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Influence of different beverages and sugars on clinically relevant endpoints

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List of Abbreviations

%E	Percent total energy
24HR	24-hour dietary recall questionnaire
AS	Added sugars
ASB	Artificially sweetened beverages
CVD	Cardiovascular disease
DGA	Dietary Guidelines for Americans
FS	Free sugars
FFQ	Food Frequency Questionnaires
FPQ	Food Preference Questionnaires
g	Gram(s)
HPL	Health Promotion Levy
HR	Hazard ratio
ICD-10	International Statistical Classification of Diseases and Related Health Problems, Tenth Revision
IHD	Ischemic heart disease
IS	Intrinsic sugars
kg	Kilogram(s)
MUP	Minimum Unit Pricing
SDIL	Soft Drinks Industry Levy
SSB	Sugar-sweetened beverages
T2DM	Type 2 diabetes mellitus
UK	United Kingdom
WHO	World Health Organization

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1. Introduction

1.1 Metabolic and vascular diseases and their complications as common causes of death

In 2021, non-communicable diseases were the leading global health challenge, responsible for 68% of the top 10 causes of death[1]. Among those, dementia and cardiovascular disease (CVD) stand out as particularly pressing concerns[1–3]. Dementia is currently the seventh leading cause of death and a major contributor to disability and dependency among older adults worldwide[2]. CVD remains the leading cause of death globally and could largely be prevented by appropriately addressing lifestyle factors such as an unhealthy diet[3]. Despite advances in medical treatments, the rising prevalence of these diseases highlights the urgent need for enhanced prevention strategies and public health interventions[2,3]. In this thesis, all-cause and cause-specific mortality, dementia, and CVD were selected as important endpoints for the analysis and they are discussed in more detail in the following subchapters.

1.1.1 Mortality

Worldwide, the World Health Organization (WHO) reported 68 million deaths in the year 2021[1]. Death from any cause, or all-cause mortality, is a clear, binary, and objective endpoint. The use of mortality as an outcome measure instead of specific conditions avoids classification bias and provides more complete reported data[4]. Therefore, all-cause mortality is a reliable indicator for assessing the overall impact of various risk factors or exposures on population health.

All-cause mortality can be further divided into more specific categories such as cancer mortality, non-cancer mortality, and CVD mortality to allow more detailed insights into the actual underlying causes of death. Cancer mortality includes deaths due to neoplastic disease, including malignant cancers (International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) codes C00-D48). Non-cancer mortality (ICD-10 codes all but C00-D48) encompasses deaths from all other causes, comprising respiratory, circulatory, infectious, mental and behavioural, as well as endocrine and metabolic diseases. CVD mortality includes deaths related to conditions affecting the cardiovascular system, including heart-specific conditions, cerebrovascular diseases, and peripheral vascular conditions impacting arteries throughout the body (ICD-10 codes I00-I79).

1.1.2 Dementia

Life expectancy is increasing worldwide, leading to a higher number of age-related diseases like dementia[5]. Currently, more than 55 million people have dementia globally[2] and 131.5 million people are expected to be affected by the disease in 2050[5]. The global burden of

dementia is particularly high since it not only impacts individuals but also poses a significant strain on families, carers, and healthcare systems[5].

The term dementia refers to a group of neurodegenerative diseases that lead to a progressive cognitive decline, affecting memory, thinking, language, and the ability to perform everyday tasks[2]. The most common form of dementia is Alzheimer's disease (ICD-10: G30), which accounts for 60-80% of cases[2,6]. Alzheimer's disease is characterised by the build-up of amyloid plaques and tau tangles in the brain, which leads to the death of neurons and damage of brain tissue and a gradual decline in memory, apathy, communication problems, and in later stages problems of motorial functions[6]. Another type of dementia is vascular dementia (ICD-10: F01), resulting from reduced blood flow to the brain due to strokes or microvascular dysfunction[6]. Further types of dementia include dementia caused by other underling diseases, e.g., Parkinson's disease (ICD-10: F02), unspecified dementia (F03), Lewy body dementia (ICD-10: G31.83), and frontotemporal dementia (G31.09)[6]. There are various modifiable risk factors for dementia, such as physical inactivity, infrequent social contact, smoking, and poor dietary habits, leading to obesity or type 2 diabetes mellitus (T2DM), which can significantly influence the likelihood of developing the disease[6,7].

1.1.3 Cardiovascular disease

Even though on a global scale the rates of CVD have dropped throughout the last three decades, CVD remains the leading cause of death worldwide, accounting for approximately 20.5 million deaths in 2021[3,8]. The CVD incidence rate is estimated to be 30% higher in middle-income as compared to high-income countries[9].

CVD represents a broad spectrum of disorders that impact the cardiovascular system, including ischemic heart disease (IHD), stroke, heart failure, arrhythmias, and peripheral artery disease[10]. It primarily develops due to a combination of atherosclerosis, inflammation, and other processes that damage the heart and blood vessels[11]. IHD, or coronary artery disease, is marked by a reduced blood flow to the heart due to atherosclerotic lesions of coronary arteries that cause narrowing or blockage of the vessel lumen and can lead to myocardial infarctions[12]. Stroke results from acute damage to central nervous system due to a disruption in blood supply, either through ischemia caused by a blocked blood vessel, i.e., ischemic stroke, or bleeding within or around the brain, i.e., haemorrhagic stroke[13]. CVD development is influenced by non-modifiable risk factors such as advanced age, male sex, and genetic predisposition, as well as modifiable behavioural risk factors like unhealthy diet, lack of physical activity, and tobacco use[10,14,15]. They can manifest in individuals as elevated blood pressure, increased blood glucose levels, elevated blood lipids, and excess body weight[3].

1.2 Dietary factors in metabolic and vascular disease

What people eat and drink every day remains one of the most important determinants of health nowadays. According to the Global Burden of Disease Study 2019, poor dietary habits are ranked among the top three leading risk factors for mortality, contributing to 13.5% of all deaths in females and 14.6% in males in 2021[16]. Improving global dietary habits should be a priority to reduce mortality rates, health complications, and the associated economic burden. As part of all dietary patterns, the consumption of different beverages, such as alcoholic beverages, coffee, tea, and sugar-sweetened beverages (SSB), plays an important role in the development of diseases. The following subchapters summarise the beverages which are particularly relevant to the development of metabolic and vascular diseases in more detail.

1.2.1 Alcohol

In 2019, worldwide alcohol per capita consumption amounted to an average of 8.2 litres for men compared to 2.2 litres for women[17]. In Germany, every year the equivalent of around 10 litres of pure alcohol is consumed per capita according to estimates by the German Centre for Addiction Issues[18].

Alcohol consumption is usually expressed in g/day and the amount of consumption is divided into different categories, e.g., no, light, moderate, and heavy drinking. Light to moderate alcohol consumption is linked to reduced all-cause mortality in many studies while heavy drinking and binge drinking are associated with increased mortality[19–21]. Furthermore, moderate alcohol consumption, i.e., <12.5 g/day, is associated with a reduced risk of dementia[22]. Alcohol impacts mortality through both beneficial and harmful pathways, such as improving high-density lipoprotein cholesterol and anti-inflammatory effects on the one hand, and promotion of hypertension, oxidative stress, and deteriorating hepatic function on the other hand[23]. Favourable neuroprotective effects include alcohol-mediated increases in levels of high density lipoprotein cholesterol, apolipoprotein A1 and adiponectin, as well as decreases in concentrations of fibrinogen[24,25]. However, excessive alcohol intake has neurotoxic effects leading to neuronal damage and brain atrophy[26].

The proposition that low alcohol consumption is beneficial for health is a matter of ongoing debate[27]. For years, many epidemiological studies reported that individuals classified as “moderate drinkers” tend to have a longer life expectancy and show a lower risk of heart disease compared to those classified as abstainers[28]. Often, a J-shaped curve is described suggesting protective effects at low alcohol consumption levels with increasing risk at higher doses. However, growing evidence suggests that these associations might be due to systematic biases that affect many studies[27,29–32]. For instance, light and moderate drinkers are in general healthier than current abstainers, while former drinkers or lifetime abstainers

may not drink due to poor health[29–32]. Studies often do not control for this “former drinker bias” in the abstainer reference group, in particular they do not remove the so-called “sick quitters” or former drinkers[29–32].

Instead of analysing total alcohol consumption, it can be divided into subgroups, such as wine and non-wine alcoholic beverages. The group of wine includes red and white wine, while non-wine alcoholic beverages contains all other categories of alcoholic drinks, such as beer, cider, spirits, fortified wine, and other alcoholic drinks. Analysing total alcohol consumption may fail to capture the distinctions between these types of alcoholic beverages. Moderate wine consumption is often associated with protective cardiovascular effects[33–36] and may also protect against cognitive decline due to wine being rich in resveratrol and other polyphenols, which have antioxidant and anti-inflammatory properties[37]. On the other hand, the impact of non-wine alcoholic beverages such as beer and spirits on health remains less clear with studies suggesting beneficial[33], neutral[36,38], or adverse[39] effects.

Hence, it is necessary to clarify the precise nature of the association between consumption of wine and non-wine alcoholic beverages and both all-cause mortality and dementia carefully controlling for former drinker bias to ensure that observed associations accurately reflect underlying risks.

1.2.2 Coffee

Coffee is hugely popular, ranking as one of the most widely consumed beverages among adults worldwide, with consumption continuing to rise[40,41]. In the 2024/25 coffee season, global coffee consumption is expected to reach 10,2 billion kg[42]. In Germany, coffee consumption amounted to 167 litres per capita in 2022[43]. Coffee contains various components that are known for their health-promoting effects, namely antioxidants and bioactive compounds such as caffeine, chlorogenic acid, trigonelline, diterpenes, and melanoids[44]. Caffeine has also neuroprotective properties, enhancing cognitive function and reducing inflammation in the brain[44].

Plenty of scientific studies suggest that a relation between coffee intake and health exists[45–49]. However, there is an ongoing discussion about the nature of its shape, since studies report U-shaped[46], J-shaped[47], inverse[45,48], positive[49], or null relations[50]. A recent large meta-analysis by Kim and colleagues including 3,852,651 subjects detects a 15% reduced risk of all-cause mortality at 3.5 cups/day compared with no coffee consumption[51]. Concerning dementia risk, a recent meta-analysis finds no association for coffee intake and dementia comparing the highest with the lowest category of coffee consumption. However, in dose-response analysis, a significant non-linear relation for 1 to 3 cups coffee/day was found with a decreased dementia risk between 8 and 12%[52].

To date, studies on coffee intake have mainly focussed on coffee consumption alone, without taking into account possible effects of other consumed beverages. Furthermore, studies treat coffee consumption as a categorical rather than a continuous variable, which can lead to loss of information for dose-response relationships.

1.2.3 Tea

After coffee, tea is one of the most frequently consumed beverages all over the world[53]. Worldwide tea consumption reached 7,2 billion kg in 2024 with a per capita average of 890 g[54]. In Germany, annual per capita tea consumption reached 69 litres in 2022[55]. Tea is known to contain high amounts of flavonoids like catechins, theaflavins, anthocyanins, and flavonols[56]. These are known for their potential to reduce the risk of many non-communicable diseases due to their anti-inflammatory and antioxidant properties[57].

Regarding tea consumption, conflicting results have been described with some studies finding an inverse[47,58–62] or positive[63] relation between tea consumption and all-cause mortality, while others find no association[64]. A recent large meta-analysis by Kim and Ye including 1,956,549 participants finds that moderate tea consumption of 2 cups/day is associated with a 9% decreased risk of all-cause mortality compared to no tea consumption[65]. Furthermore, a recent meta-analysis of 38 cohorts including 751,824 participants finds a 16% decreased risk of dementia comparing the highest with the lowest intake category of tea[52]. Especially green tea is linked to a lower risk of cognitive decline[66] due to its high polyphenol content, which exerts anti-amyloidogenic effects[67,68], while its caffeine content may help to keep the blood-brain-barrier intact[69]. An analysis of the dose-response relationship between green tea intake and all-cause mortality, however, does not find a significant association[70].

So far, studies on tea consumption have primarily assessed intake of tea alone, without considering the potential effects of other beverages consumed. Additionally, many studies only differentiate between categories of intake instead of using continuous scales, and only the latter allowing in-depth analysis of dose-dependent effects.

1.2.4 Sugar-sweetened beverages

SSB are at the centre of the public health debate due to their widespread consumption and the associated health risks. SSB are defined as any liquids that are sweetened with various forms of added sugars (AS) like brown sugar, corn sweetener, corn syrup, dextrose, fructose, glucose, high-fructose corn syrup, honey, lactose, malt syrup, maltose, molasses, raw sugar, and sucrose[71]. Recent analyses of global SSB intake in the years between 1990 and 2018 reveal that SSB consumption varies by tenfold across different world regions, ranging from 7.8 servings/week in Latin America to 0.7 in South Asia in 2018[72]. The highest SSB intake rates were observed in Mexico, Ethiopia, the United States, and Nigeria, and nearly one-third of the

185 countries studied had mean intakes of 7 or more servings per week[72]. In Germany alone, yearly per capita consumption reached 124.5 litres in 2023, highlighting the prevalence of SSB in daily diets[73]. High SSB consumption is especially concerning due to its association with a significant burden of disease and mortality, particularly in regions such as Latin America and the Caribbean[74], as well as China[75].

The role of SSB in contributing to negative health outcome is well described as they have been extensively studied for their adverse effects on CVD[76,77], obesity[76,78], T2DM[76], cancer[79], cognitive impairment[80], dementia[81,82], and mortality[83]. Negative effects of SSB are closely linked to their content of free sugars (FS). According to the WHO, total sugars can be divided into intrinsic sugars (IS) and FS[84]. IS are sugars that occur naturally in foods, like sugars from fruit, vegetables, and lactose in dairy products[84]. FS are defined as all monosaccharides and disaccharides added to foods by the manufacturer, cook or consumer, plus sugars naturally present in honey, syrups, and fruit juices[84]. AS are defined as sugars used in food preparation and as table sugar and therefore, all AS are also FS[85]. SSB are a major source of AS and FS[86,87].

A recently published umbrella review[88] associates high dietary sugar consumption with various negative health consequences[88]. However, the review includes mainly studies assessing dietary sugar exposure from SSB (n = 42) and includes only one study on FS[88]. However, FS are not only contained in beverages. Various solid foods, e.g., treats, cereals, toppings, and sauces, also contribute significantly to FS intake.

The WHO recommends limiting consumption of FS to less than 10% of total daily energy intake, with further reduction to below 5% for additional health benefits[84]. However, the WHO recommendation focuses solely on FS as such and does not take into account the source from which these originate.

Until now, only a few studies have assessed the differences between liquid and solid sources of FS on health outcomes[89–91]. Ramne and colleagues[89] describe that the association between sugar consumption and mortality depends on the sugar source. In their study, SSB are positively associated with mortality, while treats display an inverse trend. Dasgupta and colleagues[90] report that consuming at or above 5% of total energy in the form of FS from solid sources results in a 34% greater hazard for fatal or non-fatal CVD compared to consuming amounts below this threshold[90]. Debras and colleagues[91] describe that AS, FS, and sucrose, as well as sugars from sugary drinks, dairy products, and milk-based desserts, are associated with increased breast cancer risk, while no association is observed for other sugar sources and types[91].

There are several mechanisms by which the consumption of sugars, especially FS, can have a negative impact on brain health. Intake of FS is related to increased body weight[92] and being overweight or obese in midlife is associated with a higher dementia risk[93,94]. Furthermore, diets high in sugar are associated with insulin resistance and T2DM, both of which are strongly linked to Alzheimer's disease and other forms of dementia[95]. Insulin resistance limits the brain's glucose use, causing energy deficits than can accelerate cognitive decline[95,96]. Moreover, a diet high in AS can contribute to systemic inflammation and oxidative stress[97], damaging brain cells, disrupting synaptic function, and promoting formation of amyloid plaques and tau tangles[98]. In addition, SSB consumption leads to microvascular dysfunction[99], which may reduce blood flow to the brain and raise vascular dementia risk[100].

Regarding the contribution of FS to CVD, the following potential mechanisms are discussed: intake of FS is related to increased body weight[92] and the resulting excess in body fat, particularly in the abdomen, is associated with increased risk of CVD due to its impact on metabolic and inflammatory pathways[101]. Diets high in FS, in particular fructose, promote insulin resistance, which can progress to T2DM[102], an important CVD risk factor[103]. Elevated blood glucose levels and poor glycaemic control contribute to vascular damage and inflammation[103]. High amounts of AS can lead to increased systemic inflammation and oxidative stress[97] as well as *de novo* lipogenesis, dyslipidaemia, and higher circulating uric acid levels[104]. Changes in lipid profiles are risk factors for the development of atherosclerosis, a key precursor of CVD[105]. A higher intake of SSB, fructose, and glucose is directly associated with elevated blood pressure, an intermediary risk factor for CVD[106]. In addition, intake of AS leads to chronic low-grade inflammation, a key factor in CVD pathogenesis[97,107].

As outlined above, it is highly plausible that FS exert a significant impact on both brain health and CVD. However, previous studies have largely focused only on SSB and the FS they contain, while other relevant sources of FS have not been taken into account.

1.3 Research gaps

Accordingly, **four main research gaps** were analysed in the present work:

Research gap 1: How is the consumption of wine and non-wine alcoholic beverages, coffee, and tea related to all-cause mortality?

Published evidence suggests that all-cause and cause-specific mortality are dose-dependently associated with consumption of wine and non-wine alcoholic beverages, coffee, and tea[33–36,38,39,45–49,51,58–63]. However, models often include wine, non-wine, coffee, and tea consumption as either linear predictors or even discretised ordinal predictors and mutual adjustments of the four beverage types are not regularly performed. Furthermore, few studies have compared wine to non-wine consumption in relation to all-cause and cause-specific mortality risk. Additionally, former drinker bias needs to be correctly controlled for by excluding all non-alcohol drinkers from the study cohort[29,30,32].

Research gap 2: How is the intake of wine and non-wine alcoholic beverages, coffee, and tea associated with the risk for incident dementia?

Studies indicate that wine and non-wine alcoholic beverages, coffee, and tea intake are associated with the risk for dementia[22,44,52,66–69]. Nonetheless, these four beverage types have not been assessed within a large prospective cohort study with mutual adjustment. Furthermore, previous research treats wine, non-wine, coffee, and tea intake as linear variables or categorises them into discrete groups. Moreover, wine consumption has not been contrasted with non-wine intake regarding incident dementia, and effects of former drinker bias on potential protective findings of alcohol consumption have not been assessed systematically[29,30,32].

Research gap 3: How are various types of sugars, i.e., FS and their subtypes, as well as IS, related to dementia risk?

High intake of sugars, especially FS, is connected with systemic inflammation, oxidative stress, and microvascular dysfunction via various mechanisms including increased body weight, insulin resistance, and T2DM[92–98,100]. These conditions are strongly linked to an increased risk of Alzheimer's disease and other forms of dementia[93–96,98,100]. However, no study to date has systematically evaluated the association between consumption of FS from various sources including FS in beverages, beverage subtypes, solid foods, and solid food subtypes on the one hand and the risk of incident dementia on the other hand, using penalised cubic splines allowing for non-linear predictor effects. Furthermore, most existing research has focused primarily on SSB as the main source of FS[80,88,108–110], neglecting the broader range of FS sources that may also play a role in dementia risk. All relevant sources of FS are summarised in Figure 1.

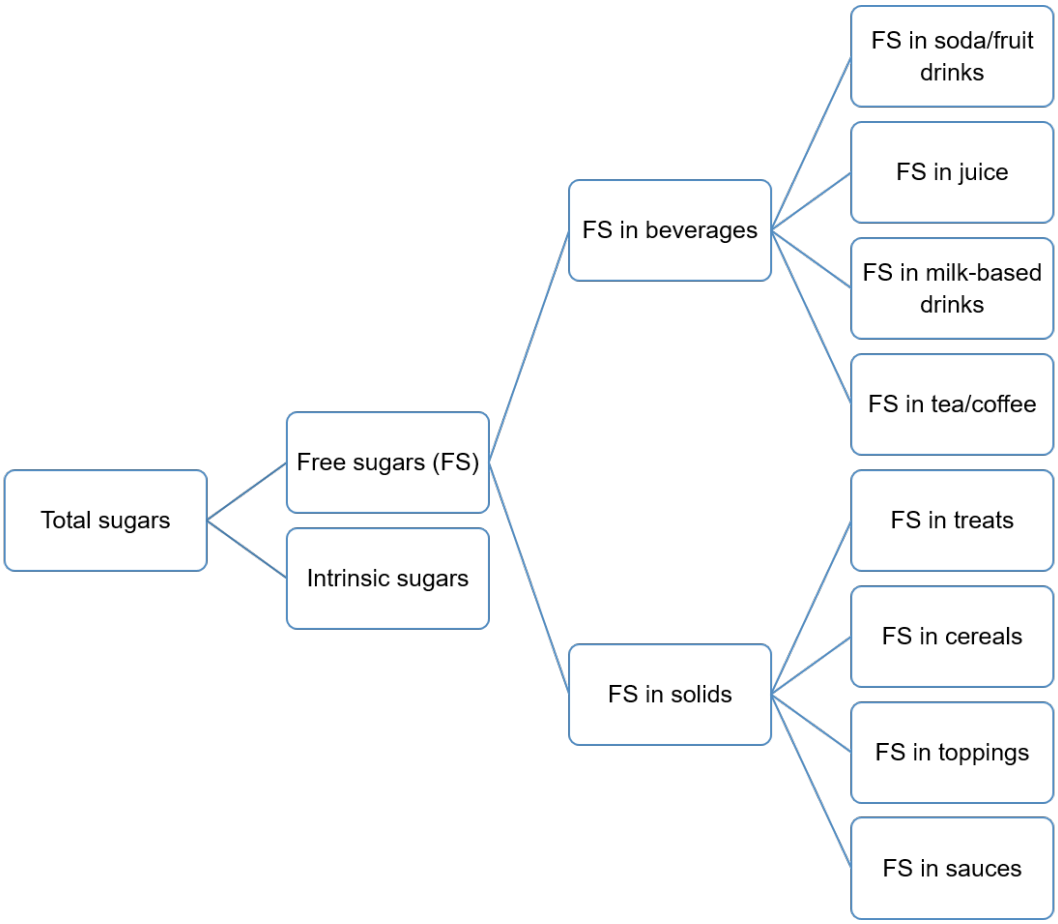

Figure 1. All relevant sources of FS analysed for research gaps 3 and 4. FS: Free sugars (own representation).

Research gap 4: How are various types of sugars, i.e., FS and their subtypes, as well as IS, associated with CVD?

High consumption of FS is linked to an increased risk of CVD via various mechanisms[88,92,97,101–107]. In contrast, fruits and vegetables as major sources for IS are generally associated with positive effects on cardiovascular health[111,112]. However, no large-scale study with over 100,000 participants has systematically examined the association between FS from all relevant sources including beverages, beverage subtypes, solid foods, and solid food subtypes on the one hand and CVD risk on the other hand, using penalised cubic splines allowing for non-linear relationships between variables. In addition, no study has evaluated the relationship between IS and incident CVD.

2. Publications

Within this doctoral thesis, four publications have addressed the research gaps summarised in subchapter 1.3 and are presented within the next subchapters.

Research gap 1: How is the consumption of wine and non-wine alcoholic beverages, coffee, and tea related to all-cause mortality?

(1) **Schaefer, S. M.**, Kaiser, A., Behrendt, I., Eichner, G., & Fasshauer, M. (2023). Association of alcohol types, coffee and tea intake with mortality: prospective cohort study of UK Biobank participants. British Journal of Nutrition, 129(1), 115-125.

Research gap 2: How is the intake of wine and non-wine alcoholic beverages, coffee, and tea associated with the risk for incident dementia?

(2) **Schaefer, S. M.**, Kaiser, A., Eichner, G., & Fasshauer M. (2022). Association of Alcohol Types, Coffee, and Tea Intake with Risk of Dementia: Prospective Cohort Study of UK Biobank Participants. Brain Sciences, 12(3), 360.

Research gap 3: How are various types of sugars, i.e., FS and their subtypes, as well as IS, related to dementia risk?

(3) **Schaefer, S. M.**, Kaiser, A., Eichner, G., & Fasshauer, M. (2023). Association of sugar intake from different sources with incident dementia in the prospective cohort of UK Biobank participants. Nutrition Journal, 22(1), 42.

Research gap 4: How are various types of sugars, i.e., FS and their subtypes, as well as IS, associated with CVD?

(4) **Schaefer, S. M.**, Kaiser, A., Eichner, G., & Fasshauer, M. (2024). Association of sugar intake from different sources with cardiovascular disease incidence in the prospective cohort of UK Biobank participants. Nutrition Journal, 23(1), 22.

2.1 Publication 1: Association of alcohol types, coffee and tea intake with mortality: prospective cohort study of UK Biobank participants

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Authors' contributions

S. M. S. and A. K. conceived the research. S. M. S., A. K. and M. F. wrote the paper. All authors performed statistical analyses. All authors have read, redacted and approved the final manuscript.

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Appendix A: Supplementary Material

Summary

Research Gap 1 was addressed in the publication "Association of alcohol types, coffee and tea intake with mortality: prospective cohort study of UK Biobank participants"[113].

Within this paper, the association of the intake of different types of alcoholic beverages, i.e., wine and non-wine, as well as coffee and tea, with all-cause, cancer, non-cancer, and CVD mortality was assessed.

This study used data from the United Kingdom (UK) Biobank, a long-term prospective cohort study established in 2006, which recruited 500,000 participants aged 40 to 69 years. For this analysis, data from 354,386 participants was included, with 20,201 deaths recorded over a mean follow-up period of 12.0 years.

Non-wine alcoholic beverages were defined as beer plus cider, spirits, fortified wine, and other alcoholic drinks. Wine and non-wine alcoholic beverages were assessed in g alcohol/day and coffee and tea in cups/day. All beverages were included in the models as continuous variables. The intake of the different types of beverages was measured using the UK Biobank's baseline questionnaire assessing participants' weekly and monthly consumption. Besides all-cause mortality, the following mortality categories were defined according to ICD-10 codes: cancer (C00-D48), non-cancer (all but C00-D48), and CVD (I00-I79). All analysis were performed in the total cohort and separated by sex. Data analysis was carried out using R version 4.0.5.[114]. Cox proportional hazard regression models were fitted with wine, non-wine, coffee, and tea mutually adjusted and included as penalised cubic splines. Furthermore, models were adjusted for age, annual household income, ethnicity, overall health rating, physical activity, percentage body fat, sex, and smoking status. In all analyses, the hazard ratio (HR)-nadir was defined as the consumption of wine, non-wine, coffee, and tea with the lowest estimated HR over the range from zero to the 99%-quantile. To address former drinker bias, primary analyses were carried out in a cohort in which all non-alcohol drinkers – defined as participants with a present alcohol intake of 0 g/day - were excluded in order to remove all participants who might not drink alcohol due to health reasons. This group included never drinkers, i.e., participants never drinking alcohol in their lifetime, and former drinkers, i.e., participants drinking alcohol in the past but not in the present. Furthermore, two sensitivity analyses were performed to assess the effect of the former drinker bias. In the first set of sensitivity analyses, only former drinkers, but not never drinkers, were excluded from the cohort. In the second set, neither former drinkers nor never drinkers were excluded, to not control for any health issues in participants not drinking alcohol and to assess the effect this would have on the study results.

The study found that wine consumption was linked to all-cause, non-cancer, and CVD mortality in a U-shaped pattern, with the HR-nadir at 20, 21, and 20 g alcohol/day, respectively. Non-wine alcoholic beverage intake was associated positively and dose-dependently with all types of mortality, except for CVD mortality in females. The HR-nadir was determined at 0 g alcohol/day for all-cause, cancer, and non-cancer mortality and at 4 g alcohol/day for CVD mortality. Coffee consumption was significantly related to all-cause and non-cancer mortality with the HR-nadir found at 2 cups coffee/day, while non-coffee drinkers had a slightly increased risk of death. Coffee intake was not significantly associated with cancer and CVD mortality. Higher tea consumption was consistently linked to a reduced risk of all types of mortality with the HR-nadir at 4 cups/day for all-cause and cancer mortality, as well as at 5 and 8 cups/day for non-cancer and CVD mortality, respectively. In the sensitivity analysis, the HR for mortality of not drinking either wine or non-wine increased further if never drinkers and all non-alcohol drinkers were included in the analysis with most pronounced changes occurring in the latter.

In summary, the study indicates that wine consumption is associated with decreased all-cause, non-cancer, and CVD mortality in a U-shaped manner, while non-wine alcoholic beverages intake is positively related to all types of mortality. Coffee consumption is not related to increased mortality with a possible minor negative dose-dependent association. Moderate-to-high tea intake is associated with a consistently decreased risk of all mortality types studied.

The published manuscript is attached.

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Association of alcohol types, coffee and tea intake with mortality: prospective cohort study of UK Biobank participants

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Abstract

The present study examines how alcohol intake from wine and non-wine alcoholic beverages (non-wine) in g/d, as well as cups of coffee and tea included as continuous covariates and mutually adjusted are associated with all-cause, cancer, non-cancer and CVD mortality. Consumption was assessed in 354 386 participants of the UK Biobank cohort who drank alcohol at least occasionally and survived at least 2 years after baseline with 20 201 deaths occurring over 4·2 million person-years. Hazard ratios (HR) for mortality were assessed with Cox proportional hazard regression models and beverage intake fitted as penalised cubic splines. A significant U-shaped association was detected between wine consumption and all-cause, non-cancer and CVD mortality. Wine consumption with lowest risk of death (nadir) ranged from 19 to 23 g alcohol/d in all participants and both sexes separately. In contrast, non-wine intake was significantly and positively associated in a dose-dependent manner with all mortality types studied except for CVD in females and with the nadir between 0 and 12 g alcohol/d. In all participants, the nadir for all-cause mortality was 2 cups coffee/d with non-coffee drinkers showing a slightly increased risk of death. Tea consumption was significantly and negatively associated with all mortality types in both sexes. Taken together, light to moderate consumption of wine but not non-wine is associated with decreased all-cause and non-cancer mortality. A minor negative association of coffee consumption with mortality cannot be excluded whereas tea intake is associated with a consistently decreased risk of all mortality types studied.

Key words: **Alcohol: Coffee: Metabolic syndrome: Mortality: Tea: UK Biobank: Wine**

Besides smoking and a sedentary lifestyle, unhealthy eating patterns are major contributors to morbidity, as well as all-cause and cause-specific mortality[1,2]. Various beverages including sugar- and artificially sweetened beverages have been implicated to contribute to metabolic and CVD, as well as cancer[3,4]. In contrast, for alcoholic drinks, coffee and tea, the association between intake and health effects is less clear.

Alcohol consumption is typically quantified in g/d and the extent of alcohol intake is frequently divided into categories, including no, light, moderate and heavy drinking. Restricted alcohol intake <16 g/d is recommended for both sexes by the National Health Service to keep health risks low[5]. Chronic light to moderate drinking was associated with decreased risks of incident type 2 diabetes mellitus[6], myocardial infarction and stroke[7] but increased risks of hypertension in men[8] and liver cirrhosis in women[9]. Moderate alcohol drinking was linked with an increased risk for oral/pharynx, oesophageal squamous cell, colorectal, liver, female breast cancer and malignant melanoma on one hand and a decreased risk for kidney, thyroid and haematologic malignancy on the other hand[10]. Based on these findings, light to moderate alcohol consumption is regarded as safe by the National Health Service; however, it is not recommended to start drinking alcohol or to drink more frequently to gain potential health benefits[5]. Several studies suggest that differences exist between wine and non-wine alcoholic beverages (non-wine) concerning their associations with incident diabetes mellitus[11], obesity[12] and cancer[13].

Coffee intake is often quantified in cups/d with moderate coffee consumption defined as 3–5 cups/d[14]. Moderate coffee consumption was associated with decreased risks of incident

Abbreviations: AHI, annual household income; CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent of task; OHR, overall health rating; PA, physical activity; Q, quartile.

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type 2 diabetes mellitus[15], obesity[16], CVD[17], as well as liver and endometrial cancer[18]. Based on these results, moderate coffee consumption is considered safe[19]. Similar to coffee, moderate tea consumption is associated with decreased morbidity from type 2 diabetes mellitus[20], ischaemic heart disease[21], as well as several cancer subtypes[22]. Therefore, tea drinking is considered safe, but no specific guidelines exist concerning optimal intake.

Besides studies on the associations of alcohol, coffee and tea intake with morbidity, published evidence suggests that all-cause and cause-specific mortality are dose-dependently associated with the three beverages[23–30]. However, only few studies have assessed the association between wine *v.* non-wine consumption and mortality. Furthermore, models often include wine, non-wine, coffee and tea consumption as either linear predictors or even discretised ordinal predictors and mutual adjustments of the four beverages are not regularly performed. To address these limitations in the present study, associations between wine, non-wine, coffee and tea intake quantified on continuous scales and all-cause, as well as cause-specific, mortality hazards are determined in a large, well-characterised population of 354 386 UK Biobank participants using penalised cubic splines to allow, in particular, non-linear predictor effects. We hypothesised that non-linear relationships exist between the four beverage types and risk of death, as well as that intake levels linked to lowest mortality hazards depend on cause of death.

Methods

Study and participants

The study design of the multicentre, prospective UK Biobank cohort is described in detail at https://www.ukbiobank.ac.uk[31]. In brief, more than 500 000 participants were recruited between 2006 and 2010 at twenty-two assessment centres across the UK with age at enrolment ranging from 38 to 73 years. At baseline, all participants were assessed by a self-completed touchscreen questionnaire, a personal interview and physical measurements as recently described[32]. The following five exclusion criteria (ec) were applied to all primary and sensitivity analyses: (1) missing smoking status; (2) missing socio-economic factors (i.e. ethnic background and/or overall health rating); (3) missing percentage body fat; (4) either missing information on beverage intake or being in the upper 0·1 % of alcohol, coffee or tea intake and (5) participants lost to follow-up or dying within 2 years after baseline (landmark analysis). All primary analyses with all outcome measures were performed in a primary cohort in which all non-alcohol drinkers were excluded in addition to ec1 to ec5 to remove all participants who might not drink alcohol due to health reasons (primary cohort; *n* 354 386; online Supplementary Fig. 1). Non-alcohol drinkers were defined as participants with a present alcohol intake of 0 g/d. This group consisted of never drinkers, that is, participants never drinking alcohol during their lifetime, and former drinkers, that is, participants drinking alcohol in the past but not in the present. In addition to the primary analyses, two sets of sensitivity analyses (cohorts S1 and S2) were run. In the first set, former drinker bias was controlled for by excluding former drinkers but not never drinkers in addition to ec1–ec5 (cohort S1; *n* 374 697). Since former drinkers include ex-drinkers who quit alcohol due to poor health, former drinker bias contributes to an apparently lower mortality of moderate drinkers[33,34]. In the second set of sensitivity analyses, only ec1–ec5 were applied, that is, non-drinkers were not excluded (cohort S2; *n* 399 866). Therefore, this set of analyses did not control for health issues in participants not drinking alcohol. The UK Biobank study was approved by the North West Multicentre Research Ethics Committee and all participants provided written informed consent before inclusion[31].

Exposure assessment

Estimation of alcohol from wine and non-wine, as well as coffee, and tea intake was performed similar as described by Bradbury and co-workers[35]. In brief, participants were asked about their weekly or monthly consumption of different alcoholic drinks during the baseline visit. Consumption of red wine and champagne plus white wine was included in the present analysis as wine intake whereas all other categories of alcoholic drinks, that is, beer plus cider, spirits, fortified wine and other alcoholic drinks, were included as non-wine. All alcoholic drinks were assumed to contain 10 g alcohol per portion except a pint of beer which was supposed to contain 20 g alcohol. Total weekly and monthly consumption of wine and non-wine was summed up for each participant. For an estimation of wine and non-wine intake in g/d, weekly and monthly consumption was divided by 7 and 30·4375, respectively. Furthermore, participants documented coffee and tea consumption as cups/d. An amount of 0·5 cups/d was assumed if 'less than one' cup of coffee or tea was recorded. Participants who did not indicate the extent of alcohol, coffee or tea intake including those answering 'do not know' or 'prefer not to answer' were excluded from the present analysis. In a subcohort of UK Biobank participants, only 'consumption of other alcoholic drinks' was not available. In these cases, this category was set to 0 g similar to Bradbury and co-workers[35].

Outcome assessment

Mortality data with date and underlying primary cause of death were provided by the National Health Service Information Centre for participants from England and Wales and by the National Health Service Central Register, Scotland for participants from Scotland[36]. Follow-up time was calculated between the date of baseline assessment and date of death or censoring (i.e. 23 March 2021), whichever came first. Besides overall mortality, the following two main mortality categories were defined according to the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (ICD-10) codes: cancer (C00-D48) and non-cancer (all but C00-D48). Furthermore, CVD (I00-I79) mortality was analysed. All analyses were performed in all participants, as well as in females and males separately.

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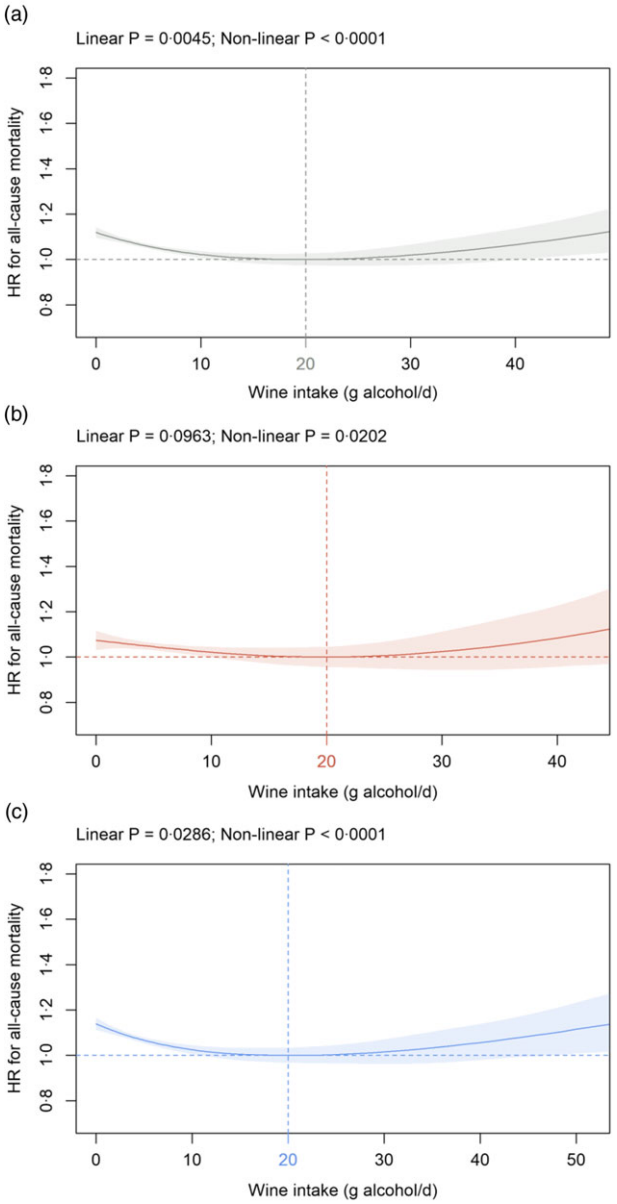

Fig. 1. Association of wine intake (g alcohol/d) in: (a) all participants; (b) females and (c) males with all-cause mortality in the primary cohort. Data are adjusted for sex (all participants only), age, AHI, ethnicity, OHR, PA, percentage body fat and smoking status. Additionally, wine, non-wine, coffee and tea intake are mutually adjusted (e.g. wine intake is additionally adjusted for non-wine, coffee and tea intake) as summarised in the Methods section. Covariates not fulfilling the proportional hazard assumption (all participants: age; females: age; males: age, OHR, percentage body fat) are stratified. The nadir is indicated in grey (total cohort), red (female) and blue (male). HR: hazard ratio; AHI, annual household income; OHR, overall health rating; PA, physical activity.

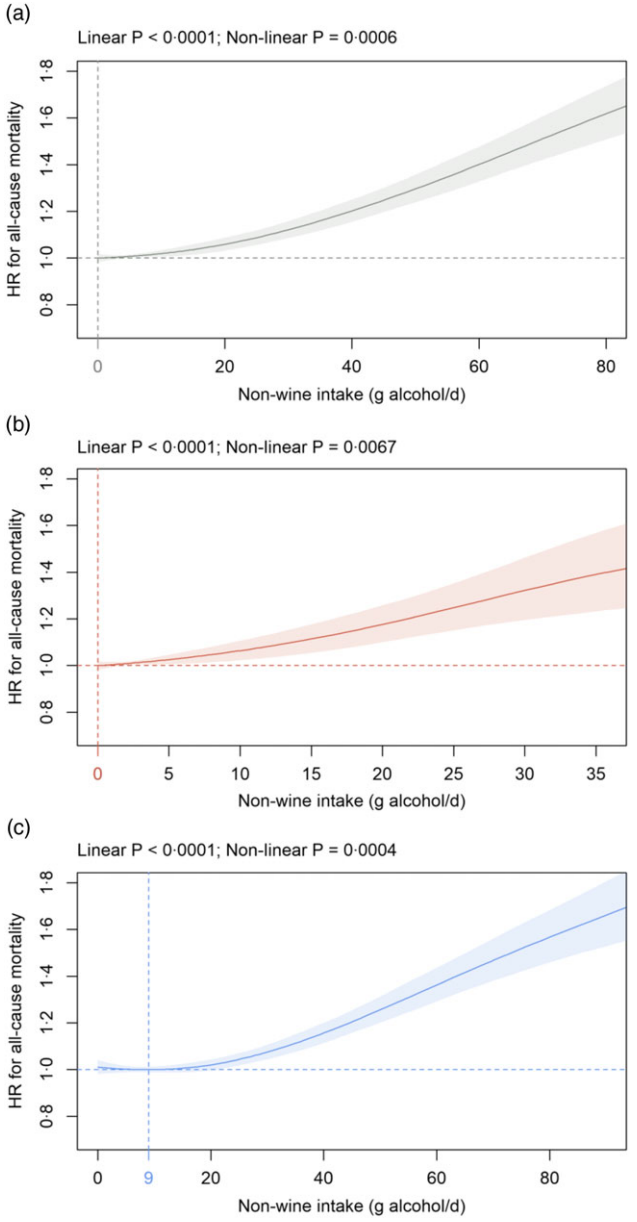

Fig. 2. Association of non-wine intake (g alcohol/d) in: (a) all participants; (b) females and (c) males with all-cause mortality in the primary cohort. Data are adjusted and presented as indicated in Fig. 1.

Statistical analyses

Data were imported, processed, analysed and graphically displayed with R version 4.0.5[37] in combination with the packages readxl[38], tidyverse[39], venn[40], skimr[41] and survival[42]. Cox proportional hazard regression models were fitted with wine, non-wine, coffee and tea mutually adjusted and included as penalised cubic splines with their degrees of freedom set to 4. The analysis of each penalised cubic spline is segregated into its linear and non-linear effects whose significances are documented by the respective *P* values (p^{lin} for the linear and $p^{non\text{-}lin}$ for the non-linear effect) of Wald-type tests for joint significance of the multiple coefficients associated with the respective linear or non-linear portion of the penalised spline fit[43,44]. These *P* values for the association of wine, non-wine, coffee and tea with mortality are depicted in Fig. 1–4, online Supplementary Fig. 2 and 3 and Supplementary Tables 2–4. In all analyses, the nadir was defined as the consumption of wine, non-wine, coffee and tea with the lowest estimated hazard ratio (HR) over the range from 0 to the 99 % quantile of consumption and the HR at the nadir was set to 1 to simplify presentations and comparisons. HR with pointwise 95 % CI are shown for all mortality analyses. In all analyses, HR^0 reflects HR in non-

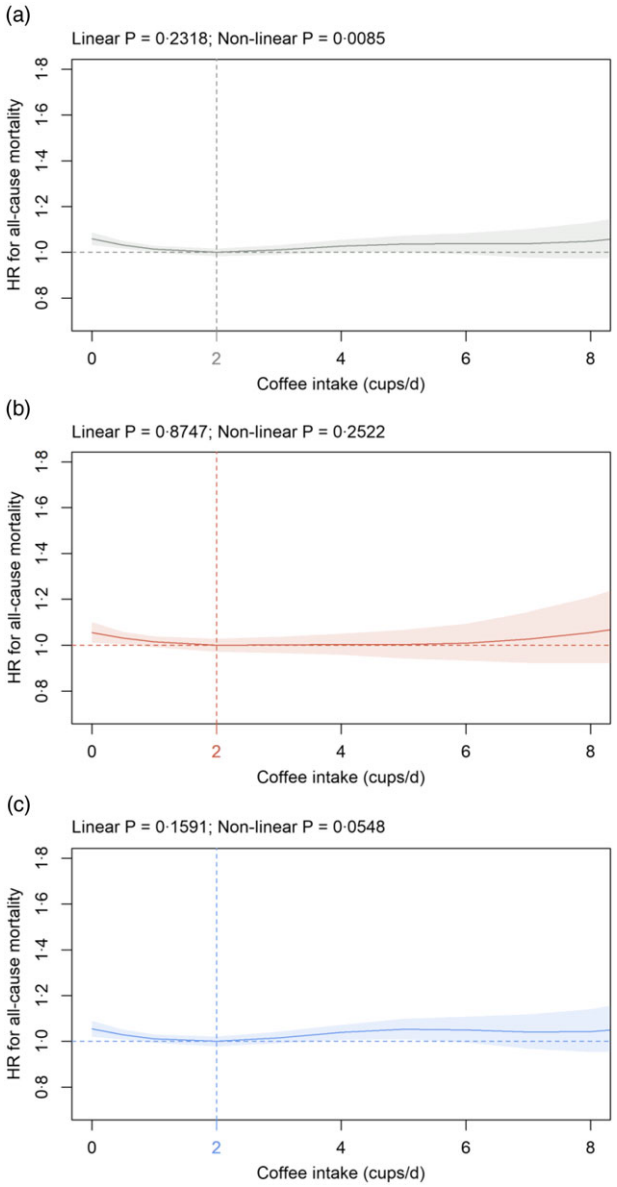

Fig. 3. Association of coffee intake (cups/d) in: (a) all participants; (b) females and (c) males with all-cause mortality in the primary cohort. Data are adjusted and presented as indicated in Fig. 1.

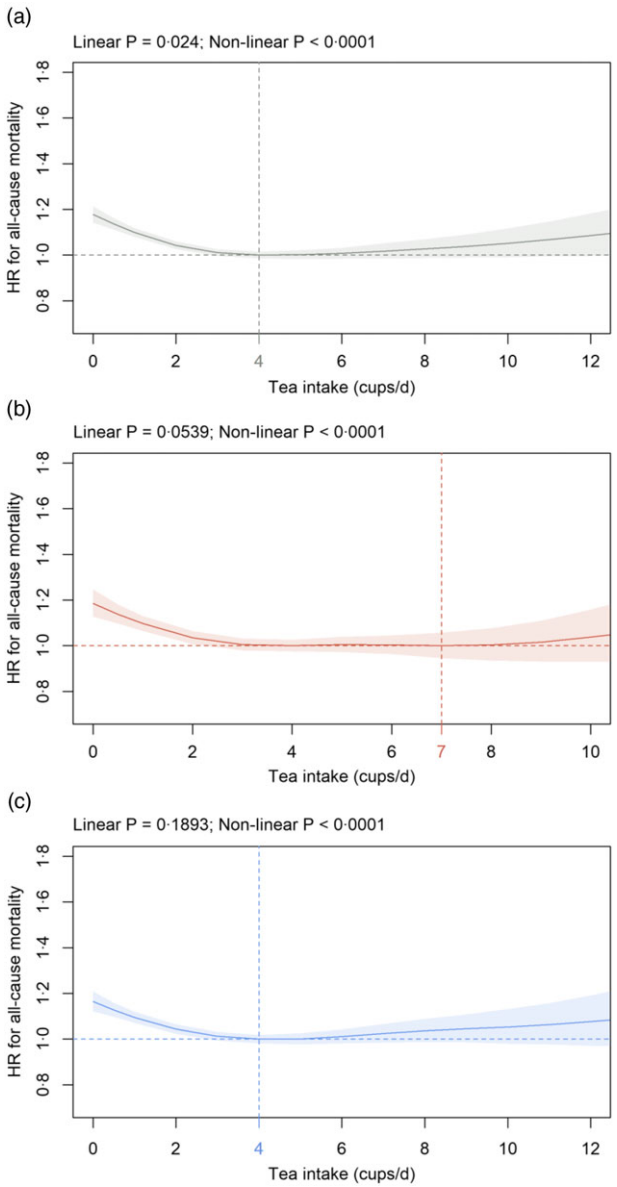

Fig. 4. Association of tea intake (cups/d) in: (a) all participants; (b) females and (c) males with all-cause mortality in the primary cohort. Data are adjusted and presented as indicated in Fig. 1.

consumers of wine, non-wine, coffee or tea relative to the HR at the nadir. If both p^{lin} and $p^{non\text{-}lin}$ were non-significant, no further interpretation of HR^0, other individual HR or of the nadir was performed. For cause-specific mortality, survival times of participants with other causes of death were considered censored at their date of death. The proportional hazard assumption was tested based on scaled Schoenfeld residuals and all covariates violating this assumption after Holm adjustment for multiple testing were stratified in the final models and are defined in the figure and table legends. Models were adjusted for age (quartiles), sex (all participants only), total physical activity (PA; metabolic equivalent of task-min/week: <1000, 1000 to <2000, 2000 to <4000, ≥4000 and unknown), smoking status (never, previous and current), annual household income (AHI; <18, 18 to <31, 31 to <52, 52 to <100, ≥100 k£ and unknown), ethnicity (White, Group combined of Mixed, Asian, Black, Chinese and Other) and overall health rating (OHR; poor, fair, good and excellent). Since percentage body fat is also an independent and significant predictor of all-cause mortality (data not shown), all analyses were adjusted for this covariate (quartiles) as well. A *P* value of < 0·05 was considered as statistically significant in all analyses.

Results

Baseline characteristics and deaths in UK Biobank participants

Baseline characteristics of the study population in total and depending on wine, non-wine, coffee and tea intake are summarised in Table 1. Median (Q (Quartile) 1, Q3) age of the study

Table 1. Baseline characteristics of the UK Biobank cohort* (median values and quartiles)

	Total cohort		Wine intake in g alcohol/d								Non-wine intake in g alcohol/d							
	n 354 386		<1 *n* 74 357		1– <8 *n* 127 737		8–<16 *n* 89 845		≥16 *n* 62 447		<1 *n* 104 546		1–<8 *n* 118 149		8– <16 *n* 58 126		≥16 *n* 73 565	
Parameter	Median	Q1, Q3	Median	Q1, Q3	Median	Q1, Q3	Median	Q1, Q3	Median	Q1, Q3	Median	Q1, Q3	Median	Q1, Q3	Median	Q1, Q3	Median	Q1, Q3
Wine intake (g alcohol/d)	5·7	1·4, 11·4	0·0	0·0, 0·0	4·3	2·9, 5·7	10·0	8·6, 12·9	21·4	17·1, 30·0	8·6	2·9, 14·3	5·7	2·9, 11·4	5·7	1·4, 12·9	2·9	0·0, 10·0
Non-wine intake (g alcohol/d)	4·3	0·0, 12·9	10·0	2·6, 25·7	2·9	0·0, 8·6	2·9	0·0, 10·0	4·3	0·0, 11·4	0·0	0·0, 0·0	2·9	2·9, 5·7	11·4	8·6, 12·9	28·6	20·0, 42·9
Coffee intake (cups/d)	2·0	0·5, 3·0	1·0	0·0, 3·0	2·0	0·5, 3·0	2·0	1·0, 3·0	2·0	1·0, 3·0	2·0	0·5, 3·0	2·0	1·0, 3·0	2·0	1·0, 3·0	2·0	0·5, 3·0
Tea intake (cups/d)	3·0	1·0, 5·0	3·0	1·0, 5·0	3·0	2·0, 5·0	3·0	1·0, 5·0	3·0	1·0, 5·0	3·0	1·0, 5·0	3·0	2·0, 5·0	3·0	1·0, 5·0	3·0	1·0, 5·0
Age (years)	58	50, 63	57	49, 63	58	50, 63	58	50, 63	57	50, 63	58	50, 63	58	50, 63	57	50, 63	57	50, 63
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Female	179 676	50·7	28 548	38·4	71 264	55·8	50 053	55·7	29 811	47·7	84 040	80·4	68 381	57·9	17 965	30·9	9290	12·6
Smoking status																		
Never	187 367	52·9	36 312	48·8	78 243	61·3	47 836	53·2	24 976	40·0	61 491	58·8	70 297	59·5	28 390	48·8	27 189	37·0
Previous	131 857	37·2	26 081	35·1	40 786	31·9	35 371	39·4	29 619	47·4	36 057	34·5	39 699	33·6	23 414	40·3	32 687	44·4
Current	35 162	9·9	11 964	16·1	8708	6·8	6638	7·4	7852	12·6	6998	6·7	8153	6·9	6322	10·9	13 689	18·6
AHI (k£)																		
<18	56 502	15·9	19 987	26·9	19 460	15·2	10 510	11·7	6545	10·5	15 118	14·5	16 891	14·3	9167	15·8	15 326	20·8
18–<31	76 979	21·7	18 087	24·3	28 599	22·4	18 451	20·5	11 842	19·0	22 113	21·2	25 146	21·3	12 594	21·7	17 126	23·3
31–<52	85 496	24·1	15 701	21·1	31 366	24·6	22 630	25·2	15 799	25·3	24 602	23·5	28 467	24·1	14 493	24·9	17 934	24·4
52–<100	71 907	20·3	8546	11·5	25 486	20·0	21 416	23·8	16 459	26·4	21 598	20·7	25 251	21·4	12 227	21·0	12 831	17·4
≥100	20 172	5·7	1209	1·6	6076	4·8	6572	7·3	6315	10·1	6914	6·6	7483	6·3	3200	5·5	2575	3·5
Unknown	43 330	12·2	10 872	14·6	16 750	13·1	10 266	11·4	5487	8·8	14 201	13·6	14 911	12·6	6445	11·1	7773	10·6
Ethnicity																		
White	342 689	96·7	69 987	94·1	122 976	96·3	88 179	98·1	61 547	98·6	100 224	95·9	114 063	96·5	56 585	97·3	71 817	97·6
Mixed, Asian, Black, Chinese, Other	11 697	3·3	4370	5·9	4761	3·7	1666	1·9	900	1·4	4322	4·1	4086	3·5	1541	2·7	1748	2·4
OHR																		
Excellent	63 715	18·0	8329	11·2	23 702	18·6	19 005	21·2	12 679	20·3	21 089	20·2	22 665	19·2	10 215	17·6	9746	13·2
Good	212 997	60·1	41 093	55·3	78 408	61·4	55 666	62·0	37 830	60·6	63 880	61·1	72 421	61·3	34 888	60·0	41 808	56·8
Fair	66 994	18·9	20 298	27·3	22 620	17·7	13 540	15·1	10 536	16·9	17 043	16·3	20 161	17·1	11 342	19·5	18 448	25·1
Poor	10 680	3·0	4637	6·2	3007	2·4	1634	1·8	1402	2·2	2534	2·4	2902	2·5	1681	2·9	3563	4·8
PA (MET-min/week)																		
Median	1804		1935		1773		1787		1773		1752		1739		1828		2031	
Q1, Q3	845, 3546		813, 4158		838, 3492		874, 3386		837, 3384		834, 3345		824, 3348		852, 3582		897, 4194	
Percentage body fat																		
Median	30·2		29·6		30·8		30·4		29·6		33·9		31·2		27·7		26·9	
Q1, Q3	24·7, 36·7		24·4, 36·2		24·8, 37·3		24·8, 36·6		24·5, 35·9		28·0, 39·2		25·0, 37·6		23·1, 33·8		23·0, 31·2	

	Coffee intake in cups/d										Tea intake in cups/d									
	0 *n* 66 840		0·5–1 *n* 98 765		2 *n* 71 654		3–4 *n* 78 677		>4 *n* 38 450		0 *n* 48 959		0·5–1 *n* 42 313		2 *n* 53 093		3–4 *n* 107 229		>4 *n* 102 792	
Parameter	Median	Q1, Q3	Median	Q1, Q3	Median	Q1, Q3	Median	Q1, Q3	Median	Q1, Q3	Median	Q1, Q3	Median	Q1, Q3	Median	Q1, Q3	Median	Q1, Q3	Median	Q1, Q3
Wine intake (g alcohol/d)	4·3	0·0, 10·0	5·7	1·6, 11·4	7·1	2·9, 12·9	7·1	2·9, 12·9	5·7	1·3, 12·9	5·7	1·0, 12·9	7·1	2·9, 14·3	7·1	2·9, 12·9	5·7	2·9, 11·4	5·7	1·3, 10·0
Non-wine intake (g alcohol/d)	4·3	0·0, 14·3	2·9	0·0, 11·4	4·3	0·0, 11·4	4·3	0·0, 12·9	5·7	1·0, 17·1	5·3	0·0, 14·3	4·3	0·0, 12·9	4·3	0·0, 11·4	4·3	0·0, 11·4	4·3	0·0, 14·3
Coffee intake (cups/d)	0·0	0·0, 0·0	1·0	0·5, 1·0	2·0	2·0, 2·0	3·0	3·0, 4·0	6·0	5·0, 6·0	3·0	2·0, 5·0	3·0	1·0, 4·0	2·0	1·0, 3·0	1·0	0·5, 3·0	1·0	0·0, 2·0
Tea intake (cups/d)	4·0	3·0, 6·0	4·0	2·0, 5·0	3·0	2·0, 4·0	2·0	0·5, 4·0	1·0	0·0, 3·0	0·0	0·0, 0·0	1·0	0·5, 1·0	2·0	2·0, 2·0	3·0	3·0, 4·0	6·0	5·0, 7·0
Age (years)	56	49, 62	58	51, 63	59	51, 64	58	51, 63	56	49, 62	56	49, 62	56	49, 63	58	50, 63	58	51, 63	58	51, 63
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Female	35 568	53·2	52 565	53·2	36 786	51·3	37 946	48·2	16 811	43·7	25 585	52·3	20 603	48·7	26 401	49·7	55 711	52·0	51 376	50·0
Smoking status																				
Never	36 708	54·9	55 019	55·7	38 650	53·9	40 452	51·4	16 538	43·0	24 636	50·3	22 005	52·0	28 446	53·6	58 668	54·7	53 612	52·2
Previous	23 771	35·6	36 493	36·9	26 954	37·6	30 004	38·1	14 635	38·1	17 989	36·7	15 757	37·2	20 038	37·7	40 046	37·3	38 027	37·0
Current	6361	9·5	7253	7·3	6050	8·4	8221	10·4	7277	18·9	6334	12·9	4551	10·8	4609	8·7	8515	7·9	11 153	10·9
AHI (k£)																				
<18	12 396	18·5	16 161	16·4	10 764	15·0	11 044	14·0	6137	16·0	7932	16·2	5584	13·2	7513	14·2	17 013	15·9	18 460	18·0
18–<31	14 331	21·4	21 763	22·0	15 808	22·1	16 986	21·6	8091	21·0	10 500	21·4	8417	19·9	11 173	21·0	23 944	22·3	22 945	22·3
31–<52	15 570	23·3	23 321	23·6	12 322	24·2	19 692	25·0	9591	24·9	11 941	24·4	10 536	24·9	12 897	24·3	25 735	24·0	24 387	23·7
52–<100	12 611	18·9	19 564	19·8	14 642	20·4	16 826	21·4	8264	21·5	9931	20·3	9766	23·1	11 625	21·9	21 194	19·8	19 391	18·9
≥100	3004	4·5	5612	5·7	4402	6·1	5006	6·4	2148	5·6	2680	5·5	3340	7·9	3579	6·7	5949	5·5	4624	4·5

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Table 1. (*Continued*)

Parameter	Coffee intake in cups/d										Tea intake in cups/d									
	0 *n* 66 840		0·5–1 *n* 98 765		2 *n* 71 654		3–4 *n* 78 677		>4 *n* 38 450		0 *n* 48 959		0·5–1 *n* 42 313		2 *n* 53 093		3–4 *n* 107 229		>4 *n* 102 792	
	Median	Q1, Q3	Median	Q1, Q3	Median	Q1, Q3	Median	Q1, Q3	Median	Q1, Q3	Median	Q1, Q3	Median	Q1, Q3	Median	Q1, Q3	Median	Q1, Q3	Median	Q1, Q3
Unknown	8928	13·4	12 344	12·5	8716	12·2	9123	11·6	4219	11·0	5975	12·2	4670	11·0	6306	11·9	13 394	12·5	12 985	12·6
Ethnicity																				
White	63 098	9·4·4	94 797	96·0	69 680	97·2	77 202	98·1	37 912	98·6	47 495	97·0	40 239	95·1	50 472	95·1	103 662	96·7	100 821	98·1
Mixed, Asian, Black, Chinese, Other	3742	5·6	3968	4·0	1974	2·8	1475	1·9	538	1·4	1464	3·0	2074	4·9	2621	4·9	3567	3·3	1971	1·9
OHR																				
Excellent	10 760	16·1	17 977	18·2	13 756	19·2	14 939	19·0	6283	16·3	8678	17·7	8322	19·7	10 266	19·3	19 439	18·1	17 010	16·5
Good	39 119	58·5	59 975	60·7	43 722	61·0	47 820	60·8	22 361	58·2	28 309	57·8	25 110	59·3	32 297	60·8	65 842	61·4	61 439	59·8
Fair	14 284	21·4	17 972	18·2	12 433	17·4	13 951	17·7	8354	21·7	10 079	20·6	7662	18·1	9156	17·2	19 278	18·0	20 819	20·3
Poor	2677	4·0	2841	2·9	1743	2·4	1967	2·5	1452	3·8	1893	3·9	1219	2·9	1374	2·6	2670	2·5	3524	3·4
PA (MET-min/week)																				
Median	1852		1836		1836		1760		1720		1760		1700		1782		1813		1888	
Q1, Q3	816, 3759		876, 3546		895, 3546		825, 3426		735, 3582		777, 3572		796, 3224		855, 3452		873, 3519		869, 3813	
Percentage body fat																				
Median	30·8		30·3		30·0		30·0		29·7		31·3		29·7		29·8		30·2		30·2	
Q1, Q3	25·2, 37·2		24·7, 36·6		24·5, 36·5		24·5, 36·6		24·5, 36·7		25·4, 37·7		24·4, 36·2		24·4, 36·2		24·7, 36·6		24·6, 36·7	

AHI, annual household income; MET, metabolic equivalent of task; OHR, overall health rating; PA, physical activity; Q, quartile.
*Categorical variables are presented as number (percentage) and continuous variables as median (Q1, Q3).

population was 58 (50, 63) with 50·7 % of participants being female. Median intake was 5·7 (1·4, 11·4) g alcohol/d from wine, 4·3 (0·0, 12·9) g alcohol/d from non-wine, 2·0 (0·5, 3·0) cups/d coffee and 3·0 (1·0, 5·0) cups/d tea (Table 1). Median (Q1, Q3) wine intake was similar in female (5·7 (2·9, 11·4) g alcohol/d) compared with male (5·7 (0·7, 11·4) g alcohol/d) participants (online Supplementary Table 1). Non-wine intake was lower in females (1·4 (0·0, 4·3) g alcohol/d) as compared with males (11·4 (4·3, 22·9) g alcohol/d) (online Supplementary Table 1). Furthermore, median coffee (females 2·0 (0·5, 3·0); males 2·0 (1·0, 3·0) cups/d) and tea (females and males 3·0 (1·0, 5·0)) intake was similar between both sexes (online Supplementary Table 1). Follow-up was 12·0 (11·3, 12·7) years with 4·2 million person-years.

