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# Free sugar, fibre intake and mood disorders:

# an epidemiological investigation

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**Declaration of Authorship**

I, Anika Knüppel, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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## Abstract

The aim of this thesis is to investigate the role of high sugar intake from sweet food / beverages and high fibre intake as predictors of mood disorders, and as moderators of the association between financial insecurity and mood disorders.

The study was based on repeat measures of diet and mood disorders in the Whitehall II cohort. Analyses used random effects models with multiple 2, 5 and 10-year follow-up cycles. Diet was measured using food frequency questionnaires and defined as sugar intake from sweet food / beverages and fibre intake. Mood disorders were defined as common mental disorder (CMD, measured with the General Health Questionnaire), depression measured using Center for Epidemiologic Studies Depression scale, and the Revised Clinical Interview Schedule.

Sugar intake from sweet food / beverages was associated with increased odds of incident CMD after 5 years in men and with recurrent depression in women. Findings in men were similar when meta-analysing associations with incident antidepressant intake in Whitehall II and the EPIC-Norfolk study. There was no evidence that mood disorders are associated with a change in sugar intake from sweet food / beverages. Fibre intake was associated with reduced odds of incident CMD after 5 and 10 years. There was no strong evidence that mood disorders are associated with a change in fibre intake. Financial insecurity consistently increased odds of mood disorders, but there was no evidence for effect modification by sugar intake from sweet food / beverages or fibre intake.

Findings suggest an adverse effect of sugar intake from sweet food / beverages and a protective role of a diet high in fibre in long-term psychological health. There was no evidence that free sugar or fibre intake could moderate associations between financial insecurity and psychological health. Future research needs to clarify whether associations reflect a causal relationship.

## Impact statement

In high income countries depressive disorders are predicted to become the leading cause of disability by 2030 (Mathers & Loncar, 2006). Costs for the management of mental health problems are already higher than for any other disease and antidepressant prescriptions are on the rise (Centre for Mental Health, 2010; McManus *et al.*, 2009; NHS England, 2015; Lubian *et al.*, 2016). Identifying potential targets for prevention could decrease the burden for individuals and economies.

Recently diet and nutrition have been suggested as a potential target for the prevention of mood disorders and a few prospective studies have suggested a link with free sugar intake and fibre intake (Cabout M. *et al.*, 2017; Guo *et al.*, 2014; Gangwisch *et al.*, 2015; Sanchez-Villegas *et al.*, 2017, 2012).

Research in this thesis adds epidemiological evidence to the currently small number of prospective studies and addressed methodological weaknesses such as the use of mood measures that had not been validated or showed low sensitivity, a lack of studies investigating recurrent disorders and alternative explanations such as reverse causation. Furthermore, this thesis is the first to explore whether free sugars and fibre intakes could amplify or buffer the effect of mental health inequalities.

This added evidence could also inform basic research in investigating biological links in mood disorders and shape future research questions.

Nutritional guidelines and policies depend on sufficient evidence to draw conclusion what action is the most likely to result in better health for the population (EFSA Panel on Dietetic Products, 2010; Scientific Advisory Committee on Nutrition, 2015). While the findings of this thesis do not offer sufficient evidence for immediate public health action it does lend support for ongoing nutritional public health interventions to reduce free sugar and increase fibre intake in the population based on associations with physical health (Hu & Malik, 2010; Malik *et al.*, 2010; Sheiham & James, 2014; Stephen *et al.*, 2017; Hartley *et al.*, 2016; Morenga, Mallard & Mann, 2013).

This project has already had impact in the scientific and wider community (see Thesis outputs). The first publication from this research was covered in major news outlets such as The Guardian, New Scientist and The Daily Telegraph and has received worldwide attention. The paper was listed as being in the 99$^{th}$ percentile of all research outputs tracked by Altmetric.com and among the highest-scoring outputs from Scientific Reports (placing 40 of 48 025 articles) (Knüppel *et al.*, 2017; Altmetric, 2018).

Impact will be further brought about by open-access scientific publication and in presentations to the research community within the United Kingdom and internationally. Impact outside of academia was and will be generated by collaborating with the UCL press office and through web channels of the European research project MooDFOOD and their collaborator, the European Association for the Study of Obesity (EASO) (Cabout M. *et al.*, 2017; EASO, 2017). These channels are intended to reach the general public, policy makers and healthcare practitioners.

## Thesis outputs

### Publication:

Knüppel, A., Shipley, M. J., Llewellyn, C. H. & Brunner, E. J. (2017). Sugar intake from sweet food and beverages, common mental disorder and depression: prospective findings from the Whitehall II study. Scientific Reports, 7(1), 6287. https://doi.org/10.1038/s41598-017-05649-7.

### Presentations:

Association between dietary fibre intake and common mental disorder: Prospective findings from Whitehall II. Nutrition Society Summer Conference 2018 'Getting energy balance right', Leeds, UK (July 2018)

Role of sugar intake in the prevention of depression. International Union of Nutritional Sciences (IUNS) 21st International Congress of Nutrition (ICN), Buenos Aires, Argentina (October 2017)

Relationships between sugar intake from sweet food and beverages, common mental disorder and depression: prospective findings from the Whitehall II cohort study. Society for Social Medicine 61st Annual Scientific Meeting, Manchester, UK (September 2017)

Association of sweet food and beverage intake with common mental disorder in Whitehall II. Hot topic conference: Dietary Sugars, Obesity & Metabolic Disease Risk 2015, Berlin, Germany (June 2015; Poster presentation)

### Related outputs not included in the thesis:

Bidirectional association between weight and waist circumference change with common mental disorder: prospective findings from the Whitehall II study. 24th European Congress on Obesity (ECO), Porto, Portugal (May 2017)

Association of the Dietary Approaches to stop Hypertension (DASH) diet score with depressive symptoms in Whitehall II. 15th Congress of the International Federation of Psychiatric Epidemiology (IFPE), Bergen, Norway (October 2015)

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## Index of abbreviations

| | |
|---|---|
| 95%-CI | 95% confidence interval |
| AGE | Advanced glycation end-products |
| AUC | Area under the curve |
| BDI | Beck's Depression Inventory |
| BDNF | Brain-derived neurotrophic factor |
| BMI | Body mass index |
| CES-D | Center for Epidemiological Studies Depression Scale |
| CIS-R | Revised Clinical Interview Schedule |
| Cm | Centimetres |
| CMD | Common mental disorder |
| CRP | C-reactive protein |
| CVD | Cardiovascular disease |
| DASH | Dietary Approaches to Stop Hypertension |
| EE | Energy expenditure |
| EFSA | European Food Safety Authority |
| EI | Energy intake |
| EPIC | European Prospective Investigation of Cancer |
| FFQ | Food Frequency Questionnaire |
| g | Grams |
| GABA | Gamma-amino butyric acid |
| GAD | Generalised anxiety disorder |
| GDS | Geriatric depression scale |
| GHQ | General Health Questionnaire |
| HAM-A | Hamilton Anxiety rating scale |
| HAM-D | Hamilton Depression rating scale |
| HC | Health check |
| HLEQ | Health and Life Experience Questionnaire |
| HM | Her Majesty's |
| HPA | Hypothalamic–pituitary–adrenal |
| HR | Hazard Ratio |
| ICD 10 | International Classification of Diseases and Related Health Problems 10th Revision |
| IL-6 | Interleukin 6 |
| kcal | Kilocalories |
| kg | Kilograms |
| LR | Likelihood ratio |
| LNAA | Large neutral amino acids |
| m | Metres |
| M | Men |

| | |
|---|---|
| MHI | Mental health index scale |
| MooDFOOD | Multi-country collaborative project on the role diet, food-related behaviour, and obesity in the prevention of depression |
| NDNS | National Diet and Nutrition Survey |
| NHS | National Health Service |
| OR | Odds Ratio |
| p | P-value |
| PHQ-9 | Patient Health Questionnaire 9 |
| PV | Predictive value |
| RCT | Randomised controlled trial |
| REM | Random effects model |
| SD | Standard deviation |
| SE | Standard error |
| SFA | Short-chain-fatty acids |
| SUN | Seguimiento University of Navarra |
| SSRI | Selective serotonin reuptake inhibitors |
| UK | United Kingdom |
| W | Women |
| WHO | World Health Organization |
| VNS | Vagus nerve stimulation |

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# Chapter 1 **Introduction**

The aim of this thesis is to investigate the role of sugar intake from sweet food / beverages and dietary fibre intake in mood disorders directly and their ability to modify an association between financial insecurity and mood disorders. The topic was developed as part of a Europe-wide research collaboration inspired by observational research that found associations between diet intake and mood disorders (Akbaraly *et al.*, 2009; Lai *et al.*, 2014; Rahe, Unrath & Berger, 2014; Cabout M. *et al.*, 2017).The 'Multi-country collaborative project on the role of diet, food-related behaviour, and obesity in the prevention of depression'(MooDFOOD) aimed to extend the understanding of the pathways and bidirectional links of food intake, nutrient status, food-related behaviours and obesity with depression (Cabout M. *et al.*, 2017).

After World War II, diets shifted towards higher energy, higher sugar and lower dietary fibre intakes in many countries (Popkin & Nielsen, 2003). In Europe and the United Kingdom (UK), current free sugar intakes are above recommended levels and fibre intakes below (Azaïs-Braesco *et al.*, 2017; Public Health England, 2018). Meanwhile, more than one in seven people suffer from anxiety or depressive disorder each year (Steel *et al.*, 2014).

Biological effects of free sugars and dietary fibre overlap with dysregulation in mood disorders. Free sugars may affect mood disorders by lowering brain-derived neurotrophic factor (BDNF) levels (Molteni *et al.*, 2002; Belmaker & Agam, 2008; Duman & Monteggia, 2006), increasing inflammation (Calder *et al.*, 2011; Dantzer *et al.*, 2008), changing dopaminergic neurotransmission (Avena, Rada & Hoebel, 2008; Dunlop & Nemeroff, 2007) and through mood and hormonal responses to blood sugar levels (Virally & Guillausseau, 1999; Schwartz *et al.*, 1987; Mitrakou *et al.*, 1991; Fanelli *et al.*, 1994). Dietary fibre intake plays an important role in shaping the composition and metabolism of the gut microbiome (Simpson & Campbell, 2015). The gut microbiome may affect mood disorders through influencing tryptophan and neurotransmitter availability (Rieder *et al.*, 2017; Jiang *et al.*, 2015), vagus nerve stimulation (Nemeroff *et al.*, 2006; Forsythe, Bienenstock & Kunze, 2014) and also the immune system (Dantzer *et al.*, 2008; Rieder *et al.*, 2017).

To date, few prospective studies have investigated the association between free sugar, sweet food and beverages, dietary fibre intake and mood disorders (Gangwisch *et al.*, 2015; Sanchez-Villegas *et al.*, 2017, 2012; Guo *et al.*, 2014; Akbaraly *et al.*, 2013). Further, no previous study has investigated the roles of sugar intake from sweet food / beverages or fibre intake in generating social inequalities in mental health.

## Thesis structure

The thesis is structured as follows: Chapter 2 introduces mood disorders, free sugars and fibre intake and the links between them. Chapter 3 sets out the thesis aims, objectives and hypotheses. Chapter 4 describes the Whitehall II cohort study, methods of data collection, statistical analysis and some characteristics of the data are investigated. Chapter 5 covers the first of the three main objectives, whether a diet high in sugar intake from sweet food and beverages is a risk factor for mood disorders. Chapter 6 investigates whether a diet high in fibre is a protective factor in mood disorders. Chapter 7 evaluates whether sugar intake from sweet food and beverages and fibre intake act as moderators in the association between financial insecurity and mood disorders. Lastly in Chapter 8 the findings, and their strengths and limitations, are discussed in epidemiological and societal context and conclusions are drawn about the extent to which psychological health at population level can be improved through dietary change, specifically changes involving reduced free sugar and increased dietary fibre intakes.

# Chapter 2 **Literature review**

## Chapter overview

This chapter introduces mood disorders, free sugar and dietary fibre intake in terms of definitions, measurement and prevalence. Potential biological explanations for associations between sugar or sweetness, fibre intake and mood disorders are mapped. The role of diet in the association between financial insecurity and mood disorders is explored before reviewing the epidemiological evidence of associations between free sugars, sweet foods and beverages, dietary fibre intake and mood disorders and interactions with financial insecurity and socio-economic position. Last, the evidence reviewed in the chapter is synthesised in order to identify gaps which if addressed successfully, will add to existing knowledge.

## 2.1 Mood disorders

### *2.1.1 Definitions and classification*

In this thesis ‘mood disorder’ is used as an umbrella term for common mental disorders (CMD) including depressive disorder. CMDs include different types of anxiety and depressive disorders that interfere with daily life (Goldberg, 1995; Goldberg & Huxley, 1992; Stansfeld *et al.*, 2016). There is no established biochemical or physiological test for depression, therefore the classification is based on descriptions of symptoms and behaviours. Distinctions, such as those between anxiety and depressive disorders remain subject to debate (Goldberg, 2010; North & Yutzy, 2010; WHO, 2015b).

In the International Statistical Classification of Diseases and Related Health Problems (ICD) mood (affective) disorders are covered by the ICD 10 codes F30-F39 describing manic episodes (F30); bipolar disorder (F31); major depressive disorder, single episode (F32); major depressive disorder, recurrent (F33); persistent mood (affective) disorders (F34); other and unspecified mood (affective) disorder (F38, 39). These disorders are dominated by prolonged disturbance of mood which are mainly feelings of depression, anxiety, elation and sometimes excitement (WHO, 2016). Mood disturbances surface as episodes lasting at least 1-2 weeks depending on type of disorder (North & Yutzy, 2010). It has to be noted, that other psychiatric illnesses can lead to symptoms of depression such as obsessive-compulsive disorders, alcohol and drug dependence disorders and schizophrenia (North & Yutzy, 2010). In this thesis these, disorders characterised by manic episodes, eating and personality disorders will not be addressed.

The majority of research on the association between diet and mood disorders has focused on depressive symptoms. Depressive episodes are characterized by the experience of at least two of a set of symptoms listed in Table 1 nearly daily over a period for at least two weeks. The number of symptoms experienced determines the severity and severe cases suffer almost always from somatic symptoms and frequently suicidal ideas. The more severe the case, the more difficulties with social, work and domestic activities are experienced (WHO, 2015b, 2016).

**Table 1 Symptoms of depression that are experienced nearly every day over at least 2 weeks based on the ICD 10 F32 definition of a depressive episode (National Collaborating Centre for Mental Health (UK), 2010; WHO, 2016)**

- Depressed mood[a]
- Loss of interest / pleasure in all activities[a]
- Feelings of worthlessness / excessive / inappropriate guilt
- Diminished ability to think / concentrate or indecisiveness
- Significant weight loss when not dieting or weight gain (e.g. 5% change in a month), or decrease or increase in appetite[b]
- Insomnia or hypersomnia[b]
- Psychomotor agitation or retardation[b]
- Fatigue or loss of energy[b]
- Thoughts of death, ideas of suicide, attempt or plan

[a]Key symptoms of depression, [b]referred to as somatic symptoms.

Around 50% of those with major depressive episodes in developed countries also suffer from anxiety disorders (Kessler *et al.*, 2010). The most common comorbidity is Generalised anxiety disorder (GAD). GAD is characterised by excessive worrying, feelings of fear and tension over a period of at least 6 months. Further symptoms include fatigue, restlessness, irritability, inability to concentrate, muscle tension, sleep disturbances and feeling of distress (WHO, 2016, 2010). It is subject to discussion whether depressive and anxiety disorders are strictly distinguishable (Goldberg, 2010). Similarities have been found in genetics, predictors at childhood and adulthood and nosology itself (Ruscio & Khazanov, 2017; Goldberg, 2010). Goldberg summarises the current discussion as *'However close or distant the disorders are, the causes of each are almost the same, and the symptoms dimensions themselves are closely related.'* (Goldberg, 2010:p.360). This suggests that even when not distinguishing depressive and anxiety disorders distinctly the results of research on causal factors are likely to be meaningful for either disorder.

### *2.1.2 Measurement*

In epidemiological research, CMDs are measured with clinical or computer assisted interviews such as the revised Clinical Interview Schedule (CIS-R), self-report questionnaires such as the Center for Epidemiological Studies Depression scale (CES-D) or the General Health questionnaire (GHQ), or derived from questions about antidepressant medication and physician diagnosis (Goldberg, 1972; Goldberg & Blackwell, 1970; Head *et al.*, 2013; Lewis *et al.*, 1988, 1992; McDowell, 2006; Radloff,

1977; Robins *et al.*, 1988; Sanchez-Villegas *et al.*, 2008). Interviews are less common in epidemiological studies as they require more resources. Self-report questionnaires are usually screening instruments designed to identify previously unrecognized cases and can overestimate prevalence (Thombs *et al.*, 2018).

Some studies have tried to overcome this issue by using self-reported physician diagnosis or antidepressant intake and hospital discharge data (Ruusunen *et al.*, 2014; Sanchez-Villegas *et al.*, 2008; Guo *et al.*, 2014). These measures should, if not misreported by the participant, underlie an examination by a health professional but are less sensitive (Sanchez-Villegas *et al.*, 2008). This is likely due to the considerable proportion of people with symptoms who do not seek treatment. Populations surveys have shown that only one quarter, and more recently one third, of people with mood disorders receive treatment (McManus *et al.*, 2009; Lubian *et al.*, 2016). It is likely that ascertainment by self-reported diagnosis or treatment might only capture more severe cases as treatment has been found to be higher in these (Lubian *et al.*, 2016). Additionally, validity could depend on accessibility of mental healthcare services and the healthcare system in the population of interest.

### *2.1.3 Prevalence and public health relevance*

In the English Adult Psychiatric Morbidity Survey 27.4% reported having ever been diagnosed with a CMD and the point prevalence of experiencing CMD symptoms was 15.7% (Stansfeld *et al.*, 2016).UK prevalence rates are in line with prevalence rates worldwide. In a meta-analysis pooling studies from across the world the lifetime prevalence for common mental disorders was estimated at 29.2%, the 12 month prevalence at 17.6% and 15.4% for mood and anxiety disorders only (Steel *et al.*, 2014). Depression prevalence is suggested to have increased in the 20th century but stable since early 1990 (Kessler *et al.*, 2005b; Spiers *et al.*, 2011; Stansfeld *et al.*, 2016; Hidaka, 2012).

In the UK the most prevalent CMD was *'CMD not otherwise specified'* a term referring to mixed anxiety and depression (7.8%), second was GAD (5.9%), followed by depression (3.3%) (Stansfeld *et al.*, 2016).

CMDs have been shown to be associated with a number of other non-communicable diseases such as hypertension (Meng et al., 2012), diabetes (Mezuk *et al.*, 2008) and coronary heart disease (Rugulies, 2002; Brunner *et al.*, 2014), and mortality (Cuijpers *et al.*, 2013; Walker, McGee & Druss, 2015). In 2016, major depression and anxiety disorders were within the top 20 causes for years lost due to premature death or lived

with disability in high income countries, and the top 10 causes of years lived with disability worldwide and depressive disorders are predicted to become the leading cause of disability in high income countries by 2030 (Abajobir *et al.*, 2017; Hay *et al.*, 2017; Murray, 1994; Mathers & Loncar, 2006).

The high prevalence of mood disorders has a substantial influence on the economy and health services. Mental health disorders are estimated to cost the UK economy and social care £105.2 billion per year and the National Health Service (NHS) spends more on mental health than any other disease group (McManus *et al.*, 2009; NHS England, 2015; Centre for Mental Health, 2010).

Depression and CMD are episodic in nature (Kessler & Bromet, 2013). In general populations around 35% of people who had a depressive episode will experience at least one recurrent episode after 15 years, with higher chances in clinical samples (Hardeveld *et al.*, 2010, 2013; Kessler & Bromet, 2013). Hardeveld et al. (2013) showed in a population sample, that after 20 years since the last depressive episode, 42% of participants had experienced at least one recurrent one.

### *2.1.4 Epidemiology of mood disorders*

A number of factors have been associated with the risk of CMDs with some being less modifiable in adulthood than others.

**Non-modifiable risk factors**

Twin studies and adoption studies suggest a heritability of unipolar depression of 30-45% (North & Yutzy, 2010; Shih, Belmonte & Zandi, 2004; Sullivan, Neale & Kendler, 2000). However, to date no genetic loci for depression have been reliably identified (Lohoff, 2010; Fakhoury, 2015; Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium *et al.*, 2013). Furthermore, the risk of CMD is shaped by adverse childhood experiences and personality traits (Tiainen *et al.*, 2013; Kendall *et al.*, 2015; Mandelli, Petrelli & Serretti, 2015).

Mood disorders are associated with age in regard to first onset and prevalence. First onset of mood disorder has been estimated to be most likely at 30 years of age (Kessler *et al.*, 2005a). In England and developed countries, rates of CMD and depression are higher in middle and young age and lower in older age (Kessler *et al.*, 2010; Stansfeld *et al.*, 2016).

### Socio-demographic factors

World and Europe wide mood and anxiety disorders are nearly twice as likely in women than men (Church & Lucey, 2011; Kessler *et al.*, 2005a; Stansfeld *et al.*, 2016; Alonso *et al.*, 2004; Steel *et al.*, 2014). In the UK, the point-prevalence of CMD symptoms was 19.1% in women and 12.2% in men in 2014 of 16 years and older adults (Stansfeld *et al.*, 2016). Gender differences are disputed and have been discussed on the basis of reporting artefacts due to gendered attitudes towards mental illness, biological differences such as hormonal influences, susceptibility and the exposure to risk factors (Kuehner, 2003, 2017; Lewin, 2011).

In middle-aged and older adults, circumstances such as marital status are associated with chances of depression. Lowest risks are often seen in those who are married (Yan *et al.*, 2011; Onrust & Cuijpers, 2006). Also, quality and quantity of social relationships beyond marriage are important. Those perceiving emotional support and few negative social interactions have lower chances for mood disorders (Santini *et al.*, 2015; Gariépy, Honkaniemi & Quesnel-Vallée, 2016; Stansfeld, Fuhrer & Shipley, 1998).

An inverse socio-economic gradient in mental health is often observed. This is discussed in section 2.5 (Fryers, Melzer & Jenkins, 2003; Lorant *et al.*, 2003).

### Modifiable risk factors

A number of modifiable behavioural factors for mood disorder have been suggested. For many, it is still unclear whether behaviours affect the risk of mood disorder or mood disorders lead to unfavourable changes in behaviour. This is the case for smoking (Fluharty *et al.*, 2017; Luger, Suls & Vander Weg, 2014), alcohol intake (Bell & Britton, 2014; Gea *et al.*, 2012), physical activity (Mammen & Faulkner, 2013; Azevedo Da Silva *et al.*, 2012), sleep deprivation as well as too long sleep (Baglioni *et al.*, 2011; Alvaro, Roberts & Harris, 2013; Zhai, Zhang & Zhang, 2015) and adiposity (Luppino *et al.*, 2010). Recently diet has been suggested to play a role as a risk factor for mood disorders as well (Lai *et al.*, 2014; Rahe, Unrath & Berger, 2014; Li *et al.*, 2017; Molendijk *et al.*, 2018; Li, Liu & Zhang, 2016).

## 2.2 Diet, free sugars and fibre

### *2.2.1 Diet measurement*

In epidemiological studies, diet is usually assessed using dietary recording methods based on self-report (Shim, Oh & Kim, 2014). Other methods such as household budget surveys or food balance sheets are more common in ecological studies (Pomerleau, Lock & McKee, 2003; Trichopoulou & Lagiou, 1997).

Individual dietary recording methods are 24-h dietary recall, in which the subject is asked by trained interviewers to recall food intake over the previous 24h; diet records or diaries in which the subject fills in an open-ended diary on what they eat throughout the time of measurement and Food frequency questionnaires (FFQ) (Shim, Oh & Kim, 2014). FFQs are the most commonly used method in longitudinal cohort studies (Shim, Oh & Kim, 2014). FFQs inquire about the frequency of consumption of a list of food items, sometimes including a possibility to quantify the portion size or to select an option provided (Willett *et al.*, 1985). While this method needs only few resources one main limitation is the reduction of detail. For example an item like *'Yoghurt'* does not distinguish between sweetened, probiotic or reduced fat types. This drawback reduces the ability to obtain precise and accurate measures of nutrient consumption from FFQs. Precision could be reduced due to too little detail such as type of food item, ingredients and portion size. Accuracy is further affected by misreporting (described below).

All commonly used data collection methods rely on self-report by participants. Therefore the participant can decide what information they want to disclose e.g. how much ice cream they eat and what they remember. This is described as dietary misreporting and most commonly results in underreporting of dietary intake, as such reporting less dietary intake than is actually consumed (Livingstone & Black, 2003). Underreporting of dietary consumption is thought to be driven by social desirability and is associated with body mass index (BMI), body dissatisfaction and potentially mood disorders (Stallone *et al.*, 1997; Bingham *et al.*, 1995; Price *et al.*, 1993; Voss *et al.*, 1998; Tyrovolas *et al.*, 2016; Lutomski *et al.*, 2011; Taren *et al.*, 1999; Whited *et al.*, 2014; Yannakoulia *et al.*, 2007). Comparing reported items by those who did report a reasonable amount of food for their height and weight with those who reported lower amounts suggest that underreporting is selective to certain food items such as foods high in sugar and high in fat (Livingstone & Black, 2003).

One way to reduce the effect of bias through misreporting is energy adjustment which allows investigating the role of a nutrient or food item relative to reported energy intake.

Energy adjustment has been found to reduce some bias by taking into account overall under- and over reporting (Stallone *et al.*, 1997) . There are several methods of energy adjustment, the standard multivariate model method, nutrient density, residual method and the energy decomposition or partition method (Willett, 2012; Willett, Howe & Kushi, 1997). The standard method uses total calorie intake in a multivariate model as any other confounder. In the nutrient density method the nutrient intake is divided by total energy intake. In the residual method, residuals for the intake of each individual are calculated from a model in which the nutrient intake is regressed on total energy intake. Energy-adjusted nutrient variables are reached by adding a constant such as predicted nutrient intake at mean energy intake to these residuals. In this method total energy intake should be additionally added to the model if associated with the outcome (Willett, 2012; Willett, Howe & Kushi, 1997; Willett & Stampfer, 1986). The energy partition method is similar to the standard multivariate method but uses, not total energy intake, but energy intake without the energy intake of the food item or nutrient in question (Howe, 1989). This method therefore describes substituting calories from a food item or nutrient while keeping *other* calories unchanged (Kipnis *et al.*, 1993).The decision on which method to use depends on whether the food item or nutrient contributes highly to calorie intake. If it does, the partition method is to be favoured, otherwise, the residual method should be preferred. These methods allow to adjust for total calorie intake while not over adjusting (Willett, 2012; Willett, Howe & Kushi, 1997; Willett & Stampfer, 1986; Kipnis *et al.*, 1993; Howe, 1989). However, it has to be noted that selective misreporting cannot be adjusted for with any of these methods.

### *2.2.2 Analysis of dietary data*

Dietary data has to be analysed on a particular level, such as dietary patterns, food groups, food items or nutrients (Jacobs & Steffen, 2003). Dietary patterns take into account a wider range of foods consumed and are generally analysed by using statistical methods, or scoring diets, based on predefined hypotheses (Hu, 2002). Food group and item analyses use per day intakes as variables, typical examples are fruit and vegetables or sugar-sweetened beverages (Li *et al.*, 2017; McMartin, Jacka & Colman, 2013). Nutrient content is calculated by multiplying all questionnaire food item intakes by nutrient content from food composition tables such as *'McCance and Widdowson's composition of foods'* (see Appendices relating to Chapter 2: Appendix 1 for details on limitations of food composition tables) (Willett, 2012; Agency & England, 2015).

### *2.2.3 Free sugars and measuring their intake*

The term ‘sugar’ refers to mono- and disaccharides that are characterised by sweet taste, occur naturally in some foods and added to others. Terms such as free sugars were adopted in response to the observation that naturally occurring sugars in for example whole fruits do not show adverse health effects (Department of Health, 1989; Scientific Advisory Committee on Nutrition, 2015). ‘Free sugars’ describe all mono- and disaccharides added to food and beverages and natural sugars present in honey, syrups and fruit juices (WHO, 2015a). Other common terms are ‘added sugars’ describing sugars and sugar-preparations added to foods and ‘non-milk extrinsic sugars’ describing sugars other than lactose not contained within a cellular structure of a food. Main differences between the terms are the inclusion or exclusion of fruit juice and naturally occurring sugars used as sweeteners (Scientific Advisory Committee on Nutrition, 2015; Department of Health, 1989; U.S. Department of Agriculture, 2000; EFSA Panel on Dietetic Products, 2010).

Free sugars are not yet covered in food composition tables and a systematic method for assessing free, added or non-milk extrinsic sugars in epidemiological research has only been described for diet diary data (Louie *et al.*, 2015; Agency & England, 2015). Studies using added sugar intake from FFQ approximated the content using total sugar intake from sugary food and beverage intakes and the MyPyramid Food Guidance System (Gangwisch *et al.*, 2015; Sanchez-Villegas *et al.*, 2017; Bowman, Friday & Moshfegh, 2008). However, the MyPyramid System did not explain calculations in detail and online references within the source have expired (Bowman, Friday & Moshfegh, 2008).

**Intakes**

In the UK two thirds to 70% (when excluding alcoholic beverages) of free sugars come from sweet foods and beverages (Public Health England, 2014) (see Figure 1). Between 2014 and 2016 adult men (19-64 years) in the UK consumed mean 64.3g (SD 46.6g) and adult women 50.0g (34.4g) free sugars per day, respectively 11.1% of total energy intake, more than double the current recommended level of 5% (Public Health England, 2018; Scientific Advisory Committee on Nutrition, 2015).

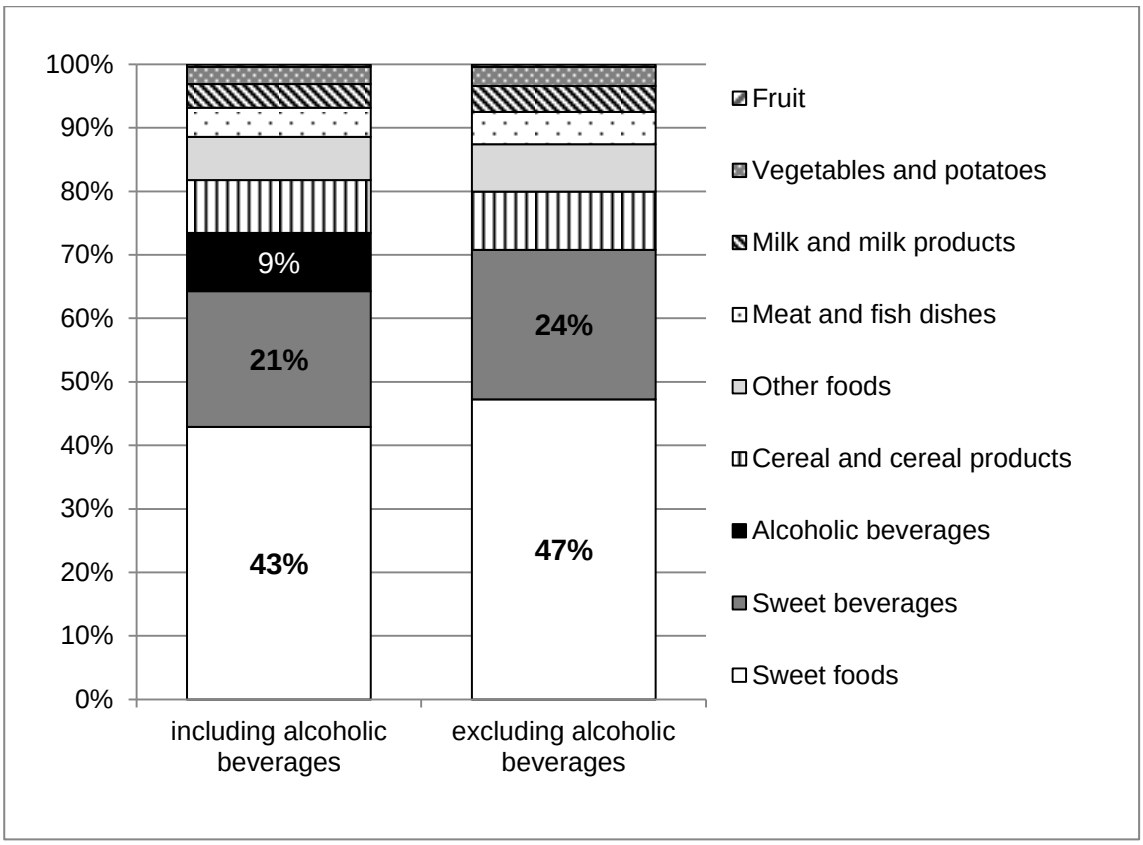


**Figure 1 Percentage contributions of food groups to average daily free sugar intake for 19-64 year olds in Britain**
Based on data from National Diet and Nutrition Survey, NDNS (Public Health England, 2018).

### Public health importance

Diets high in free sugars have been suggested to be associated with increased body weight (Morenga, Mallard & Mann, 2013), increased hypertension, dyslipidaemia (Morenga, Mallard & Mann, 2013), dental caries (Sheiham & James, 2014), CVD mortality (Yang *et al.*, 2014) and diabetes (Hu & Malik, 2010; Malik *et al.*, 2010). Associations with weight gain were partly mediated by total energy intake as naturally sugar-dense foods and beverages are high in energy (Morenga, Mallard & Mann, 2013). This has led to a debate about whether sugar intake is responsible for increased obesity rates (Kaiser *et al.*, 2013; Hu, 2013). Public health measures to reduce free sugar intakes have been introduced such as the UK levy on sugar-sweetened beverages which aims to reduce sugar-sweetened beverage intake by increasing the price in comparison to low or zero sugar alternatives.(Hu, 2013; HM Revenue & Customs, 2016).

### *2.2.4 Dietary fibre*

Dietary fibre describes carbohydrates that are neither digested nor absorbed in the small intestine. Similarly to free sugars, the definition of dietary fibre is contentious because it is an umbrella term. Most commonly dietary fibres describe cellulose, non-cellulose polysaccharides, lignin and resistant starch and non-digestible oligo-saccharides (Scientific Advisory Committee on Nutrition, 2015; Department of Health, 1989; U.S. Department of Agriculture, 2000; EFSA Panel on Dietetic Products, 2010).

**Intakes**

In the UK, adult men consume 20.7g (SD 8.7) and women 17.4g (6.4) of total fibre per day. That is about two thirds of the new recommended amount of 30g daily (Public Health England, 2016; Scientific Advisory Committee on Nutrition, 2015; Public Health England, 2018). Cereal, cereal products, vegetables and potatoes contribute mostly to the fibre intake in the British diet (Public Health England, 2018) (Figure 2).

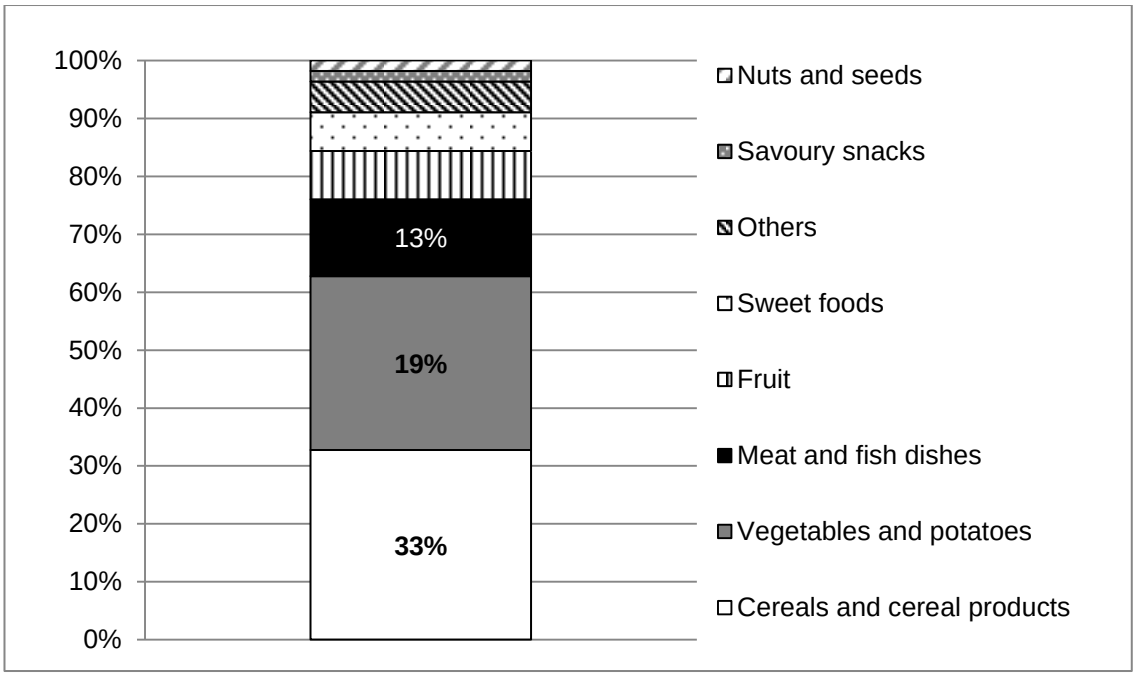


**Figure 2 Percentage contributions of food groups to average daily fibre intake for 19-64 year olds in Britain**
Based on data from NDNS (Public Health England, 2018).

**Public health importance**

Fibre intake has been found to be associated with lower low-density lipoprotein cholesterol levels (Hartley *et al.*, 2016) and non-communicable diseases such as blood pressure (Hartley *et al.*, 2016), coronary heart disease (Threapleton *et al.*, 2013b; Wu *et al.*, 2015), stroke (Threapleton *et al.*, 2013a) and CVD risk (Threapleton *et al.*, 2013b), and inflammatory bowel disease (Liu *et al.*, 2015).

## 2.3 Plausibility of an association between free sugar, fibre intake and mood disorders

Several potential biological pathways may link the biological effects of free sugars and fibre intake to mood disorders (Lang *et al.*, 2015; Rossetti, Halfon & Boutrel, 2014; Singh, 2014; Lopresti, Hood & Drummond, 2013; Benton, 2002a; Gangwisch *et al.*, 2015; Westover & Marangell, 2002; Benton & Donohoe, 1999). The following sections outline potential pathways and biological mechanisms linking high free sugar intake, low fibre intake and mood disorders.

### *2.3.1 Biological plausibility of an association between free sugars, sweetness and mood disorders*

There are five main pathways that could explain how a sugar dense or sweet diet could increase the chances of mood disorders (white arrows, Figure 3): Neuroplasticity, inflammation, reactive hypoglycaemia, the hypothalamic–pituitary–adrenal (HPA) axis and dopaminergic neurotransmission.

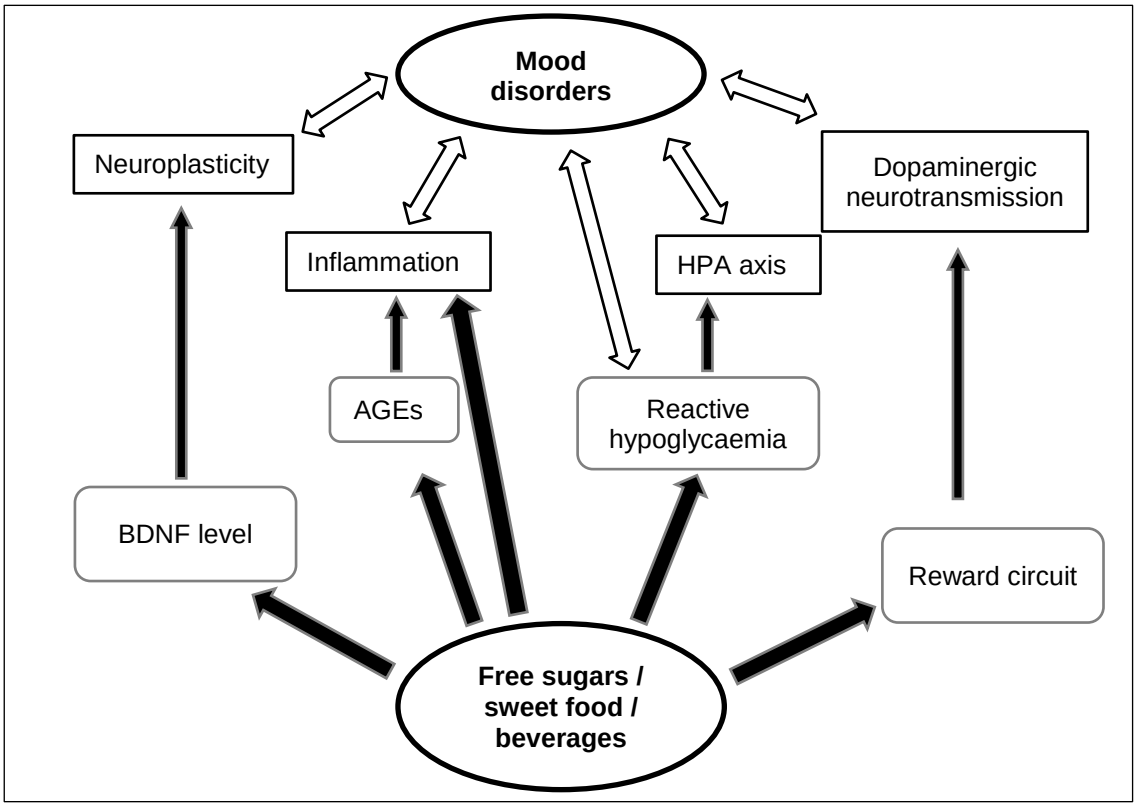


**Figure 3 Potential biological pathways linking free sugar or sweet food and beverage intake to mood disorders.**
White arrows signify the affected pathways in mood disorders, black arrows present the system that is affected by free sugars/sweetness. Text in ovals refers to main exposure and outcome. Abbreviations: BDNF, Brain-derived neurotrophic factor; AGES, advanced glycation end-products; HPA, hypothalamic-pituitary-adrenal.

### Neuroplasticity and Brain-derived neurotrophic factor (BDNF)

BDNF is involved in neuronal growth and survival, modulating neurotransmitters and neuronal plasticity (Bathina & Das, 2015). Depressed subjects have been found to have lower serum BDNF levels that normalise with antidepressant treatment (Sen, Duman & Sanacora, 2008; Molendijk *et al.*, 2014; Belmaker & Agam, 2008). These observations and observations of neural damage and atrophy in the hippocampus have led to the so-called neurotrophic hypothesis, that decreased expression of BDNF contributes to depression (Belmaker & Agam, 2008; Duman & Monteggia, 2006; Sen, Duman & Sanacora, 2008).

The hypothesis of a link between free sugar intake and BDNF levels has been tested in animal research. Studies in rodents found that long-term feeding with a high-fat high-sugar diet reduced hippocampal BDNF levels (Molteni *et al.*, 2002; Stranahan *et al.*, 2008). This was not the case after a high-fat diet, supporting the hypothesis that sugar in particular could modulate BDNF levels (Heyward *et al.*, 2012).

There is still a gap in direct evidence that reduced BDNF levels could cause depressive symptoms. BDNF-knockout mice present depressive phenotypes (Duman & Monteggia, 2006; Taliaz *et al.*, 2010) but genetic association studies of BDNF polymorphisms (Val66Met) in humans are not conclusive. The association was restricted to men, weakening the evidence of a causal link, or suggesting BDNF is important in development of depression in men but not women (Verhagen *et al.*, 2010).

### Sugar, inflammation and mood

Low grade inflammation may be a cause of depression in line with the observation that inflammation following a cold, for example, is characterised by similar symptoms to depression such as fatigue (Dantzer *et al.*, 2008). In prospective cohort studies increased inflammatory markers are associated with mood disorders at follow-up (Gimeno *et al.*, 2009; Valkanova, Ebmeier & Allan, 2013; Kivimäki *et al.*, 2014). Several dietary factors can have an effect on inflammation (Calder *et al.*, 2011). Diets with rapidly digestible carbohydrates and sugar-sweetened beverage intake have been found to increase inflammatory factors such as CRP (Liu *et al.*, 2002; Aeberli *et al.*, 2011). Higher postprandial blood glucose levels can increase oxidation and thereby activate inflammation (Ludwig, 2002; Radulian *et al.*, 2009). One pathway could involve formation of advanced glycation end-products (AGEs) that is increased by high availability of carbohydrate substrate. Receptor binding of AGEs can, among other functions, activate gene expression of pro-inflammatory cytokines increasing the load of inflammatory factors in the body (Calder *et al.*, 2011).

**Blood sugar, mood swings and the HPA axis**

After the intake of a high sugar meal some people report experiencing symptoms such as dizziness, anxiety and difficulty thinking. The condition has been attributed to reactive hypoglycaemia, the result of low blood sugar due to an exaggerated insulin response that translocates sugar from the blood into cells and organs (Virally & Guillausseau, 1999; Schwartz *et al.*, 1987; Mitrakou *et al.*, 1991; Fanelli *et al.*, 1994). Low blood sugar levels lead to the activation of the HPA axis to trigger the release of counter-regulatory hormones cortisol, norepinephrine and epinephrine. Low blood sugar causes neuroglycopenic and neurogenic symptoms, such as weakness, difficulty thinking and speaking, tiredness, anxiety, palpitations, sweating and hunger (Tesfaye & Seaquist, 2010). These feelings and anxiety-like behaviours have been shown to persist for half an hour in humans and up to two days in rodents after resolution of induced hypoglycaemia (Park *et al.*, 2012; Gold *et al.*, 1995).

A link between reactive hypoglycaemia and mood disorders could be explained, firstly by symptoms being misinterpreted as symptoms of anxiety and depression and secondly, there could be a link to mood disorders based on HPA axis regulation. The HPA axis reaction to stress is thought to show abnormalities in depressed patients (Belmaker & Agam, 2008). Depressed individuals have been found to have higher levels of cortisol and present a reduced negative feedback loop on the HPA axis (Stetler & Miller, 2011). Yet, a link between regular reactive hypoglycaemia and HPA axis dysregulation has not been investigated.

The prevalence and even the existence of reactive hypoglycaemia in non-diabetic individuals is debated (Simpson, Holdsworth & Macdonald, 2006b, 2006a). Symptoms have been ascribed to hypoglycaemia whilst the blood sugar level is above the threshold of low blood sugar (≥3.0 mmol/l). It remains unclear whether the symptoms are due to early or ongoing counter-regulatory reactions or some other cause (Simpson, Holdsworth & Macdonald, 2006b, 2006a; Benton, 2002a).

**Dopaminergic neurotransmission and sugar addiction**

Sweet and palatable foods induce the release of dopamine and endogenous opioids that facilitate reward (Dum, Gramsch & Herz, 1983; Hajnal, Smith & Norgren, 2004). Reward describes experiencing pleasure, learning through associative conditioning and building motivation of wanting more of the pleasurable substance (Berridge & Robinson, 2003). Sustained sugar intake has been shown to lead to biological changes similar to those seen in substance abuse (Avena, Rada & Hoebel, 2008; Smith, 2004; Bello, Lucas & Hajnal, 2002; Colantuoni et al., 2001).

Rodents subjected to intermittent excessive sucrose intake and repeated sugar access showed changes to mu-1 and dopamine receptor binding, density and transporter binding, and subsequently increased their intake of sucrose (Colantuoni *et al.*, 2001; Bello, Lucas & Hajnal, 2002; Colantuoni *et al.*, 2002).

Dopaminergic neurotransmission has been suggested to play a role in major depression in which reduced dopamine signalling leads to a reduced dopamine release and receptor changes (Dunlop & Nemeroff, 2007). Additionally dopaminergic neurotransmission is being discussed as one potential explanation for the strong association and comorbidity between substance dependency and mood disorders (Grant *et al.*, 2004; Stewart *et al.*, 2016; Cerdá *et al.*, 2010).

### *2.3.2 Biological plausibility of an association between dietary fibre intake and mood disorder*

Fibre intake could hold a protective role in mood disorder through its importance to the gut microbiome (Logan, 2006). The gut microbiome refers to the community of bacteria that colonize the gastrointestinal tract digesting food that is not ingested in the small intestine - mainly dietary fibre (Thomas *et al.*, 2017). A key function of dietary fibre is to maintain the gut microbiota, shaping its composition and strengthening the intestinal mucus against pathogens (Claesson *et al.*, 2012; David *et al.*, 2014; Desai *et al.*, 2016; Scott *et al.*, 2013). Dietary changes influence the gut microbiome both long- and short-term (Scott *et al.*, 2013; Walker *et al.*, 2011; Simpson & Campbell, 2015; Wu *et al.*, 2011). Populations with high intake of fibre present a higher level of bacteria of the phylum Firmicutes than those with lower intakes (Simpson & Campbell, 2015; Dominianni *et al.*, 2015).

Gut microbiota are suggested to play a role in mood disorders (Rieder *et al.*, 2017; Dash *et al.*, 2015). Case-control studies found differences in faecal microbiota between people with depression and control samples. Higher levels of Bacteroidetes and reduced levels of Firmicutes were observed in depressed patients compared to controls (Naseribafrouei *et al.*, 2014; Jiang *et al.*, 2015). Based on these observations several studies investigated how manipulating microbiota, by supplementing live bacterium cultures, so-called probiotics, affected mood. Probiotic treatments show favourable effects on mood and related processes in RCTs, strengthening the evidence of an association of gut microbiota composition and mood disorders (Wallace & Milev, 2017). Additionally the use of prebiotics, fibre fractions that are selectively fermented in the gastro-intestinal tract (Gibson *et al.*, 2004), have been shown to lower the cortisol awakening response and attentional vigilance to negative versus positive information,

suggesting substrates of gut microbiota can lead to changes in mood-related factors (Schmidt *et al.*, 2015).

Figure 4 summarises several pathways in which the gut microbiome communicates with the human body that are thought to underlie a potential association with mood disorders (Foster & McVey Neufeld, 2013; Sampson & Mazmanian, 2015; Wallace & Milev, 2017).

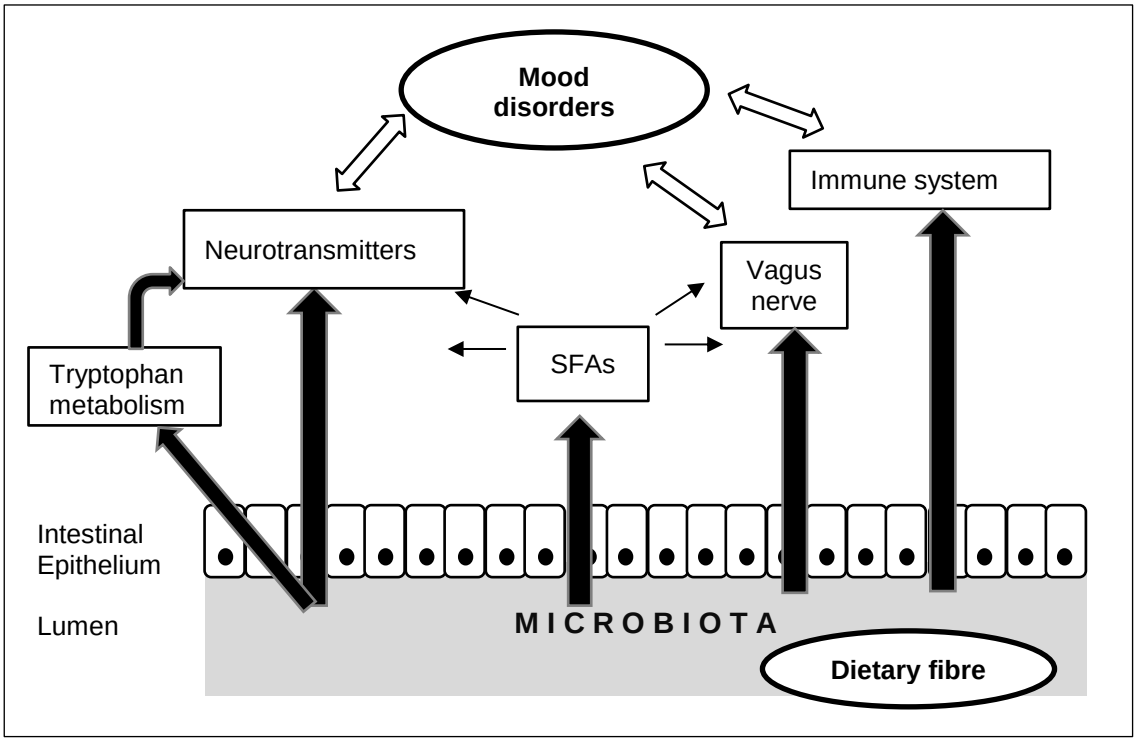


**Figure 4 Potential pathways that could explain how dietary fibre could link to mood disorders through its effect on microbiota**
White arrows signify the affected pathways in mood disorders, black arrows present the system that is affected by microbiota and metabolism of dietary fibre. Text in ovals refers to main exposure and outcome.
Abbreviations: SFA, Short-chain-fatty acids.

### Tryptophan metabolism and neurotransmitters

Tryptophan availability and ratio to other plasma neutral amino acids is a key determinant of brain serotonin synthesis (Fernstrom, 1983; Fernstrom & Wurtman, 1972). Serotonin deficiency is one biological hypothesis underlying depression and is the target of selective serotonin-reuptake inhibitors (SSRIs) that increase serotonin concentrations by blocking serotonin reuptake at the synaptic cleft (Mann, 2005; Belmaker & Agam, 2008). Other neurotransmitters such as Gamma-amino butyric acid (GABA) are being discussed in the pathology of depression and anxiety, too (Romeo *et al.*, 2018; Cryan & Kaupmann, 2005).

Microbiota can affect circulating tryptophan availability through affecting tryptophan metabolism (O'Mahony *et al.*, 2015). This could link the microbiome and depression

was shown by Jiang et al. (2015). They found increased levels of Alistipes in depression patients compared to healthy controls. Bacteria of the genus Alistipes of the phylum Bacteroidetes have the ability to metabolise tryptophan and could therefore affect its availability (Jiang *et al.*, 2015; Song *et al.*, 2006).

Additionally tryptophan is a substrate for local serotonin synthesis. Over 90% of the body's serotonin is produced in the gut (Rieder *et al.*, 2017; Yano *et al.*, 2015). Serotonin producing enterochromaffin cells are influenced by tryptophan availability, gut bacteria and their metabolites (Reigstad *et al.*, 2014; van de Wouw *et al.*, 2017). Multiple bacteria are also able to produce serotonin and other neurotransmitters such as GABA themselves (Rieder *et al.*, 2017; Cryan & Dinan, 2012).

It is subject to debate whether neurotransmitters such as GABA, norepinephrine, dopamine and serotonin produced in the gut could also directly affect neurotransmitters in the brain (Sampson & Mazmanian, 2015; Wall *et al.*, 2014) or whether they might play a role in the development of neurotransmitter related stress-reactions (O'Mahony *et al.*, 2015; Clarke *et al.*, 2013). However, it has been suggested that gut GABA could have a direct effect on the brain mediated by the vagus nerve (Bravo *et al.*, 2011).

**Short-chain-fatty acids (SFAs)**

SFAs are the result of the fermentation of dietary fibre in the colon (Besten *et al.*, 2013). SFAs can affect energy utilization, signal between host and microbes and control the pH in the colon. SFA producing bacteria (Faecalibacterium of the phylum Firmicutes) (Besten *et al.*, 2013) have been found to be more prominent in populations with diets high in fibre (Simpson & Campbell, 2015).

Specific SFAs such as n-Butyrate have an anti-inflammatory effect on human immune cells and decrease permeability in colon epithelia (see section Immune system and inflammation). Others such as propionate and acetate are substrates for enzymes in other organs such as the liver (Nicholson *et al.*, 2012). SFAs elevate neurotransmitter synthesis in enterochromaffin cells, which could play a role for mood disorder as described in the section above (Jiang *et al.*, 2015; Reigstad *et al.*, 2014). In line with the hypothesis of a link between SFA and mood disorders depressed patients have been found to present less SFA producing bacteria than healthy controls (Jiang *et al.*, 2015).

