (55.2) | 926 (60.4) | 711 (40.4) |
| **Anthropometrics** | | | | | | | | |
| BMI, kg/m2 (SD) | 27.9 (4.8) | 26.8 (4.6) | 25.3 (4.3) | 25.8 (4.7) | 28.3 (5.2) | 27.3 (5.0) | 25.7 (4.7) | 26.8 (5.2) |
| Height, m (SD) | 169.2 (9.3) | 167.4 (9.1) | 167.1 (8.7) | 166.5 (9.4) | 166.3 (9.0) | 165.0 (8.5) | 165.0 (8.6) | 163.8 (9.0) |
| **Comorbidities** | | | | | | | | |
| Prevalence of diabetes (%) | 30,733 (10.1) | 13,534 (8.2) | 494 (4.4) | 790 (8.4) | 5571 (12.2) | 2675 (10.0) | 99 (6.4) | 236 (13.2) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Prevalence of cancer (%) | 31,043 (10.2) | 18,461 (11.2) | 1171 (10.5) | 760 (8.1) | 5255 (11.5) | 3240 (12.2) | 170 (11.0) | 129 (7.2) |
| Prevalence of CVD (%) | 36,856 (12.1) | 18,461 (11.2) | 735 (6.6) | 716 (7.6) | 6727 (14.7) | 3608 (13.5) | 126 (8.1) | 212 (11.8) |
| Prevalence of other fracture (%) | 30,891 (10.1) | 16,455 (10.0) | 1206 (10.9) | 946 (10.0) | 5091 (11.1) | 2895 (10.9) | 180 (11.6) | 136 (7.6) |
| **Female-specific covariates** | | | | | | | | |
| Menopausal status (%) | | | | | | | | |
| Premenopausal | 41,426 (28.0) | 24,390 (23.8) | 2841 (35.7) | 2323 (38.4) | 5212 (18.3) | 3001 (15.5) | 325 (26.9) | 280 (25.5) |
| Postmenopausal | 106,539 (72.0) | 78,085 (76.2) | 5115 (64.3) | 3733 (61.6) | 23,342 (81.7) | 16,362 (84.5) | 885 (73.1) | 819 (74.5) |
| HRT use (%) | | | | | | | | |
| Current | 9117 (6.5) | 6169 (6.4) | 477 (6.2) | 266 (4.4) | 1732 (8.2) | 1058 (7.6) | 83 (8.7) | 54 (5.2) |
| Former | 39,940 (28.4) | 28,412 (29.3) | 1532 (19.9) | 906 (15.1) | 6415 (30.5) | 4283 (30.7) | 201 (21.0) | 133 (12.7) |
| Never | 91,388 (65.1) | 62,498 (64.4) | 5695 (73.9) | 4830 (80.5) | 12,887 (61.3) | 8626 (61.8) | 674 (70.4) | 858 (82.1) |
| ≥ 1 children (%) | 124,995 (84.0) | 81,340 (79.0) | 5566 (69.5) | 4141 (66.5) | 25,343 (86.1) | 16,269 (82.0) | 893 (70.6) | 710 (55.9) |

SD: standard deviation; METs: Metabolic equivalents; BMI: body mass index; CVD: cardiovascular disease; HRT: hormone replacement therapy.

**Table D8: Adjusted and relative means (95% confidence intervals) of potential mediators at recruitment across diet groups in the UK Biobank.**