Beverage intake and all-cause mortality

Overall, 7243 deaths occurred in females and 12 958 in males, that is, a total of 20 201 deaths.

Wine intake. In all participants, a significant U-shaped association between wine intake and all-cause mortality was detected with the nadir at 20 g alcohol/d (Fig. 1(a)). Similar findings were observed in sex-dependent analyses with the nadir for all-cause mortality at 20 g alcohol/d for both females (Fig. 1(b)) and males (Fig. 1(c)). HR^0 was 1·07 (1·03, 1·12) in females and 1·14 (1·11, 1·17) in males (Fig. 1(b)–(c)). A significant U-shaped association between wine intake and all-cause mortality was also detected in sensitivity analyses in cohorts S1 and S2 with the nadir between 19 and 20 g alcohol/d from wine in all participants, as well as in females and males separately (online Supplementary Fig. 2). In cohort S2, HR^0 for present non-alcohol drinkers was higher in both females (1·23 (1·20, 1·26); online Supplementary Fig. 2(d)) and males (1·20 (1·18, 1·22); Supplementary Fig. 2(f)) compared with the corresponding HR^0 in the primary cohort (Fig. 1(b)–(c)).

Non-wine intake. In all participants and in females, a significant positive dose-dependent association between non-wine intake and all-cause mortality was detected with the nadir at 0 g alcohol/d (Fig. 2(a)–(b)). In males, the nadir was at 9 g alcohol/d from non-wine with dose-dependent increases seen beyond 20 g alcohol/d (Fig. 2(c)). The shape of the association between non-wine intake and all-cause mortality changed towards a J-shaped curve in the sensitivity analyses with the most pronounced alterations seen in cohort S2 (online Supplementary Fig. 3). In cohort S2, the nadir was at 14, 7 and 17 g alcohol/d in all participants, females and males, respectively (online Supplementary Fig. 3(b), (d) and (f)).

Coffee intake. In all participants, coffee intake and all-cause mortality were significantly associated (Fig. 3(a)). The nadir was observed at 2 cups/d coffee and HR^0 was significantly increased at 1·06 (1·03, 1·09) (Fig. 3(a)). Association was similar in females and males; however, statistical significance was not reached in both sexes (Fig. 3(b) and (c)). Findings were similar in sensitivity analyses using cohorts S1 and S2 (data not shown).

Tea intake. In all participants, all-cause mortality risk continuously decreased from HR^0 of 1·18 (1·14, 1·21) to the nadir at 4 cups/d and no significant effects at higher consumption levels (Fig. 4(a)). Similar to all participants, HR^0 was significantly increased in both females (1·19 (1·13, 1·25)) and males (1·17 (1·12, 1·21)) compared with the HR at the nadir (females: 7, males: 4 cups/d), respectively (Fig. 4(b) and (c)). Almost identical results were obtained in sensitivity analyses in cohorts S1 and S2 (data not shown).

Beverage intake and cancer mortality

Within all-cause mortality, 4520 cancer deaths occurred in females and 6360 in males, that is, a total of 10 880 cancer deaths. All findings concerning the association between beverage intake and cancer mortality are summarised in online Supplementary Table 2.

Wine intake. In all participants and in both sexes separately, wine intake was not significantly associated with cancer mortality. Findings were numerically similar in cohorts S1 and S2, with associations reaching statistical significance in the total and male S2 cohort.

Non-wine intake. In all participants, as well as in females and males separately, non-wine intake was significantly associated with cancer mortality in a linear way. The nadir was at 0, 0 and 3 g alcohol/d from non-wine in all participants, females and males, respectively. Significant linear associations were also observed in cohorts S1 and S2. However, the nadir was seen at higher intake levels with a most pronounced shift towards higher values in cohort S2.

Coffee intake. Coffee intake was not significantly associated with cancer mortality in all participants, females and males in the primary cohort, as well as in cohorts S1 and S2.

Tea intake. Tea consumption was significantly associated in a non-linear form with cancer mortality and HR^0 was significantly increased in all participants and both sexes separately. The nadir was between 3 (females) and 4 (all participants, males) cups/d. Almost identical findings were observed in cohorts S1 and S2.

Beverage intake and non-cancer mortality

Within all-cause mortality, 2723 non-cancer deaths occurred in females and 6598 in males, that is, a total of 9321 non-cancer deaths. All findings concerning the association between beverage intake and non-cancer mortality are summarised in online Supplementary Table 3.

Wine intake. Wine consumption was significantly associated with non-cancer mortality in a U-shaped form in all participants and both sexes separately. The nadir was between 21 (all participants, females) and 23 (males) g alcohol/d from wine. HR^0 was significantly increased at 1·21 (1·18, 1·25) in all participants, 1·25 (1·17, 1·33) in females and 1·19 (1·15, 1·23) in males. Whereas the nadir was similar in cohorts S1 and S2, HR^0 was numerically higher with most pronounced increases seen in cohort S2.

Non-wine intake. In all participants and in females, a significant positive dose-dependent association between non-wine intake and non-cancer mortality was detected with the nadir at 0 g alcohol/d. In males, HR was lowest between 0 and 20 (nadir at 12) g alcohol/d from non-wine with dose-dependent increases seen beyond 20 g alcohol/d. The shape of the association between non-wine intake and non-cancer mortality changed towards a J-shaped curve in the sensitivity analyses with the most pronounced alterations seen in cohort S2. Here, the nadir was at 17, 8 and 19 g alcohol/d and HR^0 was significantly elevated at 1·11 (1·09, 1·13), 1·04 (1·02, 1·07) and 1·14 (1·11, 1·18) in all participants, females and males, respectively.

Coffee intake. Coffee intake was significantly associated with non-cancer mortality in a non-linear manner in all participants and males. The nadir was observed at 2 cups/d and HR^0 was slightly but significantly elevated at 1·08 (1·04, 1·13) and 1·07 (1·02, 1·12). In contrast, no significant association was observed in female subjects. Similar findings were obtained in cohorts S1 and S2 with $p^{non\text{-}lin}$ also becoming significant in females.

Tea intake. Tea consumption was significantly associated in a linear and non-linear way with non-cancer mortality and HR^0 was significantly elevated in all participants and both sexes separately. The nadir was between 5 (all participants, males) and 9 (females) cups/d. Similar results were observed in cohorts S1 and S2.

Beverage intake and CVD mortality

Within non-cancer deaths, 916 CVD deaths occurred in females and 2858 in males, that is, a total of 3774 CVD deaths. All findings concerning the association between beverage intake and CVD mortality are summarised in online Supplementary Table 4.

Wine intake. Wine intake was significantly associated with CVD mortality in a non-linear manner in all participants and both sexes separately. The nadir was between 19 (females) and 21 (males) g alcohol/d. HR^0 was significantly increased at 1·22 (1·16, 1·28) in all participants, 1·31 (1·17, 1·46) in females and 1·20 (1·14, 1·26) in males. Whereas the nadir was similar in cohorts S1 and S2, HR^0 was numerically higher with the most pronounced increases seen in cohort S2.

Non-wine intake. In all participants and in males, a significant positive dose-dependent association between non-wine intake and CVD mortality was detected with the nadir at 4 and 6 g alcohol/d, respectively. The shape of the association between non-wine intake and CVD mortality changed towards a J-shaped curve in the sensitivity analyses with the most pronounced alterations seen in cohort S2. Here, the nadir was at 16 and 17 g alcohol/d and HR^0 was significantly elevated at 1·08 (1·05, 1·11) and 1·08 (1·03, 1·13) in all participants and males, respectively. In contrast, no significant association was observed in females in the primary cohort, as well as in cohorts S1 and S2.

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Coffee intake. Coffee intake was not significantly associated with CVD mortality in all participants, females and males in the primary cohort, as well as in cohorts S1 and S2.

Tea intake. Tea consumption was significantly associated in a non-linear way in all participants and males, as well as in a linear negative manner in females. HR^0 was significantly increased at 1·20 (1·12, 1·29), 1·55 (1·34, 1·78) and 1·18 (1·09, 1·28) in all participants, females and males, respectively, with the nadir ranging from 4 (males) to 10 (females) cups/d. Similar findings were obtained in cohorts S1 and S2.

Discussion

In the present study, it is elucidated for the first time how wine, non-wine, coffee and tea intake included as continuous non-linear predictors and mutually adjusted are associated with all-cause and cause-specific mortality.

For all participants and in sex-dependent analyses (primary cohort), a significant U-shaped association is seen between wine intake and all-cause mortality with HR^0 significantly increased as compared with the nadir at 20 g alcohol/d. A decreased risk of death for light to moderate wine intake has also been shown in studies from the USA[45], Denmark[46], France[47] and Sweden[48] comprising 128 934, 24 523, 36 250 and 1828 individuals, respectively. To the best of our knowledge, only one study so far has assessed the sex-dependent association between different intake levels of wine and all-cause mortality. In the study by Baglietto and co-workers, HR of death is lowest in the categories 1–19 and 20–39 g alcohol/d from wine in females and males, respectively[49]. Similar to the current findings but using a different analytical approach, Jani and co-workers demonstrate convincingly in UK Biobank participants that HR for death decreases in red wine consumers up to around 20 weekly alcohol units[13]. Furthermore, red wine and champagne plus white wine intake is inversely related to all-cause mortality in another study based on UK Biobank participants in categorical analyses; however, this association largely disappears in a continuous analysis[29]. A different analytical approach and follow-up interval might well explain the differences between the latter results and our current findings. The present study is the first to elucidate the association between wine intake and non-cancer mortality. We show a significant U-shaped association in all participants and both sexes separately with increased HR^0 as compared with the nadir observed between 21 and 23 g alcohol/d from wine. Similar results are obtained for CVD with the nadir detected between 19 and 21 g alcohol/d from wine. Our CVD results are well in accordance with a meta-analysis comprising six cohort studies, and the lowest risk of death was found at 24 g alcohol/d from wine[30].

To the best of our knowledge, no study so far has contrasted non-wine with wine consumption regarding mortality after excluding non-drinkers. In contrast to wine consumption, a positive dose-dependent relation exists in the primary cohort between non-wine intake and all-cause mortality with the nadir observed at 0, 0 and 9 g alcohol/d from non-wine in all participants, females and males, respectively. Within the non-wine category, several studies have assessed the association of beer and spirits with all-cause mortality. In agreement with our non-wine results, Schutte and co-workers demonstrate convincingly that both beer/cider and spirits intake is associated with increased all-cause mortality risk in UK Biobank participants[29]. Similarly, beer/cider and spirits drinkers have a significantly higher all-cause mortality risk if compared with red wine drinkers[13]. A lower mortality risk in drinkers of any type of wine as compared with beer or spirits drinkers is also found in an independent cohort[45]. In another report, HR for all-cause mortality is increased in the highest category of beer and spirits consumption in males but not females[49]. In agreement with our findings, non-wine consumption is positively associated with cancer mortality in a cohort from Denmark[46]. Interestingly, beer/cider and spirits consumption is also associated with an increased risk for incident cancer in UK Biobank participants[29]. To the best of our knowledge, our study is the first to show a significant positive dose-dependent association between non-wine intake and non-cancer mortality. Within non-cancer, non-wine intake is positively and dose-dependently related to CVD mortality. Interestingly, beer/cider and spirits consumption is associated with an increased risk for cardiovascular events, ischaemic heart disease and cerebrovascular disease in UK Biobank participants[29]. In contrast to the current findings, a J-shaped relationship with CVD mortality is apparent for beer but not spirits[30]. However, this meta-analysis has not consistently controlled for the impact of non-drinkers on mortality[30]. Combined these findings suggest that associations between wine and non-wine consumption on the one hand and different types of mortality on the other hand show opposite directions in many cases at low to moderate drinking levels causing underestimation of mortality risk when pooled into one alcohol variable.

To the best of our knowledge, no study so far has defined the impact of not controlling for never or former alcohol drinking on the association between wine or non-wine intake and mortality. In the current study, HR^0 for wine or non-wine increases further if never drinkers (cohort S1) and all non-alcohol drinkers (cohort S2) are included in the analysis with most pronounced changes observed in cohort S2. Decreased mortality in low to moderate alcohol drinkers in cohorts S1 and S2 could be explained by a higher death risk of former and never drinkers who might have quit or not initiated alcohol consumption because of poor health[33,34]. These findings support the notion that the handling of non-drinkers has a major impact on mortality analyses and might explain some discrepancies between studies. Thus, two reports demonstrate convincingly that light to moderate wine consumption is significantly related to a lower risk of death from cancer[46,47] in contrast to our present results in the primary cohort. However, if we perform our analysis in cohort S2 similar to the approach used in both studies[46,47], we also observe a significant non-linear association between wine intake and an increased HR^0 for cancer deaths. Furthermore, non-wine intake of up to 21 drinks/week is not associated with an increased risk of death in one study[46] in contrast to the current findings in the primary cohort. However, if we perform our analysis in cohort S2 similar to the approach used in this study[46], the nadir increases to 14 g alcohol/d and risk of death is not increased up to about 25 g alcohol/d from non-wine as compared with HR^0.

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For coffee intake, the nadir is observed at 2 cups/d with non-significant effects at higher consumption levels and slightly but significantly increased HR^0 in all participants. In agreement with the present results, increased all-cause mortality risk in non-coffee drinkers is shown in previous studies[26–28,50]. However, the nadir varies and is somewhat higher compared with the present report, that is, between 3 and 7 cups/d[26–28,50–53]. Loftfield and co-workers[53] also assess UK Biobank participants with differences in study results being well explained by different exclusion criteria, follow-up time and model adjustments with coffee intake included as an ordinal variable. Coffee intake is not significantly associated with cancer mortality in the present analysis in agreement with most studies[26,54–56] except one[27]. In the current study, the nadir for non-cancer mortality is 2 cups/d coffee in all participants with no further effects at higher amounts and a significantly increased HR^0. To the best of our knowledge, no study so far has assessed the relation between coffee intake and overall non-cancer mortality. Within non-cancer, no significant association is detected between coffee consumption and CVD mortality. However, a dose-dependent decrease in CVD mortality as suggested by previous meta-analyses[26,27] cannot be ruled out since coffee consumption levels show a nadir numerically between 2 (male) and 8 (female) cups/d. Taking published and current findings into consideration, coffee is not positively related to all-cause, cancer, non-cancer and CVD mortality. A minor negative dose-dependent association remains possible.

Tea consumption shows a significant negative dose-dependent association with all-cause mortality, and HR^0 is significantly increased compared with HR at the nadir. Results are similar in both sexes. The nadir for all-cause mortality is between 4 and 7 cups/d tea similar to published results where it is found between 2 and >5 cups/d[20,24,57,58]. Similar to the present findings for all-cause mortality, tea consumption is associated with decreased cancer mortality. Although the type of tea has not been recorded during baseline assessment, the majority of tea drinkers probably consumes black tea since Great Britain has one of the highest per capita black tea consumption worldwide[59]. It is interesting to note in this context that the intake of black but not green tea has been linked with lower cancer mortality[20]. To the best of our knowledge, the present study is the first to show that HR^0 for non-cancer mortality compared with HR at the nadir (5–9 cups/d) is significantly increased in both sexes. Findings are similar for CVD in agreement with previous reports observing a negative dose-dependent association between tea and CVD mortality in both sexes[24,57,60]. Taking previous publications and the present findings into consideration, tea consumption is consistently and significantly associated with decreased all-cause, cancer, non-cancer and CVD mortality in both sexes with the nadir ranging from 3 to 10 cups/d and no increases in risk of death at higher doses.

Strengths of the current report include the prospective cohort design, a large sample size, thorough characterisation of UK Biobank participants, median follow-up time >10 years, as well as the wide range of wine, non-wine, coffee and tea intake included as continuous parameters. Limitations include that consumption of other important beverages such as sugar-sweetened beverages and milk-based drinks, as well as type of tea, has not been assessed during the baseline visit. Furthermore, the present results cannot be adjusted for energy intake since this parameter was not assessed during the UK Biobank baseline visit. Further potential limitations include residual confounding, as well as measurement errors in the assessment of the exposure variables, potential confounders and misclassification of cause of death. Two studies have evaluated the performance of the UK Biobank touchscreen dietary questionnaire. As shown convincingly by Bradbury *et al.*[61] and Carter *et al.*[62], the touchscreen questionnaire adequately discriminates between high and low intakes for selected food groups when compared with a 24-h dietary assessment (Oxford WebQ). The level of agreement is comparable with estimates reported between traditional 24-h recalls and food frequency questionnaires in previous studies[61,62]. In addition, causal mediation analysis for specific covariates, for example, percentage body fat, could not be performed since it has not been implemented in R for Cox proportional hazard regression models with covariates included as penalised cubic splines. Moreover, a 'healthy volunteer' selection bias might exist since the cohort is not demographically representative of the general UK population[63]. However, a representative population is not required to define exposure–disease relationships[63].

Summarising on a population level, the current study indicates that light to moderate consumption of wine but not non-wine is associated with decreased all-cause and non-cancer mortality. Coffee consumption is not related to increased mortality and a minor negative dose-dependent association remains possible. Tea intake is associated with a consistently decreased risk of all mortality types studied in both sexes. Further prospective studies on beverage intake in relation to morbidity from cancer and non-cancer disease are necessary to provide even more definitive conclusions.

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There are no conflicts of interest.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S000711452200040X

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2.2 Publication 2: Association of Alcohol Types, Coffee, and Tea Intake with Risk of Dementia: Prospective Cohort Study of UK Biobank Participants

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Authors' contributions

S. M. S. and A. K. conceived the research. Data analysis was performed by S. M. S., A. K., I. B., G. E. and M. F. The first draft of the manuscript was written by S. M. S. and A. K., and I. B., G. E. and M. F. commented on previous versions of the manuscript. All authors have read and agreed to the published version of the manuscript.

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Appendix B: Supplementary Material

Summary

Research Gap 2 was addressed in the publication "Association of Alcohol Types, Coffee, and Tea Intake with Risk of Dementia: Prospective Cohort Study of UK Biobank Participants"[115].

Within this paper, the association of the intake of different types of alcoholic beverages, i.e., wine and non-wine, as well as coffee and tea, with incident dementia was assessed.

The study included 351,436 UK Biobank participants with 4,270 cases of dementia occurring during a median follow-up time of 12.0 years. Non-wine alcoholic beverages were defined as beer plus cider, spirits, fortified wine, and other alcoholic drinks. Wine and non-wine alcoholic beverages were assessed in g alcohol/day and coffee and tea in cups/day. All beverages were included in the models as continuous variables. The UK Biobank's baseline questionnaire assessing participants' weekly and monthly beverage consumption was used. The primary outcome of the present study was incident dementia defined as ICD-10 codes F00, F01, F02, F03, G30, and G31. All analyses were performed in the total cohort and separated by sex. Data analysis was carried out using R version 4.0.5.[114]. Wine, non-wine, coffee, and tea were mutually adjusted within Cox proportional hazard regression models and included as penalised cubic splines. Models were additionally adjusted for age, annual household income, ethnicity, highest qualification, overall health rating, physical activity, percentage body fat, sex, and smoking status. The lowest estimated HR over the range from zero to the 99%-quantile of beverage consumption was defined as the HR-nadir. To obtain the primary cohort, all non-alcohol drinkers, i.e., participants with a present alcohol intake of 0 g alcohol/day, were removed from the analysis to exclude all participants not drinking alcohol due to health issues. The group of non-alcohol drinkers comprised lifetime abstainers and former drinkers, the latter drinking alcohol in the past but not in the present. Two sets of sensitivity analyses were performed in addition to the primary analyses. Firstly, only former drinkers but not lifetime abstainers were excluded from the analysis in addition to the exclusion criteria. Secondly, all non-drinkers were included in the analyses.

In this study, wine consumption was linked to dementia risk in a U-shaped manner, with the HR-nadir observed at 21 and 23 g alcohol/day in all participants and males. In contrast, non-wine consumption was positively and dose-dependently associated with dementia risk, with the HR-nadir at 0 g alcohol/day. No significant association was found between coffee consumption and dementia risk. In contrast, a significant U-shaped association was seen between tea intake and incident dementia in all participants and males, with the HR-nadir at 6 and 7 cups/day, respectively. Furthermore, the HR at non-consumption was higher after including all non-drinkers as compared to the primary cohort for both wine and non-wine alcoholic beverages. In addition, the association of non-wine with incident dementia was more

J-shaped, and a shift of the HR-nadir towards higher values occurred when no non-drinkers were excluded as compared to the primary cohort.

In summary, this study shows on a population level that moderate wine consumption and moderate-to-high tea intake are associated with a decreased risk of incident dementia. In contrast, non-wine alcoholic beverages intake is positively related to dementia risk in a linear fashion, and no clear association is found for coffee.

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Association of Alcohol Types, Coffee, and Tea Intake with Risk of Dementia: Prospective Cohort Study of UK Biobank Participants

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Abstract: The prevalence of dementia is increasing globally and is linked to obesity and unfavorable dietary habits. The present study analyses the association of alcohol intake from wine and non-wine alcoholic beverages (non-wine) in g/d, as well as coffee and tea in cups/d, with incident dementia. Over 4.2 million person-years, 4270 dementia cases occurred in 351,436 UK Biobank participants. Hazard ratios (HRs) for incident dementia were defined with Cox proportional hazard regression models in which beverage intake was fitted as penalized cubic splines. Wine intake showed a significant U-shaped association with the lowest risk for incident dementia (nadir) ranging from 21 to 23 g alcohol/d in all participants and in males. In contrast, non-wine consumption was significantly and dose-dependently associated with incident dementia, and the nadir was found at 0 g alcohol/d. Coffee consumption was not related to dementia risk, while moderate-to-high tea intake was negatively associated with incident dementia. Taken together, the current study shows on a population level that moderate consumption of wine and moderate-to-high tea intake is associated with a decreased risk of incident dementia. In contrast, non-wine is positively related to dementia risk in a linear fashion, and no clear association is found for coffee.

Keywords: alcohol; body weight; coffee; dementia; non-wine; obesity; prospective cohort study; tea; wine

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1. Introduction

Dementia is a condition characterized by a decline in cognitive function going beyond the common effects of biological aging [1]. Currently, there are more than 55 million people living with dementia worldwide, and almost 10 million new cases occur every year [1]. The risk of developing dementia is positively associated with overweight and obesity at younger but not older ages [2]. Despite intensive research throughout the recent decades, no effective pharmacological treatment for the main dementia types has yet been developed [3].

Lifestyle interventions, such as dietary changes, are a feasible approach not only to combat obesity [4] but also to delay the deterioration of cognitive function from mild cognitive impairment to dementia [5]. Thus, daily consumption of unprocessed or minimally processed plant-based food, such as fruits, vegetables, olive oil, and nuts, contributes to healthy body weight [6] and has neuroprotective effects [7,8]. Correspondingly, adhering to the Mediterranean diet is associated with lower body weight [9], as well as with a decreased

risk of cognitive impairment and dementia [7,10,11]. Furthermore, sugar-sweetened beverages increase the risk of both obesity and dementia [12,13]. In contrast, results for other beverages, including alcoholic drinks, coffee, and tea with incident obesity and dementia, have been less clear. Both alcoholic beverages and caffeine exert pharmacological effects on the brain. Alcoholic beverages increase microglial activation, neuroinflammation, and neuronal cell death [14]. In contrast, caffeine exerts neuroprotective effects on the brain, such as a reduction in β-amyloid peptide production via secretase suppression [15], as well as a decrease in neuroinflammation through lowering of extracellular calcium, glutamate release, and activation of microglia [16]. Therefore, it is of importance to evaluate the impact of alcohol, coffee, and tea on cognitive function.

Alcohol intake is measured in categories such as no, light (≤12 g alcohol/d), moderate (>12 to ≤24 g alcohol/d), and heavy (>24 g alcohol/d) [17]. The National Health Service recommends a restriction of alcohol intake to less than 16 g/d for both sexes to maintain good health [18]. However, guidelines do not distinguish between sources of alcohol, i.e., wine versus all non-wine alcoholic beverages combined (non-wine), including beer and spirits. Studies have suggested that the association between wine and incident obesity [19] and diabetes mellitus [20] is different as compared to non-wine. Furthermore, a negative association between wine and incident dementia has been described [17,21], while a positive [17] or no [21–23] association for beer and spirits exists. Moreover, the association of wine consumption with cognitive decline might depend on sex [24].

Coffee consumption is measured in cups/d with moderate intake between three and five cups/d [25]. Results for coffee intake and decline of cognitive function have been discordant with findings suggesting increased odds of dementia [26], no association [27], or a lower dementia risk [28,29]. Furthermore, the protective effects of coffee were more pronounced in females as compared to males [28]. Additionally, lifetime exposure to caffeine reduces the risk for incident dementia for both men and women, also with a greater effect in women [30].

Tea intake is measured using the following categories: no, light (zero to two cups/d), moderate (three to four cups/d), and high (more than five cups/d) [31]. In contrast to coffee, no specific recommendation for optimal tea intake exists. Several studies have shown a negative association between tea intake and cognitive impairment [29,32,33], Alzheimer's disease [33], and dementia [33,34]. No sex-dependent differences regarding the association between tea intake and dementia risk were observed [31,35].

To the best of our knowledge, the four beverage types, i.e., wine, non-wine, coffee, and tea, have not been assessed within a large prospective cohort study with mutual adjustment. Furthermore, previous models often include alcohol, coffee, and tea consumption as linear or discretized ordinal predictors. Moreover, wine consumption has not been contrasted with non-wine intake regarding incident dementia, and effects of abstainer bias on potential protective findings of alcohol consumption [36] have not been assessed systematically.

To address these limitations, we analyzed the associations between wine, non-wine, coffee, and tea intake and proportional hazards for incident dementia in 351,436 UK Biobank participants using penalized cubic splines. Wine was contrasted with non-wine since only wine contains substances such as resveratrol [37,38] that may have neuroprotective effects, and median intake levels between alcoholic beverage groups should be similar to improve the comparability of the data. We hypothesized that non-linear relationships exist between the four beverages and the risk for incident dementia, as well as that intake levels linked to the lowest hazards depend on the analyzed beverage.

2. Materials and Methods

2.1. Study and Participants

The UK Biobank study is a multicentre, prospective cohort study and its study design is described in more detail at https://www.ukbiobank.ac.uk [39], accessed on 7 February 2022. Between 2006 and 2010, more than 500,000 participants aged 38 to 73 years had their baseline assessment throughout the UK as described recently [40]. To all analyses, we

applied the following five exclusion criteria (ec): (1) pre-existing dementia at baseline and incident dementia within 2 years after baseline (landmark analysis), (2) missing smoking status, (3) missing socioeconomic status (i.e., annual household income (AHI), ethnicity, highest qualification and/or overall health rating (OHR)), (4) missing percentage body fat, (5) either missing information on beverage intake or being in the upper 0.1% of alcohol, coffee, or tea consumption.

To obtain the primary cohort, all non-alcohol drinkers (present alcohol intake of 0 g alcohol/d) were removed from the analysis to exclude participants not drinking alcohol due to health issues (primary cohort; n = 351,436; Supplementary Figure S1). The group of non-drinkers was comprised of lifetime abstainers and former drinkers, the latter drinking alcohol in the past but not in the present. Two sets of sensitivity analyses (S1 and S2) were performed in addition to the primary analyses. Firstly, only former drinkers but not lifetime abstainers were excluded from the analysis in addition to ec1 to ec5 (cohort S1; n = 371,153). Former drinker bias may contribute to the seemingly lower morbidity of moderate drinkers since the category of non-drinkers includes ex-drinkers who quit alcohol consumption because of poor health [41,42]. Secondly, all non-drinkers were included in the analyses, i.e., only ec1 to ec5 were applied (cohort S2; n = 395,893). Hence, this second set of analyses did not control for the abovementioned potential health issues of participants not drinking alcohol. All analyses on the influence of wine, non-wine, coffee, and tea on dementia incidence were conducted in the primary cohort, as well as in cohorts S1 and S2. All participants provided their written informed consent before inclusion in the study, which was approved by the North West Multicentre Research Ethics Committee [39].

2.2. Exposure Assessment

The assessment of alcohol intake from wine and non-wine, as well as consumption of coffee and tea, was performed as described recently by our group [43]. In brief, wine intake was defined as red wine and champagne plus white wine consumption, while all other categories of alcoholic beverages, i.e., beer plus cider, spirits, fortified wine, and other alcoholic drinks, were defined as non-wine. For all alcoholic beverages, an alcohol content of 10 g per portion was assumed, except for a pint of beer for which content of 20 g alcohol was defined. Coffee and tea intake was documented in cups/d. Participants were excluded if the extent of alcohol, coffee, or tea intake was not specified or questions concerning beverage intake were answered with "do not know" or "prefer not to answer".

2.3. Outcome Assessment

The UK Biobank provides morbidity data as the earliest record date and respective health outcome defined by three-character International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) codes [44]. Record sources were self-report at baseline assessment, as well as inpatient hospital, primary care, and death record data [44]. The primary outcome of the present study was incident dementia defined as ICD-10 codes F00, F01, F02, F03, G30, and G31. Follow-up time was calculated by subtracting the date of the baseline assessment from the date of first dementia occurrence, loss-to-follow-up, death, or censoring (i.e., 31 March 2021), whichever came first. In the case of several dementia diagnoses for a patient, the lowest duration to diagnosis was used. All analyses were performed in the total cohort and by sex.

2.4. Statistical Analyses

Data were imported, processed, analysed, and graphically displayed with R version 4.0.5 [45] and the packages readxl [46], tidyverse [47], venn [48], skimr [49], and survival [50–52]. Baseline characteristics of UK Biobank participants depending on sex were compared using Chi-squared test for categorical parameters and Mann–Whitney U test for continuous variables. Wine, non-wine, coffee, and tea were mutually adjusted within Cox proportional hazard regression models and included as penalized cubic splines as described recently [43]. The lowest estimated hazard ratio (HR) over the range from zero

to the 99%-quantile of beverage consumption was defined as the nadir and set to 1. For all morbidity analyses, HRs with pointwise 95% confidence intervals (CIs) are depicted, and HR^0 reflects HR in non-consumers relative to the HR at the nadir. No further interpretation of the nadir or HR^0 was performed if both linear and non-linear *p*-values were non-significant. All covariates violating the proportional-hazard assumption after Holm-adjustment for multiple testing were stratified in the final models. All models were adjusted for sex (all participants only), age (quartiles), AHI (<18, 18 to <31, 31 to <52, 52 to <100, ≥100 k£, and unknown), ethnicity (White, group combined of Mixed, Asian, Black, Chinese, and Other), highest qualification (none of the below, national exams at age 16 years, vocational qualifications, optional national exams at ages 17–18 years, professional, College or University), OHR (poor, fair, good, excellent), physical activity (PA: metabolic equivalent of task-min per week: <1000, 1000 to <2000, 2000 to <4000, ≥4000, and unknown), percentage body fat (quartiles), and smoking status (never, previous, current). The following sensitivity analyses were run in the primary cohort: ICD-10 code G31 was excluded from the analysis as an endpoint since it is more of a pathological diagnosis rather than a functional one. Furthermore, age and percentage body fat were included in the Cox proportional hazard regression models as continuous instead of categorical variables, with the latter being square rooted to better approximate a normal distribution. A *p*-value of < 0.05 was considered statistically significant in all analyses.

3. Results

3.1. Baseline Characteristics and Dementia Cases in UK Biobank Participants

Baseline data of the UK Biobank study population in total and depending on sex are presented in Table 1. Median (Quartile (Q) 1, Q3) age of the study population was 58 (50, 63) years, with 50.7% of participants being female (Table 1). Median (Q1, Q3) consumption was 5.7 (1.4, 11.4) g alcohol/d from wine, 4.3 (0.0, 12.9) g alcohol/d from non-wine, 2.0 (0.5, 3.0) cups/d coffee, and 3.0 (1.0, 5.0) cups/d tea (Table 1).

Table 1. Baseline characteristics of the UK Biobank cohort depending on sex [1].

Parameter	All (*n* = 351,436)	Female (*n* = 178,389)	Male [#] (*n* = 173,047)
Wine intake (g/d)	5.7 (1.4, 11.4)	5.7 (2.9, 11.4)	5.7 (0.7, 11.4)
Non-wine intake (g/d)	4.3 (0.0, 12.9)	1.4 (0.0, 4.3)	11.4 (4.3, 22.9)
Coffee intake (cups/d)	2.0 (0.5, 3.0)	2.0 (0.5, 3.0)	2.0 (1.0, 3.0)
Tea intake (cups/d)	3.0 (1.0, 5.0)	3.0 (1.0, 5.0)	3.0 (1.0, 5.0)
Age (years)	58 (50, 63)	57 (50, 63)	58 (50, 63)
AHI (k£)			
<18	55,960 (15.9)	29,328 (16.4)	26,632 (15.4)
- 18 to <31	76,591 (21.8)	39,078 (21.9)	37,513 (21.7)
- 31 to <52	85,290 (24.3)	41,302 (23.2)	43,988 (25.4)
- 52 to <100	71,810 (20.4)	33,190 (18.6)	38,620 (22.3)
- ≥100	20,161 (5.7)	9121 (5.1)	11,040 (6.4)
- Unknown	41,624 (11.8)	26,370 (14.8)	15,254 (8.8)
Ethnicity			
- White	340,001 (96.7)	172,819 (96.9)	167,182 (96.6)
- Mixed, Asian, Black, Chinese, Other	11,435 (3.3)	5570 (3.1)	5865 (3.4)
Highest Qualification			
- None of the below	50,416 (14.6)	24,189 (13.6)	26,227 (15.2)
- National exams at age 16 years	58,119 (16.5)	34,787 (19.5)	23,332 (13.5)
- Vocational qualifications	38,492 (11.0)	14,660 (8.2)	23,832 (13.8)
- Optional national exams at ages 17–18 years	26,619 (7.6)	14,469 (8.1)	12,150 (7.0)
- Professional	52,545 (15.0)	27,559 (15.4)	24,986 (14.4)
- College or University	125,245 (35.6)	62,725 (35.2)	62,520 (36.1)

Table 1. *Cont.*

Parameter	All (n = 351,436)	Female (n = 178,389)	Male # (n = 173,047)
OHR			
- Poor	10,478 (3.0)	4229 (2.4)	6249 (3.8)
- Fair	66,120 (18.8)	29,189 (16.4)	36,931 (21.3)
- Good	211,398 (60.2)	110,514 (62.0)	100,884 (58.3)
- Excellent	63,440 (18.1)	34,457 (19.3)	28,983 (16.7)
PA (MET-min/week)	1800 (845, 3546)	1764 (838, 3375)	1857 (848, 3714)
Percentage body fat	30.2 (24.7, 36.7)	36.2 (31.6, 40.7)	25.3 (21.5, 28.9)
Smoking status			
- Never	185,929 (52.9)	102,189 (57.3)	83,740 (48.4)
- Previous	130,726 (37.2)	61,360 (34.4)	69,366 (40.1)
- Current	34,781 (9.9)	14,840 (8.3)	29,941 (11.5)

[1] Categorical variables are presented as number (percentage) and continuous variables as median (Q1, Q3); AHI: Annual household income; MET: Metabolic equivalent of task; OHR: Overall health rating; PA: Physical activity; Q: Quartile, # indicates p-value < 0.001 as assessed by Chi-squared test for categorical variables and Mann–Whitney U test for continuous variables.

Wine intake was similar in both sexes (females 5.7 (2.9, 11.4); males 5.7 (0.7, 11.4) g alcohol/d); however, statistical significance was reached due to a high sample size ($p < 0.0001$) (Table 1). In contrast, non-wine intake was much lower in female (1.4 (0.0, 4.3) g alcohol/d) compared to male (11.4 (4.3, 22.9) g alcohol/d) participants ($p < 0.0001$) (Table 1). Coffee (females 2.0 (0.5, 3.0); males 2.0 (1.0, 3.0) cups/d) and tea (females and males 3.0 (1.0, 5.0)) intake was comparable between both sexes; however, statistical significance was again reached due to a high number of participants ($p < 0.0001$ for coffee; $p < 0.001$ for tea) (Table 1).

During 4.2 million person-years and a median (Q1, Q3) follow-up of 12.0 (11.3, 12.7) years, a total of 4270 incident dementia cases occurred, i.e., 1704 and 2566 cases in females and males, respectively.

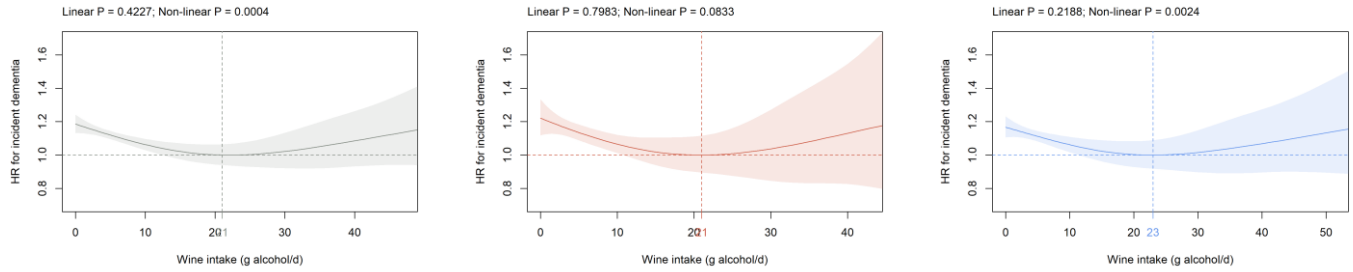
3.2. Beverage Intake and Dementia Risk

Wine intake: In all participants and in males, a significant U-shaped association between wine intake and HR for incident dementia was detected (Figure 1a,c). The nadir was observed at 21 and 23 g alcohol/d in all participants and males (Figure 1a,c). HR^0 was 1.19 (1.13, 1.24) in all participants and 1.17 (1.11, 1.23) in males (Figure 1a,c). A significant U-shaped relation between wine intake and incident dementia was also seen in cohorts S1 and S2 with the nadir between 17 and 23 g alcohol/d in all participants, as well as in both sexes separately (Supplementary Figure S2). Furthermore, an increased HR^0 was detected in cohorts S1 and S2, with a most pronounced elevation seen in the latter. Compared to the HR^0 in the primary cohort (Figure 1b,c), HR^0 in cohort S2 was higher in both females (1.40 (1.32, 1.49); Supplementary Figure S2d) and males (1.28 (1.22, 1.34); Supplementary Figure S2f). The nadir was at 29 g alcohol/d in all participants if ICD-10 code G31 was removed from the analysis (Supplementary Figure S3a). No relevant alteration was observed if age and percentage body fat were included as continuous covariates as compared to the model, including them as categorical parameters (Supplementary Figure S4a).

Non-wine intake: In all participants and both sexes, a significant positive dose-dependent association between non-wine consumption and HR for incident dementia was seen with the nadir at 0 g alcohol/d (Figure 2). The shape of the association was comparable but slightly more flattened in cohorts S1 and S2 compared to the primary cohort (Supplementary Figure S5). The nadir was detected at higher consumption levels with a most pronounced shift towards higher values in cohort S2 (Supplementary Figure S5b,d,f). Furthermore, a significant HR^0 was only seen in cohort S2 in all participants (1.08 (1.05, 1.11); Supplementary Figure S5b) and males (1.12 (1.06, 1.18); Supplementary Figure S5f). The association between non-wine intake and dementia risk was somewhat blunted but still significant in all participants if ICD-10 code G31 was removed from the

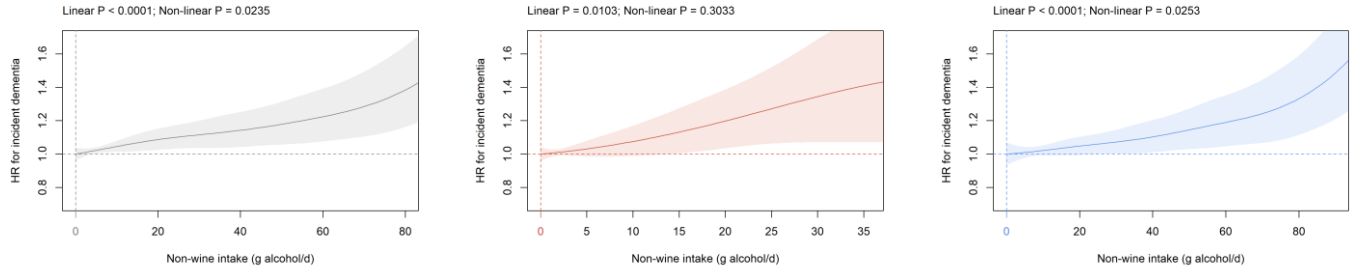
analysis (Supplementary Figure S3b). Inclusion of age and percentage body fat as continuous instead of categorical covariates did not significantly affect the association between non-wine consumption and incident dementia (Supplementary Figure S4b).

Coffee intake: Coffee consumption was not significantly associated with dementia risk in all participants, females and males in the primary cohort (Figure 3). The results remained virtually unchanged in cohorts S1 and S2 (data not shown), as well as in the analysis, including age and percentage body fat as continuous covariates in all participants (Supplementary Figure S4c). A significant dose-dependent association beyond three cups/d coffee with dementia risk was observed if ICD-10 code G31 was removed from the analysis (Supplementary Figure S3c).



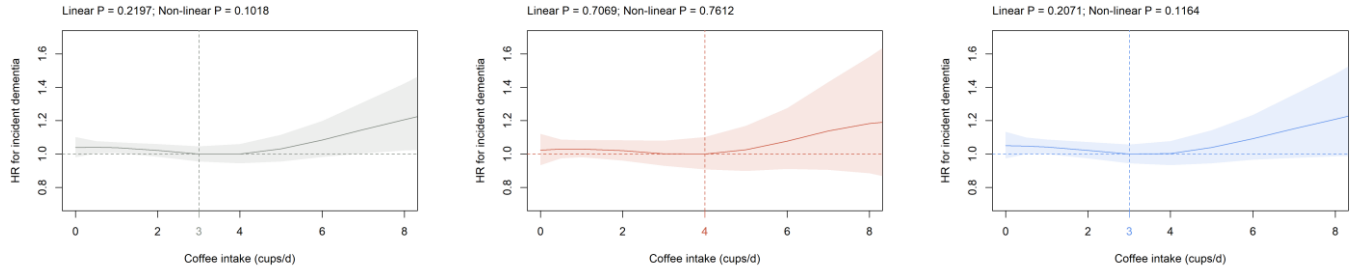
(**a**) (**b**) (**c**)

Figure 1. Association of wine intake (g alcohol/d) with dementia risk in the primary cohort in (**a**) all participants, (**b**) females, and (**c**) males. Data are adjusted for sex (all participants only), age, AHI, ethnicity, highest qualification, OHR, PA, percentage body fat, and smoking status. Wine, non-wine, coffee, and tea intake are mutually adjusted (e.g., wine intake is additionally adjusted for non-wine, coffee, and tea intake). The nadir is indicated in grey (total cohort), red (female), and blue (male). AHI: Annual household income; HR: Hazard ratio; OHR: Overall health rating; PA: Physical activity.



(**a**) (**b**) (**c**)

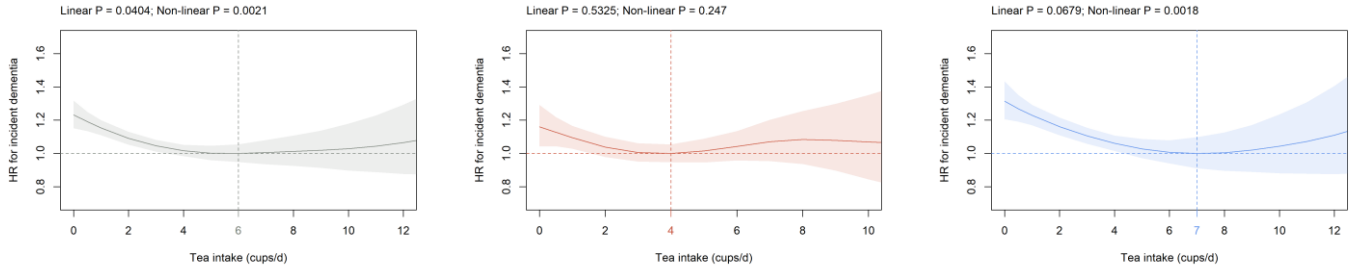
Figure 2. Association of non-wine intake (g alcohol/d) with dementia risk in the primary cohort in (**a**) all participants, (**b**) females, and (**c**) males. Data are adjusted and presented as indicated in Figure 1.



(**a**) (**b**) (**c**)

Figure 3. Association of coffee intake (cups/d) with dementia risk in the primary cohort in (**a**) all participants, (**b**) females, and (**c**) males. Data are adjusted and presented as indicated in Figure 1.

Tea intake: In all participants and males, a significant U-shaped association was seen between tea intake and incident dementia (Figure 4a,c). HR^0 was significantly increased in all participants (1.23 (1.15, 1.32); Figure 4a) and males (1.31 (1.21, 1.43); Figure 4c). The nadir was at six cups/d for all participants and seven cups/d for males (Figure 4a,c). Similar findings were observed in all participants in cohorts S1 and S2 (data not shown), after removal of ICD-10 code G31 from the analysis (Supplementary Figure S3d), as well as after inclusion of age and percentage body fat as continuous instead of categorical parameters (Supplementary Figure S4d).



(**a**) (**b**) (**c**)

Figure 4. Association of tea intake (cups/d) with dementia risk in the primary cohort in (**a**) all participants, (**b**) females, and (**c**) males. Data are adjusted and presented as indicated in Figure 1.

4. Discussion

The current study elucidates for the first time how wine, non-wine, coffee, and tea intake included as continuous non-linear predictors and mutually adjusted is associated with incident dementia. Furthermore, the impact of the abstainer bias on potential protective effects of alcohol consumption is systematically assessed.

For wine intake, we show a significant U-shaped association with incident dementia for all participants (primary cohort), and HR^0 is significantly increased compared to the nadir at 21 g alcohol/d. Compared to our current findings, varying levels of wine consumption are associated with the lowest risk of dementia, i.e., an intake of up to three daily servings [21], three to four glasses [53], or a nadir of 6 g alcohol/d [17], while no association is found in another report [23]. The current study shows a significant U-shaped association between wine consumption and incident dementia for male participants with the nadir at 23 g alcohol/d. A study from Denmark shows comparable results with monthly and weekly wine consumption linked with a decreased dementia risk in both sexes [54]. Red wine intake is negatively associated with the incidence of Alzheimer's disease in men only, while a positive association is seen in women [24]. The potential neuroprotective effect of wine might be caused by natural ingredients of wine not present in non-wine beverages, such as the phenolic substance resveratrol found in the epidermis of red grapes [38]. In rats, resveratrol inhibits the apoptosis pathway and exerts anti-oxidative effects [38]. Furthermore, resveratrol derivatives, such as stilbenoids, modulate multiple mechanisms of the neurodegenerative disease pathology, including inhibition of β-secretase, reactive oxygen intermediates generation, and β-amyloid peptide aggregation [37].

To the best of our knowledge, our study is the first to define the relationship between non-wine consumption and incident dementia. Contrary to wine intake, a significant positive dose-dependent association exists for non-wine consumption with the nadir at 0 g alcohol/d for all participants and females and males. Within non-wine beverages, several studies have examined the association of beer and/or spirits with incident dementia with conflicting results. In accordance with our findings, an elevated risk for highest versus lowest category of beer consumption is found in a large meta-analysis of prospective studies [17]. A positive association between spirits consumption and incident dementia is observed in a report in women [55]. Monthly beer but not spirits consumption is associated with higher dementia risk in another study [54]. In contrast, no significant association is found between intake of liquor and beer on the one hand and Alzheimer's disease [21,56]

or cognitive function [57] on the other hand. Together, these data suggest that even at light-to-moderate intake levels, non-wine is not consistently associated with a decreased risk of dementia and might even be related to heightened risk in contrast to wine.

To the best of our knowledge, our study is the first to systematically assess the impact of former drinkers and lifetime abstainers on the association between wine and non-wine consumption on one hand and incident dementia on the other hand. We show that HR^0 is higher after including all non-drinkers (cohort S2) as compared to the primary cohort for both wine and non-wine. In addition, the association of non-wine with incident dementia is more J-shaped, and a shift of the nadir towards higher levels in cohort S2 is detected as compared to the primary cohort. In contrast to our primary analyses, studies on wine and non-wine alcoholic beverages [17,21,23,24,53,55–57] do not exclude non-drinkers from the reference group. The category of non-drinkers might include former drinkers and never-drinkers who stopped or never initiated drinking because of bad health or emerging cognitive decline [36]. If these non-drinkers are included in the reference category, an apparent protective effect of light-to-moderate drinking may only stem from the already increased dementia risk among former and never drinkers [58]. Thus, it is important to exclude non-drinkers from the analysis since it could lessen or erase any observed protective effects and change the shape of the association [36,58].

For coffee intake, we show no significant association with dementia risk. Consistent with the present findings, no association between coffee consumption and risk of Alzheimer's disease and incident dementia is shown in a large meta-analysis of prospective studies [59]. Similarly, no reduction in the risk of cognitive decline is found in a longitudinal study [60]. Two previous studies have assessed the association between coffee intake and dementia risk in UK Biobank participants using different analytical approaches [26,34]. Based on hospital inpatient records and cubic splines, Zhang and co-workers demonstrate convincingly that the risk of dementia is lowest at two to three cups/d coffee [34]. Pham et al. show that the coffee intake category >6 as compared to the 1–2 cups/d category is associated with 53% higher odds of dementia [26]. Differences in study results may be well explained by differences in model adjustments, exclusion criteria, and follow-up period. Interestingly, light-to-moderate coffee consumption is linked to a reduced risk of any cognitive deficits or dementia in a recent meta-analysis of 29 prospective studies [29]. Taking the current findings and published studies into account, a light-to-moderate amount of coffee consumption is not positively related to dementia risk, and a minor negative association remains possible.

For tea consumption, we show a significant U-shaped association with incident dementia in all participants and males. HR^0 is significantly increased compared to the nadir at six (all participants) and seven (males) cups/d. Zhang and co-workers show convincingly that the HR for incident dementia is lowest at three to five cups/d in UK Biobank participants using hospital inpatient records and cubic splines [34]. A negative association between tea consumption and cognitive deficits was observed in a recent meta-analysis [29]. Few studies have compared green and black tea separately. Interestingly, an inverse association for incident dementia with green tea but not black tea consumption is detected in two independent cohorts [31,61]. Unfortunately, the type of tea has not been recorded for all participants during the baseline assessment of the UK Biobank; however, the UK has one of the highest per capita consumption levels of black tea worldwide [62]. The current findings and published results are in agreement with the hypothesis that overall tea consumption is associated with a lower risk of dementia. Potential differences between green and black tea need to be systematically assessed in future studies.

The current study has several strengths, such as a prospective cohort design, a large number of well-characterized participants, a long follow-up period, as well as a wide range of beverage intake. However, some limitations must be considered: No information is available concerning the consumption of other important beverages, e.g., sugar-sweetened beverages and milk-based drinks, as well as the type of tea. Furthermore, only three-character ICD-10 codes are available for morbidity data. Therefore, the diagnosis F10.6 is

not included as a dementia diagnosis in the current study since it could not be distinguished from other common codes within F10, e.g., F10.1 and F10.2. Moreover, the groups of participants not drinking coffee (n = 66,124) and tea (n = 48,568) are too small to define associations of coffee and tea intake with dementia risk in participants not drinking tea and coffee, respectively. Residual confounding, measurement errors in the assessment of the exposure variables, and a "healthy volunteer" selection bias [63] are further limitations.

Taken together, the current study shows on a population level that moderate consumption of wine and moderate-to-high tea intake is associated with a decreased risk of incident dementia. In contrast, non-wine is positively related to dementia risk in a linear fashion, and no clear association is found for coffee. Further prospective studies should elucidate potential differences between green and black tea.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/brainsci12030360/s1, Figure S1: Venn diagram depicting number of participants excluded by six exclusion criteria (primary cohort); Figure S2: Association of wine intake (g alcohol/d) in (a,b) the total cohort, (c,d) females, and (e,f) males with dementia risk in (a,c,e) cohort S1 and (b,d,f) cohort S2; Figure S3: Association of non-wine intake (g alcohol/d) in (a,b) the total cohort, (c,d) females, and (e,f) males with de-mentia risk in (a,c,e) cohort S1 and (b,d,f) cohort S2. Figure S4: Association of (a) wine intake (g alcohol/d), (b) non-wine intake (g alcohol/d), (c) coffee intake (cups/d), and (d) tea intake (cups/d) with dementia risk in all participants with age and percentage body fat included as continuous instead of categorical variables. Figure S5: Association of non-wine intake (g alcohol/d) in (a), (b) the total cohort, (c), (d) females, and (e), (f) males with dementia risk in (a), (c), (e) cohort S1 and (b), (d), (f) cohort S2.

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Institutional Review Board Statement: The UK Biobank study was conducted according to the guidelines of the Declaration of Helsinki and approved by the North West–Haydock Research Ethics Committee (REC reference: 16/NW/0274).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data supporting the results of this study are available from UK Biobank, but restrictions apply to the availability of these data, which were used under license for Application 53438, and so are not publicly available.

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2.3 Publication 3: Association of sugar intake from different sources with incident dementia in the prospective cohort of UK Biobank participants

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Authors' contributions

S. M. S. and A. K. conceived the research. Statistical analyses were performed by S. M. S., A. K., G. E., and M. F. The first draft of the manuscript was prepared by S. M. S. and A. K. All authors revised the manuscript critically for important intellectual content and gave final approval of the version to be submitted. S. M. S. and A. K. are the guarantors of the manuscript and accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Appendix C: Supplementary Material

Summary

Research gap 3 was addressed in the publication “Association of sugar intake from different sources with incident dementia in the prospective cohort of UK Biobank participants”[116].

The paper examined the association of various sources of FS, i.e., intake of FS from beverages and beverage subtypes, i.e., soda/fruit drinks, juice, milk-based drinks, and tea/coffee, as well as intake of FS from solid foods and solids subtypes, i.e., treats, cereals, toppings, and sauces, with dementia risk. Furthermore, the association between intake of IS and incident dementia was also studied.

The study comprised 186,622 participants of the UK Biobank that had a median follow-up of 10.6 years in which 1,498 incident dementia cases occurred. Sugar consumption was assessed using a web based 24-hour dietary recall questionnaire (24HR), the Oxford WebQ, and all participants who had completed the questionnaire at least once were included in the study. The primary outcome was incident all-cause dementia provided by the UK Biobank as an algorithmically defined outcome, i.e., referring to the date of the first diagnosis of dementia of any type. The HR for incident dementia was assessed with Cox proportional hazard regression multivariate nutrient density models[117] including % total energy (%E) intake of sugar from different sources and energy intake as penalised cubic splines. Furthermore, models were adjusted for alcohol intake, BMI, energy intake, ethnic background, general health status, highest qualification, physical activity, systolic blood pressure, sex, smoking status, total household income, and Townsend deprivation index. The lowest value of the HR of sugar intake in the range from zero to the 99%-quantile was called the HR-nadir. Several sensitivity analyses were performed to assess the robustness of results, e.g., excluding participants diagnosed with dementia within two years after completing the questionnaire, excluding participants with unintentional weight loss, removing participants with only one completed questionnaire, or stratifying participants according to age below or above 60 years.

Intake of total FS was significantly associated with the HR for dementia in a J-shaped fashion with the HR-nadir at 9 %E. The intake of IS was also related to dementia risk in a J-shaped fashion with the HR-nadir observed at 8 %E. Dementia risk was significantly associated with FS in beverages in an ascending approximately linear way with the HR-nadir at 2 %E. No significant association was found for FS from solid foods. Within beverages, FS in soda/fruit drinks, milk-based drinks, and - to a lesser extent in juice - were positively linked to dementia risk, whereas no such association was observed for FS in tea/coffee.

In summary, a linear-shaped association between sugar subtype intake and dementia risk is most consistently found for FS in beverages and more specifically for FS in soda/fruit drinks, as well as in milk-based drinks. These findings suggest that the source of sugar - particularly

FS in beverages - plays a crucial role in dementia risk, which could have important implications for dietary guidelines aimed at reducing dementia incidence. The study emphasises the importance of considering not just the quantity but also the source of sugar intake in the context of dementia prevention.

The published manuscript is attached.

Nutrition Journal

RESEARCH

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Association of sugar intake from different sources with incident dementia in the prospective cohort of UK Biobank participants

Sylva M. Schaefer[1*†], Anna Kaiser[1†], Gerrit Eichner[2†] and Mathias Fasshauer[1,3†]

Abstract

Background Dementia is a common disease with around 55 million cases worldwide. Therefore, dietary changes and lifestyle interventions are important approaches to delay the progress of a decline in cognitive function. The study aims to explore the association of various sources of free sugars (FS) and intrinsic sugars with dementia risk in the prospective population-based UK Biobank cohort.

Methods Sugar consumption was assessed in 186,622 UK Biobank participants with at least one web-based dietary questionnaire (Oxford WebQ). Over a mean follow-up of 10.6 (standard deviation 1.1) years, 1498 incident dementia cases occurred. The hazard ratios (HR) for incident dementia were assessed with Cox proportional hazard regression models including sugar intake from different sources as penalized cubic splines to allow for non-linear predictor effects.

Results The intake of FS and intrinsic sugar was significantly associated with dementia risk in a J-shaped fashion with the HR-nadir observed at 9% and 8% total energy (%E), respectively. FS in beverages were significantly associated with dementia risk in an ascending approximately linear way, whereas no significant association was found for FS in solids. Assessing beverage subtypes, FS in soda/fruit drinks, milk-based drinks and to a lesser extent in juice were significantly and positively related to dementia risk, whereas no association was found for FS in tea/coffee. The association between sugar subtype consumption and dementia risk remained consistent in most sensitivity analyses but changed from a J-shape to a more linear shape when the analysis was restricted to participants with at least two Oxford WebQs.

Conclusions A linear-shaped association between sugar subtype intake and dementia risk is most consistently found for FS in beverages and more specifically for FS in soda/fruit drinks, as well as in milk-based drinks.