**Vagus nerve**

The vagus nerve reaches from the medulla to the colon and its afferents can sense pressure, pain, stretch, temperature, osmotic pressure, chemical stimuli and

inflammation. The vagus nerve is involved in autonomic, cardiovascular, respiratory, gastrointestinal, immune and endocrine systems (Berthoud & Neuhuber, 2000; Yuan & Silberstein, 2016). The vagus nerve has been linked to depression after mood improvements were observed in epilepsy patients that received vagus nerve stimulation (VNS) therapy (Nemeroff *et al.*, 2006; Elger *et al.*, 2000). Later it was shown that VNS affects neurotransmitter transmission in the brain (Dorr & Debonnel, 2006). Evidence of VNS therapy for depression efficiency is weak (Martin & Martín-Sánchez, 2012), but it has been approved by the US Food and Drug Administration as a therapy for treatment-resistant depression (Shelton *et al.*, 2010) and the National Institute for Health and Care Excellence allows the procedure under special circumstances (National Institute for Health Care Excellence, 2009).

Animal studies suggest that some bacteria can activate the vagus nerve (Forsythe, Bienenstock & Kunze, 2014). For example Bravo et al. (2011) found that in mice oral administration of a Lactobacillus strain reduced anxiety-like and depression-like behaviours. However, the effect was blocked in mice that were vagotomised suggesting the vagus nerve as a pathway.

**Immune system and inflammation**

As described in 2.3.1 low grade inflammation is suggested to play a role in the mood disorders and the gut microbiome can play a crucial role in inflammation (Dantzer *et al.*, 2008; Rieder *et al.*, 2017).

At the intestinal mucosa bacteria cell wall components bind to receptors on defence cells. This binding triggers the production of cytokine such as Interleukin 6 (IL-6) activating the immune system (Rieder *et al.*, 2017; Sherwin *et al.*, 2016). Cytokines then reach the brain via the vagus nerve or directly through permeable regions of the blood brain barrier. This process plays a role in the maturation of the immune system and remains a method of communication between the gut and the brain (Sherwin *et al.*, 2016).

The inflammatory reaction is determined by the type of microbiota, intestinal permeability and SFAs and thereby linked to dietary fibre intake (Nicholson *et al.*, 2012; Aidy, Dinan & Cryan, 2015).

**Plausible explanation beyond the gut microbiome: Fibre-rich diets and micronutrients**

Beyond associations with the gut microbiome an association between mental health and fibre intake has been suggested to be potentially explained by micronutrients that are common in high fibre foods (Logan, 2006). In the UK, most fibre intake comes from

the intake of cereal, cereal products and vegetables (Public Health England, 2014). These food groups also contribute substantially to the intake of folate, magnesium, zinc and selenium, micronutrients that have been shown to be associated with a reduced risk of depression in observational studies (Benton, 2002b; Derom *et al.*, 2013; Lehto *et al.*, 2013; Li *et al.*, 2016; Public Health England, 2014; Tolmunen *et al.*, 2004; Vashum *et al.*, 2014). However, RCTs investigating the effect of folate, magnesium, zinc or selenium supplements on mood and depression have been mostly inconclusive, calling into question the causality of the association and making this alternative explanation for a link between fibre intake and mood disorders less likely (Almeida, Ford & Flicker, 2015; Derom *et al.*, 2013; Lai *et al.*, 2012; Rayman *et al.*, 2006).

### *2.3.3 Plausible explanation of adiposity mediating between free sugar intake, dietary fibre intake and mood disorders*

An association between free sugar intake, dietary fibre intake and mood disorders could potentially be explained by adiposity. Both free sugar intake and fibre intake have been found to be associated with adiposity and body weight changes (Morenga, Mallard & Mann, 2013; Wanders *et al.*, 2011). Meanwhile, adiposity and weight gain are associated with an increased chance of mood disorders (Luppino *et al.*, 2010; Forman-Hoffman *et al.*, 2007; Sutin & Zonderman, 2012; Brumpton *et al.*, 2013; Singh *et al.*, 2014; de Wit *et al.*, 2015; Fezeu *et al.*, 2015; Gibson-Smith *et al.*, 2016). Potential explanations for a link are increased inflammation (Dantzer *et al.*, 2008; Fransson *et al.*, 2010; Kivimäki *et al.*, 2014), leptin resistance (Galic, Oakhill & Steinberg, 2010; Rossetti, Halfon & Boutrel, 2014; Lu, 2007) and socio-emotional factors such as weight discrimination and body image dissatisfaction (Jackson, Beeken & Wardle, 2015; Eidsdottir *et al.*, 2014). Jackson et al. (2015) found that weight discrimination explained 41% of the association between obesity and depression in British adults and Eidsdottir et al. (2014) showed that body image dissatisfaction entirely mediated the association between weight and depression in Icelandic adolescents.

The directionality of the association between adiposity and mood disorders is still unclear. Associations have been found to be bidirectional (Luppino *et al.*, 2010) and studies using an instrumental-variable design were unable to clarify the dominant direction of the association (Hamer, Batty & Kivimaki, 2016; Kivimaki *et al.*, 2011; Jokela *et al.*, 2012). Taken together adiposity could be a mediator but also confounder in the association between free sugar intake, dietary fibre intake and mood disorders.

## 2.4 Alternative explanations

There are several ways in which high free sugars and low dietary fibre intake could be causally related to an increased risk of mood disorders, as outlined above. However, there are alternative explanations that could explain such observed associations. They are reverse causation and confounding.

### *2.4.1 Reverse causation*

Reverse causation refers to the phenomenon that an exposure-health outcome association may wholly or partly arise because the outcome state influences the exposure state or level. In the present context, it is possible that mood disorder could lead to a change in dietary pattern, giving rise to, or amplifying, the observed association between diet and mood disorder.

Depression and anxiety are defined by several symptoms that could affect dietary behaviours (WHO, 2016, 2015b). Appetite changes, experienced in some people with depression, could affect dietary behaviours and symptoms such as anhedonia and fatigue and could influence daily activities like cooking which is associated with lower sugar and higher fibre intake (Wolfson & Bleich, 2015).

Another pathway to diet changes could be the use of sweet food and beverages intake in particular as self-medication (Ulrich-Lai, 2016). Short-term experiments found that chocolate consumption can improve negative mood and that low mood initiation leads to stronger inclination towards sweet foods than after neutral mood initiation (Aguiar-Bloemer & Diez-Garcia, 2018; Macht & Mueller, 2007). Several pathways have been suggested concerning how sugar and sweetness could enhance mood (Ulrich-Lai, 2016; Corsica & Spring, 2008; Christensen, 2001; Macht, 2008; Ventura *et al.*, 2014).

The first pathway is the so-called 'Wurtman hypothesis'. Intake of a meal high in carbohydrates and low in protein is thought to increase brain serotonin synthesis by increasing the amount of the serotonin precursor, tryptophan, crossing the blood-brain-barrier (Benton & Donohoe, 1999; Shabbir *et al.*, 2013; Wurtman & Wurtman, 1995; Lieberman, Caballero & Finer, 1986). At the blood-brain barrier tryptophan is competing with large neutral amino acids (LNAA) (Fernstrom, 1983; Fernstrom & Wurtman, 1972). Insulin lowers plasma LNAA levels and thereby promotes tryptophan passage (Benton & Donohoe, 1999; Shabbir *et al.*, 2013; Wurtman & Wurtman, 1995; Lieberman, Caballero & Finer, 1986). As mentioned earlier, low serotonin levels have been linked to mood disorders (Ventura *et al.*, 2014; Belmaker & Agam, 2008). However, there are several arguments against the 'Wurtman hypothesis'. The mood

enhancement through serotonin synthesis would take approximately an hour whereas the soothing effect has been reported immediately, and protein intake can inhibit the process and sweet foods would deliver this amount already (≥4% per meal calories) (Benton & Donohoe, 1999; Ventura *et al.*, 2014). Still, this hypothesis remains a prominent argument why sweet food could be favoured following stress (Macht, 2008; Ventura *et al.*, 2014).

Secondly, the association could be rooted in memories. In infants, sweet taste has a calming effect and reduces crying (Barr *et al.*, 1999). The effect is known to decrease with age but expectations of sweetness soothing negative feelings could still be rooted in the memory and influence food choice (Gibson, 2006; Hepworth *et al.*, 2010).

Thirdly, the release of dopamine and endogenous opioids, following the consumption of sweet and palatable food, could be mood enhancing and rewarding (Dum, Gramsch & Herz, 1983; Hajnal, Smith & Norgren, 2004; Smith, 2004) (see section on Dopaminergic neurotransmission and sugar addiction).

Finally, cortisol is thought to indirectly increase food intake and especially sweet food consumption (Peckett, Wright & Riddell, 2011; Epel *et al.*, 2001).This suggests increased consumption of sweet food could be part of a stress reaction (Ventura *et al.*, 2014).

Reverse causation could also play a role through favourable diet changes. Patients of major diseases such as cancer have reported attempting changes towards healthier diets (Patterson *et al.*, 2003; Maunsell *et al.*, 2002; Salminen *et al.*, 2002). It could be possible that a diagnosis of depression or a self-diagnosis of depressive symptoms motivate healthy food choices leading, for example, to increased fibre intake.

### *2.4.2 Confounding*

The particular characteristics of observational study participants that have high intakes of free sugars or dietary fibre could confound the respective associations of interest with mood disorders.

Putative adverse dietary behaviours cluster with non-dietary health behaviours (Poortinga, 2007; Chapman *et al.*, 2012) such as low physical activity and sedentary behaviours (Pearson & Biddle, 2011; Park *et al.*, 2016), alcohol intake (Yeomans, 2010), smoking (Alkerwi et al., 2017) and sleep (Chaput, 2014). These behaviours have all been found to be associated with mood disorders and are unlikely to lie on a pathway between diet and mood disorders, meeting the criteria of confounders

(Azevedo Da Silva *et al.*, 2012; Boden Joseph M. & Fergusson David M., 2011; Fluharty *et al.*, 2017; Mammen & Faulkner, 2013; Neckelmann, Mykletun & Dahl, 2007; Staner, 2010).

Socio-demographic factors such as marital status and socio-economic position have been associated with free sugar intake, fibre intake (Vinther *et al.*, 2016; Lee *et al.*, 2005; Eng *et al.*, 2005; Roos *et al.*, 1998; Darmon & Drewnowski, 2008; Giskes *et al.*, 2010) and mood disorders (Yan *et al.*, 2011; Onrust & Cuijpers, 2006; Fryers, Melzer & Jenkins, 2003; Lorant *et al.*, 2003; Virtanen *et al.*, 2012, 2015; Marmot *et al.*, 2001; Stansfeld & Marmot, 1992; Stansfeld *et al.*, 2012; Theorell *et al.*, 2015).

Other dietary factors could confound the associations of interest. Dietary patterns including a lot of sugar dense foods and beverages have also been found to be high in fried food and meat, and low in fruits, vegetables and dietary fibre and vice versa (Pryer *et al.*, 2001; Martikainen, Brunner & Marmot, 2003; Akbaraly *et al.*, 2009). Associations of interest could be confounded by overall diet quality that has also been associated with mood disorders (Lai *et al.*, 2014; Rahe, Unrath & Berger, 2014; Li *et al.*, 2017; Molendijk *et al.*, 2018). Additionally sugar is added to coffee and tea that are probably inversely associated with mood disorders (Grosso *et al.*, 2016; Wang *et al.*, 2016).

Finally, associations between mood disorders could be confounded by obesity and prevalent disease. While obesity and diseases could lie on the pathway between diet and mood disorders they could also play a role as confounders (see Chapter 2: 2.3.3). Dietary changes could occur to following recommendations from a doctor, changes in taste and appetite (Spotten *et al.*, 2017) or as a reaction to a life-changing diagnosis (Patterson *et al.*, 2003; Maunsell *et al.*, 2002; Salminen *et al.*, 2002). Meanwhile, associations between obesity (Luppino *et al.*, 2010) and diseases such as CVD (Hare *et al.*, 2014; Brunner *et al.*, 2014), diabetes (Renn, Feliciano & Segal, 2011; Kivimaki *et al.*, 2010; Mezuk *et al.*, 2008; Nouwen *et al.*, 2010) and cancer (Krebber *et al.*, 2014; Mitchell *et al.*, 2011, 2013) and mood disorders are mostly suggested to be bidirectional.

In observational studies confounding is addressed by adjusting models for potential confounding factors. However that cannot control for all confounding. Measurement error in exposure, outcome and confounders leads to incomplete adjustment. This incomplete adjustment is described as residual confounding. Residual confounding means that it is not possible to know whether the risk factor of interest is related to an outcome even after adjustment for confounders since the association may be the

consequence of other correlated variables (Davey Smith *et al.*, 2007; Davey Smith & Phillips, 1992).

In summary, there are several biological pathways that show how diet high in sugar or sweetness and high in fibre could affect mood disorders. Alternatively, an association could be due to reverse causation and confounding. Reverse causation can be addressed by a prospective study design and confounding by adjusting for key confounders health behaviours, socio-demographic factors and other dietary factors, although residual confounding may limit interpretation of the modelled findings.

## 2.5 The role of diet in the association between financial insecurity and mood disorders

Socio-economic position and financial difficulties have been consistently found to be associated with increased chances of mood disorders and can be considered established risk factors for mood disorders (Jenkins *et al.*, 2008; Lorant *et al.*, 2003). While there is increasing evidence for an association between diet quality and mood disorders it is still based on few prospective studies and likely to have a weaker association with mental health (Lai *et al.*, 2014; Rahe, Unrath & Berger, 2014; Li *et al.*, 2017; Molendijk *et al.*, 2018). However, associations found between diet and mood disorders have led researchers to describe diet as a *'central'* mental health determinant (Sarris et al., 2015) and to call for public health action to improve diets for mental health (Dawson, Dash & Jacka, 2016). This raises the question whether an increase in diet quality could also affect associations between other risk factors and mood disorders. Lower socio-economic position is associated with higher free sugar intakes (Barrett *et al.*, 2017; James *et al.*, 1997; Maguire & Monsivais, 2015; Pechey *et al.*, 2013) and lower fibre intakes (James *et al.*, 1997; Maguire & Monsivais, 2015; Pechey *et al.*, 2013; Giskes *et al.*, 2010).

Diet quality could not only have a direct association with mood disorders but also affect associations between socio-economic position and mood disorders in a way that an improvement of diet quality could alleviate some of the increased risk for mood disorders. If diet could change the association between socio-economic position or financial difficulties and mental health, public health action to improve diet quality could additionally support the reduction of mental health inequalities and add further importance to the role of diet in mental health (Allen *et al.*, 2014).

### *2.5.1 Socio-economic position and mood disorders*

There is a strong socio-economic gradient in mood disorders. In the UK, women with low incomes have nearly 1.5 times higher rates of CMD than those with the highest household income and men nearly 3 times higher rates (McManus *et al.*, 2009). Household income is one of many measures for socio-economic position - a sociological construct classifying position in the social and material hierarchy. Several socio-economic position measures have been found to increase chances for mood disorders such as education, income, debt and occupational class (Jenkins *et al.*, 2008; Lorant *et al.*, 2003). Material circumstances and economic difficulties have been found to be more strongly associated with mood disorders than occupational social class (Stansfeld & Rasul, 2006; Fryers, Melzer & Jenkins, 2003; Weich & Lewis, 1998b,

1998a). The association between socio-economic position and mood disorder has been shown to be mostly explained by work-related and social factors and material problems, and only marginally by health behaviours, suggesting that it is unlikely for diet to mediate the association (Koster *et al.*, 2006; Stansfeld *et al.*, 2003; Virtanen *et al.*, 2008; Hanson *et al.*, 2016).

### *2.5.2 Theoretical link*

In the study of social support and health the buffering hypothesis is one of the key explanations of how social support could affect health (Stansfeld & Rasul, 2006). This hypothesis suggests that social support could buffer against psychological stressors in a way that a stressor will have a more detrimental effect when combined with low social support (Cohen, Sheldon & Mckay, Garth, 1984). Cassel (1974) hypothesised that the buffering hypothesis could not only be relevant for factors such as social support but also biological factors could modify the ability to adapt to another stressor.

Applying this to the interplay between diet, financial insecurity and mood disorders financial insecurity can be seen as a strong psychological stressor and diet as a potential buffer (Jenkins *et al.*, 2008; Lorant *et al.*, 2003). A diet high in sugar or high in fibre could modify the ability to adapt to financial insecurity (Cassel, 1974). If the theory holds for a factor such as diet, the association between financial insecurity and mood disorders should be amplified in those with high free sugar, sweet food / beverage and low fibre intake and be weaker in those with low free sugar and high fibre intake.

### *2.5.3 Food insecurity and mood disorders*

Food security is described by the FAO World Food Summit as follows: *'food security, at the individual, household, national, regional and global levels (…) exists when all people, at all times, have physical and economic access to sufficient, safe and nutritious food to meet their dietary needs and food preferences for an active and healthy life'* (FAO, 1996; Jones, 2017). The lack of food security therefore is associated with the inability of affording food as well as ensuring its quality (Hanson & Connor, 2014; Lund *et al.*, 2018).

Food insecurity has been found to be associated with mood disorders in developing countries (Weaver & Hadley, 2009) and high income countries both cross-sectionally (Carter *et al.*, 2011; Jessiman-Perreault & McIntyre, 2017; Lund *et al.*, 2010; Wang *et al.*, 2015; Okechukwu *et al.*, 2011; Siefert *et al.*, 2001; Tarasuk *et al.*, 2018; Wu & Schimmele, 2005; Jones, 2017) and prospectively (Siefert *et al.*, 2004; Power *et al.*,

2017; Jones, 2017). Participation in food assistance programmes has been found to be associated with a reduction of psychological distress (Munger, Hofferth & Grutzmacher, 2016; Oddo & Mabli, 2015). Evidence of a strong association of food insecurity with mood disorders, support the hypothesis that low dietary quality could amplify an association between financial insecurity and mental health.

### *2.5.4 Public health relevance*

A potential interaction has public heath relevance firstly because diet has a socio-economic gradient itself which could potentiate the burden in those with low socio-economic position. Added sugar intake and sugar-sweetened beverage intake has an inverse socio-economic gradient with higher levels in more deprived groups (Barrett *et al.*, 2017; James *et al.*, 1997; Maguire & Monsivais, 2015; Pechey *et al.*, 2013). Fibre intake and fibre rich food intake have been found to be higher in more prosperous groups (James *et al.*, 1997; Maguire & Monsivais, 2015; Pechey *et al.*, 2013; Giskes *et al.*, 2010). If high free sugar and low fibre intake modified the association between financial insecurity and mood disorders towards a larger effect size, those of low socio-economic position could currently be at an amplified risk for mood disorders due to financial insecurity.

Secondly, if there was evidence for an interaction, nutrition interventions effective in lower income groups such as community based strategies and policies aimed at structural changes in the environment could reduce the burden of financial insecurity on mental health (Bhattarai *et al.*, 2013; Hillier-Brown *et al.*, 2014; Maderuelo-Fernandez *et al.*, 2015; Oldroyd *et al.*, 2008; Vargas-Garcia *et al.*, 2017).

## 2.6 Literature review of the association between free sugar, fibre intake and mood disorders in population-scale studies

The aim of this review is to synthesise the existing evidence of associations between long-term free sugar and sweet food / beverages, fibre intake and mood disorders and the interaction with socio-economic measures. The evidence is observational and has not been investigated in meta-analyses. However, there are a few trials that support a potential causal link between diets high in free sugars and fibre-rich foods and mood disorders, and observational research has been meta-analysed regarding the association between dietary patterns and mood disorders.

This section will first give an overview on trials and meta-analyses investigating dietary patterns including free sugars and dietary fibre and then review the association between (1) long-term free sugar, sweet food / beverages intake and mood disorders, (2) long-term diet based fibre intake and mood disorders and (3) free sugar, sweet food / beverages and fibre intake as moderators in the association between socio-economic position and mood disorders.

### *2.6.1 Evidence from studies investigating diets including free sugars and dietary fibre*

This section will give an overview on trials and meta-analyses on dietary exposures including free sugars and fibre.

**Trial evidence**

Trials are the gold-standard to evaluate causality of an association. There have been little high quality randomised controlled trials (RCTs) in healthy samples in research on the association between habitual diet and mood disorders to date, especially for the association with unhealthy dietary factors, that allow causal conclusions. Several RCTs did not include recommendations on fibre or sugar intake or had been conducted in diseased samples, as part of weight loss trials, included supplements or a number of other non-dietary lifestyle changes (Opie *et al.*, 2015; Parletta *et al.*, 2017). Still, two studies could reflect the effect of a diet high in refined sugars and low in fibre.

Breymeyer et al. (2016) investigated the association of glycaemic load of a diet and mood in 82 participants. In a randomised cross-over design two isocaloric intervention diets were provided over two periods of 28 days with a 28 days wash-out period in between. The compared diets were a high glycaemic load diet including sweet foods, refined grains and free sugars and a low glycaemic load diet that was minimal in added

sugars and high in wholegrain foods. There was a significant reduction in CES-D scores (reduction of 0.8 point difference, p=0.002; score ranging from 0-15), fatigue/inertia, total mood disturbance and increase in vigour/activity after the low glycaemic diet than the high glycaemic diet. There was no difference in negative affect (Breymeyer *et al.*, 2016).

A second randomised-controlled trial included 67 participants with moderate to severe depression. Jacka et al. (2017) found that a 12-week intervention of regular dietary counselling sessions promoting a diet high in whole grains, fruit, vegetables, legumes, non-fat dairy, eggs, lean red meat and fish and low in sweets, refined cereal, fried fast food, processed meat and sweetened and alcoholic beverages led to lower depression and anxiety symptoms and remission in 1/3 of the participants in the intervention group as compared to 8% in the control group that received a social support intervention in the time of the dietary intervention sessions (Jacka *et al.*, 2017).

Both studies included only relatively few participants but both had a strong design. Breymeyer et al. (2016) reduced the risk of non-compliance by providing food and reduced the risk of confounding by cross-over design. Jacka et al. (2017) used a control intervention to reduce the risk that changes were only due to being enrolled in activities.

In summary, the few randomised-controlled trials that included free sugars and high fibre foods in their diets suggest a protective effect of healthy food choices including low sugar and fibre intake. Further trials on whole diet interventions including larger sample sizes are ongoing and will further elucidate the causal role of diet in mood disorders (Roca *et al.*, 2016). However, the evidence from trials so far does not allow a conclusion on the specific effect of free sugars, sweet diets/beverages and fibre intake to be made.

**Meta-analyses on the association between dietary patterns, food groups and mood disorders**

Dietary patterns and dietary indices consider a range of foods consumed within a habitual diet. To obtain dietary patterns, dietary data are analysed using factor analysis or cluster analysis resulting in scores or clusters of common underlying dimensions of food consumption in similar diets. This method is also referred to as data-driven as it depends on the dataset they are applied in (Hu, 2002). Dietary patterns focus on exploring diet disease relationships rather than being driven by potential biological hypotheses that certain foods and their combination would be likely to be associated with the outcome (Michels & Schulze, 2005). In contrast, dietary indices scores are assigned based on a priori hypotheses such as five or more fruit and vegetables per

day, a well-known example being the Mediterranean diet score (Hu, 2002; Panagiotakos, Pitsavos & Stefanadis, 2006).

Several systematic reviews and meta-analyses investigated the association between dietary patterns, indices and mood disorders (Lai *et al.*, 2014; Rahe, Unrath & Berger, 2014; Li *et al.*, 2017; Molendijk *et al.*, 2018). Table 2 gives an overview of the findings of the three meta-analyses on dietary patterns and depression. While estimates between western dietary patterns were positive and mostly non-significant, the direction was positive. In all three meta-analyses estimates including the largest number of confounder adjustments from the original studies were pooled. Differences between estimates are likely due to study selection such as the exclusion of adolescents or several studies within the same cohort (Lai *et al.*, 2014; Li *et al.*, 2017; Molendijk *et al.*, 2018).

**Table 2 Overview of results of meta-analyses on the association of dietary patterns and depression**

| | OR (95%-CI) for depression comparing highest vs. lowest intake categories | |
|---|---|---|
| | Western dietary patterns | Healthy dietary patterns |
| Lai et al. (2014) | Overall: 1.17 (0.97, 1.41)<br>Cohort studies only: N/A | Overall: 0.84 (0.78, 0.92)<br>Cohort studies only: 0.83 (0.66, 1.05) |
| Li et al. (2017) | Overall: 1.18 (1.05, 1.34)<br>Cohort studies only: 1.16 (1.01, 1.34) | Overall: 0.58 (0.46, 0.74)<br>Cohort studies only: 0.68 (0.59, 0.77) |
| Molendijk et al. (2018) | Cohort studies only: 1.05 (0.99, 1.12) | Cohort studies only: 0.77 (0.69, 0.84) |

Western dietary patterns are characterised by high intakes of fried food, processed meat, sweets and sugar-sweetened beverages (Akbaraly *et al.*, 2009; Chocano-Bedoya *et al.*, 2013; Le Port *et al.*, 2012; Rienks, Dobson & Mishra, 2013; Ruusunen *et al.*, 2014). Healthy dietary patterns are characterised by high intakes of fruit, vegetables, wholegrain and less processed foods (Akbaraly *et al.*, 2009; Chocano-Bedoya *et al.*, 2013; Le Port *et al.*, 2012). Molendijk et al. (2018) additionally analysed the association with unhealthy food groups and found stronger estimates (OR 1.09, 95%-CI 1.00, 1.19). Associations between healthy food groups and depression were weaker (OR 0.95, 95%-CI 0.87, 1.03) suggesting the strong associations with healthy dietary patterns could be explained by a pervasive dietary factor in healthy diets such as fibre.

In summary, meta-analyses on dietary pattern and food groups suggest an inverse association between healthy diets and mood disorders but no clear association between western dietary patterns and mood disorder. Dietary patterns include a variety of different food items of which some could be responsible for the associations and

others might be not which can weaken the overall effect. As shown in section 2.3 there are several plausible explanations for a potential adverse effect of sugar-dense and sweet diets and a protective effect of diets high in fibre. Therefore, the following reviews will focus on these dietary factors.

### *2.6.2 Review type and search method*

Three reviews were conducted (1) on the association between long-term free sugar, sweet food / beverages intake and mood disorders, (2) on the association between long-term diet based fibre intake and mood disorders and (3) on free sugar, sweet food / beverages and fibre intake as moderators in the association between socio-economic position and mood disorders. The three reviews were systematised presenting a brief search strategy and including key exclusion criteria but no strict evaluation criteria (Grant & Booth, 2009).

Multiple sources were systematically searched and supplemented by studies referencing and referenced by the publications found. Search terms can be found in Appendices relating to Chapter 2: Appendix 2 and Appendix 3). Studies were excluded if they were reviewing literature, conducted on animals, focused on eating disorders or included only diseased patients (except if they were mood disorder patients), children, adolescents or pregnant women. The review was further restricted to cross-sectional and prospective studies published in English and German.

### *2.6.3 Free sugars, sweet food and beverages and mood disorders*

**Cross-sectional evidence**

The association between added sugar intake, sweet food / beverages and mood disorders has mainly been studied cross-sectionally (Chamberlain, Redden & Grant, 2017; El Ansari, Adetunji & Oskrochi, 2014; Gangwisch *et al.*, 2015; Guo *et al.*, 2014; Jeffery *et al.*, 2009; Konttinen *et al.*, 2010; Mikolajczyk, El & Maxwell, 2009; Sanchez-Villegas *et al.*, 2017; Shi *et al.*, 2010; Yu *et al.*, 2014). Table 3 presents an overview of the studies found; additional descriptions of each study can be found in Appendices relating to Chapter 2: Appendix 4. Studies covered free sugar intake (n=1; 13%), sugar-dense foods and beverages intakes (n=5; 63%) and sweet beverages intakes only (n=2; 25 %). All cross-sectional studies measured depression or anxiety using self-report symptoms scales (n=8; 100%) and one study additionally used self-reported doctor diagnoses. Diet was measured using FFQs (n=6; 75%), a specific Dietary Fat and Free Sugar Short questionnaire (n=1; 13%) and a single question on soft drink intake (n=1; 13%). Most studies adjusted for socio-demographic factors (n=6; 75%)

and other dietary factors (n=5; 63%), but only few for health behaviours (n=3; 38%) and energy intake (n=2; 25%). The study cohorts included all age groups from general and student (n=3; 38%) populations based in Europe (n=4; 50%), US (n=2; 25%), China (n=1; 13%) and Australia (n=1; 13%). Sample sizes were large (1839 to 10602 participants) with one exemption that included less than 250 participants.

The majority of cross-sectional studies (n=5, 63%) found a positive association between added sugar intake, sugar-dense food intake and soft drink consumption and prevalent depressive symptoms (Chamberlain, Redden & Grant, 2017; El Ansari, Adetunji & Oskrochi, 2014; Jeffery et al., 2009; Shi et al., 2010; Yu et al., 2014). Three studies found no evidence of an association in fully adjusted models, but one of them adjusted for emotional eating which might not be a confounder (Appleton et al., 2007; Konttinen et al., 2010; Mikolajczyk, El & Maxwell, 2009). The studies lacked adjustment of important confounding factors: health behaviours and energy intake. It cannot be ruled out that associations were due to other health behaviours related to high free sugar intakes or biased by energy misreporting. Beyond that, residual confounding might be operating. However, any cross-sectional evidence is weak, due to the inability to tell whether exposure occurred before or after the outcome.

**Table 3 Cross-sectional studies on the association between free sugar, sweet food and beverages and mood disorders**

| Reference; Country; Sample size; sex; age (years); population | Assessment of mood disorders | Diet method; exposure level | Adjustment | Results |
|---|---|---|---|---|
| Free sugar intake | | | | |
| Chamberlain et al. (2017); US; 225; 40% women; mean 23; University students who gamble regularly | Hamilton Anxiety (HAM-A) and Depression (HAM-D) rating scales | Dietary Fat and Free Sugar Short questionnaire;, free sugars | sex, education | Higher free sugar intake correlated with higher HAM-D scores (partial correlation coefficient, r= 0.303, p<.001) and higher HAM-A scores (partial correlation coefficient, r= 0.303, p<.001). |
| Sweet food and beverages intakes | | | | |
| El Ansari (2014); UK; 3 706; 73% women; mean 25; University students | Beck's Depression Inventory (BDI) | FFQ; food groups | sex, university, other dietary variables | Sweets/cookies/snacks/fast food intake associated with higher BDI scores in men (unstandardized regression coefficient 0.158, p<.001) and women (0.072, p=0.001); there was no association with soft drinks (p>0.1). |
| Jeffery et al. (2009); USA; 4 655; 100% women; mean 52; Health plan members | Patient Health Questionnaire (PHQ-9) | FFQ; *'high caloric sweet'* food intake | energy intake (traditional method), BMI | Depressive symptoms were positively associated with *'high caloric sweet'* intake (non-standardised regression coefficient: 0.012, p<0.01). |
| Konttinen et al. (2010); Finland; 3 714; 55% women; 24-64; population-based | CES-D | FFQ; *'sweet energy dense food'* | age, education, BMI, physical activity, restrained eating, additional adjustment for emotional eating | Odds ratio (OR) for belonging to 4th quartile of *'sweet energy dense food'* by depressive symptoms in women: 1.48, 95%-CI 1.10, 1.99, in men: 1.42, 95%-CI 1.00, 2.02. Both models were attenuated when adjusted for emotional eating (women: 1.32, 95% 0.97, 1.80; men: 1.13, 95% 0.79, 1.64). |
| Mikolajczyk et al. (2009); central Europe: Germany, Poland, Bulgaria;1 839; 65% women; mean 21; University students | BDI | FFQ, food groups | sex, country, other dietary variables | BDI not associated with sweet food / beverages intakes. |
| Appleton et al. (2007); Northern Ireland, France; 10 602; 100% men; 50-59 years recruited from MONICA study centres | Welsh Pure Depression sub-scale | FFQ, food items (cake) | stratified by country; other dietary variables, age, housing type, number of toilets, baths, cars, work type, years at school, level of education | Cake intake was not associated with depressive symptoms after adjustment in Northern Ireland (p=0.25) and France (p=0.24). |

| | | | | |
|---|---|---|---|---|
| Sweet beverages (only) | | | | |
| Shi et al. (2010); Australia; 4 741; 51% women; 47 years; population-based | Kessler Psychological Distress scale; doctor diagnosis of anxiety, depression or other stress-related/ mental health problem | Question; Soft drinks | age, sex, education, income, area of residence, smoking, drinking, physical activity, overweight, diabetes, asthma, CVD, arthritis, osteoporosis, COPD, fruit and vegetable intake | Soft drink intake ≥ 0.5l/d was associated with increased odds of depression OR 1.63, 95%-CI 1.03, 2.58 and increased odds for psychological distress OR 1.72, 95%-CI 1.11, 2.66; not associated with anxiety. |
| Yu et al. (2014), China; 3 667; 40% women; mean 43; N/A | Zung Self-Rating Depression Scale | FFQ; Soft drinks | age, sex, BMI, smoking, drinking, physical activity, marital status, total energy intake (traditional method), income, employment status, education, visiting friends, living alone, metabolic syndrome, tea, coffee and juice intake | Weekly soft drink intake of ≥4 cups soft drink/week was associated with increased depressive symptoms (score ≥45) compared to <1 cup/week (OR 2.24, 95%-CI 1.53, 3.27). |

Abbreviations: BDI, Beck's Depression Inventory; BMI, Body Mass Index; CVD, cardiovascular disease; COPD, Chronic Obstructive Pulmonary Disease; FFQ, Food Frequency Questionnaire; HAM-A, Hamilton Anxiety scale; HAM-D, Hamilton Depression scale; OR, Odds Ratio.

**Prospective studies**

Compared to cross-sectional studies, prospective studies may allow the temporal sequence of an association to be identified. Only four prospective studies investigated the association of sugar-dense foods and beverages and mood disorders (Sanchez-Villegas *et al.*, 2017, 2012; Gangwisch *et al.*, 2015; Guo *et al.*, 2014).

Table 4 presents prospective studies that investigated added sugar, sugar-dense food and beverage intakes and mood disorders, additional descriptions of each study can be found in Appendices relating to Chapter 2: Appendix 5. All studies investigated the association between baseline added sugar intake, sweet food or drink intake and new mood disorders at follow up (Gangwisch *et al.*, 2015; Guo *et al.*, 2014; Sanchez-Villegas *et al.*, 2017, 2012). No studies were found that investigated associations with recurrent mood disorders or the reverse association between mood disorders at baseline and change of free sugar or sweet food or sweet beverage intake.

Sanchez-Villegas et al. (2012, 2017) analysed data twice in one cohort, showing positive associations between 'commercial baked goods' intake such as muffins, doughnuts and croissants and depression over 6 years of follow-up and added sugar intake and depression over up to 16 years of follow-up. All studies investigated associations with depression. The majority used self-reported doctor diagnosis or antidepressant intake (n=3; 75%) to identify cases. Gangwisch et al. (2015) identified cases using a questionnaire combining questions from the CES-D and the diagnostic interview schedule, which was not validated. All studies derived diet data from FFQs and three used data collected at one time-point (Gangwisch, et al., 2015; Guo, et al., 2014; A. Sanchez-Villegas, Toledo, De, et al., 2012). Sanchez-Villegas et al. (2017) additionally averaged dietary intake over 10 years which resulted in similar estimates. Most studies adjusted for socio-demographic factors (n=4; 100%), health behaviours (n=4; 100%), other dietary factors (n=3; 75%) and energy intake (n=4; 100%) using the partition method (n=1; 25%), residual method (n=2; 50%) and quintiles of energy intake (n=1; 25%).

All studies excluded baseline depression cases and Sanchez-Villegas et al. (2017) additionally excluded incident cases within the first 2 years of follow-up . Participants were mostly followed up for 3 to 6 years (n=3; 75%) and in one study for up to 16 years (n=1; 25%) (Gangwisch *et al.*, 2015; Guo *et al.*, 2014; Sanchez-Villegas *et al.*, 2017, 2012).

The study cohorts were based in the US (n=2; 50%) and Spain (n=2; 50%; studies in the same cohort) and all studies included large samples (8964 to 263923 participants) (Guo *et al.*, 2014; Gangwisch *et al.*, 2015; Sanchez-Villegas *et al.*, 2012, 2017).

**Table 4 Prospective studies on the association between free sugar, sweet food and beverages and mood disorders**

| Reference; Country; Sample size; sex; age (years); follow-up (years); population | Assessment of mood disorders | Diet method; exposure level | Adjustment | Results |
|---|---|---|---|---|
| | | | Free sugar intake | |
| Gangwisch et al. (2015); US; 69 954; 100% women; 50-79; 3; general population sample | Burnham 8-item scale for depressive disorders | FFQ; dietary added sugar, total and other sugar types | age, ethnicity, education, income, physical activity, alcohol, smoking, diseases, hypertension, hormone replacement therapy, major life events, social support, energy (partition method), diabetes, and energy-adjusted fatty acids, fruit, vegetables, legumes, nuts and seeds, fibre intake, Healthy Eating Index, BMI | Dietary added sugar associated with increased chance for depressive symptoms (OR for 4th quintile, mean intake 53g 1.18, 95%-CI 1.04, 1.33; 5th quintile, mean intake 79g, OR 1.23, 95%-CI 1.07, 1.41; compared to 1st quintile, mean intake 18g/day. |
| Sanchez-Villegas et al. (2017); Spain; 15 546; 59% women; 18-101; 4-16; university graduates from the Seguimiento University of Navarra (SUN) | Self-reported physician made depression diagnosis (first two years of follow-up excluded) | FFQ; Added sugar intake, sweetened beverages | sex, age, smoking, physical activity, special diets, energy intake (residual method), Mediterranean diet adherence, energy intake, BMI, CVD, dyslipidaemia, hypertension, diabetes (in sensitivity analyses) | Baseline added sugar intake was associated with increased chance for depression diagnosis at follow-up in linear analysis (HR per SD 1.08, 95%-CI 1.01, 1.17) but not significantly associated when operationalised as quartiles (HR 4th, median intake 83g vs. 1st quartile, median intake 29g 1.22, 95%-CI: 0.98, 1.50). Baseline sweetened beverages intake, only, was not associated with depression diagnosis.<br>Mean intake of added sugar intake over 10 years (overlapping with follow-up time) was associated with increased risk for depression diagnosis for both linear intakes as well as operationalised as quartiles. |
| | | | Sweet food | |
| Sanchez-Villegas et al. (2012); Spain; 8 964; 59% women; 18-101[a]; 6; university graduates from the SUN | Self-reported physician made depression diagnosis or habitual antidepressant use | FFQ; *'commercial baked goods'* | sex, age, smoking, physical activity, energy intake (residual method), fast-food and healthy food consumption, BMI | Commercial baked goods consumption non-linearly associated with depression (OR for 2nd vs. 1st quintile 1.42, 95%-CI 1.05, 1.93; OR for 5th vs. 1st quintile 1.37, 95%-CI 1.01; 1.85; p for trend 0.32). Combined the association results in an increased chance when comparing 2nd to 5th quintile with the 1st quintile (OR 1.34, 95%-CI 1.03; 1.75[b] |

| | | | | |
|---|---|---|---|---|
| Sweet beverages (only) | | | | |
| Guo et al. (2014); US; 263 923; 41% women; 50-71; 5; Members of American Association of Retired Persons | Self-reported physician made depression diagnosis | FFQ; soft drinks, fruit drinks | sex, age, ethnicity, marital status, education, smoking, alcohol intake, physical activity, energy intake (quintiles), BMI | Soft drinks intake associated with increase chance of depression (OR for ≥4 cans compared to no intake OR 1.30, 95%-Cl 1.17, 1.44, p for trend 0.0001). Fruit drinks ≥4 cans OR 1.38 (95%-Cl 1.15; 1.65) intake associated with increase chance of depression (OR for ≥4 cans compared to no intake compared to no cans/day OR 1.38, 95%-Cl 1.15, 1.65). No association with regular ice tea. When stratified by diet beverages both regular and diet soft beverages associated with increased chance, fruit drinks and ice tea restricted to diet beverages. |

Abbreviations: BMI, Body Mass Index; FFQ, Food Frequency Questionnaire; CVD, cardiovascular disease; HR, Hazard Ratio; OR, Odds Ratio.
[a]Information based on Seguí-Gómez et al. (2006).
[b]Odds ratios refer to the association with prevalent depression at follow-up; a sensitivity analysis excluding baseline depression changed the results but not the main association (Sanchez-Villegas et al., 2012).

*Free sugar intake*

Gangwisch et al. (2015) and Sanchez et al. (2017) found a dose-response relationship of added sugar intake with incident depressive symptoms and incident depression. Gangwisch et al. (2015) defined added sugar intake based on the U.S. MyPyramid equivalence database, but not all details of the calculation could be derived from this source as online documents have since expired (Bowman et al., 2008). Sanchez-Villegas et al. (2017) approximated added sugar intake from sugar intake from sweet food and beverages.

In Gangwisch et al. (2015) estimates were attenuated by 45% after adjustment for all included confounders, whereas estimates were only attenuated by 14% in Sanchez-Villegas et al. (2017). This difference could be explained by the differences in models and samples. Most of the attenuation in Gangwisch et al. (2015) was due to socio-demographic factors (73%) may be more relevant in this sample that was oversampled with minorities, whereas the SUN cohort was restricted to university graduates that might have been more homogenous in their socio-demographics. However, the strong attenuation could point towards an important role of residual confounding in the association.

*Sweet food*

In an earlier study in the SUN cohort '*commercial baked goods'* intake was associated with an increased risk of incident depression in a non-linear manner. The risk was increased in Quintile 2, 3 and 5, but showed smaller estimates when comparing Quintile 4 and 1. Adjustments for health behaviour and other dietary factors strengthened the association (6%) (Sanchez-Villegas *et al.*, 2012).

*Sweet beverages*

Guo et al. (2014) found associations between sweet drinks and depression. The research group furthermore investigated differences between regular and diet beverages and found a similar positive association for diet soft drinks, fruit drinks and ice tea suggesting that sweetness could facilitate the association rather than sugar. Only adjusted results were reported therefore model adjustment could not be investigated.

Sanchez et al. (2017) additionally investigated associations between sugar-sweetened beverages and depression but could not replicate Guo et al. (2014)'s finding of a positive association with depression.

There was some evidence for bias in the studies reviewed here. Selection bias has likely occurred in the SUN cohort as it was restricted to participants of higher education (Seguí-Gómez *et al.*, 2006), in the National Institutes of Health–American Association of Retired Persons Diet and Health Study (NIH-AARP) used in Guo et al. (2014) due to its low initial response rate of only 17.6% (Schatzkin *et al.*, 2001) and the study used in Gangwisch et al. (2015) was restricted to middle-aged postmenopausal women. Selection bias can affect the variance of the exposure and outcome in the sample. Guo et al. (2014), Sanchez-Villegas (2017) and Gangwisch et al. (2015) all tested a number of different dietary exposures which could have increased the risk of a chance finding(Rothman, Greenland & Lash, 2008). Only Gangwisch et al. (2015) corrected for this in all post hoc analyses.

All four studies found a positive association between free sugars, sugar-dense food and beverages intake at baseline and depression and depressive symptoms at follow-up (Sanchez-Villegas *et al.*, 2017, 2012; Gangwisch *et al.*, 2015; Guo *et al.*, 2014). One of two studies that investigated only associations between sweet beverages and depression at follow-up found an association suggesting that associations with free sugars were not solely driven by sugar-sweetened beverage intake (Sanchez-Villegas *et al.*, 2017; Guo *et al.*, 2014).

**Summary of the evidence**

Before summarising, it has to be noted that there are few biases that additionally have to be taken into account: Residual confounding and publication bias.

Residual confounding is an important limitation in nutritional epidemiology. As dietary data are not well measured (see Chapter 2: 2.2.1) residual confounding is likely to still operate even after adjustment for covariates (Davey Smith *et al.*, 2007; Davey Smith & Phillips, 1992; Ioannidis, 2013).

All published studies are subject to publication bias. Studies are more likely to be published, and published earlier, if they show significant or positive results, rather than those with non-significant or unexpected results (Song *et al.*, 2010). In this case free sugars, sweet foods/beverages were, only in a few cases, the sole main exposure (in cross-sectional studies n=2; 25%; in prospective studies n=1; 25%) (Guo *et al.*, 2014; Yu *et al.*, 2014; Shi *et al.*, 2010). Therefore, publication is unlikely to have highly depended on significant results in associations with free sugars or sweet foods.

Taking into account the limitations described above there was some evidence for a positive association between free sugar intake and mood disorders.

Cross-sectional studies were of lower quality including fewer participants than prospective studies and lacking control for important confounders. To my knowledge, prospective studies to date have only investigated associations with prevalent and incident depression at follow-up 3-16 years later. Associations have been based on large samples and included important confounders in their models. However, no studies have used a validated measure of mood disorder with high sensitivity, and all studies used one baseline which does not take into account the episodic nature of mood disorders.

With depressive episodes being recurrent and CMDs common, an association with recurrent mood disorder episodes is an important outcome. No studies have investigated associations between free sugar, sweet food / beverage intake and recurrent episodes. As shown in 2.4.1 associations between free sugar and mood disorders could alternatively be explained by reverse causation. No prospective studies have investigated whether mood disorders lead to changes in intake of free sugars, sweet food / beverage intake. Gaps and limitations will be summarised in detail in section 2.6.6.

### *2.6.4 Dietary fibre intake and mood disorders*

**Cross-sectional evidence**

The association between dietary fibre intake and mood disorders has mainly been studied cross-sectionally (Davison & Kaplan, 2012; Davison, Gondara & Kaplan, 2017; Fang *et al.*, 2013; Gopinath *et al.*, 2017; Green & Pope, 2000; Miki *et al.*, 2016; Woo *et al.*, 2006; Gangwisch *et al.*, 2015; Sanchez-Villegas *et al.*, 2017; Gougeon *et al.*, 2017; Akbaraly *et al.*, 2013; Xu *et al.*, 2018). Table 5 provides an overview of the cross-sectional studies. Most studies assessed mental health using the CES-D (n=3; 38%) and other symptoms scales (n=5; 50%). Green & Pope (2000) ascertained depression additionally with self-reported doctor diagnosis. Diet was measured with diet recalls (n=3; 38%), FFQs (n=3; 38%), questions on attempt of increasing fibre or fibre-rich foods (n=1; 13%), dietary records (n=1; 13%) and diet history questionnaires (n=1; 13%). Most studies adjusted for socio-demographic factors (n=7; 88%) and energy intake (n=6; 75%), but only few for health behaviours (n=3; 38%) and other dietary factors (n=1; 13%). The majority of studies used data from North America (n=4; 50%) and Asia (n=2; 25%). Sample sizes were mostly large (between 1 977 to 16 807 participants) with two exemptions that included less than 250 participants.

**Table 5 Cross-sectional studies on the association between dietary fibre intake and mood disorders**

| Reference; Country; Sample size; sex; age (years); population | Assessment of mood disorders | Diet method; exposure level | Adjustment | Results |
|---|---|---|---|---|
| Dietary fibre intake | | | | |
| Davison & Kaplan (2012);Canada; 97; 71% women; 18+; community-sample with diagnosed mood disorder | HAM-D | 3-day food records | sex, age, income, energy intake (traditional method), psychiatric medication | No significant association between fibre intake and depression scores. |
| Davison et al. (2017); Canada; 15 546; 55% women; 19-70; population based | Perceived mental health | 24h diet recall | sex, age, income, education, marital status, smoking, energy intake (traditional method) | Association between mental health and food insecurity for fibre in men between 31 and 50 years and women between 51 and 70 years; adjusted results are not presented. |
| Fang et al. (2013); US; 225; 100% women; 24-29; parents of intervention study in children | CES-D | 3-day 24h diet recalls | age, treatment group, ethnicity, energy intake (using restricted cubic splines), education, income, marital status, hormonal contraceptive use, family history of heart disease and diabetes | No association between depressive symptoms and fibre intake after adjustment for confounders. |
| Gopinath et al. (2017); Australia; 2 334, 59% women[a], 50+ & 60+; population-based cohort | Mental health index scale (MHI) & CES-D | 145-item FFQ | age, sex, energy intake (residual method), cognitive impairment, walking disability, receiving pension, antidepressant use, stroke history, arthritis | No association between total fibre intake and prevalence of depressive symptoms assessed MHI; Participants in the 2nd vs. 1st tertile of total fibre intake reduced odds of CES-D depressive symptoms (0.58, 95%-CI 0.39, 0.87), vegetable fibre intake (0.54, 95%-CI 0.36, 0.81) not significant compared to 3rd tertiles. Linear inverse association with bread/cereal fibre (trend 0.01). |
| Miki et al. (2016); Japan; 1 977; 11% women; 19-69; occupational cohort | CES-D | Diet history questionnaire | age, sex, site, marital status, job grade, shift work, overtime work, job strain, physical activity, leisure time physical activity, smoking, alcohol, green tea, coffee, sleep duration, BMI, energy intake (density method), folate intake, vitamin b6, b12, omega-3-PUFAs, magnesium, zinc | Vegetable and fruit fibre with lower chance of high depressive symptoms but attenuated when fully adjusted, models (OR for 3rd vs. 1st 0.65, 95%-CI 0.45, 0.95). Total and soluble fibre intake not associated in fully adjusted models. |

| | | | | |
|---|---|---|---|---|
| Woo et al. (2006); China; 3 357; 50% women; 65+; population sample | Geriatric depression scale (GDS) | 7d FFQ | age, sex, education, socio-economic position, medical diseases, dementia score | Intake of more than 13g/day total fibre intake was associated with reduced odds for GDS depression (OR 0.66, 95%-CI 0.46, 0.96). |
| Xu et al. (2018); US; 16 807, 51% women; 20+; population sample | Patient Health Questionnaire 9 | 24h-recall | age, sex, ethnicity, marital status, education, income, BMI, energy intake (traditional method), smoking, alcohol, physical activity, hypertension, diabetes | Total fibre intake associated with lower chance for depressive symptoms ($4^{th}$ vs. $1^{st}$ quartile OR 0.59, 95%-CI 0.44, 0.79). When analysed by source significant association with vegetable and fruit fibre, not with cereal fibre intake. |
| Attempting increase in fibre intake | | | | |
| Green & Pope (2000); US; 5 841; 60% women; 18-102; members of health maintenance organisation | History of depression assessed using symptoms list and self-reported doctor diagnosis | Question whether attempted to increase amount of fibre during last 12 months | age, sex, education, income, self-reported social class, health status | Higher OR for history of depression and depressive symptoms in those reporting to attempt increased fibre intake (OR 1.24, 95%-CI: 1.08, 1.41). |

Abbreviations: BMI, Body Mass Index; CES-D, Center for Epidemiologic Studies Depression Scale; FFQ, Food Frequency Questionnaire; GDS, Geriatric depression scale; HAM-D, Hamilton Depression scale; OR, odds ratio; PUFAs, poly unsaturated fatty acids.
[a]Information based on Cugati et al. (2007).

Two of the eight studies differed from the others, wherefore they will be described in a little detail, additional descriptions of all other studies can be found in Appendices relating to Chapter 2: Appendix 6.

Davison et al. (2017) investigated the association between fibre intake and mental health in relation to food insecurity. The researchers found that men between 31 and 50 years and women between 51 and 70 years with poor mental health and food insecurity had significantly lower fibre intakes than those without food insecurity and good mental health. However, associations were only presented in subgroups and without adjustment which leads me to believe adjusted results were statistically non-significant.

Green & Pope (2000) investigated the association between history of depressive symptoms based on recall and current dietary behaviour described as attempting to consume more fibre. They found that those with a history of depressive symptoms or diagnosis were more likely to report attempting to consume more fibre. The question does not qualify whether the attempt is representing a current diet low in fibre which is aimed to be overcome or a current attempt and engagement in healthy behaviour towards higher intakes.

Associations between fibre intake and mood disorder prevalence were mixed. Four studies found some inverse association of fibre intake with prevalent depressive symptoms (Gopinath *et al.*, 2017; Woo *et al.*, 2006; Green & Pope, 2000; Xu *et al.*, 2018) and four studies found no association or no associations after adjustment for confounding variables (Fang *et al.*, 2013; Miki *et al.*, 2016; Davison & Kaplan, 2012; Davison, Gondara & Kaplan, 2017). Two studies found slight differences by fibre source but it is likely that these were not due to specific properties of these fibre fractions but the result of confounding by other food intake which these studies and most others did not adjust for (Gopinath *et al.*, 2017; Xu *et al.*, 2018). Only one of the four studies that found an association had adjusted for health behaviours suggesting that associations could have been the result of confounding.

**Prospective**

Three prospective and one nested case-control study investigated the association of fibre intake and mood disorders (Akbaraly *et al.*, 2013; Gangwisch *et al.*, 2015; Sanchez-Villegas *et al.*, 2017; Gougeon *et al.*, 2017).

The study cohorts were based in North America (n=2; 50%), Spain (n=1; 25%) and the UK (n=1; 25%) and included large study samples (from 4 215 to 15 546 participants)

(Gougeon *et al.*, 2017; Gangwisch *et al.*, 2015; Sanchez-Villegas *et al.*, 2017; Akbaraly *et al.*, 2013).

Table 6 presents details of prospective studies on the association between dietary fibre intake and mood disorders, additional information can be found in Appendices relating to Chapter 2: Appendix 7. Two investigated the association between fibre intake and incident mood disorder, one the association with recurrent mood disorder and one the reverse hypothesis of an association between mood disorder and change in fibre intake (Gangwisch *et al.*, 2015; Sanchez-Villegas *et al.*, 2017; Akbaraly *et al.*, 2013; Gougeon *et al.*, 2017). All studies investigated associations with depressive symptoms or depression. Three studies measured depressive symptoms with a questionnaire, two added information on antidepressant intake to these measures and one study used only a self-reported doctor diagnosis of depression. Most studies used FFQ's to ascertain dietary intake (n=3; 75%). Gougeon et al. (2017) analysed data using several phases of data-collection, Sanchez-Villegas et al. (2017) used additionally averaged dietary intake over 10 years and Akbaraly et al. (2013) additionally investigated 10-year change in fibre intake. Most studies adjusted for socio-demographic factors (n=4; 100%), health behaviours (n=4; 100%), other dietary factors (n=3; 75%) and energy intake (n=3; 75%) using the partition method (n=1; 25%), residual method (n=1; 25%) and the traditional method (n=1; 25%). Follow-up ranged from one year, three and five years to up to 16 years.

**Table 6 Prospective studies on the association between dietary fibre intake and mood disorders**

| Reference; Country; Sample size; sex; age (years); follow-up years); population | Assessment of mood disorders | Diet method; exposure level | Adjustment | Results |
|---|---|---|---|---|
| Association with incident mood disorder | | | | |
| Gangwisch et al. (2015); US; 69 954; 100% women; 50-79; 3; population sample | Burnham 8-item scale for depressive disorders | FFQ; dietary fibre intake | age, ethnicity, education, income, physical activity, alcohol, smoking, diseases, hypertension, hormone replacement therapy, major life events, social support, energy (partition method), diabetes, and energy-adjusted fatty acids, fruit, vegetables, legumes, nuts and seeds, added sugar intake, Healthy Eating Index, BMI | Daily dietary fibre intake associated with reduced chance for depressive symptoms (OR 5th quintile, median intake 21g, compared to 1st quintile, median intake 11g, 0.86, 95%-CI 0.76; 0.98). |
| Sanchez-Villegas et al. (2017); Spain; 15 546; 59% women; 18-101; 4-16; university graduates | Self-reported physician made depression diagnosis | FFQ; dietary fibre intake | sex, age, smoking, physical activity, special diets, energy intake (residual method), Mediterranean diet adherence, energy intake, BMI, CVD, dyslipidaemia, hypertension, diabetes (sensitivity analyses) | Baseline dietary fibre intake was not associated with incident depression (HR per SD 1.03, 95%-CI 0.94, 1.13). |
| Association with recurrent mood disorder | | | | |
| Akbaraly et al. (2013); UK; 4215; 25% women; 50-74; 5; occupational cohort of civil servants in Whitehall II | CES-D and/or antidepressant intake | FFQ; dietary fibre intake | sex (stratified), age, ethnicity, energy intake (traditional method), socio-economic position, retirement, living alone, smoking, physical activity, coronary artery disease, diabetes, hypertension, high-density lipoprotein cholesterol, lipid-lowering drugs use, central obesity, cognitive impairment | Baseline fibre intake not associated with recurrent depression (at baseline and 5-year follow-up) in women and men. Change over 10 years not associated with depression at 10 and 15 years. |
| Nested case-control study | | | | |
| Gougeon et al. (2017); Canada; 158; 64% women; 67-82; 1; population sample | GDS and antidepressant intake | 3-day 24h dietary recalls | matched by age and sex; functional autonomy, physical activity, major life events | Fibre intakes did not differ between and within cases and controls across follow-up. |

Abbreviations: BMI, Body Mass Index; CES-D, Center for Epidemiologic Studies Depression Scale; CVD, cardiovascular disease; FFQ, Food Frequency Questionnaire; GDS, Geriatric depression scale; OR, odds ratio.