| Diet group | Cases / participants | Adjusted mean (95% CI) | Relative mean (95% CI) |
|---|---|---|---|
| **BMI** | **3503/413,914** | | |
| Regular meat-eater | 2045/256,720 | 27.74 (27.72, 27.75) | 1.00 |
| Occasional meat-eater | 1310/136,644 | 26.81 (26.78, 26.83) | 0.97 (0.97, 0.97) |
| Pescatarian | 78/9479 | 25.56 (25.47, 25.65) | 0.92 (0.92, 0.92) |
| Vegetarian | 70/7568 | 25.93 (25.83, 26.03) | 0.93 (0.93, 0.94) |
| **Heel BMD t-score** | **3016/364,864** | | |
| Regular meat-eater | 1768/229,735 | -0.21 (-0.21, -0.20) | 1.00 |
| Occasional meat-eater | 1122/122,799 | -0.21 (-0.21, -0.20) | 1.00 (1.00, 1.00) |
| Pescatarian | 66/8512 | -0.20 (-0.23, -0.18) | 1.05 (0.90, 1.10) |
| Vegetarian | 60/6834 | -0.22 (-0.25, -0.20) | 0.95 (0.81, 1.00) |
| **FFM** | **3418/408,176** | | |
| Regular meat-eater | 1990/253,148 | 54.13 (54.11, 54.15) | 1.00 |
| Occasional meat-eater | 1288/134,767 | 53.29 (53.26, 53.31) | 0.98 (0.98, 0.98) |
| Pescatarian | 74/9368 | 52.41 (52.31, 52.52) | 0.97 (0.97, 0.97) |
| Vegetarian | 66/7475 | 52.48 (52.36, 52.60) | 0.97 (0.97, 0.97) |
| **Hand grip strength** | **3483/412,770** | | |
| Regular meat-eater | 20321/256,050 | 33.39 (33.36, 33.42) | 1.00 |
| Occasional meat-eater | 1305/136,247 | 33.25 (33.21, 33.29) | 1.00 (1.00, 1.00) |
| Pescatarian | 78/9443 | 33.61 (33.46, 33.76) | 1.01 (1.00, 1.01) |
| Vegetarian | 69/7547 | 33.23 (33.06, 33.40) | 1.00 (0.99, 1.00) |
| **Vitamin D** | **3093/370,769** | | |
| Regular meat-eater | 1807/230,331 | 44.3 (44.3, 44.3) | 1.00 |
| Occasional meat-eater | 1151/122,150 | 44.3 (44.3, 44.7) | 1.00 (1.00, 1.00) |
| Pescatarian | 68/8563 | 42.9 (42.5, 43.4) | 0.99 (0.99, 0.99) |
| Vegetarian | 67/6632 | 36.6 (36.2, 37.0) | 0.95 (0.95, 0.95) |
| **IGF-1** | **3233/385,653** | | |
| Regular meat-eater | 1880/239,135 | 21.65 (21.63, 21.67) | 1.00 |
| Occasional meat-eater | 1214/127,345 | 21.42 (21.39, 21.45) | 0.99 (0.99, 0.99) |
| Pescatarian | 70/8861 | 21.37 (21.26, 21.49) | 0.99 (0.98, 0.99) |
| Vegetarian | 69/7079 | 20.39 (20.27, 20.52) | 0.94 (0.94, 0.95) |

Adjusted means were calculated from multiple linear regression models, all of which were adjusted for (all at recruitment): age, region, sex, ethnicity, Townsend Deprivation Index, live alone, smoking status, nutritional supplementation , MET minutes of physical activity per week, alcohol consumption in drinks per day, prevalence of diabetes, cancer, cardiovascular disease, and other non-hip fractures, number of children, menopausal status, and hormone replacement therapy use. Models for heel BMD, hand grip strength,

vitamin D and IGF-1 were also adjusted for BMI, whilst the model for FFM was adjusted for height. Relative means were calculated by comparing adjusted means for each diet group with that of regular meat-eaters. BMI: body mass index; FFM: fat-free mass; IGF-1: insulin-like growth factor-1; HR (95% CI): hazard ratio (95% confidence intervals).