Keywords Carbohydrates, Dementia, Sugar, UK Biobank

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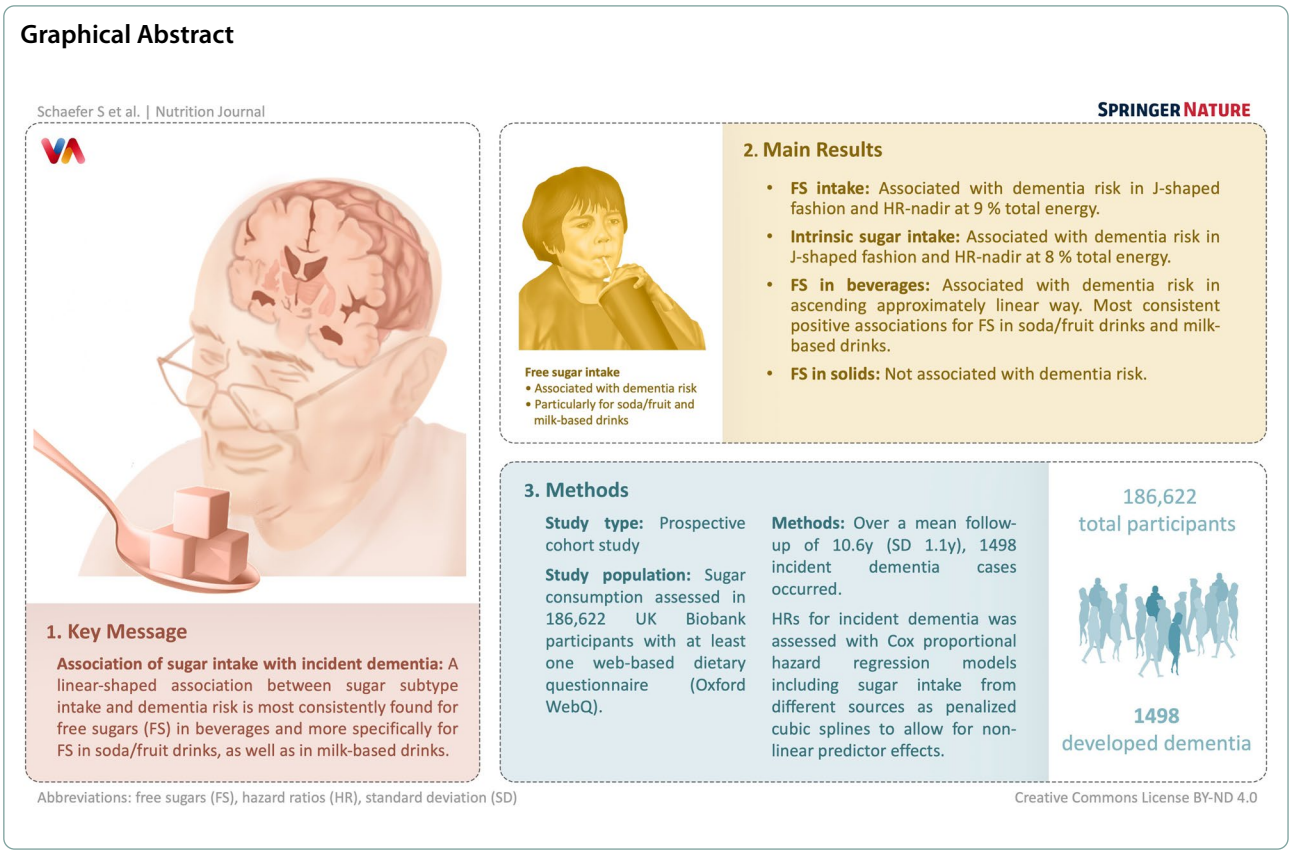
Graphical Abstract



Background

Dementia is a common disease with around 55 million cases worldwide and almost 10 million new cases every year [1]. It is characterized by a deterioration in cognitive function beyond the usual effects of biological aging [1]. Even though age is one of the most important risks factors for dementia [1], there is evidence that being overweight [2] and obese [3] in midlife is similarly associated with a higher disease risk. Despite a large amount of research that has been conducted over the past decades, no effective pharmacological treatment for the main dementia types has been developed to date [4]. Therefore, dietary changes and lifestyle interventions remain important approaches, not only to delay the progress of a decline in cognitive function [5], but also to combat overweight and obesity [6].

A common approach to decrease body weight, and improve glucose control, as well as low-grade inflammation, is to follow a diet low in carbohydrates [7, 8]. Interestingly, studies on these diets provide promising results for the treatment and prevention of dementia [9]. However, long-term adherence to low carbohydrate diets is difficult to maintain because of severe limitations in the diversity of food choices [10]. In addition, various food items that are associated with better cognitive performance such as fruits, vegetables, legumes, and whole grains might also be excluded from the diet [11, 12]. Therefore, recent interventions have investigated the reduction of specific carbohydrate subtypes with a specific focus on limiting sugars [13, 14].

Sugars are defined as all mono- and disaccharides [15] and according to the World Health Organization (WHO), they can be divided into free sugars (FS) and intrinsic sugars [16]. FS are added to foods by the manufacturer, cook, or consumer, in addition to sugars naturally present in honey, syrups, and fruit juices [16]. The WHO recommends limiting FS to less than 10% of total energy intake and ideally to less than 5%, i.e., 50 g and 25 g FS per day, respectively, for a 2000 kcal diet [16]. In agreement with WHO recommendations, the National Health Service England (NHS) limits FS intake to less than 30 g per day for adults [17].

No study so far has systematically evaluated the association between FS consumption from various sources, including FS in beverages, beverage subtypes, solid foods, and solids subtypes on the one hand, and dementia risk on the other hand. To address this open point, all major FS sources summarized in Additional file 1 Fig. S1 were analysed concerning incident dementia in

a large, well-characterized population of 186,622 UK Biobank participants.

We hypothesized that the link between FS and incident dementia depends on the FS source with a positive association found for beverages but not for solid foods similar to recent findings from our group studying all-cause mortality [18] and incident depression [19]. Furthermore, the link between intrinsic sugars, i.e., all sugars that are not FS including sugars from fruit, vegetables, and lactose in dairy products [16], and dementia risk is assessed for the first time.

Methods

Study design and participants

The UK Biobank study is a prospective cohort study that recruited more than half a million participants aged 37 to 73 across the UK between 2006 and 2010 [20]. Participants who filled out at least one web-based dietary questionnaire for the assessment of the previous 24 h dietary intakes (Oxford WebQ) [21] were selected for the current report (Additional file 1 Fig. S2, S3).

The following exclusion criteria were applied to all analyses: 1) missing lifestyle risk factors (physical activity or smoking status), 2) diagnosis of all-cause dementia before completion of the last Oxford WebQ, 3) missing socioeconomic factors (Townsend deprivation index, total household income, ethnic background, highest qualification, or overall health rating), 4) missing data of the physical exam (body mass index (BMI), systolic blood pressure (SBP)), 5) pre-existing malabsorption, 6) history of diabetes mellitus, and 7) implausible energy or carbohydrate intake, i.e., 0 kJ/d intake on at least one occasion, being in the upper 0.1% of total energy and/or carbohydrate consumption or total energy intake < 1.1 × basal metabolic rate—500 kcal (under-reporting) or > 2.5 × basal metabolic rate + 500 kcal (over-reporting). Basal metabolic rate was defined according to the Oxford equation [22].

An overview of all participants removed due to exclusion criteria is presented in Additional file 1: Fig. S2. A total of 186,622 participants were included in the present study. Written informed consent was obtained from all participants at baseline and ethical approval for the UK Biobank study was granted by the North West Multicentre Research Ethics Committee [20].

Exposure assessment

To obtain detailed dietary information which includes the consumption of 206 food items and 32 beverages, a web-based 24 h dietary recall (Oxford WebQ) was completed [23]. The Oxford WebQ was specifically developed for use in large population studies [21]. The Oxford WebQ has recently been validated against accelerometry-estimated energy expenditure and biomarkers of total sugar intake, and performed well compared to traditional 24 h interviewer-led dietary recalls especially when at least two questionnaires were completed [24]. Based on the Oxford WebQ data, intake of sugar and sugar subtypes from beverages and solids was calculated with a methodology described in two previous reports from our group [18, 19]. In brief, soda/fruit drinks, pure juice, milk-based drinks, and sugar added to tea/coffee were defined as sugary beverages whereas treats, breakfast cereals, toppings, and sauces as subtypes of sugary solids. Portion sizes for all Oxford WebQ food items were taken from the UK Food Standards Agency [25] and product labels. In the Oxford WebQ, participants reported the number of standard servings consumed of specific food items.

The intake (g/d) of the specific sugar subtype was calculated by multiplying the reported consumption frequency of each food item by the estimated content of this sugar subtype in that item in one serving. To calculate sugar subtype intake in % total energy (%E), the intake in g/d was multiplied with 17 kJ/g * 100% / total energy in kJ/d according to Willett and co-workers [26]. The difference between total sugars and FS equals intrinsic sugar.

For participants who completed more than one questionnaire, the mean %E intake of sugar subtypes was used for all primary and sensitivity analyses except when only the first completed Oxford WebQ was considered (Additional file 1 Fig. S12).

Outcome assessment

The primary outcome was incident all-cause dementia (termed dementia throughout the manuscript) which was provided by UK Biobank as an algorithmically-defined outcome, i.e., date of all-cause dementia report (data field 42,018) [27]. Follow-up time was defined as the period from the first dietary assessment to the date of the first diagnosis of dementia, loss-to-follow-up, death, or censoring, whichever came first. The analyses were censored at the censoring date for the hospital admission data, i.e., 30th of September 2021 for England, 31th of July 2021 for Scotland, and 28th of February 2018 for Wales, depending on the participants' origin.

Statistical analyses

Data analysis was performed with R version 4.2.2 [28] as described recently [19].

In brief, the hazard ratios (HR) for incident dementia were assessed with Cox proportional hazard regression multivariate nutrient density models [26] including %E intake of sugar from different sources and energy intake as penalized cubic splines with their degrees of freedom set to 4. We adjusted the models further for energy intake (penalized cubic splines), age at completion of the first

Oxford WebQ (split by quintiles), alcohol intake (< 1, 1 to < 8, 8 to < 16, ≥ 16 g/d), BMI (< 18.5, 18.5 to < 25, 25 to < 30, ≥ 30 kg/m^2), ethnic background (White, group composed of Mixed, Asian, Black, Chinese, and other), general health status (poor, fair, good, excellent), highest qualification (none of the below, national exams at age 16 years, vocational qualifications or optional national exams at ages 17–18 years, professional, College or University), history of mental illness (yes, no), physical activity (metabolic equivalent of task (MET)-minutes per week derived from the Oxford WebQ; split by quintiles), SBP (split by quintiles), sex (female, male), smoking status (never, previous, occasional, current < 10, 10 to 14, 15 to 19, ≥ 20 cigarettes per day), total household income (< 18, 18 to < 31, 31 to < 52, 52 to < 100, ≥ 100 k£, unknown), and Townsend deprivation index (split by quintiles). If there were deviations from the abovementioned adjustments, this is indicated in the figure legends. The hazard proportionality was evaluated for each covariate using scaled Schoenfeld residuals. All covariates that significantly violated the proportionality hazard assumption after Holm-adjustment for multiple testing were stratified in the final models. In each analysis, the determination of the nadir of the estimated HR as a function of the intake of a sugar subtype in %E was restricted to the range from zero to the 99%-quantile. The HR was then rescaled to a nadir of 1 to simplify the presentation. HRs with pointwise 95% confidence intervals (CIs) are shown for all Cox proportional hazard regression models. The analysis of each penalized cubic spline is divided into p^{lin} for the linear and $p^{non-lin}$ for the nonlinear effect, as recently described [29]. A *p*-value of < 0.05 was considered as statistically significant in all analyses. We performed no further interpretation of the HR-nadir or other individual HRs if both p^{lin} and $p^{non-lin}$ were non-significant.

Sensitivity analyses

To assess the robustness of the results, several sensitivity analyses were performed similarly as described in recent studies [18, 19, 30]: Reverse causation was accounted for by excluding participants who were diagnosed with dementia within two years after filling out their first Oxford WebQ (landmark analysis) (*n* = 186,580, n excluded = 24,367), who had lost weight unintentionally (*n* = 157,057, n excluded = 53,890), or had a history of cardiovascular disease (CVD) and cancer (*n* = 164,855, n excluded = 46,092). Participants who filled out only one questionnaire were removed from the analysis to address potential variation, i.e., lower reproducibility in sugar intake based on a single Oxford WebQ [24] (*n* = 115,480, n excluded = 95,467). To control for unrepresentative consumption data, participants who described their diet on the previous day as non-typical on at least one occasion were excluded (*n* = 125,313, n excluded = 85,634). Participants who followed a restricted diet due to health reasons, i.e., participants indicating their diet as being "low-calorie", "lactose-free", or "gluten-free" (*n* = 160,752, n excluded = 50,195) were excluded in another set of sensitivity analyses. In order to explore heightened dementia risk with increasing age, the analyses were re-done in the subgroup of participants ≥ 60 years (*n* = 90,571, n excluded = 120,376), as well as stratified for age below or above 60 years (*n* = 186,622, n excluded = 24,325).To focus on the nutrient intake closest to baseline assessment, analyses were repeated using only the first Oxford WebQ questionnaire (*n* = 186,622, n excluded = 24,325). To further control for residual confounding by dietary factors, a diet quality score combining five dietary components, i.e., fat, fruit, vegetables, red meat, and processed meat consumption, was included in the analysis as described in [30] (*n* = 184,271, n excluded = 26,676). To apply alternative measures for body composition, waist-to-hip ratio (WHR) and height were used instead of BMI (*n* = 186,580, n excluded = 24,367). In order to include as many participants as possible in the analysis, two additional sensitivity analyses were carried out: Firstly, all missing values for any of the covariates were included as novel "unknown" category. For example, if a BMI value was not present, the participant was assigned the BMI category "unknown" and included in the analysis (*n* = 190,205, n excluded = 20,742). Secondly, only a minimal set of exclusion criteria was applied in addition to creating the novel "unknown" category as described above. Thus, participants were only excluded if dementia was pre-existent (*n* = 80) or no energy intake was reported (*n* = 46) (*n* = 210,821, n excluded = 126).

Results

Characteristics of UK Biobank participants

Table 1 illustrates the characteristics of the study population in total and in subgroups of FS intake defined by quintiles. Mean (standard deviation (SD)) age of the study cohort at completion of the first Oxford WebQ was 58 (8) years with 57.3% of participants being female. Time of follow-up was 10.6 (1.1) years, i.e., 2.0 million person-years, with a total of 1498 incident dementia cases of which 730 occurred in females and 768 in males.

FS versus intrinsic sugars

Mean (SD) consumption of FS and intrinsic sugars was 11.4 (5.6) %E and 13.0 (5.7) %E, respectively (Table 1). FS intake was significantly associated with the HR for dementia in a J-shaped fashion (Fig. 1a). The HR-nadir was found at 9%E FS (Fig. 1a). Compared to intake at the nadir, the HR (CI) increased to 1.28 (0.98 to 1.67) and 1.36 (1.23 to 1.51), at 0 and 20%E, respectively (Fig. 1a).

Table 1 Characteristics of the UK Biobank cohort*

Parameters	Total cohort (*n* = 186,622)	FS intake (%E) split by quintiles				
		0.0 to 6.8 (*n* = 37,325)	6.8 to 9.5 (*n* = 37,324)	9.5 to 12.1 (*n* = 37,324)	12.1 to 15.5 (*n* = 37,324)	15.5 to 77.5 (*n* = 37,325)
Characteristics						
Age at completion of first Oxford WebQ (years)	58 (8)	58 (8)	58 (8)	58 (8)	58 (8)	57 (8)
BMI (kg/m^2)	26.6 (4.3)	26.8 (4.4)	26.6 (4.3)	26.4 (4.2)	26.4 (4.3)	26.6 (4.4)
Ethnic background						
- White	179,879 (96.4)	36,088 (96.7)	36,251 (97.1)	36,162 (96.9)	36,101 (96.7)	35,277 (94.5)
- Mixed, Asian, Black, Chinese, and other	6,743 (3.6)	1,237 (3.3)	1,073 (2.9)	1,162 (3.1)	1,223 (3.3)	2,048 (5.5)
General health status						
- Poor	4,515 (2.4)	814 (2.2)	697 (1.9)	725 (1.9)	873 (2.3)	1,406 (3.8)
- Fair	29,894 (16.0)	5,985 (16.0)	5,544 (14.9)	5,499 (14.7)	5,877 (15.7)	6,989 (18.7)
- Good	113,190 (60.7)	22,613 (60.6)	22,707 (60.9)	23,043 (61.7)	22,838 (61.2)	21,989 (58.9)
- Excellent	39,023 (20.9)	7,913 (21.2)	8,376 (22.4)	8,057 (21.6)	7,736 (20.7)	6,941 (18.6)
Highest qualification						
- None of the below	14,984 (8.0)	3,307 (8.9)	2,788 (7.5)	2,800 (7.5)	2,818 (7.6)	3,271 (8.8)
- National exams at age 16 years	28,062 (15.0)	5,699 (15.3)	5,352 (14.3)	5,450 (14.6)	5,509 (14.8)	6,052 (16.2)
- Vocational qualifications or optional national exams at ages 17–18 years	33,058 (17.7)	6,771 (18.1)	6,440 (17.3)	6,377 (17.1)	6,381 (17.1)	7,089 (19.0)
- Professional	28,977 (15.5)	5,543 (14.9)	5,625 (15.1)	5,930 (15.9)	5,934 (15.9)	5,945 (15.9)
- College or University	81,541 (43.7)	16,005 (42.9)	17,119 (45.9)	16,767 (44.9)	16,682 (44.7)	14,968 (40.1)
History of mental illnesses	12,278 (6.6)	2,413 (6.5)	2,288 (6.1)	2,222 (6.0)	2,409 (6.5)	2,946 (7.9)
Physical activity (MET-min/week)	4,130 (2,651)	4,069 (2,663)	4,112 (2,572)	4,133 (2,559)	4,142 (2,598)	4,194 (2,852)
SBP (mmHg)	139 (19)	139 (20)	139 (19)	139 (19)	138 (19)	138 (19)
Sex – female	106,834 (57.3)	21,447 (57.5)	21,731 (58.2)	21,512 (57.6)	21,380 (57.3)	20,764 (55.6)
Smoking status						
- Never	107,357 (57.5)	19,187 (51.4)	20,906 (56.0)	21,870 (58.6)	22,713 (60.9)	22,681 (60.8)
- Previous	65,874 (35.3)	15,128 (40.5)	13,972 (37.4)	13,146 (35.2)	12,165 (32.6)	11,463 (30.7)
- Occasional	4,461 (2.4)	1,065 (2.9)	912 (2.4)	849 (2.3)	810 (2.2)	825 (2.2)
- Current < 10 cigarettes per day	2,313 (1.2)	491 (1.3)	415 (1.1)	385 (1.0)	476 (1.3)	546 (1.5)
- Current 10 to 14 cigarettes per day	2,011 (1.1)	410 (1.1)	349 (0.9)	332 (0.9)	361 (1.0)	559 (1.5)
- Current 15 to 19 cigarettes per day	1,787 (1.0)	376 (1.0)	302 (0.8)	294 (0.8)	323 (0.9)	492 (1.3)
- Current ≥ 20 cigarettes per day	2,819 (1.5)	668 (1.8)	468 (1.3)	448 (1.2)	476 (1.3)	759 (2.0)
Total household income per year (k£)						
- < 18	24,987 (13.4)	4,730 (12.7)	4,582 (12.3)	4,692 (12.6)	5,101 (13.7)	5,882 (15.8)
- 18 to < 31	40,795 (21.9)	7,767 (20.8)	7,956 (21.3)	8,176 (21.9)	8,333 (22.3)	8,563 (22.9)
- 31 to < 52	48,423 (26.0)	9,591 (25.7)	9,806 (26.3)	9,779 (26.2)	9,669 (25.9)	9,578 (25.7)
- 52 to < 100	41,708 (22.4)	9,877 (23.8)	8,751 (23.4)	8,469 (22.7)	8,179 (21.9)	7,432 (19.9)
- ≥ 100	12,437 (6.7)	2,857 (7.7)	2,735 (7.3)	2,537 (6.8)	2,345 (6.3)	1,963 (5.3)
- Unknown	18,272 (9.8)	3,503 (9.4)	3,494 (9.4)	3,671 (9.8)	3,697 (9.9)	3,907 (10.5)
Townsend deprivation index	-1.6 (2.8)	-1.5 (2.9)	-1.7 (2.8)	-1.7 (2.8)	-1.8 (2.8)	-1.5 (2.9)
Dietary sugar subtype intake in %E						
Carbohydrates	48.6 (7.8)	44.4 (8.9)	46.8 (7.3)	48.4 (6.7)	50.1 (6.3)	53.5 (6.6)
Total sugars	24.4 (7.2)	18.8 (6.6)	21.8 (5.6)	23.9 (5.3)	26.2 (5.2)	31.1 (6.3)
Intrinsic sugars	13.0 (5.7)	14.4 (6.4)	13.6 (5.6)	13.1 (5.3)	12.5 (5.1)	11.4 (5.3)

Table 1 (continued)

Parameters	Total cohort (*n* = 186,622)	FS intake (%E) split by quintiles				
		0.0 to 6.8 (*n* = 37,325)	6.8 to 9.5 (*n* = 37,324)	9.5 to 12.1 (*n* = 37,324)	12.1 to 15.5 (*n* = 37,324)	15.5 to 77.5 (*n* = 37,325)
FS	11.4 (5.6)	4.5 (1.7)	8.2 (0.8)	10.8 (0.7)	13.7 (1.0)	19.7 (4.3)
FS beverages	4.7 (4.7)	1.1 (1.4)	2.6 (2.1)	3.9 (2.5)	5.6 (3.1)	10.5 (5.9)
- Soda/fruit drinks	1.6 (3.3)	0.2 (0.6)	0.5 (1.2)	0.9 (1.7)	1.6 (2.4)	4.6 (5.4)
- Juice	2.1 (2.8)	0.6 (1.2)	1.4 (1.8)	2.1 (2.2)	2.7 (2.6)	3.8 (4.0)
- Milk-based drinks	0.3 (0.9)	0.1 (0.5)	0.2 (0.7)	0.3 (0.9)	0.4 (1.0)	0.6 (1.3)
- Tea/coffee	0.6 (1.6)	0.2 (0.6)	0.3 (1.0)	0.5 (1.2)	0.7 (1.6)	1.4 (2.6)
FS solids	6.6 (3.5)	3.4 (1.8)	5.6 (2.1)	6.9 (2.5)	8.1 (3.0)	9.2 (4.1)
- Treats	4.4 (3.0)	2.1 (1.6)	3.6 (2.0)	4.5 (2.4)	5.3 (2.8)	6.3 (3.8)
- Cereals	0.5 (0.8)	0.3 (0.6)	0.5 (0.7)	0.5 (0.8)	0.6 (0.8)	0.6 (0.9)
- Toppings	1.2 (1.6)	0.4 (0.9)	0.9 (1.4)	1.3 (1.6)	1.6 (1.8)	1.7 (2.0)
- Sauces	0.3 (0.4)	0.2 (0.4)	0.3 (0.4)	0.3 (0.4)	0.3 (0.4)	0.3 (0.4)
Other nutrients of interest						
Alcohol (g/d)	17.3 (22.1)	26.1 (28.5)	20.2 (22.9)	16.7 (19.7)	13.7 (17.7)	9.7 (15.5)
Fat (g/d)	79.3 (28.0)	73.9 (27.4)	79.6 (27.5)	81.8 (27.8)	82.3 (27.9)	78.9 (28.5)
Protein (g/d)	74.7 (20.8)	76.5 (22.6)	76.7 (20.6)	76.0 (19.9)	74.4 (19.6)	70.1 (20.1)
Fibre (g/d)	19.1 (7.0)	19.3 (7.7)	19.8 (7.1)	19.6 (6.8)	19.1 (6.6)	17.5 (6.8)
Energy (kJ/d)	9,090 (2,309)	8,532 (2,249)	9,002 (2,236)	9,223 (2,255)	9,347 (2,290)	9,347 (2,412)
Number of Oxford WebQ	2.2 (1.2)	2.0 (1.1)	2.3 (1.2)	2.4 (1.2)	2.3 (1.2)	2.0 (1.1)

Abbreviations: BMI Body mass index, *FS* Free sugars, *g/d* Grams per day, *kg/m²* Kilogram per square meter, *kJ* Kilojoules, *MET* Metabolic equivalent of task, *mmHg* Millimetres of mercury, *%E* Percentage total energy, *SBP* Systolic blood pressure, *SD* Standard deviation

* Categorical variables are summarized as frequencies (percentages) and continuous variables as mean (SD)

All sensitivity analyses showed a significant association between FS and HR for dementia (Additional file 1 Fig. S4a to 16a) which changed from a J-shape to a more linear shape if participants who filled out only one questionnaire were removed from the analysis (Additional file 1 Fig. S7a). The intake of intrinsic sugars was also significantly related to dementia risk in a J-shaped fashion and the HR-nadir was observed at 8%E (Fig. 1b). Compared to the intake at the nadir, the HR (CI) increased to 1.30 (1.19 to 1.42) at 20%E (Fig. 1b). Intrinsic sugars remained significantly associated with dementia risk in all sensitivity analyses (Additional file 1 Fig. S4b to S16b). The relation between intrinsic sugars and dementia risk changed from a J-shape to a more linear shape in three sensitivity analyses (Additional file 1 Fig. S7b, S9b, S12b).

FS in beverages versus FS in solids

Mean (SD) intake of FS in beverages and FS in solids was 4.7 (4.7) %E and 6.6 (3.5) %E, respectively (Table 1). Dementia risk was significantly associated with FS in beverage intake in an ascending approximately linear way (Fig. 1c). The HR-nadir was observed at 2%E FS and the HRs (CIs) increased to 1.12 (1.02 to 1.22) and 1.72 (1.36 to 2.19) at 10%E and 20%E, respectively (Fig. 1c). The relation between incident dementia and FS in beverages remained similar in all sensitivity analyses (Additional file 1 Fig. S4c to S16c). The relation between FS in solids and dementia risk was not significant in the primary analysis (Fig. 1d) but in four out of the 13 sensitivity analyses (Additional file 1 Fig. S6d, S7d, S11d, S16d), changing towards a more linear shape in Additional file 1 Fig. S7d.

FS in beverage subtypes

Mean (SD) intake of FS in beverage subtypes was as follows: soda/fruit drinks 1.6 (3.3), juice 2.1 (2.8), milk-based drinks 0.3 (0.9), and tea/coffee 0.6 (1.6) %E (Table 1). FS in soda/fruit drinks were significantly approximately linearly ascending associated with dementia risk with the HR-nadir found at 1%E and HR (CI) of 1.34 (1.13 to 1.59) at 10%E FS (Fig. 2a). FS in juice were significantly related with HR for dementia in a linear manner with the HR-nadir observed at 2%E and HRs (CIs) of 1.12 (1.06 to 1.18) and 1.31 (1.06 to 1.62) at 0%E and 10%E FS, respectively (Fig. 2b). FS in milk-based drinks were significantly approximately linearly ascending associated with dementia risk with the HR-nadir detected at 0%E and increased HR (CI) of 1.39 (1.19 to 1.63) at 3%E FS but with a flattening trend at consumption levels above 4%E (Fig. 2c). These findings were robust in all sensitivity analyses

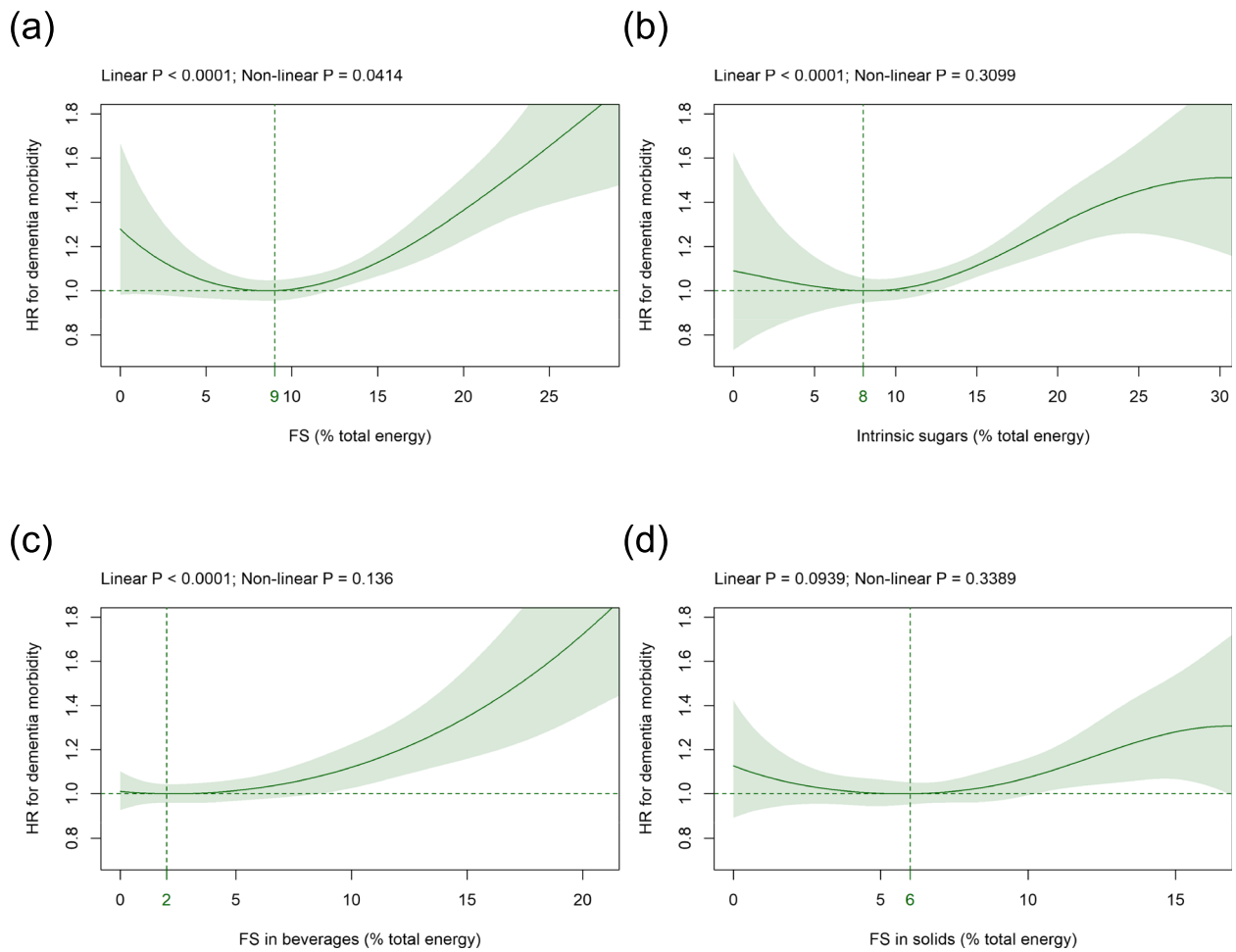


Fig. 1 Association of **a** FS, **b** intrinsic sugars, **c** FS in beverages, and **d** FS in solids intake (all %E) with dementia risk. Models are adjusted for energy intake (penalized cubic splines), age (split by quintiles), alcohol intake (< 1, 1 to < 8, 8 to < 16, ≥ 16 g/d), BMI (< 18.5, 18.5 to < 25, 25 to < 30, ≥ 30 kg/m^2), ethnic background (White, group composed of Mixed, Asian, Black, Chinese, and other), general health status (poor, fair, good, excellent), highest qualification (none of the below, national exams at age 16 years, vocational qualifications or optional national exams at ages 17–18 years, professional, College or University), history of mental illness (yes, no), physical activity (metabolic equivalent of task (MET)-minutes per week derived from the Oxford WebQ; split by quintiles), SBP (split by quintiles), sex (female, male), smoking status (never, previous, current occasional, current < 10, 10 to 14, 15 to 19, ≥ 20 cigarettes per day), total household income (< 18, 18 to < 31, 31 to < 52, 52 to < 100, ≥ 100 k£, unknown), and Townsend deprivation index (split by quintiles). Covariates not fulfilling the proportional hazard assumption are stratified. The HR-nadir is indicated by the vertical line. *Abbreviations: BMI* Body mass index, *FS* Free sugars, *HR* Hazard ratio, *kg/m^2* Kilogram per square meter, *MET* Metabolic equivalent of task, *%E* Percentage total energy, *SBP* Systolic blood pressure

except for FS in juice which only remained significantly associated with dementia in four out the 13 sensitivity analyses (Additional file 1 Fig. S4f, S14f, S15f, S16f). FS in tea/coffee were not significantly related to incident dementia (Fig. 2d) except for two sensitivity analyses (Additional file 1 Fig. S5h, S7h).

FS in solids subtypes

Mean (SD) intake of FS in solids subtypes was as follows: treats 4.4 (3.0), cereals 0.5 (0.8), toppings 1.2 (1.6), and sauces 0.3 (0.4) %E (Table 1). Concerning the solids subtypes studied, FS in treats were not significantly associated with dementia risk in the primary (Fig. 3a) and all sensitivity analyses with the exception of three sensitivity analyses (Additional file 1 Fig. S6h, S7h, S16h). FS in cereals were significantly related to incident dementia in a linear to sigmoid way in the primary analysis with the HR-nadir at 0.4%E (Fig. 3b) and all sensitivity analyses (Additional file 1 Fig. S4h to S16h). FS in toppings were not significantly related to dementia risk but became significant in three sensitivity analyses (Additional file 1 Fig. S6k, S10k, S15k). FS in sauces did not show a significant association with dementia incidence with the exception of one sensitivity analysis (Additional file 1 Fig. S9l).

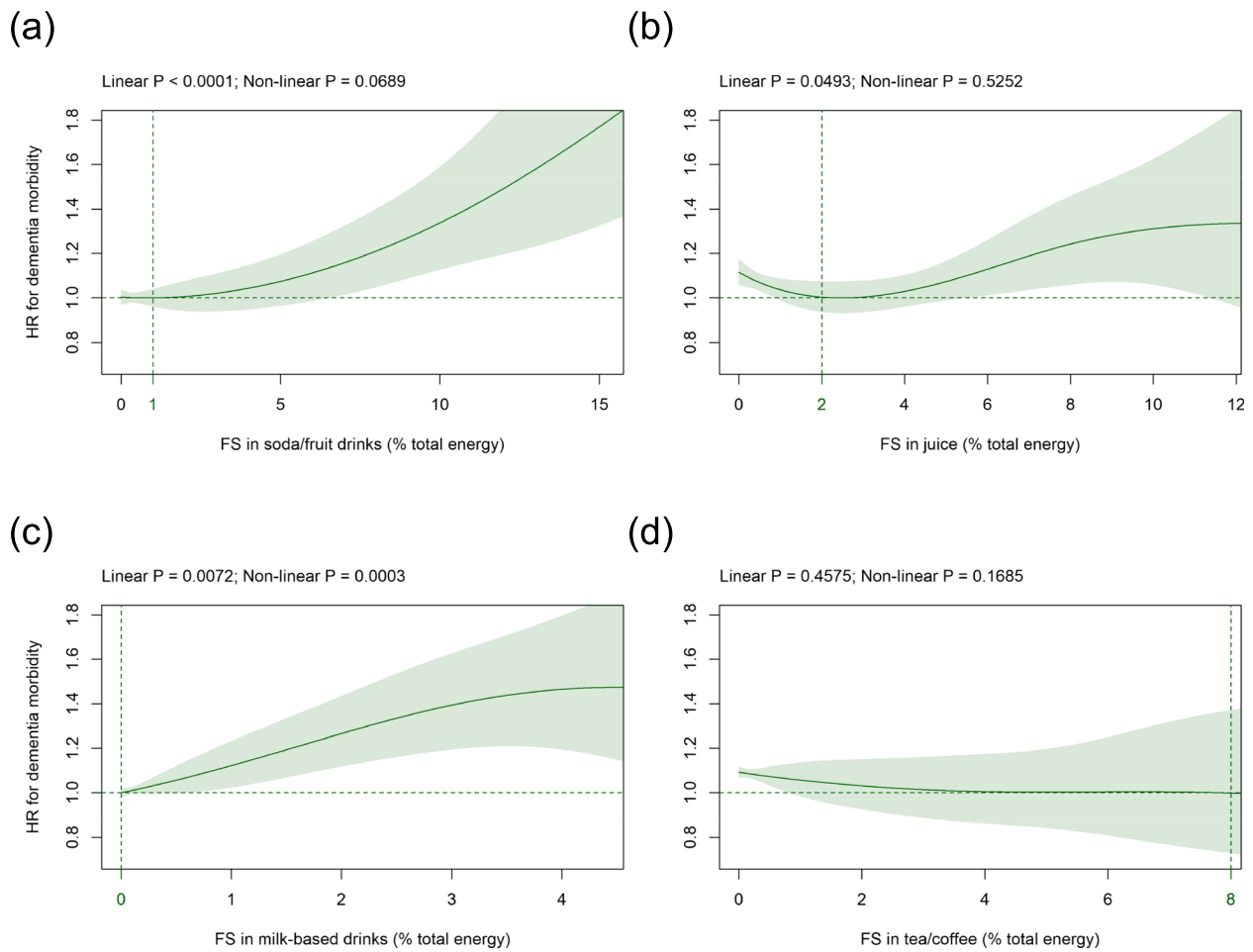


Fig. 2 Association of FS in **a** soda/fruit drinks, **b** juice, **c** milk-based drinks, and **d** tea/coffee (all %E) with dementia risk. Models are adjusted and presented as indicated in Fig. 1. *Abbreviations: %E* Percentage total energy

Discussion

Principal findings

In the current study, it is elucidated for the first time in a large prospective cohort how FS from all major liquid and solid sources and their subtypes are associated with dementia risk. Furthermore, we are the first to use penalized cubic splines to allow for non-linear predictor effects.

Overall FS intake is significantly associated with dementia risk in a J-shaped fashion with the HR-nadir found at 9%E. Similarly, intrinsic sugars are significantly related with dementia risk in a J-shaped fashion with the HR-nadir at 8%E. FS in beverages are significantly related to dementia risk in an ascending approximately linear way, whereas no association is found for FS in solids. Within the beverage subtypes, FS in soda/fruit drinks, milk-based drinks and to a lesser extent in juice are significantly and positively related to dementia risk, whereas no association is found for FS in tea/coffee. Our results highlight that the associations between FS and dementia risk depend on FS source.

Comparison with other studies

The mean FS consumption of UK Biobank participants in the present study of 11.4%E is slightly higher as compared to the median daily intake of 9%E in a representative UK population sample from the National Diet and Nutrition Survey Rolling Programme 2014–2016 [31].

To the best of our knowledge, the current study is the first to assess the association between FS from all sources and incident dementia. A cross-sectional study by Ye and co-workers in 737 participants shows convincingly that increasing added sugar intake is inversely related to cognitive function when comparing the first quintile to all other quintiles [32].

The present analysis is by far the largest study indicating a dose-dependency of FS in beverages intake and dementia risk. The majority of studies so far has focused

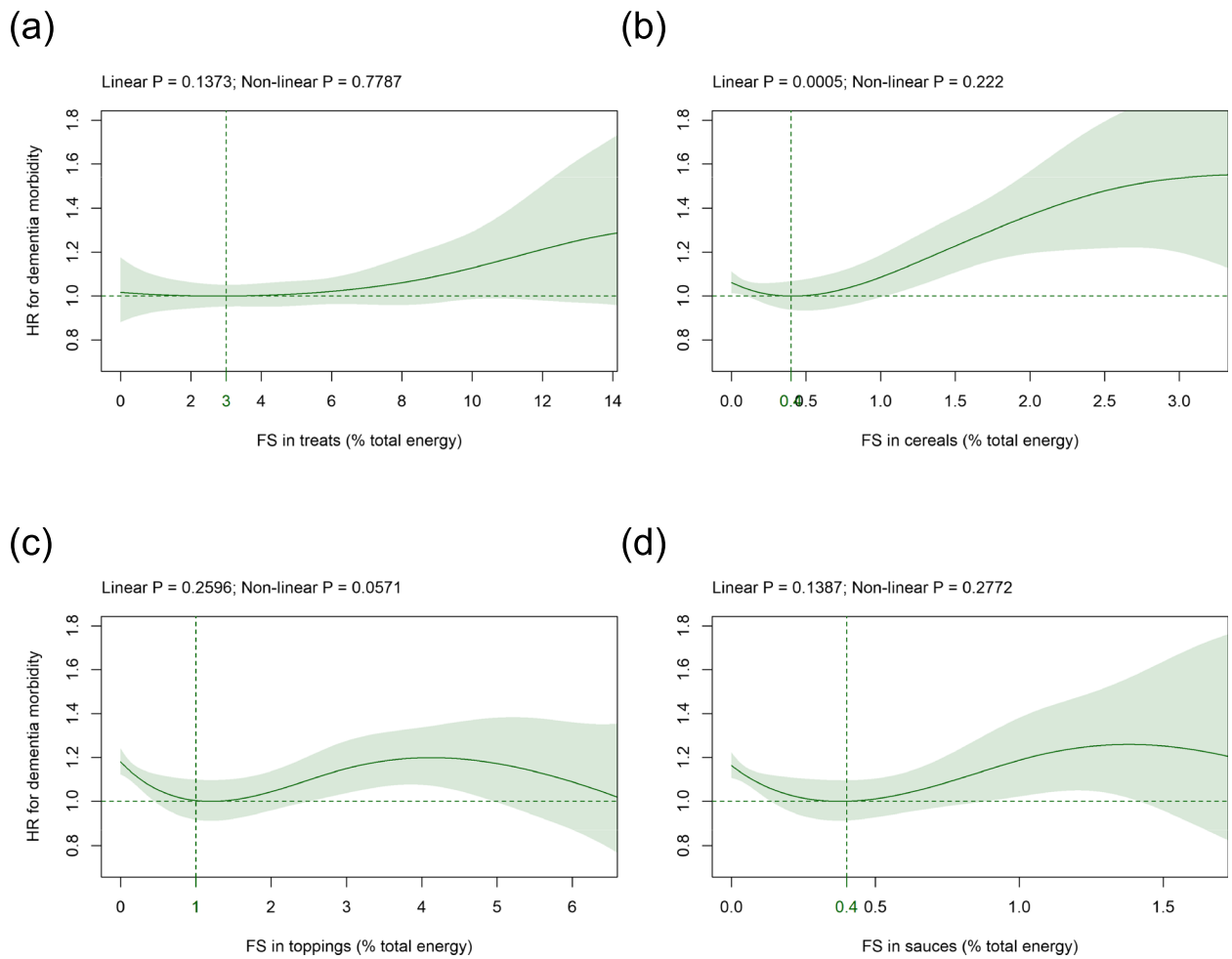


Fig. 3 Association of FS in **a** treats, **b** cereals, **c** toppings, and **d** sauces (all %E) with dementia risk. Models are adjusted and presented as indicated in Fig. 1. *Abbreviations: %E* Percentage total energy

exclusively on soda/fruit drinks with participant numbers ranging from 1384 to 22,564 and showing a positive association with dementia [33–36], similar to our present findings. Only one study in 16,948 participants does not find a significant association between soda/fruit drinks and cognitive impairment [37]. Differences in study results may be explained by relatively low consumption levels, different outcome measurements such as cognitive impairment, incident cases of Alzheimer's disease, and cognitive function, as well as varying model adjustments. Taking these and the current findings into consideration, a positive link between FS in soda/fruit drinks and incident dementia is found in the majority of studies.

In our study, intake of FS in juice is related to incident dementia in a linear manner with the HR-nadir at 2%E. Two studies show either an inverse association of juice intake > 3 times/week with HR for incident Alzheimer's disease compared to intake less often than weekly [38] or no association with cognitive function [39].

These data suggest that low to moderate juice intake is not linked to increased dementia risk and might even be a protective factor for the development of the disease. In contrast to FS in soda/fruit drinks and juice, no study so far has assessed the association between FS in milk-based sugary drinks, as well as tea/coffee, and incident dementia. FS in milk-based drinks show a positive association with dementia risk similar to FS in soda/fruit drinks while there is no relation for FS in tea/coffee.

Our study is the first to analyse the association of FS in solid foods with dementia risk and no significant link is found. In agreement with our findings, FS in solids are not associated with incident dementia in a cross-sectional study of 737 middle-aged Puerto Ricans [32].

To the best of our knowledge, the association of intrinsic sugars with dementia risk is characterized for the first time in the current study. The largest amounts of intrinsic sugars can be found in fruits and vegetables, as well as in milk with naturally present lactose and galactose [16].

Our current results of a J-shaped association between intrinsic sugars and dementia risk which even changes to a more linear shape in some sensitivity analyses are unexpected since fruits, vegetables, and dairy products have been linked with a decreased risk of dementia in several [40–43] but not all [39] studies. It is interesting to note in this context that in two recent studies from our group in the same study population intrinsic sugars are not significantly related to all-cause mortality and incident depression [18, 19]. More large-scale studies on the effect of intrinsic sugars as such on dementia risk are warranted.

Strengths and limitations

Strengths of the current study include a large sample size, the prospective cohort design, a thorough characterization of participants, a mean follow-up > 10 years, a wide range of sugar subtype intake, as well as analyses with penalized cubic splines to allow non-linear predictor effects. A recent study confirmed the applicability of the UK Biobank classification for dementia in prospective studies to identify all-cause dementia [44]. Limitations of the present study include residual confounding, which might lead to bias because estimated associations between outcome and exposure can be affected by unmeasured confounding factors. Moreover, measurement errors in the assessment of the exposure variables, and potential confounders might have occurred possibly altering the results. Since self-reported dietary assessments are vulnerable to reporting errors, only one assessment might not give a reliable insight into usual dietary habits. It is important to note in this context that the association between sugar subtypes and dementia risk changes towards a more linear association especially for intrinsic sugars and FS in solids if the analyses are restricted to participants who have completed, at a minimum, two questionnaires. The increased dementia risk in the no/low intake group might also represent a certain group of people who made dietary changes for or have a restricted diet for health reasons. This association is similar to the consistent J-shaped associations observed for alcohol intake and health outcomes, with various sources of bias and confounding potentially driving these associations [45]. Interestingly, the association of intrinsic sugars with dementia risk changes from a J-shape to a more linear shape if participants with a restricted diet due to health reasons are excluded. Reverse causality might be possible, i.e., even before dementia is diagnosed, the disease might influence dietary habits. However, results remain virtually unchanged in landmark analyses excluding all participants who have developed dementia within two years after completion of their first Oxford WebQ. Furthermore, a "healthy volunteer" selection bias is possible since it introduces a lack of representativeness into the cohort [46]. However, this is not necessarily a limitation since the size of the UK Biobank and the heterogeneity of exposure measures still allow the assessment of exposure-disease relationships [46].

Conclusions

A linear-shaped association between sugar subtype intake and dementia risk is most consistently found for FS in beverages and more specifically for FS in soda/fruit drinks, as well as in milk-based drinks. The association between intrinsic sugars and dementia risk which becomes linear in some sensitivity analyses warrants further assessment.

Further prospective studies on sugar subtype intake in relation to other disease states including CVD and cancer are necessary to provide an even more definitive conclusion.

Abbreviations

%E	Percentage total energy
BMI	Body mass index
CI	Confidence interval
CVD	Cardiovascular disease
FS	Free sugars
g/d	Grams per day
HR	Hazard ratio
kJ	Kilojoules
MET	Metabolic equivalent of task
NHS	National Health Service England
SBP	Systolic blood pressure
SD	Standard deviation
WHO	World Health Organization
WHR	Waist-to-hip-ratio

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12937-023-00871-8.

Additional file 1: Figure S1. Sugar sources relevant to the present study. **Figure S2.** Flowchart of participant selection. **Figure S3.** Venn diagram depicting number of participants excluded by seven exclusion criteria. **Figure S4.** Landmark analysis. **Figure S5.** Unintentional weight loss removed. **Figure S6.** Participants with history of CVD and cancer removed. **Figure S7.** Participants with only one completed Oxford WebQ removed. **Figure S8.** Non-typical diet removed. **Figure S9.** Special diet removed. **Figure S10.** Restricted to participants with age ≥ 60 years. **Figure S11.** Stratified by age (< 60 and ≥ 60 years). **Figure S12.** First Oxford WebQ only. **Figure S13.** Adjustment for diet quality score. **Figure S14.** Adjustment for WHR and height instead of BMI. **Figure S15.** Missing values of covariates recoded as "unknown" category. **Figure S16.** Only minimal set of exclusion criteria applied.

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Authors' contributions

SMS and AK conceived the research. Statistical analyses were performed by SMS, AK, GE, and MF. The first draft of the manuscript was prepared by SMS and AK. All authors revised the manuscript critically for important intellectual

content and gave final approval of the version to be submitted. SMS and AK are the guarantors of the manuscript and accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Availability of data and materials
The data that support the findings of this study are available from UK Biobank but restrictions apply to the availability of these data, which were used under license for Application 53,438, and, therefore, are not publicly available. Bona fide researchers can apply to use the UK Biobank dataset by registering and applying at https://www.ukbiobank.ac.uk/enable-your-research/register.

Declarations

Ethics approval and consent to participate
The UK Biobank study was conducted according to the guidelines of the Declaration of Helsinki and approved by the North West–Haydock Research Ethics Committee (REC reference: 21/NW/0157). Written informed consent was provided by all participants at baseline.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Publisher's Note

2.4 Publication 4: Association of sugar intake from different sources with cardiovascular disease incidence in the prospective cohort of UK Biobank participants

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Authors' contributions

S. M. S and A. K. conceived the research. Statistical analyses were performed by S. M. S., A. K., G. E., and M. F. S. M. S. and A. K. prepared the first draft of the manuscript and all figures. All authors revised the manuscript critically for important intellectual content and gave final approval of the version to be submitted. S. M. S. and A. K. are the guarantors of the manuscript and accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Appendix D: Supplementary Material

Summary

Research gap 4 was addressed in the publication “Association of sugar intake from different sources with cardiovascular disease incidence in the prospective cohort of UK Biobank participants”.

The paper examined the association of various sources of FS, i.e., intake of FS from beverages and beverage subtypes, i.e., soda/fruit drinks, juice, milk-based drinks, and tea/coffee, as well as intake of FS from solid foods and solids subtypes, i.e., treats, cereals, toppings, and sauces, with CVD risk. Furthermore, the association between intake of IS and incident CVD was also studied.

In total, 176,352 participants from the UK Biobank with a median follow-up period of 10.9 years and 12,355 incident cases of CVD were included in the study. Sugar intake was assessed using the 24HR Oxford WebQ, and all participants who completed the questionnaire at least once were included in the study. The primary outcome of the study was incident CVD defined as ICD codes I21-25, I60, I61, I63, and I64 and subgroup analyses were performed for IHD (ICD-10 codes I21-I25) and stroke (ICD-10 codes I60, I61, I63, and I64). The HRs for incident CVD were assessed with Cox proportional hazard regression multivariate nutrient density models[117] including %E intake of sugar from different sources and total energy intake as penalised cubic splines. Additionally, models were adjusted for age, energy intake, highest qualification, physical activity, sex, and smoking status. The lowest value of the HR of sugar intake in the range from zero to the 99%-quantile was called the HR-nadir. Several sensitivity analyses were performed to assess the robustness of results, e.g., addressing reverse causation by excluding participants diagnosed with CVD within two years after filling out the questionnaire, excluding participants with unintentional weight loss or an atypical diet, adjusting further for a diet quality score to control for residual confounding, or excluding participants from the analysis that had only completed one Oxford WebQ.

The study found that the intake of total FS was significantly linked to HR for CVD in a J-shaped fashion with the HR-nadir observed at an intake level of 9 %E. IS were related to CVD risk in a non-linear descending manner with the HR-nadir at 14 %E. FS in beverages were significantly and linearly related to CVD incidence with the HR-nadir at 3 %E. Regarding the beverages subtypes, FS in soda/fruit drinks, milk-based drinks, and tea/coffee were significantly linearly associated with CVD risk, while FS in juice were related in a U-shaped manner. For FS in solids the relation was slightly U-shaped and the HR-nadir was detected at 7 %E. FS in cereals were significantly and linearly associated with incident CVD with the HR-nadir at 0.5 %E, while FS in treats were associated in J-shaped fashion. The findings were

robust across various sensitivity analyses, including subgroup analyses focusing on IHD and stroke separately, with findings more robust for IHD than for stroke.

In summary, not all sources of FS are equally associated with CVD risk and relations are more robust for IHD as compared to stroke. Public health recommendations should focus particularly on reducing the consumption of FS from beverages, such as FS from soda/fruit drinks, milk-based drinks, tea/coffee, and in addition FS from cereals to lower CVD risk. IS may have a protective effect against CVD when consumed in moderate amounts.

The published manuscript is attached.

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Association of sugar intake from different sources with cardiovascular disease incidence in the prospective cohort of UK Biobank participants

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Abstract

Background The relation between incident cardiovascular disease (CVD) and sugar might not only depend on the quantity consumed but also on its source. This study aims to assess the association between various sources of dietary sugars and CVD incidence in the prospective population-based UK Biobank cohort.

Methods A total of 176,352 participants from the UK Biobank with at least one web-based dietary questionnaire (Oxford WebQ) for assessment of sugar intake were included in this study. Mean follow-up lasted 10.9 years (standard deviation 2.0), with 12,355 incident cases of CVD. To determine the association of free sugar (FS) and intrinsic sugar intake with incident CVD, hazard ratios (HR) were calculated using Cox proportional hazard regression models. FS intake from beverages and beverage subtypes, i.e., soda/fruit drinks, juice, milk-based drinks, and tea/coffee, as well as from solid foods and solids subtypes, i.e., treats, cereals, toppings, and sauces, was included as penalised cubic splines.

Results FS intake showed a J-shaped relationship with CVD risk, reaching the lowest HR (HR-nadir) at 9 %E, while intrinsic sugars displayed a non-linear descending association, with the HR-nadir at 14 %E. FS in beverages demonstrated a significant linear relationship with CVD with the HR-nadir at 3 %E, while FS in solids exhibited a significant non-linear U-shaped relationship with the HR-nadir at 7 %E. Within the beverage subtypes, soda/fruit drinks displayed a linear relationship, as did to a lesser extent FS in milk-based drinks and tea/coffee. Juice, however, showed a significant U-shaped relationship with CVD risk. Among solid foods subtypes, FS in treats had a J-shaped relation with the HR-nadir at 5 %E, and FS in cereals showed a linear association. In comparison, FS in toppings and sauces exhibited a U-shaped pattern with HR-nadir at 3 %E and 0.5 %E, respectively. All major results remained similar in various sensitivity analyses and were more robust for ischemic heart disease compared to stroke.

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Conclusions Only some sources of FS exhibit a robust positive association with CVD incidence. Public health efforts aiming at the reduction of CVD risk should prioritise the reduction of sugary beverages with an emphasis on soda/fruit drinks.

Keywords Carbohydrates, Cardiovascular disease, Ischemic heart disease, Stroke, Sugar, UK Biobank

Introduction

Cardiovascular disease (CVD) remains a major contributor to global mortality, accounting for approximately 32 % of all deaths worldwide [1]. CVD encompasses a spectrum of pathological conditions that affect the cardiovascular system, including diseases such as ischemic heart disease (IHD) and stroke [2, 3]. Advanced age, male sex, and genetic predisposition are important non-modifiable risk factors [3]. Major modifiable risk factors are an unhealthy diet, inadequate physical activity, harmful alcohol consumption, and tobacco use [3]. These risk factors can cause hypertension, hyperlipidaemia, type 2 diabetes mellitus, and obesity [1].

There is growing evidence that a high sugar diet is an important risk factor for CVD [2, 4] and several mechanisms have been proposed. Thus, calorie intake from sugary beverages induces less satiety, incomplete compensatory reduction in energy intake at subsequent meals, as well as a positive energy balance in humans [5]. Furthermore, dietary sugars increase hepatic de novo lipogenesis with concomitant non-alcoholic fatty liver disease (NAFLD) [6] and NAFLD is associated with increased long-term risk of CVD [7]. Further potential mechanisms linking high sugar consumption and CVD risk include increased sympathetic activity via the ventromedial hypothalamus [8] and reactive oxygen species-mediated oxidative stress [9].

Sugars include both mono- and disaccharides [10] and are classified into two different types according to the World Health Organization (WHO): free sugars (FS) and intrinsic sugars [11]. FS are all monosaccharides and disaccharides added to foods by the manufacturer, cook, or consumer, plus sugars naturally present in honey, syrups, and fruit juices [11]. In contrast, intrinsic sugars include sugars from fruit and vegetables, as well as lactose and galactose in dairy products [11]. According to the WHO, FS consumption should be reduced throughout the life course [11]. The WHO provides a strong recommendation that FS intake should be reduced to less than 10 % of total energy (%E) intake [11]. It conditionally recommends a further reduction of FS consumption to below 5 %E [11]. This corresponds to about 50 g and 25 g FS per day, respectively, in the case of a 2,000-kcal diet [11]. In agreement with the WHO, the National Health Service England recommends a daily FS intake of less than 30 g for adults [12].

High consumption of sugar, particularly in the form of sugar-sweetened beverages (SSB), is strongly associated with an increased risk of CVD [13–15]. In contrast, fruits and vegetables appear to have beneficial effects on cardiovascular health [16, 17]. However, no large study with more than 10,000 participants has systematically assessed the association between FS from all relevant sources which are summarised in Fig. S1 with CVD risk so far. Furthermore, no study has evaluated the relationship between intrinsic sugars and incident CVD. Therefore, the associations of the intake of FS, intrinsic sugars, and various FS subtypes with incident CVD were analysed in a large, well-characterised population of 176,352 UK Biobank participants using penalised cubic splines to allow non-linear predictor effects. We hypothesised that the relationship between FS and CVD risk depends on the source of FS with a positive association found for beverages, but not for solid foods, similar to recent findings from our group studying all-cause mortality [18], incident depression [19], and incident dementia [20].

Methods

Study design, participants, and exclusion criteria

The UK Biobank study is a prospective cohort study in which more than half a million participants aged 37 to 73 were recruited across the UK between 2006 and 2010 [21].

Written informed consent was obtained from all participants at baseline and ethical approval for the UK Biobank study was granted by the North West Multicentre Research Ethics Committee [21]. Participants from the UK Biobank pilot phase were removed from the analysis (n = 3,794; Fig. S2) since questions for covariates of the present study were different in some instances in the pilot as compared to the later cohort, e.g., professional qualifications were not assessed within the pilot. Since the intake of sugar and sugar subtypes was assessed based on the previous 24-h dietary intakes (Oxford WebQ) [22], participants without completing at least one dietary questionnaire had to be excluded (n = 287,620; Fig. S2). Seven exclusion criteria were applied similar to three recent studies from our group [18–20] (removed participants n = 34,593) and are depicted in Fig. S2.

Exposure assessment

Participants were asked to complete the Oxford WebQ, a web-based dietary recall tool that assesses food and beverage intake from the previous day. The Oxford WebQ provides quantitative data on 206 food and 32 beverage items, covering major foods consumed in the UK [22, 23]. While it addresses general food items, specific brands are not considered, except for occasional examples, e.g., "Chocolate bars (e.g. Crunchie, Snickers)". The Oxford WebQ is susceptible to person-specific biases, influenced by factors like age, sex, and body mass index [24–26]. Further person-specific biases include reactivity, memory, and social desirability bias [25, 27]. Moreover, inherent characteristics of the assessment tool, e.g., inadequate strategies for data collection or visual support, can also contribute to nutritional assessment errors [27]. Despite potential biases, the Oxford WebQ has been validated against accelerometry-estimated energy expenditure and biomarkers, showing good performance compared to traditional 24-hour interviewer-led dietary recalls [27]. Since underreporting of fat and carbohydrates with food records and 24-h recalls has been repeatedly demonstrated [28, 29], participants with significant underreporting of energy intake, i.e., total energy intake below 1.1 times basal metabolic rate assessed by the Oxford equation [30] minus 500 kcal, were excluded. Performance of the Oxford WebQ improves when multiple questionnaires are filled out [27], but this comes at the cost of losing more than a third of the sample size, i.e., 67,036 participants. To maintain a larger sample, main analyses were conducted on the total cohort with at least one Oxford WebQ, and additional sensitivity analyses were performed on participants with two or more questionnaires.