*Association with incident mood disorder*

Gangwisch et al. (2015) found an inverse association between fibre intake and incident depression and Sanchez-Villegas et al. (2017) did not. Estimates in Gangwisch et al. (2015) were attenuated quite substantially (66%) when adjusted for covariates but as shown for added sugar intake this could reflect the specifics of the study but could also mark a risk for residual confounding.

Differences between results of Gangwisch et al (2015) and Sanchez-Villegas et al. (2017) could be due to cohort differences or measurement and severity of depression. Gangwisch et al. (2015) analysed data from a large cohort of middle-aged US women. The SUN cohort investigated by Sanchez-Villegas et al. (2017) included university graduates of any age between 18-101 years. Sanchez-Villegas et al. (2017) assessed depression using self-reported doctor diagnosis that showed a high specificity (0.96) but a low sensitivity (0.37) when validated against a structured clinical interview in the SUN cohort study (Sanchez-Villegas *et al.*, 2008). The screening questionnaire used in Gangwisch et al. (2015) is likely to have had a higher sensitivity but lower specificity and could therefore include less severe cases. Dietary fibre intake might be only associated with mild mood disorders.

*Association with recurrent mood disorder*

One study investigated the association between fibre intake as a component of a healthy dietary index (alternative healthy eating index) and recurrent depressive symptoms in the Whitehall II cohort. The study defined ‘recurrent depression’ cases as scoring high on the CES-D or having reported antidepressant intake at baseline (in 2002-2004, data collection wave 7) and follow-up (in 2007-2009 data collection wave 9). Participants were considered as not having ‘recurrent depression’ if they scored high on the CES-D or reported antidepressant intake at neither baseline nor follow-up or at either of these data collection points. Therefore associations have to be considered partly cross-sectional as those with no CES-D case or antidepressant intake at baseline were not able to develop ‘recurrent depression’ at follow-up. (Akbaraly *et al.*, 2013).

Akbaraly et al. 2013 found an inverse association between fibre intake and recurrent depression that was attenuated after further adjustment for socio-demographic factors, diseases and other dietary factors. Change of fibre intake over 10 years (between 1991-1994, wave 3 and 2002-2004, wave 7) was not associated with recurrent depression (in 2002-2004, at wave 7) (Akbaraly *et al.*, 2013). However, the partly

cross-sectional, partly prospective design makes it difficult to determine the temporal sequence of this association.

*Nested case-control study*

Gougeon et al. (2017) investigated the role of depressive symptoms on diet changes in a nested-case control design in a sample of elderly Canadians. 158 incident cases were identified using the geriatric depression scale (GDS) and antidepressant intake at follow-up of the study. Cases were identified at three follow-up waves and matched with 158 controls by sex and age from the same cohort study of elderly Canadian adults. Fibre intake at baseline was ascertained yearly from 3-day 24h dietary recalls. Change in fibre intake between the year of incident caseness and the year prior was compared between cases and controls using general mixed models. The researchers found no significant difference in change of fibre intake between and within cases and controls suggesting that depression did not result in a subsequent change in fibre intake.

There was some evidence for bias which could have led to too little variance in outcome and exposure to detect differences (Rothman, Greenland & Lash, 2008). The Women's Health Initiative was restricted to middle-aged women (Gangwisch *et al.*, 2015), the SUN cohort restricted to participants of higher education (Seguí-Gómez *et al.*, 2006), the Whitehall II study is an occupational cohort and as later waves of data-collection were investigated loss of follow-up introduced some selection towards a healthier sample (Ferrie *et al.*, 2009; Akbaraly *et al.*, 2013). The Québec Longitudinal Study on Nutrition and Aging studied in the nested case-control study was restricted to adults over 68 years, thereby adults with bad health might have not been able to participate or were already deceased (Gougeon *et al.*, 2017).

In Gangwisch et al. (2015) associations between fibre intake and incident depression remained after applying a false discovery rate, reducing the risk that associations were due to chance.

Regarding incident depressive symptoms one of two studies found an inverse association with dietary fibre intake (Sanchez-Villegas *et al.*, 2017; Gangwisch *et al.*, 2015). There was no evidence for an association between fibre intake and recurrent depression and no evidence that depression leads to changes in fibre intake (Akbaraly *et al.*, 2013; Gougeon *et al.*, 2017).

**Summary of the evidence**

Residual confounding and publication bias could have also affected associations between fibre intake and mood disorders (Davey Smith & Phillips, 1992; Davey Smith *et al.*, 2007; Ioannidis, 2013; Song *et al.*, 2010).

In the case of fibre there were as many studies that found an association as there were that found no association suggesting that publication bias might have had little effect on the findings of this review. This is most likely due to the fact that most studies focused on several dietary exposures and only two studies focused on fibre intake as sole main exposure (Miki *et al.*, 2016; Xu *et al.*, 2018).

Considering the limitations described, there was little evidence for associations between fibre intake and depression with ambiguous findings regarding incident depression with one study suggesting an inverse association between fibre intake and incident depression. Associations found in cross-sectional studies could potentially be explained by residual confounding as all studies lacked adjustment for health behaviours. Only very few studies had investigated associations between fibre intake and mood disorders prospectively. Studies investigated associations with incident, recurrent depression and depressive symptoms and the hypothesis that mood disorder could change dietary intakes. Prospective studies had been based on large samples and included important confounders in their models. The nested-case control design used in one study reduces recall bias. However, the study based on recurrent depression was designed to be partly cross-sectional. Gaps and limitations will be summarised in detail 2.6.6.

### *2.6.5 Interactions between free sugar, sweet food and beverage intake or fibre intake in the association between socio-economic position and mood disorders*

In section 2.5 it was hypothesised that dietary intake could modify the association between financial insecurity or other socio-economic factors and mood disorders, e.g. that those with socio-economic disadvantage and high sugar intake could be more likely to experience depression and that those with socio-economic disadvantage and high fibre intake could be less likely to experience depression. No study was found investigating the role of free sugars and dietary fibre intake in the association between financial insecurity and mood disorder. One study did investigate fibre intake in the association between food insecurity and poor mental health, but association were restricted to a few age groups and were not presented adjusted which is likely due to non-significant results (Davison, Gondara & Kaplan, 2017) (see Chapter 2: 2.6.4: Cross-sectional evidence).

In sum, there is a gap in research on the potential moderating role of free sugar intake and fibre intake in the association between socio-economic factors in mood disorders.

### *2.6.6 Gaps and limitations*

Several gaps and limitations can be identified in the literature on a potential adverse effect of long-term free sugar and sweet food / beverages intake and protective effect of fibre intake on mood disorders, and an interaction with socio-economic measures.

**Cross-sectional studies that adjust for health behaviours**

Most of the cross-sectional studies between the association of free sugars, sweet food and beverages, dietary fibre and mood disorders did not adjust for health behaviours (Chamberlain, Redden & Grant, 2017; Davison, Gondara & Kaplan, 2017; Davison & Kaplan, 2012; El Ansari, Adetunji & Oskrochi, 2014; Fang *et al.*, 2013; Gopinath *et al.*, 2017; Green & Pope, 2000; Jeffery *et al.*, 2009; Miki *et al.*, 2016; Mikolajczyk, El & Maxwell, 2009; Woo *et al.*, 2006; Xu *et al.*, 2018).

Health behaviours tend to cluster in a way that for example those who consume a high fibre diet are likely to also follow other healthy behaviours like regular physical activity and low alcohol intake (Poortinga, 2007; Chapman *et al.*, 2012). As health behaviours have been found to be associated with mood disorders they could confound an association between sugar-dense diet consumption, fibre intake and mood disorders (Boden Joseph M. & Fergusson David M., 2011; Mammen & Faulkner, 2013; Azevedo Da Silva *et al.*, 2012).

Adjusting for health behaviours and other relevant confounders could reduce the chance of measuring characteristics common in people with high free sugar and low fibre intake. However, adjusting cannot avoid entirely that associations could be explained by confounding as residual confounding remains (see Chapter 2: 2.4.2) (Davey Smith *et al.*, 2007).

**Cross-sectional studies that adjust for energy intake**

Most studies on the cross-sectional association of free sugars, sweet food or beverages did not adjust for energy intake (Chamberlain, Redden & Grant, 2017; El Ansari, Adetunji & Oskrochi, 2014; Konttinen *et al.*, 2010; Mikolajczyk, El & Maxwell, 2009; Appleton *et al.*, 2007; Shi *et al.*, 2010).

Energy adjustment is an important method to reduce the effect of under- and overreporting in dietary questionnaires (Stallone *et al.*, 1997). If participants under-

reported their diet intake the amount of free sugar intake could be underestimated compared to others that reported more adequate overall diet intakes. Energy adjustment reduces both information bias due to underreporting and incorrect ranking of individuals according to their free sugar intake. Adjusting for energy intake using the partition method for analyses of free sugars and the residual method for fibre intake could reduce bias introduced by misreporting (Howe, 1989; Willett & Stampfer, 1986; Willett, Howe & Kushi, 1997; Willett, 2012).

**Prospective studies on incidence**

Overall there were a limited number of prospective studies. To date only four studies from three cohorts investigated the association between free sugars, sweet food and beverages and mood disorders and two between fibre intake and incident mood disorders (Gangwisch *et al.*, 2015; Guo *et al.*, 2014; Sanchez-Villegas *et al.*, 2017, 2012). Future studies should investigate associations between free sugar intake in cohorts outside of North America and Spain.

**Prospective studies on recurrence**

No study investigated associations between free sugar intake and recurrent mood disorders and only one study investigated the role of fibre intake in recurrent depressive symptoms (Akbaraly *et al.*, 2013). This study had a partly cross-sectional design. Studies including only participants that suffered from mood disorders at baseline would reduce the risk of reverse causation in investigating the association between free sugar, fibre and recurrent mood disorder.

**Prospective studies on reverse causation**

Associations between free sugar or fibre intake and mood disorder could be wholly or partly explained by a reverse association in which mood disorder leads to dietary changes. No study was identified that investigated associations between mood disorder and changes in free sugar intake. Only one study was found investigating the association between mood disorder and changes in fibre intake in a nested-case control design (Gougeon *et al.*, 2017). In a cohort study the association between baseline mood disorders and change of dietary intake over follow-up could be investigated to explore the role of reverse causation.

**Prospective studies using validated mood disorder assessment methods with high specificity and sensitivity**

No study has investigated the association with mood disorder using assessment measures that have been validated and shown to have high specificity and sensitivity. The depressive symptom scale used by Gangwisch et al. (2015) had not been

validated independently but was a combination of questions from other questionnaires which does not mean the questionnaire has the same ability to identify mood disorders (McDowell, 2006). Self-reported physician made depression diagnosis used by Sanchez-Villegas et al. (2017) and Guo et al. (2014) was found to have a very low sensitivity (0.37) in the SUN cohort which could have led to a large number of false-negative classifications (Sanchez-Villegas *et al.*, 2008). Investigating associations with different measures including some with high specificity and high sensitivity would reduce bias and allow the investigation of whether associations might depend on severity.

**Studies using repeated measures in a cycle approach**

Mood disorders can appear recurrently therefore analysing mood disorders as an endpoint does not reflect the cyclic nature of the disease (Hardeveld et al., 2010, 2013; Kessler & Bromet, 2013). A cycle approach, analysing multiple waves of data over several years and pooling the results using appropriate statistical models, would not only take into account the recurrent nature of the disorder but could also allow the information included in the analysis to be maximised. This approach would reduce the risk of a chance finding (a false positive or negative result) (Twisk, 2004). Only the nested-case control study used repeated data measurement occasion in this way (Gougeon et al., 2017).

**Studies investigating the role of free sugars and dietary fibre intake in the association between financial insecurity and mood disorder**

To date, no study has investigated the role of free sugars and dietary fibre intake in the association between socio-economic measures and mood disorder. Free sugar and fibre intake could not only be directly associated with mental health but also act as effect modifiers in associations with other important risk factors, in particular financial insecurity and socio-economic position. This is an important public health question when considering the effect of dietary interventions for mental health due to the burden of mental health inequalities. The link could be tested using interaction analyses investigating interactions between free sugar and fibre intake in the association between financial insecurity and mood disorders.

## 2.7 Lessons drawn from literature review

Mood disorders are highly prevalent and burden individuals and economies making them an important health outcome to study. Mood disorders appear episodic and recurrence is common meaning that research should focus on both new and recurrent cases (see Chapter 2: 2.1).

Diet data has a number of short-comings regarding precision and accuracy of measurement. As shown in section 2.2.2 adjustment for energy intake and other confounders reduces some of the bias in the measurement of diet intake. While fibre intake can be measured using FFQ data utilising food composition tables free sugar intake can only be approximated for example by using total sugar intake from the most common sources of free sugars – sweet food and beverages (see Chapter 2: 2.2).

Several biological pathways may explain the proposed links between free sugar and mood disorder, and fibre intake and mood disorder, suggesting that an association between them might reflect a causal association (see Chapter 2: 2.3) (Potischman & Weed, 1999). Still, several alternative explanations could explain an association such as reverse causation and confounding. Several pathways such as health behaviour changes in response to mood disorder symptoms or self-medication through food could lead people suffering from mood disorders to change their free sugar and fibre intake. Underlying characteristics that correlate with free sugar or fibre intake could confound the association with mood disorders (see Chapter 2: 2.4).

Apart from a direct effect on mood disorders, free sugar and fibre intake could have an indirect effect by affecting the adaptability to stressors associated with financial insecurities and low socio-economic position. It could be possible that free sugar and fibre intake moderate an association between financial insecurities and mood disorders (see Chapter 2: 2.5).

Previous research on the association between free sugar and mood disorders found some evidence for a positive association. To date, research on the association between fibre intake and mood disorders is weak. Still, research was limited to few studies and several gaps and limitations were identified (see Chapter 2: 2.6, 2.6.6).

# Chapter 3 **Aims and Objectives**

Associations between sugar intake from sweet food / beverages and dietary fibre intake, respectively, and mood disorders as well as an interaction with financial insecurity could be of great public health relevance. Review of the literature has revealed several gaps in the evidence and limitations in earlier studies.

The aim of this thesis is to investigate the role of sugar intake from sweet food / beverages and fibre intake, as predictors of mood disorders and as moderators of the association between financial insecurity and mood disorders. To investigate these associations dietary intake and several measures of mood disorders that were measured on several occasions will be analysed using random effects models (REMs) in cycles of 2, 5 and 10 years. This approach considers the recurrent nature of mood disorders while reducing the risk of chance findings.

Three objectives will be addressed.

**I$^{st}$ Objective: Is a diet high in sugar intake from sweet food / beverages a risk factor in mood disorders?**

*Hypotheses:*

- A diet high in sugar from sweet food / beverages will be positively associated with prevalent mood disorders.
- A diet high in sugar from sweet food / beverages will be associated an increased chance for incident and recurrent mood disorders.
- Mood disorders increase sugar intake from sweet food / beverages (reverse causation hypothesis).

**II$^{nd}$ Objective: Is a diet high in fibre intake a protective factor in mood disorders?**

*Hypotheses:*

- A diet high in dietary fibre will be inversely associated with prevalent mood disorders.
- A diet high in dietary fibre will be associated with a reduced chance for incident and recurrent mood disorders.
- Mood disorders change dietary fibre intake (reverse causation hypothesis).

**III$^{rd}$ Objective: Does sugar intake from sweet food / beverages, and dietary fibre intake, act as a moderator in the association between financial insecurity and mood disorders?**

*Hypotheses:*

- The association between financial insecurity and mood disorders will be stronger in those with high sugar intake from sweet food / beverages.
- The association between financial insecurity and mood disorders will be weaker in those with high fibre intake.

The hypotheses will be tested in participants of the Whitehall II study, a cohort of British civil servants that have been followed up for 30 years. The first objective will be additionally tested in the European Prospective Investigation of Cancer Norfolk (EPIC-Norfolk).

# Chapter 4 **Methodology**

This chapter describes the methods used in this thesis. Populations, variables and statistical methods are introduced. Differences between outcome variables and the structure of missing data are investigated.

## 4.1 Main study sample: The Whitehall II cohort study

The Whitehall II study was set up to examine reasons for the inverse social gradient in health and disease in both sexes. From 1985 to 1988 non-industrial civil-servants aged 35-55 years working in London offices of 20 Whitehall departments were recruited for the first data collection phase (Marmot & Brunner, 2005). With a response rate of 73% after excluding those who were ineligible, the final sample size reached 10 308, 33.1% women and 66.9% men (Marmot *et al.*, 1991). Further information on health status and death of participants was delivered by primary care and hospital records, cancer registry and NHS-Wide Clearing service notifications and the NHS Central Registry (Marmot & Brunner, 2005).

Table 7 shows dates, type of data collection and relevant factors measured at each phase of data collection. The participants were followed up via questionnaire in 1989-1990 (phase 2), 1991-1994 (phase 3), 1995-1996 (phase 4), 1997-1999 (phase 5), 2001 (phase 6), 2002-2004 (phase 7), 2006 (phase 8), 2007-2009 (phase 9) and 2012-2013 (phase 11). At phases 1, 3, 5, 7, 9 and 11 they were additionally invited for screening in a research clinic. Phase 10 (2011) consisted of a subsample of participants used for a pilot study. The main questionnaire included the GHQ questionnaire and the CES-D questionnaire from phase 7 onwards. The computer based CIS-R was part of the clinic screenings at phase 10 and 11. At phase 3, a FFQ was sent out with the main questionnaire, at phases 5, 7 and 9 it was given to participants at the clinic appointment with a post-paid return envelope (Smith, 2018).

**Table 7 Whitehall II study data collection by phase**

| Collection phase | Dates | Type | FFQ | Depression measures | n |
|---|---|---|---|---|---|
| Phase 1 | 1985-1988 | Q & S | | GHQ & Antidepressant intake | 10308 |
| Phase 2 | 1989-1990 | Q | | GHQ | 8133 |
| Phase 3 | 1991-1994 | Q & S | √ | GHQ | 8637 |
| Phase 4 | 1995-1996 | Q | | Ever told depression diagnosis (including date), Antidepressant intake | 8629 |
| Phase 5 | 1997-1999 | Q & S | √ | GHQ & Antidepressant intake | 7830 |
| Phase 6 | 2001 | Q | | GHQ & Antidepressant intake | 7344 |
| Phase 7 | 2002-2004 | Q & S | √ | GHQ & CES-D & Antidepressant intake | 6914 |
| Phase 8 | 2006 | Q | | GHQ & Antidepressant intake | 7173 |
| Phase 9 | 2007-2009 | Q & S | √ | GHQ & CES-D & Antidepressant intake | 6761 |
| Phase 10 | 2011 | Q & S | | GHQ & CES-D & CIS-R | 277* |
| Phase 11 | 2012-2013 | Q & S | | GHQ & CES-D & CIS-R & Antidepressant intake | 6318 |

Sources: (Head *et al.*, 2013; Marmot & Brunner, 2005).
Abbreviations: FFQ, Food frequency questionnaire; Q, Questionnaire; S, Clinical screening; GHQ, 30-item General health questionnaire; CES-D, Center for Epidemiologic Studies Depression Scale, CIS-R, revised Clinical Interview Schedule.
*Phase 10 was a neuroimaging substudy including a random sample of participants.

The study was approved by the Joint UCL/UCLH Committee on the Ethics of Human Research and carried out in accordance with the ethical principles set out in the Declaration of Helsinki. At every follow-up participants have been asked for informed consent.

## 4.2 Variables of interest

### *4.2.1 Diet*

Diet was assessed using FFQs (see Appendices relating to Chapter 4: Appendix 8). The questionnaire originated from the tool used in the US Nurses' Health Study, a self-administered questionnaire on habitual diet over the past 12 months (Brunner *et al.*, 2001; Willett *et al.*, 1985). In order to reflect a common diet in the UK, it has been modified and anglicised (Bingham *et al.*, 1997).

Data were validated against a 7-day diet diary at phase 3 of the Whitehall II study. Spearman rank correlations for macronutrients ranged from 0.29 to 0.48 in women and 0.32 to 0.50 in men, quartile agreement ranged from 36 to 42% and disagreement was between 3 and 7% as measured by misclassification to extreme quartiles (Brunner *et al.*, 2001). Information on nutrient content was based '*McCance and Widdowson's composition of foods, 5th edition*' (Holland *et al.*, 1991).

### *4.2.2 Measures of mood disorders*

**General Health Questionnaire (GHQ)**

The 30-item GHQ elicits melancholic and somatic symptoms over the past two weeks (Appendices relating to Chapter 4: Appendix 9). The GHQ was designed to identify minor psychiatric illness as a screening tool in practice and for research at the population level (Goldberg, 1972). All questions were answered on a Likert scale from *Better than usual*, *Same as usual*, *Less than usual* to *Much less than usual* and from to *Not at all*, *No more than usual*, *Rather more than usual* to *Much more than usual.* 0 points were given for having answered the first two categories and one point for the second two. Participants were categorised as a GHQ case if the sum of points was ≥5 (i.e. ≥5 symptoms reported) from a maximum of 30 items, or otherwise as a non-case (Goldberg & Huxley, 1992; Stansfeld & Marmot, 1992). GHQ caseness was ascertained if at least 28 of the 30 questions were answered. This case definition was found to be a sensitive and specific measure of any depressive episode compared to an interview-administered revised Clinical Interview Schedule (CIS-R) (sensitivity 78%, specificity 83%) in a validation study in Whitehall II (Head *et al.*, 2013).

**Center for Epidemiologic Studies Depression Scale (CES-D)**

The 20-item CES-D is a self-report scale to measure depressive symptoms in the general population over the past week (see Appendices relating to Chapter 4: Appendix 10) (Radloff, 1977). The CES-D comprises 20 questions which are answered

on a Likert scale from *rarely or none of the time (less than 1 day), some or a little of the time (1-2 days), occasionally or moderate amount of time (3-4 days)* to *most or all of the time (5-7 days)*, each given a value from 0 to 3. Participants scoring ≥16 out of a maximum of 60 were considered a CES-D case (Stansfeld *et al.*, 2008). CES-D caseness showed high sensitivity (89%) and specificity (86%) for depressive disorder within the same validation study mentioned above (Head *et al.*, 2013).

Figure 5 shows the distribution of GHQ and CES-D scores. The majority of participants scored 0 in the GHQ, with a mean score at 2.22. The CES-D was less zero-inflated with a median of 5 and mean of 7.25 points

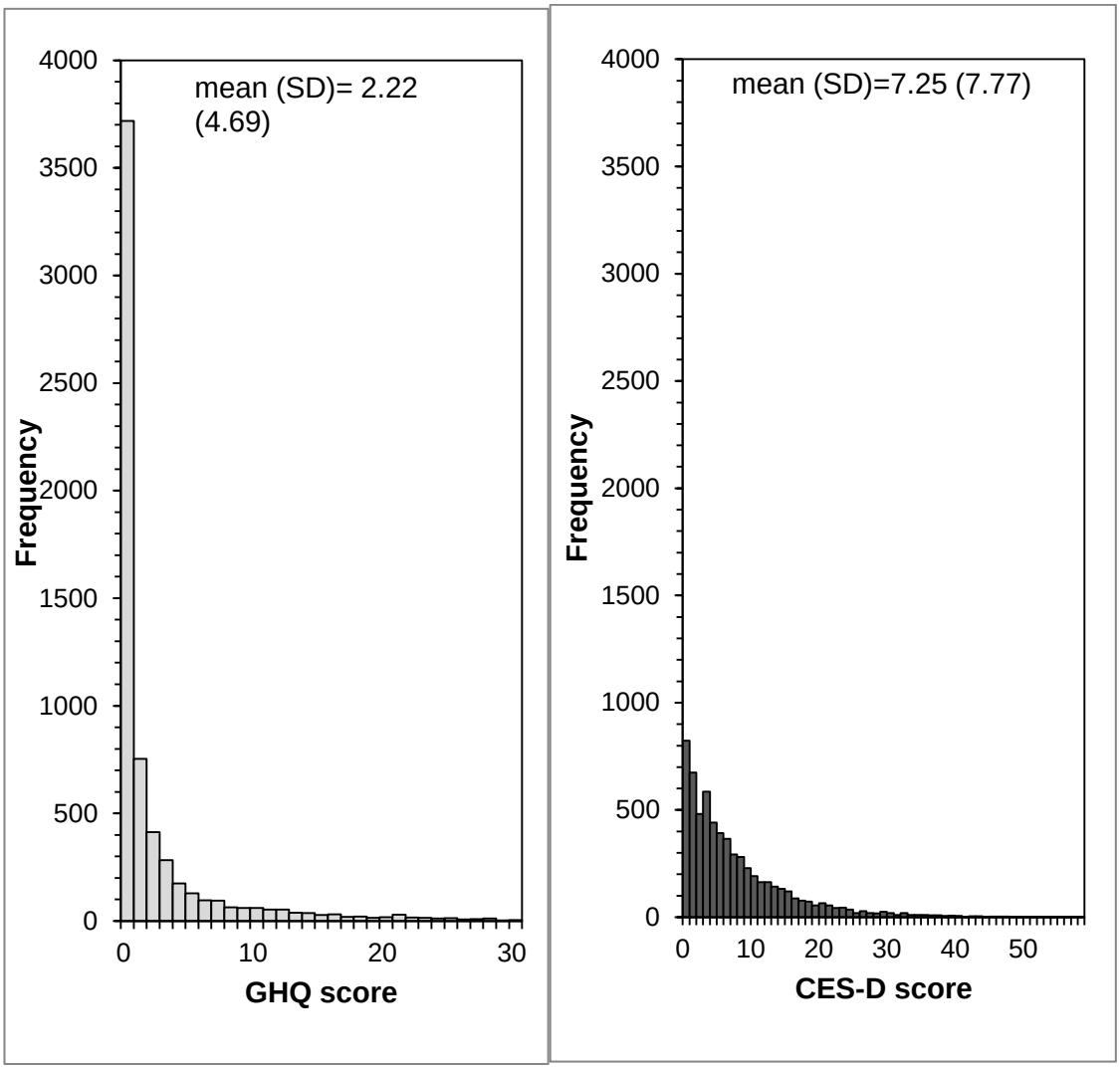


**Figure 5 Histograms and mean GHQ and CES-D scores at collection phase 9 in Whitehall II (n=6272)**
Abbreviations: GHQ, 30-item General health questionnaire; CES-D, Center for Epidemiologic Studies Depression Scale.

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**Revised Clinical Interview Schedule (CIS-R)**

The CIS-R used in Whitehall II is a computerised self-completion version of the clinical interview schedule, that assesses populations according to ICD-10 F32 criteria (Head *et al.*, 2013; Lewis *et al.*, 1992, 1988). The computerised version showed high sensitivity (75%) and very high specificity (98%) for depressive episodes when compared to an interviewer based CIS-R (Head *et al.*, 2013).

## 4.3 Covariates

Potential confounding and mediating factors were chosen based on review of the literature (see Chapter 2: 2.4.2) and restricted to variables available at phases 3, 5, 7 and 9, phases with diet data. All estimates were initially adjusted for age, ethnicity (White/ South Asian/ Black) and sex (Model 0) and a sex by age interaction where both sexes were included. Further, the following factors were chosen. Models adjusted for socio-demographic factors, health behaviours and other dietary factors were considered the final model. As described in chapter 2, 2.4.2 baseline body fatness and disease could operate as mediators or confounders, therefore models including these covariates are just included for additional information on the association.

**Socio-demographic factors:**

Marital status was categorised as married/cohabiting, single and divorced/widowed, and last employment grade level within the civil service, (high/intermediate/low) used as an overall measure for socio-economic position. It is assumed that other measures of socio-economic position, such as education and income, are partly associated with psychosocial health through their association with grade level (Singh-Manoux, Clarke & Marmot, 2002).

**Health behaviours**

Smoking was assessed as never, former, or current smoker. Alcohol intake was defined as none, moderate, heavy ≥14 units/week in women or >21 units/week in men (Jokela, 2011). Self-reported physical activity was categorised as vigorous, moderate and non/mild (Kumari, Head & Marmot, 2004). Sleep duration was assessed with one question with five possible answers ranging from ≤5 hours to ≥ 9 hours.

**Dietary factors**

Dietary data were based on FFQ data. Adjustment of energy intake depended on the chosen dietary exposure and is presented in the method sections of the results chapters 5.1, 6.1 and 7.1. To adjust for diet quality, a modified Dietary Approaches to Stop Hypertension (DASH) diet score was calculated. The score is based on 8 food and nutrient components: fruits, vegetables, nuts and legumes, whole grains, low-fat dairy, red and processed meat, sodium and sweet food or drinks (Fung *et al.*, 2008; Harrington *et al.*, 2011). The last component was excluded for the analyses in this thesis. Fish intake per day was categorised by quintiles of intake and included all types of fish. Tea and coffee consumption were included as continuous variables.

### Baseline body fatness

Baseline body fatness was defined using BMI (kg/m$^2$) and central obesity defined using waist circumference (in women ≥88cm and in men ≥102cm) (WHO, 2000).

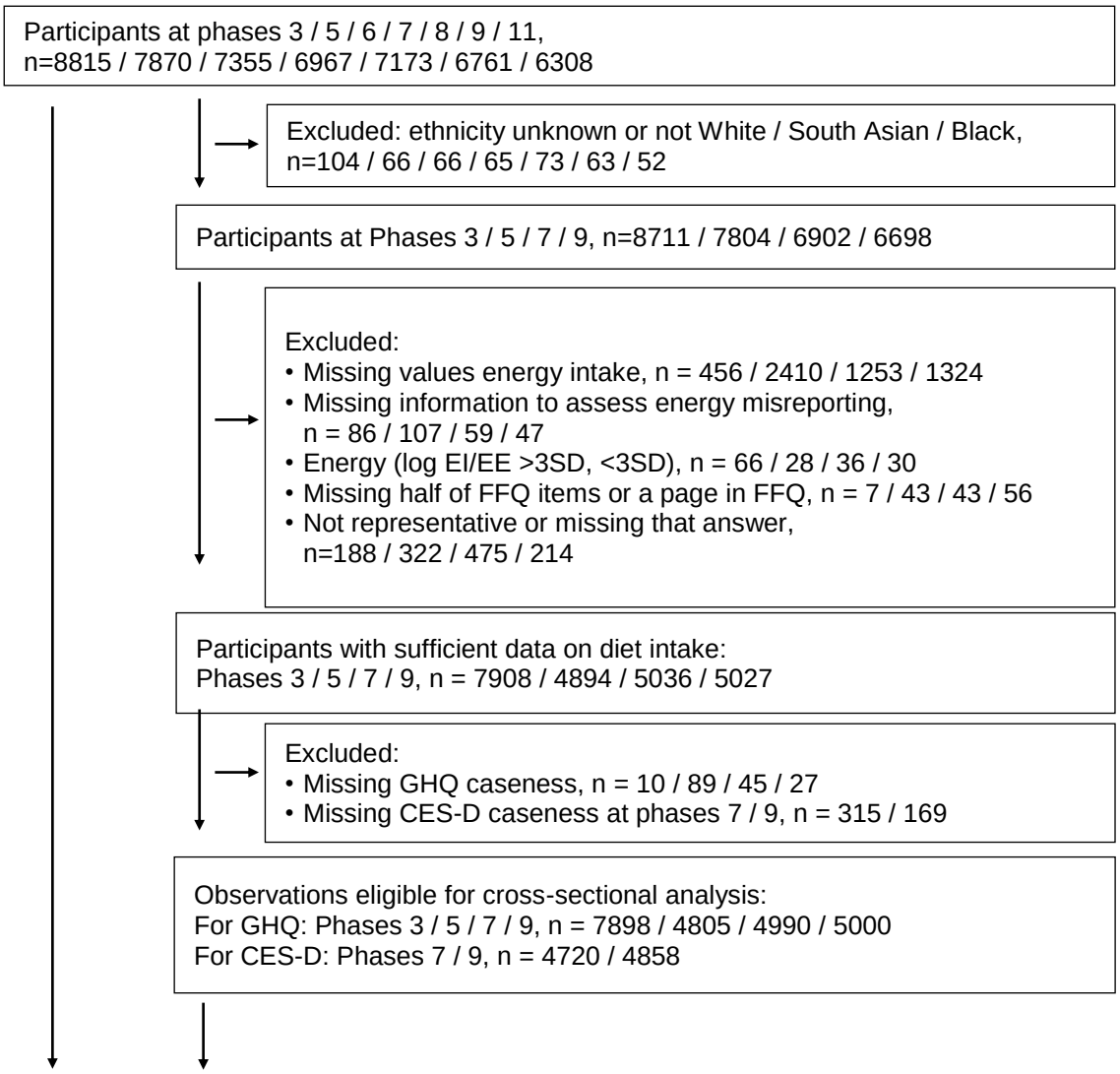
### Diseases

Diabetes status was based on self-report, diabetic medication and oral-glucose tolerance test at study examination according to the 1999 WHO classification (World Health Organization, 1999). Coronary heart disease was ascertained by self-report, information on chest-pain, electrocardiograms at study examination and validated by linkage with the NHS hospital episode statistics database and general practitioner contact. Stroke was ascertained by self-report and validated until end Phase 9 via data linkage to the NHS hospital episode statistics database and contacting general practitioners (Britton *et al.*, 2012). Coronary heart disease and stroke were combined in one variable on cardiovascular disease (CVD). Cancer prevalence was based on self-report and data linkage to the cancer registry.

## 4.4 Sample inclusion and missing data

At each phase, participants were included in analyses if their ethnicity was known to be White, Black or South Asian, they had answered at least half of all FFQ food and beverage items and at least 8 of the sweet food and beverage items (Willett, 2012), had not missed out an entire page in the FFQ, had described the FFQ as 'representative' for their dietary intake *('Are the foods listed on the previous pages representative of the foods that you ate or drank in the last 12 months?'*) and were not energy misreporters, based on methods adopted by Mosdol et al. 2007 and equations of the Department of Health (Department of Health, 1991; Mosdol *et al.*, 2007; Schofield, 1985). Misreporting was considered to have taken place where the log ratio of energy intake (EI) to estimated energy expenditure (EE) was more than 3 SD from the log mean (Mosdol *et al.*, 2007).

In addition, participants were also excluded from analyses if they had incomplete data on GHQ-, CES-D- or CIS-R caseness for outcome-specific analyses. Figure 6 shows the flow diagram to derive the analytical samples.




Observations eligible for incidence and recurrence analyses (based on GHQ-caseness at baseline):

| | Follow-up period | Outcome phases | Incidence | Recurrence |
|---|---|---|---|---|
| GHQ | 2 year | 6 / 8 | n = 3430 / 3811 | n = 851 / 899 |
| | 5 year | 5 / 7 / 9 / 11 | n = 5018 / 3451 / 3712 / 3977 | n = 1403 / 893 / 874 / 616 |
| | 10 year | 7 / 9 / 11 | n = 4752 / 3315 / 3463 | n = 1360 / 866 / 832 |
| CES-D | 5 year | 7 / 9 / 11 | n = 3176 / 3603 / 3827 | n = 807 / 851 / 588 |
| | 10 year | 7 / 9 / 11 | n = 4283 / 3216 / 3345 | n = 1221 / 843 / 795 |
| CIS-R | 5 year | 11 | n = 3755 | n = 589 |
| | 10 year | 11 | n = 3194 | n = 780 |

**Figure 6 Included sample for analyses of dietary factors with mood disorders**
Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; EI, energy intake; EE, energy expenditure; FFQ, food frequency questionnaire; GHQ, General Health Questionnaire.

### Missing data

Table 8 shows the distribution of missingness due to ethnicity, dietary data and mood disorder data. Missingness among those who participated was predominantly due to missingness in dietary data. There was a drop in FFQ participation after phase 3. This could be due to the change in how the questionnaire was distributed. At phase 3 participants received the questionnaires in conjunction with the full health questionnaire whereas at later phases they received the questionnaire at the clinic visit. Hence, all participants who did not take part in the clinic appointment did not receive a FFQ (Smith, 2018). Additionally, the completed FFQ then needed to be returned after the clinic visit, which might have led to lower response rates.

**Table 8 Distribution of missingness by data collection phase and reason**

| | Data collection phase, n (%) | | | | | | |
|---|---|---|---|---|---|---|---|
| | **3** | **5** | 6 | **7** | 8 | **9** | **11** |
| Total participation | 8815 | 7870 | 7355 | 6967 | 7173 | 6761 | 6308 |
| Reason for missingness | | | | | | | |
| ethnicity/'other' | 104 (1.17) | 66 (0.84) | 66 (0.90) | 65 (0.93) | 73 (1.02) | 63 (0.93) | 52 (0.82) |
| Dietary data | 803 (9.11) | 2898 (36.8) | n.a. | 1864 (26.8) | n.a. | 1665 (24.6) | n.a. |
| GHQ data | 508 (5.76) | 834 (10.6) | 732 (9.95) | 239 (3.43) | 372 (5.19) | 186 (2.75) | 155 (2.46) |
| CES-D data | N/A | N/A | N/A | 956 (13.7) | 456 (15.7) | 456 (6.74) | 453 (7.18) |
| CIS-R data | N/A | N/A | N/A | N/A | N/A | N/A | 799 (12.7) |

Abbreviation: GHQ, 30-item General health questionnaire.

Table 9 shows the proportion of missingness by covariates at phases 3 and 7. Missingness was more prevalent in women, in participants who were older (at phase 3), non-white, not married, in the lowest last grade level in the civil service, were non-smokers (at phase 3), less physically active, who consumed no alcohol, slept less hours, were in higher BMI classes, suffered from central obesity and diabetes, CVD and cancer (see Table 9). These associations differed only slightly in the other phases. In later phases missingness was more prevalent in GHQ cases, current smokers and not associated with age. Associations with cancer, diabetes and CVD varied across different phases (see Appendices relating to Chapter 4: Table A 2 for associations at phases 5, 9).

**Table 9 Missing data and covariates at phases 3 and 7**

| Covariates | Phase 3 | | | Phase 7 | | |
|---|---|---|---|---|---|---|
| | n | % Missing | p | n | % Missing | p |
| GHQ caseness | | | .42 | | | .001 |
| No case | 6472 | 4.82 | | 5353 | 24.9 | |
| Case (≥5 symptoms) | 1835 | 5.29 | | 1375 | 29.5 | |
| Sex | | | <.001 | | | <.001 |
| Men | 6057 | 9.43 | | 4893 | 25.5 | |
| Women | 2758 | 12.5 | | 2074 | 35.1 | |
| Age | | | <.001 | | | .18 |
| <50/60 years | 4471 | 7.07 | | 3291 | 27.3 | |
| ≥50/60 years | 4170 | 10.2 | | 3648 | 28.8 | |
| Ethnic Group | | | <.001 | | | <.001 |
| White | 7955 | 8.31 | | 6393 | 26.3 | |
| South Asian | 463 | 21.2 | | 334 | 44.3 | |
| Black | 293 | 18.4 | | 175 | 48.6 | |
| Marital Status | | | .022 | | | <.001 |
| Married/cohabiting | 6359 | 4.65 | | 5216 | 26.5 | |
| Single | 1211 | 6.19 | | 875 | 31.1 | |
| Divorced/widowed | 736 | 6.25 | | 826 | 34.0 | |
| Last grade level in Civil service | | | <.001 | | | <.001 |
| Highest | 3334 | 8.10 | | 3056 | 23.5 | |
| Intermediate | 3949 | 10.2 | | 3023 | 29.5 | |
| Lowest | 1532 | 16.1 | | 888 | 41.1 | |
| Smoking | | | .008 | | | <.001 |
| Never Smoker | 3647 | 5.73 | | 3290 | 26.9 | |
| Ex-Smoker | 3024 | 4.07 | | 3015 | 26.7 | |
| Current Smoker | 1146 | 5.24 | | 574 | 37.3 | |
| Physical activity | | | <.001 | | | <.001 |
| Non/mild | 3146 | 6.29 | | 2330 | 29.7 | |
| Moderate | 3660 | 4.23 | | 3723 | 24.7 | |
| Vigorous | 1513 | 4.49 | | 723 | 24.3 | |
| Alcohol consumption | | | <.001 | | | <.001 |
| None | 1996 | 7.21 | | 1341 | 34.8 | |
| Moderate | 4324 | 4.30 | | 3361 | 24.9 | |
| Heavy | 1992 | 4.62 | | 2049 | 23.6 | |
| Sleep duration | | | .018 | | | .10 |
| less than 7 h/day | 2125 | 5.93 | | 2729 | 27.5 | |
| ≥ 7 h/day | 6175 | 4.63 | | 4047 | 25.7 | |
| BMI | | | .002 | | | <.001 |
| Normal, <25kg/m$^2$ | 4215 | 6.22 | | 2366 | 21.0 | |
| Overweight | 3068 | 7.20 | | 2868 | 22.6 | |
| Obese, ≥30kg/m$^2$ | 791 | 9.61 | | 1216 | 27.3 | |
| Central obesity (W/M) | 7994 | | <.001 | 7994 | | <.001 |
| No | 7257 | 6.52 | | 4855 | 21.3 | |
| Yes (waist ≥88 /102cm) | 737 | 11.0 | | 1605 | 27.9 | |
| Diabetes | | | .10 | | | <.001 |
| No | 8563 | 10.3 | | 6403 | 27.8 | |
| Yes | 252 | 13.5 | | 564 | 34.9 | |
| CVD | | | .044 | | | .001 |
| No | 8504 | 10.3 | | 6247 | 27.8 | |
| Yes | 311 | 13.8 | | 720 | 33.6 | |
| Cancer | | | <.001 | | | .087 |
| No | 8676 | 10.2 | | 6576 | 28.2 | |
| Yes | 130 | 23.1 | | 385 | 32.2 | |

Abbreviations: BMI, Body mass index; CVD, cardiovascular disease; GHQ, General Health Questionnaire; M, men; W, women.

Table 10 presents the characteristics of the sample with no missing data in outcome and exposure and the missing data sample. Participants missing from analyses were more likely female, 50 years old or older, non-white, of lowest last grade level in the civil service, never smokers, none-drinkers and participants with less than seven hours of sleep per day, with general overweight or obesity, or central obesity, with cardio-vascular disease and cancer. Differences in characteristics were largely similar when comparing the sample with no missing data on exposure, outcome and covariates with the missing sample, except that there were more younger participants in the missing sample and no differences in adiposity and disease (see Appendices relating to Chapter 4: Table A 3).

**Table 10 Sample characteristics of complete case sample and missing data sample**

| Covariates | Non-missing | | Missing | | |
|---|---|---|---|---|---|
| | n | % | n | % | p |
| GHQ-caseness | | | | | .42 |
| No case | 6160 | 78.0 | 312 | 76.3 | |
| Case (≥5 symptoms) | 1738 | 22.0 | 97 | 23.7 | |
| Sex | | | | | <.001 |
| Men | 5486 | 69.5 | 571 | 62.3 | |
| Women | 2412 | 30.5 | 346 | 37.7 | |
| Age | | | | | <.001 |
| <50 years | 4155 | 52.6 | 316 | 42.5 | |
| ≥50 years | 3743 | 47.4 | 427 | 57.5 | |
| Ethnic Group | | | | | <.001 |
| White | 7294 | 92.4 | 661 | 81.3 | |
| South Asian | 365 | 4.62 | 98 | 12.05 | |
| Black | 239 | 3.03 | 54 | 6.64 | |
| Marital Status | | | | | .022 |
| Married/cohabiting | 6063 | 76.9 | 296 | 71.0 | |
| Single | 1136 | 14.4 | 75 | 18.0 | |
| Divorced/widowed | 690 | 8.75 | 46 | 11.03 | |
| Last grade level in Civil service | | | | | <.001 |
| Highest | 3064 | 38.8 | 270 | 29.4 | |
| Intermediate | 3548 | 44.9 | 401 | 43.7 | |
| Lowest | 1286 | 16.3 | 246 | 26.8 | |
| Smoking | | | | | .008 |
| Never Smoker | 3438 | 46.3 | 209 | 53.3 | |
| Ex-Smoker | 2901 | 39.1 | 123 | 31.4 | |
| Current Smoker | 1086 | 14.6 | 60 | 15.3 | |
| Physical activity | | | | | <.001 |
| Non/mild | 2948 | 37.3 | 198 | 47.0 | |
| Moderate | 3505 | 44.4 | 155 | 36.8 | |
| Vigorous | 1445 | 18.3 | 68 | 16.2 | |
| Alcohol consumption | | | | | <.001 |
| None | 1852 | 23.5 | 144 | 34.1 | |
| Moderate | 4138 | 52.4 | 186 | 44.1 | |
| Heavy | 1900 | 24.1 | 92 | 21.8 | |
| Sleep duration | | | | | .018 |
| less than 7 h/day | 1999 | 25.3 | 126 | 30.6 | |
| ≥ 7 h/day | 5889 | 74.7 | 286 | 69.4 | |

| | | | | | |
|---|---|---|---|---|---|
| BMI | | | | | .002 |
| Normal, <25kg/m$^2$ | 3953 | 52.6 | 262 | 46.9 | |
| Overweight | 2847 | 37.88 | 221 | 39.53 | |
| Obese. ≥30kg/m$^2$ | 715 | 9.51 | 76 | 13.60 | |
| Central obesity | | | | | <.001 |
| No | 6784 | 91.2 | 473 | 85.4 | |
| Yes (Waist ≥102/≥88 cm) | 656 | 8.8 | 81 | 14.6 | |
| Diabetes | | | | | .10 |
| No | 7680 | 97.2 | 883 | 96.3 | |
| Yes | 218 | 2.76 | 34 | 3.71 | |
| CVD | | | | | .044 |
| No | 7630 | 96.6 | 874 | 95.3 | |
| Yes | 268 | 3.39 | 43 | 4.69 | |
| Cancer | | | | | <.001 |
| No | 7789 | 98.7 | 887 | 96.7 | |
| Yes | 100 | 1.27 | 30 | 3.27 | |

Abbreviations: BMI, Body mass index; CVD, cardiovascular disease; GHQ, General Health Questionnaire; M, men; W, women.

Table 11 shows that the main contributors of missing data in covariates were adiposity at phases 3 and 5 and smoking at phase 3.

**Table 11 Missing data in covariates by data collection phase**

| | **Data collection phase** | | | |
|---|---|---|---|---|
| Covariates | Phase 3 | Phase 5 | Phase 7 | Phase 9 |
| Maximum sample | 7898 | 4805 | 4990 | 5000 |
| | n (% of maximum sample) | | | |
| Socio-demographic factors | | | | |
| Last grade level | 0 | 0 | 0 | 0 |
| Marital status | 9 (0.11) | 155 (3.23) | 8 (0.16) | 73 (1.46) |
| Health behaviours | | | | |
| Smoking | 473 (5.99) | 17 (0.35) | 15 (0.30) | 39 (0.78) |
| Alcohol | 8 (0.10) | 31 (0.65) | 24 (0.48) | 57 (1.14) |
| Physical activity | 0 | 0 | 0 | 0 |
| Sleep | 10 (0.13) | 30 (0.62) | 6 (0.12) | 6 (0.12) |
| Dietary behaviours | | | | |
| Tea/coffee | 0 | 0 | 0 | 0 |
| Fish | 4 (0.05) | 42 (0.87) | 93 (1.86) | 26 (0.52) |
| DASH diet score | 4 (0.05) | 0 | 2 (0.04) | 6 (0.12) |
| Adiposity | | | | |
| BMI | 383 (4.85) | 624 (13.0) | 19 (0.38) | 15 (0.30) |
| Central obesity | 458 (5.80) | 1038 (21.6) | 12 (0.24) | 10 (0.20) |
| Diseases | | | | |
| Diabetes | 0 | 0 | 0 | 0 |
| CVD | 0 | 0 | 0 | 5 (0.10) |
| Cancer | 9 (0.11) | 5 (0.10) | 5 (0.10) | 6 (0.12) |
| Total missing | 936 (11.9) | 1291 (26.9) | 171 (3.43) | 217 (4.34) |

Abbreviations: BMI, Body mass index; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension.

**Implications**

To avoid losing power and information by excluding all missing data in covariates, initial models (adjusted for age, sex and ethnicity) were analysed in the maximum eligible sample. For presentation and comparison, the sample size was then restricted to those with no missing data in socio-demographic factors, health behaviours and other dietary factors. In cases where the adjustment of adiposity and physical disease played an important role for interpretation of the results they were presented for the sample excluding missing values in these covariates. This helped with the interpretation of results.

The first (age, sex, ethnicity adjusted) model was then rerun in that reduced sample and compared to result in the maximum model to assess whether changes in estimates were due to confounding or loss of data.

## 4.5 Statistical analysis

Analyses were performed using Stata 14 and 15 (StataCorp., 2017, 2015).

To study the association of dietary exposures and financial insecurity with mood disorders random effects logistic regression models (REM) were performed using the Stata command *xtlogit* (Twisk, 2004). Random effects logistic regression modelling allows one to include all phases of data collection while accounting for the correlation between repeatedly measured data within one individual by assigning a random effect 'error' (Brunner *et al.*, 2014; Twisk, 2004; Gueorguieva & Krystal, 2004). The general form of the logistic model is given by :

$$\text{logit}\left(Y_{i(t+1)}\right) = \beta_0 + \beta_1 t + \beta_{2j} \sum_{j=1}^{J} X_{ijt} + \beta_{3m} \sum_{m=1}^{M} X_{im} + \varepsilon_i$$

$Y_{i(t+1)}$: Outcome for subject *i* at follow up time *(t+1)*
$\beta_0$: intercept
$\beta_1$: regression coefficient for time *t*, here data collection phase
$\beta_{2j}$ : regression coefficient for time dependent predictor variable j
$X_{ijt}$ : time-dependent predictor variable *j* for subject *i* at the time *t*
*J*: number of time-dependent predictor variables
$\beta_{3m}$: regression coefficient for time-independent predictor variable *m*
$X_{im}$*: the time-independent predictor variable m for subject i*
*M:* the number of time-independent variables
$\varepsilon_t$: 'error' for subject *i*, random effect (Twisk, 2004)

The initial age, sex and ethnicity adjusted model is given by:

$$\text{logit}\left(Y_{i(t+1)}\right) = \beta_0 + \beta_1 t + \beta_2 Diet\ factor_{it} + \beta_2 Age_{it} + \beta_3 Sex_i + \beta_3 Ethnicity_i + \varepsilon_i$$

Diet factor predictor variables were included as time-dependent variables at time t. Sex and ethnicity were time-independent. In addition, the model includes a sex by age interaction term which, for simplicity, has not been shown in the above equation. A diet-factor by time interaction was fitted to test whether effects differ by data collection phase (time).

For cross-sectional analyses the outcome and exposure used were both at the same phase. In prospective analyses associations were analysed in cycles of 2, 5 and 10 years where the outcome was ascertained 2, 5 and 10 years, respectively, after predictor variables (Figure 7) (Brunner *et al.*, 2014). Here mood disorders were analysed as either incident or recurrent. Incidence was assumed if no GHQ caseness

was apparent at each baseline phase (t) and recurrence if GHQ caseness was apparent at each baseline phase (t) for all depression outcomes.

Figure 7 shows the included phases for analyses using GHQ caseness as the outcome.

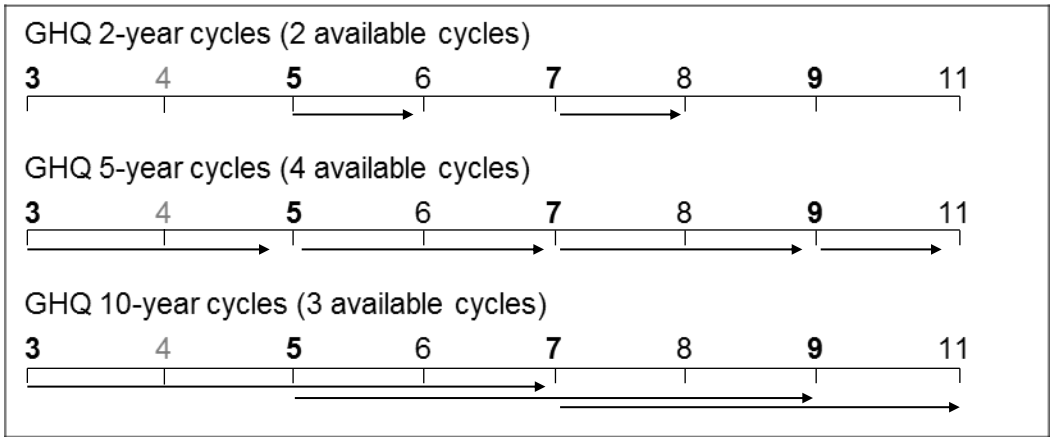



**Figure 7 Mode of analysis using cycle approach for GHQ caseness in Whitehall II**
Numbers indicate study phases. Phases with food frequency data are in bold; there was no data on GHQ available at Phase 4.
Abbreviation: GHQ, 30-item General health questionnaire.

For example, the association between the exposure variable and GHQ status 2 years later was conducted by combining the associations between the exposure variable at Phase 5 and incident GHQ caseness at Phase 6, and between the exposure variable at Phase 7 and incident GHQ caseness at Phase 8 resulting in two 2-year, four 5-year and three 10-year cycles for analyses with GHQ caseness. For CES-D, two 5-year cycles (to Phase 9 and 11) and three 10-year cycles (to Phases 7, 9 and 11) were used. CIS-R was only available at phase 11.

The applicability of the REM was tested by introducing study phase-interactions and likelihood ratio tests (LR test) to investigate whether associations within one cycle were significantly different to associations in other cycles.

**Sensitivity analyses**

Sensitivity analyses were run excluding participants who reported the use of antidepressants (ascertained by questionnaire at phase 1 and from phase 4 onwards with the question *'This question concerns any medicine that you may have taken during the last fourteen days. Have you been taking any medicines, tablets, tonics or pills within the last fourteen days?'*), or a report of a physician-made diagnosis in periods of data collection before phase 4. Additionally, those who did not answer these questions were excluded as their diagnosis and antidepressant intake are unknown. Approximately 50% of those who reported a doctor diagnosis or antidepressant intake were not GHQ cases. Participants with a diagnosis might be on the course of recovery,

not experiencing symptoms anymore, but still affected by side effects that influence mood and or other behaviours (Khawam, Laurencic & Malone, 2006; Kirsch, 2014; Tschoner *et al.*, 2007).

## 4.6 Comparison of mood disorder measures in Whitehall II

Figure 8 shows prevalence of GHQ, CES-D and CIS-R depression caseness in Whitehall II. GHQ and CES-D caseness declined over time. At phase 1, 26.9% of participants were identified as GHQ cases, compared to 17.1% at phase 11. Prevalence of CES-D caseness was approximately 5% lower than GHQ caseness and showed a similar decline. At phase 11, 3.7% of participants were identified as depressed using the CIS-R.

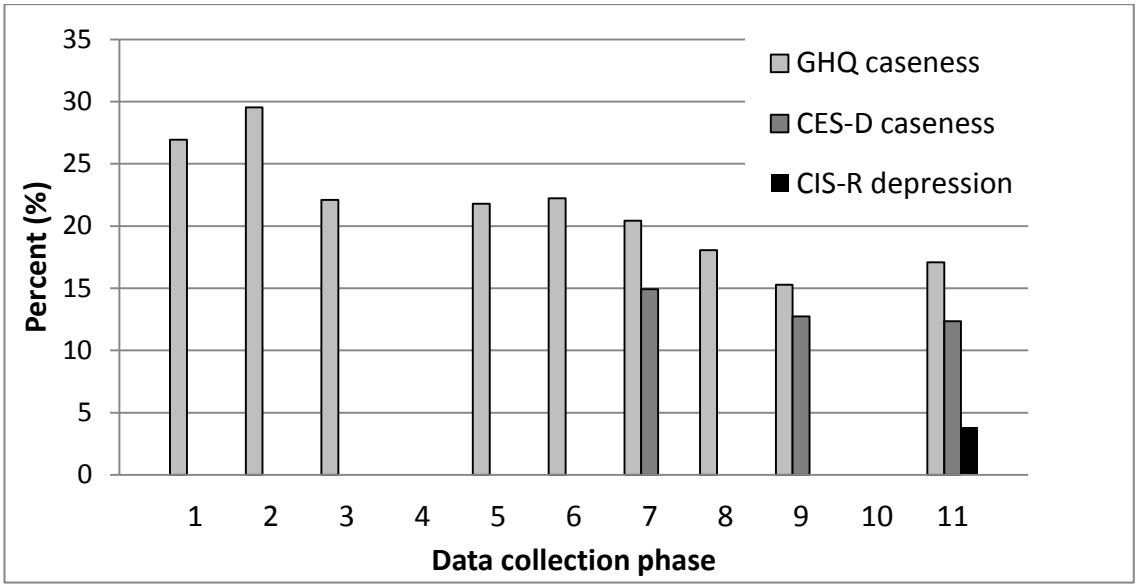



**Figure 8 Crude prevalence of GHQ, CES-D and CIS-R depression caseness by study phase**

Abbreviations: GHQ, 30-item General health questionnaire; CES-D, Center for Epidemiologic Studies Depression Scale, CIS-R, revised Clinical Interview Schedule.