**Table D9: Risk of hip fracture by diet group in the UK Biobank with varying restrictions.**

| Diet group | Cases/subjects | HR (95% CI) |
|---|---|---|
| **Adjusted model** | 3503/413,914 | |
| Regular meat-eater (reference) | 2045/258,765 | 1 |
| Occasional meat-eater | 1310/137,954 | 0.99 (0.93, 1.07) |
| Pescatarian | 78/9557 | 1.08 (0.86, 1.35) |
| Vegetarian | 70/7638 | 1.50 (1.18, 1.91) |
| **Adjusted for height and weight instead of BMI** | 3503/413,914 | |
| Regular meat-eater (reference) | 2045/258,765 | 1 |
| Occasional meat-eater | 1310/137,954 | 0.99 (0.92, 1.06) |
| Pescatarian | 78/9557 | 1.06 (0.85, 1.34) |
| Vegetarian | 70/7638 | 1.49 (1.17, 1.89) |
| **Excluding participants with < 3 years of follow-up** | 3116/410,187 | |
| Regular meat-eater (reference) | 1803/256,348 | 1 |
| Occasional meat-eater | 1179/136,748 | 1.01 (0.94, 1.09) |
| Pescatarian | 70/9496 | 1.14 (0.90, 1.45) |
| Vegetarian | 64/7595 | 1.64 (1.27, 2.11) |
| **Excluding participants on long-term treatment for illness** | 998/183,711 | |
| Regular meat-eater (reference) | 558/113,299 | 1 |
| Occasional meat-eater | 377/61262 | 0.98 (0.86, 1.12) |
| Pescatarian | 28/5096 | 1.01 (0.69, 1.48) |
| Vegetarian | 35/4054 | 1.91 (1.35, 2.70) |
| **Vegetarians and vegans separated** | 3503/413,914 | |
| Regular meat-eater (reference) | 2045/258,765 | 1 |
| Occasional meat-eater | 1310/137,954 | 0.99 (0.93, 1.07) |
| Pescatarian | 78/9557 | 1.08 (0.86, 1.35) |
| Vegetarian | 60/7238 | 1.38 (1.06, 1.79) |
| Vegan | 10/400 | 3.26 (1.75, 6.08) |
| **Accounting for death as a competing risk** | 3503/413,914 | |
| Regular meat-eater (reference) | 2045/258,765 | 1 |
| Occasional meat-eater | 1310/137,954 | 1.00 (0.93, 1.08) |
| Pescatarian | 78/9557 | 1.06 (0.85, 1.34) |
| Vegetarian | 70/7638 | 1.47 (1.15, 1.88) |

The adjusted model controlled for age, and was adjusted for the following (all at recruitment): region (England, Scotland, Wales), sex (male, female), ethnicity (white, black, Asian, mixed, other), Townsend deprivation index (continuous), live alone (yes, no), smoking (current, former, never), supplementation (yes, no), physical activity (continuous), alcohol consumption (continuous), body mass index (continuous), number of children (0, 1, 2, ≥ 3), menopausal status (premenopausal, postmenopausal), hormone

replacement therapy (current, former, never), diabetes (yes, no), cancer (yes, no), cardiovascular disease (yes, no), and other fracture (yes, no). All other models were based on the adjusted model. HR (95% CI): hazard ratio (95% confidence interval). HRT: hormone replacement therapy use at recruitment.

# Supplementary Methods

## Diet group classification

At recruitment and in the repeat assessments in 2012-2013, 2014, and in 2019, participants were asked questions on their frequency of intake of oily fish, non-oily fish, processed meat, poultry, beef, lamb/mutton, pork, eggs, and dairy products (22). Questions on meat and fish were asked in the form of "how often do you eat [specific food or beverage?]" or similar. Options were 1 "never", 2 "less than once a week", "3 once a week", 4 "2-4 times a week", 5 "5-6 times a week", or 6 "once or more daily". Responses to these individual questions were converted into weekly-based consumption frequencies as follows: 0, 0.5, 1, 3, 5.5, 7 servings/week. Participants could also answer "do not know" or "prefer not to say" for these questions. Responses to questions on intake of processed meat, poultry, beef, lamb/mutton, and pork were summed to form total meat intake (servings/week); and questions on intake of oily and non-oily fish intake were summed to form total fish intake (servings/week). Intake of eggs and dairy products was assessed by asking participants "Which of the following do you never eat?", with options of "Eggs or foods containing eggs", "Dairy products", "I eat all of the above", or "Prefer not to answer".