The intake of sugar and sugar subtypes from beverages and solids was calculated using the Oxford WebQ data similar to described in three previous reports from our group [18–20]. In brief, the definition of sugary beverages included soda/fruit drinks, pure juice, milk-based drinks, and tea/coffee with added sugar, whereas treats, breakfast cereals, toppings, and sauces were defined as subtypes of sugary solids. The size of a standard portion of these food items was taken from the UK Food Standards Agency [31] and respective product labels. To obtain the total consumed amount of sugar in each beverage and solids subtype, the reported consumption frequency of each food item was multiplied by the estimated content of this sugar subtype in that food item per serving. To calculate sugar subtype intake in %E, the intake in g/d was multiplied by 17 kJ/g * 100 % / total energy in kJ/d according to Willett and colleagues [32]. The amount of intrinsic sugars consumed was calculated from the difference between total sugars and FS. For all participants who completed more than one Oxford WebQ, their mean intake measured in %E of all sugar subtypes was used in all primary and sensitivity analyses except for Fig. S7 where only the first completed Oxford WebQ was considered.

Outcome assessment

The primary outcome of the study was incident CVD defined as International Classification of Disease 10th revision (ICD-10) codes I21-25, I60, I61, I63, and I64. Subgroup analyses were performed for IHD (ICD-10 codes I21-I25) and stroke (ICD-10 codes I60, I61, I63, and I64). Outcomes were defined as the first occurrence of these ICD-10 codes across self-report at baseline assessment, primary care, hospital in-patient records, and death record data in the UK Biobank [33]. In order to calculate the follow-up time, the date of the first dietary assessment was subtracted from the date of the first diagnosis of any CVD event, loss-to-follow-up, death, or censoring, whichever came first. In case of more than one diagnosis, the shortest duration to any diagnosis was used.

Statistical analyses

Data analysis was performed with R version 4.3.2 (R Core Team, Vienna, Austria) [34] as described recently [19]. In brief, the hazard ratios (HR) for incident CVD were assessed with Cox proportional hazard regression multivariate nutrient density models [32] including %E intake of sugar from different sources and total energy intake as penalised cubic splines with their degrees of freedom set to 4. Splines are used to produce curve shapes with a high degree of flexibility when fitting the model [35]. Penalised cubic splines impose a penalisation upon the piecewise polynomial components to optimise the model fit [35]. They are useful to identify complex patterns without the user having to specify various parameters [35]. A directed acyclic graph (produced with the R package DAGitty [36] that shows hypothesized causal relationships underlying the association between sugar and CVD incidence was used to identify an appropriate set of confounding variables to assess an unconfounded effect estimate. Hence, the following variables were selected as covariates in the analysis: age, energy intake, highest qualification, physical activity (MET per week), sex, and smoking (Fig. S3). If a significant violation of the assumption of hazard proportionality was detected using scaled Schoenfeld residuals, the respective covariates were stratified in the final models. In each analysis, the estimation of the lowest value of the hazard ratio (HR) on the sugar intake axis, called the HR–nadir, was restricted to the range of sugar intake from zero to the 99th percentile of the observed intakes. To simplify the presentation, the HR was then rescaled to a value of 1 at its nadir. In

all Cox proportional hazard regression models, the HRs are presented along with their corresponding pointwise 95 % confidence intervals. The analysis of each penalised cubic spline was divided into the linear effect (p^{lin}) and the non-linear effect ($p^{non\text{-}lin}$), as recently described [37]. In all analyses, a *p-value* of <0.05 was considered statistically significant. No further interpretation of the HR-nadir or of other individual HRs was performed if both p^{lin} and $p^{non\text{-}lin}$ were non-significant.

Sensitivity analyses

To evaluate the robustness of the results, we performed several sensitivity analyses similarly as described in recent studies [18, 19, 38]: To address reverse causation, participants who were diagnosed with CVD or lost to follow-up within two years of joining the study (landmark analysis) were excluded. Participants with unintentional weight loss were also removed in another sensitivity analysis as this might be a sign, e.g., of malignant diseases, chronic organ failure, frailty, and psychological disorders [39]. To ensure more representative consumption data, participants who reported at least once having had an atypical diet on the previous day were also excluded. To focus on nutrient intake closest to the baseline assessment, the analyses were repeated using only the first Oxford WebQ questionnaire. Additionally, a diet quality score was calculated by combining five dietary components: fat, fruit, vegetables, red meat, and processed meat consumption in order to control for potential residual confounding due to dietary factors as described by Anderson and colleagues [38]. Furthermore, participants who filled out only one Oxford WebQ were removed from the analysis to address potential variation, i.e., lower reproducibility in sugar intake based on a single Oxford WebQ [27]. Lastly, CVD outcomes were divided into the subgroups ischemic heart disease and stroke to assess whether associations remained consistent.

Results

An overview of all main results on associations of sugar subtypes with CVD risk is shown in Table S1.

Baseline data of UK Biobank participants

In total, 176,352 participants were included in the present study (Fig. S2). The baseline characteristics of the studied population in total and in subgroups of FS intake defined by %E quintiles are presented in Table 1. Mean (standard deviation (SD)) age of the study cohort at completion of the first Oxford WebQ was 57 [8] years and 58.5 % of the participants were female. The follow-up period was 10.9 (2.0) years, i.e., 1.9 million person-years. Out of the total of 12,355 cases of CVD, there were 9,950 cases of IHD and 3,066 cases of stroke, i.e., 661 participants having both diagnoses.

Main analyses

FS and intrinsic sugars

As shown in Table 1, the mean (SD) consumption of FS and intrinsic sugars was 11.4 (5.6) %E and 13.0 (5.7) %E, respectively. FS intake was significantly linked to HR for CVD in a J-shaped fashion with the HR-nadir observed at an intake level of 9 %E (Fig. 1a). In comparison to intake at the HR-nadir, the HR increased to 1.13 (1.09 to 1.17) at 20 %E (Fig. 1a). Intrinsic sugars were related with CVD risk in a non-linear descending manner with the HR-nadir at 14 %E and an increased HR of 1.26 (1.08 to 1.47) at 0 %E (Fig. 1b).

FS in beverages and FS in solids

Mean (SD) intake of FS in beverages and FS in solids was 4.7 (4.6) %E and 6.6 (3.5) %E, respectively (Table 1). For FS in beverages, a significant linear relation could be detected with the HR-nadir at 3 %E and an increase to 1.06 (1.03 to 1.09) and 1.24 (1.13 to 1.35) at 10 %E and 20 %E, respectively (Fig. 1c). For FS in solids the relation was slightly U-shaped and the HR-nadir was detected at 7 %E and increased to 1.16 (1.07 to 1.25) at 0 %E (Fig. 1d).

FS in beverage subtypes

Mean (SD) intake of FS in beverage subtypes was as follows: soda/fruit drinks 1.6 (3.2) %E, juice 2.1 (2.8) %E, milk-based drinks 0.3 (0.9) %E, and tea/coffee 0.6 (1.6) %E (Table 1). FS in soda/fruit drinks showed a significant linear association with CVD risk with the HR nadir found at 0 %E and a HR of 1.14 (1.07 to 1.22) and 1.27 (1.14 to 1.42) at 10 %E and 15 %E, respectively (Fig. 2a). FS in juice were significantly related with HR for CVD in a U-shaped fashion with HR-nadir observed at 5 %E and HRs of 1.11 (1.09 to 1.13) and 1.07 (1.00 to 1.15) at 0 %E and 10 %E FS, respectively (Fig. 2b). FS in milk-based drinks (Fig. 2c) and FS in tea/coffee (Fig. 2d) were both significantly linearly associated with CVD risk and the HR-nadir was at 0 %E for both.

FS in solids subtypes

Mean (SD) intake of FS in solids subtypes was as follows: treats 4.4 (3.0) %E, cereals 0.5 (0.8) %E, toppings 1.2 (1.6) %E, and sauces 0.3 (0.4) %E (Table 1). The relation between FS in treats and CVD risk was J-shaped with the HR-nadir at 5 %E (Fig. 3a) while the relation was U-shaped for FS in toppings and sauces with the HR-nadir at 3 %E and 0.5 %E (Fig. 3c, d), respectively. FS in cereals showed a significant linear association with incident CVD with the HR-nadir at 0.5 %E (Fig. 3b).

Table 1 Baseline characteristics of the UK Biobank cohort[a]

Parameters	Total cohort (*n*=176,352)	FS intake (%E) split by quintiles				
		0.0 to 6.8 (*n*=35,271)	6.8 to 9.5 (*n*=35,270)	9.5 to 12.1 (*n*=35,270)	12.1 to 15.4 (*n*=35,270)	15.4 to 77.5 (*n*=35,271)
Characteristics						
Age at completion of first Oxford WebQ (years)	57 (8)	57 (8)	58 (8)	58 (8)	58 (8)	57 (8)
BMI (kg/m^2)	26.5 (4.3)	26.7 (4.4)	26.5 (4.3)	26.4 (4.2)	26.3 (4.3)	26.6 (4.4)
Energy (kJ/d)	9,079 (2,307)	8,515 (2,246)	8,994 (2,236)	9,214 (2,253)	9,337 (2,287)	9,334 (2,407)
Ethnic background						
- White	169,902 (96.3)	34,095 (96.7)	34,242 (97.1)	34,158 (96.8)	34,094 (96.7)	33,313 (94.4)
- Mixed, Asian, Black, Chinese, and other	6,450 (3.7)	1,176 (3.3)	1,028 (2.9)	1,112 (3.2)	1,176 (3.3)	1,958 (5.6)
General health status						
- Poor	3,636 (2.1)	637 (1.8)	545 (1.5)	595 (1.7)	714 (2.0)	1,145 (3.2)
- Fair	26,538 (15.1)	5,299 (15.0)	4,918 (13.9)	4,875 (13.8)	5,179 (14.7)	6,267 (17.8)
- Good	107,977 (61.2)	21,579 (61.2)	21,624 (61.3)	21,943 (62.2)	21,780 (61.8)	21,051 (59.7)
- Excellent	38,201 (21.7)	7,756 (22.0)	8,183 (23.2)	7,857 (22.3)	7,597 (21.5)	6,808 (19.3)
Highest qualification						
- None of the below	13,355 (7.6)	2,914 (8.3)	2,485 (7.0)	2,523 (7.2)	2,515 (7.1)	2,918 (8.3)
- National exams at age 16 years	26,565 (15.1)	5,385 (15.3)	5,079 (14.4)	5,145 (14.6)	5,235 (14.8)	5,721 (16.2)
- Vocational qualifications or optional national exams at ages 17-18 years	31,197 (17.7)	6,390 (18.1)	6,086 (17.3)	6,009 (17.0)	6,007 (17.0)	6,705 (19.0)
- Professional	27,196 (15.4)	5,266 (14.9)	5,237 (14.8)	5,587 (15.8)	5,518 (15.6)	5,588 (15.8)
- College or University	78,039 (44.3)	15,316 (43.4)	16,383 (46.5)	16,006 (45.4)	15,995 (45.4)	14,339 (40.7)
History of cancer	14,628 (8.3)	2,829 (8.0)	2,872 (8.1)	2,970 (8.4)	3,030 (8.6)	2,927 (8.3)
History of mental illnesses	11,590 (6.6)	2,292 (6.5)	2,161 (6.1)	2,099 (6.0)	2,276 (6.5)	2,762 (7.8)
Hypertension	36,942 (21.0)	7,949 (22.5)	7,334 (20.8)	7,248 (20.6)	7,147 (20.3)	7,264 (20.6)
Physical activity (MET-min/week)	4,133 (2,647)	4,068 (2,654)	4,112 (2,566)	4,139 (2,560)	4,145 (2,597)	4,202 (2,848)
Sex – female	103,136 (58.5)	20,720 (58.7)	20,974 (59.5)	20,731 (58.8)	20,669 (58.6)	20,042 (56.8)
Smoking status						
- Never	102,774 (58.3)	18,383 (52.1)	19,970 (56.6)	20,912 (59.3)	21,752 (61.7)	21,757 (61.7)
- Previous	60,959 (34.6)	14,043 (39.8)	12,983 (36.8)	12,178 (34.5)	11,222 (31.8)	10,533 (29.9)
- Occasional	4,267 (2.4)	1,018 (2.9)	874 (2.5)	816 (2.3)	778 (2.2)	781 (2.2)
- Current <10 cigarettes per day	2,221 (1.3)	477 (1.4)	400 (1.1)	374 (1.1)	450 (1.3)	520 (1.5)
- Current 10 to 14 cigarettes per day	1,894 (1.1)	384 (1.1)	327 (0.9)	316 (0.9)	341 (1.0)	526 (1.5)
- Current 15 to 19 cigarettes per day	1,661 (0.9)	353 (1.0)	278 (0.8)	273 (0.8)	297 (0.8)	460 (1.3)
- Current ≥20 cigarettes per day	2,576 (1.5)	613 (1.7)	438 (1.2)	401 (1.1)	430 (1.2)	694 (2.0)
Total household income per year (k£)						
- <18	22,694 (12.9)	4,302 (12.2)	4,142 (11.7)	4,292 (12.2)	4,627 (13.1)	5,331 (15.1)
- 18 to <31	38,072 (21.6)	7,242 (20.5)	7,431 (21.1)	7,617 (21.6)	7,772 (22.0)	8,010 (22.7)
- 31 to <52	46,119 (26.2)	9,112 (25.8)	9,321 (26.4)	9,290 (26.3)	9,199 (26.1)	9,197 (26.1)
- 52 to <100	40,258 (22.8)	8,556 (24.3)	8,434 (23.9)	8,162 (23.1)	7,916 (22.4)	7,190 (20.4)

Table 1 (continued)

Parameters	Total cohort (*n*=176,352)	FS intake (%E) split by quintiles				
		0.0 to 6.8 (*n*=35,271)	6.8 to 9.5 (*n*=35,270)	9.5 to 12.1 (*n*=35,270)	12.1 to 15.4 (*n*=35,270)	15.4 to 77.5 (*n*=35,271)
- ≥100	12,055 (6.8)	2,773 (7.9)	2,657 (7.5)	2,450 (6.9)	2,280 (6.5)	1,895 (5.4)
- Unknown	17,154 (9.7)	3,286 (9.3)	3,285 (9.3)	3,459 (9.8)	3,476 (9.9)	3,648 (10.3)
Townsend deprivation index	-1.7 (2.8)	-1.5 (2.9)	-1.7 (2.8)	-1.7 (2.8)	-1.8 (2.8)	-1.5 (2.9)
Dietary sugar subtype intake in %E						
Intrinsic sugars	13.0 (5.7)	14.4 (6.5)	13.7 (5.6)	13.1 (5.3)	12.5 (5.1)	11.4 (5.3)
FS	11.4 (5.6)	4.5 (1.7)	8.2 (0.8)	10.8 (0.7)	13.6 (1.0)	19.6 (4.3)
FS beverages	4.7 (4.6)	1.1 (1.4)	2.6 (2.1)	3.9 (2.5)	5.6 (3.0)	10.4 (5.8)
- Soda/fruit drinks	1.6 (3.2)	0.2 (0.6)	0.5 (1.2)	0.9 (1.7)	1.6 (2.4)	4.6 (5.4)
- Juice	2.1 (2.8)	0.6 (1.2)	1.4 (1.8)	2.1 (2.2)	2.7 (2.6)	3.8 (4.0)
- Milk-based drinks	0.3 (0.9)	0.1 (0.5)	0.2 (0.7)	0.3 (0.9)	0.4 (1.0)	0.6 (1.3)
- Tea/coffee	0.6 (1.6)	0.2 (0.6)	0.3 (0.9)	0.5 (1.2)	0.7 (1.6)	1.4 (2.6)
FS solids	6.6 (3.5)	3.4 (1.8)	5.6 (2.1)	6.9 (2.5)	8.1 (3.0)	9.2 (4.1)
- Treats	4.4 (3.0)	2.1 (1.6)	3.6 (2.0)	4.5 (2.4)	5.3 (2.8)	6.3 (3.8)
- Cereals	0.5 (0.8)	0.3 (0.6)	0.5 (0.7)	0.5 (0.8)	0.6 (0.8)	0.6 (0.9)
- Toppings	1.2 (1.6)	0.4 (0.9)	0.9 (1.4)	1.3 (1.6)	1.6 (1.8)	1.7 (2.0)
- Sauces	0.3 (0.4)	0.2 (0.4)	0.3 (0.4)	0.3 (0.4)	0.3 (0.4)	0.3 (0.4)
Number of Oxford WebQs	2.2 (1.2)	2.0 (1.1)	2.3 (1.2)	2.4 (1.2)	2.3 (1.2)	2.0 (1.1)

[a] Categorical variables are summarised as frequencies (percentages) and continuous variables as mean (SD)

CVD Cardiovascular disease, *FS* Free sugars, *kJ* Kilojoules, *MET* Metabolic equivalent of task, *%E* Percentage total energy, *SD* Standard deviation

Sensitivity analyses

FS and intrinsic sugars

The association between FS and HR for CVD remained significant in all sensitivity analyses (Fig. S4a to S9a). Analysing the subgroups of CVD, the shape of the relation between FS and CVD risk was similar for IHD (Fig. S10a) but changed for stroke: the HR-nadir was at 11 %E and a considerable increase of the HR at 0 %E to 1.31 (1.10 to 1.56) was found (Fig. S10b). The relation between intrinsic sugars and CVD risk remained significant in all sensitivity analyses except for the removal of participants with a non-typical diet (Fig. S6b) and when the subgroup of stroke was analysed (Fig. 10d).

FS in beverages and FS in solids

The association between FS in beverages and CVD was virtually identical in all sensitivity analyses (Fig. S4c to S9c) and subgroup analyses (Fig. S10e, f). For FS in solids the significant U-shaped relation remained significant in the subgroup analyses and in all but one sensitivity analysis (Fig. S9d).

FS in beverage subtypes

The findings for FS in soda/fruit drinks, juice, milk-based drinks and tea/coffee were robust in all sensitivity analyses except for FS in milk-based drinks who were not significantly related to stroke incidence (S10n).

FS in solids subtypes

Findings on FS in solids subtypes changed in the following sensitivity analyses: FS in treats were linearly related to CVD when only the first Oxford WebQ was used (Fig. S7i), lost significance when only participants with more than 1 Oxford WebQ were included in the analysis (Fig. S9i), and for stroke the relation became U-shaped (Fig. S10r). FS in cereals remained significantly associated with CVD risk only in two sensitivity analyses (Fig. S5j, S8j). FS in toppings remained significantly associated with CVD morbidity in all sensitivity analyses (Fig. S4k to S9k) and in the subgroup analysis (Fig. S10u, v). FS in sauces remained significantly associated with CVD in two sensitivity analyses (Fig. S6l, S8l). In subgroup analysis, FS in sauces were significantly associated with IHD risk (Fig. 10w) but not with incident stroke (Fig. 10x).

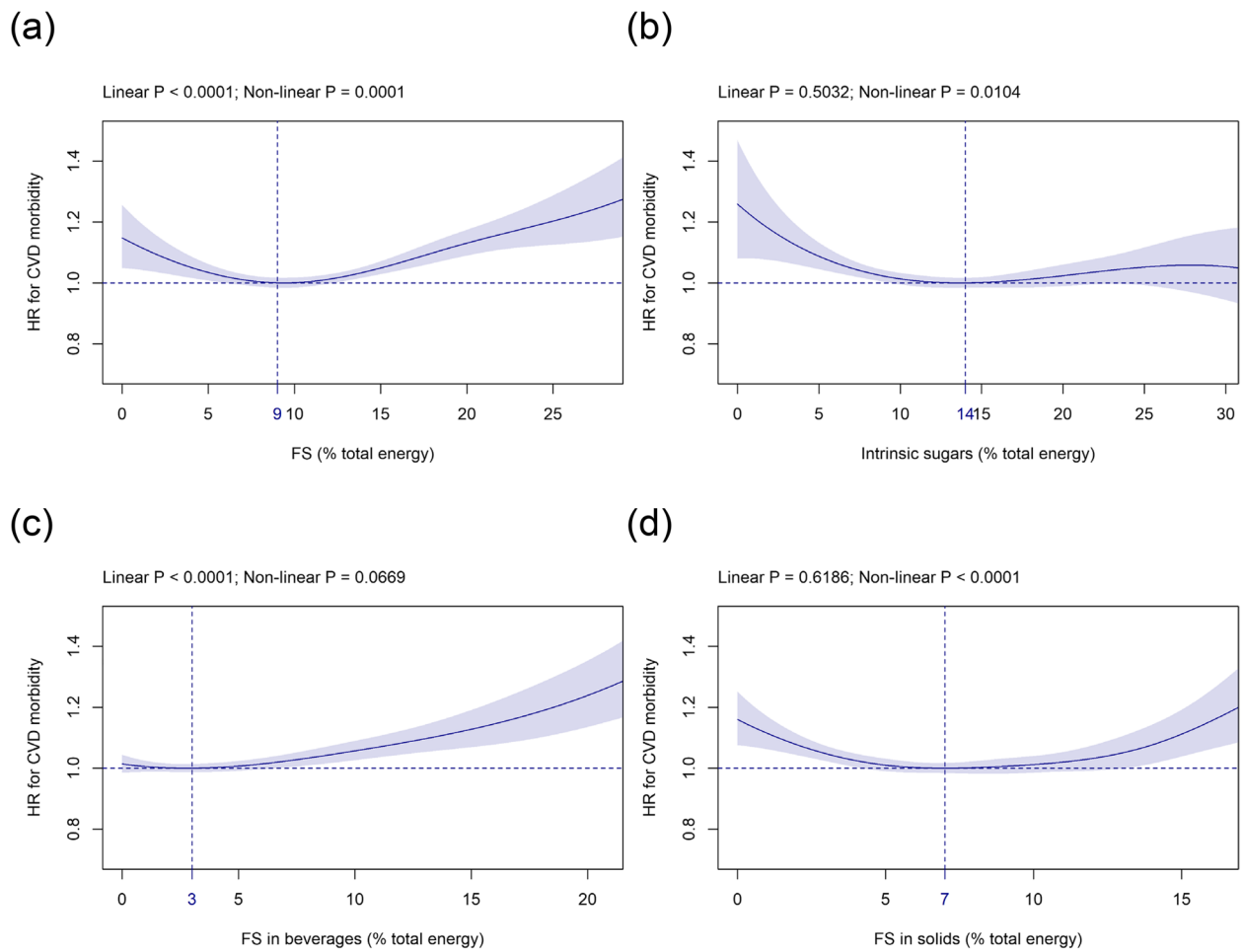

Fig. 1 Association of (**a**) FS, (**b**) intrinsic sugars, (**c**) FS in beverages, and (**d**) FS in solids intake (all %E) with CVD risk. Models are adjusted for age (split by quintiles), energy intake (penalised cubic splines), highest qualification (none of the below, national exams at age 16 years, vocational qualifications or optional national exams at ages 17-18 years, professional, College or University), physical activity (metabolic equivalent of task-minutes per week derived from the Oxford WebQ; split by quintiles), sex (female, male), and smoking status (never, previous, current occasional, current <10, 10 to 14, 15 to 19, ≥20 cigarettes per day). Covariates not fulfilling the proportional hazard assumption are stratified. The vertical line indicates the HR-nadir. Abbreviations: CVD, Cardiovascular disease; FS, Free sugars; HR, Hazard ratio; %E, Percentage total energy

Discussion

Principal findings

This study aims to assess the relationship between FS and incident CVD in a large prospective cohort. The analysis comprehensively examines FS intake from all relevant sources, including beverages and solids, using penalised cubic splines to account for non-linear relationships. FS intake show a J-shaped relationship with CVD risk, reaching the HR-nadir at 9 %E, while intrinsic sugars display a non-linear descending association, with the HR-nadir at 14 %E. There is a significant linear relationship between FS in beverages and HR for incident CVD, while a U-shaped relation can be detected for FS in solids with the lowest risk at 7 %E. FS in soda/fruit drinks, milk-based drinks, and tea/coffee are significantly linearly related with the HR-nadir at 0 %E, while juice shows a U-shaped association with the lowest HR at 5 %E. FS in treats show a J-shaped relation with the HR-nadir at 5 %E while FS in cereals are linearly associated with CVD risk. FS in toppings and sauces exhibit a U-shaped pattern with the HR-nadir at 3 %E and 0.5 %E, respectively. Major findings remain robust in various sensitivity analyses. Since results including the diet quality score as a covariate are not substantially different as compared to the main analyses, the association between FS subtypes and CVD risk cannot be simply explained by overall diet quality.

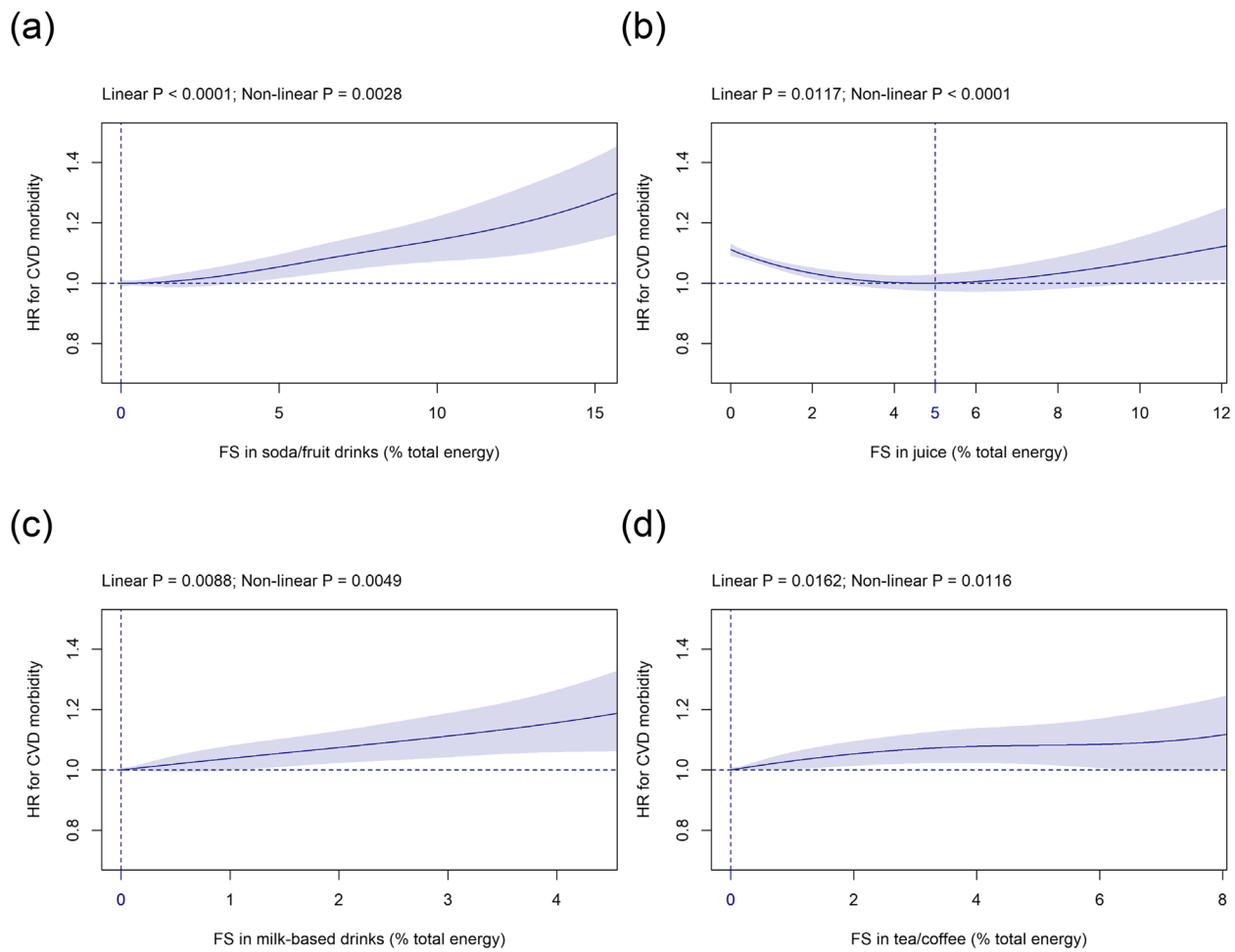

Fig. 2 Association of FS in (**a**) soda/fruit drinks, (**b**) juice, (**c**) milk-based drinks, and (**d**) tea/coffee (all %E) with CVD risk. Models are adjusted and presented as indicated in Fig. 1. Abbreviations: %E, Percentage total energy

Comparison with other studies

Other studies focusing on added sugars or FS have reached inconclusive results [40–43]. Our findings align with a Swedish report that observes a U-shaped trend for added sugars and incident stroke with the lowest risk for consumers in the 7.5 %E to 10 %E group and an increasing risk among the lowest and highest intake groups [40]. In a meta-analysis, a threshold for harm is identified for added sugars at 13 %E in relation to CVD mortality; however, the evidence is rated as low to very low certainty [41]. A study in 109,034 women from the Women's Health Initiative shows that the consumption of added sugars of ≥15.0 %E is positively associated with total CVD and IHD risk [42]. However, another recent study in Canadians does not show conclusive associations for FS above vs. below a threshold of 10 %E [44]. In a previous well-conducted study in UK Biobank participants, each 5 %E increment of FS intake is positively associated with CVD, IHD, and stroke incidence [43]. Taking these and the current results into consideration, FS intake appears not to be linearly related to CVD risk but limiting FS consumption to no more than 10 %E might be beneficial for CVD prevention.

In the present study, FS in beverages are significantly associated with CVD, IHD, and stroke incidence in a linear way. To the best of our knowledge, only one small study (n = 8,422) has assessed the association of FS in liquid foods with CVD incidence [44]. CVD risk for FS intake above as compared to below a threshold of 5 %E in liquid foods is numerically higher but does not reach statistical significance [44]. Differences in results may be well attributable to the much larger sample size (n = 176,352) and the use of splines in the present analysis.

Within beverage subtypes, FS in soda/fruit drinks are significantly associated with CVD, IHD, and stroke incidence in a linear way in the present analysis. Consistent with our findings, a network meta-analysis of 21 cohort studies shows that the consumption of SSB is

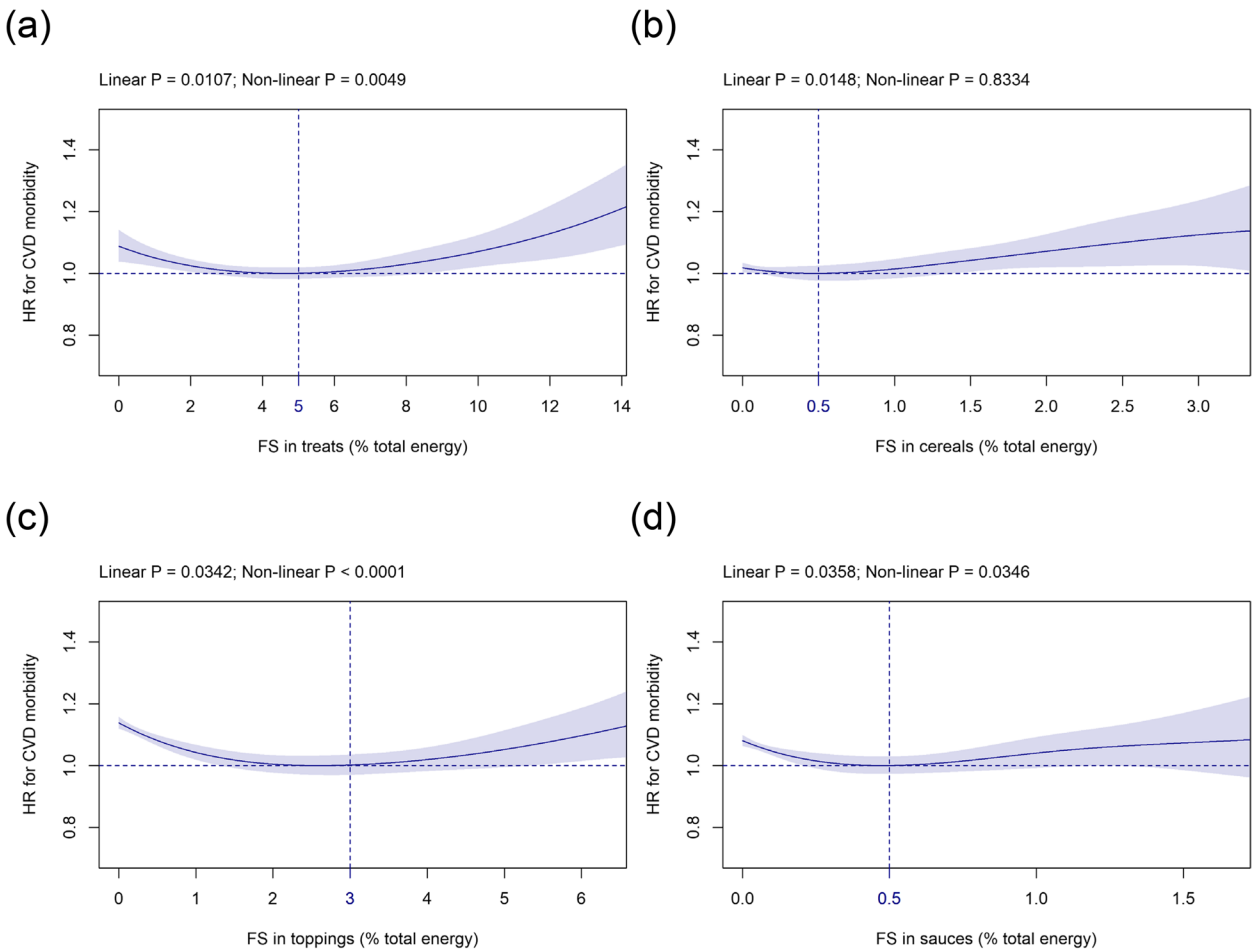

Fig. 3 Association of FS in (**a**) treats, (**b**) cereals, (**c**) toppings, and (**d**) sauces (all %E) with CVD risk. Models are adjusted and presented as indicated in Fig. 1. Abbreviations: %E, Percentage total energy

associated with a 14 % higher risk of CVD and a 13 % higher risk of stroke, respectively [42]. Results from the Women's Health Initiative also show an elevated risk of CVD and stroke with an intake of ≥1 serving of SSB per day [42]. In our study, the intake of FS in juice is significantly related to CVD incidence in a U-shaped fashion with the HR-nadir at 5 %E and with an 11 % higher risk in non-consumers. In CVD subgroups, the association remains significant for both IHD and stroke. Scheffers and co-workers observe a significant association of fruit juice intake up to 7 glasses per week with a reduced risk of CVD, but not beyond ≥8 glasses [45]. A significantly decreased risk of stroke is observed at intake levels of 1 to 4 and 4 to 8 glasses juice per week as compared to non-drinkers [45]. Our study is the first to elucidate the association between FS in milk-based drinks and FS added to tea/coffee on the one hand and CVD risk on the other hand. FS in milk-based drinks and FS added to tea/coffee show a linear association with CVD risk similar to FS in soda/fruit drinks. Assessing the subgroups of CVD, FS in milk-based drinks show a similar association for IHD and no significant relation with stroke. In contrast, FS in tea/coffee are significantly related with both IHD and stroke. Combined, these data and published evidence suggest that the association between FS and incident CVD depends on beverage type with a significant linear relationship observed in soda/fruit drinks and to a lesser extent in milk-based drinks and tea/coffee. In contrast, consuming a low to moderate amount of juice is not associated with an elevated risk of CVD and may even have a protective effect. This potential link should be assessed in further studies.

In the current report, FS in solids show a significant non-linear U-shaped association with the HR-nadir at 7 %E. In the subgroup analysis, the association for FS in solids and HR remains significant for both IHD and stroke. Using a different approach, Dasgupta and co-workers find a 34 % higher HR for CVD in men aged 55-75 years who consume more compared to men who consume less than 5 %E FS from solids [44]. In our study,

FS in treats exhibit a J-shaped relation, FS in cereals a linear relation and FS in toppings and sauces are related in a U-shaped manner with HR for CVD. In agreement with our results, Janzi and co-workers [40] show that the highest risk of stroke and coronary events is found in the intake group of treats with ≤2 servings/week, however, they detect no association for toppings intake. Taken together, these results indicate that a linear association between FS intake and CVD risk can only be observed for beverages, especially soda/fruit drinks, milk-based drinks and FS added to tea/coffee and only to a smaller extent for FS in cereals. Different associations of FS in beverages and solids with CVD could be in part explained by faster gastric emptying of sugary liquids [46, 47]. More rapid absorption of FS from beverages triggers less satiety which leads to an incomplete compensatory reduction in energy intake at subsequent meals and a positive energy balance [5].

The present study is the first to show that intrinsic sugars are significantly associated with CVD risk in a non-linear descending way. Intrinsic sugars can be found in high amounts incorporated within the structure of intact fruit and vegetables or as naturally present lactose and galactose in dairy products [11]. It is important to note in this context that the CVD risk is reduced by 28 % in participants with an intake of 800 g per day of fruit and vegetables combined as compared to no intake in a large meta-analysis of 12 studies [48]. In agreement with these findings, comparing the highest to the lowest category of intake, an inverse association of vegetable and fruit consumption with risk of IHD and stroke is found in a meta-analysis of 123 studies [49]. In contrast, milk and dairy-product intake is not significantly related to CVD risk in a meta-analysis of 17 studies [50]. Takings these findings into consideration, intrinsic sugars are not or even inversely related to CVD risk and a moderate consumption may be beneficial for CVD prevention. It remains to be elucidated whether intrinsic sugars per se are neutral in contrast to FS concerning CVD risk or whether adverse effects of this sugar subtype are neutralised or even overcompensated by other beneficial ingredients and/or the plant matrix of intrinsic sugar-rich sources [51].

Some differences are observed between IHD and stroke. Thus, we find a significant non-linear descending association of intrinsic sugars with IHD but not with stroke risk. FS in milk-based drinks and in sauces are only significantly linearly related with incident IHD but not with stroke.

These different associations might be in part explained by different pathophysiologic mechanisms of IHD and stroke. Thus, atherosclerotic plaques in coronary arteries are the most common cause of IHD with plaque rupture and concomitant thrombosis leading to myocardial infarction [52]. In contrast, strokes are caused by a broader range of mechanisms including thrombotic and embolic events and they can be ischemic or haemorrhagic [52]. Further studies need to elucidate which mechanisms contribute to the different associations observed in the current analysis.

Strengths and limitations

The strengths of the current study encompass a prospective cohort design, a large sample size, comprehensive characterisation of participants, a long follow-up period >10 years, systematic analyses of sugar consumption by sugar subtype, and the use of penalised cubic splines to allow non-linear relations. Some limitations of our findings have to be acknowledged. These include potential residual confounding, measurement errors in assessing the exposure variables, as well as the presence of potential confounders, mediators, and further covariates not included in the models which might significantly and independently affect the current results. It should be noted that all consumption data in this study were self-reported and not independently assessed. Participants recruited to the UK Biobank are mostly of white European ancestry and are typically healthier than the overall population [53]. Therefore, our findings may not be generalisable and further research in other populations is warranted.

Conclusions

The association with incident CVD varies depending on the source of the sugars. Thus, FS and FS in treats are related to CVD risk in a J-shaped fashion. FS in beverages, FS in soda/fruit drinks, and to a lesser extent FS in milk-based drinks, FS in tea/coffee, and FS in cereals are significantly linearly associated with incident CVD. Furthermore, FS in solids, FS in juice, FS in toppings, and FS in sauces are significantly related to CVD risk in a U-shaped fashion. In contrast, a significant non-linear descending association of intrinsic sugars with CVD risk is found.

In sensitivity analyses, these relations are more robust for ischemic heart disease as compared to stroke. To improve CVD risk reduction strategies, public health efforts should prioritise the reduction of beverages with an emphasis on soda/fruit drinks when targeting different FS subtypes. Additional prospective studies are needed to investigate the consumption of specific sugar subtypes and their association with other relevant diseases including various types of cancer. In addition, a possible protective effect of fruit juice should be investigated in further studies.

Abbreviations

BMI	Body mass index
CVD	Cardiovascular disease
FS	Free sugars
g/d	Grams per day
HR	Hazard ratio
ICD-10	International classification of disease 10th revision
IHD	Ischemic heart disease
kJ	Kilojoules
%E	Percentage total energy
SD	Standard deviation
WHO	World Health Organization
WHR	Waist-to-hip-ratio

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12937-024-00926-4.

Supplementary Material 1.

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Authors' contributions
S.M.S and A.K. conceived the research. Statistical analyses were performed by S.M.S., A.K., G.E., and M.F. S.M.S. and A.K. prepared the first draft of the manuscript and all figures. All authors revised the manuscript critically for important intellectual content and gave final approval of the version to be submitted. S.M.S. and A.K. are the guarantors of the manuscript and accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Availability of data and materials
The data that support the findings of this study are available from UK Biobank but restrictions apply to the availability of these data, which were used under license for Application 53438, and, therefore, are not publicly available. Bona fide researchers can apply to use the UK Biobank dataset by registering and applying at https://www.ukbiobank.ac.uk/enable-your-research/register .

Declarations

Ethics approval and consent to participate
The UK Biobank study was conducted according to the guidelines of the Declaration of Helsinki and approved by the North West Multicentre Research Ethics Committee (REC reference: 21/NW/0157). Written informed consent was provided by all participants at baseline.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Publisher's Note

3. Discussion

Within the doctoral thesis, the four research gaps mentioned in chapter 1.3 have been addressed through the publications summarised in chapter 2.

3.1 Major conclusions

The following major conclusions can be drawn based on the findings of the present thesis:

1) Wine intake is significantly associated in a U-shaped manner with all-cause, non-cancer, and CVD mortality with the HR-nadir at 20, 21, and 20 g alcohol/day, respectively (publication 1).
2) Non-wine alcoholic beverage intake is associated positively and dose-dependently with all types of mortality studied with the HR-nadir at 0 g alcohol/day for all-cause, cancer, and non-cancer mortality and at 4 g alcohol/day for CVD mortality (publication 1).
3) Coffee consumption is significantly associated with all-cause and non-cancer mortality with the HR nadir at 2 cups coffee/day but not significantly related to cancer and CVD mortality (publication 1).
4) Tea consumption is consistently linked with a decreased risk for all-cause, cancer, non-cancer, and CVD mortality with the HR-nadir ranging from 4 to 8 cups/day (publication 1).
5) Wine intake is significantly associated in a U-shaped fashion with the HR-nadir for incident dementia at 21 g alcohol/day (publication 2).
6) Non-wine alcoholic beverage consumption is significantly and dose-dependently associated with incident dementia with the HR-nadir at 0 g alcohol/day (publication 2).
7) Coffee intake is not significantly related to dementia risk (publication 2).
8) Tea intake is associated in a U-shaped manner with incident dementia with the HR-nadir at 6 cups/day (publication 2).
9) Not controlling for former drinker bias leads to an elevated mortality and dementia risk in non-drinkers, thus, possibly introducing bias (publications 1 and 2).
10) Intake of total FS and IS are significantly associated with dementia risk in a J-shaped fashion with the HR-nadir at 9 and 8 %E, respectively (publication 3).
11) FS in beverages consumption is significantly associated with dementia risk with the HR-nadir at 2 %E (publication 3).
12) FS in solids intake is not associated with incident dementia risk (publication 3).
13) Intake of total FS is associated with CVD risk in a J-shaped fashion, with the HR-nadir at 9 %E, while consumption of IS are associated in a non-linear descending fashion with the HR-nadir at 14 %E (publication 4).

14) FS in beverages consumption is significantly and linearly related to CVD with the HR-nadir at 3 %E (publication 4).
15) FS in solids intake exhibits a significant non-linear and slightly U-shaped relationship with the HR-nadir at 7 %E (publication 4).

3.2 Comparison with other studies and future research

Taking into account the findings of the studies included in this thesis, the following section will outline the next sensible steps for research concerning alcoholic beverages, coffee and tea, FS and their subtypes, as well as the assessment of dietary habits in general (Figure 2).

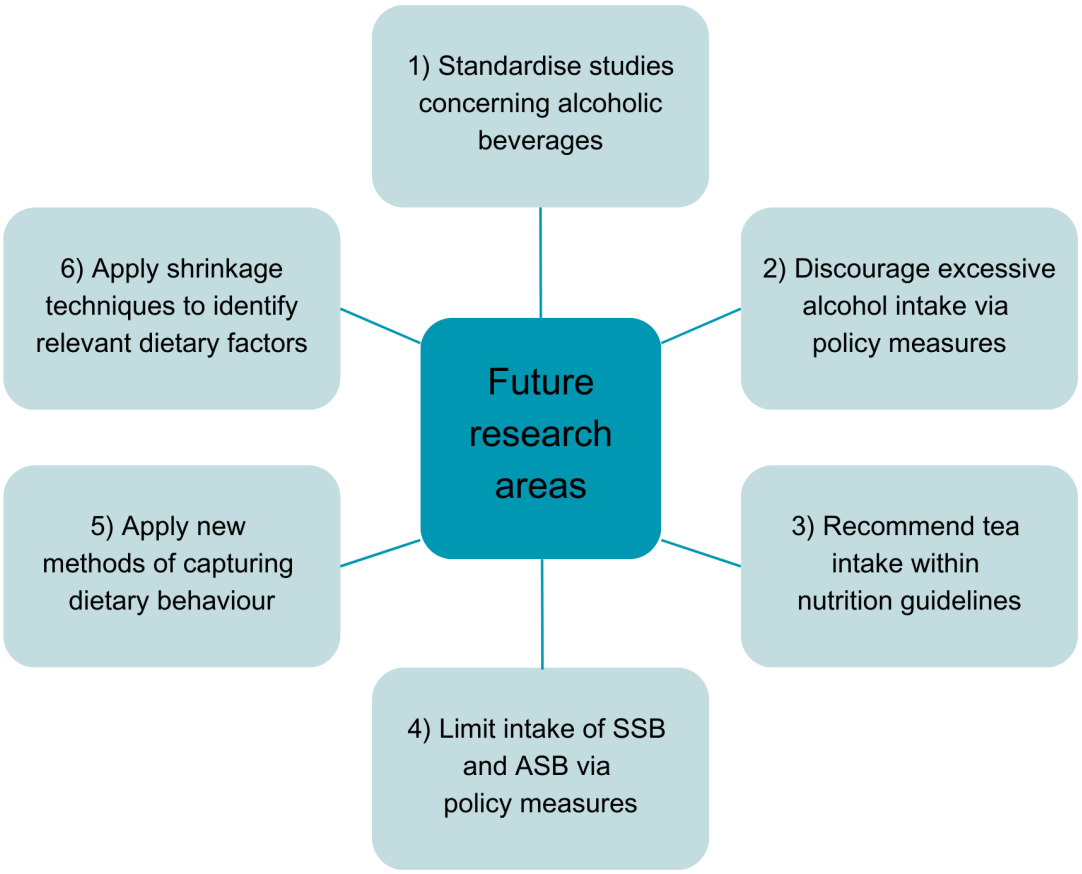

Figure 2. Future research areas. ASB: Artificially sweetened beverages; FS: Free sugars; SSB: Sugar-sweetened beverages (own representation).

1) Standardise studies concerning alcoholic beverages

Firstly, all future studies should adequately **adjust for former drinker bias**. The current analyses (publications 1 and 2) reveal that not controlling for former drinker bias could lead to a distortion of the relation between alcoholic beverage intake and health risks by elevating the mortality risk in non-drinkers. Studies on wine and non-wine alcoholic beverages often do not exclude non-drinkers from the reference group[22,28,118–121]. If these non-drinkers are included in the reference category, a seemingly protective effect of light-to-moderate drinking might simply result from the comparison with already ill participants who have abstained from alcohol for health reasons[29,30]. Thus, future studies on alcohol intake and health outcomes need to

appropriately exclude all non-alcohol drinking participants from the studied cohort at least within sensitivity analyses to ensure results are not biased.

Secondly, all future studies should be **stratified by alcoholic beverage type** allowing for a more differentiated analysis of potential effects. Both studies on alcohol consumption (publications 1 and 2) suggest that wine and non-wine alcoholic beverages considerably vary concerning their associations with mortality and dementia. These findings are well in accordance with publications by other groups indicating that light-to-moderate wine consumption has beneficial health effects[33–36,122,123]. By stratifying for type of alcoholic beverage, it is possible to elucidate which types are most strongly associated with positive and negative health consequences, respectively.

2) Discourage excessive alcohol intake via policy measures

Based on the current results, excessive consumption of alcoholic beverages is associated with increased risk for both all-cause mortality and dementia (publications 1 and 2). One of the most effective strategies to reduce alcohol consumption in general is the implementation of taxes on alcohol. Governments can discourage excessive alcohol consumption, particularly among heavy drinkers, by increasing the retail price of alcoholic beverages through **excise taxes**. According to the WHO[124], 148 countries worldwide are already applying excise taxes on alcohol at the national level, with an excise tax share of 17.2% on beer and 26.5% on spirits in the weighted average price of the most-sold brands[124]. According to data from the European Commission of 2024, Finland, the United Kingdom (UK) and Ireland levy the highest excise taxes with, e.g., a tax of 0.60€ per 330 millilitres beer bottle in Finland and of 0.41€ in the UK[125]. Bulgaria, Germany, Luxembourg, and Spain levy the European Union's minimum tax rate of 0.03€ per bottle[125]. In addition to taxes, another policy aimed at reducing alcohol-related harm is **Minimum Unit Pricing (MUP).** By setting a minimum price/unit of alcohol, countries like Scotland have effectively restricted the sale of very cheap alcohol[126–128]. An evaluation of the impact of MUP shows that it has led to a reduction of alcohol-related deaths by 13.4% in Scotland compared to England as the control area[129]. Another approach is **volumetric taxation**, where alcoholic beverages are taxed based on their alcohol content. This practice has been adopted by Australia, for example, and ensures that stronger alcoholic drinks are taxed at a higher rate, thus discouraging consumption[130]. Research suggests that volumetric taxation can reduce excessive drinking without disproportionately affecting moderate drinkers[131]. To summarise, limiting the consumption of excessive alcohol consumption through targeted measures, such as excise taxes, MUP, and volumetric taxation can be very effective in reducing alcohol-related harm.

3) Recommend tea intake within nutrition guidelines

Tea intake is negatively associated with all the studied outcomes, i.e., all-cause, cancer, non-cancer, and CVD mortality, as well as incident dementia (publications 1 and 2). Thus, of all the beverages analysed, tea provides the most convincing association with beneficial health outcomes. This is confirmed by a recent large umbrella review describing a reduced risks of total mortality, cardiac death, coronary artery disease, stroke, and T2DM with an increment of two to three cups/day[132]. Only very hot tea (55-60°C) should be consumed with caution, since it can increase risk of oesophageal and stomach cancer[132]. In a recent meta-analysis, an inverse association for dementia risk is found for all tea and green tea consumption, but not for oolong tea and black tea[52]. Most national and international guidelines recommend tea primarily for hydration, without addressing the growing evidence of its health benefits. The German Nutrition Society[133], the Dietary Guidelines for Americans (DGA)[71], the British Eatwell Guide[134], and the Australian Dietary Guidelines[135], e.g., consider unsweetened tea to be a healthy fluid option. Currently, there is an ongoing discussion about whether daily tea consumption should be recommended in the next version of the DGA, given its potential to modify the risk of several chronic and degenerative diseases[136].

Based on the current findings of this thesis and the studies summarised above, all national and international guidelines should more thoroughly **address the potential health benefits of tea** beyond its role in hydration, and more actively recommend its consumption.

4) Limit intake of SSB and artificially sweetened beverages (ASB) via policy measures

FS in beverages are positively associated with both risk for dementia and CVD, while the relation for FS in solids is less clear (publications 3 and 4). These findings support the WHO recommendation to focus public health initiatives especially on SSB by introducing taxation to reduce SSB intake[87]. To date, SSB taxes have been introduced in 117 countries and territories worldwide, covering 57% of the world's population[137]. In 2014, the world's first tax on SSB has been introduced in Mexico, one of the largest soft drink markets in the world[138]. This **volumetric tax** of 1 peso/litre on SSB has led to a prize increase of 11% resulting in a 37% decrease in SSB purchases compared to the year before[139]. The UK has implemented a tiered tax on SSB in 2018, the so-called **Soft Drinks Industry Levy** (SDIL)[140]. This tax is a two-tiered levy that taxes producers according to a drink's sugar concentration, with different rates for different sugar levels[140]. The SDIL incentivises sugar reduction in SSB[141]. Within 4 years after its introduction sugar content of SSB has been reduced by 43.7%[142] and sugar consumption from SSB has been reduced by 35.4%[142]. South Africa has been the first African nation to introduce a 10% tax on SSB, known as the **Health Promotion Levy** (HPL), which applies to all sugary drinks except fruit juices[143]. The HPL is based on the sugar content of

beverages, with a rate of 0.021 ZAR/g of sugar when beverages exceed the threshold of 4 g/100 millilitres[143]. The tax has resulted in a 29% reduction in the purchase of SSB, while the sugar content in these beverages decreased by 51%[144].

These data provide compelling evidence that taxing SSB is an effective strategy to reduce consumption across various populations. However, a key concern remains that consumers and industry will replace SSB with ASB. ASB are often exempt from the abovementioned taxes since they contain no sugar. Between 2007 and 2019 the per capita volume of non-sugar sweeteners from beverages replacing sugar in SSB has increased by 36% globally[145]. This substitution may carry its own health risks, as ASB consumption has been linked to several negative outcomes. A large WHO review and meta-analysis reports that a higher artificial sweetener intake is associated with increased body weight, risk of T2DM, CVD, and all-cause mortality[87]. This is confirmed by a recent umbrella review, linking ASB consumption with an elevated risk of obesity, T2DM, hypertension, CVD, and all-cause mortality[146]. Based on these findings, the WHO points out that any short term benefits of using artificial sweeteners, such as weight loss, are outweighed by their adverse health effects[87].

Taking these results, as well as the findings of the present thesis, into consideration, taxes should not only target SSB but also ASB to effectively address public health risks including obesity and its complications.

5) Apply new methods of capturing dietary behaviour

A persistent challenge in nutritional epidemiological studies is the ascertainment of dietary intake[147]. Nowadays, food frequency questionnaires (FFQ) are the most commonly used tools in nutritional epidemiology research due to their cost-effectiveness, simplicity, and capacity to capture dietary behaviour at different time points[148]. The studies included in this thesis have obtained data using either FFQ (publications 1 and 2) or 24HRs (publications 3 and 4). However, FFQ and 24HRs face challenges measuring food choices since they are often subject to bias, e.g., social desirability bias[149]. Furthermore, memory and health status can influence participants' perceptions of the reported intake[150]. Food preferences are an alternative measure of dietary behaviour and play a significant role in shaping eating habits[151]. If foods are not perceived positively in their appearance, smell, texture, or taste, they are unlikely to be eaten[152]. Therefore, food preference questionnaires (FPQ) could serve as a valuable alternative tool for capturing dietary behaviour based on likes and dislikes. In contrast to factual memory-based FFQ, FPQ rely on affective memory, which can be assessed even when factual memory is compromised[153,154]. Furthermore, food preferences are a stable measure over time[155].

The **study of food preferences in terms of their ability to predict health outcomes** is therefore promising, as it can provide valuable information for the assessment of dietary habits going beyond FFQ and 24HR data. It is important to note in this context that FPQ data covering 150 items have recently become available from >180.000 participants of the UK Biobank. Therefore, studying the association of food preferences with important endpoints, including mortality, dementia, and CVD is now possible, and a statistical approach similar to the one used in the current thesis can be applied.

6) Apply shrinkage techniques to identify relevant dietary factors

Various shrinkage techniques have been developed to **identify dietary factors and food preferences most closely linked with important health outcomes**. Among these, **Least Absolute Shrinkage and Selection Operator (LASSO) regression** is used to reduce the number of predictors by shrinking the coefficients to zero, effectively excluding redundant predictors and simplifying the model[156,157]. Thus, it helps to mitigate the effects of multicollinearity, which occurs when predictor variables in a model are highly correlated[156,157]. Using LASSO regression, the relation between dietary intake patterns and childhood obesity is studied using FFQ data from the National Health and Nutrition Examination Survey[158]. This innovative variable shrinkage technique should also be applied to the UK Biobank data to identify the nutritional factors most closely associated with the endpoints studied in the present thesis, namely all-cause and cause-specific mortality, dementia, and CVD.

In conclusion, the findings of the present doctoral thesis, along with the proposed future research will improve our current understanding of dietary factors contributing to decreased life expectancy, as well as dementia and CVD risk. Furthermore, they will improve the scientific basis for policy measures to decrease the consumption of alcoholic beverages, as well as SSB and ASB.

4. Summary

Poor dietary habits are ranked among the top three leading risk factors for mortality and non-communicable diseases worldwide. As various beverages are part of every diet, their potential health consequences need to be investigated. CVD and dementia are of particular concern, as they contribute to a high number of deaths, especially as the global population ages.

Four major research gaps were identified and addressed in this thesis: 1) How is the consumption of wine and non-wine alcoholic beverages, coffee, and tea related to all-cause mortality? 2) How is the intake of wine and non-wine alcoholic beverages, coffee, and tea associated with the risk for incident dementia? 3) How are various types of sugars, i.e., FS and their subtypes, as well as IS, related to dementia risk? 4) How are various types of sugars, i.e., FS and their subtypes, as well as IS, associated with CVD? These research gaps have been addressed in four publications.

In the **first publication**, light to moderate consumption of wine is associated with decreased all-cause, non-cancer and CVD mortality. Non-wine is positively related to all types of mortality. Coffee intake is significantly associated with all-cause and non-cancer mortality, whereas tea intake is associated with a consistently decreased risk of all mortality types studied. In the **second publication**, moderate consumption of wine is related to dementia risk in a U-shaped fashion. In contrast, non-wine intake is positively related to incident dementia. No significant association is found for coffee, while tea intake is related in a U-shaped fashion with dementia risk. In the **third publication**, a linear-shaped association between FS subtype intake and dementia risk is most consistently found for FS in beverages. No significant association is found for FS in solids. In the **fourth publication**, associations of incident CVD depend on the source of the sugars with a linear relation for FS in beverages but different associations for other sources of FS. Relations are more robust for ischemic heart disease as compared to stroke.

Further research should focus on the following six areas: 1) Studies concerning alcoholic beverages should be better standardised especially concerning former drinker bias and alcoholic beverage type. 2) Excessive alcohol intake should be discouraged via policy measures including excise taxes, MUP, and volumetric taxation to reduce the burden of alcohol-related health risks. 3) Tea intake should be recommended within nutrition guidelines to better reflect data on its health-promoting effects. 4) Intake of SSB and ASB should be limited through policy measures to reduce SSB- and ASB-mediated negative health outcomes. 5) New methods of assessing diets such as FPQ should be applied to provide a more comprehensive capture of dietary intake. 6) Shrinkage techniques like LASSO regression should be applied to identify the dietary factors most closely linked with important health outcomes.

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6. Further publications

1. Kaiser, A., **Schaefer, S. M.**, Behrendt, I., Eichner, G., & Fasshauer, M. (2023). Association of all-cause mortality with sugar intake from different sources in the prospective cohort of UK Biobank participants. Br J Nutr., 130(2), 294-303.

2. Kaiser, A., **Schaefer, S. M.**, Behrendt, I., Eichner, G., & Fasshauer, M. (2023). Association of sugar intake from different sources with incident depression in the prospective cohort of UK Biobank participants. Eur J Nutr, 62(2), 727-738.

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7. Declaration

Declaration in accordance with the Doctoral Regulations of the Faculty 09 in the version of 29.05.2019 § 17 (2)

“I declare that the doctoral thesis here submitted is entirely my own work, written without any unauthorised help by a third party and solely with the assistance referred to in the thesis. I have indicated in the text those texts that have been quoted from already published sources, either verbatim or by analogy and all statements based on verbally conveyed information. During the research carried out by me and referred to in the doctoral thesis, I have at all times followed the principles of good scholarly practice as defined in the Statute of Justus Liebig University Giessen for Ensuring of Good Academic Practice."

Giessen, 27.11.2024

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Sylva Mareike Schäfer

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9. Appendix

Appendix A Supplementary Material:

Association of alcohol types, coffee and tea intake with mortality: prospective cohort study of UK Biobank participants.

Schaefer, S. M., Kaiser, A., Behrendt, I., Eichner, G., & Fasshauer, M. (2023). Association of alcohol types, coffee and tea intake with mortality: prospective cohort study of UK Biobank participants. British Journal of Nutrition, 129(1), 115-125.

Appendix B Supplementary Material:

Association of Alcohol Types, Coffee, and Tea Intake with Risk of Dementia: Prospective Cohort Study of UK Biobank Participants.

Schaefer, S. M., Kaiser, A., Behrendt, I., Eichner, G., & Fasshauer, M. (2022). Association of alcohol types, coffee, and tea intake with risk of dementia: prospective cohort study of UK Biobank participants. Brain Sciences, 12(3), 360.

Appendix C Supplementary Material:

Association of sugar intake from different sources with incident dementia in the prospective cohort of UK Biobank participants.

Schaefer, S. M., Kaiser, A., Eichner, G., & Fasshauer, M. (2023). Association of sugar intake from different sources with incident dementia in the prospective cohort of UK Biobank participants. Nutrition Journal, 22(1), 42.

Appendix D Supplementary Material:

Association of sugar intake from different sources with cardiovascular disease incidence in the prospective cohort of UK Biobank participants.