Head et al. (2013) investigated the association of CES-D measured depression and GHQ measured CMD with clinical depression. The association between CES-D caseness and GHQ caseness has not been investigated in Whitehall II and no sufficient literature from other cohort studies comparing these two measures was found.

Three approaches were chosen to investigate differences between the mood disorder measures: (1) sensitivity, specificity and area under the curve (AUC), (2) differences and selective missingness, (3) comparison of univariate associations with covariates.

### Receiver Operating Characteristic (ROC) analysis

For these analyses, the sample was restricted to participants who had data on both GHQ and CES-D at phase 9. The analysis was repeated for incident cases, by including only those with no GHQ caseness at phase 7, and for recurrent cases by including only those with GHQ caseness at phase 7. The Stata command *diagt* was used to calculate values and 95%-confidence intervals for sensitivity, specificity and

AUC. Analyses were repeated for men and women separately to assess potential differences. 63.1% of CES-D cases were also cases when ascertained using GHQ and 46.2% of GHQ cases were non-CES-D cases (Table 12).

**Table 12 Cross-tabulation of GHQ and CES-D caseness at phase 9, without missing values**

| | No CES-D case | CES-D case | Total |
|---|---|---|---|
| **Caseness** | | n (%) | |
| **no GHQ case, n** | 5049 (92.2) | 293 (36.9) | 5342 |
| **GHQ case, n** | 430 (7.8) | 500 (63.1) | 930 |
| **Total** | 5479 (100) | 793 (100) | 6272 |

Abbreviations: GHQ, 30-item General health questionnaire; CES-D, Center for Epidemiologic Studies Depression Scale.

Table 13 presents the ROC analysis for GHQ caseness using CES-D caseness to ascertain depression. GHQ was a highly specific measure for CES-D caseness in phase 9 but only weakly sensitive, resulting in a positive predictive value of 54%. The predictive value of GHQ for CES-D depression differed depending on incidence and recurrence. Among those without GHQ caseness 5 years earlier specificity was very high, but sensitivity low (Table 13: Incidence). Among those with GHQ caseness 5 years earlier, both sensitivity and specificity were somewhat high (Table 13: Recurrence). Associations did not differ by sex (Table A 4).

**Table 13 Sensitivity and specificity for GHQ caseness as measure of depression with CES-D ascertained depression caseness as the criterion, at phase 9**

| | Prevalence | Incidence[a] | Recurrence[b] |
|---|---|---|---|
| N | 6272 | 4623 | 1131 |
| Cases | 793 | 345 | 369 |
| Sensitivity (95%-CI) | 63.1 (59.6, 66.4) | 50.7 (45.3, 56.1) | 73.7 (68.9, 78.1) |
| Specificity (95%-CI) | 92.2 (91.4, 92.9) | 94.0 (93.3, 94.7) | 81.1 (78.1, 83.8) |
| +PV | 0.54 | 0.41 | 0.65 |
| -PV | 0.95 | 0.96 | 0.84 |
| +LR | 8.03 | 8.51 | 3.90 |
| -LR | 0.40 | 0.52 | 0.32 |
| AUC (95%-CI) | 0.78 (0.76; 0.79) | 0.72; (0.70; 0.75) | 0.77 (0.75; 0.80) |

Abbreviations: AUC, area under the receiver operating characteristic (ROC) curve; CES-D, Center for Epidemiologic Studies Depression Scale; GHQ, 30-item General health questionnaire; +LR, positive likelihood ratio; -LR, negative likelihood ratio; +PV, positive predictive value; -PV, negative predictive value.
[a] Among participants with no GHQ caseness at phase 7.
[b] Among participants with GHQ caseness at phase 7.

### Selective Missingness

Missingness in GHQ and CES-D was defined as either omission of the entire questionnaire section or omission of too many questions with the result that scores

could not be calculated. All missing values were investigated via cross-tabulation and logistic regression with missingness as outcome variables.

Table 14 shows the distribution of missing values in GHQ and CES-D scores by phase. Only a few participants who completed the CES-D questionnaire had not completed the GHQ questionnaire. Missing in CES-D only was more common, especially at phase 7. This could be due to a page break within that questionnaire, which led participants to overlook the second set of questions (University College London, 2007). This page break was deleted in subsequent CES-D questionnaires. At later phases, CES-D caseness was missing in approximately 5% of participants that had answered the GHQ questionnaire. At all phases, the GHQ questionnaire was placed before the CES-D questionnaire, which could explain the unbalanced missingness.

**Table 14 Distribution of missing values in GHQ and CES-D, n (%)**

| | Not missing in GHQ and CES-D | Missing GHQ only | Missing CES-D only |
|---|---|---|---|
| Phase 7 | 5892 (86.1) | 119 (1.74) | 836 (12.2) |
| Phase 9 | 6272 (94.9) | 33 (0.50) | 303 (4.59) |
| Phase 11 | 5811 (93.8) | 44 (0.71) | 342 (5.52) |

Abbreviations: GHQ, 30-item General health questionnaire; CES-D, Center for Epidemiologic Studies Depression Scale.

Table 15 shows that odds ratios of having missing data in GHQ and CES-D was affected by caseness in the other measure. GHQ caseness was associated with 26 to 79% increased odds of having missing CES-D data. CES-D caseness resulted in double to triple the odds of having missing GHQ scores. Further adjustment for grade level did not change the associations (Table A 5).

**Table 15 Odds ratios of having missing values by GHQ and CES-D caseness by phase adjusted for age, sex, age*sex and ethnicity (white versus black / south Asian)**

| | Outcome: CES-D/GHQ missingness | | |
|---|---|---|---|
| **Exposure** | n / missing | OR (95%-CI) | p |
| **GHQ** | | | |
| Phase 7 | 6667 / 824 | 1.26 (1.05; 1.50) | .011 |
| Phase 9 | 6516 / 298 | 1.69 (1.27; 2.23) | <.001 |
| Phase 11 | 6102 / 337 | 1.79 (1.39; 2.30) | <.001 |
| **CES-D** | | | |
| Phase 7 | 5935 / 92 | 1.79 (1.10; 2.91) | .020 |
| Phase 9 | 6249 / 31 | 2.93 (1.32; 6.52) | .008 |
| Phase 11 | 5808 / 43 | 3.04 (1.58; 5.85) | .001 |

Abbreviations: GHQ, 30-item General health questionnaire; CES-D, Center for Epidemiologic Studies Depression Scale.

The lower odds ratios at phase 7 compared to the other phases are likely due to the page break mentioned above.

### Mood disorders and covariates

Table 16 shows the prevalence of GHQ and CES-D caseness according to covariates at phase 7, the first phase in which both questionnaires were included. For both measures, cases were more prevalent in women, younger, white, unmarried or non-cohabiting participants, those in the lower grade levels, who were current smokers, physically inactive, non-drinkers and those having fewer hours of sleep. Prevalence was higher in men with either BMI defined or central obesity and participants with CVD. Additionally, GHQ caseness was associated with adiposity in women. CES-D caseness was more prevalent in those who drank less than one cup coffee or tea per day and diabetics. Associations of GHQ caseness with covariates at phases 3 and 5 showed similar associations (Table A 6)

**Table 16 Crude association of GHQ and CES-D caseness with covariates at phase 7**

| **Covariates at phase 7** | **GHQ caseness** | | | **CES-D caseness** | | |
|---|---|---|---|---|---|---|
| | n | % | p | n | % | p |
| CES-D / GHQ caseness | | | <.001 | | | <.001 |
| No | 4026 | 11.8 | | 4026 | 11.8 | |
| Yes | 654 | 64.8 | | 654 | 64.8 | |
| Sex | | | <.001 | | | <.001 |
| Men | 3643 | 18.1 | | 3458 | 12.61 | |
| Women | 1347 | 23.2 | | 1222 | 17.84 | |
| Age | | | <.001 | | | <.001 |
| < median | 2392 | 23.7 | | 2265 | 16.11 | |
| > median | 2598 | 15.5 | | 2415 | 11.97 | |
| Ethnic Group in Whitehall II | | | <.001 | | | <.001 |
| White | 4714 | 19.0 | | 4436 | 13.05 | |
| South Asian | 186 | 30.6 | | 174 | 35.63 | |
| Black | 90 | 20.0 | | 70 | 18.57 | |
| Marital Status | | | <.001 | | | <.001 |
| Married/cohabiting | 3834 | 18.1 | | 3604 | 11.60 | |
| Single | 603 | 23.7 | | 566 | 22.79 | |
| Divorced/widowed | 545 | 24.4 | | 503 | 21.07 | |
| Last grade level in Civil service | | | <.001 | | | <.001 |
| Highest | 2980 | 18.0 | | 2702 | 10.81 | |
| Intermediate | 2920 | 22.4 | | 2640 | 16.67 | |
| Lowest | 828 | 22.3 | | 669 | 24.96 | |
| Smoking | | | 0.036 | | | <.001 |
| Never Smoker | 2406 | 19.4 | | 2249 | 13.74 | |
| Ex-Smoker | 2209 | 18.7 | | 2080 | 12.84 | |
| Current Smoker | 360 | 24.4 | | 338 | 21.60 | |
| Physical activity | | | <.001 | | | <.001 |
| Non/mild | 1638 | 26.1 | | 1519 | 19.75 | |
| Moderate | 2805 | 16.9 | | 2647 | 11.45 | |
| Vigorous | 547 | 12.4 | | 514 | 9.92 | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Alcohol consumption | | | 0.002 | | | <.001 |
| None | 875 | 23.7 | | 814 | 22.36 | |
| Moderate | 2525 | 18.5 | | 2367 | 12.29 | |
| Heavy | 1566 | 18.6 | | 1478 | 11.98 | |
| Sleep duration | | | <.001 | | | <.001 |
| less than 7 h/day | 1978 | 27.9 | | 1861 | 20.85 | |
| ≥ 7 h/day | 3006 | 13.9 | | 2814 | 9.38 | |
| Energy intake (kcal) | | | .40 | | | .97 |
| < median | 2442 | 19.0 | | 2280 | 13.99 | |
| > median | 2548 | 19.9 | | 2400 | 13.96 | |
| Modified DASH diet score | | | .021 | | | .002 |
| < median | 2476 | 20.6 | | 2326 | 15.48 | |
| > median | 2422 | 18.0 | | 2274 | 12.31 | |
| Fish intake | | | .38 | | | .32 |
| < median | 2608 | 19.9 | | 2454 | 14.43 | |
| > median | 2374 | 18.9 | | 2221 | 13.42 | |
| Coffee and tea | | | .37 | | | .016 |
| ≤ 1 cup of either/day | 200 | 17.0 | | 185 | 20.00 | |
| > 1 cup of either/day | 4790 | 19.5 | | 4495 | 13.73 | |
| BMI (M) | | | .005 | | | .007 |
| Normal, <25kg/m$^2$ | 1327 | 16.7 | | 1263 | 11.8 | |
| Overweight | 1748 | 17.5 | | 1648 | 11.8 | |
| Obese. ≥30kg/m$^2$ | 556 | 22.8 | | 538 | 16.7 | |
| BMI (W) | | | .008 | | | .35 |
| Normal, <25kg/m$^2$ | 541 | 22.0 | | 496 | 16.3 | |
| Overweight | 471 | 20.2 | | 426 | 17.8 | |
| Obese. ≥30kg/m$^2$ | 328 | 29.3 | | 294 | 20.4 | |
| Central obesity (M) | | | .005 | | | .004 |
| No | 2915 | 17.2 | | 2765 | 11.8 | |
| Yes (Waist ≥102 cm) | 720 | 21.7 | | 688 | 15.8 | |
| Central obesity (W) | | | .061 | | | .84 |
| No | 905 | 21.7 | | 832 | 17.7 | |
| Yes (Waist ≥88 cm) | 438 | 26.3 | | 386 | 18.1 | |
| Diabetes | | | .62 | | | .019 |
| No | 4623 | 19.4 | | 4340 | 13.64 | |
| Yes | 367 | 20.4 | | 340 | 18.24 | |
| CVD | | | .051 | | | .015 |
| No | 4512 | 19.1 | | 4229 | 13.57 | |
| Yes | 478 | 22.8 | | 451 | 17.74 | |
| Cancer | | | .65 | | | .54 |
| No | 4724 | 19.5 | | 4431 | 14.06 | |
| Yes | 261 | 18.4 | | 245 | 12.65 | |

Abbreviations: BMI, Body mass index; CES-D, Center for Epidemiologic Studies Depression Scale; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension; GHQ, General Health Questionnaire; M, men; W, women.

To investigate whether associations with CIS-R depression were consistent with those for GHQ and CES-D, associations were compared at Phase 11. There was little difference between the associations at this phase with those seen at the previous phases, and the CIS-R depression associations were also similar (Table A 7).

**Implications**

While specificity in measuring CES-D measured depression was independent of type of caseness, sensitivity was lower for incident GHQ caseness and higher for recurrent caseness. This suggests that associations are likely to differ more between CES-D and GHQ when investigating incident mood disorders.

Many participants who answered the GHQ questionnaire did not finish the CES-D questionnaire, only few participants had answered the CES-D but not the GHQ questionnaire. The selective missingness in the CES-D measure could result in underestimation and bias of the association when using CES-D compared to using GHQ.

Associations with covariates were similar between the three measures: GHQ, CES-D and CIS-R depression.

# Chapter 5 **Objective I: Is a diet high in sugar intake from sweet food and beverages a risk factor in mood disorders?**

This chapter presents associations of sugar intake from sweet food / beverages and mood disorders in two British cohorts. Firstly (analyses A), the association of sugar intake from sweet food / beverages with three measures of mood disorder were assessed cross-sectionally and prospectively using data from the Whitehall II cohort study. Secondly (analyses B), analyses were repeated using antidepressant intake as outcome measure and data from the EPIC-Norfolk cohort.

## 5.1 Methods

In the following 'analysis A' will describe analyses on the association of sugar intake from sweet food / beverages with three measures of mood disorder using data from the Whitehall II cohort study and 'analyses B' will describe analyses on the associations of sugar intake from sweet food / beverages with antidepressant intake in Whitehall II and EPIC-Norfolk.

### *5.1.1 Study samples*

Whitehall II was described in chapter 4.1.

EPIC-Norfolk aimed to elucidate the association of diet and cancer. The study included middle-aged adults (45 to 74 years) from the area of Norfolk, UK recruited from general health practices between 1993 and 1997. Of those invited, 39.2% consented to the first health check (HC1, 55% women, 45% men) (Hayat et al., 2014). The study has been found to be representative in terms of anthropometric variables, blood pressure and serum lipids, though included fewer current smokers when compared to data from the Healthy Survey of England (Day *et al.*, 1999). Figure 9 shows the data collection flow in EPIC-Norfolk.

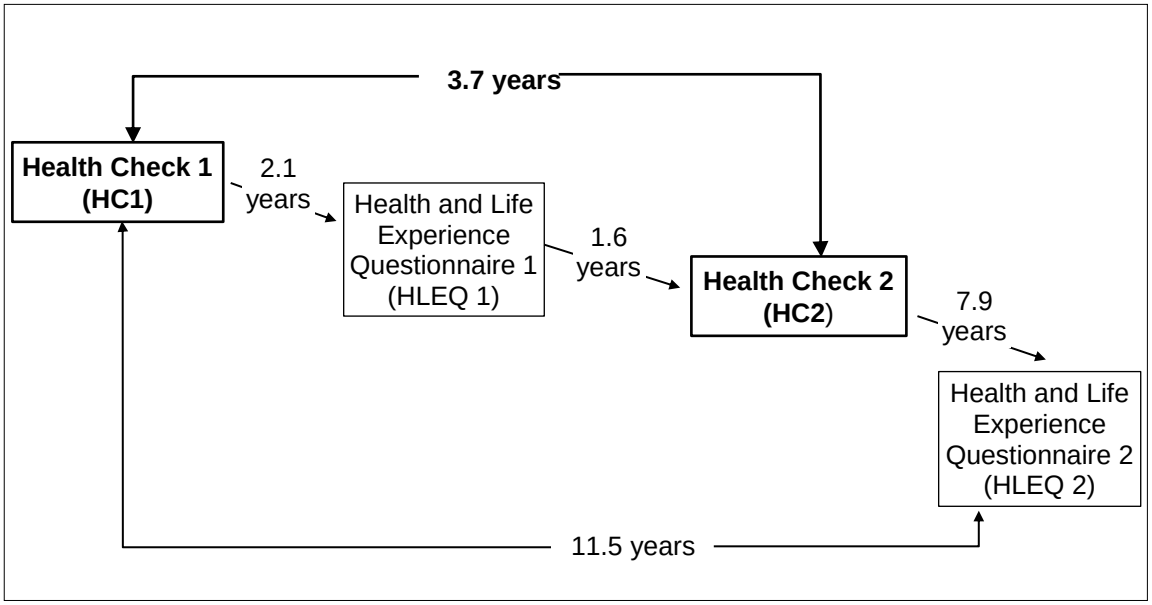



**Figure 9 EPIC-Norfolk data collection by phase**
Sources: (Day *et al.*, 1999; Hayat *et al.*, 2014; Leng *et al.*, 2014; Surtees, Wainwright & Brayne, 2000).

Table 17 shows the data collection dates and what types of data have been collected. After ascertainment of their health, measures of participants' mood were assessed using the Health and Life Experiences Questionnaire (HLEQ), but these were not contemporaneous with FFQ data collection (Table 17).

**Table 17 EPIC-Norfolk data collection by phase**

| Collection phase | Dates | Type | FFQ | Available mood disorder measures* | n[a] |
|---|---|---|---|---|---|
| HC1 | 1993-1997 | Q & S | √ | Ever told depression diagnosis (including date), Antidepressant intake | 30445 |
| HLEQ 1 | 1996-2000 | Q | | Major depression assessed by questionnaire | 20921 |
| HC2 | 1997-2000 | Q & S | √ | Ever told depression diagnosis (including date), Antidepressant intake | 19560 |
| HLEQ 2 | 2006-2007 | Q | | Major depression assessed by questionnaire | 12897 |

Sources: (Day et al., 1999; Hayat et al., 2014; Leng et al., 2014; Surtees, Wainwright & Brayne, 2000).
Abbreviations: HC, Health check, HLEQ, Health and Life Experience questionnaire; Q, questionnaire; S, clinical screening; FFQ, food frequency questionnaire.
[a]Data sharing with EPIC-Norfolk resulted in only parts of the data being obtained.

The study was approved by the Norwich District Health Authority Ethics Committee and participants gave informed consent at each follow-up.

### *5.1.2 Free sugar intake*

Diet was assessed using FFQs (see Chapter 4: 4.2.1, Appendices relating to Chapter 4: Appendix 1). Both questionnaires originated from the tool used in the US Nurses' Health Study, a self-administered questionnaire on habitual diet over the past 12 months (Bingham *et al.*, 2001; Willett *et al.*, 1985). A detailed description of validation studies for Whitehall II has been described in 4.2.1. In EPIC-Norfolk, FFQ data were validated against weighed diet records, obtained at 4 occasions over a year on 4 consecutive days. Quartile agreement ranged from 38 to 47% and disagreement from 2 to 5% (Bingham *et al.*, 1997).

Sugar intake was calculated by multiplying sweet food / beverage consumption frequencies per day by their sugar content and portion size based *on 'McCance and Widdowson's composition of foods, 5th edition'* (Holland *et al.*, 1991). Table 18 presents food items that cover sweet food and beverage intake.

**Table 18 Sources of sugar intake from sweet food / beverages in Whitehall II and EPIC-Norfolk**

| | Whitehall II | EPIC-Norfolk |
|---|---|---|
| **Sweet foods** | | |
| | sweet biscuits | plain biscuits |
| | | chocolate biscuits |
| | cakes | cakes (readymade & homemade) |
| | buns or pastries | buns (readymade & homemade) |
| | fruit pies, tarts or crumbles | fruit pies (readymade & homemade) |
| | milk puddings, sponge puddings | sponges (readymade & homemade) |
| | | milk puddings |
| | ice cream | ice cream |
| | chocolates or chocolate bars | chocolates |
| | | chocolate bars |
| | sweets, toffees or mints | sweets |
| | added sugar | added sugar |
| | jam, marmalade or honey | Jam |
| **Beverages** | | |
| | fizzy soft drinks | fizzy drinks |
| | fruit squash or cordial | squash |
| | fruit juice | Juices |
| | malted milk drinks, such as Horlicks | horlicks |
| | cocoa or hot chocolate | Cocoa |

### *5.1.3 Mood disorder assessment*

For analyses A mood disorders were assessed using GHQ, CES-D and CIS-R depression (a detailed description can be found in chapter 4.2.2). All measures were dichotomized; which allowed prevalent cases at baseline to be excluded in prospective analyses. GHQ caseness will henceforth be referred to as CMD, CES-D caseness as depression and CIS-R depression caseness as clinical depression.

For analyses B mood disorder was assessed using antidepressant intake. As shown in Chapter 4.11 diet intake and mood questionnaires in EPIC-Norfolk were not conducted at the same time. Therefore to allow for dietary intake and mood to be assessed at the same time for prospective analyses of incidence, only antidepressant intake or ever told depression diagnosis were available. To maximise comparison between Whitehall II and EPIC-Norfolk and reduce heterogeneity, reported antidepressant intake was used as a measure for mood disorder. Antidepressant intake was based on the questions *'This question concerns any medicine that you may have taken during the last fourteen days. Have you been taking any medicines, tablets, tonics or pills within the last fourteen days?'* asked from phase 4 onwards in Whitehall II and *'In the last week, have you taken any drugs or medicines, either prescribed by your doctor or bought from the chemist'* in EPIC-Norfolk.

### *5.1.4 Confounders*

Description of confounders can be found in Chapter 4: 4.3. Socio-demographic factors included last grade level in the civil service and marital status; health behaviours included physical activity, alcohol consumption, smoking and sleep duration; measures of adiposity included BMI and central obesity and physical health included diabetes, cardio-vascular disease and cancer.

In analyses B sleep duration was excluded as there was no comparable measure in EPIC-Norfolk and ethnicity could not be included due to zero cells, meaning there were too little cases in the small sample of participants of ethnicity other than white. The following covariates were collected and defined similarly to Whitehall II in EPIC-Norfolk: marital status, smoking, weight, waist circumference, alcohol and dietary intake. CVD, cancer and diabetes were based on self-report. Social position was based on a social class variable derived from own and partner's occupation coded as professional, managerial and technical, skilled non-manual, manual, partly skilled and unskilled occupations (Office of Population Censuses and Surveys general register office for Scotland, 1992). For this analysis professional and managerial, and partly and unskilled were combined. Physical activity was based on self-report and categorised into 4 groups inactive, moderately inactive, moderately active and active (University of Cambridge, 2018)

### *5.1.5 Dietary Confounders*

To adjust for energy intake a modified partition method was used, subtracting not only the calories from the nutrient (sugar) from overall calorie intake, but also the calories from the sweet food / beverages (Howe, 1989). Energy content from sweet food / beverages due to sugar was an average 58% of the total energy content per food item, consequently sugar intake from sweet food / beverages was strongly correlated with energy intake from other sources (Pearson's correlation 0.56). Other dietary confounders were the modified DASH diet score, fish, coffee and tea consumption. In analyses A. fibre intake derived from the entire FFQ was added as a confounder to harmonise sample inclusion with Objective II (see Chapter 4: 4.4).

### *5.1.6 Statistical analysis: Analyses A*

Interactions of mood disorders and depression with sex were tested in the initial model (Model 0: adjusted for age, sex and ethnicity) using LR test since sex-differences have been reported in a prior study on the association of diet and depression in the Whitehall

II cohort (Akbaraly *et al.*, 2013). Further adjustments were grouped into four hierarchical models: baseline socio-demographic factors and health behaviours (Model 1), diet-related factors (Model 2), BMI and central obesity (Model 3), and physical health (Model 4). Models 0 to 2 are considered to include actual confounders, whereas factors included in Model 3 and 4 could also lie on the pathway and mediate the association. Therefore, model 2 is considered the final model.

**Inclusion criteria**

Inclusion criteria and flow diagram can be found in Chapter 4: 4.4, Figure 6. The results of the initial age, sex and ethnicity adjusted model are presented in the maximum eligible sample, following models are restricted to those with no missing data in the final model. Estimates from the initial model in the maximum sample were compared to estimates in the reduced sample and reported when different.

**Analyses**

In all analyses, daily sweet food and beverage intake were modelled as continuous variables, expressed per 30g of sugar which is close to the standard deviation (SD in phase 3 / 5 / 7 / 9: 32.73 / 33.59 / 32.44 / 31.10), as well as sex-specific tertiles based on the distribution at phase 3 (in men <39.5, ≥39.5 to <67.0 and ≥67.0g/day; in women <30.0, ≥30.0 to <51.0 and ≥51.0g/day). To describe the samples at baseline, mood disorders and sugar intake by covariate were compared using descriptive statistics.

To study the association of sugar intake from sweet food and beverages, a random effects logistic regression model (REM) was performed using the Stata command *xtlogit* (Twisk, 2004), with exposures at phases 3, 5, 7 and 9 for GHQ caseness, and at phases 7 and 9 for CES-D caseness. The applicability of the REM was tested by introducing study phase-interactions and LR test. The prospective association of sugar intake from sweet food / beverages on incident and recurrent CMD and depression was examined in 2, 5 and 10-year cycles (Brunner *et al.*, 2014).

In sensitivity analyses, main analyses were repeated by: (a) excluding participants with extreme values of sugar intake (>7 SD; at phases 3/ 5/ 7 / 9: 5 / 3 / 4 / 4) and (b) excluding participants with unknown or reported doctor diagnosis of depression at each baseline (at phases 3/ 5/ 7 / 9: 164 / 124 / 166 / 197 individuals) in models concerning incidence.

To check for reverse causation, that depressive symptoms may affect subsequent sugar intake, linear regression models of 5-year absolute change in sugar intake from sweet food / beverages and multinomial models for change in tertiles were fitted for

each cycle, from phases 3 to 5, 5 to 7 and 7 to 9, with CMD at phases 3, 5, 7 respectively, and for change from phase 7 to 9 with depression at phase 7.

### 5.1.7 Statistical analysis: Analyses B

Analyses were conducted by sex. All models were adjusted for age and ethnicity (in Whitehall II) and further adjustments were grouped in four hierarchical models: baseline socio-demographic factors and health behaviours (Model 1), diet-related factors (Model 2), BMI and central obesity (Model 3), and physical health (Model 4). In line with analysis A model 2 is considered the final model.

**Inclusion criteria**

Participants were included if they had answered at least 8 of the FFQ sweet food and beverage items (Willett, 2012), their ethnicity was known to be either White, Black or South Asian, and participants were not energy misreporters, as defined by the methods adopted by Mosdol et al. 2007 and based on basal metabolic rate equations of the Department of Health (Department of Health, 1991; Mosdol *et al.*, 2007; Schofield, 1985). Misreporting was considered where the log ratio of energy intake (EI) to estimated energy expenditure (EE) was more than 3 SD from the log mean. As sugar intake from sweet food / beverages was not derived from the entire questionnaire, and to ensure maximal case numbers, participants were not excluded on the basis of representativeness. Figure 10 depicts how the samples were reached.

The results of the minimally adjusted model (including age, sex and ethnicity in Whitehall II) are presented in the maximum eligible sample; following models are restricted to those with no missing data in the final model. Estimates from the minimally adjusted model in the maximum sample were compared to those and presented when different.

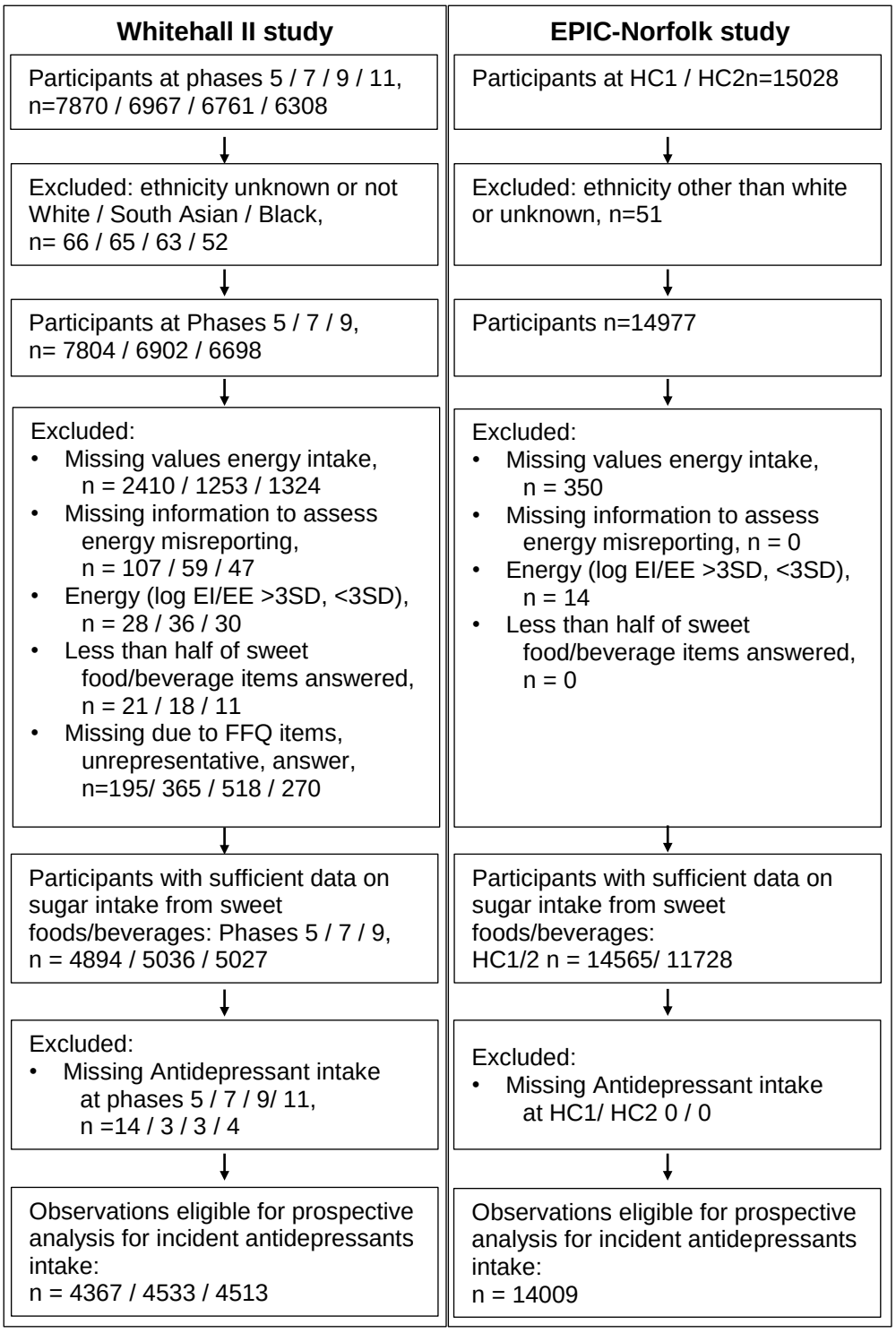



**Figure 10 Included sample for comparison study Whitehall II and EPIC-Norfolk**
Abbreviations: EI, Energy intake; EE, Energy expenditure; FFQ, Food Frequency Questionnaire; HC, Health Check.

**Analyses**

Daily sweet food and beverage intake were modelled as continuous variables, expressed per 30g of sugar and sex-specific tertiles based on the distribution at phase 3 in Whitehall II (see definitions in section 5.1.6) and based on HC1 in EPIC-Norfolk (in men <43.5, ≥43.5 to <76.0 and ≥76.0g/day; in women <32.0, ≥32.0 to <58.5 and ≥58.5 g/day). To describe the samples at baseline antidepressant intake and sugar intake by covariate were compared using descriptive statistics.

The prospective association of sugar intake from sweet food / beverages and antidepressant intake was modelled separately using logistic regression. Incident antidepressant intake was assumed when no antidepressant intake was reported at each baseline phase in Whitehall II and HC1 in EPIC, respectively. Whitehall II data were analysed using REM and 5-year cycles from phases 5 to 7, 7 to 9 and 9 to 11, data from EPIC-Norfolk was analysed using simple logistic regression and from HC1 to HC2 (mean follow-up period 3.7 years).

Findings on the association of sugar intake from sweet food and beverages and incident antidepressant intake were meta-analysed using the Stata command *metan*.

Finally, the potential role of reverse causation was investigated using change of sugar intake from sweet food / beverages as outcome and baseline antidepressant intake as exposure variable. In Whitehall II this was analysed using linear regressions for each cycle and in EPIC-Norfolk by modelling the effect of antidepressant intake on change of sugar intake from sweet food / beverages from HC1 to HC2. Associations of baseline antidepressant intake with change in tertile of sugar intake sugar intake from sweet food / beverages were examined using multinomial regression.

## 5.2 Descriptive results

### *5.2.1 Population characteristics*

Table 19 shows the sample characteristics in Whitehall II at phase 5 and EPIC Norfolk HC1. Participants in Whitehall II at phase 5 were younger than those in EPIC Norfolk. In Whitehall II there was a higher proportion of singles and fewer men in lowest measure of socio-economic position (grade level in the civil service) but more women in lowest measure of socio-economic position than participants in EPIC. The proportions of smokers were comparable between the studies, there were slightly higher proportion of vigorously active participants in EPIC Norfolk, but categorisation was not fully comparable. There were a higher proportion of heavy drinking men and women in Whitehall than in EPIC Norfolk. There were slightly more men with normal weight and without central obesity in Whitehall II. In Whitehall there was a higher proportion of participants with diabetes, women with CHD and a lower proportion of participants with cancer.

**Table 19 Sample characteristics of Whitehall II (Phase 5) and EPIC-Norfolk (HC1)**

| | **Whitehall II, n (%)** | | | **EPIC Norfolk, n (%)** | | |
|---|---|---|---|---|---|---|
| Study characteristics at phase 5 / at HC1 | Men (n=3747) | Women (n=1375) | | Men (n=6375) | Women (n=8190) | |
| Age, | | | 0.001 | | | <0.001 |
| <55 years | 1761 (50.2) | 617 (44.9) | | 2092 (32.8) | 3258 (39.8) | |
| ≥55 years | 1744 (49.8) | 758 (55.1) | | 4283 (67.2) | 4932 (60.2) | |
| Marital Status | | | <0.001 | | | <0.001 |
| Married/cohabiting | 2908 (85.4) | 815 (61.9) | | 5628 (88.8) | 6333 (77.7) | |
| Single | 297 (8.7) | 259 (19.7) | | 254 (4.0) | 338 (4.2) | |
| Divorced/widowed | 199 (5.9) | 242 (18.4) | | 459 (7.2) | 1482 (18.2) | |
| Last grade level in Civil service / (Social class in EPIC) | | | <0.001 | | | <0.001 |
| Highest (prof / management) | 1916 (54.7) | 288 (21.0) | | 3120 (49.6) | 3565 (44.4) | |
| Intermediate (skilled non manual) | 1435 (40.9) | 655 (47.6) | | 810 (12.9) | 1600 (19.9) | |
| (skilled manual) | | | | 1435 (22.8) | 1623 (20.2) | |
| Lowest(semiskilled/non skilled) | 154 (4.4) | 432 (31.4) | | 922 (14.7) | 1624 (20.2) | |
| Smoking | | | <0.001 | | | <0.001 |
| Never Smoker | 1665 (47.7) | 765 (56.1) | | 2294 (36.2) | 4844 (59.6) | |
| Ex-Smoker | 1547 (44.3) | 454 (33.3) | | 3448 (54.5) | 2555 (31.4) | |
| Current Smoker | 282 (8.1) | 145 (10.6) | | 590 (9.3) | 728 (9.0) | |
| Physical activity | | | <0.001 | | | <0.001 |
| Non/mild | 1114 (31.8) | 736 (53.5) | | 1609 (25.2) | 2681 (32.7) | |
| Vigorous | 575 (16.4) | 115 (8.4) | | 1427 (22.4) | 1402 (17.1) | |
| Alcohol consumption | | | <0.001 | | | <0.001 |
| None | 417 (12.0) | 406 (29.8) | | 889 (14.0) | 2763 (34.0) | |
| Moderate | 1586 (45.6) | 746 (54.8) | | 3884 (61.3) | 4802 (59.1) | |
| Heavy | 1478 (42.5) | 210 (15.4) | | 1568 (24.7) | 564 (6.9) | |

| | | | | | | |
|---|---|---|---|---|---|---|
| BMI | | | <0.001 | | | <0.001 |
| Normal, <25kg/m2 | 1271 (42.1) | 559 (45.5) | | 2213 (34.7) | 3897 (47.6) | |
| Overweight | 1424 (47.2) | 444 (36.2) | | 3397 (53.3) | 3075 (37.6) | |
| Obese. ≥30kg/m2 | 321 (10.6) | 225 (18.3) | | 761 (11.9) | 1210 (14.8) | |
| Central obesity | | | <0.001 | | | 0.19 |
| No | 2316 (86.5) | 861 (74.7) | | 4957 (77.9) | 6302 (77.0) | |
| Yes (Waist ≥102/≥88 cm) | 361 (13.5) | 292 (25.3) | | 1408 (22.1) | 1887 (23.0) | |
| Diabetes | | | 0.088 | | | <0.001 |
| No | 3347 (95.5) | 1297 (94.3) | | 6200 (97.3) | 8090 (98.8) | |
| Yes | 158 (4.5) | 78 (5.7) | | 172 (2.7) | 95 (1.2) | |
| CHD | | | 0.19 | | | <0.001 |
| No | 3270 (93.3) | 1297 (94.3) | | 5993 (94.1) | 8030 (98.1) | |
| Yes | 235 (6.7) | 78 (5.7) | | 378 (5.9) | 157 (1.9) | |
| Cancer | | | <0.001 | | | <0.001 |
| No | 3430 (97.9) | 1316 (95.9) | | 6143 (96.4) | 7633 (93.2) | |
| Yes | 73 (2.1) | 56 (4.1) | | 230 (3.6) | 555 (6.8) | |

Abbreviations: BMI, Body mass index; CVD, cardiovascular disease; GHQ, General Health Questionnaire; HC, Health Check; M, men; W, women.

### *5.2.2 Mood disorders*

Associations of CMD, depression and clinical depression with covariates are described in chapter 4.6, Table 16, Table A 6, Table A 7.

Table 20 shows the distribution of antidepressant intake by covariates for Whitehall II Phase 5 and EPIC-Norfolk HC1. In both cohorts, antidepressant intake was associated with sex, marital status, physical activity and alcohol intake. In Whitehall II, antidepressant intake was additionally associated with socio-economic position measured by last grade of civil service, coffee or tea intake, in EPIC with smoking, diet quality, BMI and central obesity.

**Table 20 Crude association of antidepressant intake in Whitehall II (Phase 5) and EPIC-Norfolk (HC1) with covariates**

| | | **Antidepressant intake** | | | | |
|---|---|---|---|---|---|---|
| Covariates at phase 5 / at HC1 | | Whitehall II | | | EPIC-Norfolk | |
| | n | % | p | n | % | p |
| Sex | | | .007 | | | <.001 |
| Men | 3505 | 2.25 | | 6375 | 2.62 | |
| Women | 1375 | 3.64 | | 8190 | 4.75 | |
| Age | | | .20 | | | .27 |
| <50 years | 2378 | 2.94 | | 5350 | 3.59 | |
| ≥50 years | 2502 | 2.36 | | 9215 | 3.95 | |
| Ethnic Group in Whitehall II | | | .65 | | | |
| White | 4589 | 2.64 | | N/A | | |
| South Asian | 189 | 2.12 | | | | |
| Black | 102 | 3.92 | | | | |
| Marital Status | | | .047 | | | <.001 |
| Married/cohabiting | 3723 | 2.31 | | 11961 | 3.47 | |
| Single | 556 | 3.78 | | 592 | 5.74 | |
| Divorced/widowed | 441 | 3.63 | | 1941 | 5.41 | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Last grade level in Civil service // (Social class in EPIC) | | | .016 | | | .13 |
| Highest (prof / management) | 2204 | 2.04 | | 6685 | 3.66 | |
| Intermediate (skilled non manual) | 2090 | 2.87 | | 2410 | 4.44 | |
| (skilled manual) | | | | 3058 | 3.30 | |
| Lowest(semiskilled/non skilled) | 586 | 4.10 | | 2172 | 4.10 | |
| Smoking | | | .69 | | | .025 |
| Never Smoker | 2430 | 2.55 | | 7138 | 3.64 | |
| Ex-Smoker | 2001 | 2.65 | | 6003 | 3.68 | |
| Current Smoker | 427 | 3.28 | | 1318 | 5.16 | |
| Physical activity | | | <.001 | | | <.001 |
| Non/mild | 1850 | 4.49 | | 3882 | 5.20 | |
| Vigorous | 690 | 1.30 | | 2829 | 2.83 | |
| Alcohol consumption | | | .006 | | | .032 |
| None | 823 | 4.25 | | 3652 | 4.52 | |
| Moderate | 2332 | 2.49 | | 8686 | 3.60 | |
| Heavy | 1688 | 2.13 | | 2132 | 3.42 | |
| Energy intake from other diet | | | .55 | | | .44 |
| < median | 2408 | 2.78 | | 7284 | 3.94 | |
| > median | 2472 | 2.51 | | 7281 | 3.69 | |
| Modified DASH diet score | | | .63 | | | .026 |
| < median | 2661 | 2.71 | | 8181 | 4.13 | |
| > median | 2174 | 2.48 | | 6378 | 3.42 | |
| Fish intake | | | .31 | | | .63 |
| < median | 2565 | 2.85 | | 8777 | 3.87 | |
| > median | 2312 | 2.38 | | 5781 | 3.72 | |
| Tea / coffee | | | .004 | | | .98 |
| ≤ 1 cup of either/day | 162 | 6.17 | | 710 | 3.80 | |
| > 1 cup of either/day | 4718 | 2.52 | | 13855 | 3.82 | |
| BMI (M) | | | .84 | | | .220 |
| Normal, <25kg/$m^2$ | 1271 | 2.28 | | 2213 | 2.17 | |
| Overweight | 1424 | 2.04 | | 3397 | 2.80 | |
| Obese. ≥30kg/$m^2$ | 321 | 2.49 | | 761 | 3.15 | |
| BMI (W) | | | .77 | | | <.001 |
| Normal, <25kg/$m^2$ | 559 | 3.76 | | 3897 | 3.62 | |
| Overweight | 444 | 2.93 | | 3075 | 5.69 | |
| Obese. ≥30kg/$m^2$ | 225 | 3.56 | | 1210 | 6.03 | |
| Central obesity (M) | | | .54 | | | .020 |
| No | 2316 | 2.25 | | 4957 | 2.36 | |
| Yes (Waist ≥102cm) | 361 | 2.77 | | 1408 | 3.48 | |
| Central obesity (W) | | | .49 | | | .13 |
| No | 861 | 3.25 | | 6302 | 4.55 | |
| Yes (Waist ≥88 cm) | 292 | 4.11 | | 1887 | 5.41 | |
| Diabetes | | | .25 | | | .80 |
| No | 4644 | 2.58 | | 14290 | 3.81 | |
| Yes | 236 | 3.81 | | 267 | 4.12 | |
| CVD | | | .09 | | | .13 |
| No | 4567 | 2.54 | | 14023 | 3.77 | |
| Yes | 313 | 4.15 | | 535 | 5.05 | |
| Cancer | | | .15 | | | .56 |
| No | 4746 | 2.57 | | 13776 | 3.80 | |
| Yes | 129 | 4.65 | | 785 | 4.20 | |

Abbreviations: BMI, Body mass index; CES-D, Center for Epidemiologic Studies Depression Scale; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension; GHQ, General Health Questionnaire; HC, Health Check; M, men; W, women.

### *5.2.3 Sugar intake from sweet food / beverages*

Table 21 shows the association of sugar intake with covariates at phase 3 in Whitehall II. Sugar intake from sweet food / beverages was higher in men, Whites, married/cohabiting or single participants, those in higher last grade of civil service, non-smokers, those with higher physical activity, those who did not consume alcohol, those with higher energy intake from other foods, those with higher coffee/tea intake, higher fibre intake, higher BMI and central obesity, diabetes and CVD. When operationalised as sex-specific tertiles, sugar intake from sweet food / beverages was additionally associated with lower fish intake.

There was little difference in associations at later phases, except that at later phases ex-smokers had the lowest sugar intake, there was no association with CVD and at phase 9 those with cancer presented higher sugar intakes (see Table A 8).

**Table 21 Crude association of sugar intake from sweet food / beverages with covariates in Whitehall II at phase 3**

| Covariates at phase 3 | **Sugar intake from sweet food / beverages, grams** | | | **Sugar intake from sweet food / beverages, %** | | | |
|---|---|---|---|---|---|---|---|
| | n | Mean ± SD | p | Tertile 1 | Tertile 2 | Tertile 3 | p |
| Sex | | | <.001 | | | | .90 |
| Men | 5486 | 57.7 ± 33.6 | | 69.4 | 69.8 | 69.2 | |
| Women | 2412 | 45.4 ± 29.0 | | 30.6 | 30.2 | 30.8 | |
| Age | | | .76 | | | | .80 |
| <50 years | 4155 | 54.0 ± 32.6 | | 53.1 | 52.2 | 52.5 | |
| ≥50 years | 3743 | 53.8 ± 32.9 | | 46.9 | 47.8 | 47.5 | |
| Ethnic Group | | | <.001 | | | | <.001 |
| White | 7294 | 54.8 ± 32.9 | | 90.1 | 92.2 | 94.7 | |
| South Asian | 365 | 41.7 ± 28.5 | | 6.38 | 4.75 | 2.77 | |
| Black | 239 | 46.5 ± 31.4 | | 3.51 | 3.07 | 2.51 | |
| Marital Status | | | <.001 | | | | <.001 |
| Married/cohabiting | 6063 | 54.3 ± 32.3 | | 76.0 | 78.9 | 75.7 | |
| Single | 1136 | 55.6 ± 34.5 | | 14.0 | 12.7 | 16.5 | |
| Divorced/widowed | 690 | 47.9 ± 32.9 | | 10.06 | 8.37 | 7.83 | |
| Last grade level in Civil service | | | <.001 | | | | .035 |
| Highest | 3064 | 56.8 ± 32.7 | | 36.7 | 40.1 | 39.6 | |
| Intermediate | 3548 | 53.7 ± 32.7 | | 45.7 | 44.0 | 45.1 | |
| Lowest | 1286 | 47.4 ± 32.2 | | 17.6 | 16.0 | 15.3 | |
| Smoking | | | <.001 | | | | <.001 |
| Never Smoker | 3438 | 55.9 ± 33.0 | | 42.3 | 47.4 | 49.1 | |
| Ex-Smoker | 2901 | 52.7 ± 32.5 | | 42.1 | 38.4 | 36.8 | |
| Current Smoker | 1086 | 51.2 ± 32.3 | | 15.5 | 14.3 | 14.1 | |
| Physical activity | | | <.001 | | | | .006 |
| Non/mild | 2948 | 50.7 ± 31.2 | | 40.0 | 36.7 | 35.3 | |
| Moderate | 3505 | 55.7 ± 33.5 | | 42.0 | 45.4 | 45.7 | |
| Vigorous active | 1445 | 56.2 ± 33.6 | | 18.0 | 17.9 | 19.0 | |
| Alcohol consumption | | | <.001 | | | | <.001 |
| None | 1852 | 57.1 ± 35.6 | | 20.4 | 22.0 | 28.0 | |
| Moderate | 4138 | 55.0 ± 32.5 | | 48.9 | 54.2 | 54.2 | |
| Heavy | 1900 | 48.4 ± 29.7 | | 30.7 | 23.8 | 17.8 | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Sleep duration | | | .14 | | | | .23 |
| less than 7 h/day | 1999 | 53.0 ± 33.0 | | 26.5 | 24.5 | 25.1 | |
| ≥ 7 h/day | 5889 | 54.3 ± 32.7 | | 73.5 | 75.5 | 74.9 | |
| Energy intake from other diet | | | <.001 | | | | <.001 |
| < median | 3899 | 38.0 ± 21.4 | | 74.8 | 53.8 | 21.8 | |
| > median | 3999 | 69.4 ± 34.4 | | 25.2 | 46.2 | 78.2 | |
| Modified DASH diet score | | | <.001 | | | | <.001 |
| < median | 4447 | 56.6 ± 33.4 | | 51.1 | 56.0 | 61.8 | |
| > median | 3447 | 50.5 ± 31.5 | | 48.9 | 44.0 | 38.2 | |
| Fish intake | | | .16 | | | | .022 |
| < median | 4486 | 53.5 ± 32.3 | | 56.3 | 58.9 | 55.2 | |
| > median | 3412 | 54.5 ± 33.4 | | 43.7 | 41.1 | 44.8 | |
| Tea / Coffee | | | <.001 | | | | <.001 |
| ≤ 1 cup of either/day | 690 | 47.1 ± 31.3 | | 10.9 | 8.40 | 6.96 | |
| > 1 cup of either/day | 7208 | 54.6 ± 32.8 | | 89.1 | 91.6 | 93.0 | |
| Fibre intake | | | <.001 | | | | <.001 |
| 1st Tertile | 2475 | 44.8 ± 27.9 | | 40.5 | 31.8 | 22.0 | |
| 2nd Tertile | 2821 | 54.0 ± 31.2 | | 33.8 | 38.3 | 35.1 | |
| 3rd Tertile | 2602 | 62.4 ± 36.2 | | 25.7 | 29.9 | 43.0 | |
| BMI | | | <.001 | | | | <.001 |
| Normal, <25kg/m2 | 3953 | 56.7 ± 33.5 | | 47.9 | 52.0 | 57.7 | |
| Overweight | 2847 | 52.0 ± 31.4 | | 40.8 | 39.0 | 34.0 | |
| Obese. ≥30kg/m2 | 715 | 48.4 ± 32.5 | | 11.4 | 9.0 | 8.3 | |
| Central obesity (M/W) | | | .002 | | | | .18 |
| No | 6784 | 54.4 ± 32.8 | | 90.4 | 91.2 | 91.9 | |
| Yes (Waist ≥102/88 cm) | 656 | 50.2 ± 31.8 | | 9.6 | 8.8 | 8.1 | |
| Diabetes | | | <.001 | | | | <.001 |
| No | 7680 | 54.2 ± 32.8 | | 96.1 | 97.5 | 98.1 | |
| Yes | 218 | 44.2 ± 30.4 | | 3.9 | 2.5 | 1.9 | |
| CVD | | | .028 | | | | .006 |
| No | 7630 | 54.1 ± 32.8 | | 95.8 | 96.7 | 97.3 | |
| Yes | 268 | 49.6 ± 32.2 | | 4.2 | 3.3 | 2.7 | |
| Cancer | | | .78 | | | | .33 |
| No | 7789 | 53.9 ± 32.8 | | 98.7 | 99.0 | 98.5 | |
| Yes | 100 | 54.8 ± 30.3 | | 1.3 | 1.0 | 1.5 | |

Abbreviations: BMI, Body mass index; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension; M, men; W, women.

Table 22 shows the association between sugar intake from sweet food / beverages and covariates at phase 3 by gender. Associations with age, ethnicity, smoking, sleep duration, alcohol intake, energy intake from other diet, modified DASH diet score, fibre intake, tea and coffee intake and cancer did largely not differ by gender. In women, there was no significant association with last grade level in the civil service, physical activity, BMI, diabetes and CVD. While both men and women who were single had the highest sugar intake from sweet food / beverages, divorced or widowed men, but married and cohabiting women had the lowest intakes. Men who had a normal BMI and no central obesity had the highest sugar intakes from sweet food / beverages. In contrast, women with central obesity had higher grams of sugar intake from sweet food / beverages but there was no association when operationalised as sex-specific tertiles (see table Table A 9).

**Table 22 Crude association of sugar intake from sweet food / beverages with covariates in Whitehall II by gender**

| Covariates at phase 3 | Sugar intake from sweet food / beverages, grams | | | | | |
|---|---|---|---|---|---|---|
| | Men (n=5486) | | | Women (n=2412) | | |
| | n | Mean ± SD | p | n | Mean ± SD | p |
| Age | | | .93 | | | .11 |
| <50 years | 3023 | 57.6 ± 33.80 | | 1132 | 44.4 ± 27.07 | |
| ≥50 years | 2463 | 57.7 ± 33.38 | | 1280 | 46.3 ± 30.56 | |
| Ethnic Group | | | <.001 | | | .066 |
| White | 5172 | 58.5 ± 33.61 | | 2122 | 45.7 ± 29.01 | |
| South Asian | 227 | 42.9 ± 30.37 | | 138 | 39.8 ± 24.98 | |
| Black | 87 | 48.0 ± 31.29 | | 152 | 45.6 ± 31.52 | |
| Marital Status | | | <.001 | | | .001 |
| Married/cohabiting | 4536 | 57.8 ± 33.03 | | 1527 | 43.8 ± 27.65 | |
| Single | 643 | 60.3 ± 36.95 | | 493 | 49.5 ± 29.90 | |
| Divorced/widowed | 302 | 49.6 ± 33.70 | | 388 | 46.6 ± 32.32 | |
| Last grade level in Civil service | | | .001 | | | .085 |
| Highest | 2684 | 58.9 ± 32.92 | | 380 | 42.4 ± 26.55 | |
| Intermediate | 2454 | 57.2 ± 34.08 | | 1094 | 46.1 ± 27.99 | |
| Lowest | 348 | 51.7 ± 34.90 | | 938 | 45.8 ± 30.95 | |
| Smoking | | | <.001 | | | .007 |
| Never Smoker | 2297 | 60.2 ± 34.06 | | 1141 | 47.1 ± 28.64 | |
| Ex-Smoker | 2198 | 55.8 ± 33.42 | | 703 | 42.8 ± 26.93 | |
| Current Smoker | 681 | 54.8 ± 32.13 | | 405 | 45.2 ± 31.62 | |
| Physical activity | | | <.001 | | | .20 |
| Non/mild | 1715 | 55.0 ± 32.23 | | 1233 | 44.6 ± 28.61 | |
| Moderate | 2553 | 59.0 ± 34.27 | | 952 | 46.7 ± 29.46 | |
| Vigorous active | 1218 | 58.4 ± 33.92 | | 227 | 44.4 ± 28.91 | |
| Alcohol consumption | | | <.001 | | | <.001 |
| None | 954 | 64.9 ± 37.32 | | 898 | 48.8 ± 31.53 | |
| Moderate | 2846 | 60.1 ± 33.47 | | 1292 | 43.8 ± 27.21 | |
| Heavy | 1680 | 49.5 ± 29.85 | | 220 | 40.4 ± 26.91 | |
| Sleep duration | | | .51 | | | .38 |
| less than 7 h/day | 1339 | 57.1 ± 34.07 | | 660 | 44.6 ± 29.01 | |
| ≥ 7 h/day | 4142 | 57.8 ± 33.47 | | 1747 | 45.8 ± 28.98 | |
| Energy intake from other diet | | | <.001 | | | <.001 |
| < median | 2382 | 39.4 ± 21.64 | | 1563 | 35.9 ± 20.62 | |
| > median | 3104 | 71.6 ± 34.45 | | 849 | 62.9 ± 33.64 | |
| Modified DASH diet score | | | <.001 | | | <.001 |
| < median | 3093 | 60.4 ± 34.30 | | 1354 | 47.8 ± 29.60 | |
| > median | 2390 | 54.1 ± 32.36 | | 1057 | 42.3 ± 27.91 | |
| Fish intake | | | .23 | | | .004 |
| < median | 3235 | 57.2 ± 33.11 | | 1251 | 43.8 ± 27.84 | |
| > median | 2251 | 58.3 ± 34.31 | | 1161 | 47.1 ± 30.09 | |
| Tea / Coffee | | | <.001 | | | .001 |
| ≤ 1 cup of either/day | 409 | 51.9 ± 33.78 | | 281 | 40.1 ± 25.64 | |
| > 1 cup of either/day | 5077 | 58.1 ± 33.56 | | 2131 | 46.1 ± 29.33 | |
| Fibre intake | | | <.001 | | | <.001 |
| 1st Tertile | 1611 | 47.3 ± 28.03 | | 864 | 40.1 ± 27.05 | |
| 2nd Tertile | 1983 | 57.5 ± 32.15 | | 838 | 45.9 ± 27.11 | |
| 3rd Tertile | 1892 | 66.7 ± 36.76 | | 710 | 51.1 ± 32.13 | |
| BMI | | | <.001 | | | .39 |
| Normal, <25kg/m$^2$ | 2781 | 61.8 ± 34.62 | | 1172 | 44.7 ± 27.24 | |
| Overweight | 2093 | 53.9 ± 31.82 | | 754 | 46.5 ± 29.63 | |
| Obese. ≥30kg/m$^2$ | 370 | 51.1 ± 33.38 | | 345 | 45.5 ± 31.24 | |
| Central obesity (M/W) | | | <.001 | | | .028 |
| No | 4821 | 58.3 ± 33.74 | | 1963 | 44.9 ± 28.32 | |
| Yes (Waist ≥102/≥88 cm) | 360 | 51.3 ± 32.55 | | 296 | 48.8 ± 30.77 | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Diabetes | | | <.001 | | | .33 |
| No | 5331 | 58.0 ± 33.61 | | 2349 | 45.5 ± 29.00 | |
| Yes | 155 | 45.2 ± 31.26 | | 63 | 41.8 ± 28.43 | |
| CVD | | | .012 | | | .55 |
| No | 5287 | 57.9 ± 33.58 | | 2343 | 45.4 ± 29.07 | |
| Yes | 199 | 51.8 ± 33.94 | | 69 | 43.3 ± 25.96 | |
| Cancer | | | .10 | | | .59 |
| No | 5431 | 57.6 ± 33.66 | | 2358 | 45.4 ± 28.98 | |
| Yes | 53 | 65.2 ± 28.32 | | 47 | 43.1 ± 28.25 | |

Abbreviations: BMI, Body mass index; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension; M, men; W, women.