Participants were then classified as regular meat-eaters (ate meat ≥ 5 times/week), occasional meat-eaters (ate meat < 5 times/week), pescatarians (ate fish but not meat), vegetarians (ate eggs or dairy but not meat or fish), or vegans (did not eat meat, fish, eggs, or dairy) at recruitment and at the latest point of available follow-up in each participant, with vegans combined into the vegetarian group. Diet group classifications at recruitment were used to represent diet group over follow-up. We considered non-responders for each specific question to be non-consumers of that food item, however the final complete-case analysis did not include any non-responders for questions related to meat and fish intake. Participants who answered "do not know" or "prefer not to say" to questions on meat, fish, eggs, or dairy intake were coded as missing, and were excluded from analyses, unless there was sufficient data to classify the participant into a diet group (e.g. if a participant reported consuming ≥ 5 servings/week of a specific type of meat but had missing data for other meat types, that participant could be classified as a regular meat-eater).

## Other dietary measurements

From April 2009 to September 2010, the Oxford WebQ 24h dietary recall was added to assessment centres to provide a more detailed assessment of diet. After that, the WebQ questionnaire was administered online once every 3-4 months from February 2011 until June 2012, resulting in four follow-up instances. In each instance, participants were asked to report the number of portions for each item they consumed over the prior 24 h. These were multiplied by standard portion sizes to calculate daily intake in grams per day for each specific food item at each instance (22). Nutrient intakes were calculated automatically in the WebQ via built-in-algorithms using daily intakes of food items and food composition data from the UK Nutrient Databank – this process is described in detail elsewhere (23). We then summed relevant items (in g/day) together (e.g. for fruit intake, we summed reported intakes of apples and pears, berries, citrus, dried fruit, other fruit, and stewed fruit). In participants who completed at least one 24h recall (n=181,142 after applying the exclusion criteria and excluding participants with missing covariate data), we averaged each participant's reported intake of each food item, food group, or nutrient intake across all available instances, as suggested in a previous study (23).

## Derivation of potential mediators

### Body mass index (BMI)

Body weight and standing height were measured at the assessment centre visit at recruitment. BMI was calculated as a participant's body weight (kg) divided by the square of their height (m).

### Other anthropometric measures

Bioimpedance was measured at the assessment centre visit at recruitment using the Tanita Bc418ma bioimpedance device, from which body fat percentage, whole-body fat mass, whole-body fat-free mass were estimated.

Hand grip strength (for each hand) was measured using the Jamar Hydraulic hand dynamometer, and the highest score of either hand was used in this study.

Calcaneal bone mineral density (BMD) was measured using a Norland McCue Contact Ultrasound Bone Analyzer, from which a heel BMD t-score was calculated for each participant. In participants with BMD measures for the left and right heels, we used the highest BMD t-score value.

### Biomarkers

Participants provided blood samples at recruitment, from which serum vitamin D and insulin-like Growth Factor-1 (IGF-1) were measured by Chemiluminescence Immunoassay (CLIA) analysis on a DiaSorin Ltd. LIASON XL. A full description of the biomarker measurements can be found on the UK Biobank website (https://www.ukbiobank.ac.uk/media/gnkeyh2q/study-rationale.pdf).

## Derivation of covariates

### Age at recruitment

Calculated as date of recruitment minus date of birth, truncated to whole year.

### Sex

Genetic sex as determined from genotyping analysis.

### Region

At recruitment, participants attended one of 22 assessment centres across the UK. We grouped the centres into three regions as follows: England (Barts, Birmingham, Bristol, Bury, Croydon, Hounslow, Leeds, Liverpool, Manchester, Middlesborough, Newcastle, Nottingham, Oxford, Reading, Sheffield, Stockport, Stoke), Scotland (Edinburgh, Glasgow), and Wales (Cardiff, Swansea, and Wrexham).

### Ethnicity

At recruitment, participants were asked in the touchscreen questionnaire to select their ethnic group among “White”, “Mixed”, “Asian or Asian British”, “Black or black British”, “Chinese”, “Other ethnic group”, “Do not know”, or “Prefer not to say”. We regrouped participants into the following ethnicity categories: White, Mixed race, Asian, Black, and Other.

### Socio-economic status

The Townsend deprivation index was used as in index of socio-economic status (as a continuous variable). This variable was previously created in the UK biobank resource based on national census output areas. Each participant was assigned a score corresponding to the output area in which their postcode was located.