Schaefer, S. M., Kaiser, A., Eichner, G., & Fasshauer, M. (2024). Association of sugar intake from different sources with cardiovascular disease incidence in the prospective cohort of UK Biobank participants. Nutrition Journal, 23(1), 22.

Appendix A

Supplementary Material:

Association of alcohol types, coffee and tea intake with mortality: prospective cohort study of UK Biobank participants.

Schaefer, S. M., Kaiser, A., Behrendt, I., Eichner, G., & Fasshauer, M. (2023). Association of alcohol types, coffee and tea intake with mortality: prospective cohort study of UK Biobank participants. British Journal of Nutrition, 129(1), 115-125.

Online Supplementary Material

British Journal of Nutrition

Association of alcohol types, coffee and tea intake with mortality: prospective cohort study of UK Biobank participants

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Supplementary Table 1 Baseline characteristics of the UK Biobank cohort depending on sex[1]

Parameter	All (n=354386)	Female (n=179676)	Male (n=174710)
Wine intake (g/d)	5.7 (1.4, 11.4)	5.7 (2.9, 11.4)	5.7 (0.7, 11.4)
Non-wine intake (g/d)	4.3 (0.0, 12.9)	1.4 (0.0, 4.3)	11.4 (4.3, 22.9)
Coffee intake (cups/d)	2.0 (0.5, 3.0)	2.0 (0.5, 3.0)	2.0 (1.0, 3.0)
Tea intake (cups/d)	3.0 (1.0, 5.0)	3.0 (1.0, 5.0)	3.0 (1.0, 5.0)
Age (years)	58 (50, 63)	57 (50, 63)	58 (50, 64)
Smoking status			
- Never	187367 (52.9)	102908 (57.3)	84459 (48.3)
- Previous	131857 (37.2)	61792 (34.4)	70065 (40.1)
- Current	35162 (9.9)	14976 (8.3)	20816 (11.6)
AHI (£)			
- <18000	56502 (15.9)	29534 (16.4)	26968 (15.4)
- 18000-30999	76979 (21.7)	39204 (21.8)	37775 (21.6)
- 31000-51999	85496 (24.1)	41385 (23.0)	44111 (25.2)
- 52000-99999	71907 (20.3)	33229 (18.5)	38678 (22.1)
- ≥100000	20172 (5.7)	9127 (5.1)	11045 (6.3)
- Unknown	43330 (12.2)	27197 (15.1)	16133 (9.2)
Ethnicity			
- White	342689 (96.7)	174006 (96.8)	168683 (96.6)
- Mixed, Asian, Black, Chinese, Other	11697 (3.3)	5670 (3.2)	6027 (3.4)
OHR			
- Excellent	63715 (18.0)	34584 (19.2)	29131 (16.7)
- Good	212997 (60.1)	111268 (61.9)	101729 (58.2)
- Fair	66994 (18.9)	29529 (16.4)	37465 (21.4)
- Poor	10680 (3.0)	4295 (2.4)	6385 (3.7)
PA (MET-min/week)	1804 (845, 3546)	1764 (838, 3380)	1862 (850, 3732)
Percentage body fat	30.2 (24.7, 36.7)	36.2 (31.6, 40.7)	25.3 (21.5, 28.9)

[1]Categorical variables are presented as number (percentage) and continuous variables as median (Q1, Q3). AHI, Annual household income; MET, Metabolic equivalent of task; OHR, Overall health rating; PA, Physical activity; Q, Quartile.

Supplementary Table 2 Association of beverage intake with cancer mortality[1]

Beverage	Primary cohort									Cohort S1			Cohort S2		
	P^{lin} / $P^{non-lin}$	nadir	HR^0	HR at intake						P^{lin} / $P^{non-lin}$	nadir	HR^0	P^{lin} / $P^{non-lin}$	nadir	HR^0
Wine				**10**	**20**	**30**	**40**	**50**	**60**						
All	0.2978 / 0.2558	14	1.05 (1.02, 1.08)	1.00 (0.98, 1.02)	1.00 (0.97, 1.04)	1.02 (0.96, 1.09)	1.04 (0.96, 1.14)	1.06 (0.94, 1.20)	1.08 (0.91, 1.28)	0.2616 / 0.0600	14	1.07 (1.04, 1.10)	0.3109 / **0.0005**	16	1.11 (1.08, 1.13)
Female	0.6086 / 0.7113	4	1.00 (0.95, 1.05)	1.00 (0.97, 1.03)	1.02 (0.96, 1.07)	1.03 (0.93, 1.14)	1.03 (0.88, 1.21)	1.01 (0.79, 1.30)	0.99 (0.69, 1.40)	0.5727 / 0.5197	11	1.04 (1.00, 1.09)	0.6225 / 0.1137	14	1.08 (1.04, 1.12)
Male	0.3748 / 0.0841	17	1.09 (1.06, 1.13)	1.01 (0.98, 1.04)	1.00 (0.95, 1.05)	1.02 (0.95, 1.10)	1.05 (0.95, 1.17)	1.09 (0.94, 1.26)	1.12 (0.93, 1.36)	0.3464 / 0.0595	17	1.10 (1.06, 1.13)	0.3832 / **0.0035**	17	1.13 (1.10, 1.16)
Non-Wine				**10**	**20**	**30**	**40**	**50**	**60**						
All	**<0.0001** / 0.0610	0	1.00 (0.98, 1.02)	1.02 (1.00, 1.04)	1.06 (1.03, 1.10)	1.13 (1.08, 1.18)	1.21 (1.14, 1.28)	1.30 (1.22, 1.39)	1.40 (1.30, 1.52)	**<0.0001** / 0.0602	1	1.00 (0.98, 1.02)	**<0.0001** / 0.0537	11	1.02 (1.00, 1.04)
Female	**0.0017** / 0.1802	0	1.00 (0.98, 1.02)	1.04 (0.99, 1.10)	1.14 (1.05, 1.25)	1.26 (1.10, 1.44)	1.31 (1.08, 1.58)	1.30 (0.99, 1.70)	1.36 (0.97, 1.90)	**0.0020** / 0.3648	3	1.00 (0.98, 1.03)	**0.0045** / 0.5583	6	1.02 (1.00, 1.04)
Male	**<0.0001** / 0.0728	3	1.00 (0.96, 1.04)	1.01 (0.99, 1.02)	1.03 (1.00, 1.07)	1.09 (1.05, 1.14)	1.18 (1.11, 1.24)	1.28 (1.20, 1.36)	1.38 (1.28, 1.49)	**<0.0001** / 0.0530	6	1.00 (0.96, 1.04)	**<0.0001** / **0.0182**	14	1.04 (1.01, 1.08)
Coffee				**2**	**4**	**6**	**8**	**10**	**12**						
All	0.3076 / 0.4262	2	1.04 (1.00, 1.07)	1.00 (0.98, 1.02)	1.02 (0.99, 1.06)	1.03 (0.97, 1.10)	1.07 (0.96, 1.18)	1.13 (0.96, 1.32)	1.14 (0.84, 1.54)	0.3215 / 0.3343	2	1.04 (1.01, 1.08)	0.2519 / 0.2044	2	1.04 (1.01, 1.08)

Female	0.1309 / 0.3243	1	1.01 (0.96, 1.07)	1.00 (0.96, 1.04)	1.00 (0.95, 1.06)	1.04 (0.94, 1.15)	1.18 (1.00, 1.40)	1.36 (1.05, 1.77)	1.47 (0.89, 2.43)	0.1352 / 0.2944	2	1.02 (0.97, 1.07)	0.0973 / 0.3848	2	1.02 (0.97, 1.07)
Male	0.7369 / 0.4809	2	1.05 (1.00, 1.10)	1.00 (0.97, 1.03)	1.04 (0.99, 1.08)	1.03 (0.96, 1.12)	1.01 (0.89, 1.16)	1.03 (0.84, 1.26)	1.01 (0.69, 1.48)	0.7428 / 0.3688	2	1.05 (1.00, 1.10)	0.7361 / 0.3034	2	1.06 (1.01, 1.10)
Tea				**2**	**4**	**6**	**8**	**10**	**12**						
All	0.9086 / **0.0009**	4	1.12 (1.07, 1.17)	1.02 (1.00, 1.05)	1.00 (0.98, 1.02)	1.02 (0.99, 1.05)	1.05 (1.00, 1.11)	1.09 (1.01, 1.19)	1.12 (1.00, 1.27)	0.9551 / **0.0003**	4	1.12 (1.08, 1.17)	0.9035 / <**0.0001**	4	1.12 (1.08, 1.17)
Female	0.7112 / **0.0409**	3	1.13 (1.06, 1.20)	1.02 (0.98, 1.06)	1.00 (0.97, 1.03)	1.01 (0.96, 1.06)	1.03 (0.94, 1.12)	1.08 (0.94, 1.24)	1.12 (0.92, 1.37)	0.7568 / **0.0089**	3	1.15 (1.08, 1.22)	0.8577 / **0.0006**	4	1.14 (1.08, 1.21)
Male	0.8692 / **0.0393**	4	1.11 (1.05, 1.17)	1.02 (0.99, 1.05)	1.00 (0.97, 1.03)	1.02 (0.98, 1.07)	1.07 (0.99, 1.14)	1.10 (0.99, 1.21)	1.12 (0.97, 1.30)	0.8167 / **0.0377**	4	1.10 (1.04, 1.16)	0.9127 / **0.0358**	4	1.10 (1.05, 1.16)

[1]Linear (p^{lin}) and non-linear ($p^{non-lin}$) p-values for associations, the nadir, as well as HRs (95% confidence intervals) at 0 g alcohol/d or cups/d (HR^0) are given for wine, non-wine, coffee, and tea in the primary cohort, cohort S1, and cohort S2. In addition, HRs (95% confidence intervals) at defined intake levels are shown for the primary cohort. For wine and non-wine, consumption is given as g alcohol/d. For coffee and tea, intake is given as cups/d. Covariates not fulfilling the proportional hazard assumption (primary cohort – all participants: OHR; males: age, OHR; cohort S1 – all participants: OHR; males: age, OHR; cohort S2 – all participants: OHR; males: age, OHR) are stratified.

Supplementary Table 3 Association of beverage intake with non-cancer mortality[1]

Beverage	Primary cohort									Cohort S1			Cohort S2		
	P^{lin} / $P^{non\text{-}lin}$	nadir	HR^0	HR at intake						P^{lin} / $P^{non\text{-}lin}$	nadir	HR^0	P^{lin} / $P^{non\text{-}lin}$	nadir	HR^0
Wine				**10**	**20**	**30**	**40**	**50**	**60**						
All	**0.0023** / **<0.0001**	21	1.21 (1.18, 1.25)	1.05 (1.03, 1.08)	1.00 (0.96, 1.04)	1.02 (0.95, 1.09)	1.09 (0.99, 1.20)	1.22 (1.07, 1.38)	1.39 (1.18, 1.63)	**0.0015** / **<0.0001**	21	1.27 (1.24, 1.31)	**0.0075** / **<0.0001**	21	1.35 (1.31, 1.38)
Female	**0.0148** / **<0.0001**	21	1.25 (1.17, 1.33)	1.09 (1.05, 1.13)	1.00 (0.93, 1.08)	1.04 (0.91, 1.20)	1.20 (0.98, 1.47)	1.52 (1.15, 2.00)	2.09 (1.47, 2.96)	**0.0103** / **<0.0001**	20	1.42 (1.35, 1.49)	**0.0162** / **<0.0001**	20	1.53 (1.46, 1.60)
Male	**0.0228** / **<0.0001**	23	1.19 (1.15, 1.23)	1.04 (1.01, 1.07)	1.00 (0.96, 1.05)	1.01 (0.94, 1.09)	1.06 (0.95, 1.18)	1.15 (0.99, 1.32)	1.25 (1.04, 1.50)	**0.0226** / **<0.0001**	21	1.21 (1.17, 1.25)	**0.0400** / **<0.0001**	21	1.28 (1.24, 1.32)
Non-Wine				**10**	**20**	**30**	**40**	**50**	**60**						
All	**<0.0001** / **0.0066**	0	1.00 (0.98, 1.03)	1.01 (0.99, 1.03)	1.05 (1.01, 1.09)	1.10 (1.05, 1.16)	1.18 (1.12, 1.25)	1.28 (1.20, 1.36)	1.38 (1.29, 1.49)	**<0.0001** / **0.0026**	10	1.02 (0.99, 1.04)	**<0.0001** / **<0.0001**	17	1.11 (1.09, 1.13)
Female	**<0.0001** / **0.0190**	0	1.00 (0.97, 1.03)	1.09 (1.03, 1.16)	1.23 (1.10, 1.36)	1.41 (1.22, 1.64)	1.62 (1.33, 1.98)	1.84 (1.42, 2.39)	2.12 (1.55, 2.90)	**<0.0001** / 0.2634	4	1.01 (0.98, 1.03)	**<0.0001** / 0.3807	8	1.04 (1.02, 1.07)
Male	**<0.0001** / **0.0031**	12	1.02 (0.98, 1.07)	1.00 (0.98, 1.02)	1.01 (0.98, 1.05)	1.06 (1.02, 1.11)	1.14 (1.08, 1.20)	1.24 (1.16, 1.32)	1.35 (1.25, 1.45)	**<0.0001** / **0.0006**	14	1.04 (1.00, 1.08)	**<0.0001** / **<0.0001**	19	1.14 (1.11, 1.18)
Coffee				**2**	**4**	**6**	**8**	**10**	**12**						
All	0.5153 / **0.0058**	2	1.08 (1.04, 1.13)	1.00 (0.98, 1.03)	1.03 (0.99, 1.07)	1.04 (0.97, 1.11)	1.02 (0.92, 1.14)	1.11 (0.94, 1.30)	1.36, 1.04, 1.79)	0.4395 / **0.0020**	2	1.09 (1.06, 1.13)	0.4607 / **0.0014**	2	1.09 (1.05, 1.12)

Female	0.1246 / 0.1786	8	1.30 (1.21, 1.39)	1.15 (1.10, 1.20)	1.16 (1.07, 1.25)	1.10 (0.97, 1.26)	1.00 (0.79, 1.26)	0.99 (0.68, 1.43)	1.07 (0.53, 2.16)	0.0531 / **0.0170**	8	1.31 (1.24, 1.40)	0.1052 / **0.0297**	8	1.28 (1.21, 1.35)
Male	0.0949 / **0.0444**	2	1.07 (1.02, 1.12)	1.00 (0.97, 1.03)	1.04 (1.00, 1.09)	1.07 (0.99, 1.15)	1.08 (0.95, 1.21)	1.18 (0.99, 1.41)	1.46 (1.09, 1.96)	**0.0312** / 0.0562	2	1.06 (1.01, 1.10)	**0.0194** / **0.0319**	2	1.07 (1.02, 1.11)
Tea				**2**	**4**	**6**	**8**	**10**	**12**						
All	**0.0029** / **<0.0001**	5	1.24 (1.19, 1.30)	1.07 (1.04, 1.09)	1.00 (0.98, 1.03)	1.00 (0.97, 1.04)	1.01 (0.95, 1.07)	1.02 (0.93, 1.11)	1.05 (0.93, 1.19)	**0.0012** / **<0.0001**	9	1.25 (1.20, 1.30)	**0.0107** / <**0.0001**	5	1.22 (1.18, 1.27)
Female	**0.0120** / **0.0005**	9	1.34 (1.24, 1.46)	1.10 (1.05, 1.15)	1.04 (1.00, 1.08)	1.03 (0.97, 1.10)	1.00 (0.89, 1.13)	1.01 (0.84, 1.22)	1.09 (0.83, 1.41)	**0.0009** / **0.0006**	9	1.41 (1.31, 1.52)	**0.0015** / **0.0016**	9	1.34 (1.26, 1.44)
Male	**0.0424** / **<0.0001**	5	1.23 (1.17, 1.30)	1.07 (1.04, 1.10)	1.01 (0.98, 1.03)	1.00 (0.96, 1.05)	1.02 (0.95, 1.09)	1.03 (0.93, 1.14)	1.05 (0.91, 1.21)	0.0765 / **<0.0001**	5	1.21 (1.15, 1.28)	0.3020 / **<0.0001**	5	1.21 (1.15, 1.27)

[1]Linear (p^{lin}) and non-linear ($p^{non-lin}$) p-values for associations, the nadir, as well as HRs (95% confidence intervals) at 0 g alcohol/d or cups/d (HR^0) are given for wine, non-wine, coffee, and tea in the primary cohort, cohort S1, and cohort S2. In addition, HRs (95% confidence intervals) at defined intake levels are shown for the primary cohort. For wine and non-wine, consumption is given as g alcohol/d. For coffee and tea, intake is given as cups/d. Covariates not fulfilling the proportional hazard assumption (primary cohort – all participants: age, OHR, percentage body fat, sex, smoking status; females: age, percentage body fat; males: age, OHR, percentage body fat, smoking status; cohort S1 – all participants: age, OHR, percentage body fat, sex, smoking status; females: age, percentage body fat; males: age, OHR, percentage body fat, smoking status; cohort S2 – all participants: age, OHR, PA, percentage body fat, sex, smoking status; females: age, percentage body fat, smoking status; males: age, OHR, percentage body fat, smoking status) are stratified.

Supplementary Table 4 Association of beverage intake with CVD mortality[1]

Beverage	Primary cohort									Cohort S1			Cohort S2		
	P^{lin} / $P^{non\text{-}lin}$	nadir	HR^0	HR at intake						P^{lin} / $P^{non\text{-}lin}$	nadir	HR^0	P^{lin} / $P^{non\text{-}lin}$	nadir	HR^0
Wine				**10**	**20**	**30**	**40**	**50**	**60**						
All	0.7612 / **0.0004**	20	1.22 (1.16, 1.28)	1.05 (1.01, 1.08)	1.00 (0.94, 1.06)	1.03 (0.93, 1.15)	1.09 (0.93, 1.27)	1.12 (0.91, 1.38)	1.14 (0.86, 1.50)	0.6862 / **<0.0001**	19	1.28 (1.22, 1.33)	0.7552 / **<0.0001**	19	1.32 (1.27, 1.37)
Female	0.4298 / **0.0439**	19	1.31 (1.17, 1.46)	1.09 (1.02, 1.16)	1.00 (0.88, 1.15)	1.13 (0.88, 1.45)	1.36 (0.95, 1.96)	1.63 (0.97, 2.74)	1.95 (0.99, 3.83)	0.3496 / **0.0003**	19	1.50 (1.36, 1.64)	0.3235 / **<0.0001**	19	1.51 (1.40, 1.64)
Male	0.9431 / **0.0031**	21	1.20 (1.14 1.26)	1.04 (1.00, 1.08)	1.00 (0.93, 1.08)	1.01 (0.90, 1.14)	1.03 (0.87, 1.22)	1.04 (0.83, 1.30)	1.02 (0.76, 1.39)	0.9504 / **0.0011**	21	1.21 (1.15, 1.27)	0.9580 / **<0.0001**	20	1.25 (1.19, 1.30)
Non-Wine				**10**	**20**	**30**	**40**	**50**	**60**						
All	**<0.0001** / 0.5215	4	1.00 (0.96, 1.04)	1.00 (0.97, 1.04)	1.03 (0.97, 1.09)	1.08 (1.01, 1.16)	1.15 (1.05, 1.25)	1.23 (1.11, 1.35)	1.30 (1.16, 1.46)	**<0.0001** / 0.4402	12	1.03 (0.99, 1.06)	**<0.0001** / 0.1075	16	1.08 (1.05, 1.11)
Female	0.3146 / 0.8300	9	1.03 (0.97, 1.09)	1.00 (0.89, 1.12)	1.05 (0.86, 1.28)	1.18 (0.88, 1.59)	1.30 (0.87, 1.94)	1.34 (0.76, 2.35)	1.33 (0.65, 2.71)	0.3545 / 0.5315	13	1.13 (1.08, 1.18)	0.3239 / 0.4776	13	1.14 (1.09, 1.19)
Male	**<0.0001** / 0.4663	6	1.00 (0.94, 1.07)	1.00 (0.98, 1.03)	1.02 (0.98, 1.07)	1.07 (1.01, 1.14)	1.14 (1.06, 1.24)	1.23 (1.12, 1.35)	1.32 (1.18, 1.47)	**<0.0001** / 0.4045	11	1.02 (0.96, 1.08)	**<0.0001** / 0.1224	17	1.08 (1.03, 1.13)
Coffee				**2**	**4**	**6**	**8**	**10**	**12**						
All	0.4841 / 0.2896	2	1.07 (1.01, 1.14)	1.00 (0.96, 1.04)	1.03 (0.97, 1.10)	1.08 (0.98, 1.19)	1.07 (0.90, 1.26)	1.13 (0.88, 1.46)	1.27 (0.81, 1.98)	0.3571 / 0.1904	2	1.08 (1.02, 1.14)	0.3173 / 0.3403	2	1.06 (1.00, 1.11)

Female	0.1988 / 0.2331	8	1.35 (1.19, 1.52)	1.11 (1.03, 1.21)	1.09 (0.95, 1.24)	1.07 (0.85, 1.35)	1.00 (0.67, 1.50)	0.97 (0.48, 1.93)	0.80 (0.20, 3.26)	0.3151 / 0.0731	3	1.26 (1.13, 1.40)	0.5401 / 0.3851	8	1.21 (1.10, 1.33)
Male	0.1376 / 0.6148	2	1.03 (0.96, 1.11)	1.00 (0.96, 1.05)	1.05 (0.98, 1.12)	1.11 (1.00, 1.24)	1.11 (0.93, 1.34)	1.18 (0.90, 1.55)	1.35 (0.85, 2.16)	0.0872 / 0.5759	2	1.02 (0.95, 1.09)	0.0941 / 0.5722	2	1.02 (0.96, 1.09)
Tea				**2**	**4**	**6**	**8**	**10**	**12**						
All	0.3439 / **0.0016**	8	1.20 (1.12, 1.29)	1.06 (1.02, 1.10)	1.01 (0.98, 1.05)	1.01 (0.96, 1.07)	1.00 (0.91, 1.10)	1.01 (0.88, 1.16)	1.08 (0.89, 1.30)	0.2289 / **0.0011**	9	1.22 (1.14, 1.30)	0.2187 / **0.0003**	4	1.21 (1.13, 1.28)
Female	**0.0370** / 0.3050	10	1.55 (1.34, 1.78)	1.35 (1.25, 1.46)	1.29 (1.20, 1.39)	1.20 (1.07, 1.35)	1.05 (0.86, 1.30)	1.00 (0.72, 1.39)	1.07 (0.67, 1.73)	**0.0150** / 0.2592	10	1.63 (1.44, 1.86)	**0.0371** / 0.3498	10	1.38 (1.23, 1.55)
Male	0.9355 / **0.0055**	4	1.18 (1.09, 1.28)	1.04 (1.00, 1.09)	1.00 (0.96, 1.04)	1.02 (0.96, 1.08)	1.04 (0.94, 1.15)	1.07 (0.92, 1.24)	1.13 (0.92, 1.40)	0.9382 / **0.0036**	4	1.19 (1.10, 1.29)	0.9312 / **0.0007**	4	1.21 (1.13, 1.31)

[1]Linear (p^{lin}) and non-linear ($p^{non-lin}$) p-values for associations, the nadir, as well as HRs (95% confidence intervals) at 0 g alcohol/d or cups/d (HR^0) are given for wine, non-wine, coffee, and tea in the primary cohort, cohort S1, and cohort S2. In addition, HRs (95% confidence intervals) at defined intake levels are shown for the primary cohort. For wine and non-wine, consumption is given as g alcohol/d. For coffee and tea, intake is given as cups/d. Covariates not fulfilling the proportional hazard assumption (primary cohort – all participants: age, percentage body fat, sex; cohort S1 – all participants: age, percentage body fat, sex; cohort S2 – all participants: age, percentage body fat, sex, smoking status; males: OHR) are stratified.

Appendix B

Supplementary Material:

Association of Alcohol Types, Coffee, and Tea Intake with Risk of Dementia: Prospective Cohort Study of UK Biobank Participants.

Schaefer, S. M., Kaiser, A., Eichner, G., & Fasshauer M. (2022). Association of Alcohol Types, Coffee, and Tea Intake with Risk of Dementia: Prospective Cohort Study of UK Biobank Participants. Brain Sciences, 12(3), 360.

Online Supplementary Material

Association of alcohol types, coffee, and tea intake with risk of dementia: prospective cohort study of UK Biobank participants

Schaefer SM et al.

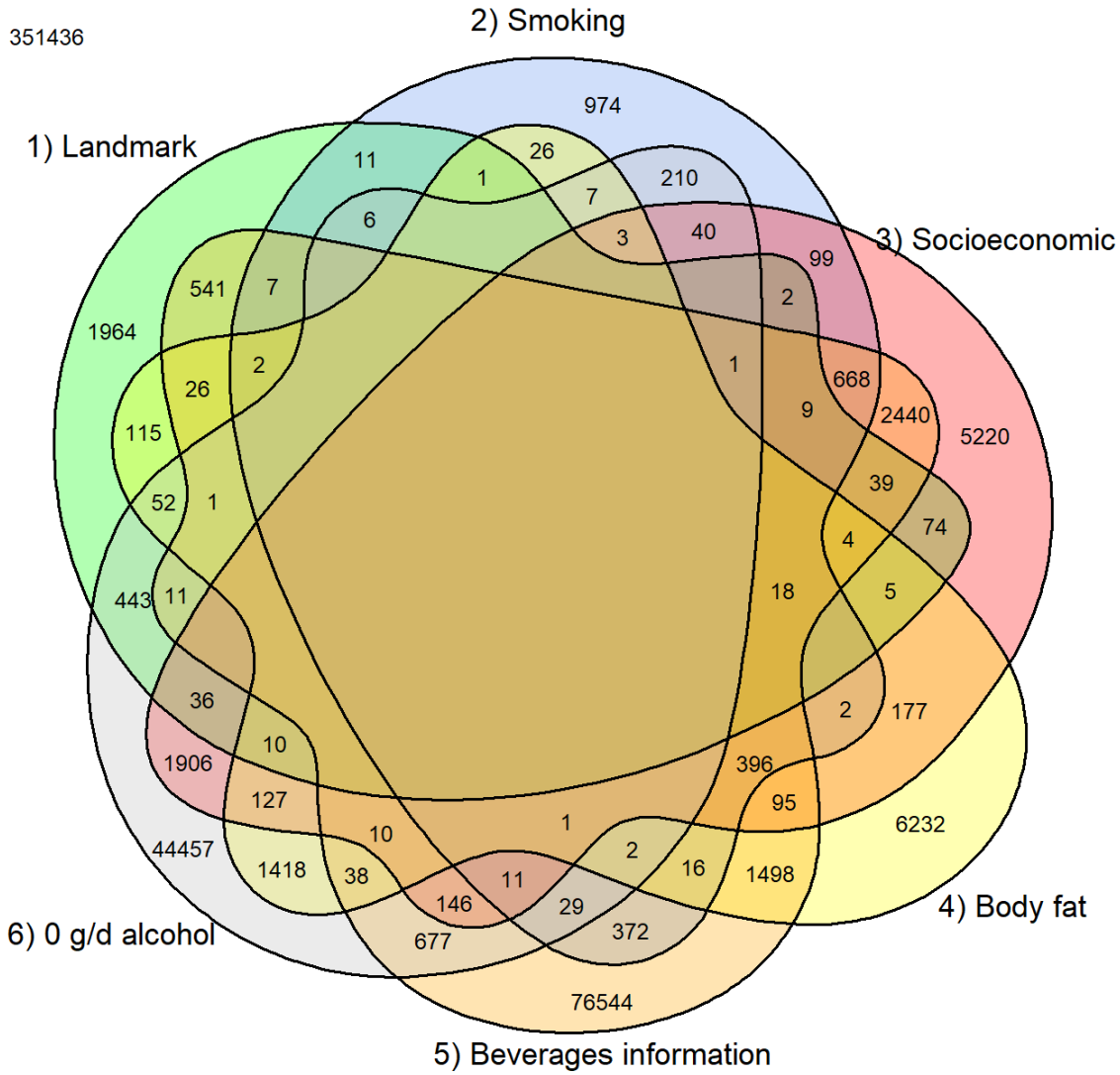

Figure S1. Venn diagram depicting number of participants excluded by six exclusion criteria (primary cohort). The number of participants for which exclusion criteria apply is depicted as colored shape and labelled as follows: Participants with 1) pre-existing dementia at baseline and incident dementia within 2 years after baseline in green, 2) missing smoking status in blue, 3) missing socioeconomic factors (i.e., annual household income (AHI), ethnicity, highest qualification, and/or overall health rating (OHR)) in red, 4) missing percentage body fat in yellow, 5) either missing information on beverage intake or being in the upper 0.1 % of alcohol, coffee, or tea consumption in orange, 6) present alcohol intake of 0 g alcohol/d in grey.

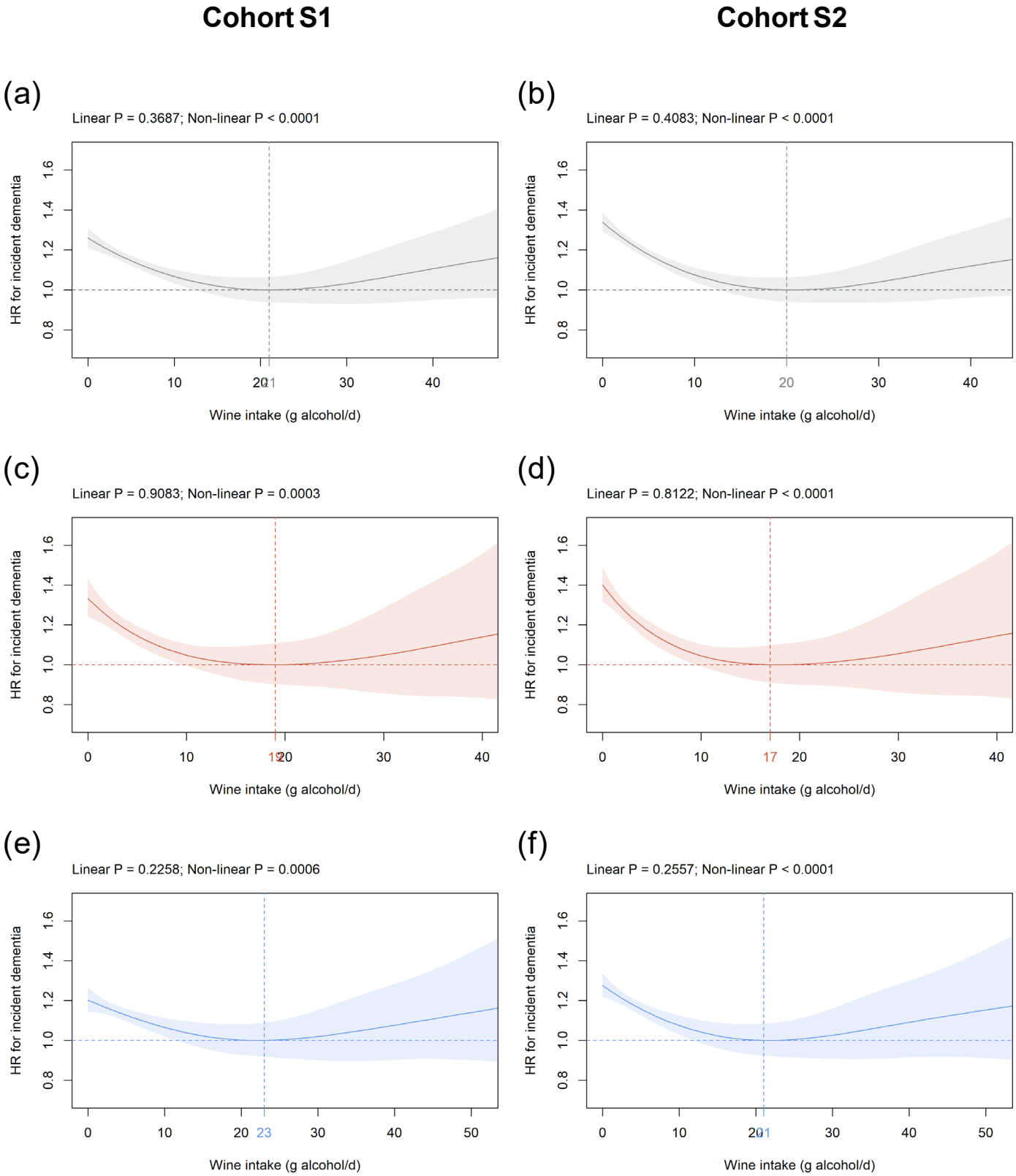

Figure S2. Association of wine intake (g alcohol/d) in (a), (b) the total cohort, (c), (d) females, and (e), (f) males with dementia risk in (a), (c), (e) cohort S1 and (b), (d), (f) cohort S2. Data are adjusted for sex (all participants only), age, AHI, ethnicity, highest qualification, OHR, PA, percentage body fat, and smoking status. Additionally, wine, non-wine, coffee, and tea intake are mutually adjusted (e.g., wine intake is additionally adjusted for non-wine, coffee, and tea intake) as summarized in the Materials and Methods section. Covariates not fulfilling the proportional hazard assumption are stratified. The nadir is indicated in grey (total cohort), red (female), and blue (male). AHI, Annual household income; HR, Hazard ratio; OHR, Overall health rating; PA, Physical activity.

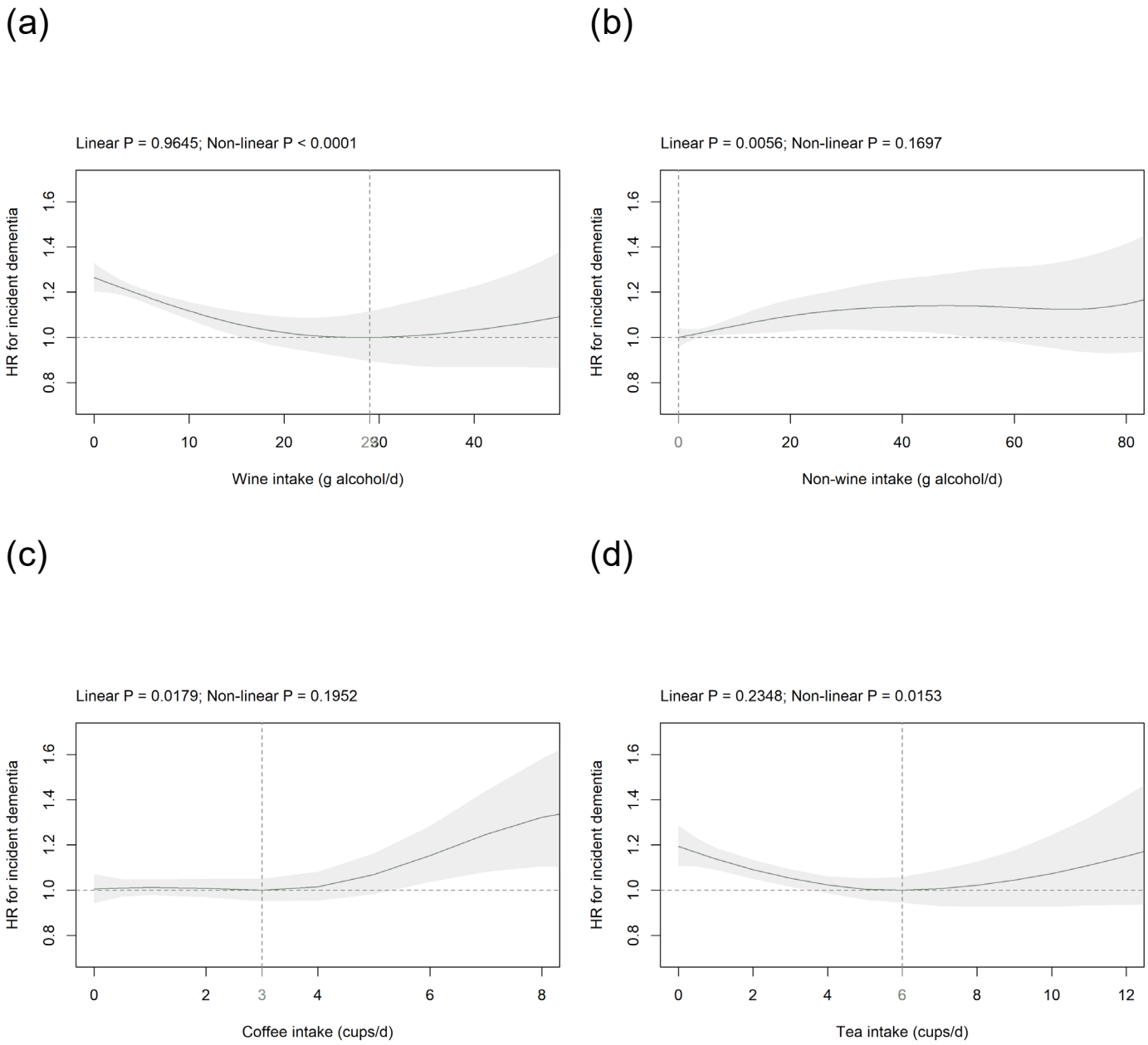

Figure S3. Association of (a) wine intake (g alcohol/d), (b) non-wine intake (g alcohol/d), (c) coffee intake (cups/d), and (d) tea intake (cups/d) with dementia risk in all participants after removal of ICD code G31. Data are adjusted and presented as indicated in Supplementary Figure S2.

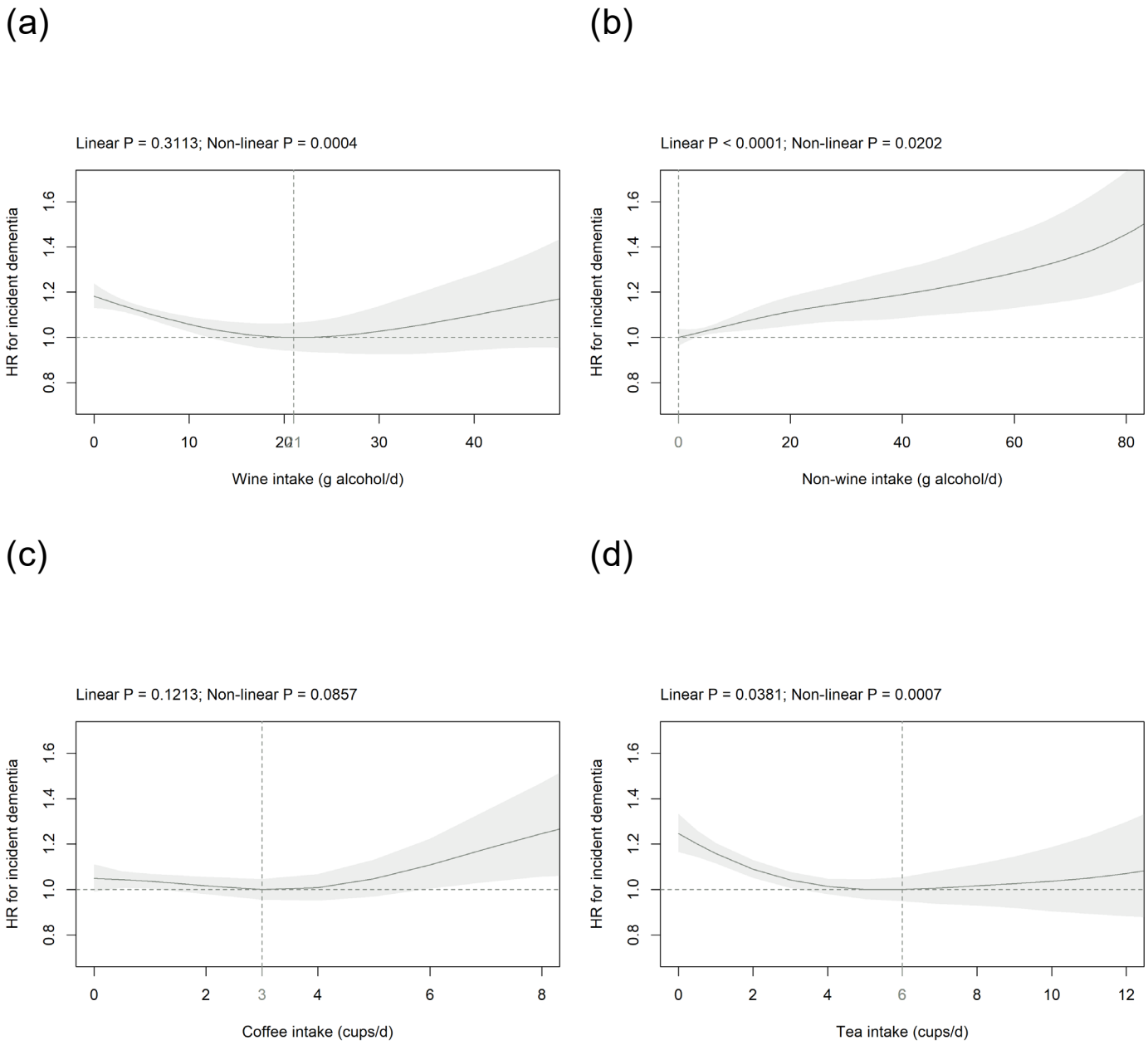

Figure S4. Association of (a) wine intake (g alcohol/d), (b) non-wine intake (g alcohol/d), (c) coffee intake (cups/d), and (d) tea intake (cups/d) with dementia risk in all participants with age and percentage body fat included as continuous instead of categorical variables. Data are adjusted and presented as indicated in Supplementary Figure S2.

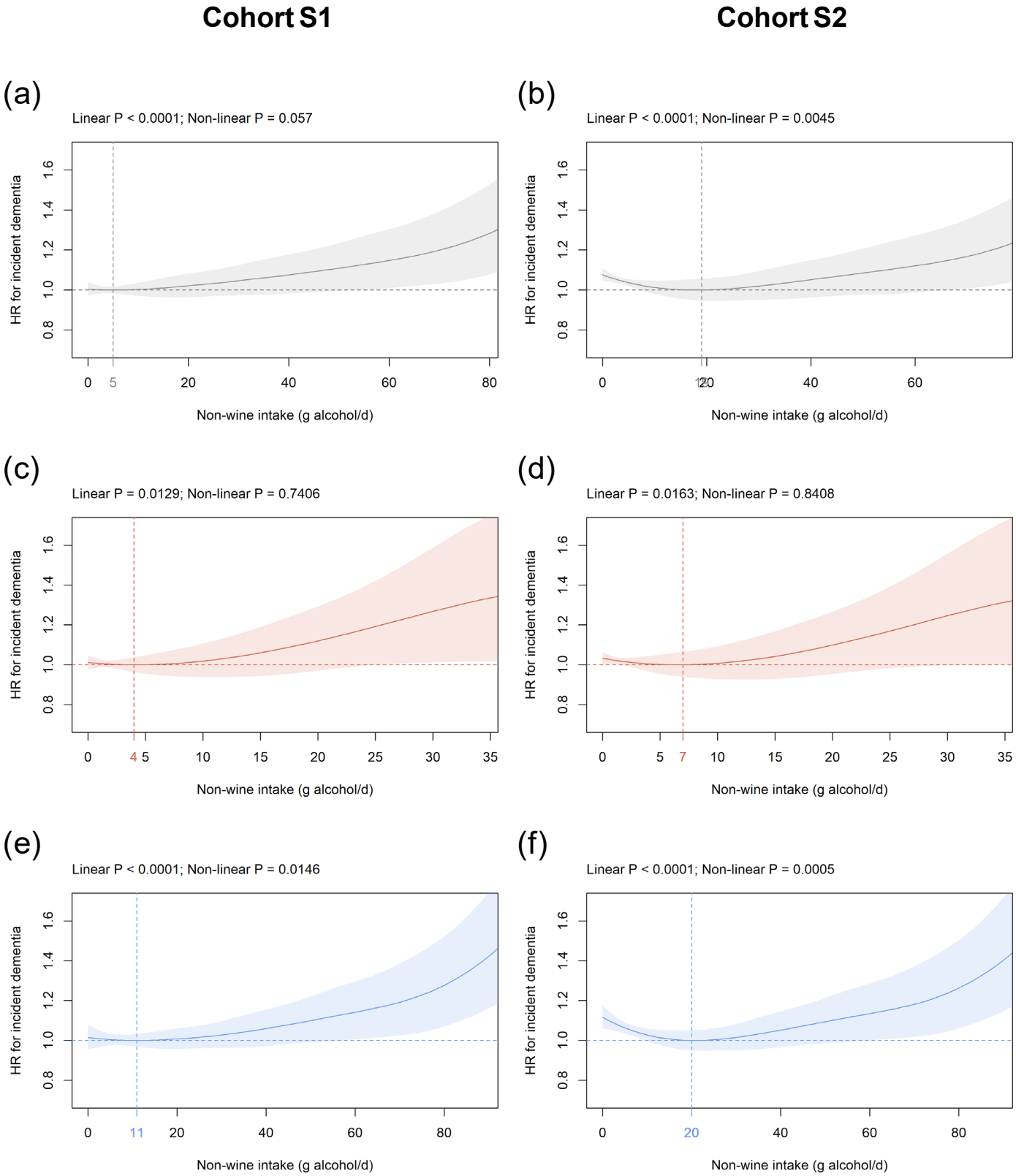

Figure S5. Association of non-wine intake (g alcohol/d) in (a), (b) the total cohort, (c), (d) females, and (e), (f) males with dementia risk in (a), (c), (e) cohort S1 and (b), (d), (f) cohort S2. Data are adjusted and presented as indicated in Supplementary Figure S2.

Appendix C

Supplementary Material:

Association of sugar intake from different sources with incident dementia in the prospective cohort of UK Biobank participants

Schaefer, S. M., Kaiser, A., Eichner, G., & Fasshauer, M. (2023). Association of sugar intake from different sources with incident dementia in the prospective cohort of UK Biobank participants. Nutrition Journal, 22(1), 42.

Supplementary Information

Nutrition Journal

Association of sugar intake from different sources with incident dementia in the prospective cohort of UK Biobank participants

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Additional File 1: Figures

Figure S1

Sugar sources relevant to the present study.

Figure S2

Flowchart of participant selection

Figure S3

Venn diagram depicting number of participants excluded by seven exclusion criteria: 1) missing lifestyle risk factors (physical activity or smoking status), 2) diagnosis of all-cause dementia before completion of the last Oxford WebQ, 3) missing socioeconomic factors (Townsend deprivation index, total household income, ethnic background, highest qualification, or overall health rating), 4) missing data of the physical exam (body mass index (BMI), systolic blood pressure (SBP)), 5) pre-existing malabsorption, 6) history of diabetes mellitus, and 7) implausible energy or carbohydrate intake, i.e., 0 kJ/d intake on at least one occasion, being in the upper 0.1 % of total energy and/or carbohydrate consumption or total energy intake <1.1 × basal metabolic rate - 500 kcal (under-reporting) or >2.5 × basal metabolic rate + 500 kcal (over-reporting) resulting in a study population of 186,622 participants.

Figure S4

Landmark analysis

Association of **a** FS, **b** intrinsic sugars, as well as FS in **c** beverages, **d** solids, **e** soda/fruit drinks, **f** juice, **g** milk-based drinks, **h** tea/coffee, **i** treats, **j** cereals, **k** toppings, and **l** sauces (all %E) with dementia risk (landmark analysis; n=186,580; number of cases=1,456). Models are adjusted for energy intake, age, alcohol intake, BMI, ethnic background, general health status, highest qualification, history of mental illnesses, physical activity, SBP, sex, smoking status, total household income, and Townsend deprivation index. Covariates not fulfilling the proportional hazard assumption are stratified. The nadir is indicated by the vertical line. *Abbreviations*: *BMI* Body mass index, *FS* Free sugars, *HR* Hazard ratio, *%E* Percentage total energy, *SBP* Systolic blood pressure

Figure S5

Unintentional weight loss removed

Association of **a** FS, **b** intrinsic sugars, as well as FS in **c** beverages, **d** solids, **e** soda/fruit drinks, **f** juice, **g** milk-based drinks, **h** tea/coffee, **i** treats, **j** cereals, **k** toppings, and **l** sauces (all %E) with dementia risk (unintentional weight loss removed; n=157,057; number of cases=1,223). Models are adjusted and presented as indicated in Additional file 1 Fig. S4. *Abbreviations*: *FS* Free sugars, *HR* Hazard ratio, *%E* Percentage total energy

Figure S6

Participants with history of CVD and cancer removed

Association of **a** FS, **b** intrinsic sugars, as well as FS in **c** beverages, **d** solids, **e** soda/fruit drinks, **f** juice, **g** milk-based drinks, **h** tea/coffee, **i** treats, **j** cereals, **k** toppings, and **l** sauces (all %E) with dementia risk (participants with history of CVD and cancer removed; n=164,855; number of cases=1,180). Models are adjusted and presented as indicated in Additional file 1 Fig. S4. *Abbreviations*: *FS* Free sugars, *HR* Hazard ratio, *%E* Percentage total energy

Figure S7

Participants with only one completed Oxford WebQ removed

Association of **a** FS, **b** intrinsic sugars, as well as FS in **c** beverages, **d** solids, **e** soda/fruit drinks, **f** juice, **g** milk-based drinks, **h** tea/coffee, **i** treats, **j** cereals, **k** toppings, and **l** sauces (all %E) with dementia risk (participants with only one completed Oxford WebQ removed; n=115,480; number of cases=776). Models are adjusted and presented as indicated in Additional file 1 Fig. S4. *Abbreviations*: *FS* Free sugars, *HR* Hazard ratio, *%E* Percentage total energy

Figure S8

Non-typical diet removed

Association of **a** FS, **b** intrinsic sugars, as well as FS in **c** beverages, **d** solids, **e** soda/fruit drinks, **f** juice, **g** milk-based drinks, **h** tea/coffee, **i** treats, **j** cereals, **k** toppings, and **l** sauces (all %E) with dementia risk (non-typical diet removed; n=125,313; number of cases=1,185). Models are adjusted and presented as

indicated in Additional file 1 Fig. S4. *Abbreviations*: *FS* Free sugars, *HR* Hazard ratio, *%E* Percentage total energy

Figure S9

Special diet removed

Association of **a** FS, **b** intrinsic sugars, as well as FS in **c** beverages, **d** solids, **e** soda/fruit drinks, **f** juice, **g** milk-based drinks, **h** tea/coffee, **i** treats, **j** cereals, **k** toppings, and **l** sauces (all %E) with dementia risk (special diet removed; n=160,752; number of cases=1,274). Models are adjusted and presented as indicated in Additional file 1 Fig. S4. *Abbreviations*: *FS* Free sugars, *HR* Hazard ratio, *%E* Percentage total energy

Figure S10

Restricted to participants with age ≥ 60 years

Association of **a** FS, **b** intrinsic sugars, as well as FS in **c** beverages, **d** solids, **e** soda/fruit drinks, **f** juice, **g** milk-based drinks, **h** tea/coffee, **i** treats, **j** cereals, **k** toppings, and **l** sauces (all %E) with dementia risk (restricted to participants with age ≥ 60 years; n=90,571; number of cases=1,361). Models are adjusted and presented as indicated in Additional file 1 Fig. S4. *Abbreviations*: *FS* Free sugars, *HR* Hazard ratio, *%E* Percentage total energy

Figure S11

Stratified by age (< 60 and ≥ 60 years)

Association of **a** FS, **b** intrinsic sugars, as well as FS in **c** beverages, **d** solids, **e** soda/fruit drinks, **f** juice, **g** milk-based drinks, **h** tea/coffee, **i** treats, **j** cereals, **k** toppings, and **l** sauces (all %E) with dementia risk (models were further stratified by age; n=186,622; number of cases=1,498). Models are adjusted and presented as indicated in Additional file 1 Fig. S4 except for the age covariate being replaced by a strata of age </≥ 60 years. *Abbreviations*: *FS* Free sugars, *HR* Hazard ratio, *%E* Percentage total energy

Figure S12

First Oxford WebQ only

Association of **a** FS, **b** intrinsic sugars, as well as FS in **c** beverages, **d** solids, **e** soda/fruit drinks, **f** juice, **g** milk-based drinks, **h** tea/coffee, **i** treats, **j** cereals, **k** toppings, and **l** sauces (all %E) with dementia risk (only the first Oxford WebQ was used for intake estimation; n=186,622; number of cases=1,498). Models are adjusted and presented as indicated in Additional file 1 Fig. S4. *Abbreviations*: *FS* Free sugars, *HR* Hazard ratio, *%E* Percentage total energy

Figure S13

Adjustment for diet quality score

Association of **a** FS, **b** intrinsic sugars, as well as FS in **c** beverages, **d** solids, **e** soda/fruit drinks, **f** juice, **g** milk-based drinks, **h** tea/coffee, **i** treats, **j** cereals, **k** toppings, and **l** sauces (all %E) with dementia risk (models were further adjusted for diet quality score; n=184,271; number of cases=1,457). Models are adjusted and presented as indicated in Additional file 1 Fig. S4. *Abbreviations*: *FS* Free sugars, *HR* Hazard ratio, *%E* Percentage total energy

Figure S14

Adjustment for WHR and height instead of BMI

Association of **a** FS, **b** intrinsic sugars, as well as FS in **c** beverages, **d** solids, **e** soda/fruit drinks, **f** juice, **g** milk-based drinks, **h** tea/coffee, **i** treats, **j** cereals, **k** toppings, and **l** sauces (all %E) with dementia risk (models were adjusted for WHR and height instead of BMI; n=186,580; number of cases=1,498). Models are adjusted and presented as indicated in Additional file 1 Fig. S4. *Abbreviations*: *FS* Free sugars, *HR* Hazard ratio, *%E* Percentage total energy

Figure S15

Missing values of covariates recoded as “unknown” category

Association of **a** FS, **b** intrinsic sugars, as well as FS in **c** beverages, **d** solids, **e** soda/fruit drinks, **f** juice, **g** milk-based drinks, **h** tea/coffee, **i** treats, **j** cereals, **k** toppings, and **l** sauces (all %E) with dementia risk (missing values of covariates recoded as “unknown” category; n=190,205; number of cases=1,546). Models are

adjusted and presented as indicated in Additional file 1 Fig. S4. *Abbreviations*: *FS* Free sugars, *HR* Hazard ratio, *%E* Percentage total energy

Figure S16

Only minimal set of exclusion criteria applied

Association of **a** FS, **b** intrinsic sugars, as well as FS in **c** beverages, **d** solids, **e** soda/fruit drinks, **f** juice, **g** milk-based drinks, **h** tea/coffee, **i** treats, **j** cereals, **k** toppings, and **l** sauces (all %E) with dementia risk (only minimal set of exclusion criteria applied; n=210,821; number of cases=1,859). Models are adjusted and presented as indicated in Additional file 1 Fig. S4. *Abbreviations*: *FS* Free sugars, *HR* Hazard ratio, *%E* Percentage total energy

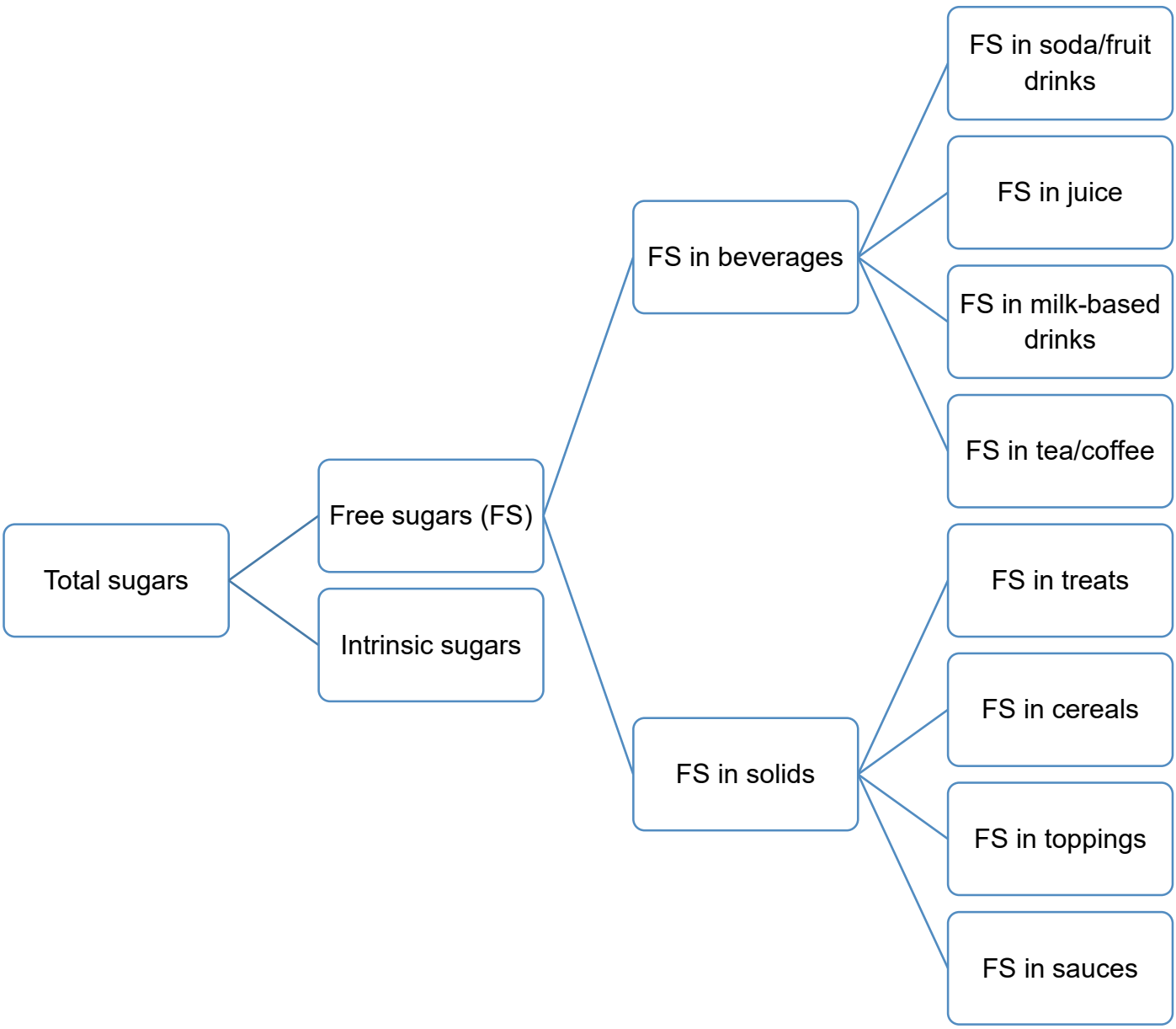

Total sugars
Free sugars (FS)
Intrinsic sugars
FS in beverages
FS in solids
FS in soda/fruit drinks
FS in juice
FS in milk-based drinks
FS in tea/coffee
FS in treats
FS in cereals
FS in toppings
FS in sauces