Sugar intake from sweet food and beverages was higher in EPIC-Norfolk than in Whitehall II. Mean reported sugar consumption from sweet food / beverages in Whitehall II was 53.9g per day (SD 33.8) at phase 3, 53.1 (SD 33.3) at phase 5, 49.9 (SD 32.4) at phase 7 and 48.3 (SD 31.1) at phase 9. Mean reported sugar intake from sweet food / beverages in EPIC was 64.9g per day (SD 45.9) at HC1.

Table 23 shows the association of sugar intake with covariates at HC1 in EPIC-Norfolk. In EPIC-Norfolk sugar intake from sweet food / beverages was associated with sex, age, marital status, social class, smoking, energy intake from other sources, diet quality, coffee/tea intake, fish intake, BMI, central obesity and diabetes. Sugar intake from sweet food / beverages was associated with alcohol consumption and CVD only when operationalised continuously suggesting differences might have been explained by sex-differences in alcohol intake as tertiles were calculated sex-specific.

**Table 23 Crude association of sugar intake from sweet food / beverages in EPIC-Norfolk**

| Covariates at phase at HC1 | Sugar intake from sweet food / beverages, grams | | | Sugar intake from sweet food / beverages, % | | | |
|---|---|---|---|---|---|---|---|
| | n | Mean ± SD | p | Tertile 1 | Tertile 2 | Tertile 3 | p |
| Sex | | | <.001 | | | | .78 |
| Men | 6375 | 66.9 ± 44.1 | | 44.0 | 43.4 | 44.0 | |
| Women | 8190 | 52.0 ± 36.1 | | 56.0 | 56.6 | 56.0 | |
| Age | | | <.001 | | | | <.001 |
| <60 years | 7798 | 54.7 ± 38.7 | | 59.0 | 54.7 | 47.0 | |
| ≥60 years | 6767 | 63.0 ± 41.9 | | 41.0 | 45.3 | 53.0 | |
| Marital Status | | | <.001 | | | | .22 |
| Married/cohabiting | 11961 | 59.1 ± 40.4 | | 81.7 | 83.1 | 82.7 | |
| Single | 592 | 59.4 ± 42.0 | | 4.0 | 4.0 | 4.3 | |
| Divorced/widowed | 1941 | 55.4 ± 40.5 | | 14.3 | 12.9 | 13.0 | |
| Social Class | | | <.001 | | | | <.001 |
| Prof / Management | 6685 | 55.8 ± 39.2 | | 50.8 | 47.1 | 42.2 | |
| Skilled, non-manual | 2410 | 57.8 ± 38.5 | | 16.4 | 16.6 | 17.5 | |
| Skilled manual | 3058 | 62.0 ± 42.2 | | 19.5 | 21.1 | 23.5 | |
| Semiskilled/non skilled | 2172 | 62.8 ± 43.2 | | 13.4 | 15.3 | 16.8 | |
| Smoking | | | .044 | | | | <.001 |
| Never Smoker | 7138 | 57.8 ± 38.0 | | 45.1 | 51.1 | 51.9 | |
| Ex-Smoker | 6003 | 58.9 ± 42.5 | | 46.0 | 39.9 | 38.7 | |
| Current Smoker | 1318 | 60.6 ± 43.2 | | 8.9 | 9.0 | 9.4 | |
| Physical activity | | | <.001 | | | | .19 |
| Non/mild | 3882 | 59.2 ± 42.1 | | 27.1 | 26.1 | 26.7 | |
| Moderate inactive | 4290 | 56.5 ± 38.5 | | 29.8 | 30.0 | 28.5 | |
| Moderate | 3564 | 58.4 ± 39.7 | | 24.5 | 24.6 | 24.2 | |
| Vigorous | 2829 | 61.0 ± 41.7 | | 18.5 | 19.2 | 20.6 | |
| Alcohol consumption | | | <.001 | | | | .<.001 |
| None | 3652 | 61.0 ± 42.4 | | 21.4 | 24.8 | 29.5 | |
| Moderate | 8686 | 59.3 ± 40.4 | | 58.6 | 60.9 | 60.6 | |
| Heavy | 2132 | 51.3 ± 36.7 | | 20.0 | 14.3 | 9.9 | |
| Energy intake from other diet | | | <.001 | | | | <.001 |
| < median | 7284 | 49.2 ± 36.0 | | 62.8 | 50.8 | 36.5 | |
| > median | 7281 | 67.9 ± 42.4 | | 37.2 | 49.2 | 63.5 | |
| Modified DASH diet score | | | <.001 | | | | <.001 |
| < median | 8181 | 64.5 ± 42.6 | | 45.7 | 55.8 | 67.0 | |
| > median | 6378 | 51.0 ± 36.1 | | 54.3 | 44.2 | 33.0 | |
| Fish intake | | | .20 | | | | .074 |
| < median | 8777 | 58.2 ± 40.5 | | 61.1 | 60.8 | 59.0 | |
| > median | 5781 | 59.1 ± 40.3 | | 38.9 | 39.2 | 41.0 | |
| Tea/Coffee | | | <.001 | | | | .001 |
| ≤ 1 cup of either/day | 710 | 52.2 ± 38.4 | | 5.8 | 4.6 | 4.2 | |
| > 1 cup of either/day | 13855 | 58.9 ± 40.5 | | 94.2 | 95.4 | 95.8 | |
| BMI (M) | | | <.001 | | | | <.001 |
| Normal, <25kg/m$^2$ | 2213 | 71.9 ± 44.0 | | 27.7 | 36.9 | 39.5 | |
| Overweight | 3397 | 65.6 ± 43.9 | | 56.6 | 51.6 | 51.8 | |
| Obese. ≥30kg/m$^2$ | 761 | 58.4 ± 43.5 | | 15.7 | 11.5 | 8.70 | |
| BMI (F) | | | .002 | | | | <.001 |
| Normal, <25kg/m$^2$ | 3897 | 52.7 ± 35.9 | | 45.6 | 48.3 | 49.0 | |
| Overweight | 3075 | 52.5 ± 36.9 | | 37.7 | 36.5 | 38.5 | |
| Obese. ≥30kg/m$^2$ | 1210 | 48.7 ± 34.4 | | 16.7 | 15.2 | 12.5 | |
| Central obesity (M) | | | <.001 | | | | <.001 |
| No | 4957 | 68.2 ± 44.4 | | 74.7 | 77.4 | 81.5 | |
| Yes (Waist ≥102 cm) | 1408 | 62.2 ± 42.7 | | 25.3 | 22.6 | 18.5 | |
| Central obesity (W) | | | 0.18 | | | | .026 |
| No | 6302 | 52.3 ± 36.2 | | 75.2 | 77.4 | 78.2 | |
| Yes (Waist ≥88 cm) | 1887 | 51.1 ± 35.7 | | 24.8 | 22.6 | 21.8 | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Diabetes | | | <.001 | | | | <.001 |
| No | 14290 | 58.9 ± 40.4 | | 96.5 | 98.6 | 99.4 | |
| Yes | 267 | 38.6 ± 35.4 | | 3.5 | 1.4 | 0.6 | |
| CVD | | | .009 | | | | .27 |
| No | 14023 | 58.4 ± 40.4 | | 96.1 | 96.7 | 96.2 | |
| Yes | 535 | 63.0 ± 42.2 | | 3.9 | 3.3 | 3.8 | |
| Cancer | | | .37 | | | | .11 |
| No | 13776 | 58.5 ± 40.4 | | 95.0 | 94.7 | 94.1 | |
| Yes | 785 | 59.8 ± 40.8 | | 5.0 | 5.3 | 5.9 | |

Abbreviations: BMI, Body mass index; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension; M, men; W, women.

Table 24 shows the crude association between sugar intake from sweet food / beverages with covariates in EPIC Norfolk by gender. Associations did not differ for age, social class, alcohol consumption, energy intake from other diet, modified DASH diet score, fish intake and diabetes. After stratification by gender there was no association between sugar intake from sweet food / beverages and marital status, smoking in men, tea and coffee intake in women. Sugar intake from sweet food / beverages was lowest in women who were ex-smokers, men with CVD, and women without CVD and without cancer.

**Table 24 Crude association of sugar intake from sweet food / beverages with covariates in EPIC Norfolk by gender**

| | **Sugar intake from sweet food / beverages, grams** | | | | | |
|---|---|---|---|---|---|---|
| Covariates at phase at HC1 | Men (n=6375) | | | Women (n=8190) | | |
| | n | Mean ± SD | p | n | Mean ± SD | p |
| Age | | | <.001 | | | <.001 |
| <60 years | 2092 | 63.0 ± 42.1 | | 3258 | 47.4 ± 34.3 | |
| ≥60 years | 4283 | 68.8 ± 44.9 | | 4932 | 55.1 ± 36.8 | |
| Marital Status | | | **.37** | | | **.47** |
| Married/cohabiting | 5628 | 67.2 ± 44.0 | | 6333 | 45.7 ± 29.01 | |
| Single | 254 | 66.8 ± 47.0 | | 338 | 39.8 ± 24.98 | |
| Divorced/widowed | 459 | 64.2 ± 43.5 | | 1482 | 45.6 ± 31.52 | |
| Social Class | | | <.001 | | | <.001 |
| Prof / Management | 3120 | 63.8 ± 42.8 | | 3565 | 48.8 ± 34.2 | |
| Skilled, non-manual | 810 | 66.8 ± 41.2 | | 1600 | 53.2 ± 36.2 | |
| Skilled manual | 1435 | 71.4 ± 46.3 | | 1623 | 53.7 ± 36.1 | |
| Semiskilled/non skilled | 922 | 70.6 ± 46.3 | | 1250 | 57.0 ± 39.8 | |
| Smoking | | | .10 | | | <.001 |
| Never Smoker | 2294 | 67.4 ± 41.8 | | 4844 | 53.3 ± 35.2 | |
| Ex-Smoker | 3448 | 66.0 ± 45.4 | | 2555 | 49.3 ± 36.1 | |
| Current Smoker | 590 | 70.0 ± 44.6 | | 728 | 53.0 ± 40.5 | |
| Physical activity | | | <.001 | | | .008 |
| Non/mild | 1757 | 66.4 ± 45.4 | | 2125 | 53.2 ± 38.1 | |
| Moderate inactive | 1609 | 64.7 ± 41.9 | | 2681 | 51.5 ± 35.5 | |
| Moderate | 1582 | 66.8 ± 42.5 | | 1982 | 51.7 ± 36.0 | |
| Vigorous | 1427 | 70.2 ± 46.3 | | 1402 | 51.7 ± 34.1 | |
| Alcohol consumption | | | <.001 | | | <.001 |
| None | 889 | 75.3 ± 50.2 | | 2763 | 56.4 ± 38.4 | |
| Moderate | 3884 | 69.8 ± 44.1 | | 4802 | 50.8 ± 34.8 | |
| Heavy | 1568 | 54.9 ± 37.6 | | 564 | 41.3 ± 32.3 | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Energy intake from other diet | | | <.001 | | | <.001 |
| < median | 2608 | 55.2 ± 39.2 | | 4676 | 45.9 ± 33.7 | |
| > median | 3767 | 75.0 ± 45.4 | | 3514 | 60.2 ± 37.5 | |
| Modified DASH diet score | | | <.001 | | | <.001 |
| < median | 3553 | 73.2 ± 46.0 | | 4628 | 57.8 ± 38.4 | |
| > median | 2821 | 59.0 ± 40.1 | | 3557 | 44.6 ± 31.1 | |
| Fish intake | | | .13 | | | .13 |
| < median | 3976 | 66.3 ± 43.9 | | 4801 | 51.5 ± 36.2 | |
| > median | 2397 | 68.0 ± 44.4 | | 3384 | 52.8 ± 35.8 | |
| Tea/Coffee | | | .001 | | | .059 |
| ≤ 1 cup of either/day | 247 | 58.2 ± 38.2 | | 463 | 49.0 ± 38.1 | |
| > 1 cup of either/day | 6128 | 67.3 ± 44.3 | | 7727 | 52.2 ± 35.9 | |
| BMI | | | <.001 | | | .002 |
| Normal, <25kg/m$^2$ | 2213 | 71.9 ± 44.0 | | 3897 | 52.7 ± 35.9 | |
| Overweight | 3397 | 65.6 ± 43.9 | | 3075 | 52.5 ± 36.9 | |
| Obese. ≥30kg/m$^2$ | 761 | 58.4 ± 43.5 | | 1210 | 48.7 ± 34.4 | <.001 |
| Central obesity (M/W) | | | <.001 | | | 0.18 |
| No | 4957 | 68.2 ± 44.4 | | 6302 | 52.3 ± 36.2 | |
| Yes (Waist ≥102/88 cm) | 1408 | 62.2 ± 42.7 | | 1887 | 51.1 ± 35.7 | |
| Diabetes | | | <.001 | | | <.001 |
| No | 6200 | 67.7 ± 44.1 | | 8090 | 52.2 ± 36.0 | |
| Yes | 172 | 38.8 ± 32.9 | | 95 | 38.3 ± 39.7 | |
| CVD | | | .014 | | | .001 |
| No | 5993 | 67.1 ± 44.2 | | 8030 | 51.9 ± 35.9 | |
| Yes | 378 | 63.7 ± 41.3 | | 157 | 61.4 ± 44.5 | |
| Cancer | | | .22 | | | .022 |
| No | 6143 | 66.8 ± 44.0 | | 7633 | 51.8 ± 35.9 | |
| Yes | 230 | 70.4 ± 45.0 | | 555 | 55.4 ± 38.0 | |

Abbreviations: BMI, Body mass index; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension; M, men; W, women

Associations of sugar intake from sweet food / beverages with covariates differed by study for age, measures of grade level, smoking, adiposity in women and CVD. Those in the highest level of Civil Service in Whitehall II had higher sugar intakes and those in the lowest level of social class in EPIC-Norfolk had the lowest intakes. Sugar intakes were highest in never smokers in Whitehall II and current smokers in EPIC-Norfolk, not associated with BMI in women and higher in women with central adiposity in Whitehall II and in EPIC-Norfolk women with generalised and central obesity had lowest sugar intakes and sugar intake was significantly higher in older participants and CVD cases in EPIC-Norfolk.

## 5.3 Analyses A: Association of sugar intake from sweet food / beverages with mood disorders in Whitehall II

### *5.3.1 Cross-sectional association*

Cross-sectionally, sugar intake from sweet food / beverages was associated with increased odds of CMD in Whitehall II independent of socio-demographic factors, health behaviours and diet-related factors (see Table 25) and when additionally adjusted for measures of adiposity and disease status (OR per 30g per day increment: 1.06, 95%-CI: 1.01, 1.12; p=0.019). The association with depressive symptoms was attenuated when other dietary factors were included in the model.

Estimates found in age, sex and ethnicity adjusted models did not differ when analysed in a sample restricted to those with no missing data in socio-demographic factors, health behaviours and diet-related factors (not shown). There was no evidence for an interaction by sex (LR test p=0.65 for CMD and p=0.87 for depression), phase (LR test p=0.22 for CMD and p=0.81 for depression) and exclusion of those with extreme sugar intakes (>7 SD) did not change the results.

**Table 25 Cross-sectional association of sugar intake from sweet food / beverages and prevalent CMD and depression in men and women[a]**

| | | **Prevalent CMD, OR (95% CI)** | | |
|---|---|---|---|---|
| | events / person observations | Model 0[b] | Model 1[c] | Model 2[d] |
| Sugar intake from sweet food / beverages | | | | |
| Lowest Tertile | 1432 / 7934 | 1 (reference) | 1 (reference) | 1 (reference) |
| Middle Tertile | 1342 / 7075 | 1.09 (0.98, 1.22) | 1.12 (1.00, 1.25) | 1.09 (0.97, 1.21) |
| Highest Tertile | 1374 / 6585 | 1.23*** (1.10, 1.38) | 1.27*** (1.13, 1.44) | 1.19** (1.05, 1.35) |
| p for trend | | <.001 | <.001 | .006 |
| Continuous (30g/day increment) | 4148 / 21594 | 1.08** (1.03, 1.13) | 1.09*** (1.04, 1.14) | 1.06* (1.01, 1.11) |
| | | **Prevalent depression, OR (95% CI)** | | |
| Sugar intake from sweet food / beverages | | | | |
| Lowest Tertile | 459 / 3758 | 1 (reference) | 1 (reference) | 1 (reference) |
| Middle Tertile | 333 / 2990 | 1.05 (0.83, 1.32) | 0.97 (0.77, 1.23) | 0.90 (0.71, 1.14) |
| Highest Tertile | 349 / 2520 | 1.37* (1.07, 1.76) | 1.26 (0.98, 1.61) | 1.06 (0.82, 1.38) |
| p for trend | | .018 | .094 | .75 |
| Continuous (30g/day increment) | 1141 / 9268 | 1.19*** (1.09, 1.31) | 1.13* (1.03, 1.24) | 1.05 (0.95, 1.16) |

* p<.05, **p<.005, *** p<.001.
[a]Cross-sectional association across phases 3, 5, 7, 9 for CMD and 7, 9 for depression.
[b]CMD model 0 (4387 events / 22693 person observations), Depression model 0 (1200 events / 9578 person observations): adjusted for age, sex and their interaction and ethnicity.
[c]Model 1: additionally adjusted for marital status, last grade level in civil service, smoking, alcohol intake, physical activity, sleep duration.

[d]Model 2: additionally adjusted for energy intake from other foods, modified DASH diet score, fish, coffee, tea and fibre intake.

### *5.3.2 Prospective associations: Incidence*

Figure 11 gives an overview over prospective associations of sugar intake from sweet food / beverages with mood disorders in Whitehall II. In age, sex and ethnicity adjusted models sugar intake from sweet food / beverages was associated with incident CMD over 5-year cycles, but not after 2 and 10 years, with incident depression and clinical depression after 5 years. There was an inverse association between sugar intake from sweet food / beverages and incident depression in women over 5-year cycles and a positive association with incident clinical depression after 10 years in men.

There were significant differences by sex in the association of sugar intake from sweet food / beverages and incident CMD after 2 (LR test p=0.044), 5 years (LR test p=0.043), depression after 5 years (LR test p=0.050) and clinical depression after 10 years (LR test p=.004). There were no sex differences in associations with incident CMD and depression after 10 years (LR test for CMD after 10 years p=0.43, for depression after 10 years p=0.39) and clinical depression after 5 years (LR test p=0.37).

There were no significant differences by phase in the association of sugar intake from sweet food / beverages, incident CMD and depression (LR test for CMD after 2 years in men p=0.95, in women p=0.75, after 5 years in men p=0.97, in women p=0.83, after 10 years p=0.11, for depression after 5 years in men p=0.15, in women p=0.58, after 10 years p=0.91).

Age, sex and ethnicity adjusted associations between sugar intake from sweet food / beverages with incident mood disorders did not differ when analysed in samples restricted to those with no missing data in socio-demographic factors, health behaviours and diet-related factors (not shown).

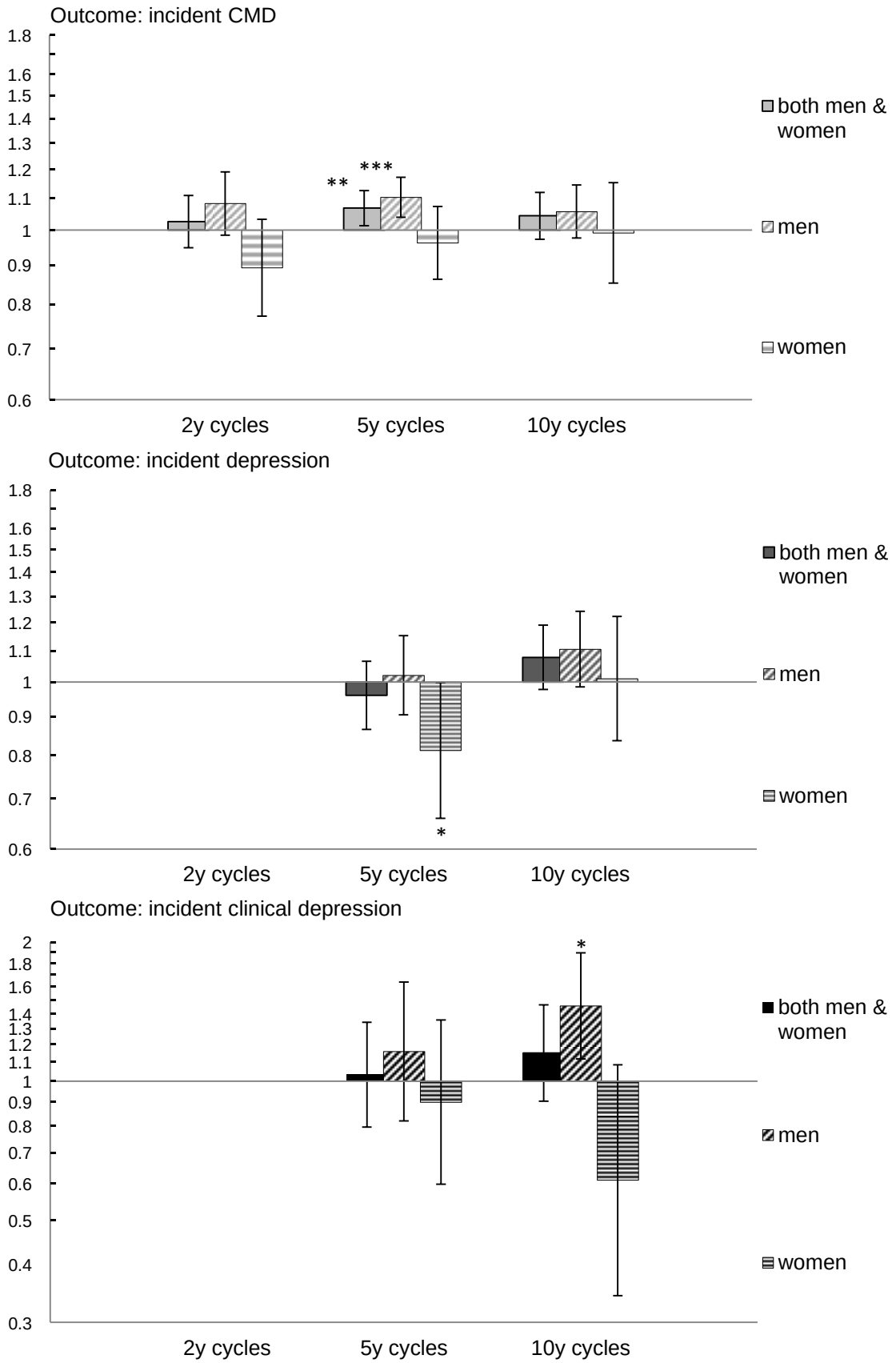



**Figure 11 Overview of odds ratios for incident mood disorders per 30g sugar intake from sweet food / beverages over 2, 5, 10-year cycles, adjusted for age, sex and ethnicity**

Sample sizes and data are presented in Table A 10.

* p<.05, **p<.005, *** p<.001.

### Associations with incident CMD

Sugar intake from sweet food / beverages was positively associated with CMD after 5 years in men (Table 26). Additional adjustment for adiposity, CVD, diabetes and cancer resulted in similar estimates (OR per 30g/day increment: 1.08, 95%-CI 1.01, 1.16). There was no association in women in base and adjusted models (OR for CMD after 5 years per 30g/day increment: 0.96, 95%-CI: 0.86, 1.07).

**Table 26 Prospective association of sugar intake from sweet food / beverages and incident CMD after 5 years in men[a]**

| | | Incident CMD after 5 years, OR (95% CI) | | |
|---|---|---|---|---|
| | events / person observations | Model 0[b] | Model 1[c] | Model 2[d] |
| Sugar intake from sweet food / beverages | | | | |
| Lowest Tertile | 450 / 4239 | 1 (reference) | 1 (reference) | 1 (reference) |
| Middle Tertile | 424 / 3783 | 1.05 (0.89, 1.23) | 1.06 (0.90, 1.25) | 1.04 (0.88, 1.23) |
| Highest Tertile | 447 / 3396 | 1.28** (1.08, 1.51) | 1.28** (1.08, 1.52) | 1.21* (1.01, 1.45) |
| p for trend | | .004 | .004 | .038 |
| Continuous (30g/day increment) | 1321 / 11418 | 1.10** (1.04, 1.17) | 1.10** (1.04, 1.17) | 1.08* (1.01, 1.15) |

* p<.05, **p<.005, *** p<.001.
[a]Prospective association across phases 3, 5 for 2-year and 3, 5, 7, 9 for 5-year incident CMD.
[b]5-year model 0 (1381 events / 11875 person observations): adjusted for age and ethnicity.
[c]Model 1: additionally adjusted for marital status, last grade level in civil service, smoking, alcohol intake, physical activity, sleep duration.
[d]Model 2: additionally adjusted for energy intake from other foods, modified DASH diet score, fish, coffee, tea and fibre intake.

Sensitivity analyses excluding person-observations with high sugar intakes and baseline antidepressant intake strengthened the results (Table A 10).

### Associations with incident depression

There was an inverse association between sugar intake from sweet food / beverages and CES-D depression in women (OR per 30g per day increment: 0.81, 95%-CI: 0.66, 1.00; p=.048; Table A 12) and no association in men (OR per 30g/day increment: 1.02, 95%-CI: 0.90, 1.15; p=.74). The association in women attenuated when additionally adjusted for socio-demographic factors (OR per 30g/day increment: 0.83, 95%-CI: 0.68, 1.02; p=.076) and when excluding person-observations with extreme sugar intakes (OR per 30g/day increment in models adjusted for age and ethnicity: 0.81, 95%-CI: 0.66, 1.00; p=.053).

**Associations with incident clinical depression**

There was no association with CIS-R after 5-years (OR per 30g per day increment, 1.03, 95%-CI: 0.79, 1.34), but there was an association after 10-years. Here it has to be noted that findings are based on very small case numbers (Table 27). When participants with baseline antidepressant intake were excluded the association in women remained significant in model 2 (OR per 30g per day increment, 0.42, 95%-CI: 020, 0.89), but was then based on 20 cases and 732 participants.

**Table 27 Association with clinical depression after 10 years by sex**

| | Incident clinical depression after 10year (events / participants) | | | |
|---|---|---|---|---|
| | Men (30 / 2374) | | Women (23 / 750) | |
| | OR (95% CI) | p | OR (95% CI) | p |
| Sugar intake from sweet food / beverages(30g/day increment) | | | | |
| Model 0[a] | 1.45* (1.12, 1.90) | .006 | 0.61 (0.34; 1.08) | .10 |
| Model 1[b] | 1.44 (1.10, 1.90) | .009 | 0.54 (0.29; 1.01) | .053 |
| Model 2[c] | 1.19 (0.88, 1.64) | .74 | 0.55 (0.28; 1.06) | .075 |

* p<.05, **p<.005, *** p<.001.

[a]Model 0 Men (30 cases / 2423 participants), Women (23 cases / 771 participants) adjusted for age, ethnicity (binary white, non-white).

[b]Model 1: Additionally adjusted for Marital status (binary married/cohabiting vs. other), last grade level in civil service, smoking, alcohol intake, physical activity, sleep duration (recoded 1-4), recoded due to avoid zero-cells.

[c]Model 2: Additionally adjusted for energy intake from other foods, modified DASH diet score, fish intake, coffee, tea and fibre intake.

### *5.3.3 Prospective associations: Recurrence*

Figure 12 depicts the association of sugar intake from sweet food / beverages with recurrent mood disorder. In models adjusted for age, sex and ethnicity there was no significant association with recurrent CMD, but depression and clinical depression after 5 years, not 10 years.

There was a statistical significant difference by sex in the association of sugar intake from sweet food / beverages and recurrent depression after 5 years (LR test p=0.003). Otherwise there were no sex differences in models for recurrent CMD and depression (LR test for CMD after 2 years p=0.44, after 5 years p=0.51, after 10 years p=0.31, for depression after 10 years p=0.79 and clinical depression after 5 years p=0.19 and 10 years p=0.41).

There were no significant differences by phase in the association of sugar intake from sweet food / beverages and recurrent CMD and depression (LR test for CMD after 2 years p=0.07, after 5 years p=0.45, after 10 years p=0.30, for depression after 5 years p=0.075, after 10 years p=0.95).

Age, sex and ethnicity adjusted associations between sugar intake from sweet food / beverages with recurrent mood disorders did not differ when analysed in samples restricted to those with no missing data in socio-demographic factors, health behaviours and diet-related factors (not shown).

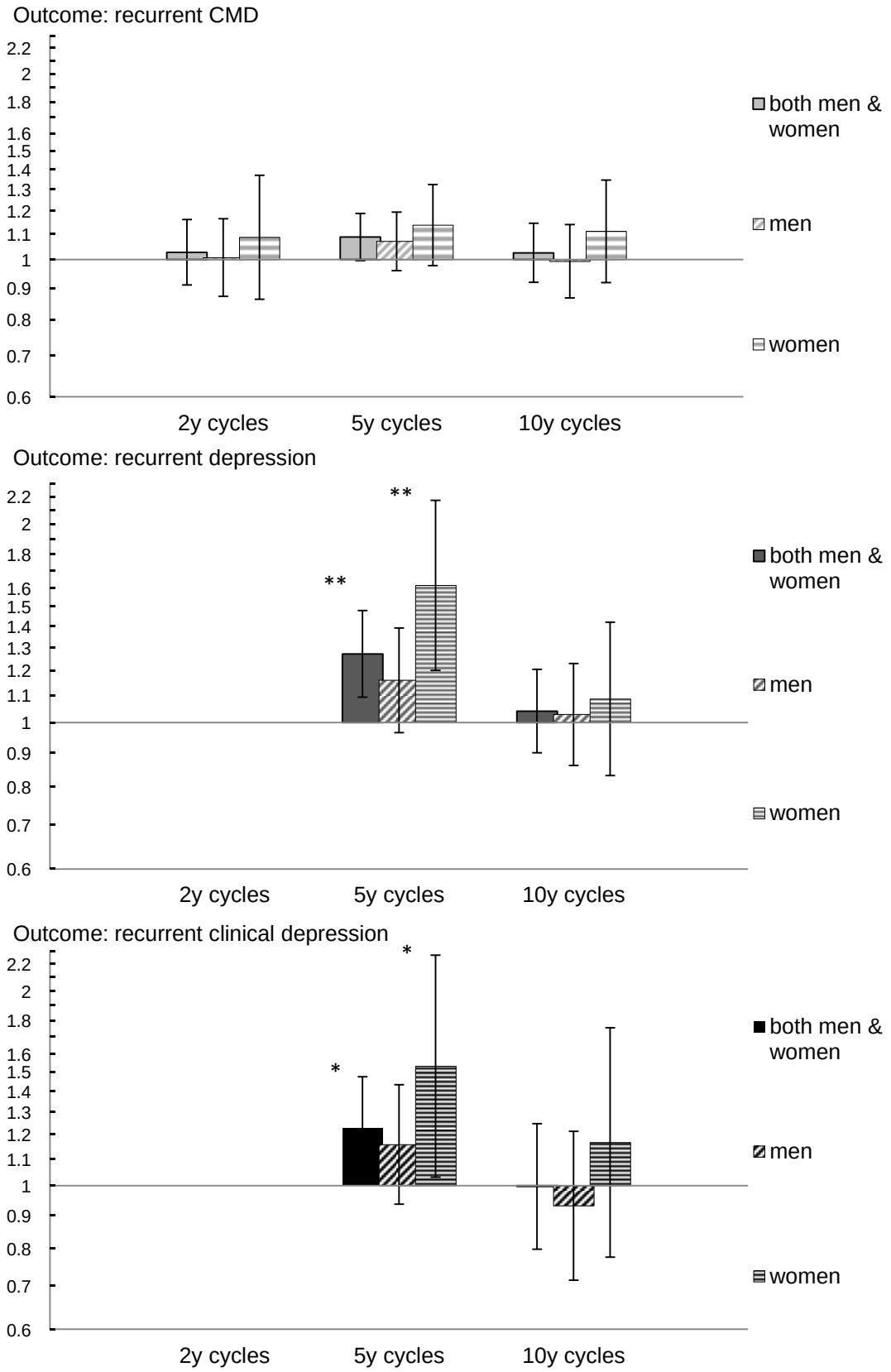



**Figure 12 Overview of odds ratios for recurrent mood disorder per 30g sugar intake from sweet food / beverages over 2, 5, 10-year cycles, adjusted for age, sex and ethnicity**

Sample sizes and data presented in Table A 13.

* p<.05, **p<.005, *** p<.001.

### Association with recurrent CMD

In base adjusted models sugar intake from sweet food / beverages was associated with increased odds for recurrent GHQ after 5 years (OR per 30g/day increment: 1.09, 95%-CI: 1.00, 1.19, p=0.062), but the association was entirely attenuated when other dietary factors were introduced in the model (Model 2, OR per 30g/day increment: 1.03, 95%-CI 0.94, 1.14).

### Association with recurrent depression

Sugar intake from sweet food / beverages was associated with recurrent depression after 5 years in women. However, there was an overall effect for both sexes and the association in men was in the same direction as associations in women (Table 28). Adjustment for diet-related factors attenuated the association. Further adjustment for adiposity (Model 3) and disease (Model 4) attenuated the association in women (Model 3, OR per 30g/day increment: 1.37, 95%-CI: 0.97, 1.94; p=0.074; Model 4: 1.36, 95%-CI: 0.96, 1.93; p=0.083). There were no women with extreme sugar intakes in this analysis.

**Table 28 Prospective association of sugar intake from sweet food / beverages and recurrent depression after 5 years[a]**

| | | Recurrent depression after 5 years, OR (95% CI)[b] | | |
|---|---|---|---|---|
| | events / person observations | Model 0[b] | Model 1[c] | Model 2[d] |
| **Women & Men** | | | | |
| Sugar intake from sweet food / beverages | | | | |
| Lowest Tertile | 230 / 775 | 1 (reference) | 1 (reference) | 1 (reference) |
| Middle Tertile | 207 / 694 | 1.30 (0.87, 1.94) | 1.19 (0.80, 1.79) | 1.16 (0.77, 1.75) |
| Highest Tertile | 246 / 678 | 1.86** (1.22, 2.82) | 1.68* (1.10, 2.57) | 1.56 (0.99, 2.44) |
| p for trend | | .004 | .017 | .055 |
| Continuous (30g/day increment) | 683 / 2147 | 1.27** (1.09, 1.48) | 1.23** (1.05, 1.43) | 1.19* (1.01, 1.41) |
| **Women** | | | | |
| Sugar intake from sweet food / beverages | | | | |
| Lowest Tertile | 75 / 235 | 1 (reference) | 1 (reference) | 1 (reference) |
| Middle Tertile | 65 / 212 | 1.02 (0.53, 1.95) | 1.03 (0.53, 2.00) | 1.04 (0.51, 2.10) |
| Highest Tertile | 106 / 240 | 2.54** (1.32, 4.91) | 2.36* (1.18, 4.71) | 2.14* (1.00, 4.57) |
| p for trend | | .005 | .014 | .052 |
| Continuous (30g/day increment) | 246 / 687 | 1.62** (1.20, 2.17) | 1.52** (1.11, 2.07) | 1.43* (1.02, 2.01) |
| **Men** | | | | |
| Sugar intake from sweet food / beverages | | | | |
| Lowest Tertile | 155 / 540 | 1 (reference) | 1 (reference) | 1 (reference) |
| Middle Tertile | 142 / 482 | 1.42 (0.85, 2.37) | 1.24 (0.73, 2.10) | 1.23 (0.71, 2.10) |
| Highest Tertile | 140 / 438 | 1.45 (0.83, 2.51) | 1.35 (0.76, 2.38) | 1.26 (0.69, 2.30) |
| p for trend | | .18 | .30 | .44 |
| Continuous (30g/day increment) | 439 / 1460 | 1.16 (0.97, 1.39) | 1.13 (0.93, 1.37) | 1.11 (0.90, 1.36) |

* p<.05, **p<.005, *** p<.001.

[a]Prospective association across phases 7, 9 for recurrent depression.

[b]Model 0 (724 events / 2246 person observations; in women 262 events / 723 person observations and in men 462 events / 1523 person-observations) adjusted for age, sex and their interaction and ethnicity.

[c]Model 1: additionally adjusted for marital status, last grade level in civil service, smoking, alcohol intake, physical activity, sleep duration.

[d]Model 2: additionally adjusted for energy intake from other foods, modified DASH diet score, fish, coffee, tea and fibre intake.

### Associations with recurrent clinical depression

Continuous sugar intake from sweet food / beverages was associated with increased odds with recurrent depression measured using CIS-R (Table 29). Associations attenuated when adjusted for socio-demographic and health behaviours. The initial association was also attenuated when those with extreme intakes were excluded (Model 0: OR per 30g/day increment: 1.20, 95%-CI: 0.98, 1.46, p=0.075).

**Table 29 Prospective association of sugar intake from sweet food / beverages and recurrent clinical depression after 5 years[a]**

| | Recurrent clinical depression after 5 years (81 events / 557 participants) | |
|---|---|---|
| | OR (95% CI) | p |
| Sugar intake from sweet food / beverages (30g/day increment) | | |
| Model 0[b] | 1.23 (1.02, 1.47)* | .029 |
| Model 1[c] | 1.19 (0.97, 1.45) | .091 |
| Model 2[d] | 0.99 (0.76, 1.29) | .92 |

* p<.05, **p<.005, *** p<.001.
[a]Prospective association across phase 9 to 11.
[b]Clinical depression model 0 (88 events / 589 participants): adjusted for age age, sex and their interaction and ethnicity.
[c]Model 1: additionally adjusted for marital status, last grade level in civil service, smoking, alcohol intake, physical activity, sleep duration.
[d]Model 2: additionally adjusted for energy intake from other foods, modified DASH diet score, fish, coffee, tea and fibre intake.

### *5.3.4 Mood disorders and change in sugar intake from sweet food / beverages*

From phase 3 to 5 sugar intake from sweet food / beverages decreased by 2.18g per day (SD 28.6; 95% CI 1.36, 3.01), from phase 5 to 7 by 3.26g per day (SD 28.0; 95% CI 2.35, 4.17) and from phase 7 to 9 by 1.51g per day (SD 25.8; 95% CI 0.71, 2.32). Sugar intake change was normally distributed (Figure A 1, Figure A 2). Mean 5-year change was approximately 31g sugar from sweet food / beverages per day in the decrease group, -0.8g in the stable intake group and 28g in the increase group.

Table 30 shows the association of mood disorders with 5-year change in sugar intake from sweet food / beverages and the chance of not changing or increasing sugar intake as compared to increasing sugar intake. Neither CMD, nor depression predicted 5-year changes in sugar intake (Table 30).

**Table 30 Association of CMD and depression with subsequent 5-year change in sugar intake from sweet food / beverages**

| | 5-year change in intake from sweet food / beverages | | | |
|---|---|---|---|---|
| | Events | Participants | OR (95% CI) *β-Coefficient*[a] *(95% CI)* | p |
| **CMD** | | | | |
| **At phase 3 – Sugar intake from sweet food / beverages change: phase 3 to 5** | | | | |
| Reduction | 237 | 1091 | 1 (reference) | |
| No change | 544 | 2649 | 0.95 (0.80, 1.13) | 0.57 |
| Increase | 177 | 883 | 0.91 (0.73, 1.14) | 0.43 |
| Continuous change in grams per day | 958 | 4623 | *0.18 (-1.86, 2.23)* | 0.86 |
| **At phase 5 – Sugar intake from sweet food / beverages change: phase 5 to 7** | | | | |
| Reduction | 175 | 870 | 1 (reference) | |
| No change | 401 | 2116 | 0.93 (0.76, 1.14) | 0.49 |
| Increase | 149 | 619 | 1.25 (0.97, 1.61) | 0.08 |
| Continuous change in grams per day | 725 | 3605 | *1.29 (-1.02, 3.60)* | 0.27 |
| **At phase 7 – Sugar intake from sweet food / beverages change: phase 7 to 9** | | | | |
| Reduction | 176 | 819 | 1 (reference) | |
| No change | 433 | 2383 | 0.83 (0.68, 1.01) | 0.06 |
| Increase | 133 | 736 | 0.83 (0.64, 1.07) | 0.15 |
| Continuous change in grams per day | 855 | 3938 | *-0.99 (-3.06, 1.09)* | 0.35 |
| **Depression** | | | | |
| **At phase 7 – Sugar intake change from sweet food / beverages: phase 7 to 9** | | | | |
| Reduction | 104 | 765 | 1 (reference) | |
| No change | 291 | 2266 | 0.97 (0.76, 1.24) | 0.82 |
| Increase | 84 | 688 | 0.92 (0.68, 1.26) | 0.62 |
| Continuous change in grams per day | 479 | 3719 | *0.88 (-1.62, 3.38)* | 0.49 |

[a]Change in sugar intake in cases compared with non-cases, adjusted for age, sex and ethnicity.

Associations did not differ by sex (LR test p>0.40) and for socio-demographic factors and health behaviours did not change the associations (not shown). Excluding participants with extreme sugar intakes at baseline and follow-up phases did not change conclusions (Table A 12).

## 5.4 Analyses B: Association of sugar intake from sweet food / beverages with antidepressant intake in EPIC-Norfolk & Whitehall II

### *5.4.1 Prospective association with antidepressant intake*

Table 31 presents the association of sugar intake from sweet food / beverages and incident antidepressant intake in Whitehall II after 5 years and EPIC-Norfolk after approximately 4 years. In men, there was a positive association of sugar intake from sweet food / beverages and antidepressant intake in Whitehall II, however the association did not show a clear trend but rather an increased in odds in tertiles 2 and 3 compared to tertile 1. Associations failed to reach statistical significance in some models based on operationalization and degree of adjustment. There was a smaller positive association of sugar intake from sweet food / beverages and antidepressant intake in men in the EPIC-Norfolk study, but the associations were not statistically significant. Associations in the minimally adjusted model did not differ when analysed in samples restricted to those with no missing data in covariates included in the final model.

**Table 31 Association of sugar intake from sweet food / beverages and antidepressant intake in men in Whitehall II[a] & EPIC-Norfolk**

| | | **Whitehall II: Antidepressant intake, OR (95% CI)** | | |
|---|---|---|---|---|
| | events / person observations | Model 0[b] | Model 1[c] | Model 2[d] |
| Sugar intake from sweet food / beverages | | | | |
| Lowest Tertile | 42 / 3687 | 1 (reference) | 1 (reference) | 1 (reference) |
| Middle Tertile | 64 / 3120 | 2.20** (1.32, 3.65) | 2.04** (1.24, 3.36) | 1.98** (1.20, 3.25) |
| Highest Tertile | 54 / 2661 | 2.19** (1.27, 3.78) | 2.04** (1.19, 3.48) | 1.88* (1.08, 3.28) |
| p for trend | | 0.005 | 0.009 | 0.024 |
| Continuous (30g/day increment) | 160 / 9468 | 1.22* (1.03, 1.44) | 1.20* (1.01, 1.42) | 1.15 (0.96, 1.38) |
| | | **EPIC-Norfolk: Antidepressant intake, OR (95% CI)** | | |
| Sugar intake from sweet food / beverages | | | | |
| Lowest Tertile | 42 / 2022 | 1 (reference) | 1 (reference) | 1 (reference) |
| Middle Tertile | 54 / 2008 | 1.31 (0.87, 1.97) | 1.33 (0.88, 2.00) | 1.35 (0.89, 2.04) |
| Highest Tertile | 54 / 2035 | 1.36 (0.91, 2.05) | 1.34 (0.88, 2.04) | 1.40 (0.90, 2.18) |
| p for trend | | 0.14 | 0.17 | 0.14 |
| Continuous (30g/day increment) | 150 / 6065 | 1.07 (0.96, 1.18) | 1.06 (0.96, 1.18) | 1.07 (0.96, 1.20) |

* p<.05, **p<.005, *** p<.001.
[a]Association across phases 5, 7, 9.
[b]Model 0 (Whitehall II: 163 events / 9782 person observations; EPIC-Norfolk: 152 events / 6259 person observations): adjusted for age, ethnicity (in Whitehall II).
[c]Model 1: additionally adjusted for marital status, last grade level in civil service/social class, smoking, alcohol intake, physical activity.
[d]Model 2: additionally adjusted for energy intake from other foods, modified DASH diet score,

fish, coffee and tea intake.

Figure 13 depicts the meta-analysed associations between sugar intake from sweet food / beverages and incident antidepressant intake in men in Whitehall II and EPIC-Norfolk in models adjusted for age, ethnicity (in Whitehall II), socio-demographic factors, health behaviours and diet-related factors. While all the associations were positive, only the association per tertile of sugar intake from sweet food / beverages reached statistical significance. Associations were slightly changed when further adjusted for adiposity, diabetes, CVD and cancer resulting in a higher estimate for the 3rd tertile as compared to the 2nd tertile compared to the lowest in Whitehall II Figure A 3.

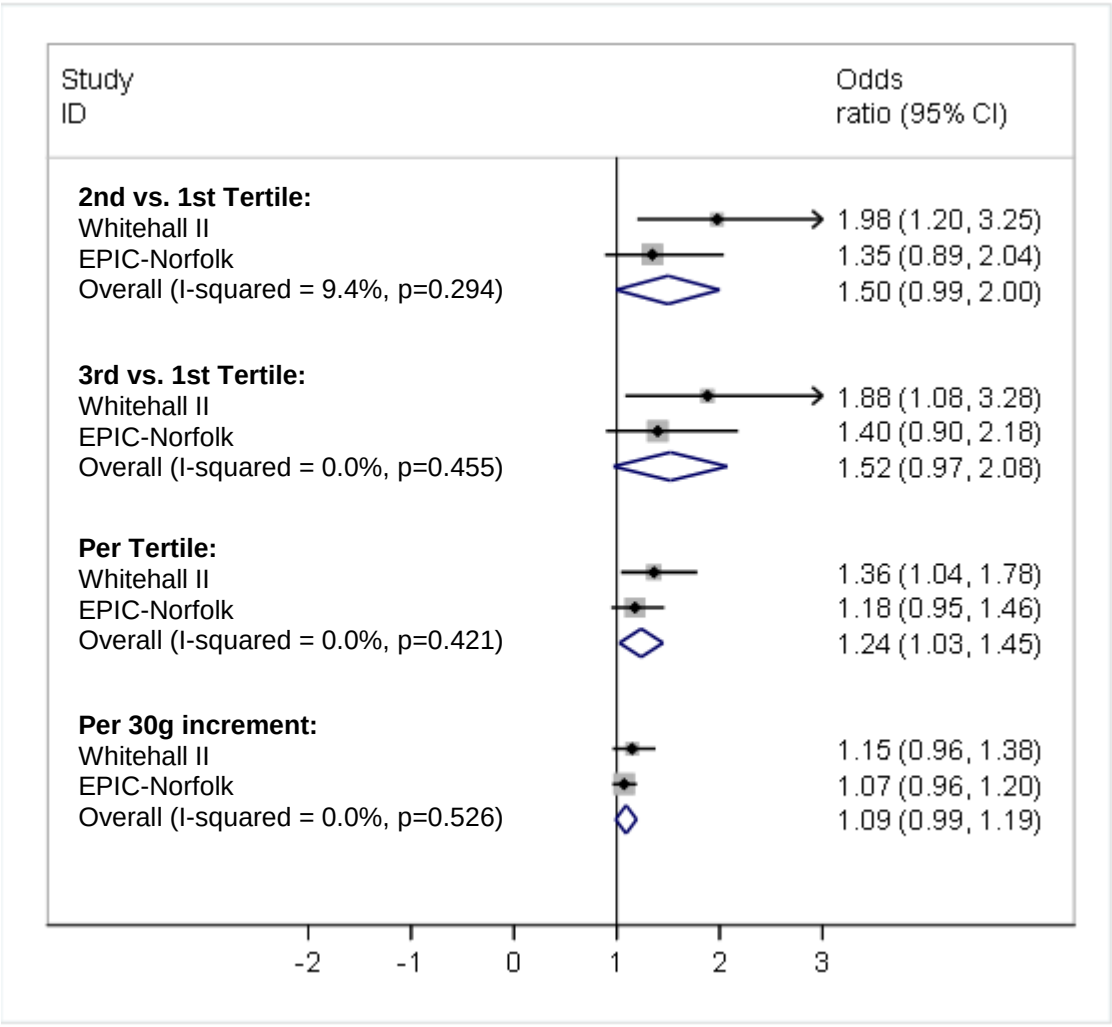



**Figure 13 Association of sugar intake from sweet food / beverages with incident antidepressant intake in men**
2nd vs 1st, 3rd vs 1st, Tertile trend, adjusted for age, ethnicity (in Whitehall II), socio-demographic factors, health behaviours and diet-related factors.

Figure 14 depicts associations in women. There was no association between sugar intake from sweet food / beverages with incident antidepressant intake in women. Associations did not change when further adjusted for adiposity, diabetes, CVD and cancer (not shown).

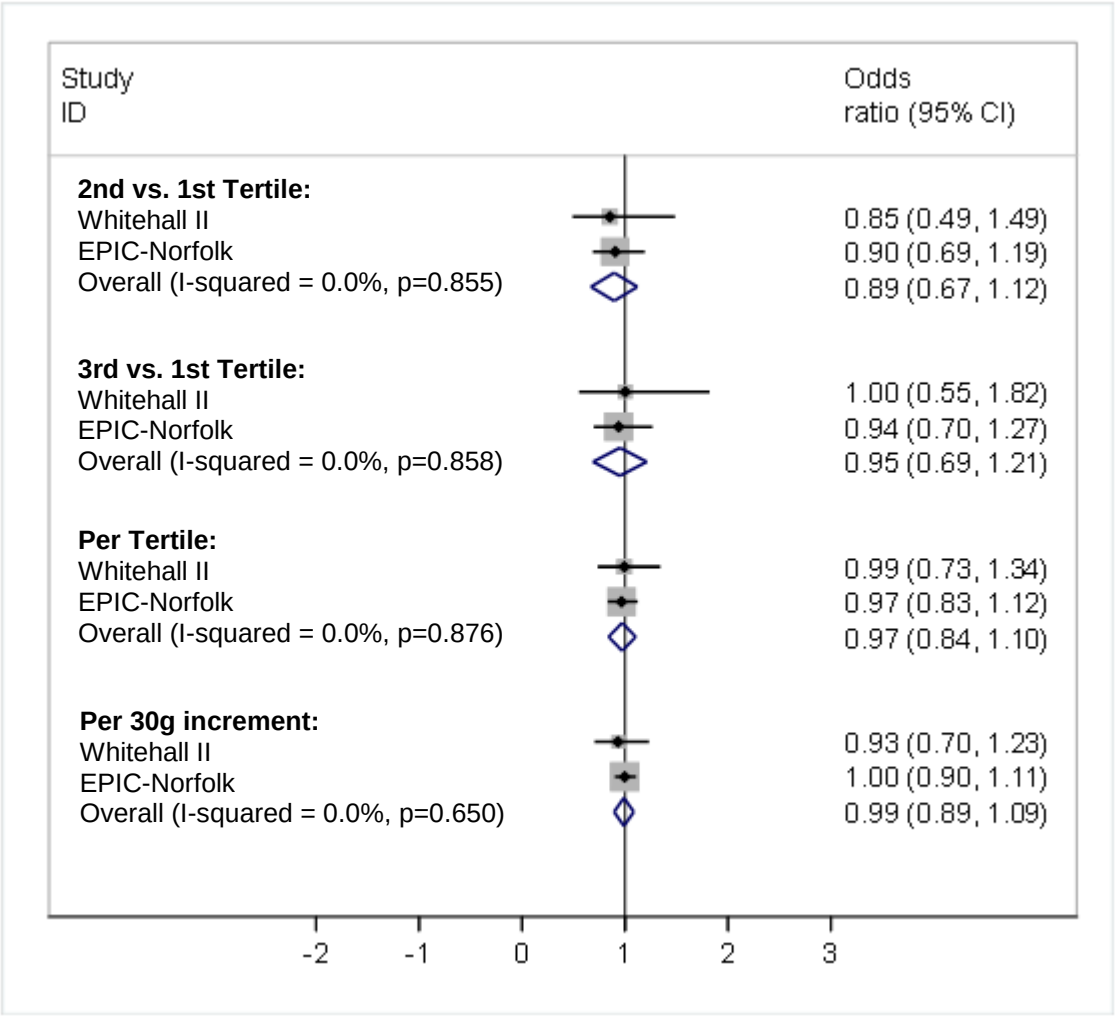



**Figure 14 Association of sugar intake from sweet food / beverages with incident antidepressant intake in women**
$2^{nd}$ vs 1st, $3^{rd}$ vs $1^{st}$, Tertile trend, adjusted for age, ethnicity (in Whitehall II), socio-demographic factors, health behaviours and diet-related factors.

### *5.4.2 Antidepressant intake and change in sugar intake from sweet food/beverages*

There was no association of antidepressant intake with change in sugar intake in either study, suggesting that there was no reverse effect (Table 32). There were no sex-differences between these associations.

**Table 32 Association of antidepressant intake with change in sugar intake from sweet food / beverages**

| Antidepressant intake | **5-year change in intake from sweet food / beverages** | | | |
|---|---|---|---|---|
| | Events | Participants | OR (95% CI) *β-Coefficient*[a] *(95% CI)* | p |
| **Whitehall II study** | | | | |
| **At phase 5 – Sugar intake from sweet food / beverages change: phase 5 to 7** | | | | |
| Reduction | 28 | 967 | 1 (reference) | |
| No change | 55 | 2297 | 0.84 (0.53, 1.32) | 0.45 |
| Increase | 16 | 690 | 0.71 (0.42, 1.45) | 0.42 |
| Continuous change in grams per day | 99 | 3954 | *-0.22 (-5.84, 5.40)* | 0.94 |
| **At phase 7– Sugar intake from sweet food / beverages change: phase 7 to 9** | | | | |
| Reduction | 24 | 857 | 1 (reference) | |
| No change | 79 | 2486 | 1.14 (0.71, 1.81) | 0.58 |
| Increase | 25 | 769 | 1.16 (0.66, 2.06) | 0.60 |
| Continuous change in grams per day | 128 | 4112 | *0.58 (-3.97, 5.12)* | 0.80 |
| **EPIC-Norfolk study** | | | | |
| **At HC1 – Sugar intake from sweet food / beverages change: phase HC1 to HC2** | | | | |
| Reduction | 100 | 2617 | 1 (reference) | |
| No change | 232 | 6865 | 0.88 (0.69, 1.12) | 0.31 |
| Increase | 93 | 2091 | 1.16 (0.87, 1.54) | 0.33 |
| Continuous change in grams per day | 425 | 11573 | *2.28 (-1.04, 5.61)* | 0.18 |

[a]Change in sugar intake in cases compared with non-cases, adjusted for age, sex and ethnicity.