### Living alone

In the touchscreen questionnaire at recruitment, participants were asked “Including yourself, how many people are living together in your household?”. From this, we defined the variable “live alone” (yes, no).

### Physical activity

Physical activity in total metabolic equivalent task (MET) minutes per week was calculated based on a series of questions that asked about frequency and duration of walking, moderate activity, and vigorous activity.

### Smoking status

At recruitment, participants were asked in the touchscreen questionnaire “Do you smoke tobacco now?” and “In the past, how often have you smoked tobacco?” to determine their smoking status as current, previous, or never.

### Alcohol consumption

In the touchscreen questionnaire at recruitment, participants were asked about their weekly and monthly intake of glasses of red wine, glasses of champagne plus white wine, pints of beer plus cider, measures of spirits or liqueurs, glasses of fortified wine, and glasses of other alcohol. Participants could input any number, “do not know”, or “prefer not to say”. We summed participants weekly and monthly alcohol intakes, respectively. Weekly total alcohol intake was converted into daily total alcohol intake (drinks/day). Non-responders for weekly and monthly intake of specific alcohol types were considered non-consumers of that specific alcohol type. For

participants who answered “do not know” or “prefer not to say” for any question on weekly alcohol intake, monthly intakes were used, if available. Otherwise, we used responses to a question in the touchscreen questionnaire at recruitment that asked “how often do you drink alcohol?” with options of 1 “daily or almost daily”, 2 “three or four times a week”, 3 “once or twice a week”, 4 “one to three times a month”, 5 “special occasions only”, 6 “never”, or 7 “prefer not to answer”.

### Nutritional supplementation

Participants were asked in the touchscreen questionnaire at recruitment to select which, if any, of the following supplements they consume regularly: vitamin A, vitamin B, vitamin C, vitamin D, vitamin E, folic acid or folate, multivitamins/minerals, fish oil, glucosamine, calcium, zinc, iron, selenium, none of the above, or prefer not to answer. Participants who reported consuming ≥ 1 type of supplement were classified as supplement users. Non-responders and participants who responded “none of the above” were coded as not taking any supplements.

### Comorbidities

We identified prevalence of hip fracture (yes, no), osteoporosis (yes, no), other non-hip fractures (yes, no), diabetes (yes, no), cardiovascular disease (yes, no), and cancer (yes, no) at recruitment using self-reported information from questions on health and medical history asked in the touchscreen questionnaire, and through use of hospital records and cancer registries (with the date of diagnosis being before or on the date of recruitment).

### Number of children

At recruitment in the touchscreen questionnaire, women were asked “how many children have you given birth to?”. We grouped responses as 0, 1, 2, 3, or ≥ 4 children.

### Menopausal status

At recruitment in the touchscreen questionnaire, women were asked multiple questions relating to menopausal status. Women were defined as premenopausal or postmenopausal at recruitment using the following criteria:

**Premenopausal:** answered "no" to the question that asked about having gone through menopause, or answered "not sure", and:

- Were < 55 years old, did not report having a bilateral oophorectomy or hysterectomy, and did not report using hormone replacement therapy (HRT), or;
- Were < 55 years old, did not report having a bilateral oophorectomy or hysterectomy, and reported menstruating on the day of recruitment.

**Postmenopausal:** answered "yes" to having gone through menopause, or answered "not sure", and were ≥ 55 years old or had a bilateral oophorectomy.

### Hormone replacement therapy (HRT)

At recruitment in the touchscreen questionnaire, women were asked "Have you ever used hormone replacement therapy?" and if yes, "How old were you when you last used hormone replacement therapy?" We categorised HRT use based on these questions as "Current", "Former", "Never".