Figure S1

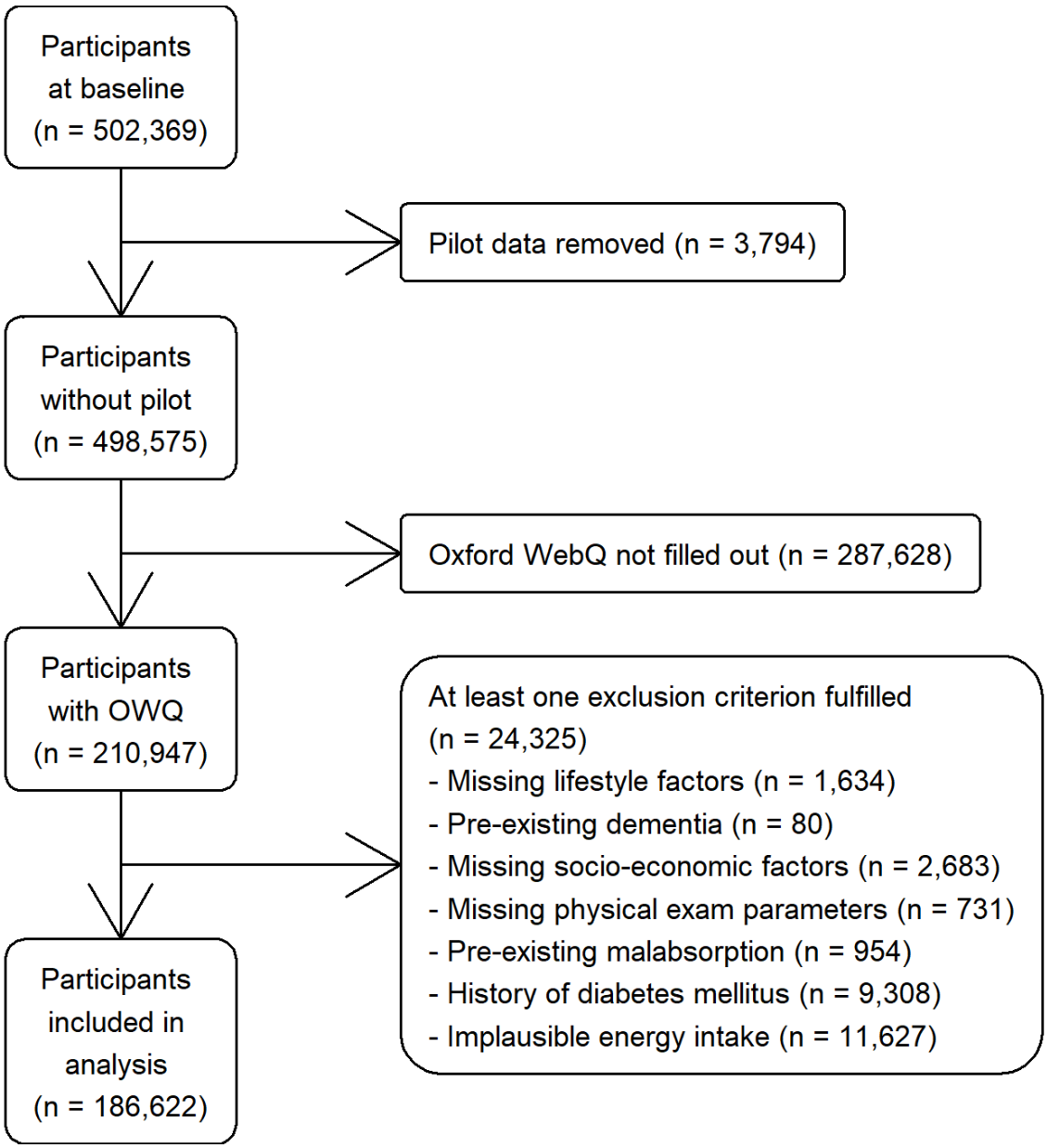

Participants at baseline (n = 502,369)
Pilot data removed (n = 3,794)
Participants without pilot (n = 498,575)
Oxford WebQ not filled out (n = 287,628)
Participants with OWQ (n = 210,947)
At least one exclusion criterion fulfilled (n = 24,325)
- Missing lifestyle factors (n = 1,634)
- Pre-existing dementia (n = 80)
- Missing socio-economic factors (n = 2,683)
- Missing physical exam parameters (n = 731)
- Pre-existing malabsorption (n = 954)
- History of diabetes mellitus (n = 9,308)
- Implausible energy intake (n = 11,627)
Participants included in analysis (n = 186,622)

Figure S2

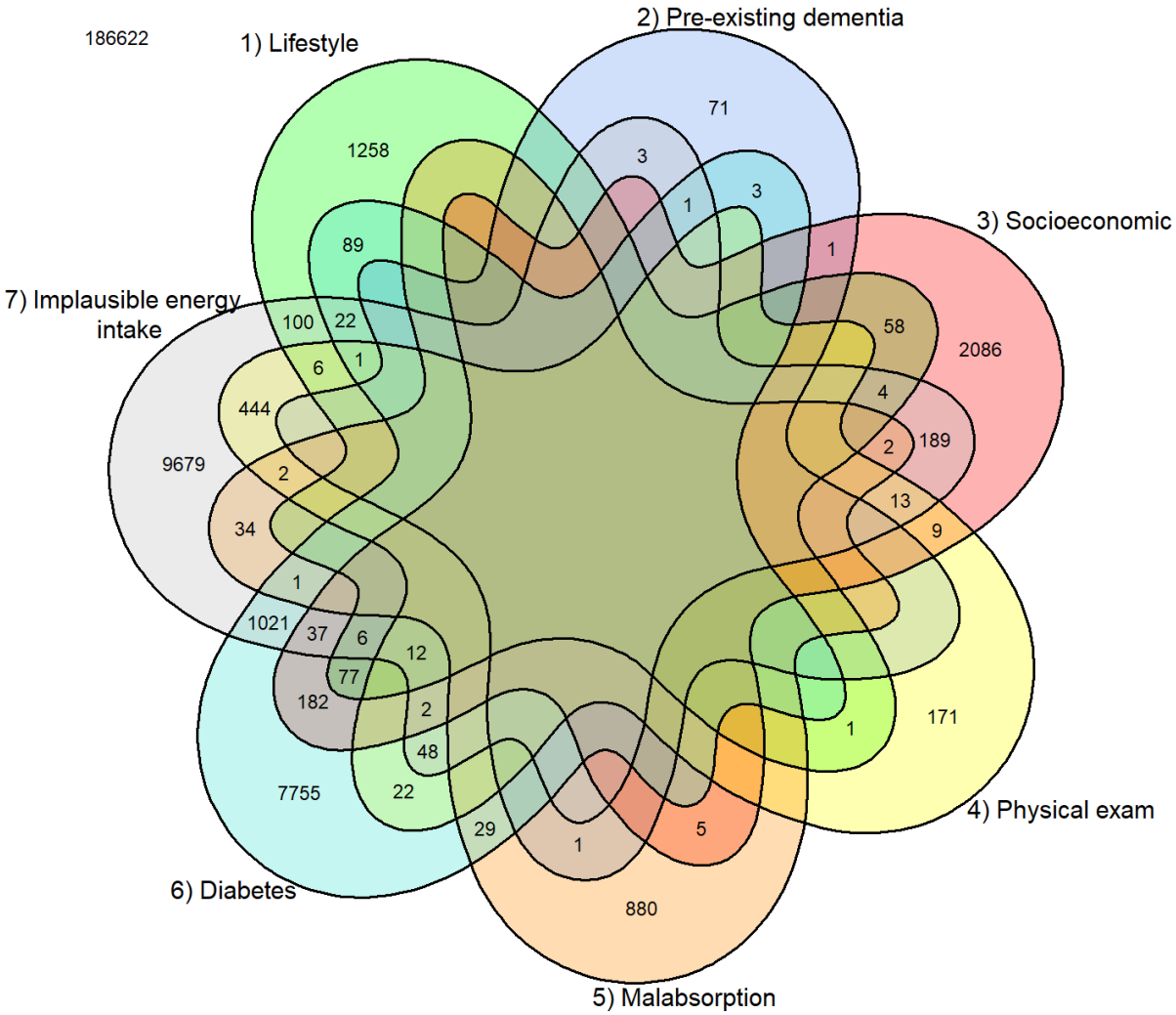
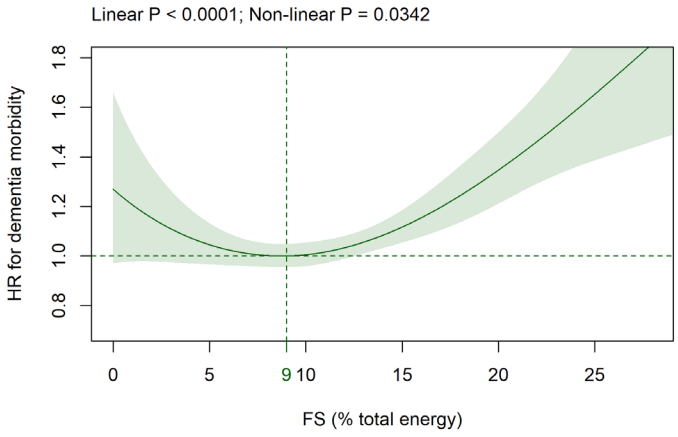
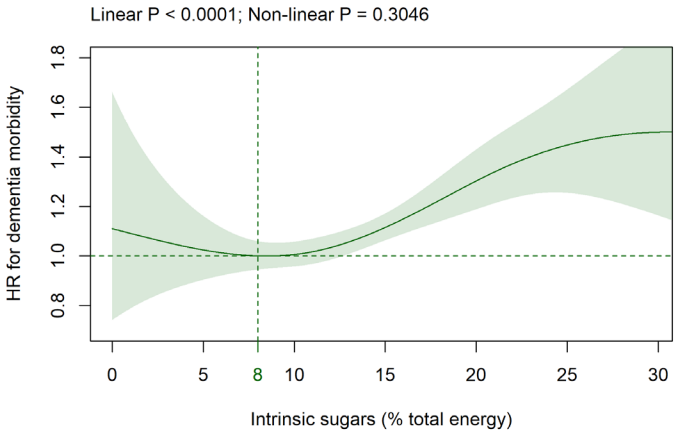

186622
1) Lifestyle
2) Pre-existing dementia
3) Socioeconomic
4) Physical exam
5) Malabsorption
6) Diabetes
7) Implausible energy intake
1258
71
3
1
3
89
1
100
22
6
1
58
2086
444
4
2
189
9679
2
13
34
9
1
1021
37
6
12
77
182
2
48
171
1
7755
22
29
1
5
880

Figure S3

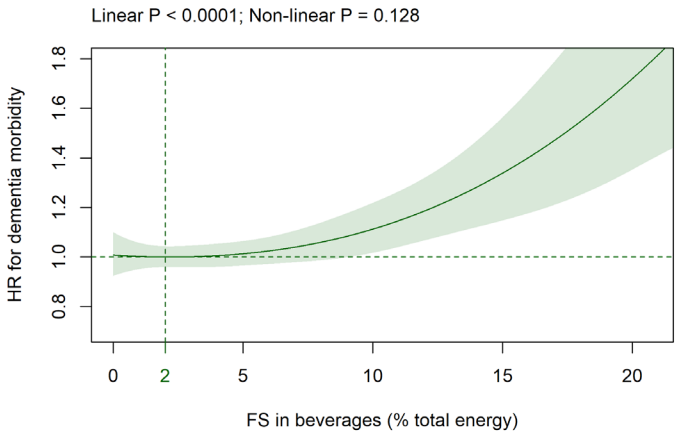
(a)



(b)



(c)



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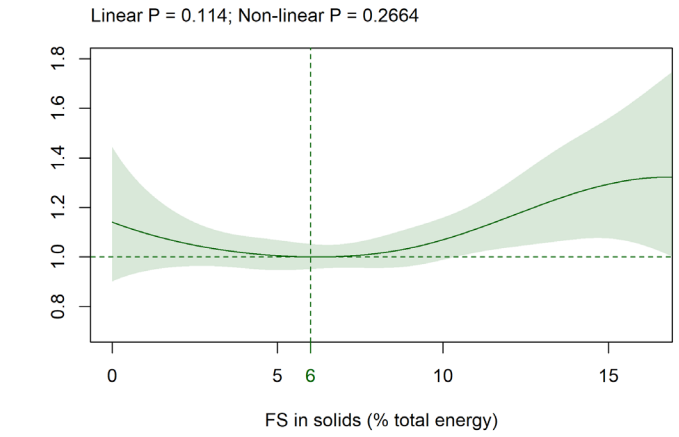


Figure S4

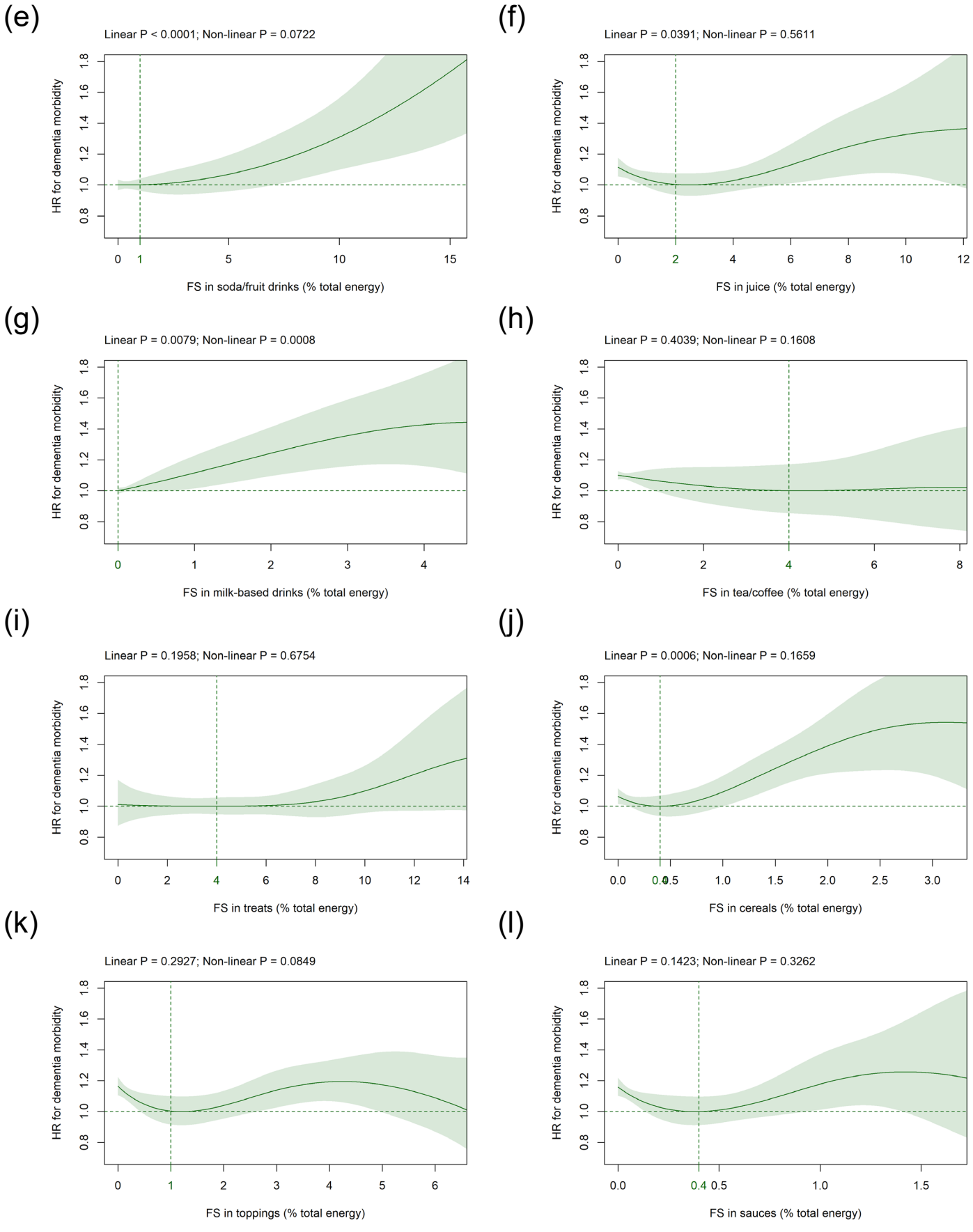


Figure S4 continued

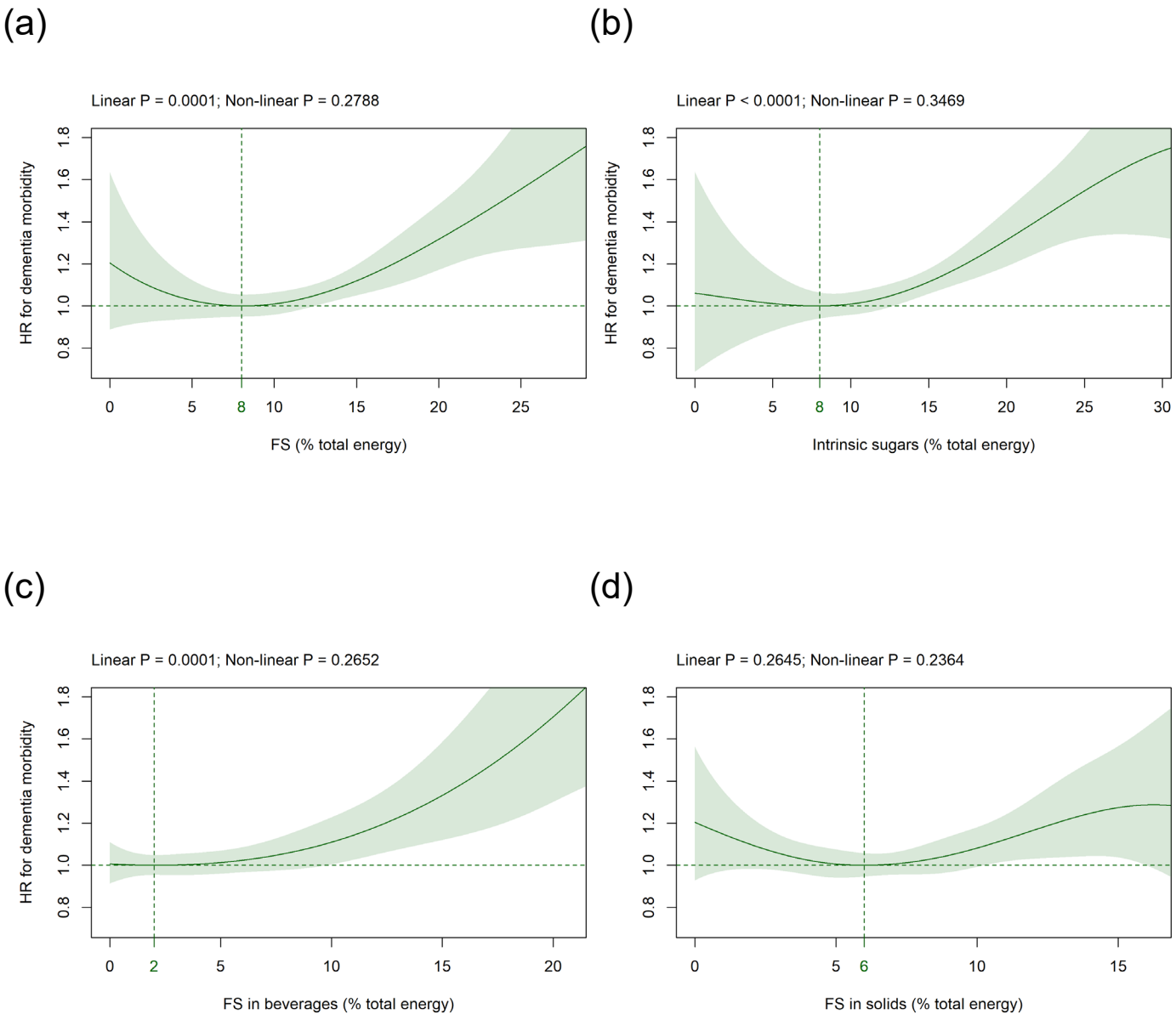

(a)
Linear P = 0.0001; Non-linear P = 0.2788
HR for dementia morbidity
0.8
1.0
1.2
1.4
1.6
1.8
0
5
8
10
15
20
25
FS (% total energy)
(b)
Linear P < 0.0001; Non-linear P = 0.3469
HR for dementia morbidity
0.8
1.0
1.2
1.4
1.6
1.8
0
5
8
10
15
20
25
30
Intrinsic sugars (% total energy)
(c)
Linear P = 0.0001; Non-linear P = 0.2652
HR for dementia morbidity
0.8
1.0
1.2
1.4
1.6
1.8
0
2
5
10
15
20
FS in beverages (% total energy)
(d)
Linear P = 0.2645; Non-linear P = 0.2364
0.8
1.0
1.2
1.4
1.6
1.8
0
5
6
10
15
FS in solids (% total energy)

Figure S5

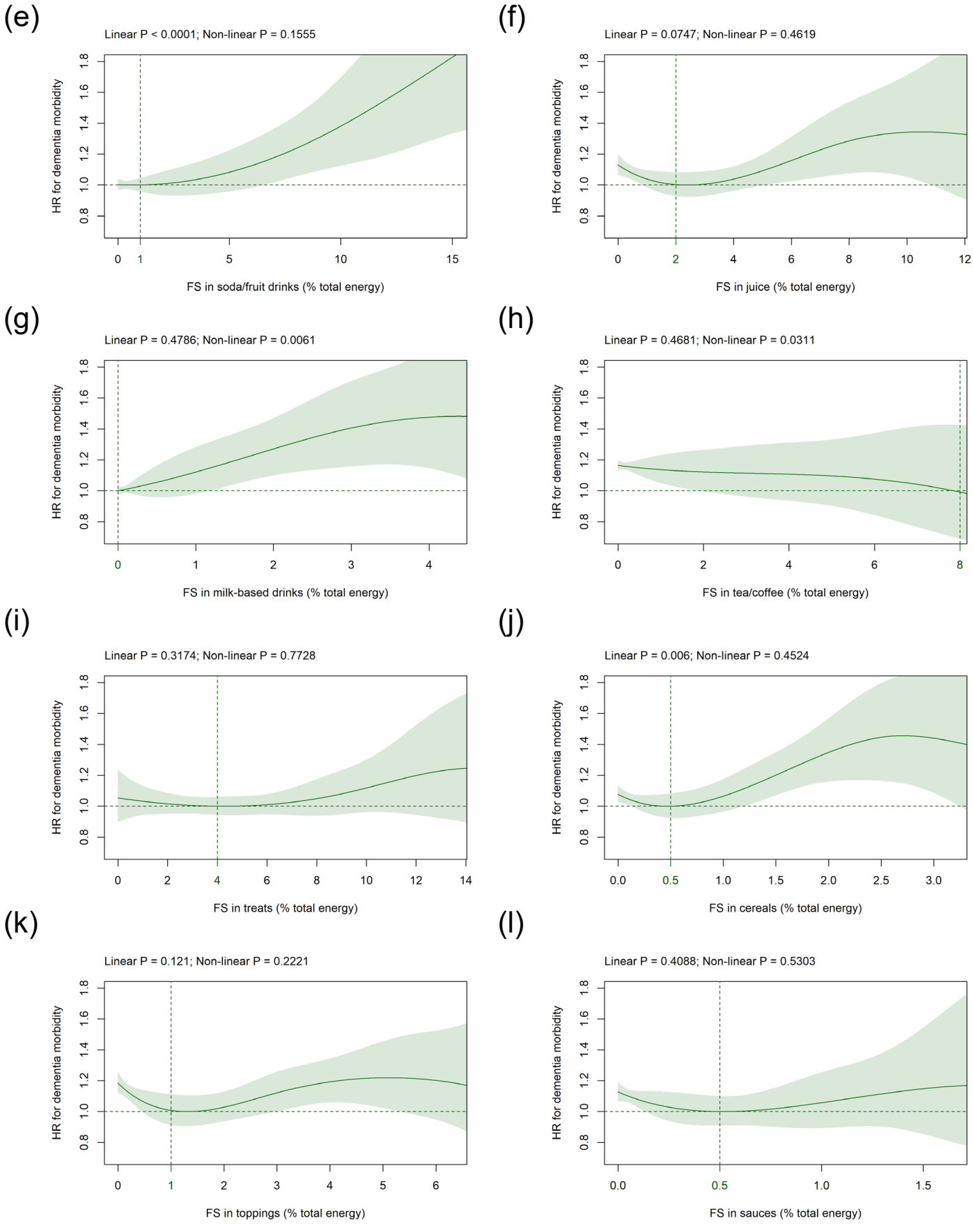
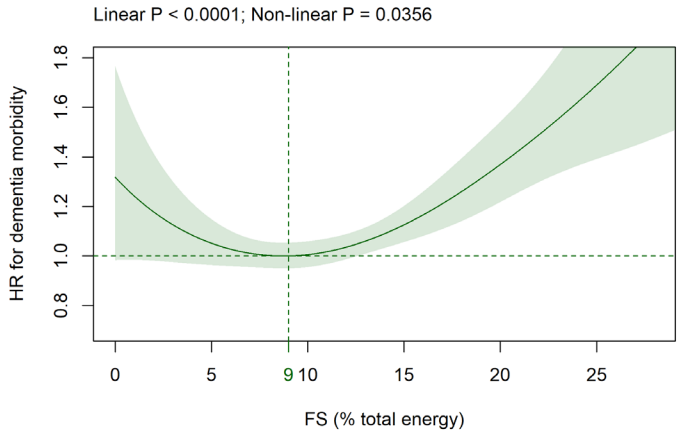


Figure S5 continued

(a)



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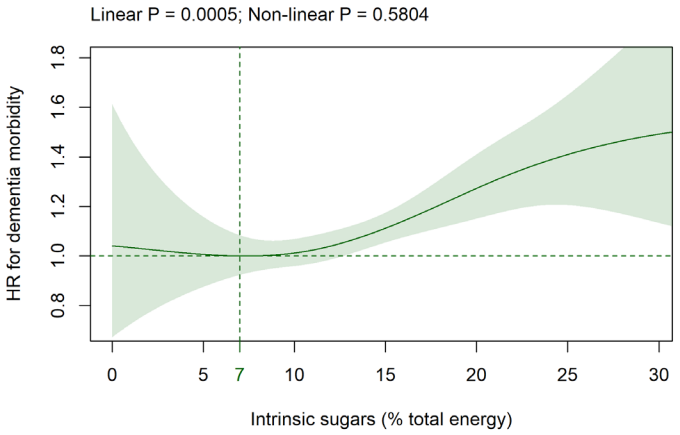

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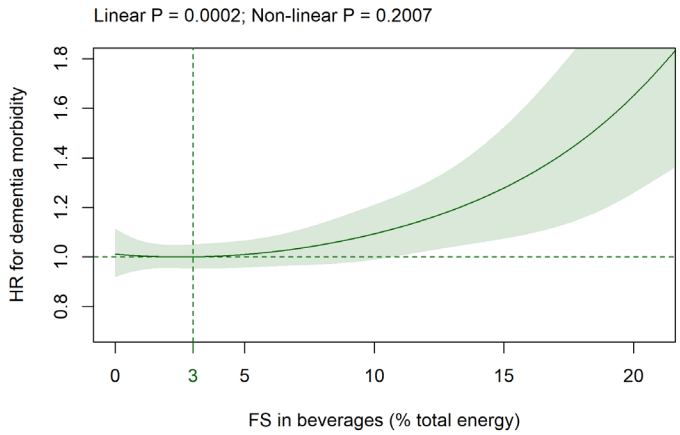

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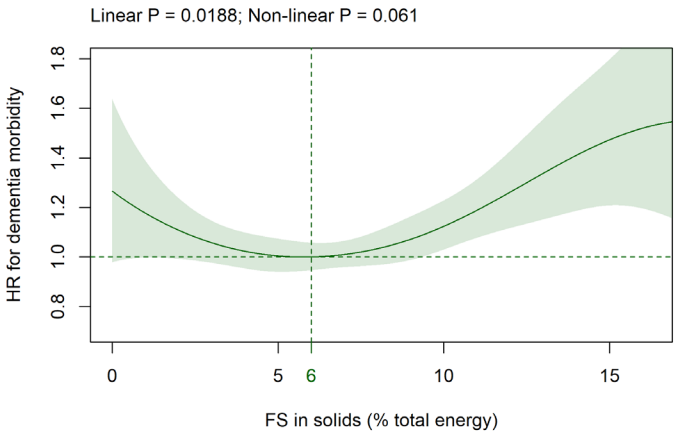


Figure S6

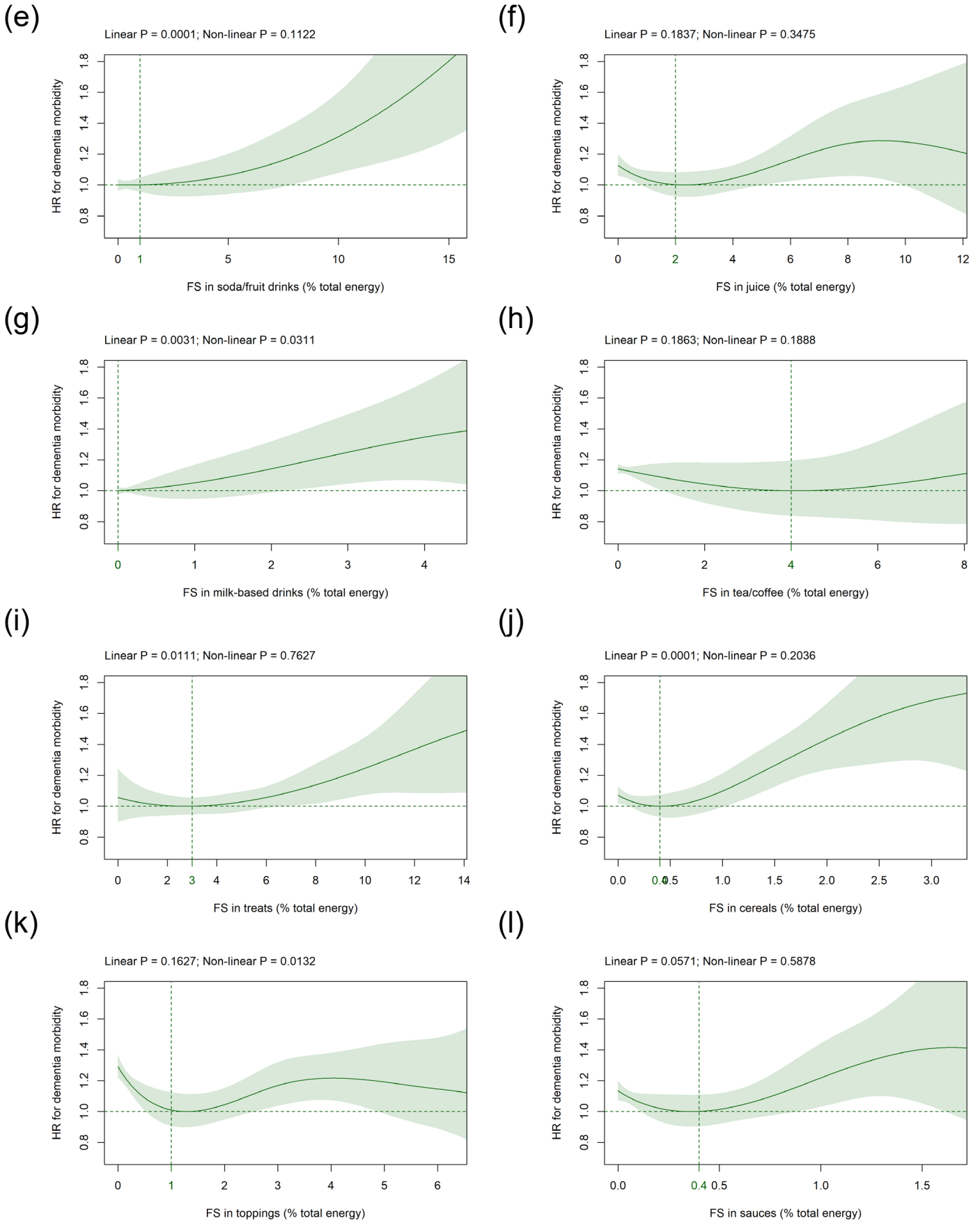
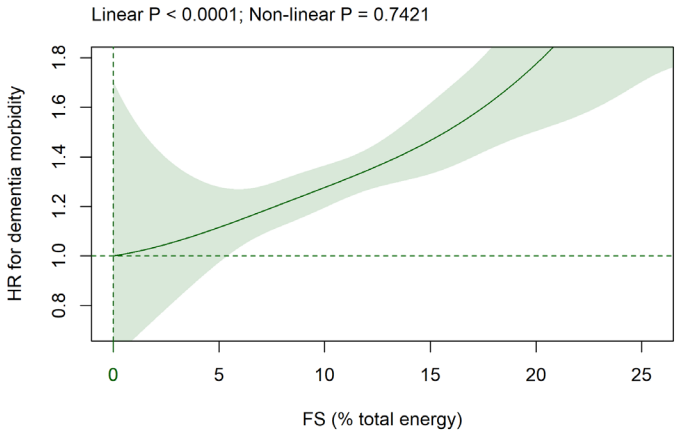


Figure S6 continued

(a)



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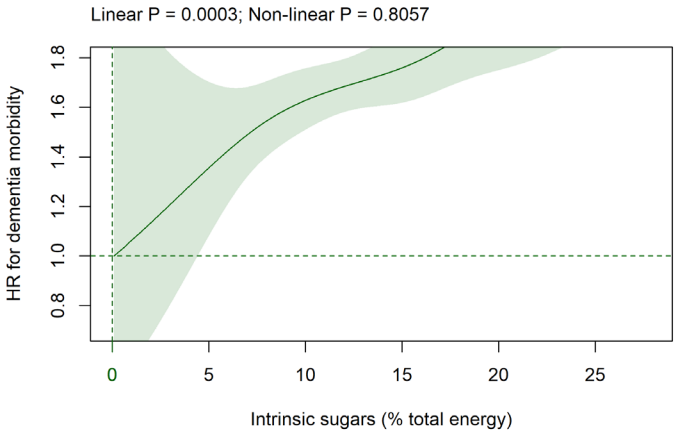

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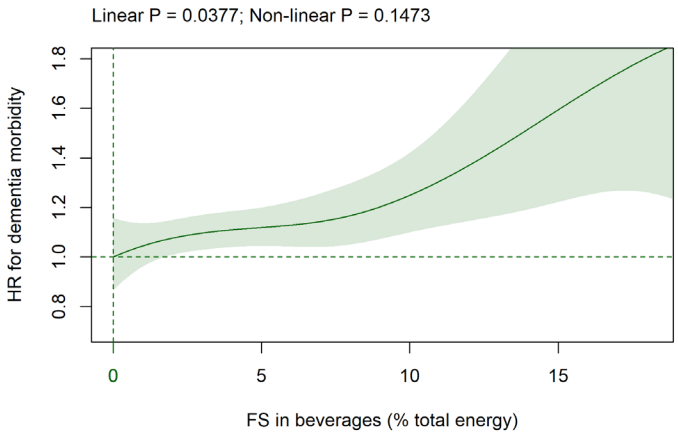

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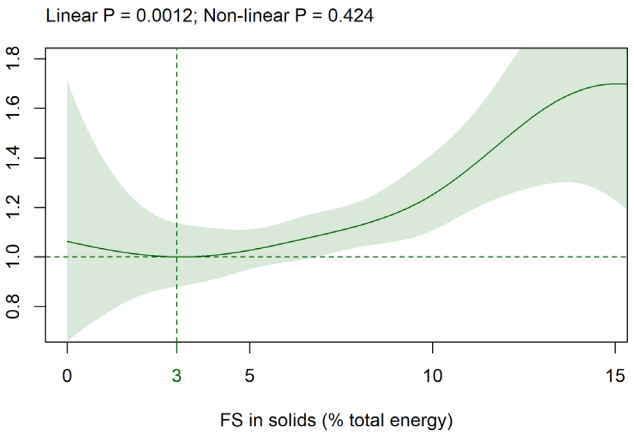


Figure S7

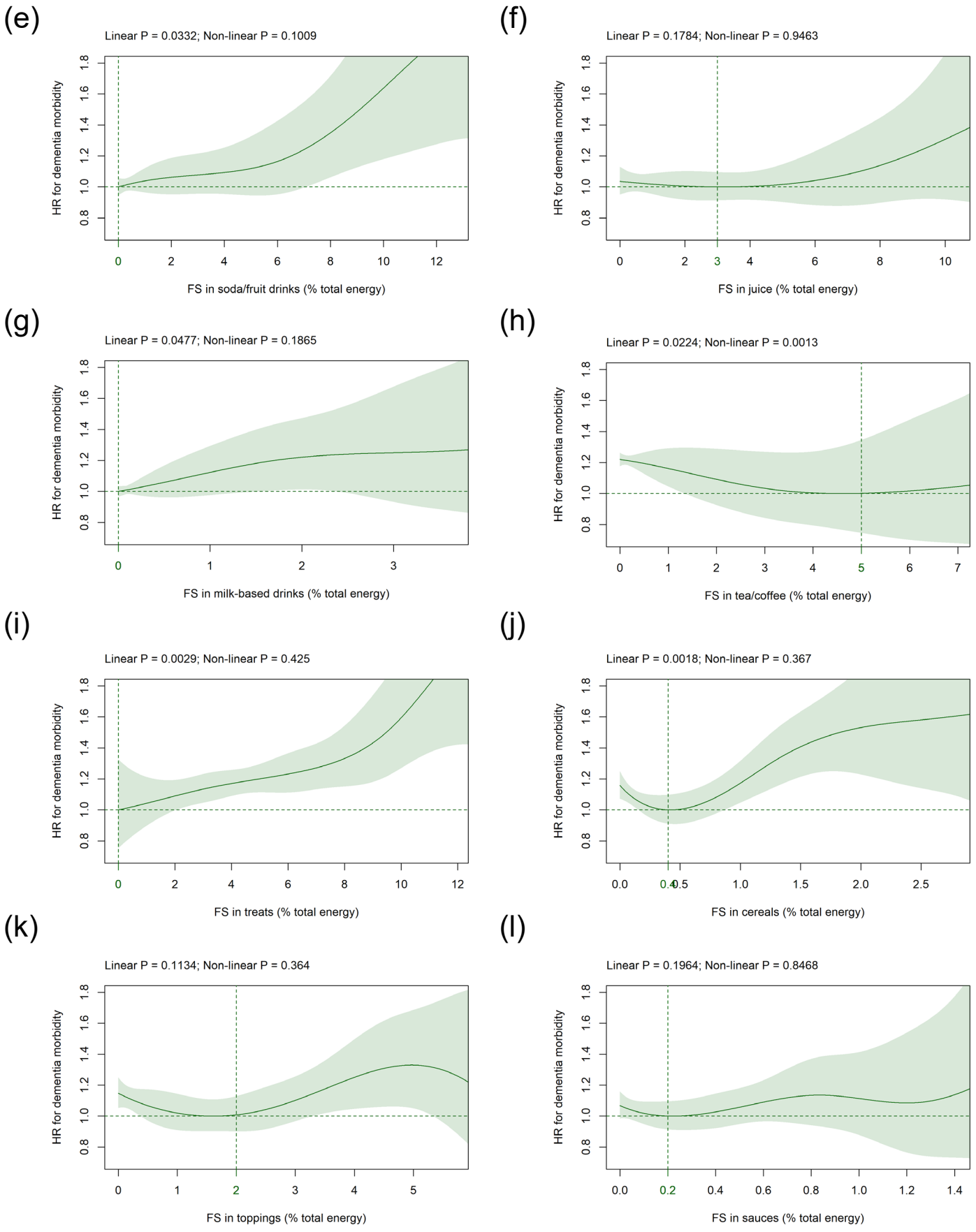
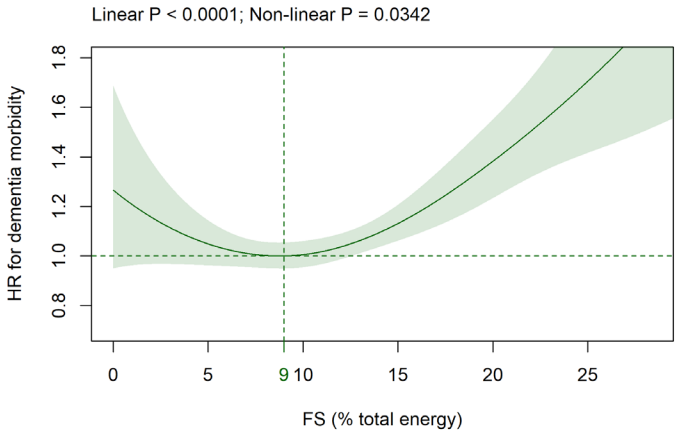


Figure S7 continued

(a)



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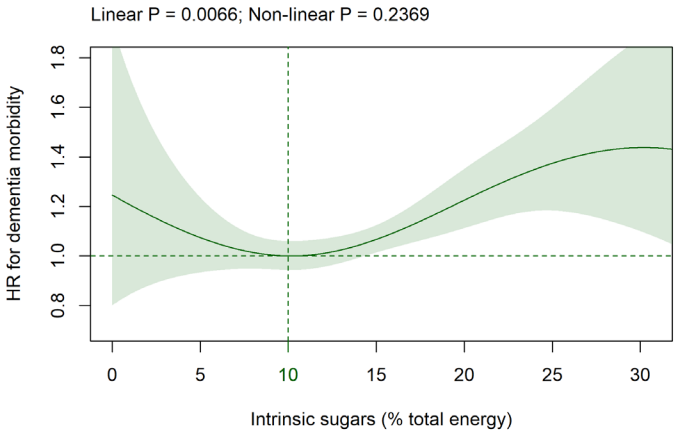

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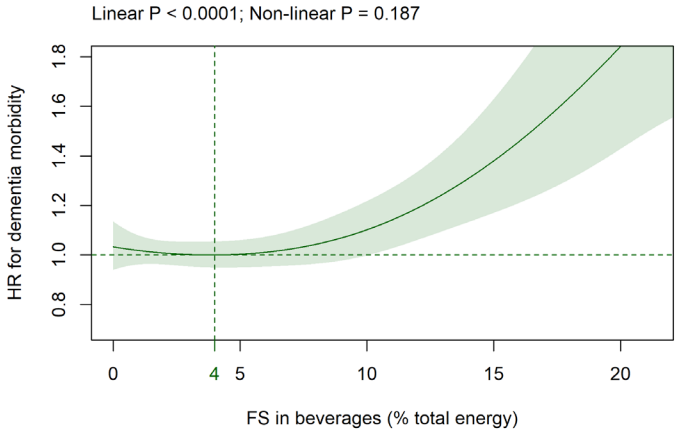

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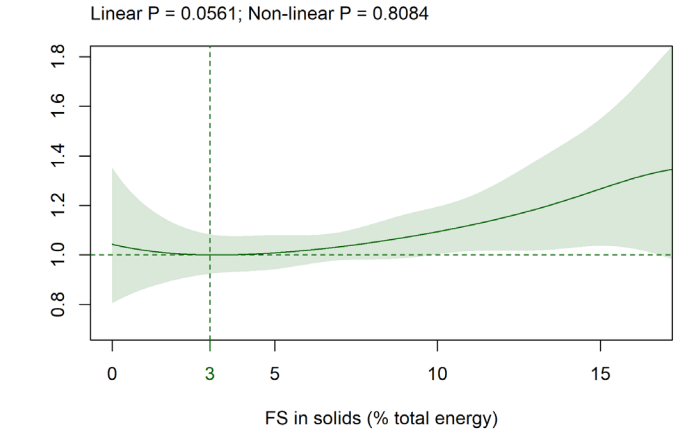


Figure S8

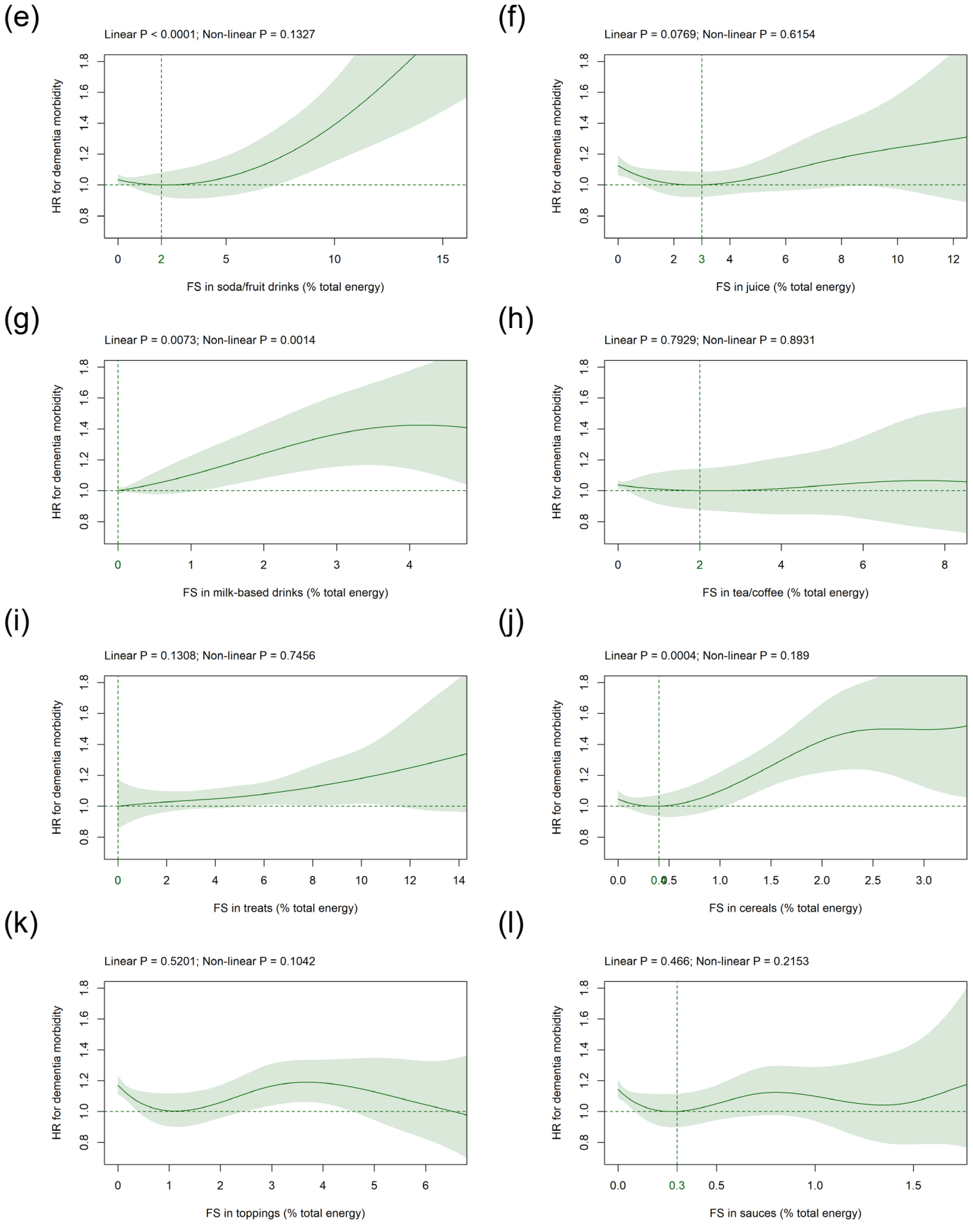
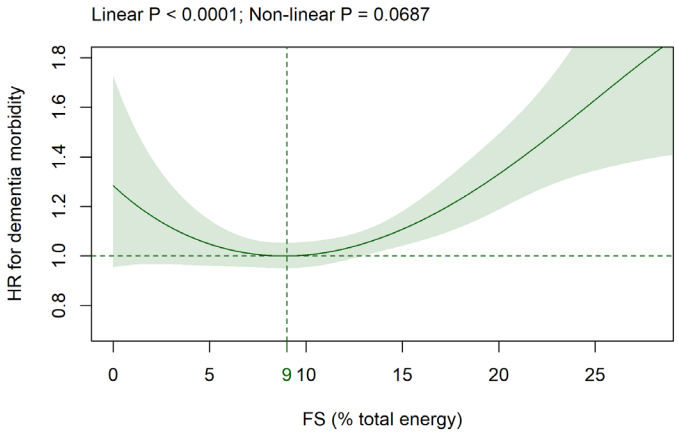


Figure S8 continued

(a)



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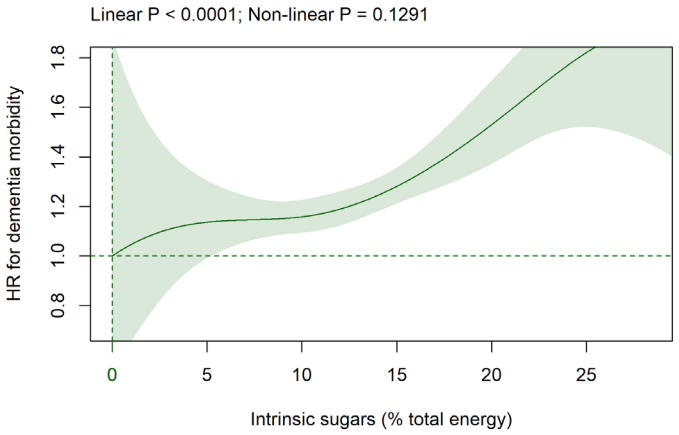

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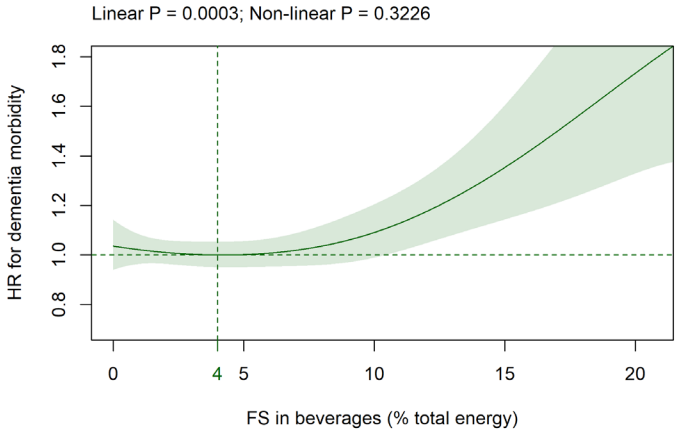

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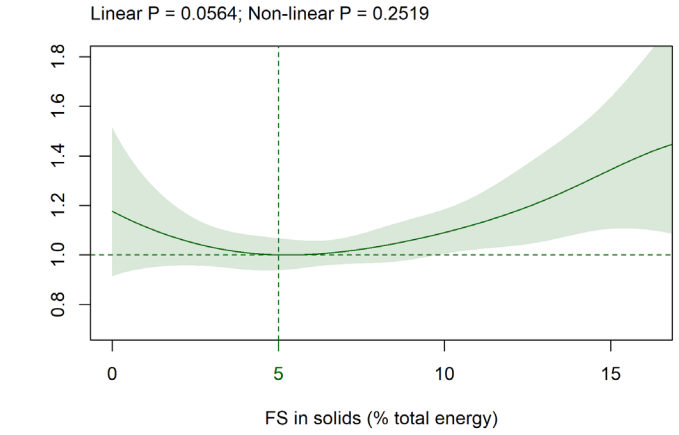


Figure S9

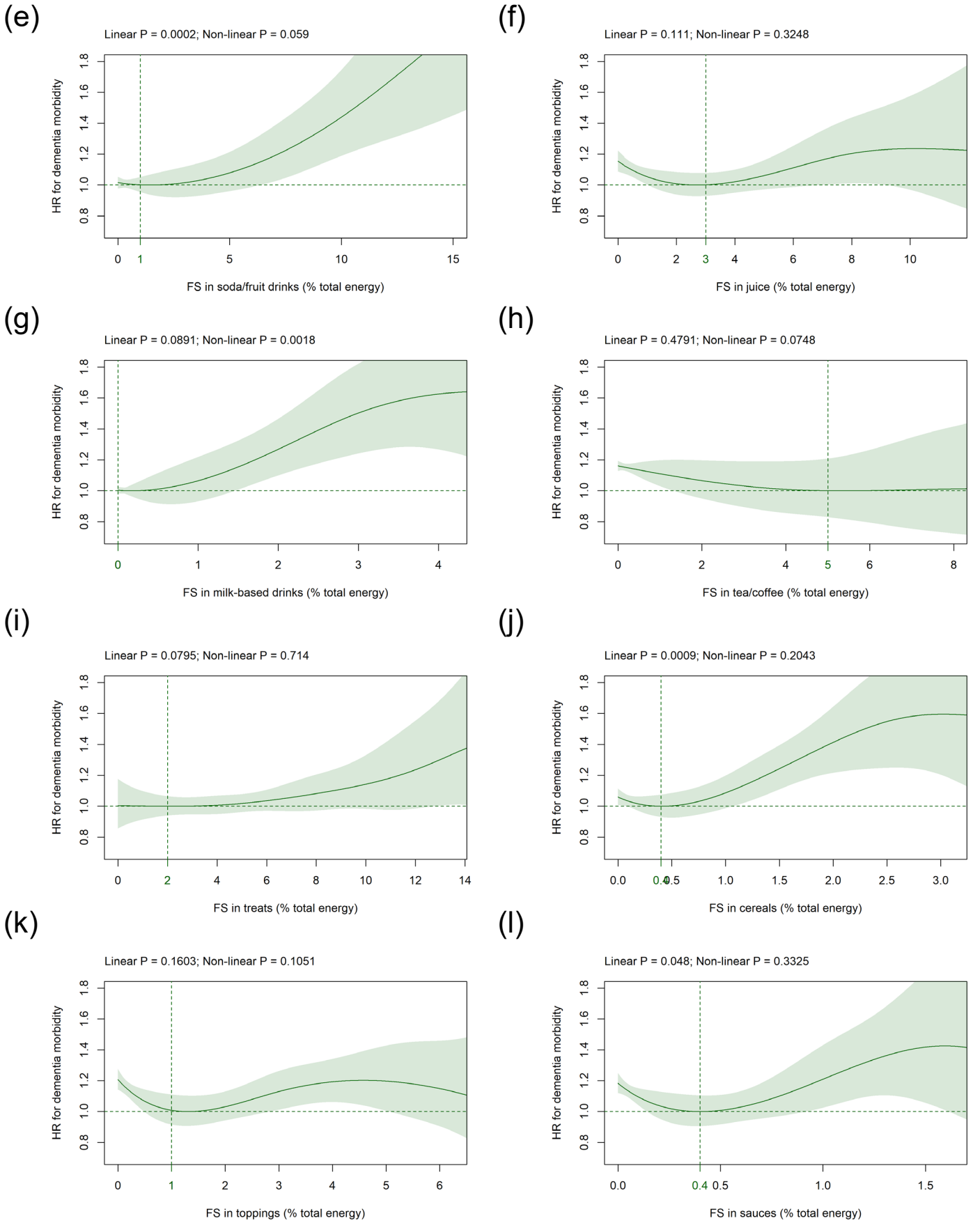
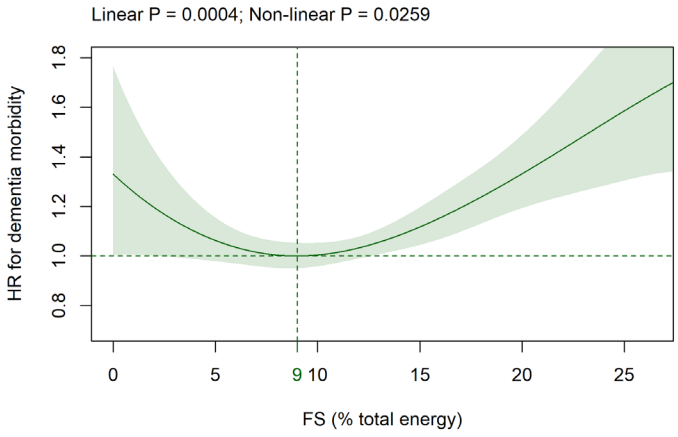


Figure S9 continued

(a)



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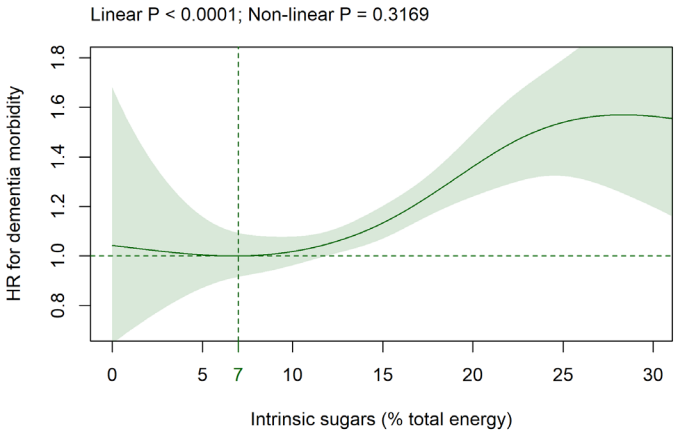

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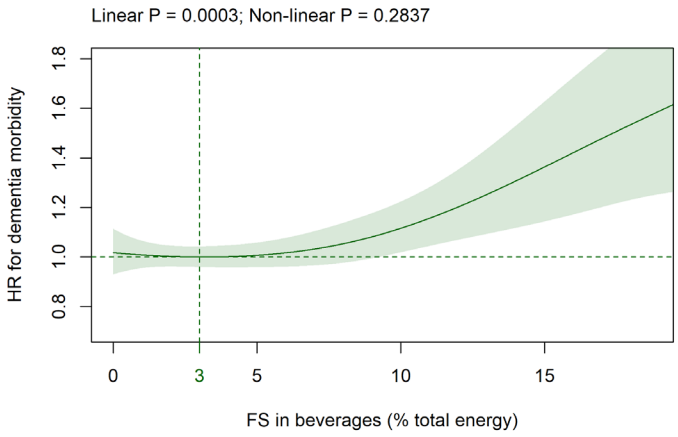

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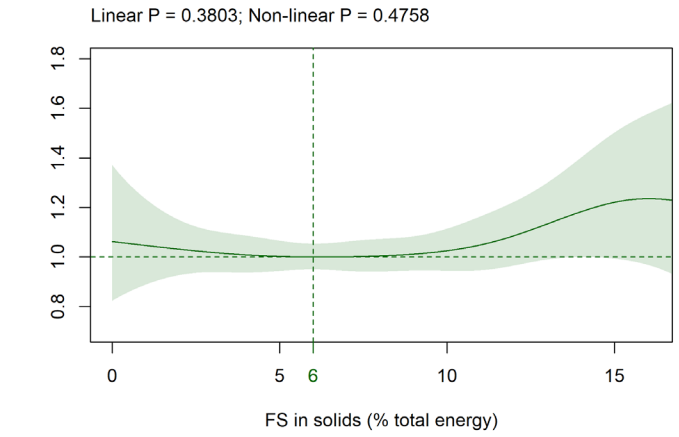
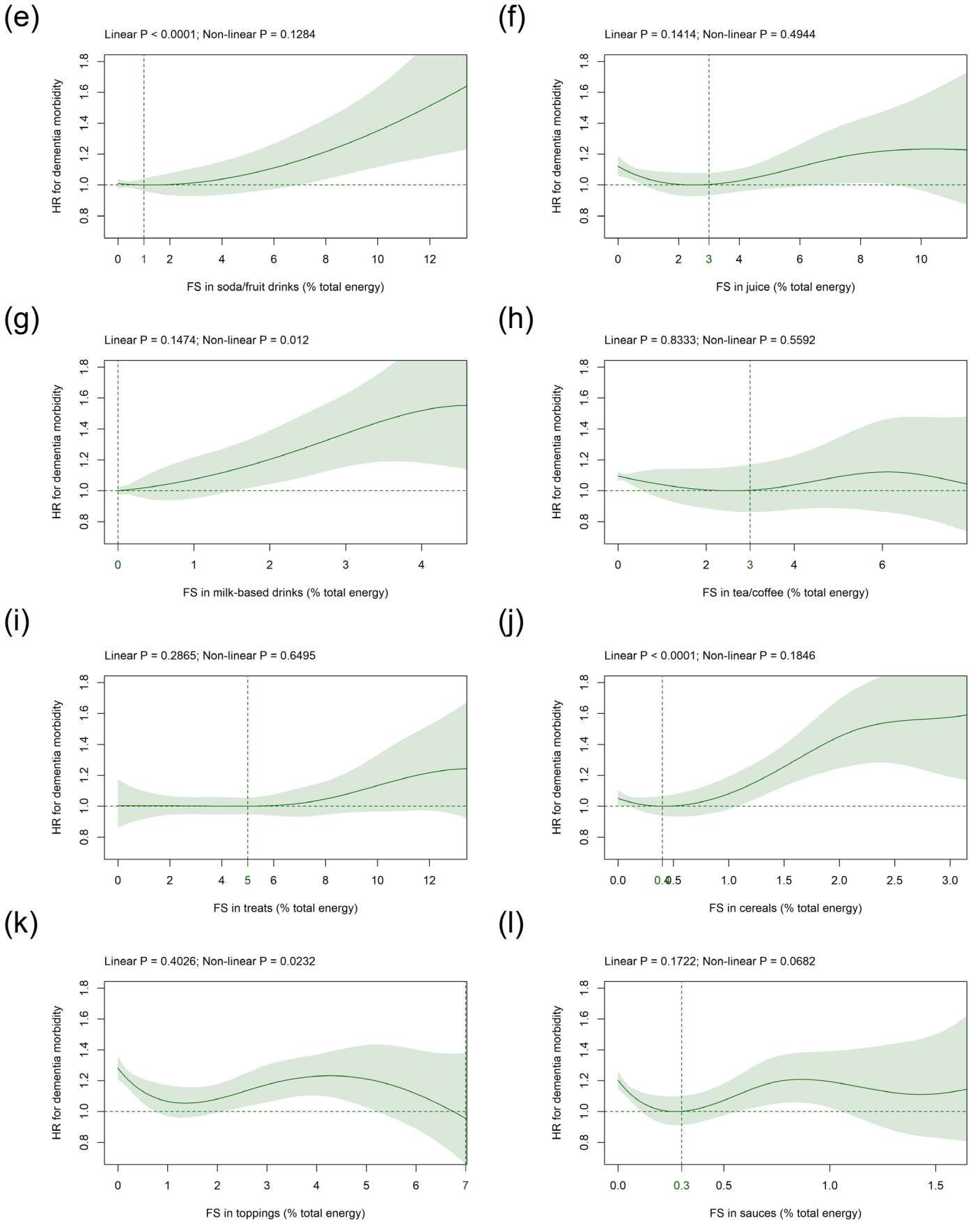