## 5.5 Interim discussion and summary

The current chapter addressed objective I, whether a diet high in sugar from sweet food and beverages was a risk factor in mood disorders and whether mood disorders affect change in habitual sugar intake from sweet food / beverages. An analysis in Whitehall II confirmed a positive association of sugar intake from sweet food / beverages on incident mood disorders in men but not in women with evidence of a sex interaction. To further investigate this paradox, a replication study was conducted using antidepressant intake in Whitehall II and EPIC-Norfolk, a population sample. Meta-analyses of the two studies showed similar sex differences and a positive trend between sugar intake from sweet food / beverages and incident antidepressant intake in men. In neither Whitehall II nor EPIC-Norfolk was there any evidence for reverse causation.

**Analyses A: Association of sugar intake from sweet food / beverages with CMD and depression in Whitehall II**

We conducted REMs over 20 years to investigate the association of sugar intake from sweet food / beverages in Whitehall II. Higher sugar intake from sweet food / beverages was associated with prevalent CMD in men and women independent of socio-demographic factors, health behaviours, diet-related factors, adiposity and CVD, diabetes and cancer. Associations with depression could be explained by other dietary factors. This cross-sectional association was consistent with previous literature (Chamberlain, Redden & Grant, 2017; El Ansari, Adetunji & Oskrochi, 2014; Jeffery *et al.*, 2009; Shi *et al.*, 2010; Yu *et al.*, 2014).

Prospectively sugar intake from sweet food / beverages was associated with incident CMD after 5 years in men but not in women. There was no association with incident depression and no association with clinical depression after 5 years. There was an increased chance for incident clinical depression after 10 years in men before adjustment for energy intake. A positive association between sugary foods, drinks and added sugars was in line in previous research (Guo *et al.*, 2014; Sanchez-Villegas *et al.*, 2012, 2017; Gangwisch *et al.*, 2015). However, they did not find differences between men and women or were based on women only (Guo *et al.*, 2014; Sanchez-Villegas *et al.*, 2017; Gangwisch *et al.*, 2015).

Sugar intake from sweet food / beverages was associated with increased chance of recurrent CMD, depression and clinical depression after 5 years. Associations with recurrent CMD and clinical depression could be entirely explained by confounding factors. The association with recurrent depression differed significantly by sex, but both

men and women showed a positive association between sugar intake from sweet foods / beverages and recurrent depression. Associations in women remained significant upon adjustment for socio-demographic factors, health behaviours, diet-related factors, but attenuated after adjustment for BMI and central obesity suggesting that weight changes might lie on the pathway between sugar intake from sweet food / beverages and recurrent mood disorder. We found no prospective cohort studies investigating the particular role of sugar-dense diets with recurrent depression. A randomised controlled trial in 67 participants with moderate to severe depression in Australia found that a dietary intervention that recommended, among other dietary changes a reduction of sweets and refined drinks led to a reduction of anxiety and depressive symptoms as well as remission of depression (in 1/3 in the intervention group) when compared to a social support control intervention (8% in the control group) (Jacka *et al.*, 2017).

There was no evidence for reverse causation. Neither baseline CMD nor prevalent CES-D caseness were associated with a subsequent change in sugar intake from sweet food / beverages. To date, no studies prospectively investigated the association between mood disorders and subsequent change in sugar-dense food or drinks were found (see Chapter 2: 2.6.3).

Table 33 summarises the results of all analysis modes.

**Table 33 Summary of associations between sugar intake from sweet food / beverages and three measures of mood disorder in Whitehall II**

| Analysis A | CMD | CES-D Depression | CIS-R Depression | Summary |
|---|---|---|---|---|
| **Exposure: Sugar intake from sweet food / beverages** | | | | |
| **Cross-sectional** | √ | X | N/A | Associated with CMD |
| **Prospective** | | | | |
| Incident mood disorder | | | | Associated with CMD after 5years in men. |
| after 2 years | X | X | N/A | |
| after 5 years | M: √; W: X | X | X | |
| after 10 years | X | X | X | |
| Recurrent mood disorder | | | | Associated with CES-D depression after 5years in women. |
| after 2 years | X | N/A | N/A | |
| after 5 years | X | M: X; W: √ | X | |
| after 10 years | X | X | X | |
| **Exposure: Mood disorder** | | | | |
| Change in sugar intake from sweet food / beverages | X | X | N/A | Not associated. |

√=associated in final model; X=not associated in final model; N/A=not available; Brackets mark limitations.

**Analyses B: Association of sugar intake from sweet food / beverages with antidepressant intake in EPIC-Norfolk and Whitehall II**

The second study aimed to investigate the sex difference found in the association between sugar intake from sweet food / beverages and CMD in men. Therefore, data from Whitehall II was reanalysed using REM and antidepressant intake as outcome measure. EPIC-Norfolk data were analysed similarly. In both studies there was a positive but non-significant association between high sugar intake from sweet food and beverages and incident antidepressant intake in men. Meta-analyses showed evidence for a positive trend but non-significant associations by tertile and for 30g increments. In both studies there was no association between sugar intake from sweet food / beverages in women.

There was no evidence that antidepressant intake increased habitual sugar intake from sweet food and beverages in Whitehall II and EPIC-Norfolk.

Table 34 summarises the results.

**Table 34 Summary of associations between sugar intake from sweet food / beverages and incident antidepressant intake in Whitehall II, EPIC Norfolk and meta-analyses of both studies**

| Analysis B | Antidepressant intake | Summary |
|---|---|---|
| **Exposure: Sugar intake from sweet food / beverages** | | |
| **Prospective** | | |
| Incident Antidepressant intake after 5/3.5 years | | Associated in Whitehall II and in meta-analysis in men, but restricted to per tertile estimate. |
| **Whitehall II** | M: (√); W: X | |
| **EPIC Norfolk** | M: X; W: X | |
| **Meta-analysis** | M: (√); W: X | |
| **Exposure: Mood disorder** | | |
| **C**hange in sugar intake from sweet food / beverages | X | Not associated. |
| | | |

√=associated in final model; X=not associated in final model; N/A=not available; Brackets mark limitations.

In sum, this chapter found some evidence for sugar intake from sweet food / beverages increase chances for mood disorders.

# Chapter 6 **Objective II: Is a diet high in fibre intake a protective factor in mood disorders?**

This chapter presents associations of fibre intake and mood disorders in the Whitehall II cohort study. The association of fibre intake with three measures of mood disorder was assessed cross-sectionally and prospectively.

## 6.1 Methods

### *6.1.1 Study sample*

Whitehall II was described in chapter 4.1.

### *6.1.2 Dietary fibre intake*

Diet data were based on FFQs (see Chapter 4: 4.2.1, Appendices relating to Chapter 4: Appendix 1). Fibre intake was derived from all foods included in the FFQ. Fibre content was based on *'McCance and Widdowson's composition of foods, 5th edition'* (Holland *et al.*, 1991). When validated against a 7-day diet diary at phase 3 spearman rank correlations for energy adjusted fibre intake was 0.60 in women and 0.62 in men, quartile agreement was 43% in women and 47% in men and 1 and 2% were misclassified to extreme quartiles (Brunner *et al.*, 2001).

### *6.1.3 Mood disorder assessment*

For this chapter mood disorders from Whitehall II were assessed using GHQ, CES-D and CIS-R questionnaire data (a detailed description can be found in Chapter 4, 4.2.2). GHQ caseness will henceforth be referred to as CMD, CES-D caseness as depression and CIS-R depression caseness as clinical depression.

### *6.1.4 Confounders*

Description of confounders can be found in Chapter 4: 4.3. Socio-demographic factors included last grade level in the civil service and marital status; health behaviours included physical activity, alcohol consumption, smoking and sleep duration; measures of adiposity included BMI and central obesity and physical health included diabetes, CVD and cancer.

### *6.1.5 Dietary confounders*

To adjust for energy intake the residual method was used as fibre does not contribute any meaningful number of calories but is correlated with amount of food consumed (Pearson r 0.64 at phase 3). Residuals from a model using total calorie intake as exposure were calculated and added to the mean fibre intake per 2200 kcal in men and per 1900 kcal in women (Willett & Stampfer, 1986). Additionally, fish intake,

categorised as quintiles of intake per day, the modified DASH diet score, coffee and tea intake, sugar intake from sweet food / beverages and a sugar intake from sweet food / beverages by sex interaction were included as covariates.

### *6.1.6 Statistical analysis*

Interactions with sex and data collection phase were tested using LR test in the initial model (Model 0: adjusted for age, sex and ethnicity). Further adjustments were grouped into four hierarchical models: baseline socio-demographic factors and health behaviours (Model 1), diet-related factors (Model 2), BMI and central obesity (Model 3), and physical health (Model 4), all models were energy adjusted. Models 0 to 2 are considered to include confounding factors and Models 3 and 4 factors that could both confound or mediate the association. Model 2 was therefore considered the final model.

Inclusion criteria and flow diagram can be found in Chapter 4: 4.4, Figure 6. The results of the initial age, sex and ethnicity adjusted model are presented in the maximum eligible sample; following models are restricted to those with no missing data in the final model. Estimates from the initial model in the maximum sample were compared to estimates in the reduced sample and reported when different.

Energy adjusted fibre intake was modelled both continuously and expressed per 10g which was close to the standard deviation (SD of non-adjusted fibre intake in phase 3 / 5 / 7 / 9: 9.82 / 10.36 / 10.06 / 9.76) as well as tertiles based on the distribution at phase 3 (≤22, >22 to ≤28 and >28g/day). The association of energy adjusted fibre intake with baseline characteristics of the sample at phase 3 were compared using descriptive statistics.

REM were performed using the Stata 14 (StataCorp., 2015) command *xtlogit* (Twisk, 2004) with fibre intake at phases 3, 5, 7 and 9 as the exposure and CMD and depression as outcomes. To assess the applicability of the REM model across the phases, interactions by collection phase were tested using LR test. The prospective effects were examined using REM in 2, 5 and 10-year cycles and by restricting the outcomes as incident and recurrent cases (Brunner *et al.*, 2014). This mode of analysis is presented in chapter 4.5.

Finally, linear and multinomial regression models of 5-year change in fibre intake, energy adjusted and non-adjusted were fitted for each cycle, from phases 3 to 5, 5 to 7 and 7 to 9, with CMD at phases 3, 5, 7 and depression at phase 7, respectively.

In sensitivity analyses, the main analyses were repeated by: (a) excluding participants with extreme values of fibre intake (>7 SD) at phases 3/ 5/ 7 / 9: n=12 / 18 / 19 / 15 individuals respectively) and (b) excluding participants with unknown or reported doctor diagnosis of depression at each baseline (at phases 3/ 5/ 7 / 9: n=164 / 124 / 166 / 197) in models concerning incidence.

## 6.2 Descriptive results

Mean fibre intake was 25.6 g/day (SD 9.8) at phase 3, 26.6 (SD 10.4) at phase 5, 26.6 (SD 10.1) at phase 7 and 25.8 (SD 9.8) at phase 9. At phase 3, energy adjusted fibre intake was higher in men and in those who were, 50 years and older, married or cohabiting, in higher last grade level in the Civil service, took more vigorous physical activity, consumed no or moderate alcohol intake, slept for more hours, had higher energy intakes, with a higher diet quality, fish intake and lower sugar intake from sweet food / beverages, high BMI, without central obesity and had diabetes and CVD (see Table 35).

The associations were similar using tertiles of fibre intake but showed no statistically significant association with sleep duration, central obesity in men or diabetes.

Most factors showed similar associations with fibre intake across phases 5, 7 and 9 (Table A 15). However, grade level was not associated with fibre intake at phases 5 and 9, and marital status and tea/coffee intake were not associated at phase 5. Sleep duration and CVD were only associated at phase 9, and central obesity only associated at phases 7 and 9.

**Table 35 Crude association of energy adjusted fibre intake and covariates at phase 3**

| Covariates at phase 3 | | **Fibre intake, grams** | | **Fibre intake, %** | | | |
|---|---|---|---|---|---|---|---|
| | n | Mean ± SD | p | Tertile 1 | Tertile 2 | Tertile 3 | p |
| Sex | | | <.001 | | | | <.001 |
| Men | 5486 | 26.0 ± 7.39 | | 64.9 | 70.2 | 73.3 | |
| Women | 2412 | 24.8 ± 7.82 | | 35.1 | 29.8 | 26.7 | |
| Age | | | .012 | | | | .031 |
| <50 years | 4155 | 25.4 ± 7.47 | | 53.8 | 53.5 | 50.5 | |
| ≥50 years | 3743 | 25.9 ± 7.61 | | 46.2 | 46.5 | 49.5 | |
| Ethnic Group | | | .002 | | | | .003 |
| White | 7294 | 25.6 ± 7.47 | | 93.6 | 91.4 | 92.0 | |
| South Asian | 365 | 26.9 ± 7.67 | | 3.34 | 5.63 | 4.91 | |
| Black | 239 | 26.2 ± 9.21 | | 3.04 | 2.95 | 3.09 | |
| Marital Status | | | <.001 | | | | <.001 |
| Married/cohabiting | 6063 | 25.8 ± 7.41 | | 73.8 | 78.4 | 78.4 | |
| Single | 1136 | 25.0 ± 7.67 | | 16.3 | 13.2 | 13.7 | |
| Divorced/widowed | 690 | 25.1 ± 8.40 | | 9.91 | 8.39 | 7.93 | |
| Last grade level in Civil service | | | <.001 | | | | <.001 |
| Highest | 3064 | 26.0 ± 7.22 | | 35.8 | 38.9 | 41.8 | |
| Intermediate | 3548 | 25.6 ± 7.39 | | 45.7 | 44.6 | 44.5 | |
| Lowest | 1286 | 24.9 ± 8.59 | | 18.6 | 16.5 | 13.8 | |
| Smoking | | | <.001 | | | | <.001 |
| Never Smoker | 3438 | 26.3 ± 7.39 | | 41.3 | 46.7 | 51.1 | |
| Ex-Smoker | 2901 | 26.0 ± 7.56 | | 36.6 | 40.3 | 40.4 | |
| Current Smoker | 1086 | 22.5 ± 7.22 | | 22.1 | 13.0 | 8.59 | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Physical activity | | | <.001 | | | | <.001 |
| Non/mild | 2948 | 25.0 ± 7.52 | | 41.9 | 35.5 | 34.4 | |
| Moderate | 3505 | 25.6 ± 7.11 | | 42.9 | 45.5 | 44.8 | |
| Vigorous | 1445 | 26.9 ± 8.40 | | 15.2 | 19.0 | 20.8 | |
| Alcohol consumption | | | <.001 | | | | <.001 |
| None | 1852 | 26.5 ± 8.43 | | 20.9 | 23.2 | 26.4 | |
| Moderate | 4138 | 26.1 ± 7.25 | | 47.1 | 53.8 | 56.4 | |
| Heavy | 1900 | 23.8 ± 6.93 | | 32.0 | 22.9 | 17.2 | |
| Sleep duration | | | .012 | | | | .140 |
| less than 7 h/day | 1999 | 25.3 ± 7.45 | | 26.6 | 25.3 | 24.2 | |
| ≥ 7 h/day | 5889 | 25.8 ± 7.57 | | 73.4 | 74.7 | 75.8 | |
| Energy intake | | | .002 | | | | <.001 |
| < median | 3899 | 25.4 ± 6.53 | | 48.7 | 55.4 | 44.0 | |
| > median | 3999 | 25.9 ± 8.41 | | 51.3 | 44.6 | 56.0 | |
| Modified DASH diet score | | | <.001 | | | | <.001 |
| < median | 4447 | 22.5 ± 6.16 | | 86.5 | 53.5 | 28.6 | |
| > median | 3447 | 29.7 ± 7.24 | | 13.5 | 46.5 | 71.4 | |
| Fish intake | | | <.001 | | | | <.001 |
| < median | 4486 | 25.2 ± 7.41 | | 60.1 | 57.9 | 52.3 | |
| > median | 3412 | 26.2 ± 7.68 | | 39.9 | 42.1 | 47.7 | |
| Tea / coffee | | | .001 | | | | .085 |
| ≤ 1 cup of either/day | 690 | 26.6 ± 8.11 | | 7.82 | 8.88 | 9.52 | |
| > 1 cup of either/day | 7208 | 25.6 ± 7.48 | | 92.2 | 91.1 | 90.5 | |
| Sugar intake | | | <.001 | | | | <.001 |
| 1st Tertile | 2618 | 27.2 ± 7.48 | | 25.1 | 34.6 | 39.8 | |
| 2nd Tertile | 2608 | 25.8 ± 6.96 | | 30.7 | 35.9 | 32.5 | |
| 3rd Tertile | 2672 | 24.0 ± 7.80 | | 44.2 | 29.5 | 27.7 | |
| BMI | | | <.001 | | | | <.001 |
| Normal, <25kg/m2 | 3953 | 26.0 ± 7.61 | | 50.3 | 51.3 | 56.2 | |
| Overweight, 25-29.9kg/m2 | 2847 | 25.3 ± 7.09 | | 39.3 | 38.6 | 35.7 | |
| Obese. ≥30kg/m2 | 715 | 25.2 ± 8.62 | | 10.4 | 10.0 | 8.1 | |
| Central obesity (M/W) | | | .036 | | | | .063 |
| No | 6784 | 25.7 ± 7.40 | | 90.1 | 91.5 | 92.0 | |
| Yes (Waist ≥102/ 88 cm) | 656 | 25.1 ± 8.73 | | 9.9 | 8.5 | 8.0 | |
| Diabetes | | | .009 | | | | .054 |
| No | 7680 | 25.6 ± 7.52 | | 97.5 | 97.6 | 96.6 | |
| Yes | 218 | 27.0 ± 8.12 | | 2.48 | 2.41 | 3.39 | |
| CVD | | | <.001 | | | | .001 |
| No | 7630 | 25.6 ± 7.53 | | 97.5 | 96.6 | 95.7 | |
| Yes | 268 | 27.2 ± 7.67 | | 2.48 | 3.41 | 4.30 | |
| Cancer | | | .70 | | | | .887 |
| No | 7789 | 25.7 ± 7.53 | | 98.6 | 98.8 | 98.8 | |
| Yes | 100 | 25.4 ± 8.57 | | 1.35 | 1.23 | 1.22 | |

Abbreviations: BMI, Body mass index; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension; M, men; W, women.

Table 41 presents the crude association between energy adjusted fibre intake and covariates by gender. Associations with smoking, physical activity, alcohol consumption, diet quality, fish, coffee and tea intake and sugar intake did not differ by gender.

In women there was no association between dietary fibre intake and ethnic group, marital status, last grade level, sleep duration, central obesity, diabetes, CVD and cancer. Men with seven or more hours of sleep had higher fibre intake; there was no association between energy adjusted fibre intake energy intake. There was a strong association with BMI category in men, with those in the normal weight group having the

highest fibre intakes; in women those with overweight had the lowest fibre intakes. Additionally, men with central obesity had higher intakes than those without (see Table 34).

**Table 36 Crude association of energy adjusted fibre intake and covariates at phase 3 by gender**

| Covariates at phase 3 | Fibre intake, grams | | | | | |
|---|---|---|---|---|---|---|
| | Men (n=5486) | | | Women (2412) | | |
| | n | Mean ± SD | p | n | Mean ± SD | p |
| Age | | | <.001 | | | .88 |
| <50 years | 3023 | 25.7 ± 7.37 | | 1132 | 24.8 ± 7.71 | |
| ≥50 years | 2463 | 26.4 ± 7.39 | | 1280 | 24.8 ± 7.93 | |
| Ethnic Group | | | <.001 | | | .32 |
| White | 5172 | 25.9 ± 7.34 | | 2122 | 24.7 ± 7.72 | |
| South Asian | 227 | 27.8 ± 8.12 | | 138 | 25.4 ± 6.64 | |
| Black | 87 | 27.3 ± 7.75 | | 152 | 25.5 ± 9.91 | |
| Marital Status | | | <.001 | | | .19 |
| Married/cohabiting | 4536 | 26.2 ± 7.31 | | 1527 | 24.6 ± 7.56 | |
| Single | 643 | 24.7 ± 7.55 | | 493 | 25.4 ± 7.82 | |
| Divorced/widowed | 302 | 25.6 ± 7.92 | | 388 | 24.8 ± 8.76 | |
| Last grade level in Civil service | | | .127 | | | .15 |
| Highest | 2684 | 26.2 ± 7.31 | | 380 | 24.8 ± 6.42 | |
| Intermediate | 2454 | 25.8 ± 7.30 | | 1094 | 25.1 ± 7.58 | |
| Lowest | 348 | 26.2 ± 8.51 | | 938 | 24.5 ± 8.57 | |
| Smoking | | | <.001 | | | <.001 |
| Never Smoker | 2297 | 26.7 ± 7.36 | | 1141 | 25.4 ± 7.38 | |
| Ex-Smoker | 2198 | 26.3 ± 7.38 | | 703 | 25.4 ± 8.06 | |
| Current Smoker | 681 | 23.0 ± 6.71 | | 405 | 21.8 ± 7.96 | |
| Physical activity | | | <.001 | | | .012 |
| Non/mild | 1715 | 25.4 ± 7.29 | | 1233 | 24.5 ± 7.82 | |
| Moderate | 2553 | 25.9 ± 7.00 | | 952 | 24.8 ± 7.36 | |
| Vigorous | 1218 | 27.0 ± 8.18 | | 227 | 26.2 ± 9.46 | |
| Alcohol consumption | | | <.001 | | | <.001 |
| None | 954 | 27.4 ± 7.72 | | 898 | 25.6 ± 9.03 | |
| Moderate | 2846 | 26.7 ± 7.26 | | 1292 | 24.7 ± 7.04 | |
| Heavy | 1680 | 24.0 ± 6.99 | | 220 | 22.4 ± 6.26 | |
| Sleep duration | | | .015 | | | .57 |
| less than 7 h/day | 1339 | 25.6 ± 7.41 | | 660 | 24.7 ± 7.51 | |
| ≥ 7 h/day | 4142 | 26.2 ± 7.38 | | 1747 | 24.9 ± 7.93 | |
| Energy intake | | | .477 | | | .025 |
| < median | 2351 | 25.9 ± 6.39 | | 1548 | 24.5 ± 6.64 | |
| > median | 3135 | 26.1 ± 8.06 | | 864 | 25.3 ± 9.57 | |
| Modified DASH diet score | | | <.001 | | | <.001 |
| < median | 3093 | 22.9 ± 6.22 | | 1354 | 21.5 ± 5.91 | |
| > median | 2390 | 30.0 ± 6.87 | | 1057 | 29.0 ± 7.98 | |
| Fish intake | | | <.001 | | | <.001 |
| < median | 3235 | 25.6 ± 7.22 | | 1251 | 24.1 ± 7.78 | |
| > median | 2251 | 26.5 ± 7.60 | | 1161 | 25.6 ± 7.81 | |
| Tea / coffee | | | .016 | | | .002 |
| ≤ 1 cup of either/day | 409 | 26.9 ± 7.68 | | 281 | 26.2 ± 8.70 | |
| > 1 cup of either/day | 5077 | 25.9 ± 7.36 | | 2131 | 24.6 ± 7.69 | |
| Sugar intake | | | <.001 | | | <.001 |
| 1st Tertile | 1816 | 27.6 ± 7.17 | | 802 | 26.3 ± 8.08 | |
| 2nd Tertile | 1820 | 26.0 ± 6.97 | | 788 | 25.5 ± 6.95 | |
| 3rd Tertile | 1850 | 24.5 ± 7.68 | | 822 | 22.7 ± 7.91 | |

| | | | | | | |
|---|---|---|---|---|---|---|
| BMI | | | .001 | | | .007 |
| Normal, <25kg/m$^2$ | 2781 | 26.4 ± 7.59 | | 1172 | 25.2 ± 7.57 | |
| Overweight | 2093 | 25.7 ± 7.09 | | 754 | 24.1 ± 6.96 | |
| Obese. ≥30kg/m$^2$ | 370 | 25.2 ± 7.23 | | 345 | 25.2 ± 9.90 | |
| Central obesity | | | .033 | | | .87 |
| No | 4821 | 26.1 ± 7.40 | | 1963 | 24.8 ± 7.33 | |
| Yes (Waist ≥102/≥88 cm) | 360 | 25.2 ± 7.18 | | 296 | 24.9 ± 10.32 | |
| Diabetes | | | .021 | | | .23 |
| No | 5331 | 26.0 ± 7.36 | | 2349 | 24.8 ± 7.82 | |
| Yes | 155 | 27.4 ± 8.17 | | 63 | 26.0 ± 7.98 | |
| CVD | | | .001 | | | .31 |
| No | 5287 | 25.9 ± 7.36 | | 2343 | 24.8 ± 7.84 | |
| Yes | 199 | 27.7 ± 7.81 | | 69 | 25.8 ± 7.08 | |
| Cancer | | | .651 | | | .77 |
| No | 5431 | 26.0 ± 7.38 | | 2358 | 24.8 ± 7.80 | |
| Yes | 53 | 25.6 ± 8.26 | | 47 | 25.1 ± 8.99 | |

Abbreviations: BMI, Body mass index; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension; M, men; W, women.

## 6.3 Association of dietary fibre intake and mood disorders

### *6.3.1 Cross-sectional association*

Cross-sectionally, energy adjusted fibre intake, both continuous and when operationalised as tertiles of intake, was associated with reduced odds of CMD and depression in models adjusted for age, sex and ethnicity (Table 37: Model 0).

There was no evidence for an interaction by sex (LR test p=0.51 for CMD and p=0.67 for depression) or phase for depression (p0.84), but there was evidence for interaction by phase for CMD (LR test p=0.023, discussed in Table 39).

The associations with CMD were attenuated when adjusted for socio-demographic factors and health behaviours (see Table 37: Model 1). Further adjustment for adiposity, CVD, diabetes and cancer had little effect on the association (not shown).

Being in the highest tertile of energy adjusted fibre intake was associated with 31% lower odds of depression compared to those in the lowest tertile (Table 37:).

Estimates found in age, sex and ethnicity adjusted models did not differ when analysed in a sample restricted to those with no missing data in socio-demographic factors, health behaviours and diet-related factors (not shown).

There was no significant association with continuous fibre intake. The association was attenuated when adjusted for socio-demographic factors and health behaviours. Adjustment of other diet-related factors explained the association entirely (see Table 37:: Model 2). Further adjustment for adiposity, CVD, diabetes and cancer did not change the associations (not shown).

**Table 37 Cross-sectional association of energy adjusted fibre intake and prevalent CMD and depression in men and women[a]**

| | | Prevalent CMD, OR (95% CI) | | |
|---|---|---|---|---|
| | events / person observations | Model 0[b] | Model 1[c] | Model 2[d] |
| Fibre intake | | | | |
| Lowest Tertile | 1477 / 6990 | 1 (reference) | 1 (reference) | 1 (reference) |
| Middle Tertile | 1380 / 7397 | 0.85** (0.77, 0.95) | 0.90 (0.80, 1.00) | 0.93 (0.83, 1.05) |
| Highest Tertile | 1227 / 6812 | 0.85* (0.76, 0.96) | 0.91 (0.81, 1.02) | 0.93 (0.81, 1.08) |
| p for trend | | .006 | .11 | .37 |
| Continuous (10g/day increment) | 4084 / 21199 | 0.92* (0.87, 0.98) | 0.95 (0.89, 1.01) | 0.96 (0.89, 1.04) |
| | | **Prevalent depression, OR (95% CI)** | | |
| Fibre intake | | | | |
| Lowest Tertile | 401 / 2841 | 1 (reference) | 1 (reference) | 1 (reference) |
| Middle Tertile | 404 / 3272 | 0.84 (0.66, 1.05) | 0.96 (0.76, 1.22) | 1.08 (0.84, 1.39) |
| Highest Tertile | 297 / 2845 | 0.69** (0.53, 0.88) | 0.73* (0.56, 0.95) | 0.94 (0.69, 1.28) |
| p for trend | | .004 | .022 | .68 |
| Continuous (10g/day increment) | 1102 / 8958 | 0.93 (0.81, 1.06) | 0.96 (0.84, 1.10) | 1.12 (0.95, 1.31) |

* p<.05, **p<.005, *** p<.001.
[a]Cross-sectional association across phases 3, 5, 7, 9 for CMD and 7, 9 for depression.
[b]CMD model 0 (4387 events / 22693 person observations); Depression model 0 (1200 events / 9578 person observations); adjusted for age, sex and their interaction and ethnicity.
[c]Model 1: additionally adjusted for marital status, last grade level in civil service, smoking, alcohol intake, physical activity, sleep duration.
[d]Model 2: additionally adjusted fish intake, modified DASH diet score, coffee and tea intake, sugar intake from sweet food / beverages, sugar intake from sweet food / beverages*sex and total calories.

Excluding extreme fibre intakes (>7 SD) 47 (12 cases) and 21 (8 cases), respectively resulted in slightly different estimates for the association with continuous fibre intake explaining partly the difference between tertile and continuous associations (see Table 38). Adjustment for dietary factors including modified DASH score and sugar intake from sweet food and beverages did not change the association with prevalent depression as drastically as before (see Table 38: Model 2). There were no changes in associations with tertiles of fibre intake (not shown).

**Table 38 Cross-sectional association of energy adjusted fibre intake and prevalent CMD and depression in men and women after exclusion of extreme fibre intakes (>7 SD)[a]**

| | | Prevalent CMD, OR (95% CI) | | |
|---|---|---|---|---|
| | events / person observations | Model 0[b] | Model 1[c] | Model 2[d] |
| Fibre intake Continuous (10g/day increment) | 4136 / 21549 | 0.90** (0.84, 0.96) | 0.93* (0.87, 0.99) | 0.94 (0.86, 1.02) |
| | | **Prevalent depression, OR (95% CI)** | | |
| Fibre intake Continuous (10g/day increment) | 1133 / 9248 | 0.85* (0.74, 0.98) | 0.92 (0.79, 1.05) | 1.03 (0.86, 1.23) |

* p<.05, **p<.005, *** p<.001.
[a]Cross-sectional association across phases 3, 5, 7, 9 for CMD and 7, 9 for depression.
[b]CMD (4375 events / 22646 person observations) and depression model 0 (1192 events / 9557 person observations): adjusted for age, sex and their interaction and ethnicity.
[c]Model 1: additionally adjusted for marital status, last grade level in civil service, smoking, alcohol intake, physical activity, sleep duration.
[d]Model 2: additionally adjusted fish intake, modified DASH diet score, coffee and tea intake, sugar intake from sweet food / beverages, sugar intake from sweet food / beverages*sex and total calories.

Excluding participants with unknown or self-reported doctor diagnosis changed the estimates only marginally.

Analyses for each phase separately showed that the significant interaction by study phase was due to a strongly negative association at phase 9 (see Table 39). Excluding this phase lead to a LR test of 0.98, and to an overall OR per 10g increment of 0.96 with a 95%-CI of 0.90, 1.03 (p=0.23).

**Table 39 Cross-sectional association of energy adjusted fibre intake and prevalent CMD and depression in men and women by data collection phase**

| | | Prevalent CMD |
|---|---|---|
| Phase | events / participants | OR[a] (95% CI) |
| Fibre intake (10g/day increment) | | |
| Phase 3 | 1738 / 7898 | 0.95 (0.89, 1.02) |
| Phase 5 | 990 / 4808 | 0.95 (0.86, 1.04) |
| Phase 7 | 970 / 4990 | 0.97 (0.88, 1.07) |
| Phase 9 | 689 / 5000 | 0.76*** (0.67, 0.85) |
| Test for interaction | | p=.023 |

* p<.05, **p<.005, *** p<.001.
[a]Adjusted for age, sex and their interaction and ethnicity.

### *6.3.2 Prospective associations: Incidence*

Figure 15 gives an overview over the prospective associations of fibre intake with mood disorders in Whitehall II for all participants combined and separately in men and women. In age, sex and ethnicity adjusted models fibre intake was associated with reduced chances of incident CMD in 5-year, 10-year cycles and of depression in 10-years cycles. There were associations with depression after 5 years and with clinical depression after 5 years in men with borderline significance. Fibre intake was not associated with CMD in 2-year cycles and clinical depression after 10 years.

There was no significant difference by sex in the association between energy adjusted fibre intake and CMD (LR test after 2 years p=0.86, 5 years p=0.45 and 10 years p=0.89) or depression (LR test after 5 years p=0.47, after 10 years p=0.15). There was a significant difference by sex in models of clinical depression after 5 years, but not after 10 years (LR test after 5 years p=0.011, after 10 years p=0.93).

There were no significant differences by phase in the association of energy adjusted fibre intake when using CMD and depression (LR test for CMD after 2 years p=0.47, after 5 years p=0.59, after 10 years p=0.31, for depression after 5 years p=0.23, after 10 years p=0.32).

Age, sex and ethnicity adjusted associations between fibre intake with incident mood disorders did not differ when analysed in samples restricted to those with no missing data in socio-demographic factors, health behaviours and diet-related factors (not shown).

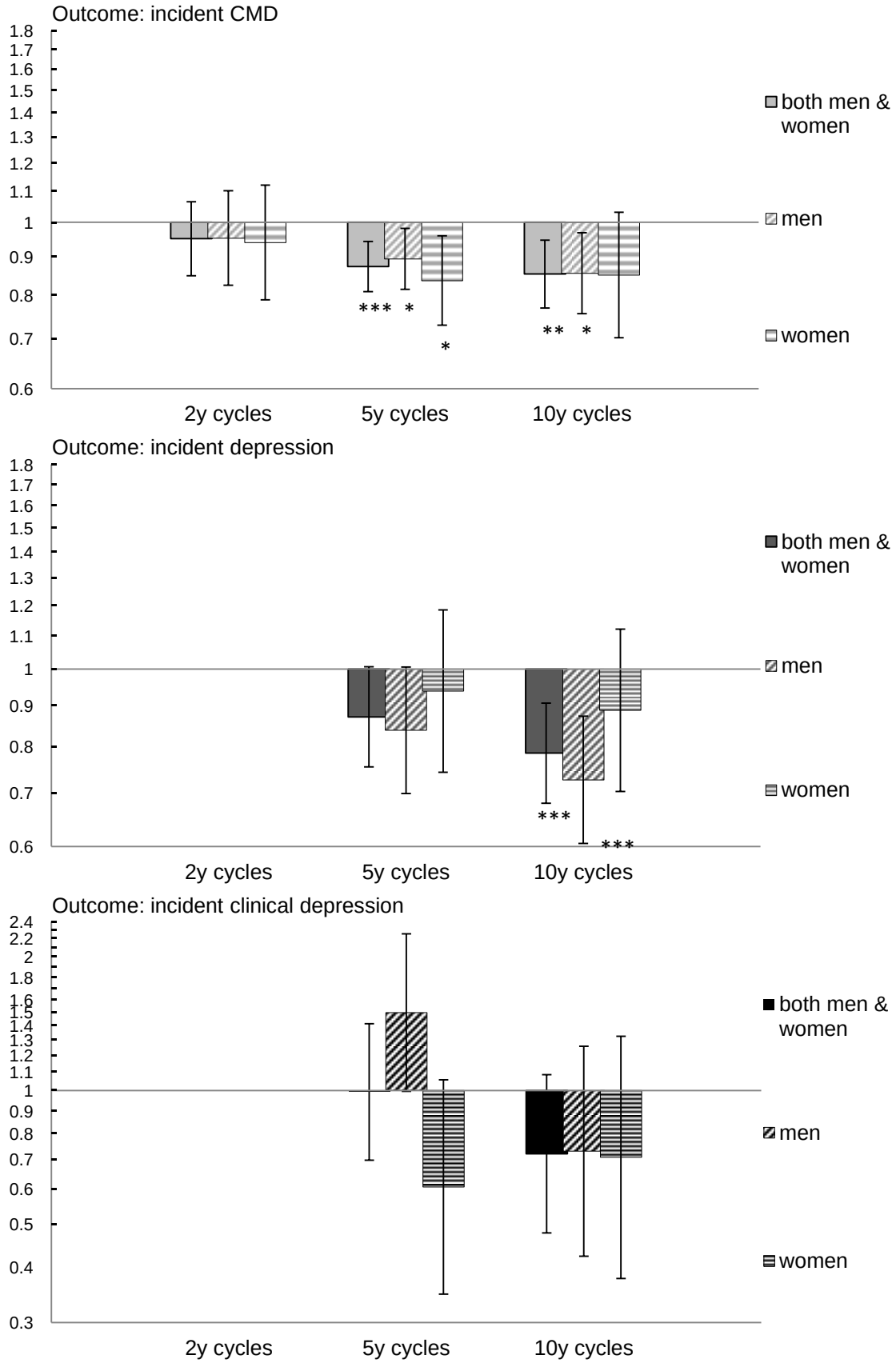



**Figure 15 Overview of odds ratios for incident mood disorder measures per 10g energy adjusted fibre intake over 2, 5, 10-year cycles, adjusted for age, sex and ethnicity**

Sample sizes and data can be found in Table A 17.

* p<.05, **p<.005, *** p<.001.

**Associations with incident CMD**

Higher energy adjusted fibre intake was associated with lower incidence of CMD after 5 and 10 years (Table 40: Model 0). Associations remained significant and were only slightly attenuated when additionally adjusted for socio-demographic factors, health behaviours and dietary factors (Table 40: Model 2). Additional adjustment for adiposity and disease did not change the associations (not shown). The associations were strong both in analyses using tertiles and continuous fibre intake.

**Table 40 Prospective association of energy adjusted fibre intake and incident CMD after 5 and 10 years[b]**

| | | Incident CMD, OR (95% CI) | | |
|---|---|---|---|---|
| | events / person observations | Model 0[b] | Model 1[c] | Model 2[d] |
| **After 5 years** | | | | |
| Fibre intake | | | | |
| Lowest Tertile | 721 / 4941 | 1 (reference) | 1 (reference) | 1 (reference) |
| Middle Tertile | 658 / 5477 | 0.81** (0.71, 0.92) | 0.82** (0.71, 0.93) | 0.83* (0.72, 0.96) |
| Highest Tertile | 577 / 5069 | 0.76*** (0.66, 0.87) | 0.75*** (0.65, 0.86) | 0.74*** (0.62, 0.88) |
| p for trend | | <.001 | <.001 | .001 |
| Continuous (10g/day increment) | 1956 / 15487 | 0.87*** (0.81, 0.94) | 0.86*** (0.79, 0.93) | 0.86** (0.78, 0.95) |
| **After 10 years** | | | | |
| Fibre intake | | | | |
| Lowest Tertile | 507 / 3536 | 1 (reference) | 1 (reference) | 1 (reference) |
| Middle Tertile | 430 / 3807 | 0.76** (0.64, 0.91) | 0.75** (0.62, 0.90) | 0.75** (0.62, 0.92) |
| Highest Tertile | 428 / 3681 | 0.74** (0.62, 0.89) | 0.75** (0.62, 0.91) | 0.73* (0.58, 0.92) |
| p for trend | | .001 | .003 | .009 |
| Continuous (10g/day increment) | 1365 / 11024 | 0.85** (0.77, 0.95) | 0.85** (0.77, 0.95) | 0.84* (0.73, 0.96) |

* p<.05, **p<.005, *** p<.001.
[b]Prospective association across phases 3, 5, 7, 9 for 5y cycle and 3, 5, 7 for 10year cycles.
[c]Model 0 for incident CMD after 2y 0 (910 events / 7246 person observations); after 5 years (2044 events / 16158 person observations); after 10 years (1421 events / 11530 person observations); adjusted for age, sex and their interaction and ethnicity.
[d]Model 1: additionally adjusted for marital status, last grade level in civil service, smoking, alcohol intake, physical activity, sleep duration.
[e]Model 2: additionally adjusted fish intake, modified DASH diet score, coffee and tea intake, sugar intake from sweet food / beverages, sugar intake from sweet food / beverages*sex and total calories.

Excluding 27 (3 cases) and 16 (1 case) person-observations with extreme fibre intakes (>7 SD) did not change estimates (not shown). Associations did also not change when person-observations with baseline unknown or self-reported doctor diagnosis of depression were excluded (not shown).

### Associations with incident depression

Being in the highest tertile of energy adjusted fibre intake was associated with a lower chance of depression after 5 years (Table 41: Model 1). There was no significant association with continuous fibre intake. The association with tertiles of fibre intake was attenuated when adjusted for socio-demographic factors, but borderline statistically significant when further adjusted. Excluding those with extreme fibre intake (23 of which 2 cases) and with baseline unknown or self-reported doctor diagnosis of depression did not change the estimates for associations with depression after 5 years (not shown).

There was a strong association of continuous fibre intake with incident depression after 10 years which remained irrespective of adjustments (Table 41, Table A 18). It has to be noted that when adjusting further for adiposity and disease, associations with incident depression after 5 years returned to statistical significance which was likely the result of bias introduced by the reduction of the sample size to no missings in BMI and physical health measures (see Table A 18).

**Table 41 Prospective association of energy adjusted fibre intake and incident depression after 5 and 10 years[a]**

| | | Incident Depression, OR (95% CI) | | |
|---|---|---|---|---|
| | events / person observations | Model 0[b] | Model 1[c] | Model 2[d] |
| **After 5 years** | | | | |
| Fibre intake | | | | |
| Lowest Tertile | 296 / 3366 | 1 (reference) | 1 (reference) | 1 (reference) |
| Middle Tertile | 277 / 3836 | 0.77* (0.61, 0.98) | 0.83 (0.65, 1.06) | 0.81 (0.63, 1.06) |
| Highest Tertile | 225 / 3409 | 0.69* (0.53, 0.90) | 0.78 (0.60, 1.01) | 0.73 (0.53, 1.00) |
| p for trend | | .006 | .057 | .052 |
| Continuous (10g/day increment) | 798 / 10611 | 0.87 (0.76, 1.01) | 0.92 (0.80, 1.06) | 0.90 (0.75, 1.07) |
| **After 10 years** | | | | |
| Fibre intake | | | | |
| Lowest Tertile | 324 / 3310 | 1 (reference) | 1 (reference) | 1 (reference) |
| Middle Tertile | 304 / 3574 | 0.88 (0.69, 1.11) | 0.90 (0.71, 1.15) | 0.93 (0.72, 1.21) |
| Highest Tertile | 260 / 3493 | 0.69** (0.53, 0.89) | 0.75* (0.58, 0.97) | 0.76 (0.56, 1.04) |
| p for trend | | .005 | .029 | .088 |
| Continuous (10g/day increment) | 888 / 10377 | 0.78*** (0.68, 0.91) | 0.81** (0.70, 0.93) | 0.78** (0.65, 0.94) |

* p<.05, **p<.005, *** p<.001.
[a]Prospective association across phases 5, 7, 9 for 5 years and 3, 5, 7 for 10 year depression.
[b]Model 0 for incident depression after 5 years (797 events / 10606 person observations); after 10 years (947 events / 10844 person observations); adjusted for age, sex and their interaction and ethnicity.
[c]Model 1: additionally adjusted for marital status, last grade level in civil service, smoking, alcohol intake, physical activity, sleep duration.
[d]Model 2: additionally adjusted fish, total calorie intake, modified DASH diet score, sugar intake from sweet food / beverages*sex, coffee and tea intake.

The association with depression after 10 years was strengthened when 14 person-observations (2 cases) with extreme intakes were excluded (OR per 10g increment for model 4: 0.72, 95%-CI 0.59, 0.88; p=0.001; data not shown).

### Associations with incident clinical depression

Higher energy adjusted fibre intake was associated with increased odds for clinical depression after 5 years in men (Table 42: Main analysis). However, this association was due to participants with extreme fibre intakes (>7 SD). After excluding these extreme values, the interaction by sex disappeared (LR test p=0.21) and associations in men were attenuated (Table 42: Sensitivity analysis (a)).

**Table 42 Prospective association of energy adjusted fibre intake and incident clinical depression after 5 years by sex, with and without exclusion of extreme fibre intakes (>7 SD)[a]**

| | Incident clinical depression after 5 years (events / participants) | | | |
|---|---|---|---|---|
| **Main analysis** | | | | |
| | Men (26 / 2699) | | Women (32 / 929) | |
| | OR (95%-CI) | p | OR (95%-CI) | p |
| Fibre intake (10g/day increment) | | | | |
| Model 0[b] | 1.50 (1.00, 2.25) | .053 | 0.61 (0.35, 1.06) | .078 |
| Model 1[c] | 1.63* (1.06, 2.51) | .027 | 0.57 (0.31, 1.02) | .059 |
| Model 2[d] | 1.41 (0.83, 2.42) | .21 | 0.42* (0.19, 0.91) | .028 |
| **Sensitivity analysis (a), exclusion of extreme fibre intakes (>7 SD)** | | | | |
| | Men (25 / 2690) | | Women (32 / 924) | |
| | OR (95%-CI) | p | OR (95%-CI) | p |
| Fibre intake (10g/day increment) | | | | |
| Model 0[b] | 1.01 (0.58, 1.78) | .96 | 0.61 (0.35, 1.08) | .089 |
| Model 1[c] | 1.15 (0.65, 2.05) | .63 | 0.57 (0.31, 1.03) | .062 |
| Model 2[d] | 0.78 (0.36, 1.70) | .54 | 0.42* (0.19, 0.92) | .029 |

* p<.05, **p<.005, *** p<.001.
[a]Prospective association across phase 9 to 11.
[b]Model 0 for before exclusion men(27 events / 2778 participants), women (33 events / 977 participants); after excluding fibre intakes (>7 SD) men (26 events / 2773 person observations), women (33 events / 972 participants); adjusted for age, ethnicity.
[c]Model 1: additionally adjusted for marital status, last grade level in civil service, smoking, alcohol intake, physical activity, sleep duration.
[d]Model 2: additionally adjusted fish, total calorie intake, modified DASH diet score, sugar intake from sweet food / beverages, coffee and tea intake.

After exclusion of extreme fibre intakes higher energy adjusted fibre intakes were associated with lower odds ratios of clinical depression in men and women after 5 years when other dietary factors were adjusted for, additionally to socio-demographic and health behaviours Further adjustment for adiposity did not affect the association, but on adjustment for CVD, diabetes and cancer the association became non-significant (Table 43: Sensitivity analysis (a): Model 4).

Exclusion of person-observations with a baseline unknown or known depression diagnosis strengthened the association (Table 43: Sensitivity analysis (b)).

**Table 43 Prospective association of energy adjusted fibre intake and incident clinical depression after 5 years after exclusion of extreme fibre intakes (>7 SD) (a) and after additional exclusion those with unknown or known depression diagnosis at baseline (b)[a]**

| | Incident clinical depression after 5 years (events / participants) | | | |
|---|---|---|---|---|
| | Sensitivity analysis (a) (57 / 3602) | | Sensitivity analysis (b) (50 / 3498) | |
| | OR (95%-CI) | p | OR (95%-CI) | p |
| Fibre intake (10g/day increment) | | | | |
| Model 0[c] | 0.78 (0.53, 1.17) | .24 | 0.68 (0.44, 1.05) | .084 |
| Model 1[d] | 0.77 (0.52, 1.16) | .22 | 0.68 (0.44, 1.06) | .086 |
| Model 2[e] | 0.58* (0.34, 0.99) | .048 | 0.53* (0.30, 0.95) | .034 |
| Model 3[f] | 0.57* (0.34, 0.99) | .045 | 0.53* (0.30, 0.95) | .032 |
| Model 4[g] | 0.59 (0.35, 1.01) | .055 | 0.55* (0.31, 0.98) | .042 |

* p<.05, **p<.005, *** p<.001.
[a]Prospective association across phase 9 to 11.
[b]Model 0 for sensitivity analysis a (59 cases / 3745 participants), sensitivity analysis b (52 cases / 3636 participants); adjusted for age, ethnicity.
[c]Model 1: additionally adjusted for marital status, last grade level in civil service, smoking, alcohol intake, physical activity, sleep duration.
[d]Model 2: additionally adjusted fish, total calorie intake, modified DASH diet score, sugar intake from sweet food / beverages, sugar intake from sweet food / beverages*sex, coffee and tea intake.
[e]Model 3: additionally adjusted for BMI and central adiposity.
[f]Model 4: additionally adjusted for baseline CVD, diabetes and cancer.

Energy adjusted fibre intake was associated with lower odds of clinical depression after 10 years in models additionally adjusted for other dietary factors (Table 44: Model 2). This association was attenuated in models excluding those with extreme fibre intakes (Table 44, Sensitivity analysis (a): Model 2) and those with a depression diagnosis at each baseline (Table 44, Sensitivity analysis (b): Model 2).

**Table 44 Prospective association of energy adjusted fibre intake and incident clinical depression after 10 years, after exclusion of extreme fibre intakes (>7 SD) (a) and after additional exclusion of those with unknown or self-reported doctor diagnosis of depression at baseline (b)[a]**

| | Incident clinical depression after 10 years (events / participants) | | | | | |
|---|---|---|---|---|---|---|
| | Main analysis (53 / 3121) | | Sensitivity analysis (a) (53 / 3114) | | Sensitivity analysis (b) (48 / 3051) | |
| | OR (95% CI) | p | OR (95% CI) | p | OR (95% CI) | p |
| Fibre intake (10g/day increment) | | | | | | |
| Model 0[b] | 0.72 (0.48, 1.08) | .12 | 0.72 (0.48, 1.09) | .13 | 0.72 (0.47, 1.12) | .15 |
| Model 1[c] | 0.67 (0.45, 1.01) | .059 | 0.68 (0.45, 1.03) | .067 | 0.68 (0.43, 1.05) | .081 |
| Model 2[d] | 0.58* (0.34, 0.99) | .048 | 0.58 (0.34, 1.02) | .057 | 0.62 (0.35, 1.13) | .12 |

* p<.05, **p<.005, *** p<.001.
[a]Prospective association across phase 7 to 11.
[b]Model 0 in main analysis (53 cases / 3194 participants), in sensitivity analysis a (53 cases / 3187 participants), n sensitivity analysis b (48 cases / 3123); adjusted for age, sex and their interaction and ethnicity.
[c]Model 1: additionally adjusted for marital status, last grade level in civil service, smoking, alcohol intake, physical activity, sleep duration.
[d]Model 2: additionally adjusted fish, total calorie intake, modified DASH diet score, sugar intake from sweet food / beverages*sex, coffee and tea intake.

### *6.3.3 Prospective associations: Recurrence*

Figure 16 depicts the associations of energy adjusted fibre intake with recurrent mood disorders after adjustment for age, sex and ethnicity. There was no significant association with CMD, depression after 5 years and clinical depression. There was one significant association; those with higher fibre intake had lower chances for recurrent depression after 10 years. Women with higher fibre intakes had lower chances developing incident CMD 2 years later, but the association was statistically non-significant.

There was no significant difference in the associations by sex in models using recurrent CMD (LR test after 2 years p=0.15, 5 years p=0.69 and 10 years p=0.95), depression (LR test after 5 years p=0.83, after 10 years p=0.26) and clinical depression (LR test after 5 years p=0.83, after 10 years p=0.26).

There were no significant differences by phase in models of recurrent CMD (after 2 years p=0.14, after 5 years p=0.58, after 10 years p=0.62) and depression (after 5 years p=0.07, after 10 years p=0.92).

Age, sex and ethnicity adjusted associations between fibre intake with incident mood disorders did not differ when analysed in samples restricted to those with no missing data in socio-demographic factors, health behaviours and diet-related factors (not shown).

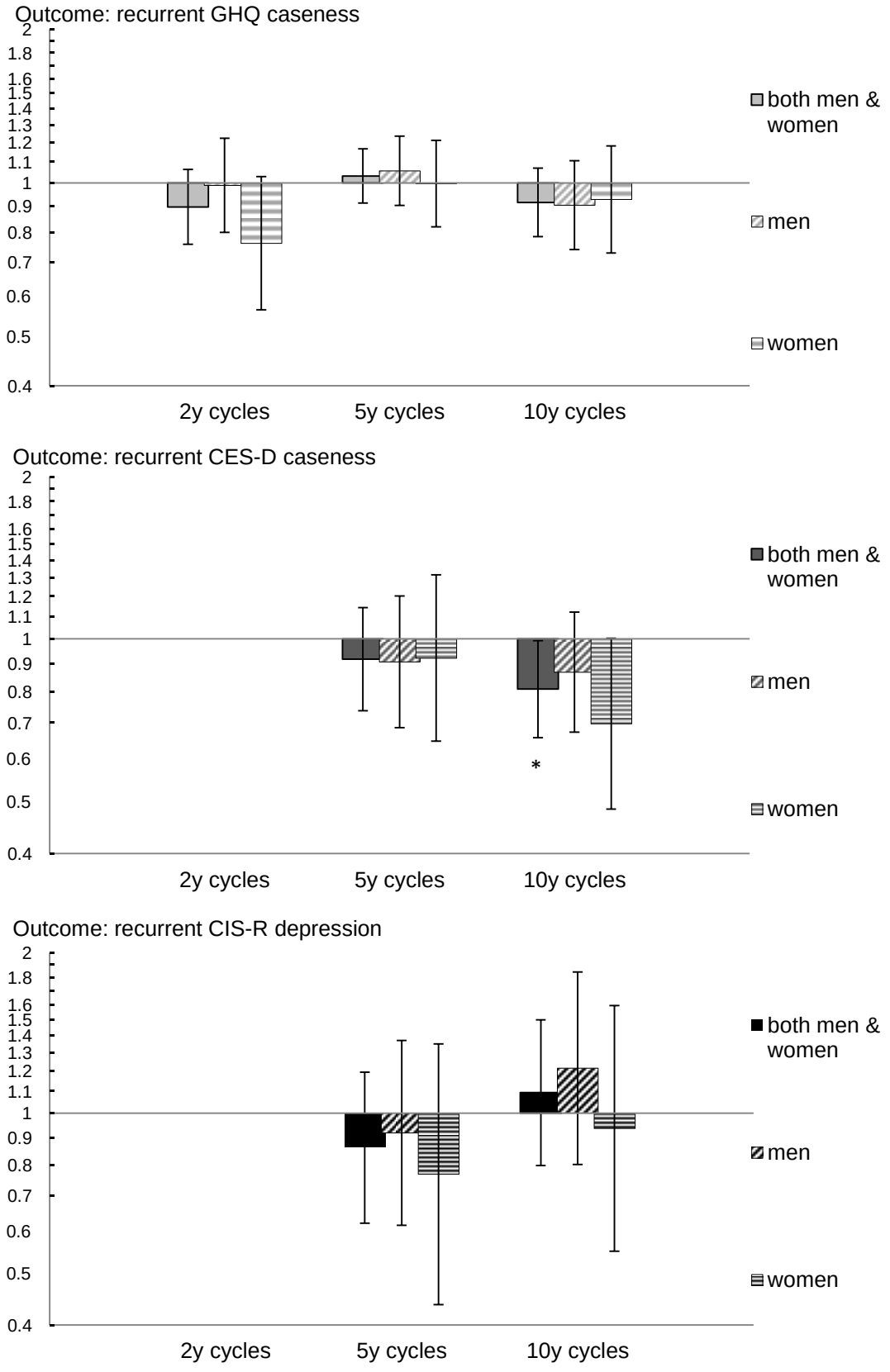



**Figure 16 Overview of odds ratios for recurrent mood disorder measures per 10g energy adjusted fibre intake over 2, 5, 10-year cycles, adjusted for age, sex and ethnicity**

See Table A 19 for sample sizes and data.

* p<.05, **p<.005, *** p<.001.

### Associations with recurrent CMD

In models using continuous intakes adjusted for age, sex and ethnicity there was no significant association with recurrent CMD after 2, 5 and 10 years (Figure 16), but being in the highest tertile of fibre intake was associated with reduced chances of a recurrent CMD after 2 years with a significant trend across the tertiles in models only adjusted for age, sex and ethnicity (Table 45: Model 0). The association attenuated after additional adjustment of socio-demographic factors, health behaviours, fish and calorie intake, but was strengthened when additionally adjusted for sugar intake from sweet food / beverages and modified DASH diet score (see Table 45: Model $2_{A, B}$). This association remained when further adjusted for adiposity and disease, and when 8 (3 cases) person-observations were excluded for extreme fibre intakes (>7 SD) (not shown). There was no association with continuously operationalised fibre intake.