## Calculating absolute risk differences

To determine if any relative risk differences between diet groups are clinically significant, we calculated the absolute risk difference between each diet group and regular meat-eaters as the difference between the predicted incidence per 1000 people over 10 years per diet group. Predicted incidences were calculated using hazard ratios (HR) and 95% confidence intervals (95% CI's) expressed as floating absolute risks, which assign a 95% CI to all groups including the reference group, allowing estimation of precision for the predicted incidence in regular meat-eaters without arbitrarily assigning a diet group as the reference group (7, 25, 26). Predicted incidence in regular meat-eaters per 1000 people over 10 years was calculated as (1 – Sr) x 1000, where Sr = (1 – observed incidence in regular meat-eaters)$^{10}$, representing the predicted 10-year non-incidence (survival) rate in regular meat-eaters. Predicted incidence in occasional meat-eaters, pescatarians, and vegetarians over the same timeframe was calculated as (1-$SR^{HR\ or\ 95\%\ CI}$) x 1000, where HR or 95% CI represents the adjusted hazard ratio or confidence intervals for hip fracture risk per diet group compared to regular meat-eaters, and $Sr^{HR\ or\ 95\%\ CI}$ represents the

predicted 10-year non-incidence (survival) rate in each diet group compared to regular meat-eaters, after accounting for potential confounders.

## Mediation analyses

All steps of mediation analyses are summarised in **Table D3**. Mediation analyses were only conducted if a) an association was observed between a diet group and risk of hip fracture, and b) a significant difference in the mediator of interest was observed between a given diet group and regular meat-eaters.

To determine if body mass index (BMI), heel bone mineral density (BMD), fat-free mass (FFM), hand grip strength, serum vitamin D, and insulin-like growth factor-1 (IGF-1) significantly differed between diet groups at recruitment, we used a multivariable linear regression model for each mediator (independent variable = diet group, dependent variable = mediator of interest). All models were adjusted for (all at recruitment): age, region, sex, ethnicity, Townsend Deprivation Index, live alone, smoking status, any nutritional supplementation, MET minutes of physical activity per week, alcohol consumption in drinks per day, prevalence of diabetes, cancer, cardiovascular disease, and other non-hip fractures, number of children, menopausal status, and hormone replacement therapy use. Models for heel BMD, hand grip strength, serum vitamin D and IGF-1 were also adjusted for BMI, whilst the model for FFM was further adjusted for height.

The inverse odds ratio weighting (IORW) method was used to estimate mediation of any significant diet group – hip fracture associations through each of the aforementioned potential mediators. This method leverages the invariance property of an odds ratio (OR; the OR for the relationship between the exposure and mediator is the same regardless of which variable is defined as dependent or independent) to condense the relationship between the exposure and any number of mediators of interest into a single OR, conditional on covariates, by regressing the exposure on the mediator(s) and covariates (4, 27, 28). The inverse of the covariate-adjusted exposure-mediator OR can then be applied as a weight in main regression analyses of the outcome on the exposure. By using mediators to construct weights, mediators are never entered into Cox regression models with the outcome, meaning that the exposure and mediator(s) remain independent (28). The resulting weighted Cox regression model thereby estimates the

natural direct effect (NDE) of the exposure on the outcome when the mediating pathway(s) of interest is/are deactivated. The natural indirect effect (NIE) (the exposure – outcome association only through mediator(s) pathways of interest) can then be calculated as the total effect minus the NDE. The IORW method can be applied to Cox regression, accommodates use of multiple mediators of a categorical, discrete, or continuous nature, and is agnostic of exposure-mediator interactions (28). Key assumptions made include: no unmeasured exposure-mediator, mediator-outcome, or exposure-outcome confounding; and no unmeasured mediator-outcome confounding that could be affected by the exposure (4, 27, 28).

We ran the IORW method separately for each mediator (all continuous variables). In each case, weights for each mediator were estimated from logistic regression models adjusted for relevant confounders (as in multivariable linear regression models from step 1) where the binary diet group (regular meat-eater or vegetarian) was the dependent variable, and the mediator was the independent variable. For each mediator, inverse odds ratio weights were derived for each participant by taking the inverse of the predicted diet group – mediator OR. Regular meat-eaters (reference group) were assigned a weight of 1, and vegetarians were assigned the inverse odds ratio weights. Multivariable Cox regression models with weights applied were then fit to estimate the direct effect. The indirect effect was then calculated as the HR for the total effect divided by the HR for the direct effect. Percentage mediation (the proportion of the exposure – outcome association mediated by the mediator of interest) was calculated as [[ln(HR total) - ln HR direct] / ln(HR total)] x 100. 95% CI's for total, direct, and indirect effects, as well as percentage mediation estimates, were estimated by bootstrapping their respective HRs using 300 replications. In line with existing recommendations, we report percentile-based CI's (29, 30). Participants not in the binary diet group of interest (occasional meat-eaters and pescatarians) or with missing data for a variable required in each mediation analysis were excluded from that analysis.