Figure S10



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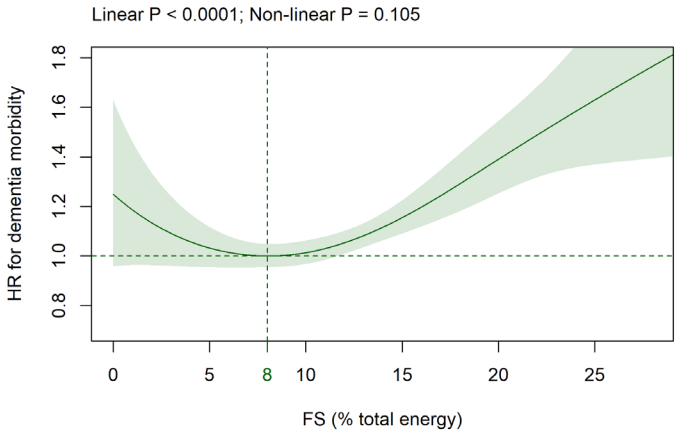

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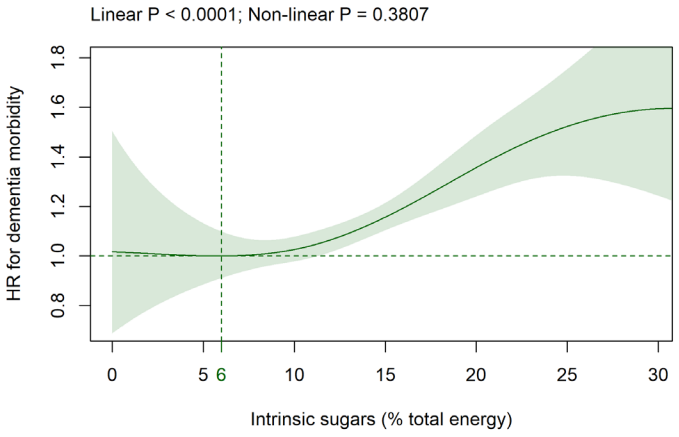

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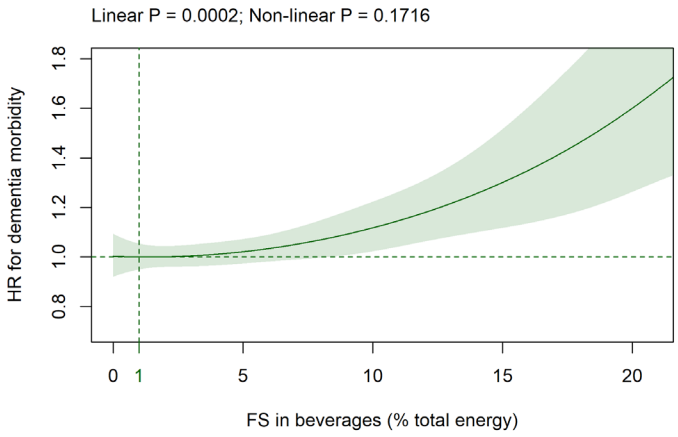

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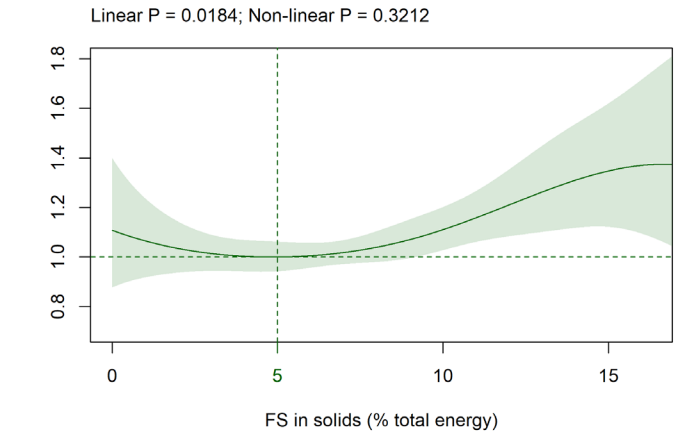

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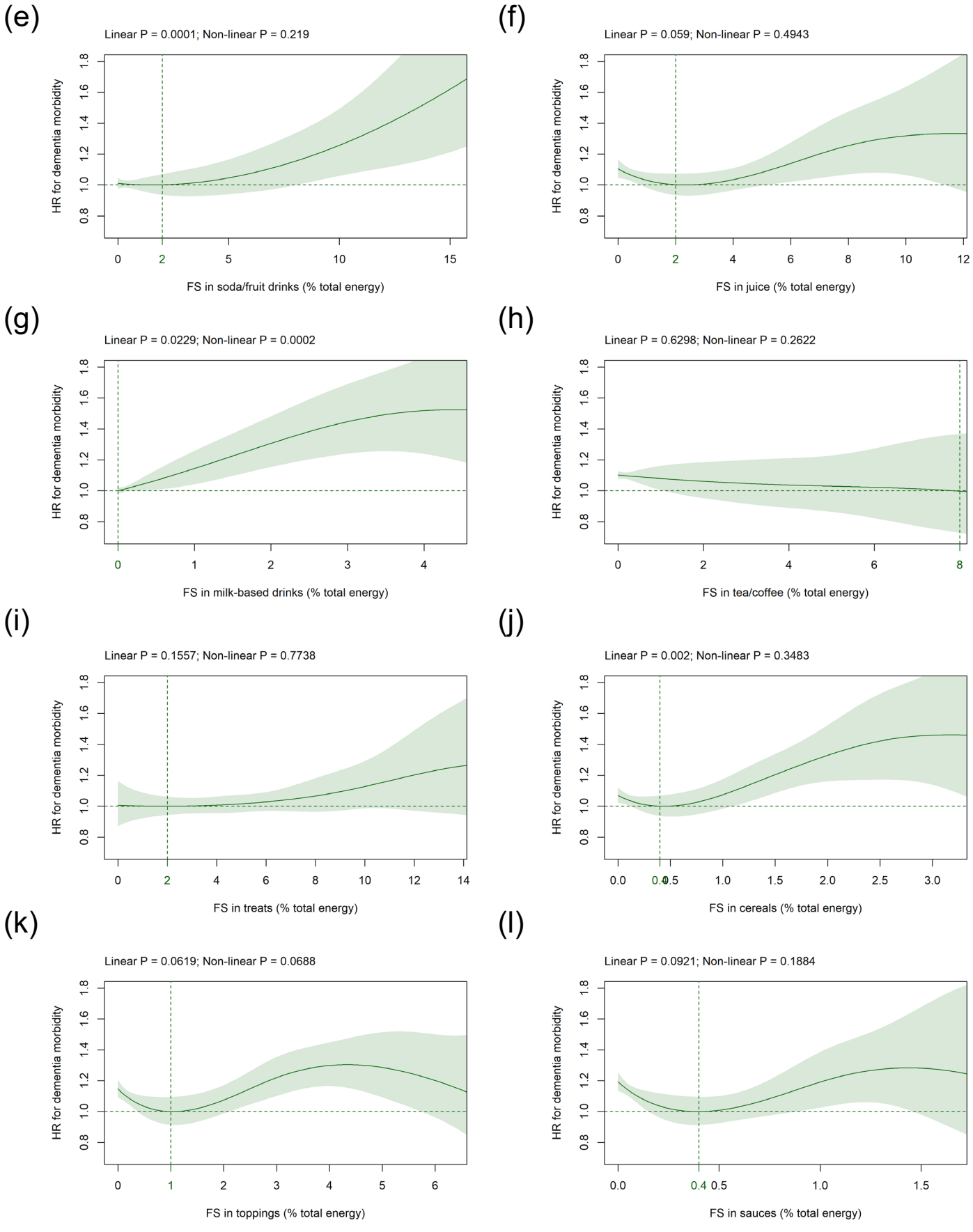

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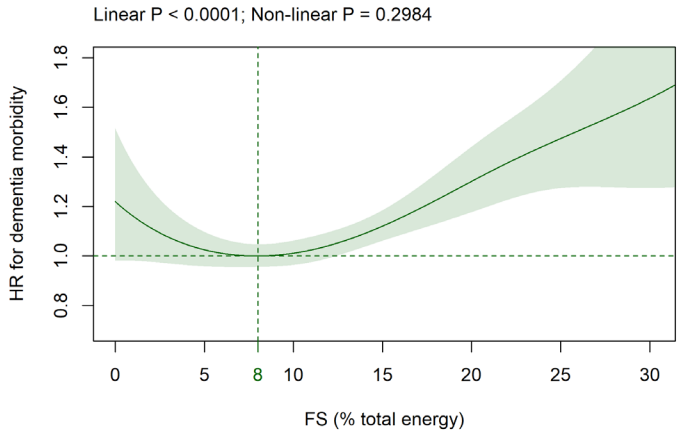

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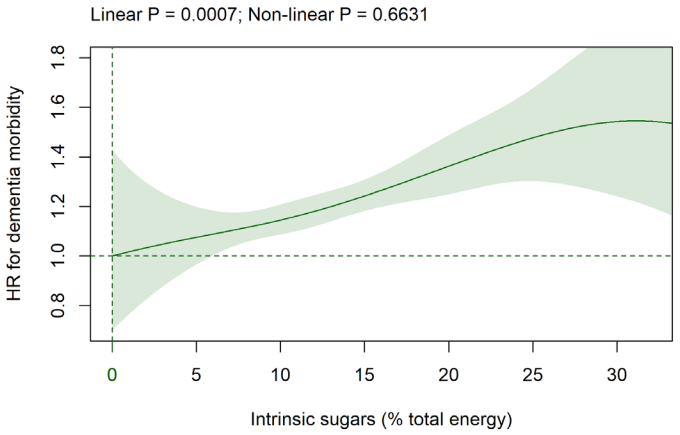

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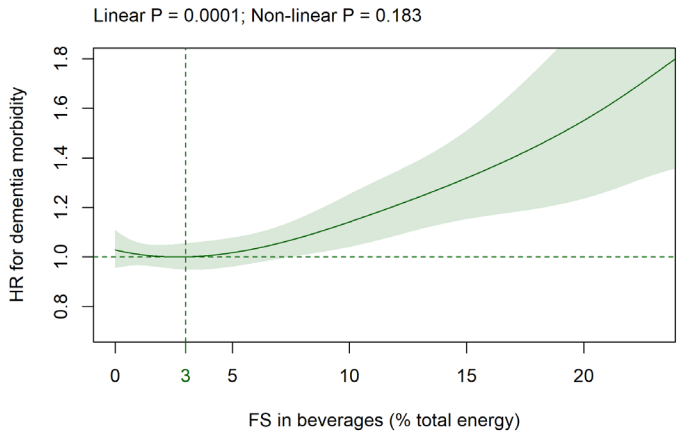

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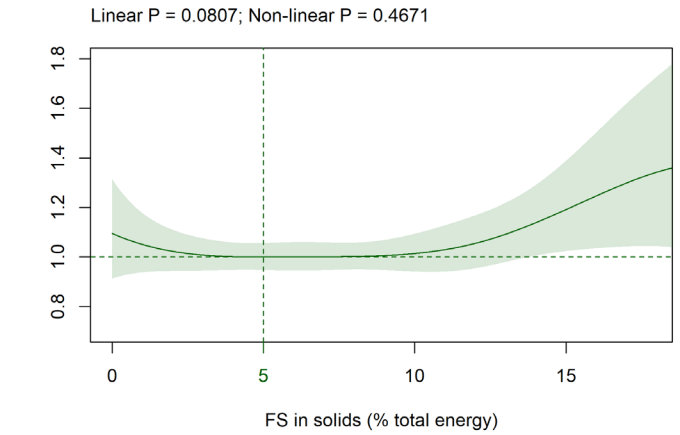

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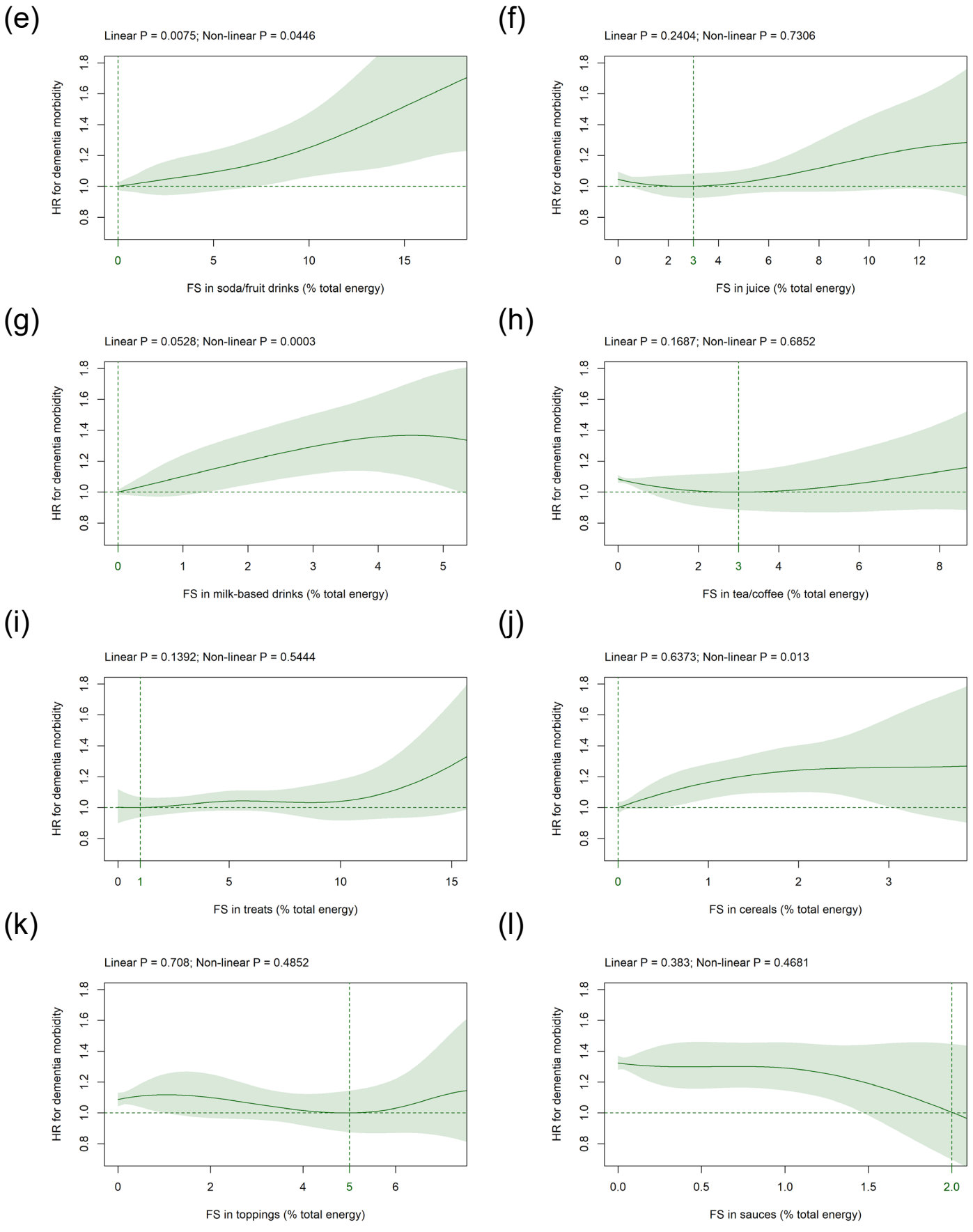

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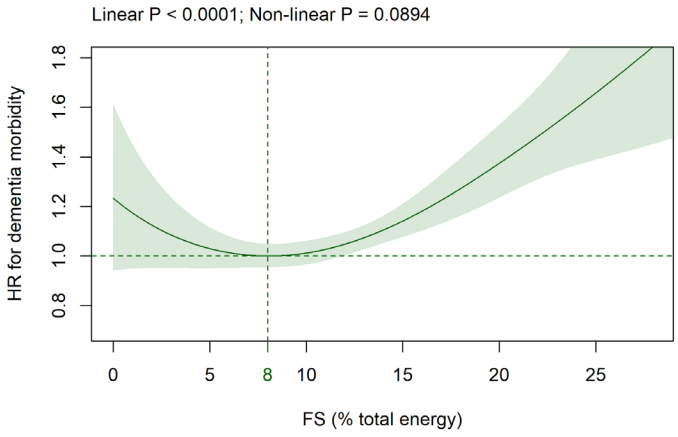

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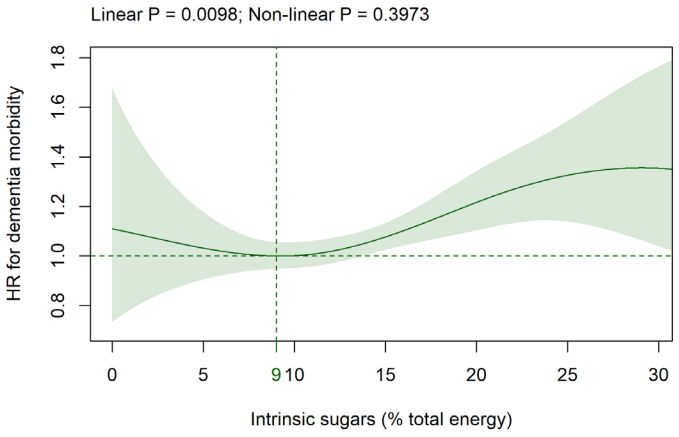

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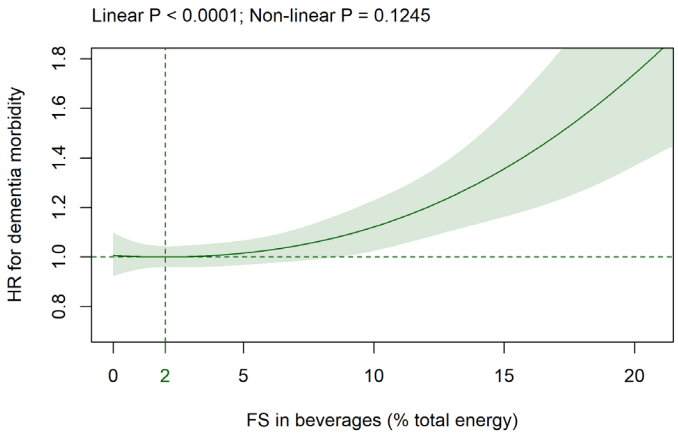

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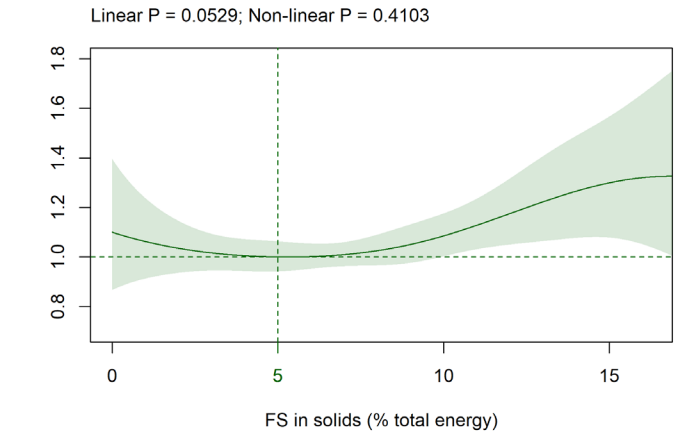

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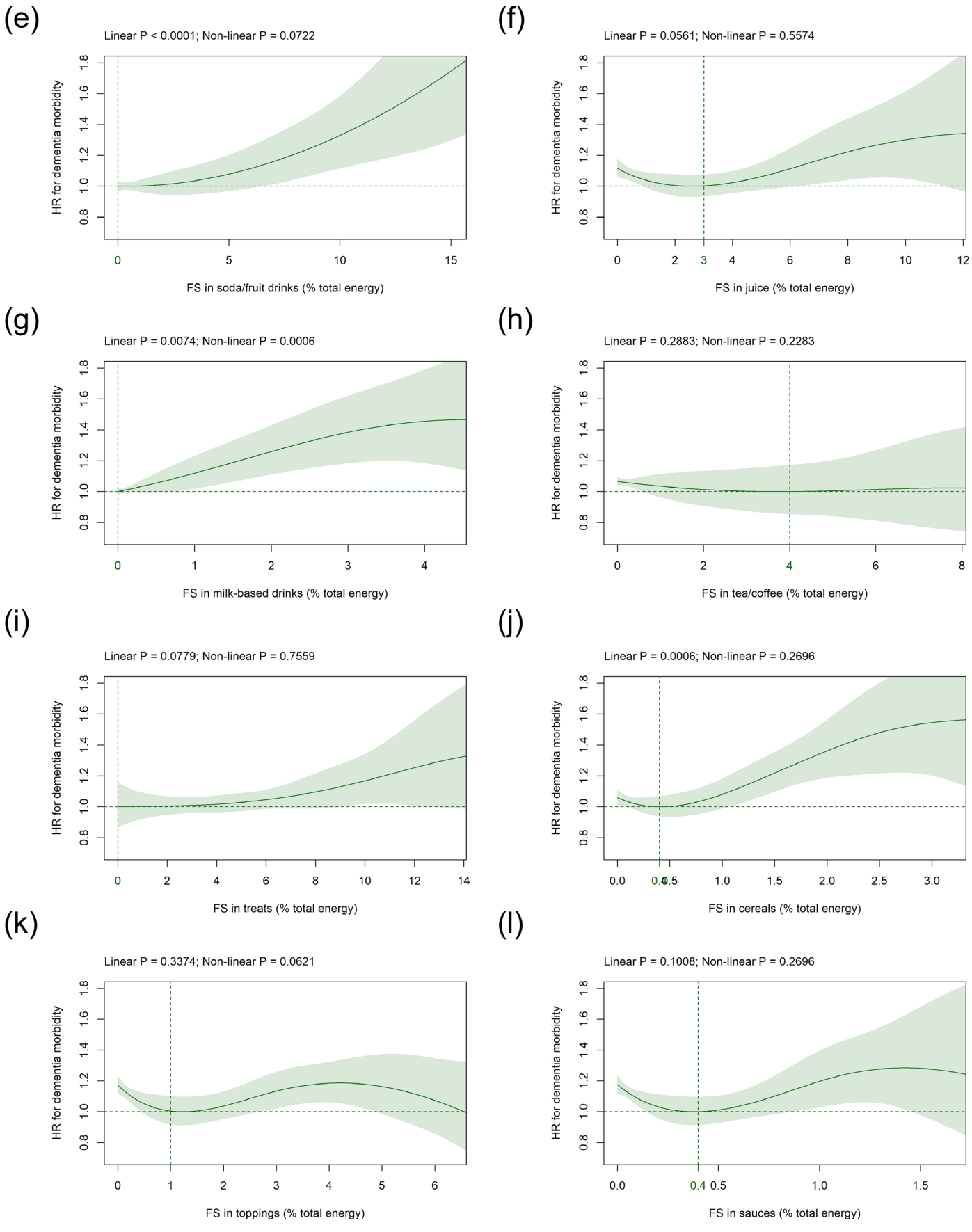

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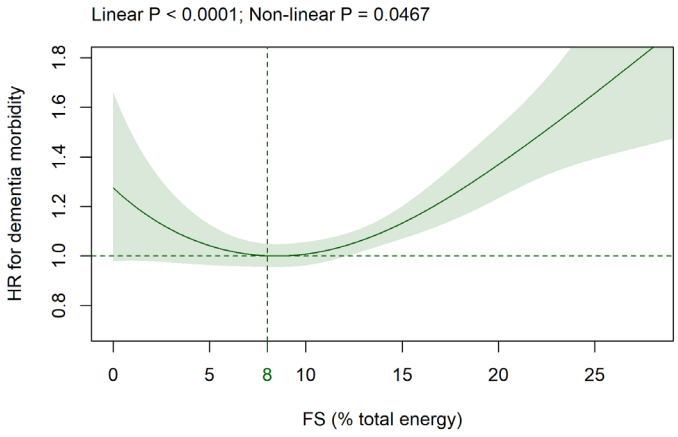

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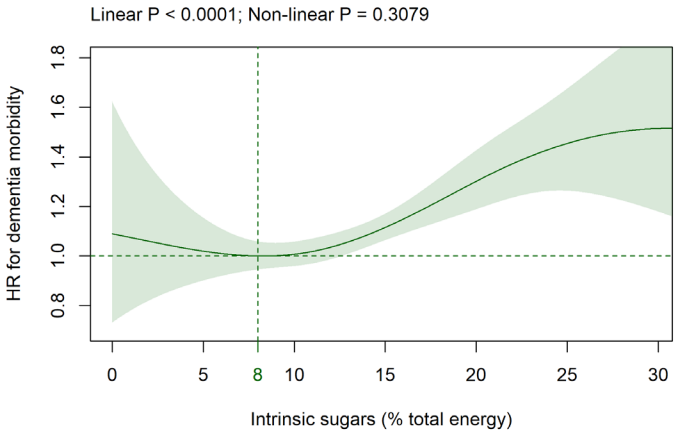

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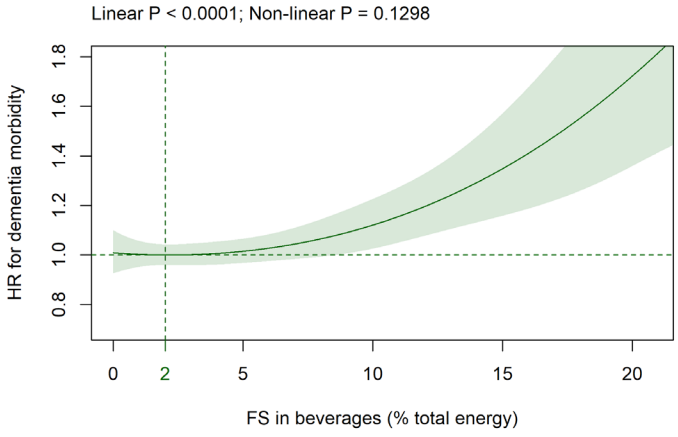

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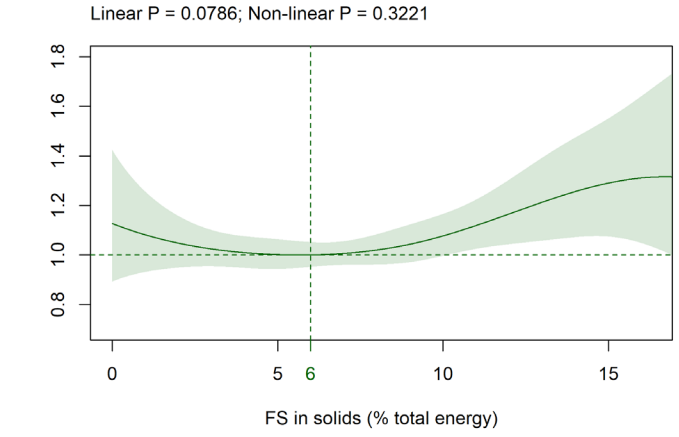

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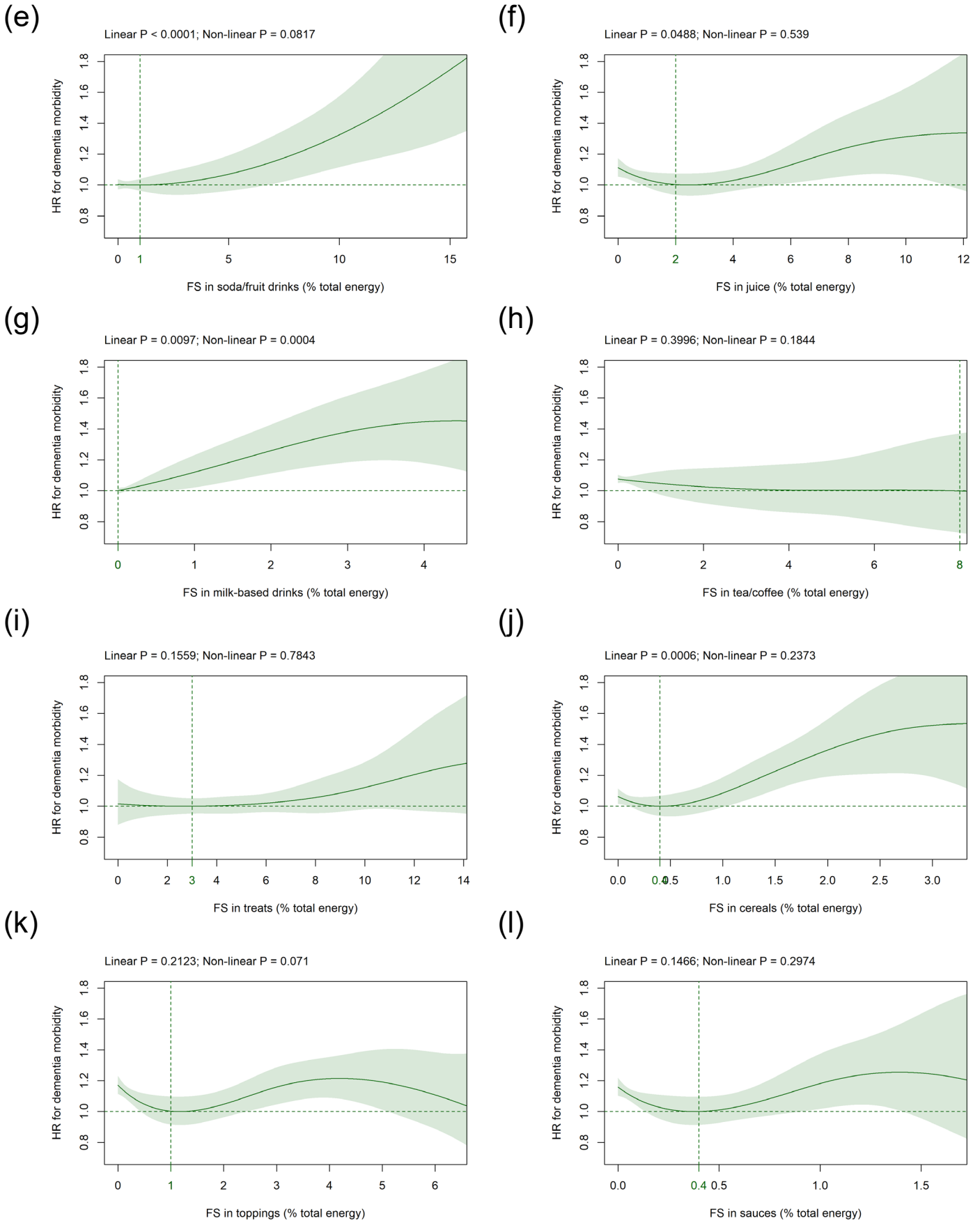

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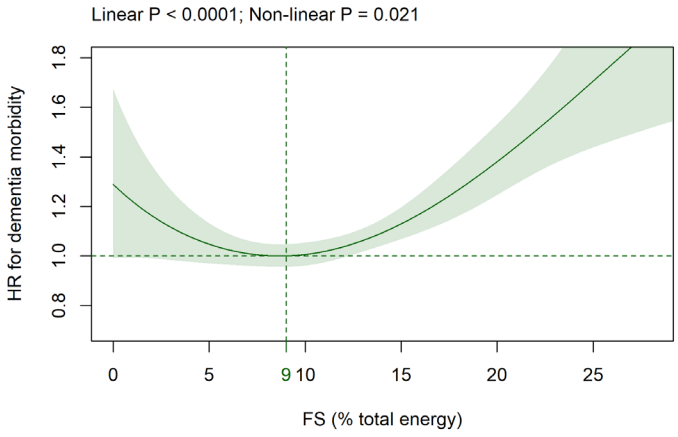

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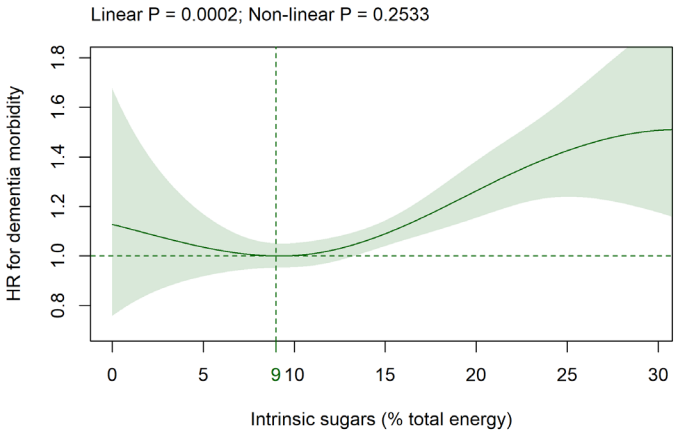

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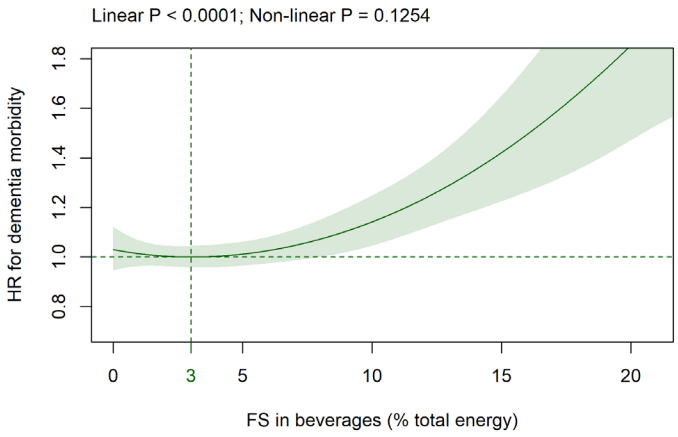

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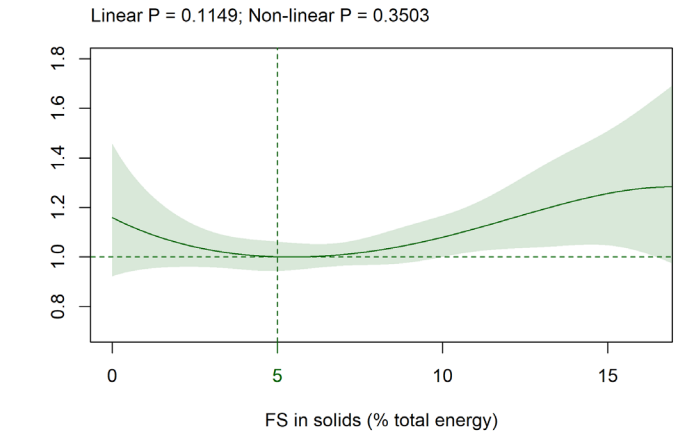

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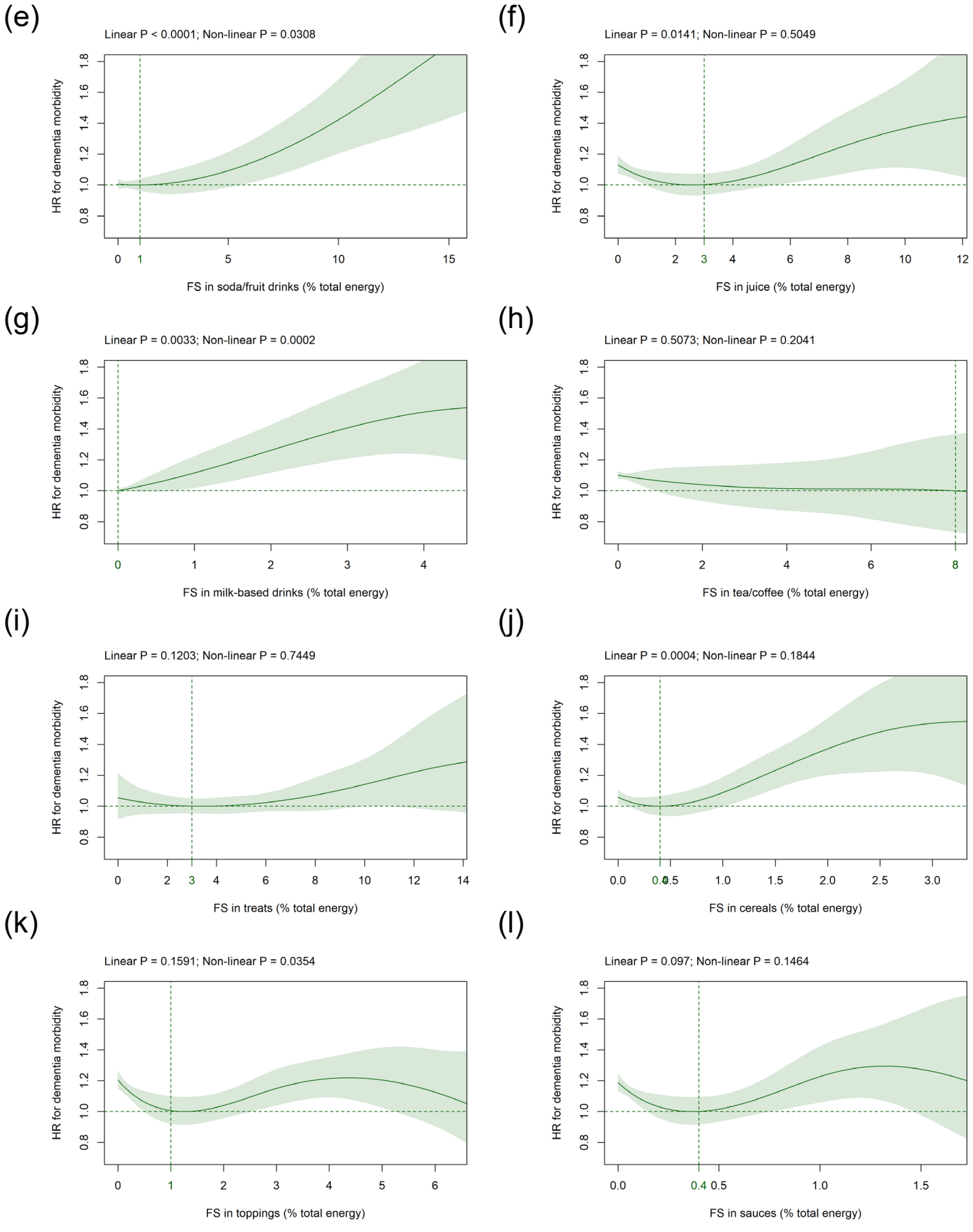

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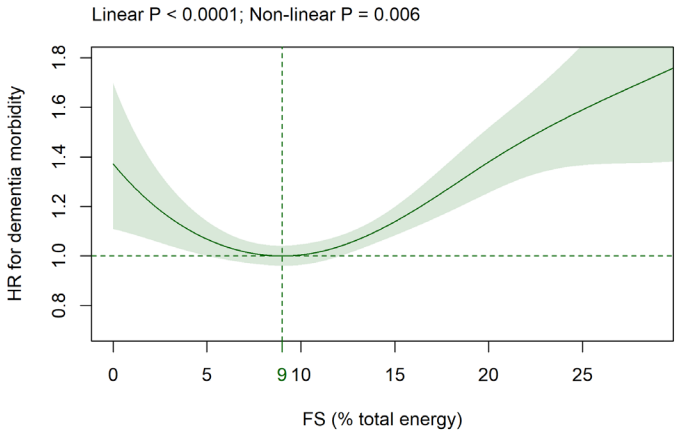

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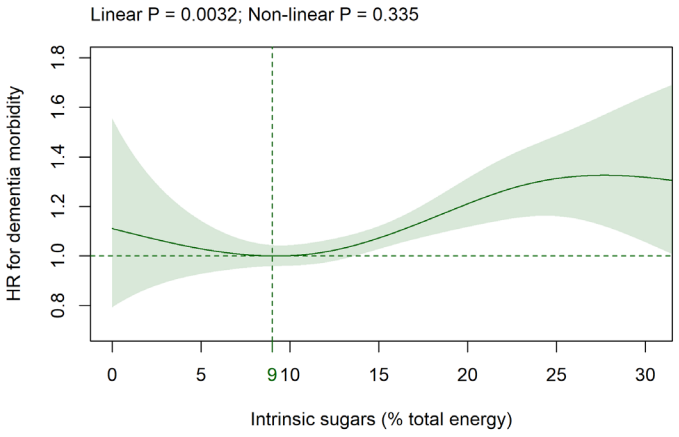

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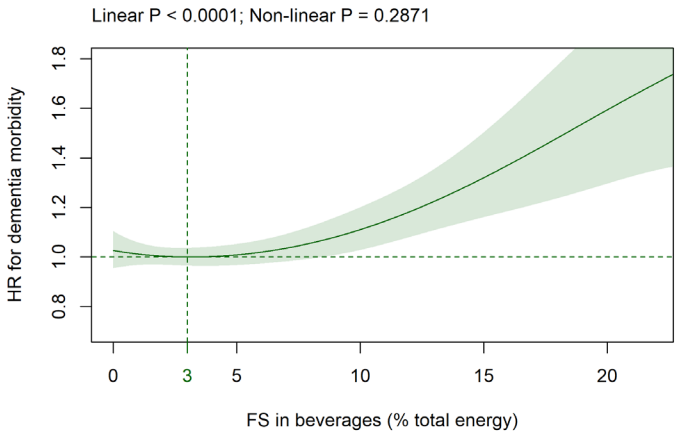

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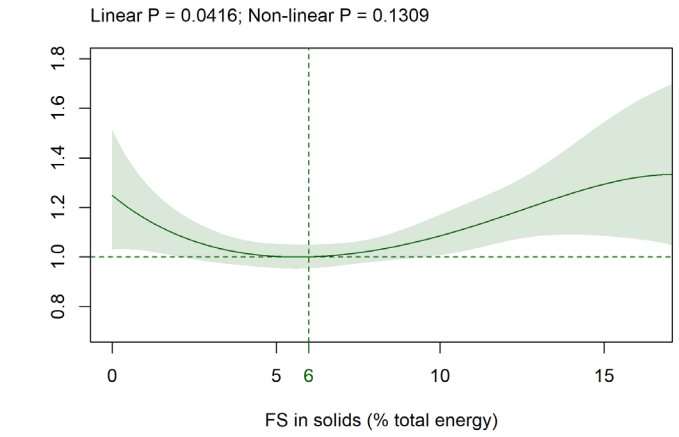

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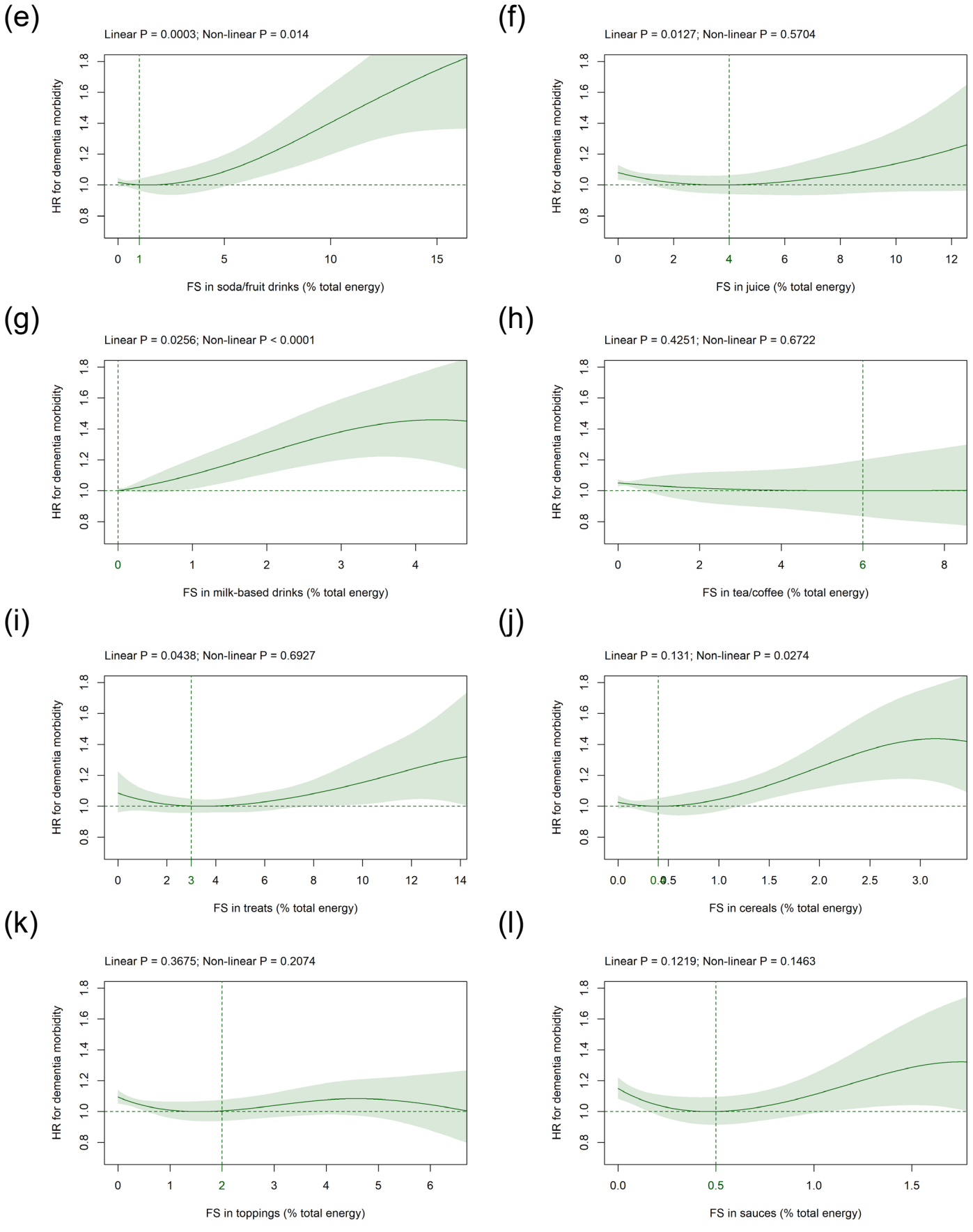

Figure S16 continued

Appendix D

Supplementary Material:

Association of sugar intake from different sources with cardiovascular disease incidence in the prospective cohort of UK Biobank participants.

Schaefer, S. M., Kaiser, A., Eichner, G., & Fasshauer, M. (2024). Association of sugar intake from different sources with cardiovascular disease incidence in the prospective cohort of UK Biobank participants. Nutrition Journal, 23(1), 22.

Supplementary Material

Nutrition Journal

Association of sugar intake from different sources with cardiovascular disease incidence in the prospective cohort of UK Biobank participants

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[#]SMS and AK contributed equally to this work and are joint first authors.

[§]GE and MF contributed equally to this work and are joint senior authors.

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Figure S1

Sugar sources relevant to the present study

Abbreviations: FS, Free sugars

Figure S2

Flowchart of participant selection

The following exclusion criteria were applied to all analyses: 1) missing lifestyle risk factors (physical activity or smoking status), 2) diagnosis of ischemic heart disease (IHD) or stroke before completion of the last Oxford WebQ (=pre-existing CVD, Cardiovascular disease), 3) missing socio-economic factors (Townsend deprivation index, total household income, ethnic background, highest qualification, or overall health rating), 4) missing data of the physical exam (body mass index (BMI), systolic blood pressure (SBP)), 5) pre-existing malabsorption or diabetes, 6) current pregnancy or the possibility of being pregnant, and 7) implausible energy or carbohydrate intake, i.e., 0 kJ/d intake on at least one occasion, being in the upper 0.1 % of total energy and/or carbohydrate consumption or total energy intake <1.1 × basal metabolic rate - 500 kcal (under-reporting) or >2.5 × basal metabolic rate + 500 kcal (over-reporting). Basal metabolic rate was defined according to the Oxford equation (1).

Figure S3

Directed acyclic graph

Directed acyclic graph representing the assumed relationships between variables that may affect the relationship between sugar intake (green disc with inscribed triangle; exposure) and risk of CVD (blue disc with inscribed vertical bar; outcome). Other blue discs denote ancestors of the outcome, i.e., direct or indirect predecessors of the outcome; white discs denote covariates for which the model was adjusted, i.e., age, energy intake, highest qualification, physical activity (MET per week), sex, and smoking. Grey discs denote other variables and pink discs denote ancestors of both exposure and outcome. Green arrows indicate causal paths.

Abbreviations: BMI, Body mass index; CVD, Cardiovascular disease; MET, Metabolic equivalent of task

Figure S4

Landmark analysis

Association of (a) FS, (b) intrinsic sugars, as well as FS in (c) beverages, (d) solids, (e) soda/fruit drinks, (f) juice, (g) milk-based drinks, (h) tea/coffee, (i) treats, (j) cereals, (k)

toppings, and (l) sauces (all %E) with CVD risk (landmark analysis; n=175,789; number of events=11,991). Models are adjusted for age, energy intake, highest qualification, physical activity, sex, and smoking status. Covariates not fulfilling the proportional hazard assumption are stratified. The vertical line indicates the nadir. Abbreviations: CVD, Cardiovascular disease; FS, Free sugars; HR, Hazard ratio

Figure S5

Unintentional weight loss removed

Association of (a) FS, (b) intrinsic sugars, as well as FS in (c) beverages, (d) solids, (e) soda/fruit drinks, (f) juice, (g) milk-based drinks, (h) tea/coffee, (i) treats, (j) cereals, (k) toppings, and (l) sauces (all %E) with CVD risk (unintentional weight loss removed; n=148,640; number of events=10,315). Models are adjusted and presented as indicated in Figure S4. Abbreviations: CVD, Cardiovascular disease; FS, Free sugars; HR, Hazard ratio

Figure S6

Non-typical diet removed

Association of (a) FS, (b) intrinsic sugars, as well as FS in (c) beverages, (d) solids, (e) soda/fruit drinks, (f) juice, (g) milk-based drinks, (h) tea/coffee, (i) treats, (j) cereals, (k) toppings, and (l) sauces (all %E) with CVD risk (non-typical diet removed; n=117,966; number of events=8,732). Models are adjusted and presented as indicated in Figure S4. Abbreviations: CVD, Cardiovascular disease; FS, Free sugars; HR, Hazard ratio

Figure S7

First Oxford WebQ only

Association of (a) FS, (b) intrinsic sugars, as well as FS in (c) beverages, (d) solids, (e) soda/fruit drinks, (f) juice, (g) milk-based drinks, (h) tea/coffee, (i) treats, (j) cereals, (k) toppings, and (l) sauces (all %E) with CVD risk. Only the first Oxford WebQ was used for intake estimation (n=176,352; number of events=12,355). Models are adjusted and presented as indicated in Figure S4. Abbreviations: CVD, Cardiovascular disease; FS, Free sugars; HR, Hazard ratio

Figure S8

Adjustment for diet quality score

Association of (a) FS, (b) intrinsic sugars, as well as FS in (c) beverages, (d) solids, (e) soda/fruit drinks, (f) juice, (g) milk-based drinks, (h) tea/coffee, (i) treats, (j) cereals, (k) toppings, and (l) sauces (all %E) with CVD risk. Models were further adjusted for diet quality score (n=174,164; number of events=12,145). Models are adjusted and presented as

indicated in Figure S4. Abbreviations: CVD, Cardiovascular disease; FS, Free sugars; HR, Hazard ratio

Figure S9

Only participants with >1 Oxford WebQ

Association of (a) FS, (b) intrinsic sugars, as well as FS in (c) beverages, (d) solids, (e) soda/fruit drinks, (f) juice, (g) milk-based drinks, (h) tea/coffee, (i) treats, (j) cereals, (k) toppings, and (l) sauces (all %E) with CVD risk. Only participants who completed more than one Oxford WebQ were included in the analysis (n=109,316; number of events=7,124). Models are adjusted and presented as indicated in Figure S4. Abbreviations: CVD, Cardiovascular disease; FS, Free sugars; HR, Hazard ratio

Figure S10

IHD + Stroke

Association of FS (a + b), intrinsic sugars (c + d), FS in beverages (e + f), FS in solids (g + h), FS in beverage subtypes (i to p) and FS in solids subtypes (q to x) (all %E) with IHD (n=176,929; number of events=9,950) and stroke (n=179,082; number of events=3,066). Models are adjusted and presented as indicated in Figure S4. Covariates not fulfilling the proportional hazard assumption are stratified. Abbreviations: FS, Free sugars; HR, Hazard ratio; IHD, Ischemic heart disease

Table S1

Overview of main results

Linear (p^{lin}) and non-linear ($p^{non\text{-}lin}$) p-values for associations with CVD, the nadir, as well as HRs (95% confidence intervals) at 0 %E of respective sugar (HR^0), and shape of the curve in case of significance. Abbreviations: CVD, Cardiovascular disease; %E; Percent total energy; FS, Free sugars; HR, Hazard ratio; NA, not applicable since non-significant results for p^{lin} and $p^{non\text{-}lin}$

References

1. Henry CJK. Basal metabolic rate studies in humans: measurement and development of new equations. Public Health Nutr 2005; 8(7A):1133–52.