**Table 45 Prospective association of energy adjusted fibre intake and recurrent CMD after 2 years[a]**

| | | Recurrent CMD after 2 years, OR (95% CI)[b] | | | |
|---|---|---|---|---|---|
| | events / person observations | Model 0[b] | Model 1[c] | Model $2_A$[d] | Model $2_B$[e] |
| Fibre intake | | | | | |
| Lowest Tertile | 268 / 575 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| Middle Tertile | 250 / 587 | 0.82 (0.60, 1.13) | 0.85 (0.62, 1.18) | 0.87 (0.63, 1.21) | 0.77 (0.54, 1.09) |
| Highest Tertile | 203 / 510 | 0.71* (0.51, 1.00) | 0.72 (0.51, 1.02) | 0.72 (0.51, 1.02) | 0.57*(0.37, 0.88) |
| p for trend | | .046 | .063 | .068 | .012 |
| Continuous (10g/day increment) | 721 / 1672 | 0.90 (0.76, 1.07) | 0.90 (0.76, 1.07) | 0.90 (0.76, 1.07) | 0.81 (0.65, 1.02) |

*p<.05, **p<.005, *** p<.001.
[a]Prospective association across phases 3, 5 for 2-year recurrent CMD.
[b]CMD model 0:(759 events / 1750 person observation); adjusted for age, sex and their interaction and ethnicity.
[c]Model 1: additionally adjusted for marital status, last grade level in civil service, smoking, alcohol intake, physical activity, sleep duration.
[d]Model $2_A$: additionally adjusted for fish intake, calorie intake, coffee and tea intake.
[g]Model $2_B$: additionally adjusted for modified DASH diet score, sugar intake from sweet food / beverages*sex.

### Associations with recurrent depression

Being in the second or third tertile of adjusted fibre intake was associated with a reduced chance of recurrent depression after 5 years in models adjusted for age, sex and ethnicity (Table 46: Model 0). There was no association with continuous fibre intake. The associations were not affected by adjustment for socio-demographic factors and health behaviours but were attenuated when further adjusted for other diet-related factors (Table 46: Model 2). Excluding 7 (5 cases) person-observations for extreme fibre intakes attenuated associations with continuous fibre intake but did not change associations overall (Table 46, Sensitivity analysis (a): Model 0).

**Table 46 Prospective association of energy adjusted fibre intake and recurrent depression after 5 years[a] with and without exclusion of extreme fibre intakes (>7SD)**

| | Recurrent depression after 5 years, OR (95% CI) | | | |
|---|---|---|---|---|
| | events / person observations | Model 0[b] | Model 1[c] | Model 2[d] |
| **Main analyses** | | | | |
| Fibre intake | | | | |
| Lowest Tertile | 271 / 770 | 1 (reference) | 1 (reference) | 1 (reference) |
| Middle Tertile | 222 / 740 | 0.62* (0.42, 0.92) | 0.63* (0.42, 0.95) | 0.65 (0.41, 1.02) |
| Highest Tertile | 190 / 637 | 0.62* (0.40, 0.95) | 0.63* (0.40, 0.97) | 0.59 (0.34, 1.03) |
| p for trend | | .024 | .033 | .062 |
| Continuous (10g/day increment) | 683 / 2147 | 0.91 (0.73, 1.14) | 0.94 (0.75, 1.17) | 0.99 (0.75, 1.31) |
| **Sensitivity analysis (a), exclusion of extreme fibre intakes (>7 SD)** | | | | |
| Fibre intake | | | | |
| Lowest Tertile | 271 / 770 | 1 (reference) | 1 (reference) | 1 (reference) |
| Middle Tertile | 222 / 740 | 0.62* (0.42, 0.92) | 0.63* (0.42, 0.94) | 0.65 (0.41, 1.02) |
| Highest Tertile | 185 / 630 | 0.60* (0.39, 0.92) | 0.61* (0.39, 0.94) | 0.59 (0.34, 1.01) |
| p for trend | | .017 | .022 | .056 |
| Continuous (10g/day increment) | 678 / 2140 | 0.84 (0.66, 1.06) | 0.85 (0.67, 1.09) | 0.91 (0.67, 1.23) |

*p<.05, **p<.005, *** p<.001.
[a]Prospective association across phases 5, 7, 9 for 5-year recurrent depression.
[b]Depression model 0:(5-year cycles: 724 events / 2246 person observations; exclusion of extreme fibre intakes (>7 SD): 719 events / 2239 person observations); adjusted for age, sex and their interaction and ethnicity.
[c]Model 1: additionally adjusted for marital status, last grade level in civil service, smoking, alcohol intake, physical activity, sleep duration.
[d]Model 2: additionally adjusted fish, total calorie intake, modified DASH diet score, sugar intake from sweet food / beverages*sex, coffee and tea intake.

Energy adjusted fibre intake was associated with recurrent depression after 10 years in models adjusted for sex, age and ethnicity, but was attenuated after adjustment for socio-demographic factors and health behaviours (Table A 20). Additional exclusion of 8 participants with extreme fibre intake attenuated the association (Model 0: OR per 10g increment 0.86, 95%-CI 0.69, 1.06) suggesting that the association was driven by these outliers.

### Associations with recurrent clinical depression

There was no association between fibre intake and recurrent clinical depression after 5 and 10 years (Figure 16).

### *6.3.4 Mood disorders and change in dietary fibre intake*

From phase 3 to 5 daily fibre intake increased by 0.47g per day (SD 9.89; 95% CI 19, 0.76), did not change from phase 5 to 7 (mean change 0.05g per day, SD 9.05; 95%-CI -0.24, 0.35) and decreased from phase 7 to 9 by 0.85g per day (SD 9.23; 95%-CI 0.56, 1.14). Energy adjusted fibre intakes decreased from phase 3 to 5 by 0.62g per day (SD 7.52; 95%-CI 0.40, 0.84), increased from phase 5 to 7 by 0.47g per day (SD 6.99; 95%-CI 0.24, 0.70) and decreased from phase 7 to 9 by -0.44 (SD 7.03; 95-CI% 0.22, 0.66).

The association of mood disorders with changes in non-energy adjusted fibre intake did not follow a clear pattern (Table 47). Overall associations of baseline CMD and depression with fibre intake change compared to those without CMD or depression were inconsistent and showed no overall effect on fibre intake.

There was no difference in fibre intake change from phases 3 and 5 between those with CMD at phase 3 as compared to those without CMD. Those with CMD at phase 5 had a reduced chance to reduce their fibre intake compared to non-cases and had overall increased their fibre intake from phase 5 to 7. However, those with CMD at phase 7 had a reduced chance to increase their fibre intake compared to those without CMD and there was no association with continuous change in fibre intake. Those with depression at phase 7 had a smaller chance of reducing their fibre intake, as well as a smaller chance of increasing their fibre intake (p=0.06), thus suggesting that they had a higher chance of not changing their fibre intake compared to those without depression (Table 47).

When using energy adjusted fibre intake, there was no association between mood disorders and subsequent change in energy adjusted fibre intake (Table 47).

Associations did not differ by sex (LR test >0.05) and adjustments for socio-demographic factors and health behaviours did not change the associations (not shown). The associations were not affected by excluding those with extreme fibre intakes (Table A 21).

**Table 47 Association of CMD and depression with subsequent 5-year change in dietary fibre intake**

| | 5-year change in fibre intake | | | | | |
|---|---|---|---|---|---|---|
| | Not adjusted for energy intake | | | Energy adjusted | | |
| | events / participants | OR (95% CI) *β-coefficient*[a] *(95% CI)* | p | events / participants | OR (95% CI) *β-coefficient*[a] *(95% CI)* | p |
| **CMD** | | | | | | |
| **At phase 3 –Fibre intake change: phase 3 to 5** | | | | | | |
| Reduction | 231 / 1086 | 1.07 (0.89, 1.27) | .49 | 259 / 1228 | 1.03 (0.87, 1.22) | .74 |
| No change | 492 / 2412 | 1 (reference) | | 499 / 2418 | 1 (reference) | |
| Increase | 235 / 1125 | 1.02 (0.86, 1.22) | .82 | 200 / 978 | 0.99 (0.82, 1.20) | .95 |
| Continuous change in grams per day | 958 / 4623 | *-0.02 (-0.73, 0.69)* | .95 | 958 / 4623 | *0.00 (-0.54, 0.54)* | 1.00 |
| **At phase 5 – Fibre intake change: phase 5 to 7** | | | | | | |
| Reduction | 136 / 787 | 0.78* (0.63, 0.97) | .028 | 150 / 738 | 1.02 (0.83, 1.27) | .83 |
| No change | 408 / 1996 | 1 (reference) | | 385 / 1956 | 1 (reference) | |
| Increase | 181 / 822 | 1.08 (0.89, 1.33) | .43 | 190 / 911 | 1.01 (0.83, 1.23) | .88 |
| Continuous change in grams per day | 725 / 3605 | *1.07* (0.32, 1.82)* | .005 | 725 / 3605 | *0.36 (-0.22, 0.94)* | .22 |
| **At phase 7 – Fibre intake change: phase 7 to 9** | | | | | | |
| Reduction | 182 / 987 | 0.88 (0.73, 1.07) | .20 | 200 / 970 | 1.15 (0.95, 1.39) | .16 |
| No change | 433 / 2192 | 1 (reference) | | 404 / 2170 | 1 (reference) | |
| Increase | 127 / 759 | 0.80* (0.64, 0.99) | .037 | 138 / 798 | 0.94 (0.76, 1.17) | .58 |
| Continuous change in grams per day | 742 / 3938 | *-0.40 (-1.15, 0.34)* | .29 | 742 / 3938 | *-0.39 (-0.96, 0.17)* | .17 |
| **Depression** | | | | | | |
| **At phase 7 – Fibre intake change: phase 7 to 9** | | | | | | |
| Reduction | 100 / 934 | 0.69** (0.54, 0.89) | .004 | 111 / 919 | 0.93 (0.73, 1.18) | .52 |
| No change | 294 / 2070 | 1 (reference) | | 270 / 2044 | 1 (reference) | |
| Increase | 85 / 715 | 0.78 (0.60, 1.01) | .063 | 98 / 756 | 1.01 (0.79, 1.30) | .92 |
| Continuous change in grams per day | 479 / 3719 | *0.01 (-0.88, 0.89)* | .99 | 479 / 3719 | *-0.11 (-0.78, 0.57)* | .76 |

*p<.05, **p<.005, *** p<.001.
[a]Change in fibre intake in cases compared with non-cases, adjusted for age, sex and ethnicity.

## 6.4 Interim discussion and summary

This chapter addressed objective II, whether a diet high in fibre could be a protective factor in mood disorders. The hypothesised association of higher fibre intake being associated with lower long-term odds was confirmed for odds of incident CMD after 5 and 10 years. Similar but weak associations were found for incident and clinical depression. Mood disorders did not change fibre intake over 5 years.

We conducted REM over 20 years to investigate the association of fibre intake in Whitehall II. Higher fibre intake was associated with lower odds of prevalent depression before but not after adjustment for health behaviours. REM models were not applicable for associations with CMD, as there was a significant difference between phases, with reduced chance for CMD at phase 9 only.

Prospectively, being in the third tertile of fibre intake (>28g/day) was associated with 24% reduced chance of incident CMD and 31% reduced chance of incident depression after 5 years. The association with incident CMD remained significant after adjustment for socio-demographic factors, health behaviours, adiposity and disease and was not affected by sensitivity analyses. The association with depression was restricted to tertile analyses and attenuated when adjusted for socio-demographic factors and health behaviours, and when participants with unknown or self-reported doctor diagnosis of depression at baseline were excluded. The finding of a protective association was in line with results from the American Women's Health Initiative in which participants in the 5$^{th}$ Quintile of fibre intake (median intake 21g/day) had 14% reduced odds for incident depression 3 years later (Gangwisch *et al.*, 2015).

In our study, fibre intake seemed to have a more long-term effect on mood disorder risk. Per 10g fibre intake the chance for incident CMD after 10 years was reduced by 16% and for incident depression was reduced by 13%. This was in contrast to findings from the Spanish SUN cohort that investigated the risk of depression diagnosis over 16 years and did not find an association (Sanchez-Villegas *et al.*, 2017). In comparison to Whitehall II, participants in the SUN cohort were younger with 55% of the cohort below the age of 45 years at baseline (Seguí-Gómez *et al.*, 2006). This discrepancy could suggest that the association may be more relevant in older age. Participants in the American Women's Health Initiative had a similar age range to participants in Whitehall (age at recruitment 50-79 years old) (Hays *et al.*, 2003).

In models adjusted for dietary factors, fibre intake was associated with a reduction in odds of clinical depression after 5 years and 10 years. This suggests they might have been masked by differences in diet-related factors, such as DASH score, sugar intake

from sweet food / beverages. These associations have to be interpreted with caution as they were based on few cases, were not robust to sensitivity analyses and showed stronger estimates than expected in nutritional research (0.8-1.2) (Potischman & Weed, 1999). Still, they underscore the consistency between the associations with different measures of mood disorder, throughout all measures there was a trend of fibre intake being inversely associated with mood disorder risk.

There was little evidence of an association of fibre intake with recurrent mood disorders. In minimally adjusted models being in the third tertile of fibre intake was associated with a reduced chance of recurrent CMD 2 years later and recurrent depression 5 years later. The association with recurrent CMD after 2 years was attenuated by further adjustment but then strengthened when adjusted for other dietary factors, suggesting it might have been driven by inverse associations with these factors. The association with recurrent depression was attenuated when adjusted for other dietary factors. Overall, both associations were weak as they were restricted to analyses in tertiles.

Finally, there was no clear association between mood disorders and fibre intake change. This was in line with findings of a nested case-control study, that found no difference in change in fibre intake between cases and controls and no significant change in fibre intake in year of depression incidence (Gougeon *et al.*, 2017).

Table 52 summarises the results of all analysis modes.

**Table 48 Summary of associations between fibre intake and three measures of mood disorder in Whitehall II**

| | CMD | CES-D Depression | CIS-R Depression | Summary |
|---|---|---|---|---|
| **Exposure: Fibre intake** | | | | |
| **Cross-sectional** | X | X | N/A | Not associated. |
| **Prospective** | | | | |
| Incident mood disorder | | | | Associated with CMD after 5 years and 10 years and with restrictions with CES-D depression after 10 years and CIS-R depression after 5 and 10 years. |
| after 2 years | X | X | N/A | |
| after 5 years | √ | X | (√) | |
| after 10 years | √ | (√) | (√) | |
| Recurrent mood disorder | | | | Associated with CMD after 2 years in highest tertile, only. |
| after 2 years | (√) | N/A | N/A | |
| after 5 years | X | X | X | |
| after 10 years | X | X | X | |
| **Exposure: Mood disorder** | | | | |
| **Change in fibre intake** | X | (X) | N/A | Not associated.<br>CES-D depression was associated with reduction in fibre intake, only, but not continuously and not after energy adjustment. |
| | | | | |

√=associated in final model; X=not associated in final model; N/A=not available; Brackets mark limitations.

In sum, this chapter found some evidence that fibre intake could reduce the odds for mood disorders.

# Chapter 7 **Objective III: Does sugar intake from sweet food and beverages, and dietary fibre intake, act as a moderator in the association between financial insecurity and mood disorders?**

Aim of this chapter was to investigate whether sugar intake from sweet food / beverages, and fibre intake act as a moderator in the association between financial insecurity and mood disorders using data from the Whitehall II cohort study. Additionally, the role of these factors in the association between grade level in the civil service and mood disorders was analysed.

## 7.1 Methods

### *7.1.1 Study sample*

Whitehall II was described in Chapter 4: 4.1.

### *7.1.2 Financial insecurity*

Financial insecurity was ascertained at phases 1, 2, 3, 5, 7 and 9 by two questions: *How often does it happen that you do not have enough money to afford the kind of food or clothing you/your family should have?* with five responses: *Always, often, sometimes, seldom, never;* and, *How much difficulty do you have in meeting the payment of bills?* with responses: *Very great, great, some, slight, very little.*

The variables were dichotomised to compare the response *never* versus *seldom*, *sometimes, often* or *always,* and, *very little* versus *slight, some, great* and *very great.* These two dichotomised variables were then combined into a single variable of financial insecurity as having either not enough money or not being able to pay bills.

### *7.1.3 Grade level*

Current grade level refers to the grade level in the civil service. The 12 non-industrial grades were combined into three groups in order of decreasing salary: the highest level grades including administrative senior management, intermediate grades including professional executive grades and the lowest grade including clerical and support staff (Marmot *et al.*, 1991). As participants left the civil service or retired, last grade level, refers to the last recorded grade level.

### *7.1.4 Diet measures*

Diet was operationalised as continuous sugar intake from sweet food / beverages (detailed description Chapter 5: 5.1.2) and energy adjusted fibre intake (detailed description Chapter 6: 6.1.2). Both variables were centred about their means (Kontopantelis *et al.*, 2017).

### *7.1.5 Mood disorder assessment*

For this chapter mood disorders were assessed using GHQ and CES-D questionnaire data (a detailed description can be found in chapter 4.2.2). GHQ caseness will be referred to as CMD and CES-D caseness as depression.

### *7.1.6 Confounders*

Confounders were chosen to cover both confounding factors of the association of financial insecurity with mood disorders and diet and mood disorders (detailed description in Chapter 4: 4.3) and included marital status; health behaviours such as physical activity, alcohol consumption, smoking and sleep duration; BMI, central obesity and diabetes, CVD and cancer. The following dietary factors were adjusted for: fish intake, categorised as quintiles of intake per day, the modified DASH diet score, coffee and tea intake. Analyses of sugar intake from sweet food / beverages were additionally adjusted for fibre intake and calorie intake from other food (method described in Chapter 5: 5.1.5); analyses of fibre intake were additionally adjusted for sugar intake from sweet food / beverages and total calorie intake (method described in Chapter 6: 6.1.5). Models adjusted for socio-demographic factors, health behaviours and other dietary factors were considered the final model.

### *7.1.7 Statistical analyses*

Inclusion criteria were described in Chapter 4: 4.4, Figure 6. The sample was further restricted to participants without extreme sugar intake (phase 3 / 5 / 7 / 9: 5 / 3 / 3 / 4) and extreme fibre intakes (phase 3 / 5 / 7 / 9: 9 / 15 / 12 / 11) as these have been shown to affect some results and missing data on financial insecurities (phase 3 / 5 / 7 / 9: 6 / 45 / 38 / 41) resulting in sample sizes for phase 3 / 5 / 7 / 9 of 7882 / 4817 / 4979 / 4971. For analyses including current grade level at phases 3 / 5 / 7 / 9: 6/ 2608 / 3459 / 4392 participants had to be excluded (resulting in phase 3 / 5 / 7 / 9: 7876 / 2209 / 1520 / 579 participants).

Associations were modelled using REM models for incident CMD and depression after 5 years only to ensure high power for interaction analyses. Incidence was defined as having a case while having been without current CMD at baseline. To accommodate sex differences found in the association of sugar intake from sweet food and beverages and CMD all models were run including an interaction between the dietary factor and sex. Initial models of financial insecurity and grade level with mood disorders were tested for sex interactions and interactions by data collection phase.

Interactions with dietary factors were tested against models adjusted for the dietary factor. The results are presented using estimated odds ratios for the association of financial insecurity and grade level plotted against sugar intake from sweet food / beverages and fibre intake, respectively. The post estimation command *lincom* was used to calculate Odds ratios at dietary intakes of 'mean – 1SD', 'mean' and 'mean +1SD' in men with financial insecurity or the lowest grade level, respectively. The presentation for men only is attributed to the inclusion of sex interactions with dietary factors.

Sensitivity analyses were run excluding participants with unknown or self-reported doctor diagnosis at each baseline.

## 7.2 Descriptive results

Nearly half of the sample experienced financial insecurities at collection phase 3, driven by not having enough money. In the later phases the prevalence reduced to a quarter, with 20% of the sample having difficulties with money and 14% with paying their bills. Table 49 shows the prevalence of financial insecurity by phase.

**Table 49 Prevalence of financial insecurities by phase**

| | Not having enough money | | Problems paying bills | | Any financial insecurity | |
|---|---|---|---|---|---|---|
| | Never | Ever | Never | Ever | Never | Ever |
| Phase 3 | 4337 (55.0) | 3545 (45.0) | 6131 (77.8) | 1751 (22.2) | 4111 (52.2) | 3771 (47.9) |
| Phase 5 | 3121 (64.8) | 1696 (35.2) | 3889 (80.8) | 928 (19.2) | 2970 (61.8) | 1847 (38.3) |
| Phase 7 | 3735 (75.0) | 1244 (25.0) | 4107 (82.4) | 872 (17.6) | 3517 (70.6) | 1462 (29.4) |
| Phase 9 | 3972 (79.9) | 999 (20.1) | 4264 (85.8) | 707 (14.2) | 3772 (75.9) | 1199 (24.1) |

Financial insecurity was more prevalent in those with CMD, more prevalent in younger, non-white participants, those who were divorced or widowed, those in lower grade levels in the civil service, smokers, non-drinker and those with less than 7 hours of sleep per day (Table 50). Participants with generalised overweight or obesity and central obesity had higher prevalence of financial insecurity than those with recommended weight for height and waist circumferences (Table 50). Diabetics and people suffering from CVD were more likely to experience financial insecurity (Table 50). Most associations were similar at later phases. At later phases financial insecurity was more prevalent in women and participants who were less physically active (see Table A 22).

**Table 50 Crude association of financial insecurity with covariates at phase 3**

| Covariates at phase 3 | | Any financial insecurity | |
|---|---|---|---|
| | n | % | p |
| Sex | | | .16 |
| Men | 5474 | 47.3 | |
| Women | 2404 | 49.0 | |
| Age | | | <.001 |
| < median | 4144 | 50.3 | |
| > median | 3734 | 45.2 | |
| Ethnic Group | | | <.001 |
| White | 7276 | 45.9 | |
| South Asian | 364 | 71.4 | |
| Black | 238 | 71.4 | |
| Marital Status | | | <.001 |
| Married/cohabiting | 6052 | 48.1 | |
| Single | 1131 | 39.5 | |
| Divorced/widowed | 686 | 59.5 | |
| Last grade level in Civil service | | | <.001 |
| Highest | 3058 | 34.5 | |
| Intermediate | 3543 | 53.6 | |
| Lowest | 1277 | 63.8 | |
| Smoking | | | <.001 |
| Never Smoker | 3430 | 43.4 | |
| Ex-Smoker | 2893 | 48.7 | |
| Current Smoker | 1083 | 57.2 | |
| Physical activity | | | .28 |
| Non/mild non active | 2943 | 47.0 | |
| Moderate | 3498 | 48.9 | |
| Vigorous active | 1437 | 47.3 | |
| Alcohol consumption | | | <.001 |
| None | 1840 | 53.3 | |
| Moderate | 4133 | 46.9 | |
| Heavy | 1897 | 44.5 | |
| Sleep duration | | | <.001 |
| less than 7 h/day | 1993 | 54.1 | |
| ≥ 7 h/day | 5875 | 45.7 | |
| BMI | | | <.001 |
| Normal, <25kg/$m^2$ | 3944 | 44.9 | |
| Overweight | 2844 | 50.6 | |
| Obese. ≥30kg/$m^2$ | 709 | 54.0 | |
| Central obesity (W / M) | | | <.001 |
| No | 6771 | 47.2 | |
| Yes (Waist ≥88/ 102cm) | 651 | 54.7 | |
| Diabetes | | | .004 |
| No | 7660 | 47.6 | |
| Yes | 218 | 57.3 | |
| CVD | | | .032 |
| No | 7611 | 47.6 | |
| Yes | 267 | 54.3 | |
| Cancer | | | .86 |
| No | 7769 | 47.9 | |
| Yes | 100 | 47.0 | |

Abbreviations: BMI, Body mass index; CVD, cardiovascular disease; GHQ, General Health Questionnaire; M, men; W, women.

Prevalence of financial insecurity was higher in participants with lower diet quality scores, men with higher sugar intake from sweet food / beverages, and men and women with lower fibre intakes (see Table 51). These associations were less stable over time (see Table A 23). At later phases association with sugar intake from sweet food / beverages and fibre intakes were weaker and partly disappeared. Additionally, there was an association with lower energy and coffee/tea intakes (see Table A 20).

**Table 51 Crude association of financial insecurity with diet at phase 3**

| Covariates at phase 3 | | **Any financial insecurity** | |
|---|---|---|---|
| | n | % | p |
| Energy intake (kcal) | | | .26 |
| < median | 3939 | 48.5 | |
| > median | 3939 | 47.2 | |
| Modified DASH diet score | | | .007 |
| < median | 4439 | 49.2 | |
| > median | 3435 | 46.1 | |
| Fish intake | | | .45 |
| < median | 4475 | 48.2 | |
| > median | 3403 | 47.4 | |
| Tea/coffee | | | .92 |
| ≤ 1 cup of either/day | 689 | 48.0 | |
| > 1 cup of either/day | 7189 | 47.8 | |
| Sugar intake from sweet food / beverages (M) | | | .002 |
| < median | 2434 | 49.7 | |
| > median | 3040 | 45.4 | |
| Sugar intake from sweet food / beverages (W) | | | .36 |
| < median | 1505 | 49.8 | |
| > median | 899 | 47.8 | |
| Fibre intake (energy adj.) (M) | | | <.001 |
| < median | 2605 | 49.8 | |
| > median | 2869 | 45.1 | |
| Fibre intake (energy adj.) (W) | | | .020 |
| < median | 1333 | 51.2 | |
| > median | 1071 | 46.4 | |

Abbreviations: DASH, Dietary Approaches to Stop Hypertension; M, men; W, women.

## 7.3 Results

### *7.3.1 Association between financial insecurity with CMD*

Financial insecurity was associated with increased odds of incident CMD after 5 years (Table 52: Model 0) in models adjusted for age, sex, ethnicity and after adjustment for socio-demographic factors, health behaviours including dietary factors, adiposity and disease (Table 45: Model 3). Associations did not differ by sex (LR-test p=0.63), data collection phase (LR-test p=0.76) and when those with unknown or self-reported doctor diagnosis at each baseline were excluded from the analysis (not shown).

**Table 52 Association of financial insecurity and incident CMD after 5 years[a]**

| | | Incident CMD 5y later, OR (95%-CI) | | | | |
|---|---|---|---|---|---|---|
| | events / person-observations | Model 0[b] | Model 0*[c] | Model 1[d] | Model 2[e] | Model 3[f] |
| Financial insecurity | | | | | | |
| never | 742 / 4545 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| ever | 1076 / 9817 | 1.48*** (1.32, 1.66) | 1.47*** 1.30, 1.66) | 1.48*** (1.31, 1.68) | 1.47*** (1.30, 1.67) | 1.47*** (1.30, 1.67) |

* p<.05, **p<.005, *** p<.001.
[a]Prospective association across phases 3, 5, 7, 9 for CMD.
[b]CMD model 0 (2032 events / 16029 person observations); adjusted for age, sex, ethnicity.
[c]Model 0*: Model 0 in sample without missing in covariates for Models 1-3.
[d]Model 1: additionally adjusted for marital status, last grade level in civil service, smoking, alcohol intake, physical activity, sleep duration.
[e]Model 2: additionally adjusted fish intake, modified DASH diet score, coffee and tea intake, fibre intake, sugar intake from sweet food / beverages and total calories.
[f]Model 3: additionally adjusted for BMI, central adiposity, baseline CVD, diabetes and cancer.

**Interaction with sugar intake from sweet food / beverages**

In the association between financial insecurity and CMD there was no statistically significant interaction between financial insecurity and sugar intake from sweet food / beverages before ($OR_{interaction}$ 1.04, 95%-CI 0.94, 1.15; p=0.44, Figure 17: Model 0) and after adjustment ($OR_{interaction}$ 1.04, 95%-CI 0.93, 1.16; p=0.50; Figure 17: Model 3). Figure 17 shows the estimated odds ratio in men of incident CMD 5 years later for financial insecurity in comparison to those with no financial insecurity at sugar intakes from sweet food / beverages of 'mean – 1SD', 'mean' and 'mean +1SD'. There was a non-significant trend to higher odds of incident CMD 5 years later with higher intakes of sugar from sweet food / beverages.

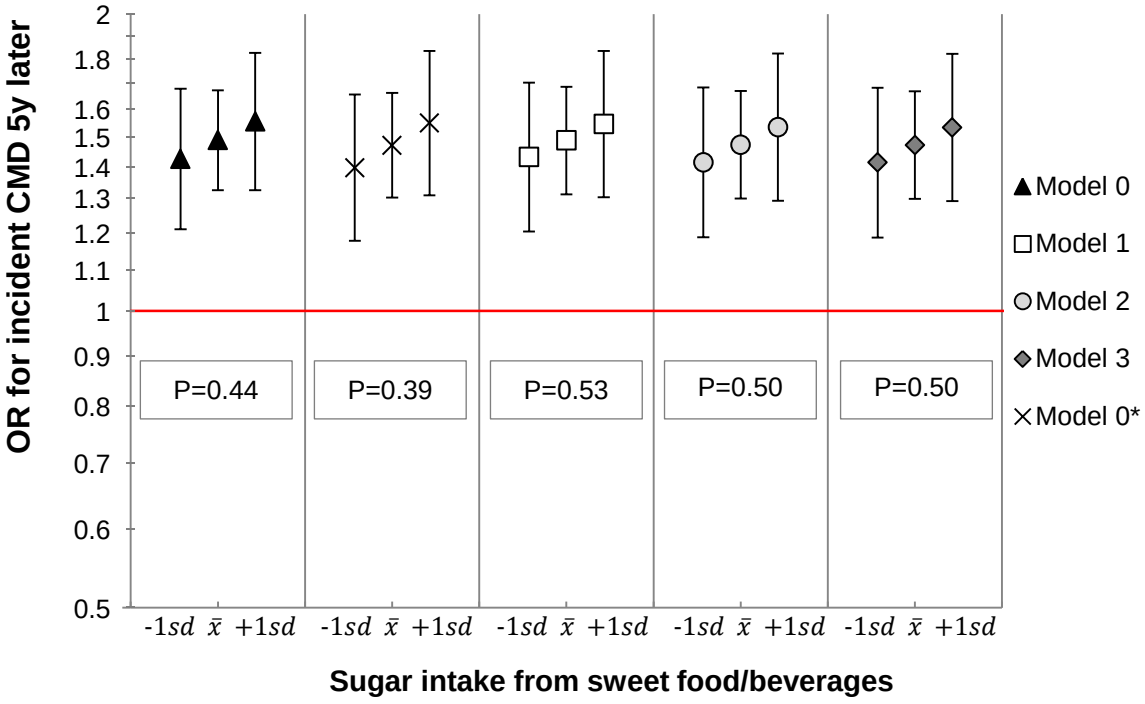



**Figure 17 Association, in men, of financial insecurity with incident CMD 5y later, estimated at the mean and mean ±1 SD of sugar intake from sweet food / beverages (Reference: OR=1 indicates no association between financial insecurity and incident CMD 5y later)**

P-values are for test of interaction of the effect of financial insecurity on incident CMD 5y later with sugar intake from sweet food / beverages.
Model 0 adjusted for age, sex, ethnicity, sugar intake from sweet food beverages and sugar intake from sweet food beverages*sex in the maximum eligible sample: 2032 events / 16029 person observations.
Model 0*: Model 0 in sample without missing in covariates for Models 1-3: 1818 cases / 14362 Person observations.
Model 1: additionally adjusted for marital status, last grade level in civil service, smoking, alcohol intake, physical activity, sleep duration.
Model 2: additionally adjusted fish, total calorie intake, modified DASH diet score, fibre intake*sex, coffee and tea intake.
Model 3: additionally adjusted for BMI, central adiposity, baseline CVD, diabetes and cancer.

### Interaction with dietary fibre intake

Figure 18 shows the estimated odds ratio in men for the association of financial insecurity with incident CMD 5 years later, at 'mean – 1SD', 'mean' and 'mean +1SD' of fibre intake. The association between financial insecurity and incident CMD 5 years later did not differ by fibre intake in minimally adjusted models ($OR_{interaction}$ 0.94, 95%-CI 0.80, 1.10; p=0.42) in the maximum eligible sample (see Figure 18: Model 0). Excluding participants with missing data in covariates strengthened the interaction considerably suggesting a lower chance of developing CMD 5 years later in those with lower fibre intakes, but this association remained statistically insignificant ($OR_{interaction}$ 0.89, 95%-CI 0.75, 1.05; p=0.16; Figure 18: Model 0*). Further adjustment marginally attenuated the association ($OR_{interaction}$ 0.88, 95%-CI 0.75, 1.04; p=0.13; Figure 18: Model 3).

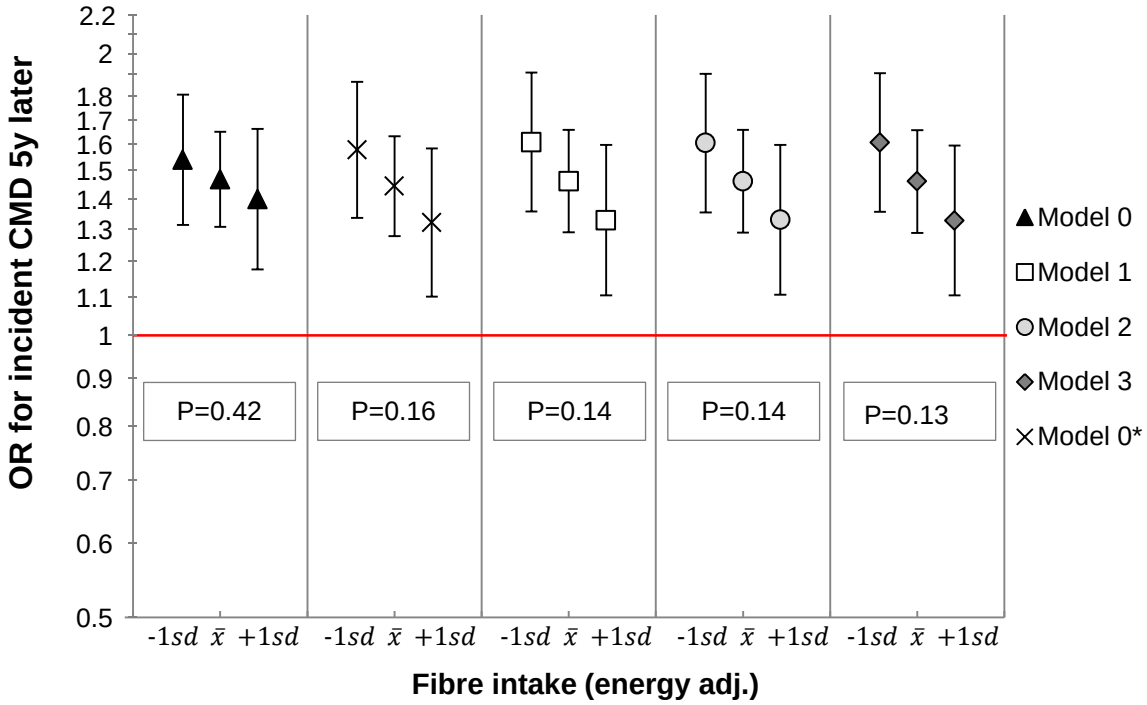



**Figure 18 Association, in men, of financial insecurity with incident CMD 5y later, estimated at the mean and mean ±1 SD of fibre intake (Reference: OR=1 indicates no association between financial insecurity and incident CMD 5y later)**

P-values are for test of interaction of the effect of financial insecurity on incident CMD 5y later with fibre intake.

Model 0 adjusted for age, sex, ethnicity, sugar intake from fibre intake from fibre intake*sex in the maximum eligible sample: 2032 events / 16029 person observations.

Model 0*: Model 0 in sample without missing in covariates for Models 1-3: 1818 cases / 14362 Person observations.

Model 1: additionally adjusted for marital status, last grade level in civil service, smoking, alcohol intake, physical activity, sleep duration.

Model 2: additionally adjusted fish, total calorie intake, modified DASH diet score, sugar intake from sweet food / beverages*sex, coffee and tea intake.

Model 3: additionally adjusted for BMI, central adiposity, baseline CVD, diabetes and cancer.

Associations did not differ when those with unknown or self-reported doctor diagnosis at each baseline were excluded from the analysis.

### *7.3.2 Association of financial insecurity with depression*

Participants with financial insecurity had twice the odds of incident depression after 5 years than those without (Table 53: Model 0) in models adjusted for age, sex, ethnicity. This association remained after further adjustment for socio-demographic factors, health behaviours including dietary factors, adiposity and diseases (Table 53: Model 3). The association between financial insecurity and depression did not differ by sex (LR-test p=0.90), data collection phase (LR-test p=0.87) and when those with unknown or self-reported doctor diagnosis at each baseline were excluded from the analysis (not shown).

**Table 53 Association of financial insecurity and incident depression after 5 years[a]**

| | | Incident depression 5y later, OR (95%-CI) | | | | |
|---|---|---|---|---|---|---|
| | events / person-observations | Model 0[b] | Model 0*[c] | Model 1[d] | Model 2[e] | Model 3[f] |
| Financial insecurity | | | | | | |
| never | 284 / 6965 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| ever | 418 / 2459 | 2.09*** (1.68, 2.62) | 2.18*** (1.72, 2.76) | 2.01*** (1.59, 2.54) | 2.01*** (1.59, 2.54) | 2.00*** (1.58, 2.53) |

* p<.05, **p<.005, *** p<.001.
[a]Prospective association across phases 7, 9 for depression.
[b]Depression model 0 (789 events / 10501 person observations); adjusted for age, sex, ethnicity
[c]Model 0*: Model 0 in sample without missing in covariates for Models 1-3.
[d]Model 1: additionally adjusted for marital status, last grade level in civil service, smoking, alcohol intake, physical activity, sleep duration.
[e]Model 2: additionally adjusted fish intake, modified dash score, coffee and tea intake, fibre intake, sugar intake from sweet food / beverages and total calories.
[f]Model 3: additionally adjusted for BMI, central adiposity, baseline CVD, diabetes and cancer.

**Interaction with sugar intake from sweet food / beverages**

There was no statistical significant interaction of sugar intake from sweet food / beverages in the association between financial insecurity and incident depression 5 years later before ($OR_{interaction}$ 1.09, 95%-CI 0.89, 1.33; p=0.41; Figure 19: Model 0) and after adjustment for all covariates ($OR_{interaction}$ 1.06, 95%-CI 0.86, 1.30; p=0.59; Figure 19: Model 3). Figure 19 shows the estimated odds ratio for the association of financial insecurity with incident depression 5 years later at 'mean–1SD', 'mean' and 'mean+1SD' intake of sugar from sweet food / beverages in men.

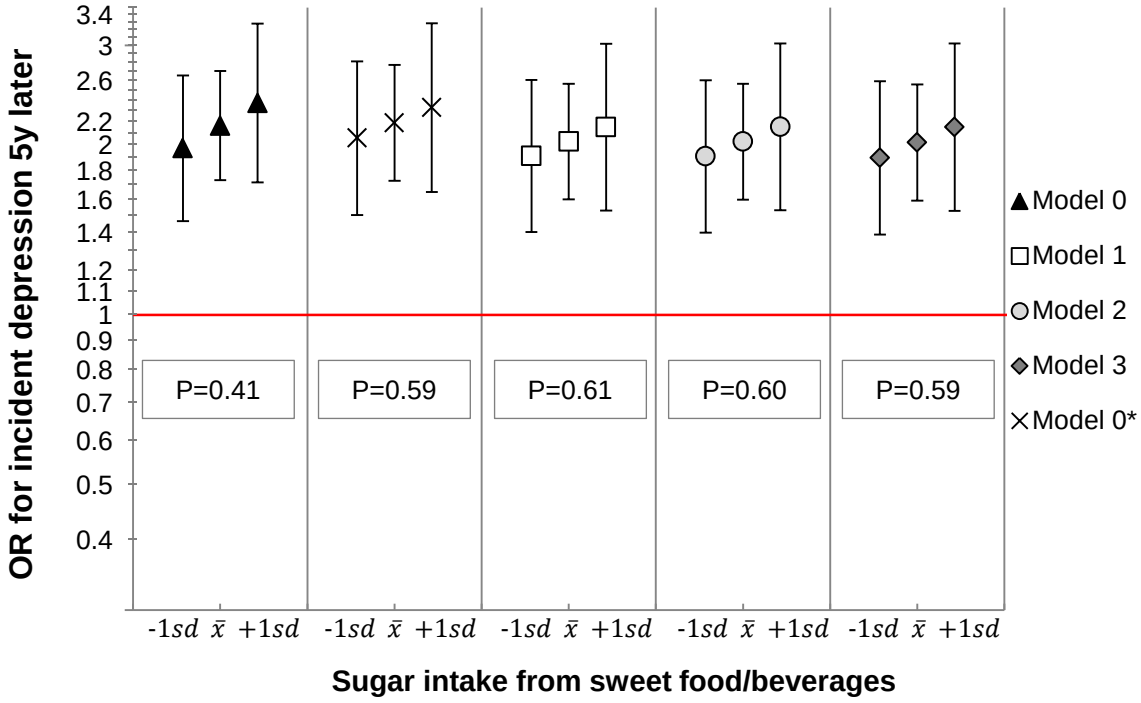



**Figure 19 Association, in men, of financial insecurity with incident depression 5y later, estimated at the mean and mean ±1 SD of sugar intake from sweet food / beverages (Reference: OR=1 indicates no association between financial insecurity and incident depression 5y later)**

P-values are for test of interaction of the effect of financial insecurity on incident depression 5y later with sugar intake from sweet food / beverages.
Model 0 adjusted for age, sex, ethnicity, sugar intake from sweet food beverages and sugar intake from sweet food beverages*sex in the maximum eligible sample; 789 events / 10501 person observations.
Model 0*: Model 0 in sample without missing in covariates for Models 1-3: 702 events / 9424 person observations.
Model 1: additionally adjusted for marital status, last grade level in civil service, smoking, alcohol intake, physical activity, sleep duration.
Model 2: additionally adjusted fish, total calorie intake, modified DASH diet score, fibre intake*sex, coffee and tea intake.
Model 3: additionally adjusted for BMI, central adiposity, baseline CVD, diabetes and cancer.

The interaction was slightly strengthened when person-observations with unknown or self-reported doctor diagnosis at each baseline were excluded, both before ($OR_{interaction}$ 1.11, 95%-CI 0.91, 1.36; p=0.29) and ($OR_{interaction}$ 1.09, 95%-CI 0.89, 1.34 p=0.42) after adjustment.

**Interaction with dietary fibre intake**

Figure 20 shows the estimated odds ratio in men for the association of financial insecurity with incident depression 5 years later, at 'mean – 1SD', 'mean' and 'mean +1SD' of fibre intake. Fibre intake did not change the association between financial insecurity and incident depression 5 years later in minimally adjusted models ($OR_{interaction}$ 1.00, 95%-CI 0.74, 1.36, p=0.98) in the maximum eligible sample (Figure 20: Model 0). Excluding participants with missing data in covariates strengthened the interaction marginally ($OR_{interaction}$ 0.93, 95%-CI 0.68, 1.27; p=0.67; Figure 20: Model 0*). Further adjustment did not change the results ($OR_{interaction}$ 0.91, 95%-CI 0.66, 1.23; p=0.53; Figure 20: Model 3). There was no evidence that energy adjusted fibre intake reduced the odds for incident depression in those with financial insecurity. This association did not differ when person-observations with unknown or self-reported doctor diagnosis at each baseline were excluded from the analysis (not shown).

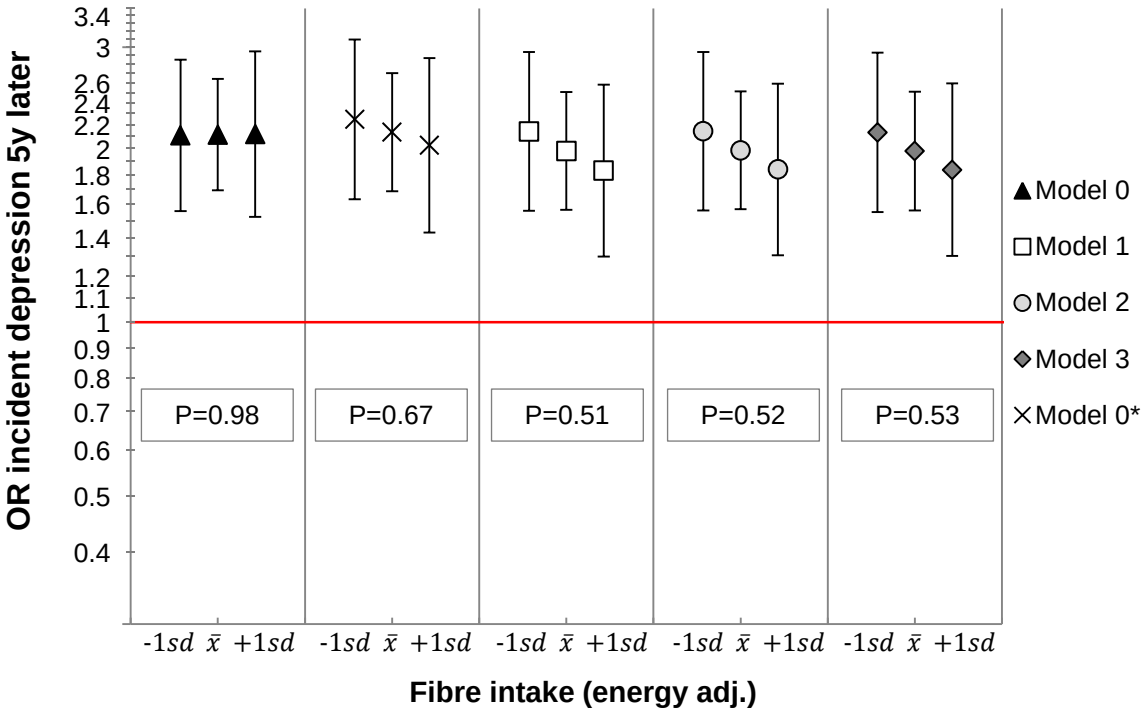



**Figure 20 Association, in men, of financial insecurity with incident depression 5y later, estimated at the mean and mean ±1 SD of fibre intake (Reference: OR=1 indicates no association between financial insecurity and incident depression 5y later)**

P-values are for test of interaction of the effect of financial insecurity on incident depression 5y later with fibre intake.
Model 0 adjusted for age, sex, ethnicity, sugar intake from fibre intake and fibre intake*sex in the maximum eligible sample: 789 events / 10501 person observations.
Model 0*: Model 0 in sample without missing in covariates for Models 1-3: 702 events / 9424 person observations.
Model 1: additionally adjusted for marital status, last grade level in civil service, smoking, alcohol intake, physical activity, sleep duration.
Model 2: additionally adjusted fish, total calorie intake, modified DASH diet score, sugar intake from sweet food / beverages*sex, coffee and tea intake.
Model 3: additionally adjusted for BMI, central adiposity, baseline CVD, diabetes and cancer.

### *7.3.3 Association of last grade level in civil service and CMD*

Grade level was not associated with CMD 5y later in models adjusted for age, sex and ethnicity (see Table 54). Adjustment for health behaviours and marital status attenuated the association further (Table 54: Model 1). There was no association of current grade level with incident CMD 5 years later. Associations did not differ by sex (LR-test for last grade level p=0.54, for current grade level p=0.77), data collection phase (LR-test p=0.48 and p=0.38) and when person-observations with self-reported depression diagnosis at baseline were excluded (not shown).

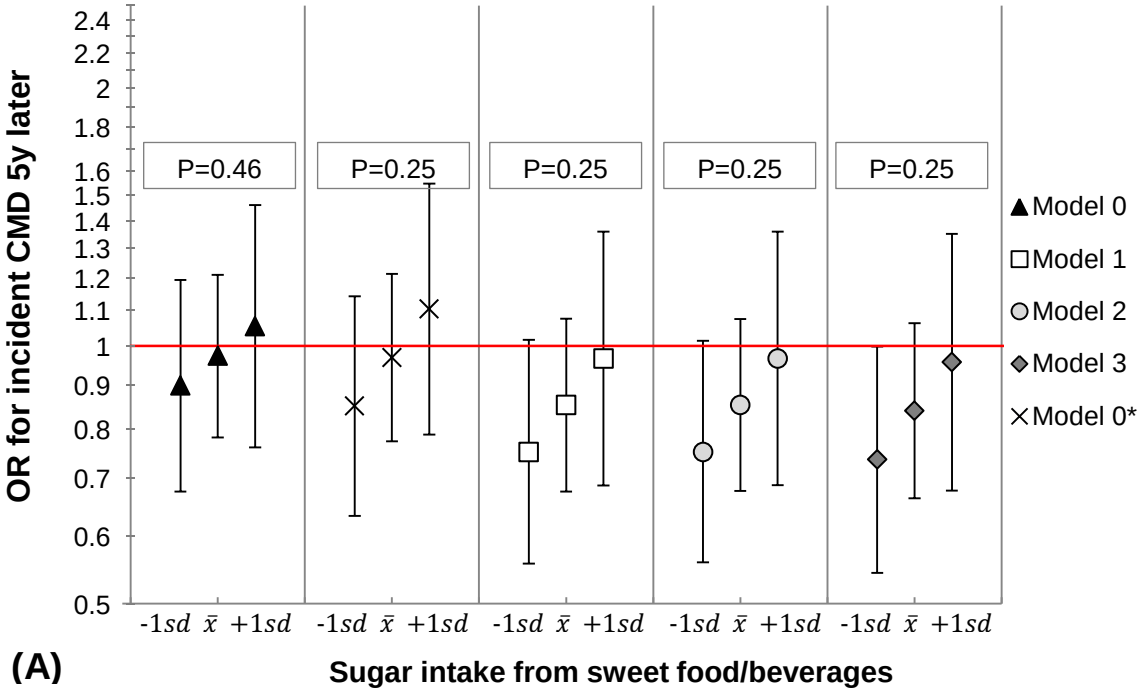
**Table 54 Associations of last and current grade level and incident CMD 5 years later[a]**

| | | Incident CMD 5y later, OR (95%-CI) | | | | |
|---|---|---|---|---|---|---|
| | events / person-observations | Model 0[b] | Model 0*[c] | Model 1[d] | Model 2[e] | Model 3[f] |
| **Last grade level in civil service** | | | | | | |
| high | 793 / 6667 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| medium | 809 / 6134 | 1.07 (0.94, 1.22) | 1.01 (0.88, 1.15) | 0.96 (0.84, 1.10) | 0.97 (0.85, 1.11) | 0.97 (0.85, 1.11) |
| low | 216 / 1561 | 0.96 (0.78, 1.20) | 0.91 (0.72, 1.13) | 0.82 (0.66, 1.04) | 0.82 (0.65, 1.04) | 0.82 (0.65, 1.04) |
| p for trend | 1818 / 14362 | .81 | .58 | .15 | .17 | .16 |
| **Current grade level in civil service** | | | | | | |
| high | 428 / 3052 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| medium | 459 / 3157 | 0.91 (0.76, 1.09) | 0.89 (0.74, 1.06) | 0.89 (0.74, 1.07) | 0.89 (0.74, 1.07) | 0.91 (0.76, 1.09) |
| low | 148 / 883 | 1.06 (0.80, 1.41) | 0.98 (0.73, 1.31) | 0.99 (0.74, 1.33) | 0.99 (0.74, 1.33) | 1.06 (0.80, 1.41) |
| p for trend | 1035 / 7092 | .89 | .51 | .57 | .57 | .89 |

* p<.05, **p<.005, *** p<.001.
[a]Prospective association across phases 3, 5, 7, 9 for last grade level and current grade level.
[b]CMD model 0 for last grade level (2032 events / 16029 person observations); for current grade level (1162 events / 8001 person observations); adjusted for age, sex, ethnicity.
[c]Model 0*: Model 0 in sample without missing in covariates for Models 1-3.
[d]Model 1: additionally adjusted for marital status, smoking, alcohol intake, physical activity, sleep duration.
[e]Model 2: additionally adjusted fish intake, modified DASH diet score, coffee and tea intake, fibre intake, sugar intake from sweet food / beverages and total calories.
[f]Model 3: additionally adjusted for BMI, central adiposity, baseline CVD, diabetes and cancer.

**Interaction with sugar intake from sweet food / beverages**

Figure 21 shows the estimated odds ratio in men of incident CMD 5 years later for last grade level (A) and current grade level (B) in comparison to those with highest (last / current) grade level at sugar intakes from sweet food / beverages of 'mean – 1SD', 'mean' and 'mean +1SD'.



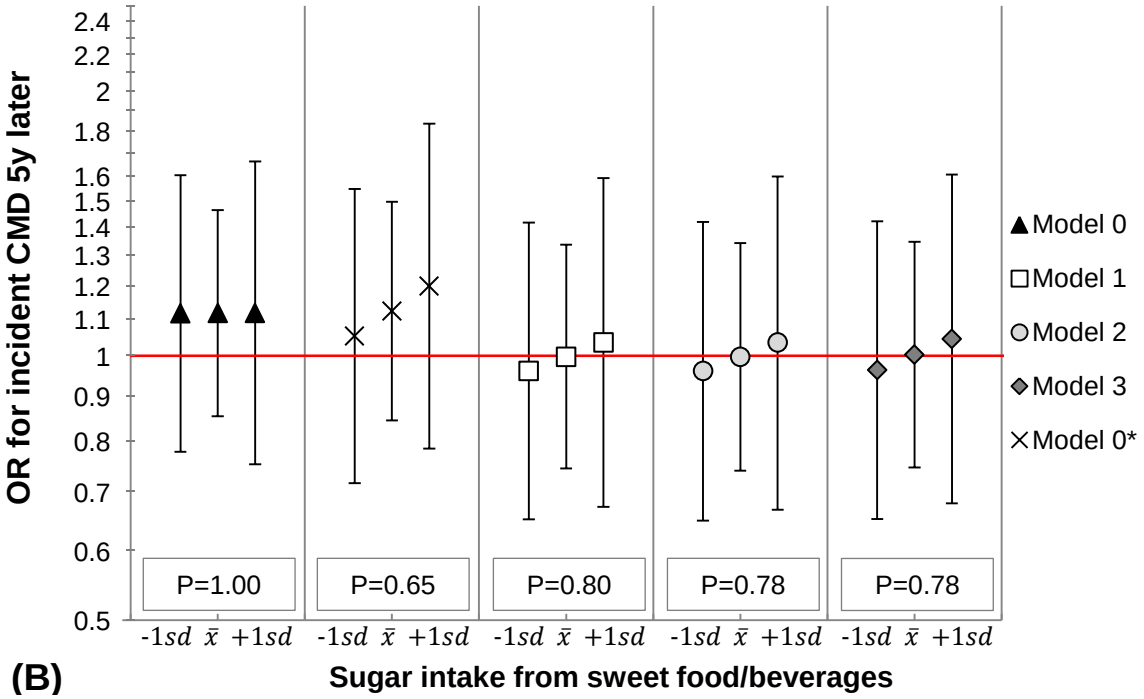




**Figure 21 Association, in men, of lowest last (A) and current (B) grade level in civil service with incident CMD 5y later, estimated at the mean and mean±1SD of sugar intake from sweet food / beverages (Reference: OR=1 indicates no association between last (A) or current (B) grade level and incident CMD 5y later)**
P-values are for test of interaction of the effect of lowest grade level on incident CMD 5y later with sugar intake from sweet food / beverages.