## Supplementary results

### Diet group at recruitment and follow-up

The agreement of diet group in 57,730 participants with measures at recruitment and at least one instance of follow-up (using the latest available instance per participant) was generally high (**Table D4**). Of 35,801 regular meat-eaters at recruitment, 27,277 (762%) remained regular meat-eaters, with 8,043 (22.5%) becoming occasional meat-eaters. Of 19,009 occasional meat-eaters at recruitment, 11,487 (60.4%) remained occasional meat-eaters, and 6,966 (36.6%) became regular meat-eaters. Of 1621 pescatarians at recruitment, 1306 (80.6%) remained pescatarian, with 157 (9.7%) becoming occasional meat-eaters, and 105 (6.5%) becoming vegetarian. Of 1223 vegetarians at recruitment, 1058 (86.5%) remained vegetarian, with 81 (6.6%) becoming pescatarian, and 50 (4.1%) becoming vegan. Of 76 vegans at recruitment, 54 (71.1%) remained vegan, with 19 becoming vegetarian (25.0%). The proportion of regular meat-eaters decreased over follow-up (35,801 (62.0%) to 34,284 (59.4%)), whilst the proportion of all other diet groups increased (**Table D4**).

### Dietary characteristics at recruitment

Dietary intake of foods, beverages, and nutrients across diet groups at recruitment are summarised in **Table D5**. Compared to regular meat-eaters, vegetarians and pescatarians ate more fruit and vegetables, wholegrains, and meat substitutes per day, and consumed fewer sugar-sweetened beverages. Consumption of dairy products was broadly similar across diet groups, though compared to regular meat-eaters, vegetarians consumed less milk (161.7 ml/day vs 108.9 ml/day) and more cheese (126.8 g/day vs 16.6 g/day).

Total protein intake was lowest in vegetarians (63.1 g/day) and highest in regular meat-eaters in both absolute terms (63.1 vs 84.8 g/day) and relative to body weight (0.91 vs 1.1 g/kg body weight/day). Vegetarians were also less likely to meet the recommended daily protein intake of 0.75 g/kg body weight/day, with 31.8% of vegetarians below this threshold compared to 14.8% for regular meat-eaters. Dietary calcium intakes were similar across diet groups, and on average, all groups exceeded the UK recommended intake of 700 mg/day (31). Unsurprisingly, vegetarians

did not consume haem iron. Dietary iodine, niacin, selenium, vitamin B12, and vitamin D intakes were lower in vegetarians compared to other diet groups (iodine: vegetarians 161.0 µg/day vs average across all diet groups 221.3 µg/day; niacin: 29.3 mg/day vs average across all diet groups 38.3 mg/day; selenium: 34.8 µg/day vs average across diet groups 52.5 µg/day; vitamin B12: 3.7 µg/day vs average across diet groups 6.2 µg/day; vitamin D: 2.1 µg/day vs average across diet groups 3.6 µg/day). Dietary retinol intakes were also lower in pescatarians (345.8 µg/day) and vegetarians (338.9 µg/day) than in regular meat-eaters (498.1 µg/day).

## Descriptive characteristics at recruitment with varying restrictions

Characteristics of participants across diet groups at recruitment including or restricting to those with missing covariate data are shown in **Table D7**. Compared to participants who were included in the study (with complete covariate data), participants with missing covariate data included a greater proportion of females, were less likely to have a degree, had a lower Townsend Deprivation Index, had lower values for height, and included a greater proportion of postmenopausal women, despite small differences in age, across all diet groups. Vegetarians with missing covariate data included a higher proportion of Asian participants, reported higher physical activity levels, were more likely to report never having smoked, had a slightly higher BMI, and were less likely to have children than vegetarians with complete covariate data.