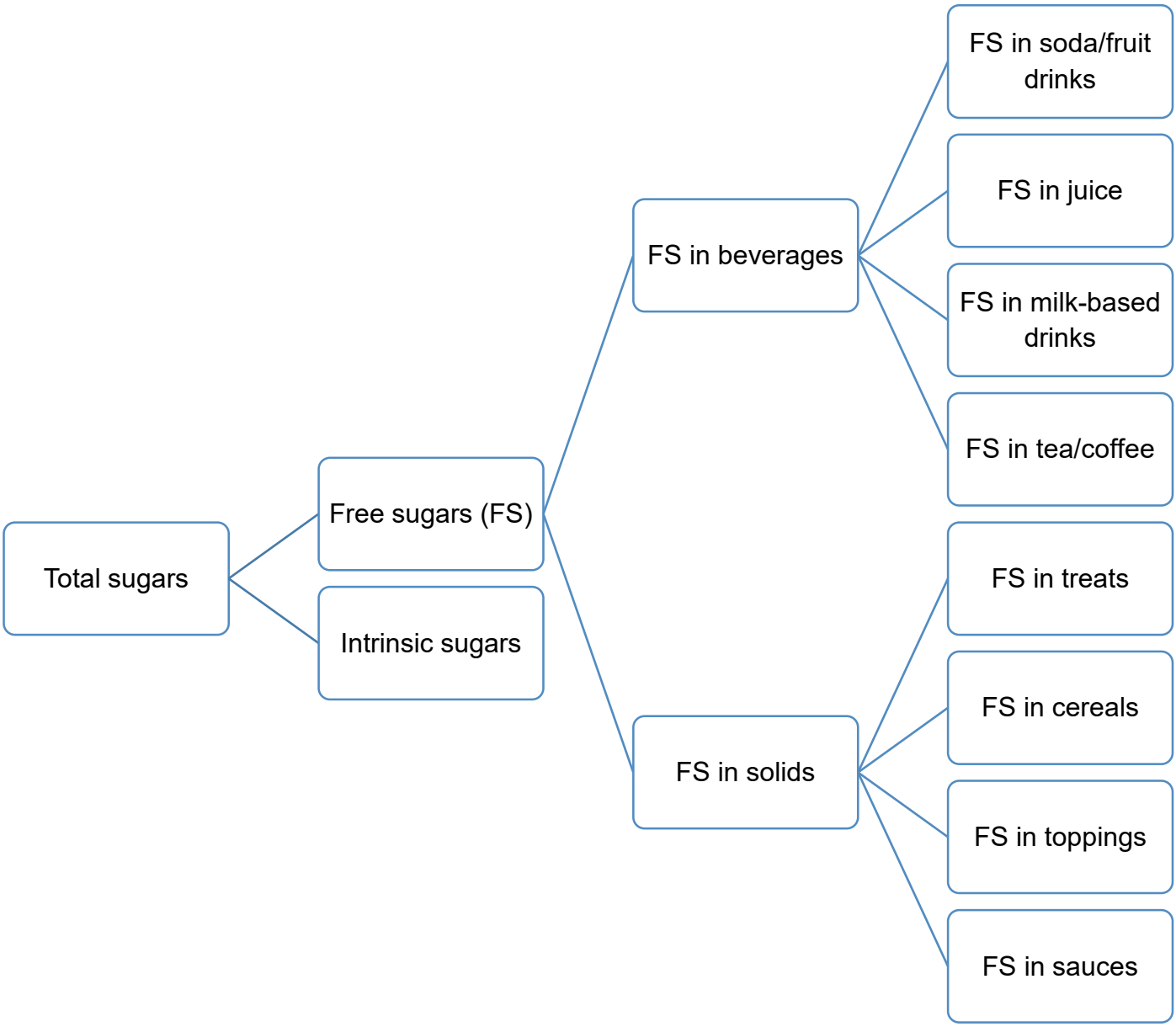

Figure S1 Sugar sources relevant to the present study

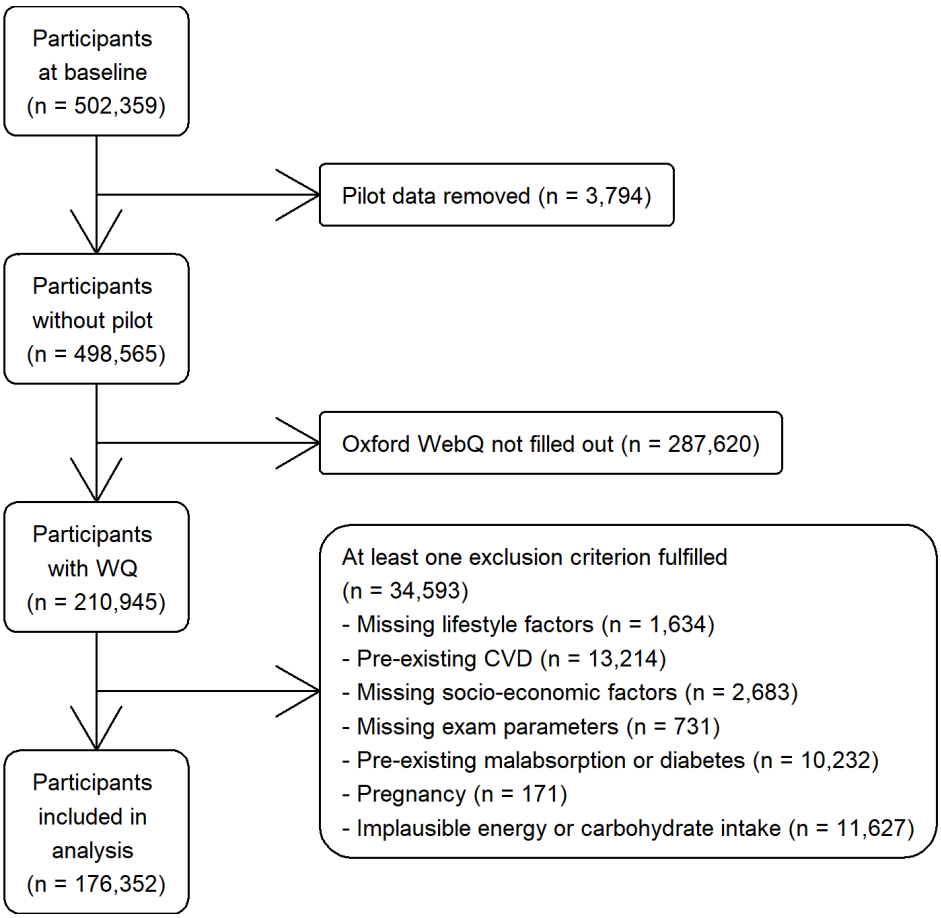

Figure S2 Flowchart of participant selection

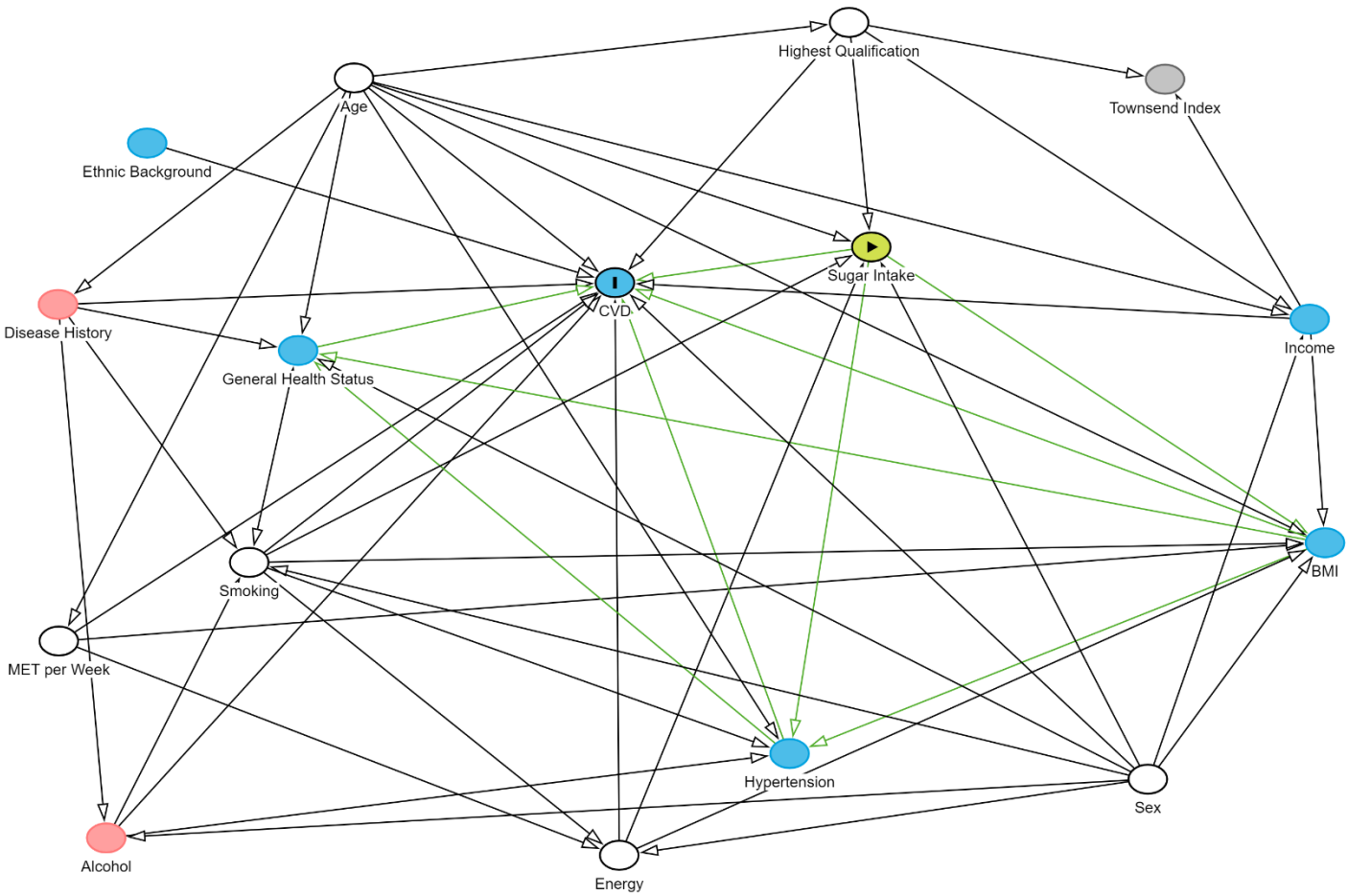

Figure S3 Directed acyclic graph

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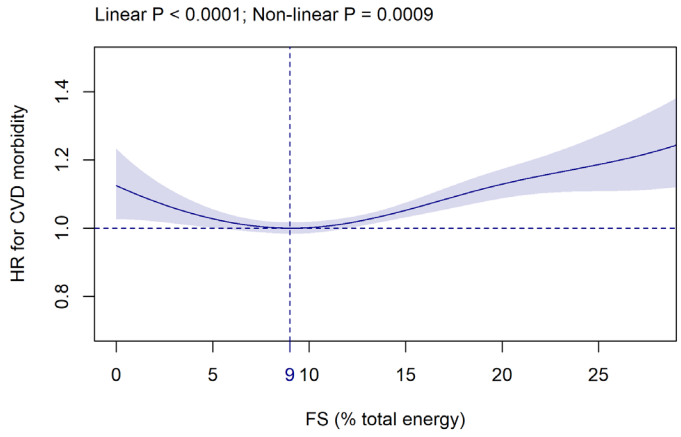

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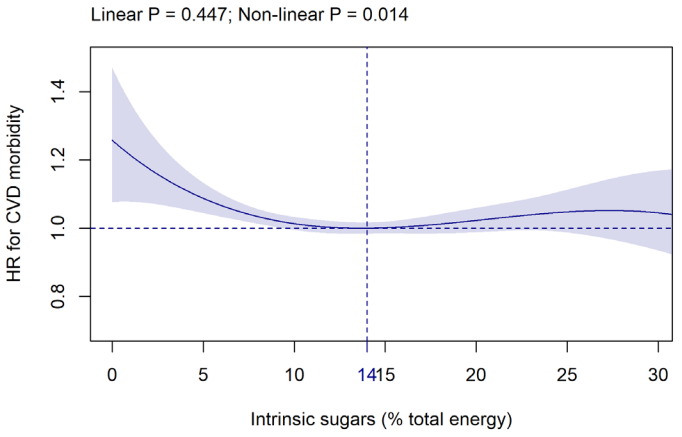

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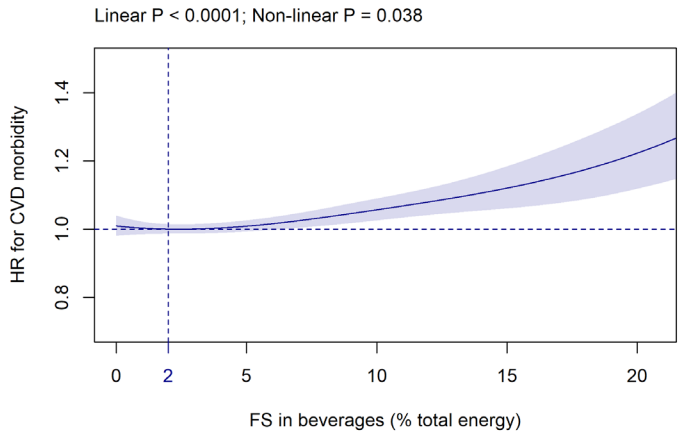

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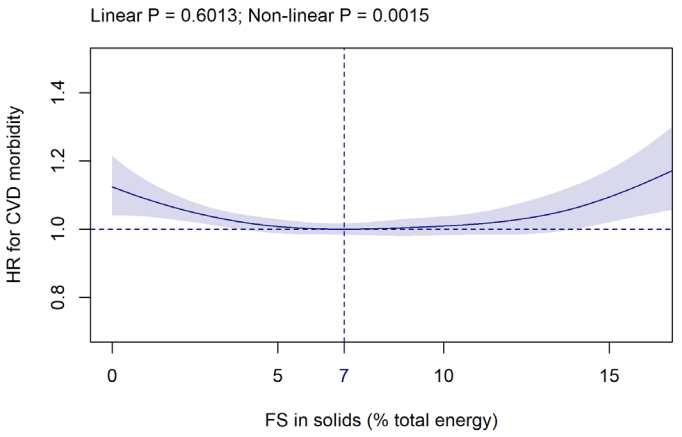


Figure S4 Landmark analysis

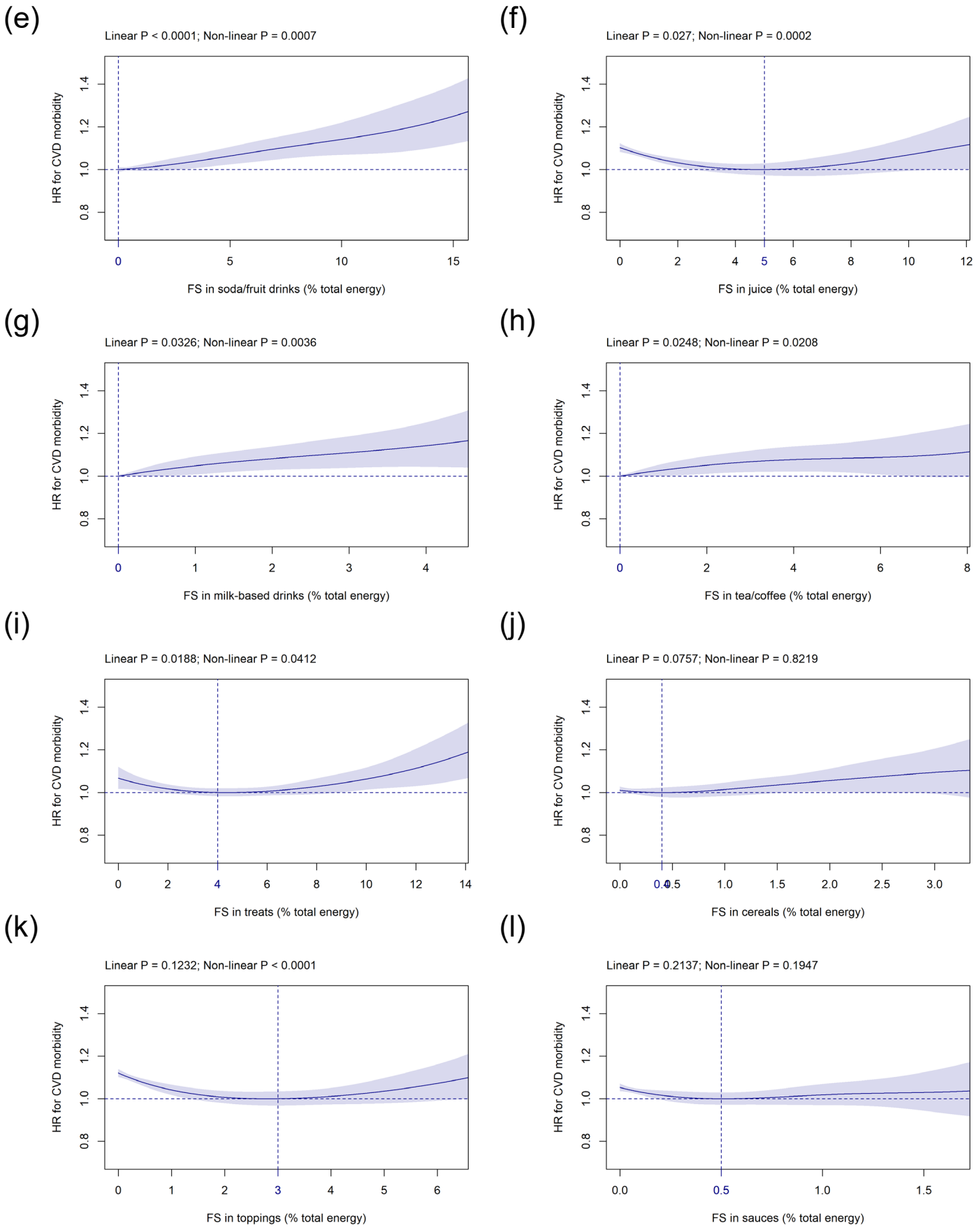


Figure S4 Landmark analysis continued

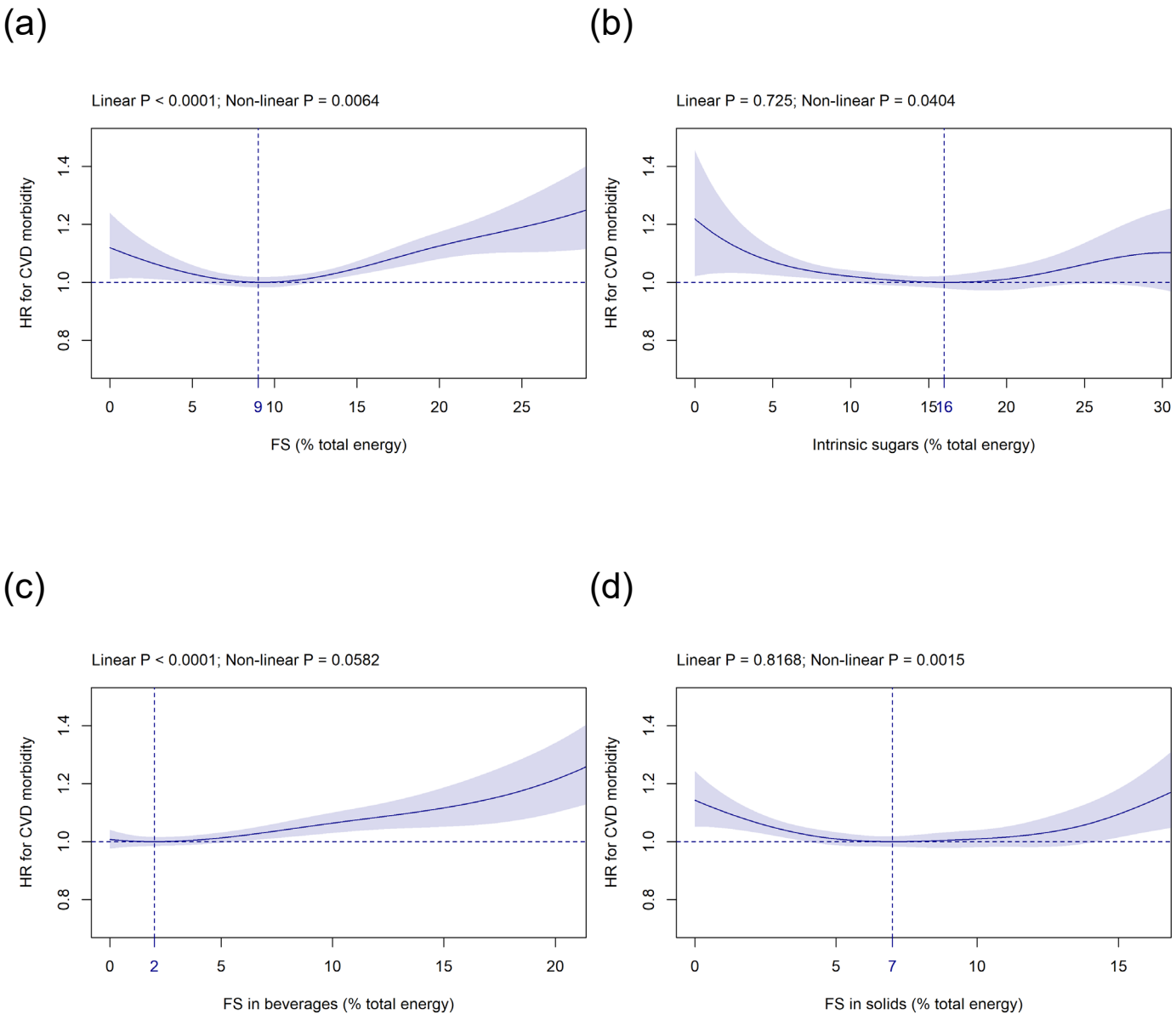


Figure S5 Unintentional weight loss removed

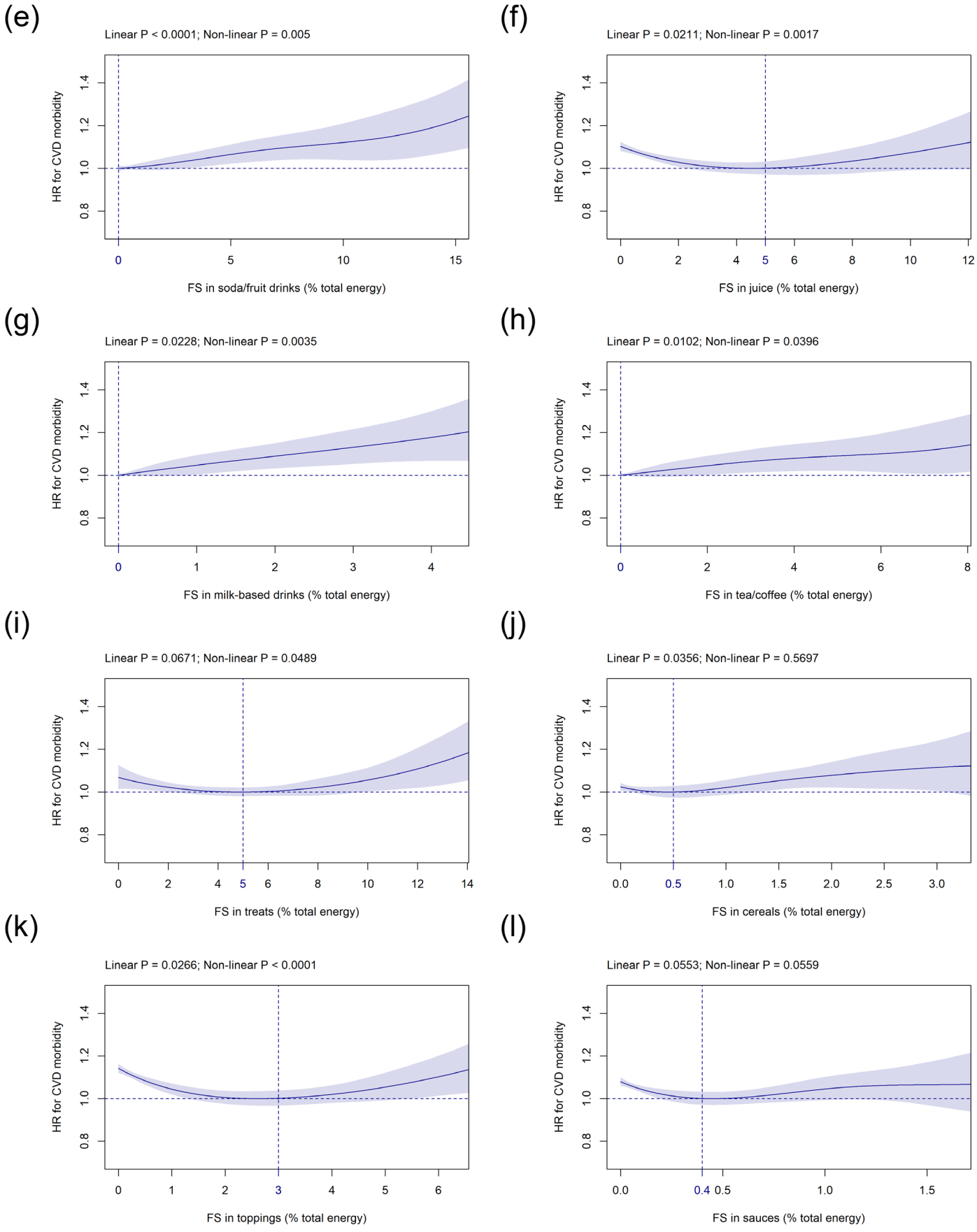


Figure S5 Unintentional weight loss removed continued

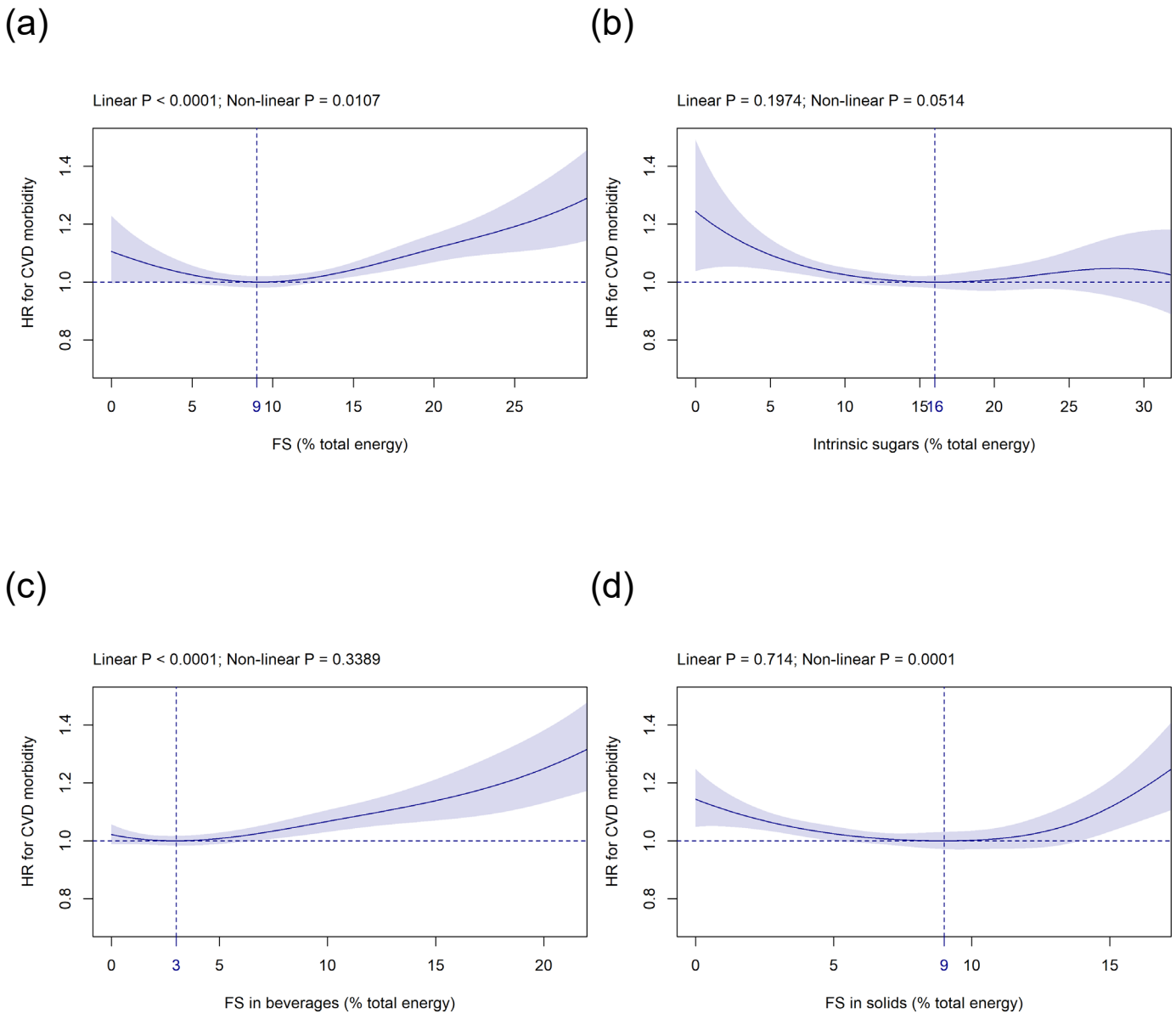


Figure S6 Non-typical diet removed

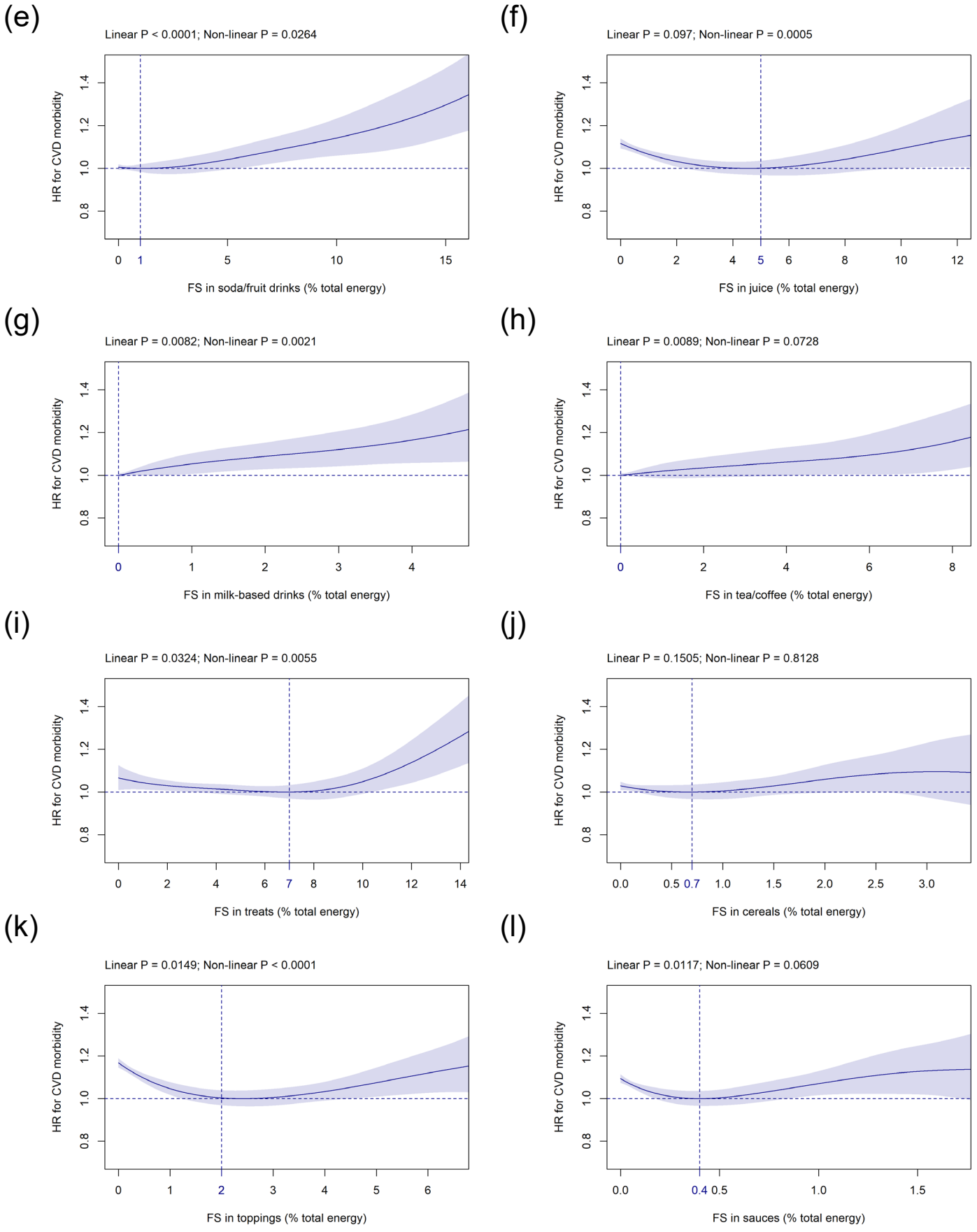
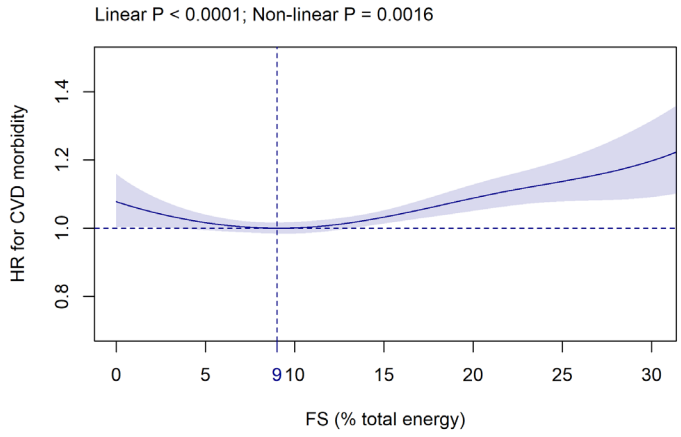
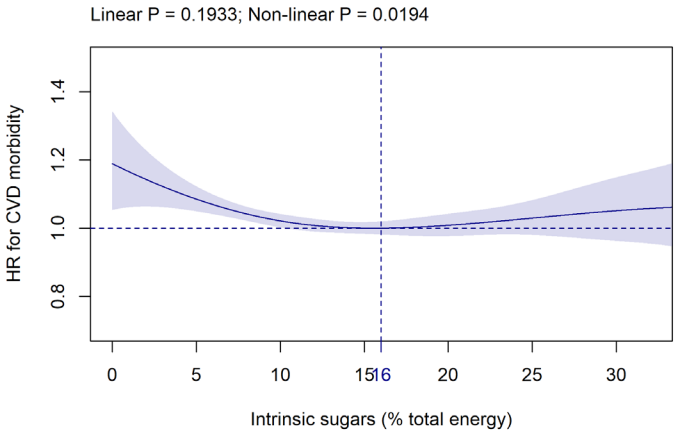


Figure S6 Non-typical diet removed continued

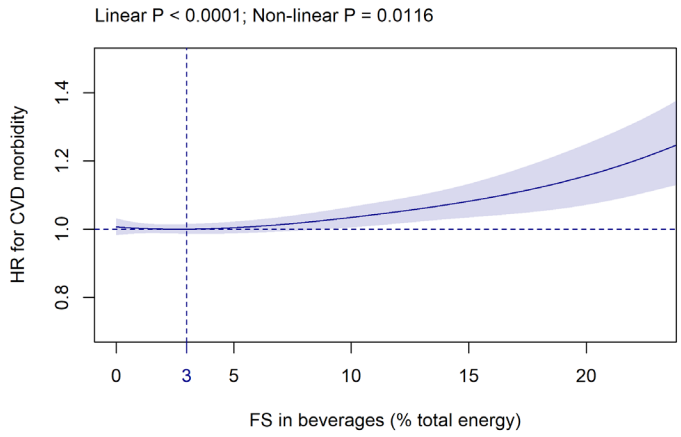
(a)



(b)



(c)



(d)

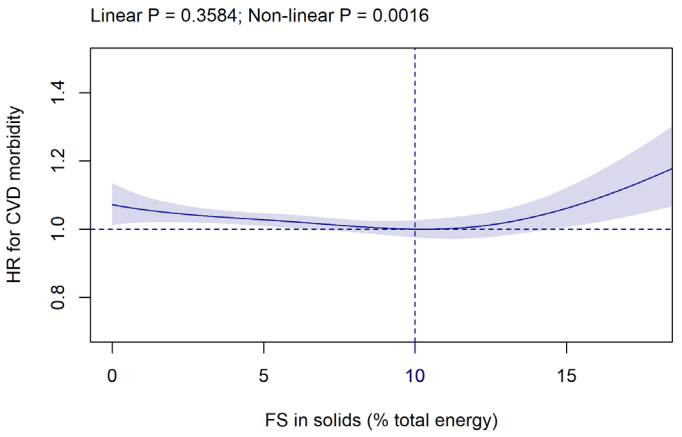


Figure S7 First Oxford WebQ only

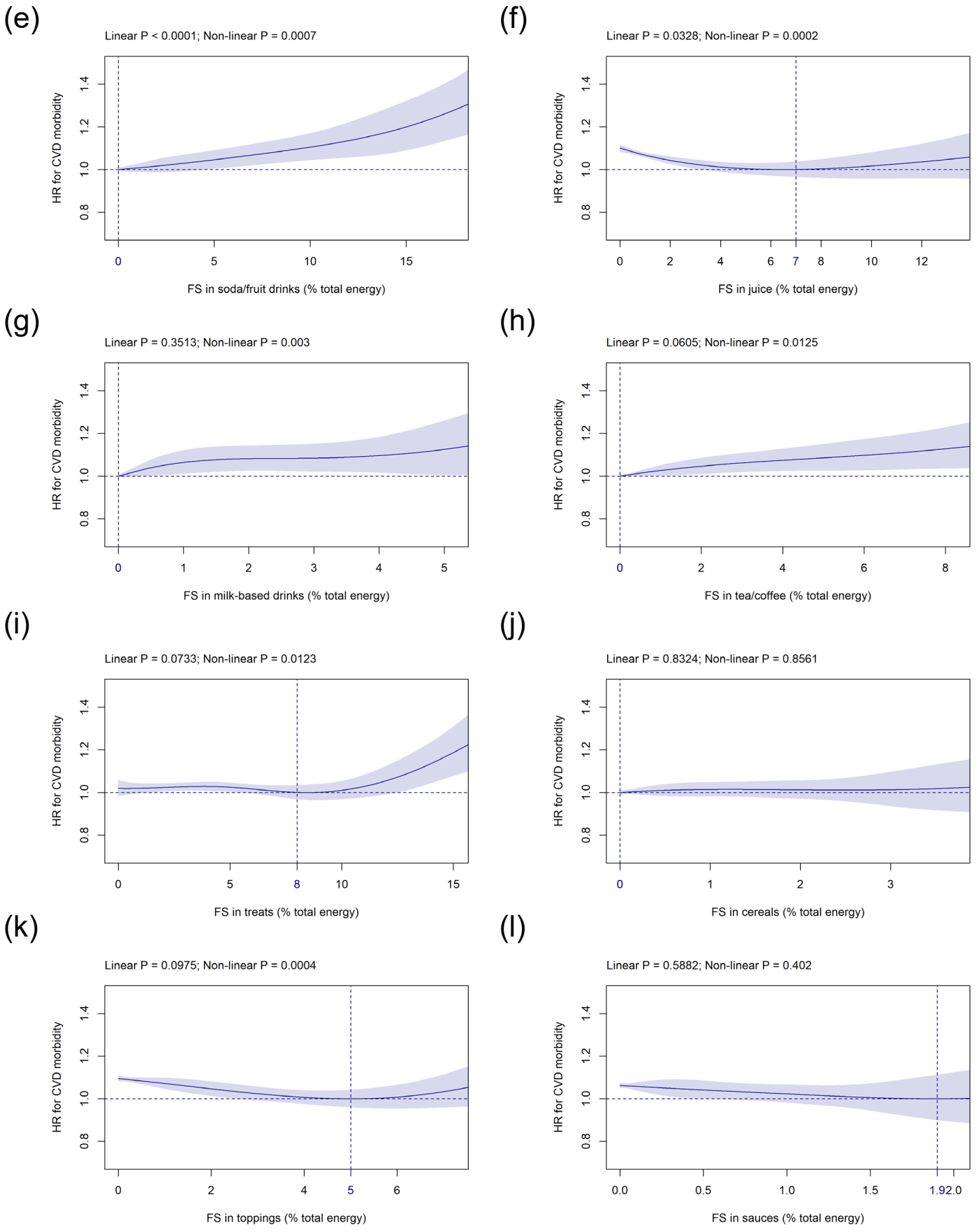
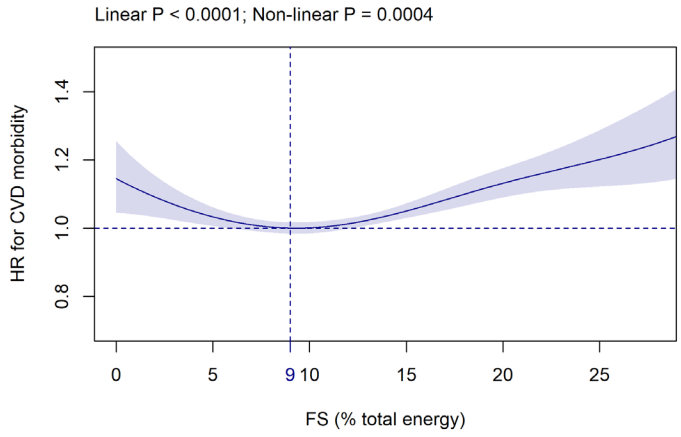
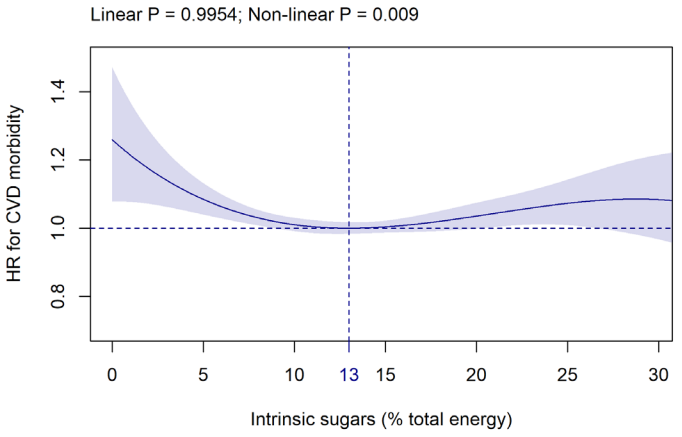


Figure S7 First Oxford WebQ only continued

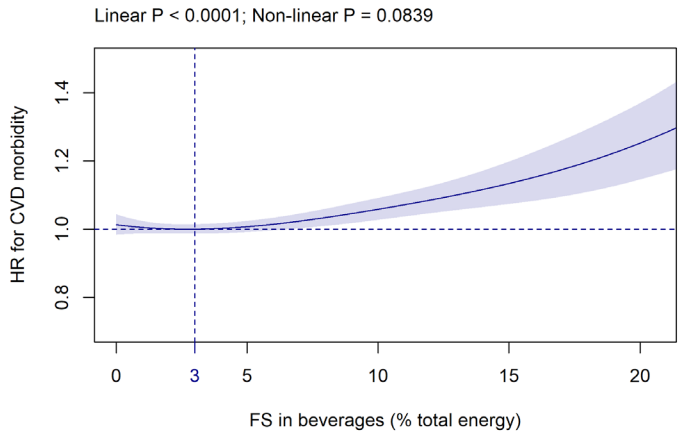
(a)



(b)



(c)



(d)

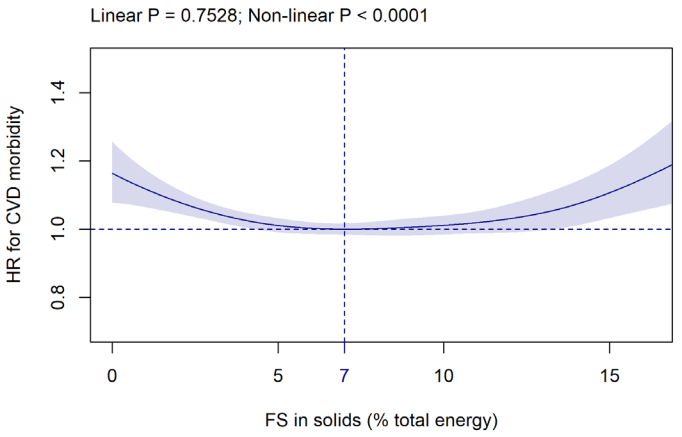


Figure S8 Adjustment for diet quality score

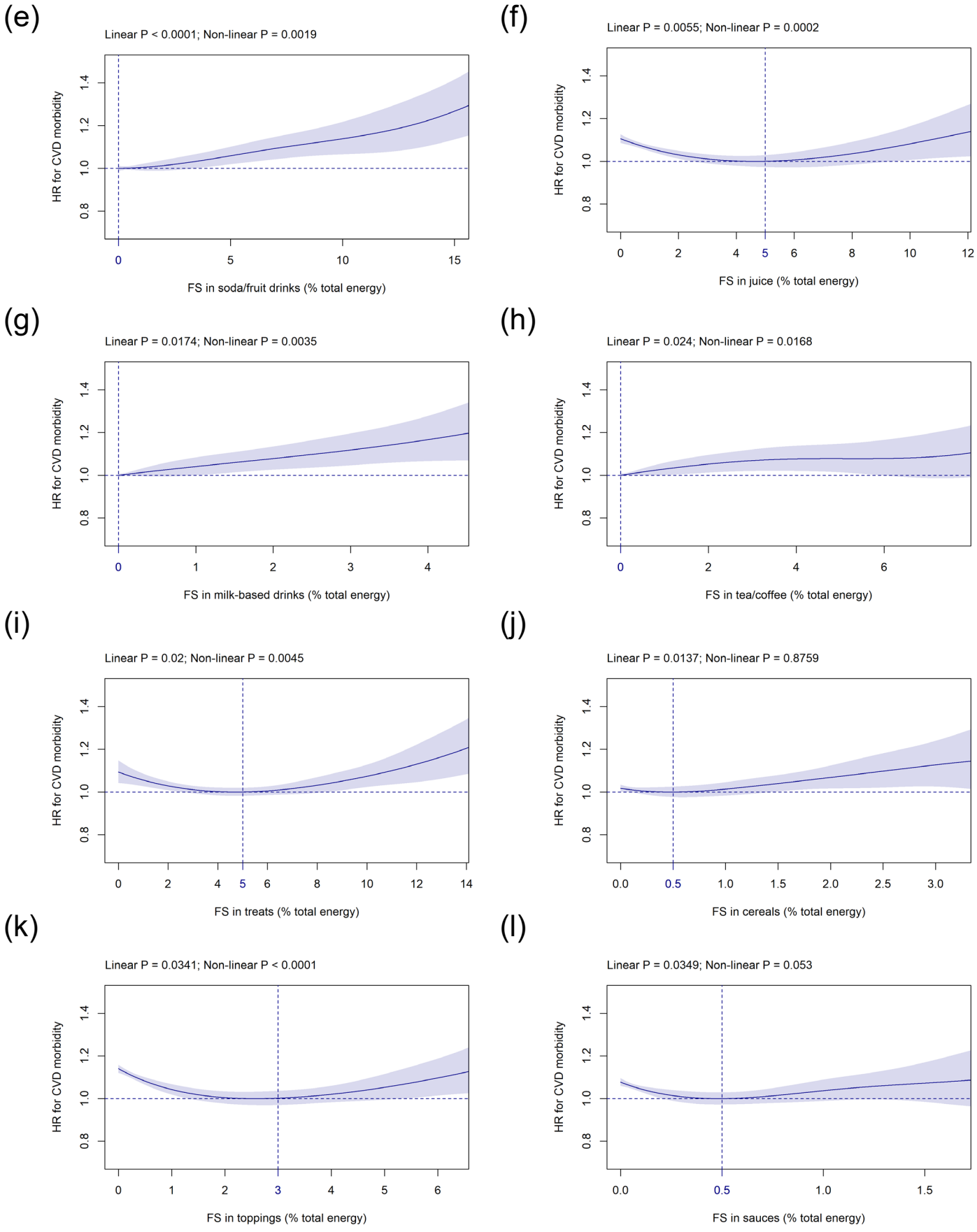


Figure S8 Adjustment for diet quality score continued

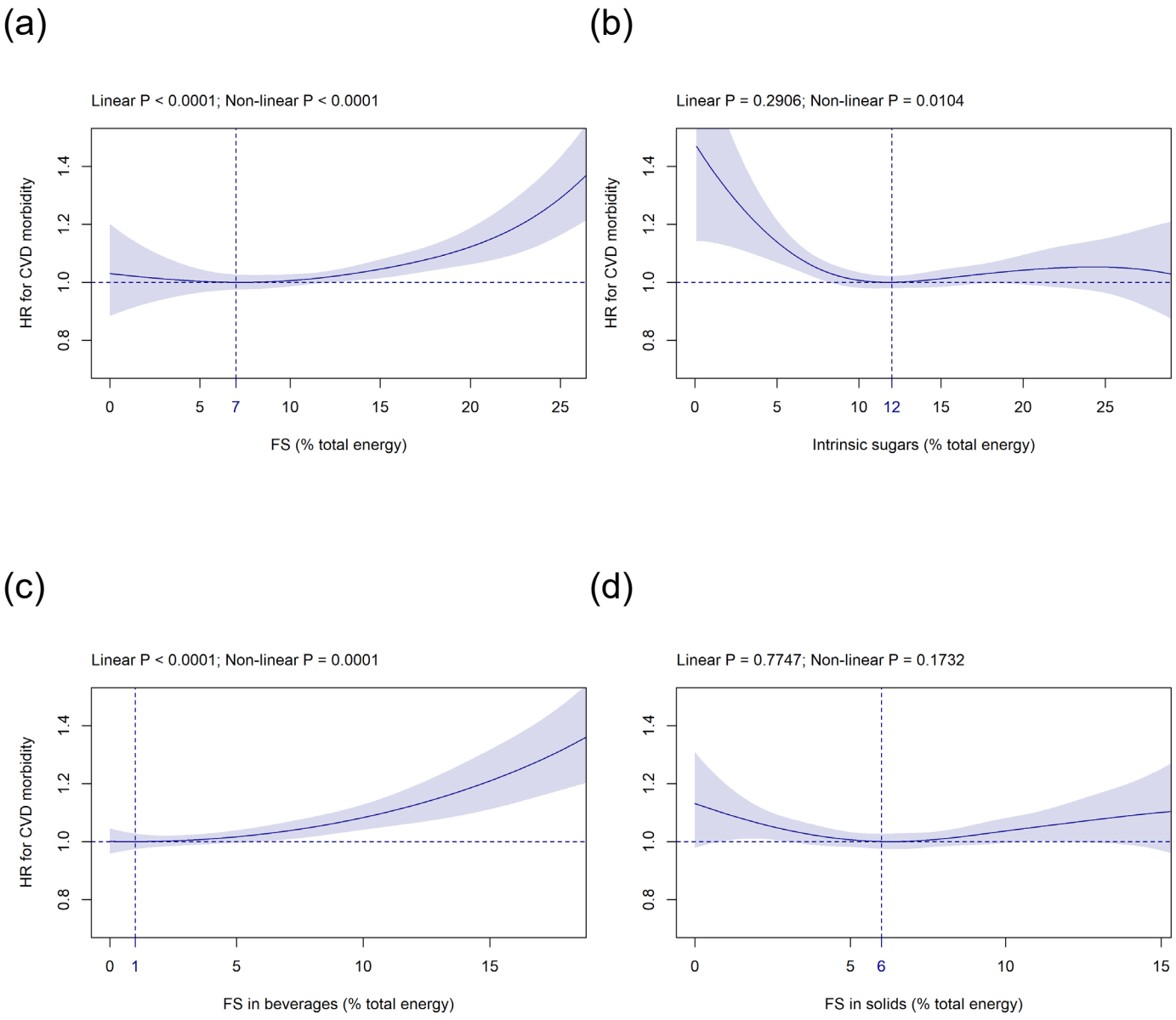


Figure S9 Only participants with >1 Oxford WebQ

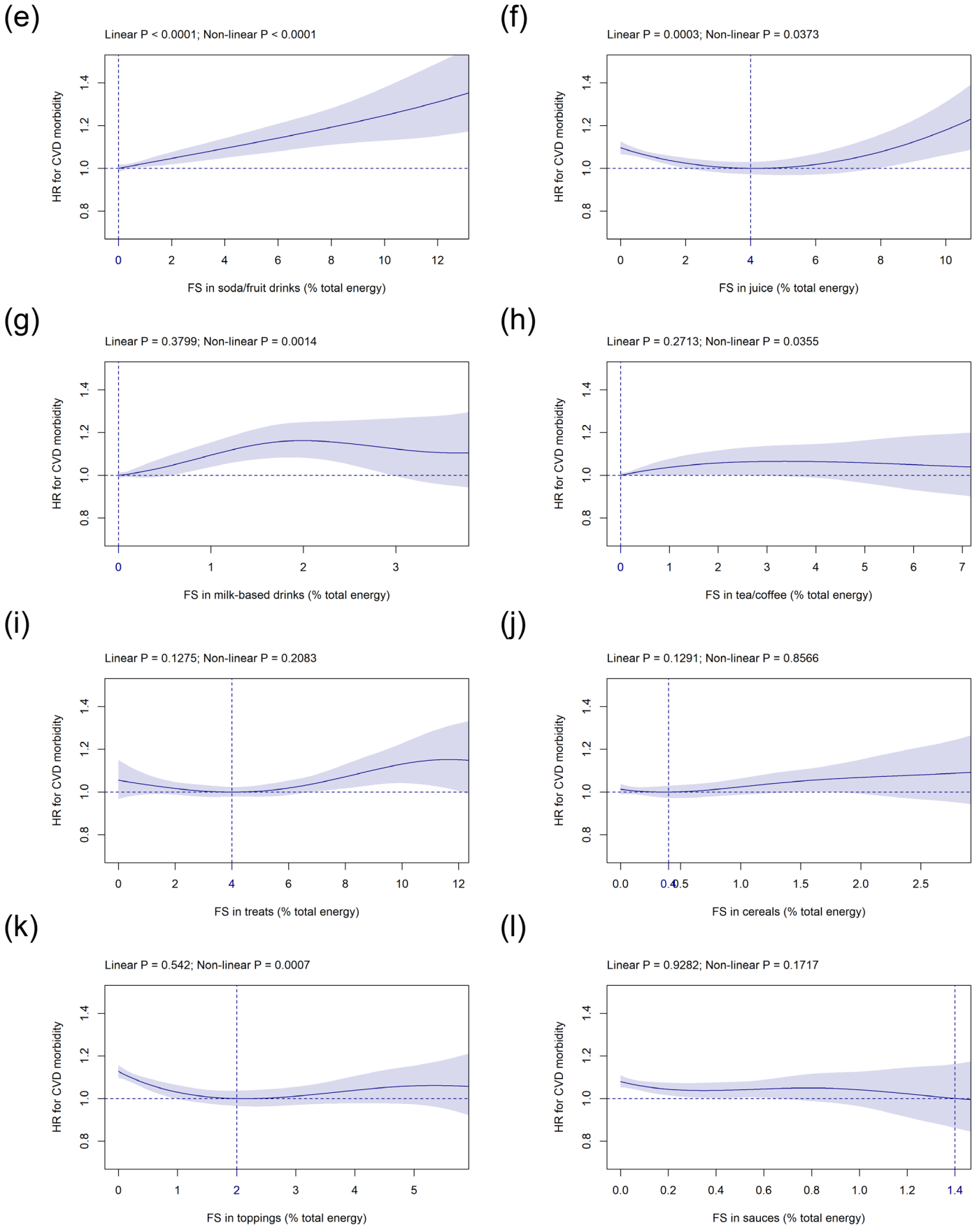


Figure S9 Only participants with >1 Oxford WebQ continued

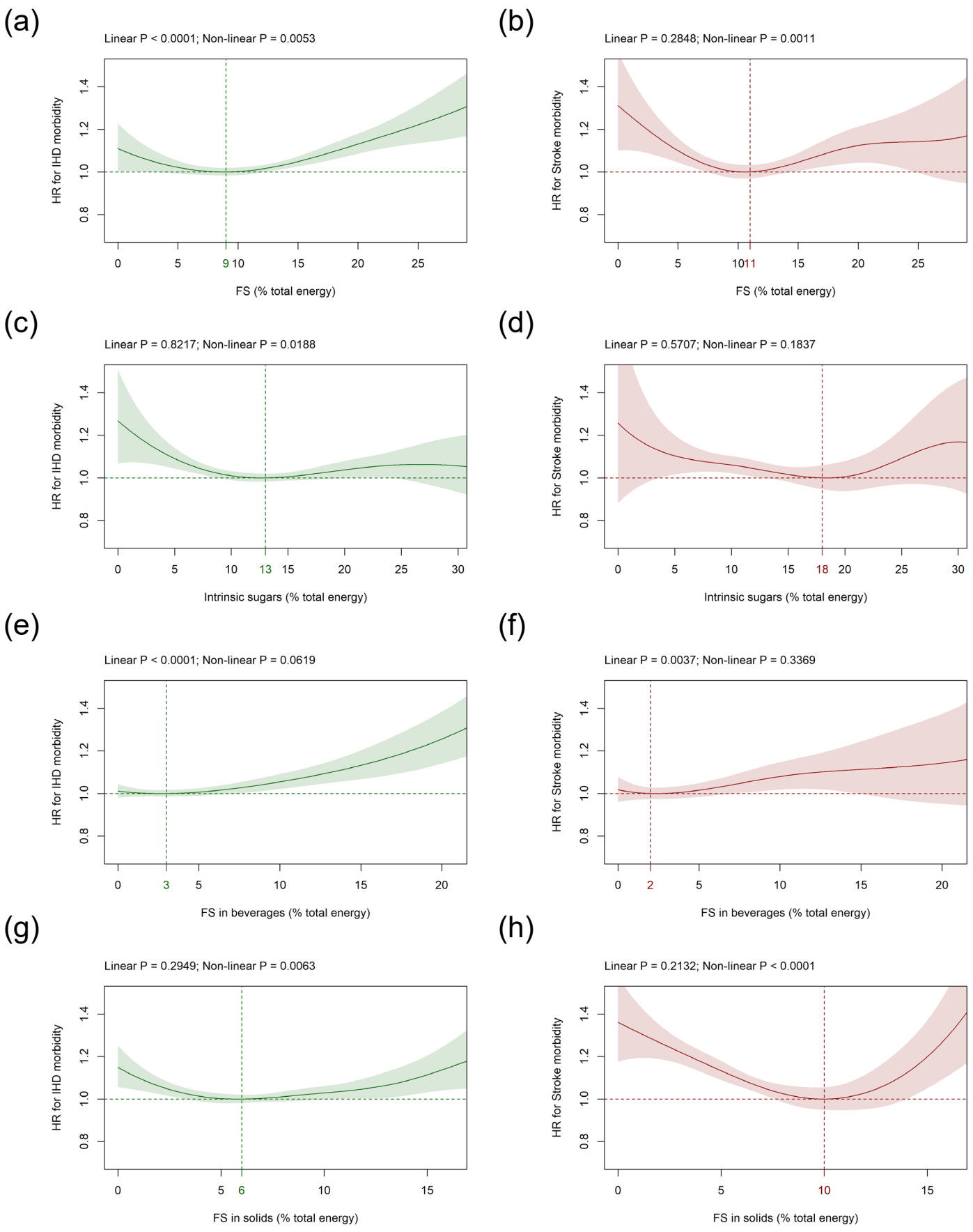


Figure S10 IHD + Stroke

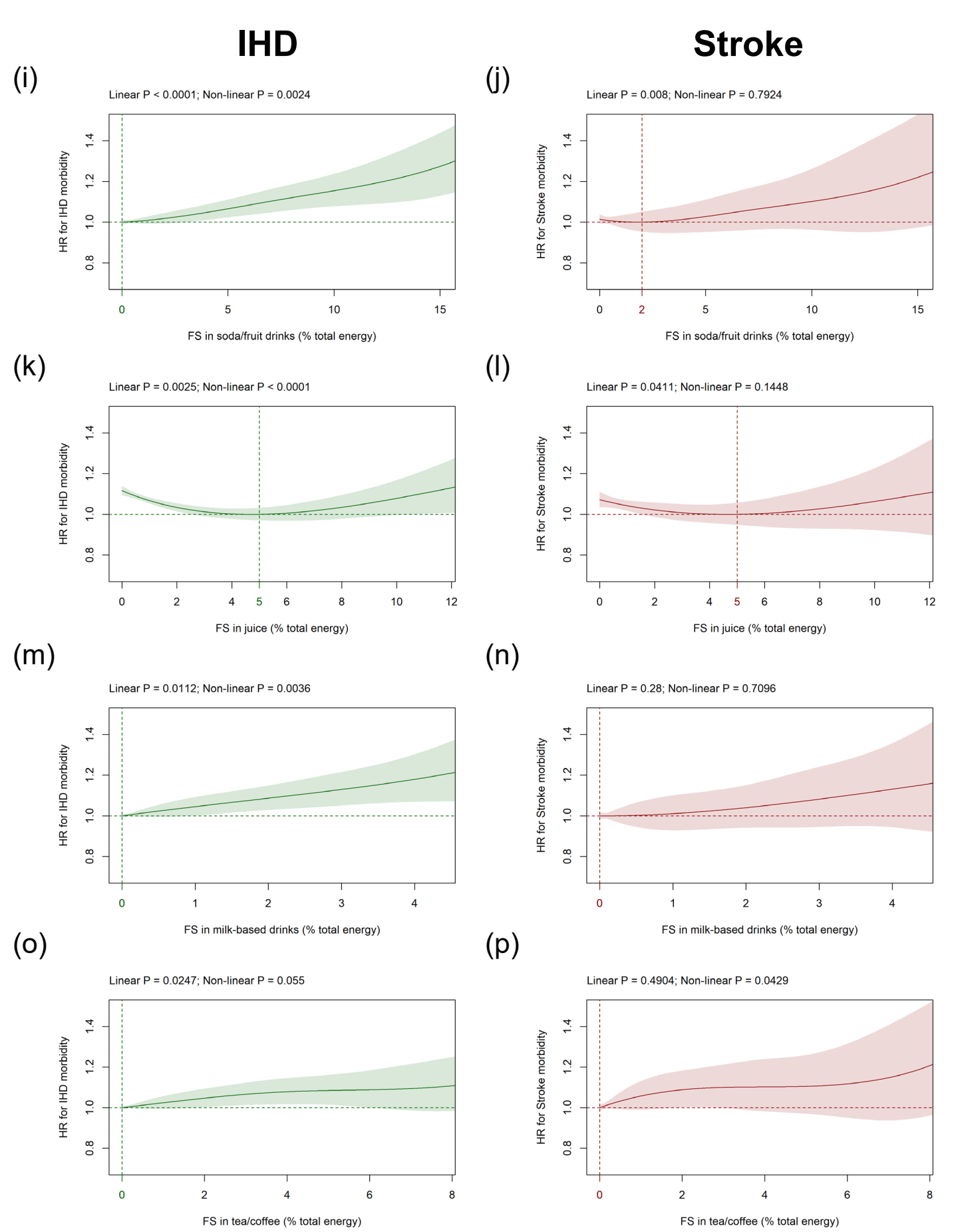


Figure S10 IHD + Stroke continued

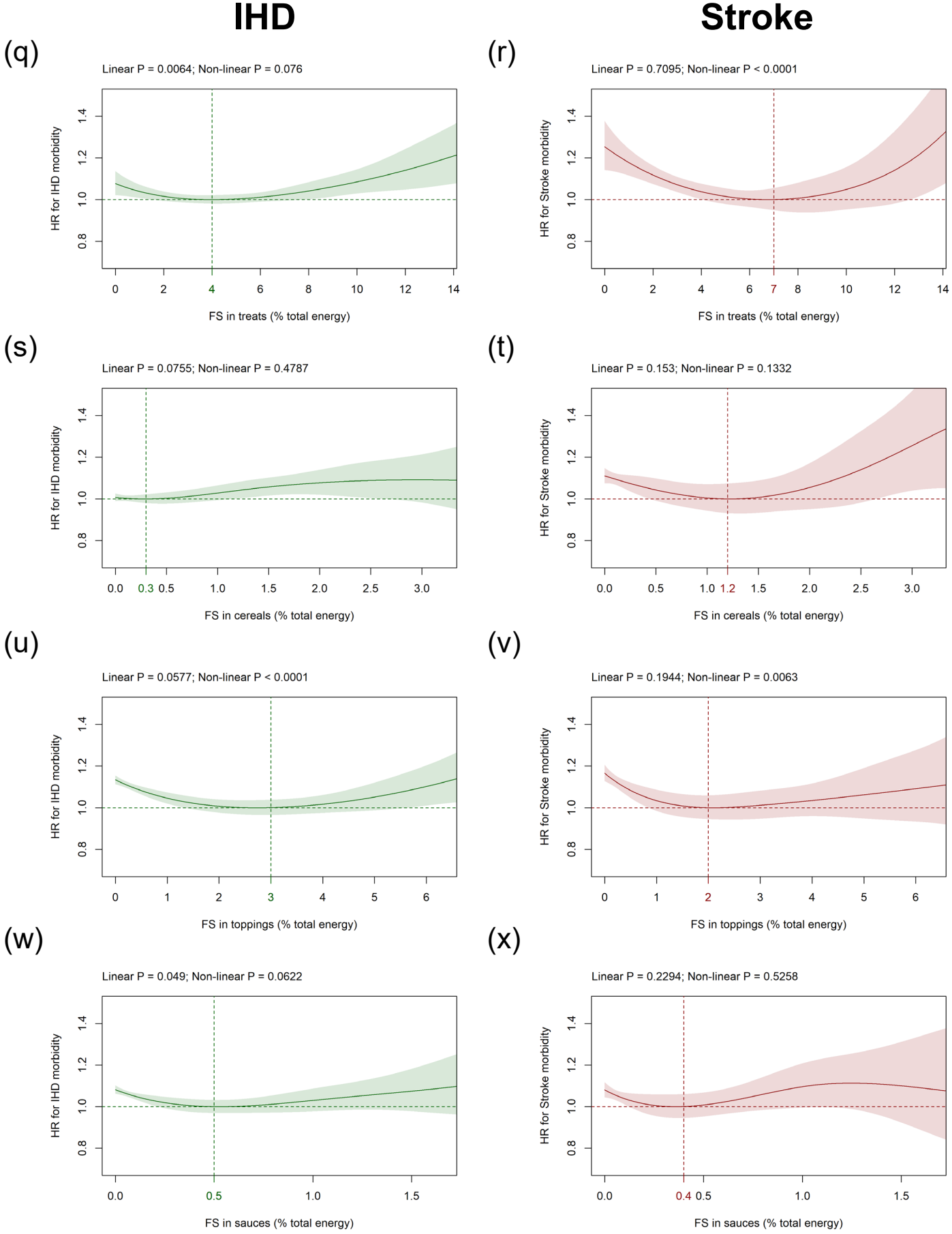


Figure S10 IHD + Stroke continued

Table S1 Overview of main results[1]

Type of sugar (%E)	p^{lin} / $p^{non\text{-}lin}$	Nadir (%E)	HR^0	Shape
FS	**<0.0001** / **0.0001**	9	1.15 (1.05, 1.26)	J-shaped
Intrinsic sugar	0.5032 / **0.0104**	14	1.26 (1.08 1.47)	Non-linear descending
FS in beverages	**<0.0001** / 0.0669	3	1.01 (0.99, 1.04)	Linear
FS in solids	0.6186 / **<0.0001**	7	1.16 (1.07, 1.25)	U-shaped
FS in soda/fruit drinks	**<0.0001** / 0.**0028**	0	1.00 (0.99, 1.01)	Linear
FS in juice	0.0117 / **<0.0001**	5	1.11 (1.09, 1.13)	U-shaped
FS in milk-based drinks	**0.0088** / **0.0049**	0	1.00 (0.99, 1.01)	Linear
FS in tea/coffee	0.**0162** / **0.0116**	0	1.00 (0.99, 1.01)	Linear
FS in treats	0.**0107** / 0.**0049**	5	1.09 (1.04, 1.14)	J-shaped
FS in cereals	**0.0148** / 0.8334	0.5	1.02 (1.00, 1.03)	Linear
FS in toppings	**0.0342** / **<0.0001**	3	1.14 (1.12, 1.16)	U-shaped
FS in sauces	**0.0358** / **0.0346**	0.5	1.08 (1.06, 1.10)	U-shaped

[1]Linear (p^{lin}) and non-linear ($p^{non\text{-}lin}$) p-values for associations with CVD, the nadir, as well as HRs (95% confidence intervals) at 0 %E of respective sugar (HR^0), and shape of the curve in case of significance. Abbreviations: CVD, Cardiovascular disease; %E; Percent total energy; FS, Free sugars; HR, Hazard ratio