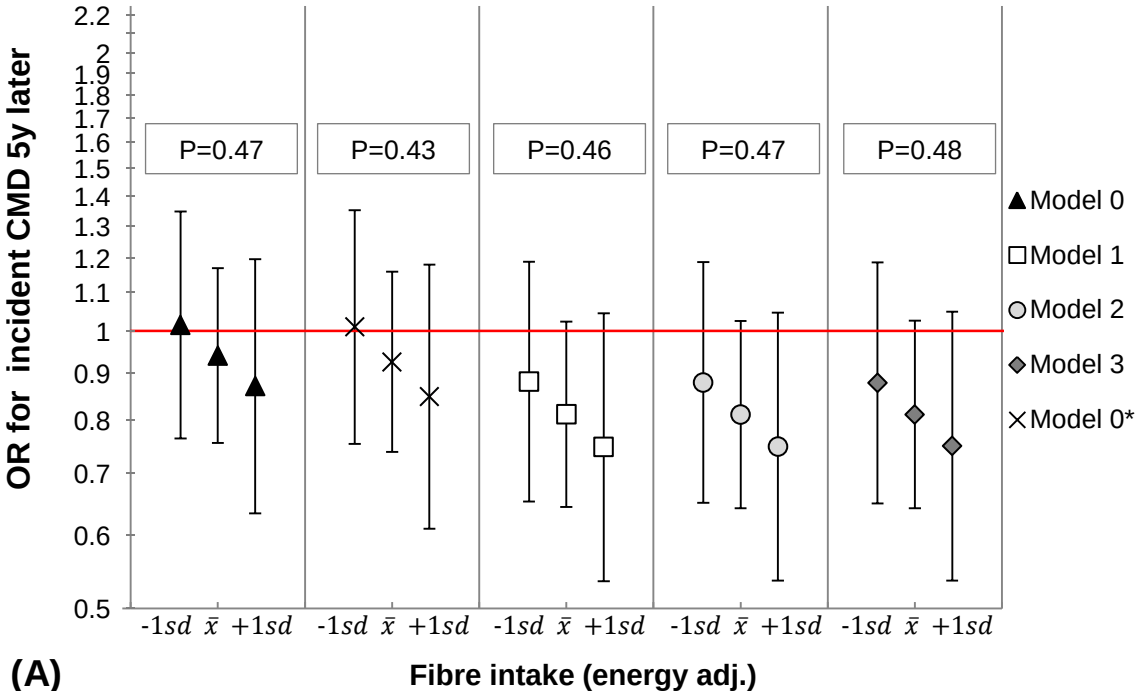
Model 0 adjusted for age, sex, ethnicity, sugar intake from sweet food beverages and sugar intake from sweet food beverages*sex in the maximum eligible sample for last grade level: 2032 events / 16029 person observations and for current grade level: 1162 events / 8001 person observations.
Model 0*: Model 0 in sample without missing in covariates for Models 1-3 for last grade level: 2032 cases / 16029 person observations, for grade 1162 cases / 8001 person observations.
Model 1: additionally adjusted for marital status, smoking, alcohol intake, physical activity, sleep duration.
Model 2: additionally adjusted fish, total calorie intake, modified DASH diet score, fibre intake*sex, coffee and tea intake.
Model 3: additionally adjusted for BMI, central adiposity, baseline CVD, diabetes and cancer.

There was no statistical significant interaction between sugar intake from sweet food / beverages and lowest last grade level ($OR_{interaction}$ 1.08, 95%-CI 0.88, 1.31; p=0.46; Figure 21 (A): Model 0) and lowest current grade level ($OR_{interaction}$ 1.00, 95%-CI 0.78, 1.28; p=1.00; Figure 21 (B): Model 0) in the associations between last grade level and current grade with incident CMD 5 years later. Reducing the sample to those with no missing data in covariates, resulted in slightly stronger interactions with lowest last grade level ($OR_{interaction}$ 1.13, 95%-CI 0.92, 1.39; p=0.25; Figure 21 (A): Model 0*), and lowest current grade level ($OR_{interaction}$ 1.06, 95%-CI 0.82, 1.38; p=0.65; Figure 21 (B): Model 0). Further adjustment did not affect the interactions with last grade level ($OR_{interaction}$ 1.13, 95%-CI 0.92, 1.39; p=0.25; Figure 21 (A): Model 3) and current grade level ($OR_{interaction}$ 1.04, 95%-CI 0.80, 1.35; p=0.78; Figure 21 (B): Model 3).

There were no significant interactions with sugar intake from sweet food / beverages and intermediate last and current grade level in the association of intermediate grade level and incident CMD 5y years later (not shown).The interaction with last grade level weakened when person-observations with baseline self-reported depression diagnosis were excluded before ($OR_{interaction}$ 1.04, 95%-CI 0.85, 1.28; p=0.68) and after adjustment ($OR_{interaction}$ 1.09, 95%-CI 0.98, 1.35; p=0.41).

**Interaction with dietary fibre intake**

Figure 22 shows the estimated odds ratio in men of incident CMD 5 years later for last grade level (A) and current grade level (B) in comparison to those with highest (last / current) grade level at fibre intakes of 'mean – 1SD', 'mean' and 'mean +1SD'.



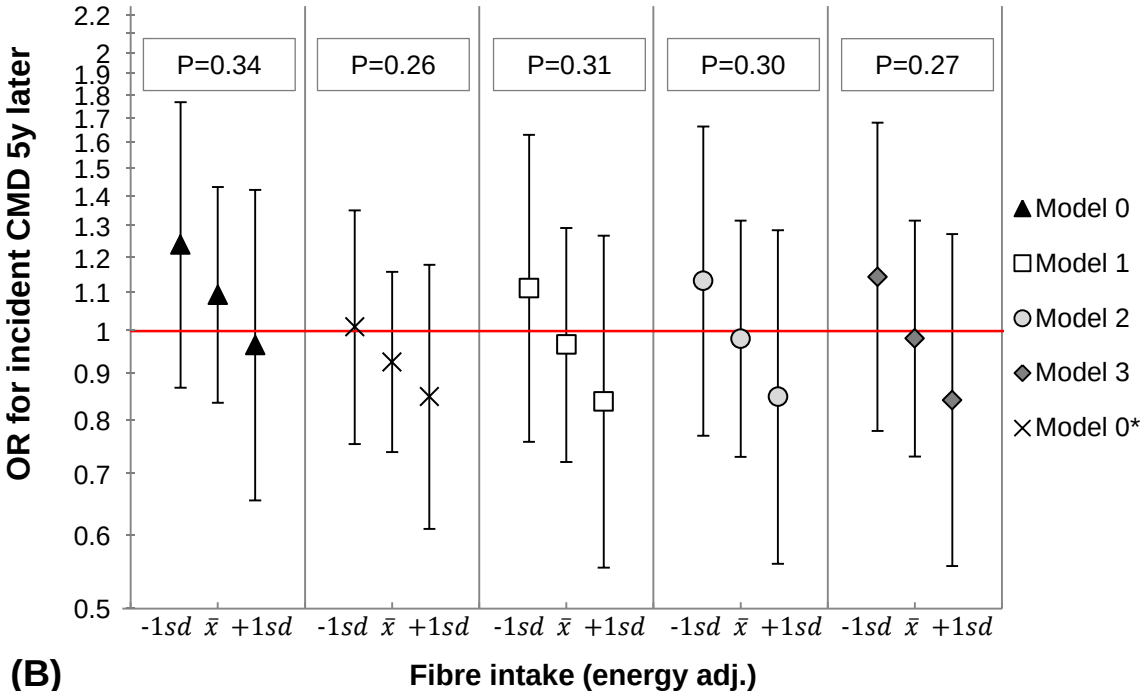




**Figure 22 Association, in men, of lowest last (A) and current (B) grade level in civil service with incident CMD 5y later, estimated at the mean and mean ±1 SD of fibre intake (Reference: OR=1 indicates no association between highest grade level and incident CMD 5y later)**

P-values are for test of interaction of the effect of lowest grade level on incident CMD 5y later with fibre intake.

Model 0 adjusted for age, sex, ethnicity, fibre intake and fibre intake *sex in the maximum eligible sample for last grade level: 2032 events / 16029 person observations and for current grade level: 1162 events / 8001 person observations.
Model 0*: Model 0 in sample without missing in covariates for Models 1-3 for last grade level: 2032 cases / 16029 person observations, for grade 1162 cases / 8001 person observations.
Model 1: additionally adjusted for marital status, smoking, alcohol intake, physical activity, sleep duration.
Model 2: additionally adjusted fish, total calorie intake, modified DASH diet score, sugar intake from sweet food / beverages*sex, coffee and tea intake.
Model 3: additionally adjusted for BMI, central adiposity, baseline CVD, diabetes and cancer.

In the association between last grade level and current grade and incident CMD 5 years later there was no statistically significant interaction between fibre intake and lowest last grade level ($OR_{interaction}$ 0.90, 95%-CI 0.69, 1.19; p=0.47; Figure 22 (A): Model 0) or lowest current grade level ($OR_{interaction}$ 0.85, 95%-CI 0.60, 1.19; p=0.34; Figure 22 (B): Model 0). Reducing the sample to those with no missing data in covariates did not affect the interactions with last grade level ($OR_{interaction}$ 0.89, 95%-CI 0.67, 1.19; p=0.43; Figure 22 (A: Model 0*) and only slightly changed that with current grade level ($OR_{interaction}$ 0.81, 95%-CI 0.56, 1.17; p=0.26; Figure 22 (B): Model 0*). There was a non-significant trend of lower odds for incident CMD 5 years later by fibre intake, that was not affected by further adjustments (Last grade level: $OR_{interaction}$ 0.90, 95%-CI 0.68, 1.20; p=0.48; Figure 22 (A): Model 3; current grade level: $OR_{interaction}$ 0.81, 95%-CI 0.57, 1.17; p=0.27; Figure 22 (B): Model 3).

There were no significant interactions with fibre intake and intermediate last and current grade level in the association with incident CMD 5y years later (not shown). Excluding person-observations with unknown or self-reported depression diagnosis at baseline did not change results.

### *7.3.4 Association of last grade level in civil service and depression*

Having been in the lowest grade level in the civil service was associated a 64% increased chance of depression in models adjusted for age, sex and ethnicity (Table 55: Model 0). Marital status and health behaviours explained the association of low current grade level with incident depression 5 years later. The association between last grade level and current grade level with depression did not differ by sex (LR-test p=0.86 and p=0.91) or data collection phase (LR-test p=0.97 and p=0.84) and when person-observations with unknown or self-reported depression diagnosis at baseline were excluded (not shown).

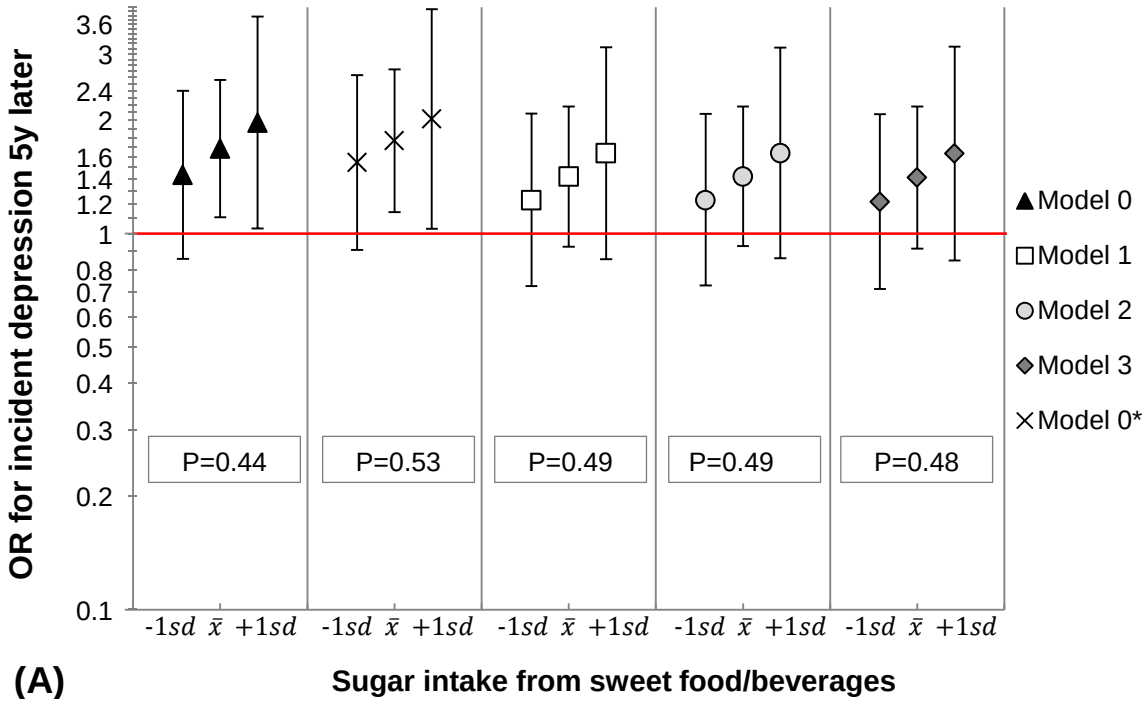
**Table 55 Association of last and current grade level and incident depression 5 years later[a]**

| | | Incident depression 5y later, OR (95%-CI) | | | | |
|---|---|---|---|---|---|---|
| | events / person-observations | Model 0[b] | Model 0*[c] | Model 1[d] | Model 2[e] | Model 3[f] |
| **Last grade level in civil service** | | | | | | |
| high | 262 / 4640 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| medium | 328 / 3918 | 1.35* (1.05, 1.73) | 1.39* (1.07, 1.81) | 1.21 (0.93, 1.56) | 1.22 (0.94, 1.58) | 1.23 (0.94, 1.59) |
| low | 112 / 866 | 1.64* (1.09, 2.47) | 1.71* (1.12, 2.62) | 1.35 (0.89, 2.05) | 1.35 (0.89, 2.05) | 1.35 (0.88, 2.07) |
| p for trend | 702 / 9424 | .006 | .004 | .097 | .095 | .093 |
| **Current grade level in civil service** | | | | | | |
| high | 72 / 1157 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| medium | 76 / 1005 | 0.97 (0.61, 1.54) | 0.96 (0.58, 1.58) | 0.80 (0.49, 1.32) | 0.77 (0.46, 1.29) | 0.76 (0.45, 1.30) |
| low | 25 / 247 | 1.47 (0.70, 3.10) | 1.42 (0.63, 3.22) | 0.87 (0.39, 1.96) | 0.82 (0.36, 1.90) | 0.79 (0.34, 1.87) |
| p for trend | 173 / 2409 | .49 | .59 | .53 | .44 | .40 |

* p<.05, **p<.005, *** p<.001.
[a]Prospective association across phases 3, 5, 7, 9 for last grade level and current grade level.
[b]Depression model 0 for last grade level (789 events / 10501 person observations); for current grade level (199 events / 2867); adjusted for age, sex, ethnicity.
[c]Model 0*: Model 0 in sample without missing in covariates for Models 1-3.
[d]Model 1: additionally adjusted for marital status, smoking, alcohol intake, physical activity, sleep duration.
[e]Model 2: additionally adjusted fish intake, modified DASH score, coffee and tea intake, fibre intake, sugar intake from sweet food / beverages and total calories.
[f]Model 3: additionally adjusted for BMI, central adiposity, baseline CVD, diabetes and cancer.

#### Interaction with sugar intake from sweet food / beverages

Figure 23 shows the estimated odds ratio in men of incident depression 5 years later for last grade level (A) and current grade level (B) in comparison to those with highest (last / current) grade level at sugar intakes from sweet food / beverages of ‘mean – 1SD’, ‘mean’ and ‘mean +1SD’.



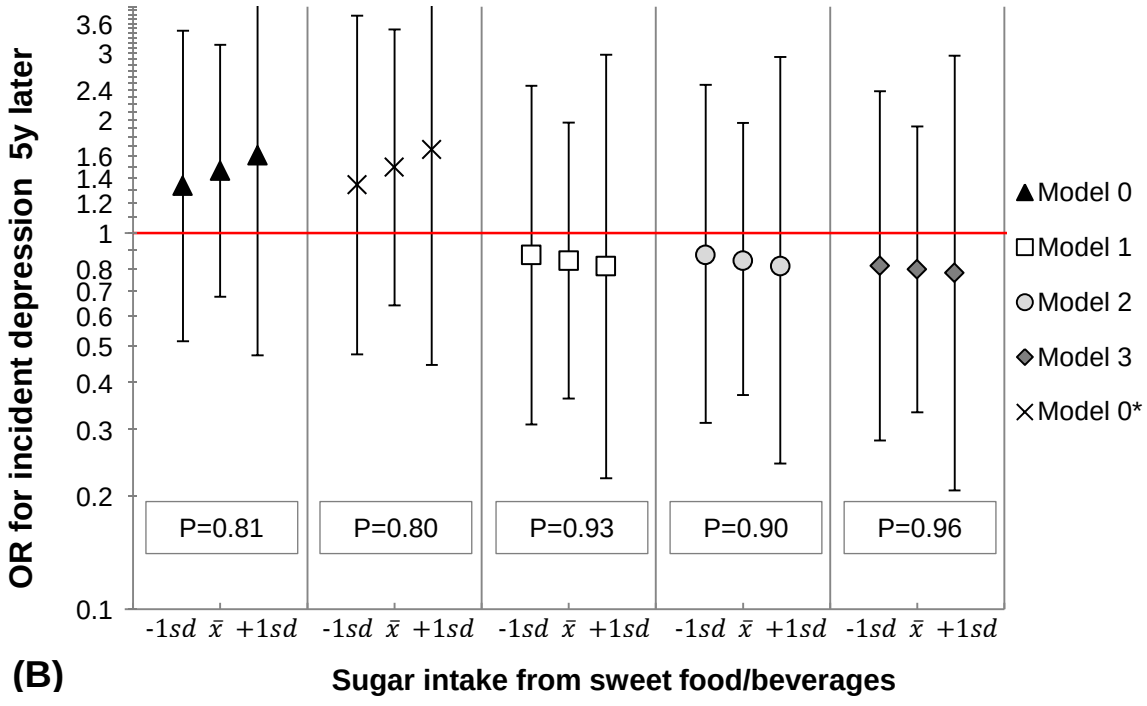




**Figure 23 Association, in men, of lowest last (A) and current (B) grade level in civil service with incident depression 5y later, estimated at the mean and mean ±1 SD of sugar intake from sweet food / beverages (Reference: OR=1 indicates no association between highest grade level and incident depression 5y later)**

P-values are for test of interaction of the effect of lowest grade level on incident depression 5y later with sugar intake from sweet food / beverages.

Model 0 adjusted for age, sex, ethnicity, sugar intake from sweet food beverages and sugar intake from sweet food beverages*sex in the maximum eligible sample for last grade level: 789 events / 10501 person observations and for current grade level: 199 events / 2867 person observations.

Model 0*: Model 0 in sample without missing in covariates for Models 1-3 for last grade level: 702 cases / 9424 person observations, for grade 173 cases / 2485 person observations

Model 1: additionally adjusted for marital status, smoking, alcohol intake, physical activity, sleep duration.

Model 2: additionally adjusted fish, total calorie intake, modified DASH diet score, fibre intake*sex, coffee and tea intake.
Model 3: additionally adjusted for BMI, central adiposity, baseline CVD, diabetes and cancer.

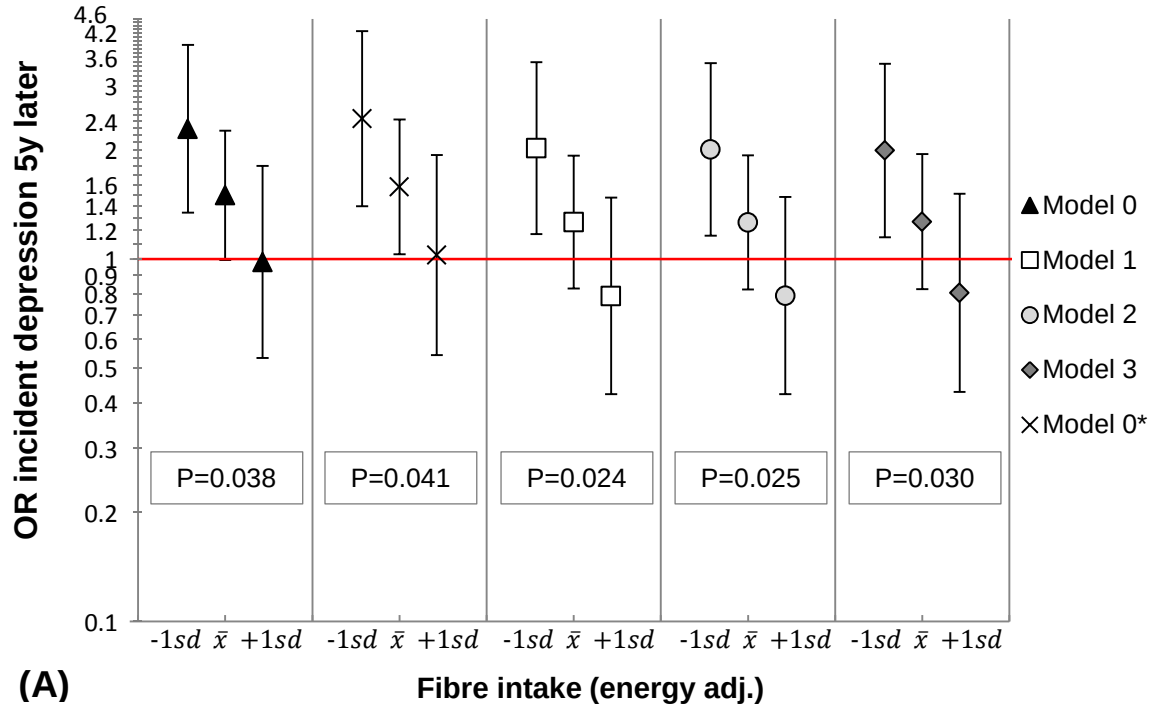
In the association of grade level with incident depression 5 years later, there was no statistically significant interaction between lowest last grade level ($OR_{interaction}$ 1.16, 95%-CI 0.80, 1.69; p=0.44; Figure 23 (A): Model 0) or lowest current grade level ($OR_{interaction}$ 1.09, 95%-CI 0.53, 2.23; p=0.81; Figure 23 (B): Model 0) with sugar intake from sweet food / beverages. After adjustment for health behaviours there was no association of current grade level and with incident depression entirely independent of sugar intake from sweet food / beverages ($OR_{interaction}$ 0.97, 95%-CI 0.46, 2.05; p=0.93; Figure 23 (B): Model 3).

Furthermore, there were no significant interactions between intermediate last and current grade level and sugar intake from sweet food / beverages in the association of intermediate grade level and incident depression 5y years later (not shown).

The association between lowest last grade level ($OR_{interaction}$ 1.19, 95%-CI 0.82, 1.73; p=0.36) and lowest current grade level ($OR_{interaction}$ 1.22, 95%-CI 0.60, 2.45; p=0.59) were slightly strengthened when person-observations with baseline unknown or self-reported doctor diagnosis of depression were excluded and the direction of the interaction with lowest current grade level remained after adjustment ($OR_{interaction}$ 1.17, 95%-CI 0.55, 2.59; p=0.69).

**Interaction with dietary fibre intake**

Figure 24 shows the estimated odds ratio in men of incident depression 5 years later for last grade level (A) and current grade level (B) in comparison to those with highest (last / current) grade level at fibre intakes of 'mean – 1SD', 'mean' and 'mean +1SD'.



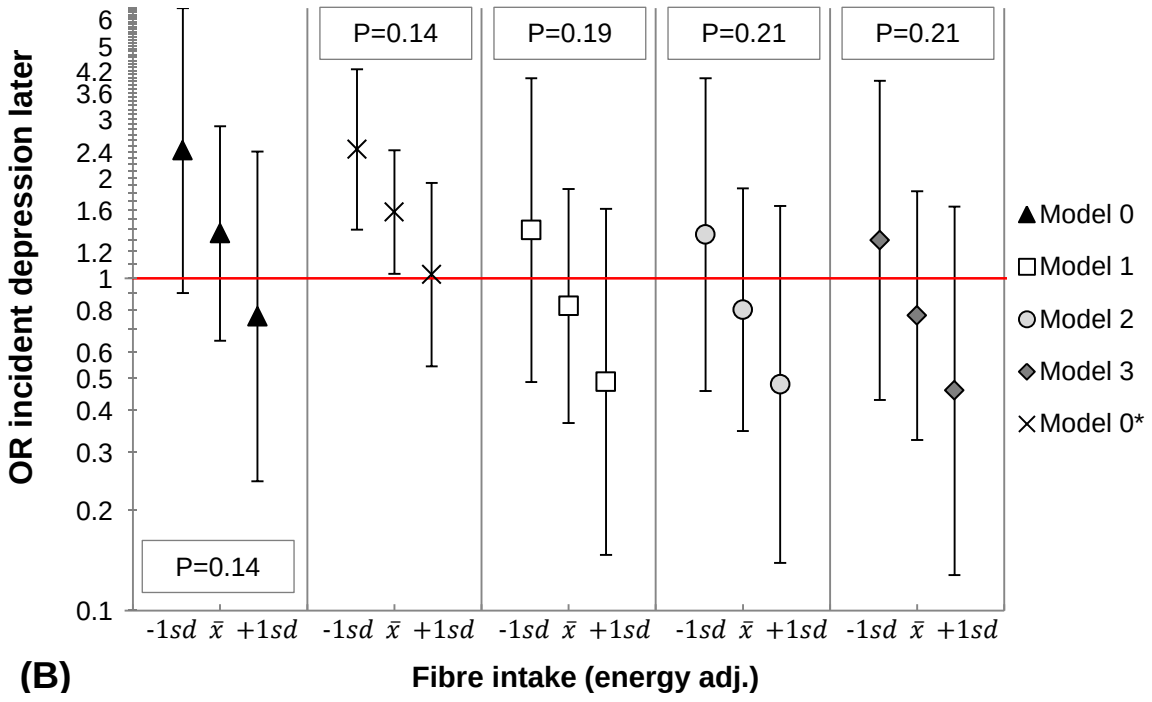




**Figure 24 Association, in men, of lowest last (A) and current (B) grade level in civil service with incident depression 5y later, estimated at the mean and mean ±1 SD of fibre intake (Reference: OR=1 indicates no association between highest grade level and incident depression 5y later)**

P-values are for test of interaction of the effect of lowest grade level on incident depression 5y later with fibre intake.

Model 0 adjusted for age, sex, ethnicity, fibre intake and fibre intake *sex in the maximum eligible sample for last grade level: 789 events / 10501 person observations and for current grade level: 199 events / 2867 person observations.
Model 0*: Model 0 in sample without missing in covariates for Models 1-3 for last grade level: 702 cases / 9424 person observations, for grade 173 cases / 2485 person observations.
Model 1: additionally adjusted for marital status, smoking, alcohol intake, physical activity, sleep duration.
Model 2: additionally adjusted fish, total calorie intake, modified DASH diet score, sugar intake from sweet food / beverages*sex, coffee and tea intake.
Model 3: additionally adjusted for BMI, central adiposity, baseline CVD, diabetes and cancer
P-values are for test of interaction of the effect of lowest grade level on incident depression 5y later with sugar intake from sweet food / beverages.

There was a statistically significant interaction between dietary fibre intake and lowest last grade level in the association with incident depression 5 years later ($OR_{interaction}$ 0.57, 95%-CI 0.33, 0.97; p=0.038; Figure 24 (A): Model 0). In fully adjusted models this resulted in estimated OR of 1.99 (95%-CI 1.15, 3.46) in men consuming 1SD less fibre than mean intakes, and 0.81 (95%-CI 0.43, 1.51) in men with 1SD more fibre intake than the mean (Figure 24 (A): Model 3; $OR_{interaction}$ 0.55, 95%-CI 0.32, 0.94; p=0.030).

There was a similar trend of lower chances for incident depression 5 years later in those in the lowest current grade level with higher fibre intakes compared to those in the lowest current grade level with lower fibre intakes ($OR_{interaction}$ 0.47, 95%-CI 0.17, 1.29; p=0.14; Figure 24 (B): Model 0). While the association of current grade level and incident depression 5 years later was explained by differences in health behaviours (Table 55: Model 3), the interaction with fibre intake was not affected (Model 3: $OR_{interaction}$ 0.50, 95%-CI 0.17, 1.47; p=0.21; Figure 24 (B): Model 3).

There were no significant interactions between intermediate last and current grade level and fibre intake in the association with incident depression 5y years later (not shown).

When person-observations with baseline unknown or self-reported doctor diagnosis of depression were excluded interactions with lowest last grade level were strengthened (minimally adjusted model: $OR_{interaction}$ 0.55, 95%-CI 0.32, 0.93; p=0.027; fully adjusted model: $OR_{interaction}$ 0.52, 95%-CI 0.30, 0.89; p=0.018) and current grade level (minimally adjusted model: $OR_{interaction}$ 0.46, 95%-CI 0.17, 1.25; p=0.13; fully adjusted model: $OR_{interaction}$ 0.49, 95%-CI 0.17, 1.47; p=0.20).

## 7.4 Interim discussion and summary

The aim of this chapter was to investigate the role of dietary factors, sugar intake from sweet food / beverages and fibre intake, as moderators in the association between financial insecurity and mood disorders. Additionally, the role in the association of grade level in the civil service and mood disorders was examined.

The interactions were mostly in the expected directions, but insignificant. It was hypothesised that those with financial insecurities and higher sugar intakes from sweet food / beverages would have higher odds for mood disorders, and those with financial insecurities and higher fibre intakes lower odds of mood disorders, but interactions were not significant and therefore did not support this hypothesis. The strongest interaction was reached in the interaction of fibre intake and financial insecurity with incident CMD 5 years later, but was above the 5% significance level ($p=0.13$). However, the association was lower in minimally adjusted models, suggesting that the association was affected by selection bias.

Interactions in the association of grade level and mood disorders were investigated as a proof of concept, whether interventions in diet could reduce health inequalities in mental health. Grade level was operationalised as grade level when last in the civil service and current grade level while still working in the civil service. It should to be noted, that although these grade levels may not be currently held, they can be seen as a measure of social position overall and midlife occupational position has been found to increase chances for post-retirement depressive symptoms (Virtanen et al., 2015). In our study the association of current grade level and depression showed a similar direction but did not reach statistical significance. This was most likely due to loss of power as 74% (person-observations: 7015) of person-observations had to be excluded from these analyses as participants had left the civil service.

There was a trend for lower odds of common mental disorder in participants in the lowest last grade level and lower sugar intakes from sweet food / beverages ($p=0.25$), which could not be replicated in models with current grade level. Participants in the lowest grade level when last in the civil service and higher fibre intakes had significantly lower chances of becoming new depression cases within 5 years than those in the same grade level but lower fibre intakes ($p<0.05$). This association was similar for those in the lowest grade level currently, but not statistically significant ($p=0.22$). Confidence intervals were substantially bigger in analyses of current grade level as the sample size was drastically reduced.

# Chapter 8 **Discussion**

In this chapter the findings are discussed. First findings, strengths and limitations of analyses in this thesis are summarised. Then internal and external validity are investigated and judgements are made in regard to the initial objectives. Finally, future research questions and policy implications are suggested and overall conclusions of the thesis are drawn.

## 8.1 Summary of principal findings

This thesis investigated the role of sugar intake from sweet food / beverages and fibre intake as predictors of mood disorders and as moderators of an association between financial insecurity and mood disorders.

Three objectives were investigated:

1st Objective: Is a diet high in sugar intake from sweet food and beverages a risk factor in mood disorders?

2nd Objective: Is a diet high in fibre intake a protective factor in mood disorders?

3rd Objective: Does sugar intake from sweet food / beverages, and dietary fibre intake, act as a moderator in the association between financial insecurity and mood disorders?

It was hypothesised that sugar intake from sweet food / beverages could increase the chance of mood disorders, and dietary fibre intake could decrease the chance of mood disorders. Finally, it was hypothesised that the association between financial insecurity and mood disorders could be strengthened by increased sugar intake from sweet food / beverages and weakened by high fibre intake.

### *8.1.1 Objective I: Association between sugar intake from sweet food / beverages and mood disorders*

There was a cross-sectional association between sugar intake from sweet food / beverages and CMD independent adjustment for all confounders. The prospective results supported the hypothesis in part. Per 30g additional sugar intake per day from either sweet food or beverages, equivalent to the sugar in one chocolate bar (53g) or a can of cola, the odds of being classified as having new minor psychiatric morbidity (CMD) after 5 years was increased by 9% among men (11418 person-observations) in Whitehall II. This association was independent of confounding factors (further discussed in 8.4.3). There were no statistically significant associations with incident CMD after 2 and 10 years, incident depressive symptoms and clinical depression in fully adjusted models. Sugar intake from sweet food and beverages was associated with an increased chance for recurrent but not new depression during follow-up in women (687 person-observations).

Because of the evidence of a sex interaction described above in Whitehall II it appeared valuable and necessary to test the sugar-depression hypothesis in an independent sample. The prospective analysis was repeated in data from the EPIC-

Norfolk cohort that recruited 30445 participants from the general population and included 55% women. The outcome measure of mood disorder in the replication cohort was incident antidepressant intake. The same sex difference was evident but the positive association between sugar intake from sweet food / beverages and incident antidepressant intake in men was weak (further discussed in 8.5.1 Dose-response relationship).

The availability of four waves of food intake in the Whitehall II data allowed useful extension of the analysis. The analyses assessed the presence of reverse causation: an association between baseline mood disorder and changes in sugar intake from sweet food / beverages over five years of follow-up. There was no evidence in this mode of analysis for this alternative explanation of the link between sugar intake and mood disorder.

### *8.1.2 Objective II: Association between dietary fibre intake and mood disorders*

There was no cross-sectional association between fibre intake and CMD after adjustment for socio-demographic factors and health behaviours. However, prospective results supported the hypothesis. Per 10g additional fibre intake per day, equivalent to one can of baked beans (200g) or 130g of oats, the odds of being a CMD case after 5 years was decreased by 16% and 20% after 10 years among men and women (15487 person-observations) in Whitehall II. The odds of being classified as having depression after 10 years was decreased by 22%, but the association was only evident when fibre intake was operationalised continuously. Associations were independent of confounders (further discussed in 8.4.3). After adjustment for confounders and exclusion of an outlier, odds of having clinical depression was decreased by 42% per 10g additional fibre intake. There were no statistically significant associations with CMD after 2 years and incident depressive symptoms after 5 years in fully adjusted models. The hypothesised association with reduced odds for recurrent disorders was not supported as associations were attenuated by adjustment for other dietary factors.

There was no evidence for an association between baseline mood disorders and change in fibre intake over 5 years of follow-up.

### *8.1.3 Objective III: Moderation analysis of the association between financial insecurity and mood disorders by sugar intake from sweet food / beverages and dietary fibre intake*

Associations between sugar intake from sweet food / beverages, fibre intake and mood disorders were modest. In the third objective it was investigated whether these dietary factors could also act as moderators of an association between financial insecurity and mood disorders. This third and last novel hypothesis was investigated using interaction analyses. Largely, it was not supported by the data. Neither sugar intake from sweet food and beverages nor fibre intake moderated the associations of financial insecurity with mood disorders. However, associations between financial insecurity and CMD tended to be lower in those with high fibre intakes (p for interaction <0.20).

As a proof of concept, interactions were also investigated in the association between current and last grade level and mood disorders. There were significantly lower odds (over 40%) of incident depression after 5 years in those in the lowest last grade of the civil service and higher fibre intakes (per standard deviation).

## 8.2 Strengths

The analyses of this thesis have several strengths stemming from the dataset, measures, study design and the partial replication in EPIC-Norfolk.

### *8.2.1 Whitehall II study*

The rich Whitehall II dataset is the source of many strengths in this study (Marmot & Brunner, 2005). The study had a high initial response rate and continuing large sample size over all follow-ups providing the analyses with high statistical power. Between the baseline examination and the 11th follow-up in 2012/13 approximately 71% (n=6308) of participants remained in the study, excluding those who died during follow-up (n=1414) (Whitehall II Webpage, 2018; Marmot *et al.*, 1991).

Data on socio-demographic measures, health behaviours and health outcomes including mood disorders and diet were collected at several follow-ups using subjective and objective methods, where possible. Data collection methods were standardised and changed minimally across phases of follow-up allowing for time-variant adjustment (Marmot & Brunner, 2005).

As an occupational cohort the Whitehall II study is not representative for the British population (presented in more detail in 8.3.1) but results could still have important implications. Firstly, because mean sugar intakes from sweet food / beverages and fibre intakes were just slightly below and above those observed in the National Diet and Nutrition Survey, suggesting that results could potentially underestimate the true association (see Table 56) (Public Health England, 2018).

**Table 56 Comparison of dietary intakes between Whitehall II and the National Diet and Nutrition Survey (NDNS) for ages 19-65 years (Public Health England, 2018)**

| Intake (grams per day) | Women | | Men | |
|---|---|---|---|---|
| | Whitehall II | NDNS | Whitehall II | NDNS |
| Sugar from sweet food / beverages and free sugars in NDNS | 45.5 | 50.0 | 57.7 | 64.3 |
| Total dietary fibre | 24.8 | 17.4 | 26.0 | 20.7 |

Secondly, because the prevalence of mood disorders was mostly in line with the UK Adult Psychiatric Morbidity survey (Public Health England, 2018; Stansfeld *et al.*, 2016). CIS-R measured depressive episodes affected 3.8% of participants in Whitehall II at phase 11 as compared to 4.4% at ages 55-64 and 2.1% at ages 65-74 in the UK population (Stansfeld *et al.*, 2016). Antidepressant intakes were higher in Whitehall II

(2.7% at phase 3, 1991-1994) and EPIC-Norfolk (3.9% at HC1, 1993-1997) in comparison to the point prevalence reported in a representative UK sample (1.6%) at a similar time point (1994) (Ohayon *et al.*, 1998).

Finally, there is evidence that risk factor-health outcome associations seen in Whitehall II are comparable to those in population-based studies. Batty et al. (2014) found comparable hazard ratios for the association between classic risk factors and coronary heart disease when comparing associations from Whitehall II to a UK-wide general population based study (the British Regional Heart study), despite that the occurrence of exposures and outcomes differed (Batty *et al.*, 2014).

### *8.2.2 Dietary assessment*

Diet was assessed using validated questionnaires and analysed to reduce the chance of bias. The FFQ was validated against a 7-day diet diary in a subsample of 865 cohort members at phase 3 (Brunner *et al.*, 2001). A 7-day diet diary has reduced recall bias and provides more detailed diet data than a FFQ making it a higher quality measurement (Shim, Oh & Kim, 2014). The validation study showed that the FFQ could rank individuals according to their nutrient intake. Energy-adjusted fibre intake measured with FFQ correlated well with 7-day diet diary measured intake (spearman rank correlation: women 0.60, men 0.62) (Brunner *et al.*, 2001).

To reduce bias to some extent participants with unrealistic energy intakes were excluded from analyses and energy intake was adjusted for (Mosdol *et al.*, 2007; Howe, 1989; Willett & Stampfer, 1986; Willett, 2012). Energy adjustment of fibre intake had been found to reduce bias by underreporting in Whitehall II (Stallone *et al.*, 1997).

### *8.2.3 Mood disorder measures*

In this thesis, four measures of mood disorders were used of which three had been validated against an interviewer administered CIS-R in 256 participants in Whitehall II. All three were found to have high specificity and high sensitivity to measure a depressive episode (Head *et al.*, 2013). The use of self-reported antidepressant intake will be discussed below (see Chapter 8: 8.2.5). High specificity is important for reducing bias from misclassification and a high sensitivity further supports finding the true association (Copeland *et al.*, 1977).

### *8.2.4 Design*

**Random effect models (REM)**

As presented in Chapter 2 mood disorders appear in episodes and are recurrent. Therefore analysing mood disorders restricted to one endpoint as done in previous research undermines the nature of this disease (Sanchez-Villegas *et al.*, 2012, 2017; Guo *et al.*, 2014; Gangwisch *et al.*, 2015). In this study REMs were used as they allow analysis of cohort data in multiple cycles of several years without restricting the outcome or exposure to one time point (Twisk, 2004).

REMs have the advantage of reducing the chance of random error by increasing the number of observations and reducing selection bias by including data from participants that participated only once for cross-sectional or twice for prospective analyses (Twisk, 2004).

**Confounding**

Chapter 2 identified a gap in cross-sectional studies that adjusted for health behaviours and total energy intake. This was addressed by adjusting associations for health behaviours and energy intake as well as socio-demographic factors, other diet intake, and additionally measured BMI and central obesity, and CVD, diabetes and cancer.

**Temporality and reverse causation**

Chapter 2 identified a gap in studies that systematically investigated the association with prevalence, incidence and recurrence. In this thesis this gap was addressed by analysing in several ways: cross-sectionally, prospectively regarding incident mood disorders, and prospectively regarding recurrent mood disorders over medium-term (2 year) and longer-term (5-10 year) follow-up intervals. Prospective analyses allow investigating the temporal association. By excluding cases at time of dietary assessment within each cycle, for example at phase 3 for the 5-year cycle from phase 3 to phase 5, I was able to ensure that participants' dietary intakes were not recorded within a phase of low mood reducing bias by reverse causation. In a second analysis only CMD cases were included at each baseline investigating whether dietary intake during a mood disorder affects recurrence.

To investigate the role of reverse causation, the association between mood disorders and change in dietary intake over a 5-year follow-up was analysed separately.

### *8.2.5 Replication of Objective I in EPIC-Norfolk*

In Chapter 5 a sex-difference was identified between men and women in the association between sugar intake from sweet food / beverages and mood disorders. To investigate whether this difference was specific to the Whitehall II cohort, analyses were repeated in EPIC-Norfolk. A study that recruited participants from the general population making it more representative of women (Day *et al.*, 1999; Hayat *et al.*, 2014). EPIC-Norfolk used a similar FFQ to the one used in Whitehall II (Brunner *et al.*, 2001; Bingham *et al.*, 1997, 1997; Willett *et al.*, 1985, 1988). To reduce heterogeneity, mood disorders were measured with antidepressant intake which was available in both studies.

## 8.3 Limitations

Several limitations and sources of bias in analyses in this thesis need to be acknowledged. The effect of these limitations on validity will be discussed in 8.4.

### *8.3.1 Generalisability of findings*

As mentioned above the Whitehall II study is not representative of the UK population. This is even more so the case after several years of follow-up. Inevitably cohort attrition occurs due to mortality and drop-out and participants who remained in the study were shown to behave more healthfully and had lower rates of obesity and disease (Ferrie *et al.*, 2009). In analyses in this thesis an additional 10.4% (n=917, at phase 3) to 38.9% (n=3065, at phase 5) of participants had to be excluded from analyses mostly due to missing or unreliable dietary data. In Chapter 4 it was shown that this missingness was more prevalent in women, unmarried and non-white participants, participants in lower grade levels of the civil service, who were less physically active, drink no alcohol, sleep less hours, were overweight or obese and suffered from diabetes, CVD and cancer (more details see Chapter 8: 8.4.1)

EPIC-Norfolk participants were recruited from the general population but the initial response rate was low (39%) and smokers were underrepresented, a sign of potential underrepresentation of participants with unfavourable health behaviours (Day *et al.*, 1999; Hayat *et al.*, 2014).

Both cohorts covered middle-aged to elderly adults and generations from 1930 to 1953 for Whitehall II and 1919 to 1952 for EPIC-Norfolk. It cannot be ruled out, that findings could differ in younger generations, as the increased availability of sugar and sugary foods and beverages between the 1960s and 2000s and changes in food consumption from high fibre to lower fibre diets could have affected dietary preferences and consumption over time (National Food Survey Committee, 2000; Popkin, Adair & Ng, 2012; Popkin & Nielsen, 2003).

In sum, this means that results of both studies are not fully generalisable to the British population and might be subject to selection bias (further discussed in 8.4.1).

### *8.3.2 Measurement error in exposures and outcomes*

**Dietary intake**

A major limitation in this thesis was the use of semi-quantitative FFQs to assess dietary intake which leads to inaccurate and imprecise assessment of dietary intakes and was

restricted to covering long-term habitual diet (see Chapter 2: 2.2.1 and Chapter 8: 8.3.2).

Misreporting has been shown to be evident in Whitehall II and EPIC-Norfolk (Stallone *et al.*, 1997; Lentjes *et al.*, 2014). Underreporting is thought to be driven by social desirability and has been found to be especially prevalent in participants with high BMI or dissatisfaction with their body size (Stallone *et al.*, 1997; Bingham *et al.*, 1995; Price *et al.*, 1993; Voss *et al.*, 1998; Tyrovolas *et al.*, 2016; Lutomski *et al.*, 2011; Taren *et al.*, 1999).

Energy adjustment can reduce bias by misreporting but not eliminate it (Stallone *et al.*, 1997; Willett, 2012). For energy adjustment to be effective, the misreporting would have to be proportionally distributed over all types of food, which it was not. Those reporting lower energy intakes than possible have been found to report eating less sweet foods such as cakes and candy than those reporting reasonable energy intakes (Livingstone & Black, 2003). However, the full extent of this selective underreporting cannot be estimated as no diet collection method can measure actual dietary intake without including self-report or the risk that participants adjust their dietary intake over the reporting period (Livingstone & Black, 2003; Shim, Oh & Kim, 2014; Macdiarmid & Blundell, 1997, 1998).

Estimated nutrient contents, sugar content from sweet food / beverages and fibre are imprecise even if they were reported correctly. Firstly, because semi-quantitative FFQs do not include exact portion sizes; secondly, because the information about the type of product is limited so differences in ingredients cannot be taken into account and thirdly, because nutrient content was based on food composition tables from 1991 (Brunner *et al.*, 2001). Nutrient contents of foods change over time in response to regulations, or cost, demand and availability of ingredients. Therefore sugar or fibre content estimates might have become even more inaccurate in later data collection phases (Hendry *et al.*, 2015). That being said, comparing food composition tables showed that sugar contents in included sweet food / beverages were more stable than other foods (Appendices relating to Chapter 2: Appendix 1) (Holland *et al.*, 1991; McCance, 2002; Agency & England, 2015).

Finally, the FFQs used in this thesis were based on 12-month habitual intake. This has three implications: short-term changes are not captured and potential short-term changes that would have an effect on the average 12-month consumption might have not been recorded. FFQ questions are based on the average frequency per month, week or day over the 12-month period; it could be difficult to estimate the average if there was a spike in intake or avoidance of a certain foods over a few months only.

Also a change might not be remembered or incorrectly recalled as recall bias may operate (Rohan & Potter, 1984; Coughlin, 1990).

**Mood disorders**

CMD and depression were assessed using population screening tools: the GHQ, the CES-D and a computer assisted CIS-R which are prone to misclassification. Among other things, they might not be able to distinguish between non-psychiatric conditions that cause similar symptoms and misreport has been shown to be evident as well (Head *et al.*, 2013; Thombs *et al.*, 2018; Stansfeld & Marmot, 1992) (bias discussed in more detail 8.4.2).

### *8.3.3 Residual confounding*

Residual confounding could operate in the adjusted models used to test the hypotheses of interest. Most covariates were based on self-report which is often imperfect. For example does self-reported physical activity correlate only weakly with accelerometer-assessed physical activity (Spearman's r=0.33) (Sabia *et al.*, 2014). The fact that confounders, dietary exposures and mood disorders have not been perfectly measured increases the risk of residual confounding (Davey Smith & Phillips, 1992; Fewell, Davey Smith & Sterne, 2007).

Furthermore, some potential confounding variables were not included because they had not been measured at phases 3, 5, 7, 9 (phases with dietary data collection), never measured or because their association with the exposures and outcome was unknown. Examples are social support and personality traits and the wider context of eating such as snacking or eating alone (Tiainen *et al.*, 2013; Kendall *et al.*, 2015; Santini *et al.*, 2015; Henriksen, Torsheim & Thuen, 2014; Le Port *et al.*, 2012; Tani *et al.*, 2015). Residual confounding could also come from ingredients that could not be identified by the FFQ such as caffeine content in carbonated drinks which is suggested to be associated with mood disorders (Grosso *et al.*, 2016; Wang *et al.*, 2016).

### *8.3.4 Multiple testing*

Analyses were set out a priori to include several outcomes, time-frames and analyses regarding cross-sectional associations, incidence and recurrence using REM. This was done to reflect the different abilities of the CIS-R, CES-D and GHQ to measure a depressive episode (Head *et al.*, 2013). Multiple comparisons increase the risk of a chance finding (Feise, 2002). A limitation of this thesis was that this risk was not further addressed in analyses.

One way to address this issue would have been to set the significance level at a lower level using Bonferroni correction (Bland & Altman, 1995). Considering all prospective analyses for sugar intake from sweet food beverages (20 tests) the significance level would have been reduced to 0.05/20= 0.0025, for associations with fibre intake (16 tests) to 0.05/16=0.0031 and for interactions (12 tests) to 0.05/12= 0.0042 (in Appendices relating to Chapter 8: Appendix 11 test numbers explained). Under this correction, the associations between sugar intake from sweet food beverages and incident CMD in men, recurrent depression in women and interactions between fibre intake and last grade level would have been rejected. The finding of an inverse association between fibre intake and incident CMD after 5 years would still be considered statistically significant (p=0.0029).

### *8.3.5 Caveats in the analysis*

**Comparison between different mood disorder measures**

Associations between sugar intake from sweet food / beverages, fibre intake with the different measures of mood disorders were not fully comparable between each other.

First of all, the measures do not represent the exact same concepts. The GHQ and CES-D were developed aiming to identify different disorders, suggesting the construct validity may differ. The GHQ was developed as a screening tool for common mental disorders including both symptoms of depression and anxiety and was not intended to distinguish among disorders, whereas the CES-D focusses on depressive symptoms (Goldberg, 1972; Radloff, 1977; McDowell, 2006). It is possible that associations that differ by measure might reflect that the dietary exposures are only associated with certain sets of symptoms covered by the particular questionnaire.

Secondly, associations between dietary exposures and GHQ, CES-D and CIS-R differed in power. This is because measures had been introduced at different phases, which reduced the number of cycles used in the analysis and thereby person-observations available as compared to the GHQ (see Figure 25). The CIS-R was only available at one phase (11) and the CES-D only from phase 7 onward. Additionally, there was less reliable FFQ data available at later phases. Only 63% of participants had reliable FFQ data at phase 5 as compared to 91% at phase 3.

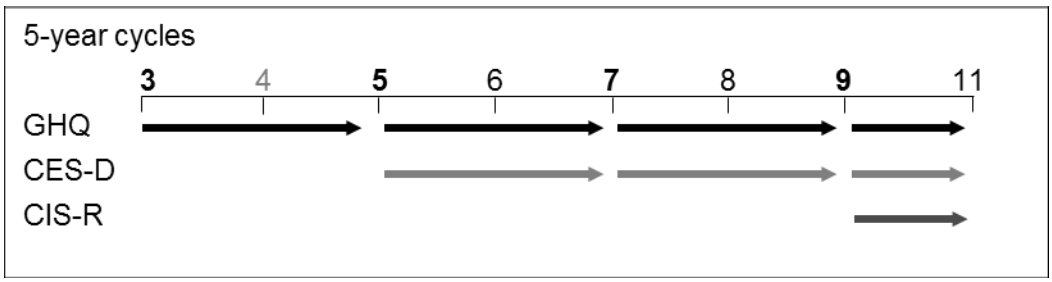



**Figure 25 Mode of analyses cycle approach for 5-year cycles and GHQ, CES-D, CIS-R**

Numbers indicate study phases. Phases with food frequency data are in bold; there was no data on common mental disorder available at Phase 4.
Abbreviations: GHQ, 30-item General health questionnaire; CES-D, Center for Epidemiologic Studies Depression Scale, CIS-R, revised Clinical Interview Schedule.

Thirdly, the power could have been affected by selection bias in the CES-D measure. It was shown that participants who reported a GHQ case were selectively less likely to answer the CES-D questionnaire which was presented second (Chapter 4: 4.6). Therefore, person-observations (n=1450) with a higher chance for caseness were additionally lost in CES-D analyses. Finally, there was a page-break in the first CES-D questionnaire that increased missing data in this measure even further.

**Comparison between different time-frames**

Comparison between different time-frames was restricted as well due to reduced power. The number of cycles and therefore person-observations and power differed by time-frame. For associations with GHQ two 2-year cycles, four 5-year cycles and three 10-year cycles were available. Therefore, associations with 5 years cycles had the largest power to detect a significant association.

## 8.4 Internal validity

Before asking the question whether observed associations could be the result of a causal association several alternative explanations need to be taken into account namely bias, confounding and chance (Grimes & Schulz, 2002).

### *8.4.1 Selection bias*

Selection bias describes distortions introduced by the sample selection procedures and from factors influencing study participation and drop-out (Rothman, Greenland & Lash, 2008). As described in section 8.3.1 selection bias was evident in all cohorts studied in this thesis.

The Whitehall II study was selective, based on the definition of the target population (Rothman, Greenland & Lash, 2008). As an occupational cohort the study is subject to the 'healthy worker effect'. The 'healthy worker effect' means it is likely that participants, recruited while in Civil Service employment, are to a certain degree selected for health (McMichael, Spirtas & Kupper, 1974). As a result of recruiting civil servants, the study included less people with unhealthy behaviours than expected in the general population (see Chapter 8: 8.3.1). The EPIC-Norfolk study was not selective based on the definition of the target population, but due to self-selection that occurred in those participating (39% of those invited), who showed more favourable health behaviours (Day *et al.*, 1999; Hayat *et al.*, 2014). Secondly, those who remained in Whitehall II over several follow-ups and those with adequate data for analyses were found to be exposed to less risk factors for mood disorders (see Chapter 8: 8.3.1) (Ferrie *et al.*, 2009). This selection could have led to reduced variability in exposure and outcome and therefore reduced ability to detect an association.

On the other hand, overall drop-out in Whitehall II was low and exposure and outcome rates were roughly within the range found in the general population (see Chapter 8: 8.2.1). REM used in Whitehall II could reduce the effect of attrition to some extent as those who dropped out earlier were included in analyses. Additionally, analyses were initially analysed in the maximum eligible sample to avoid further restricting the analytical sample. Estimates were then compared between the maximal sample and a sample excluding those with missing data on covariates. In analyses for Objectives I and II estimates were found similar before and after exclusion of participants with missing data in covariates (not shown). However, selection bias was evident in Objective III where an interaction between financial insecurity and fibre intake ($p<0.2$)

was only evident when participants with missing data on covariates were excluded, suggesting that associations might be restricted to healthier participants.

### *8.4.2 Information bias*

Information bias is caused by measurement error in the variables used in analyses. As shown in 8.3.2 and 8.3.3 dietary intake, mood disorders and covariates were not measured perfectly.

**(1) Measurement error and misclassification of dietary intake**

As shown in 8.3.2 FFQ data are prone to error and sugar and fibre content might have been incorrectly estimated. Generally bias in diet misreporting would lead to bias towards null because those with low nutrient or food intakes would be contaminated by those with high intakes (Thomas, Stram & Dwyer, 1993). However, bias could differ in the case of sugar intake of sweet food / beverages as compared to fibre intake. Measurement error in sugar intake from sweet food / beverages is affected by selective underreporting, suggesting that participants who ate more sweet food / beverages may report less (Pryer *et al.*, 1997; Bingham *et al.*, 1995; Lutomski *et al.*, 2011; Livingstone & Black, 2003). Assuming that was the case for the majority of participants underreporting could lead to opposite ranking in which those with truly low intakes reporting these correctly being ranked higher than those with truly high intakes reporting these substantially lower (Stallone *et al.*, 1997; Kuhnle *et al.*, 2015). Then associations would present the opposite direction of a true effect (Wacholder, Dosemeci & Lubin, 1991).

**(2) Measurement error in mood disorder measures**

As shown in 8.3.2 bias could have been introduced by misclassification of mood disorders, incidence and recurrence.

In prospective analyses levels of misclassification of mood disorders should predominantly be independent of the level of the exposures, leading to estimates biased towards the null. Bias through misclassification of the outcome is estimated to be higher if specificity is low and the outcome rare (Copeland *et al.*, 1977).This was not the case here as the computer-assisted CIS-R, CES-D and GHQ were shown to have a high specificity (see Chapter 8: 8.2.3) and CMD and depressive episodes are common (see Chapter 2: 2.1.2, 2.1.3, Chapter 4: 4.2.2) (Copeland *et al.*, 1977; Head *et al.*, 2013; Steel *et al.*, 2014; Stansfeld *et al.*, 2016). The specificity and sensitivity regarding antidepressant medications is unknown but results from a validation study of

a similar measure, self-reported diagnosis, suggests the specificity could be high too (Sanchez-Villegas *et al.*, 2008).

Furthermore, misclassification could have occurred based on the definition of incidence and recurrence. Figure 26 depicts the mode of analyses for different measures. To investigate associations with incidence and recurrence, participants were excluded based on GHQ caseness at each baseline (presented as a box: 'GHQ case yes/no' in Figure 26). This approach was chosen to ensure a maximal number of cycles and sample sizes for each measure. However, this could have led to further misclassification of incident and recurrent cases in analyses of CES-D depression and CIS-R caseness as the baseline mood disorders were assessed using the GHQ. In Chapter 4, 4.6, it could be shown that specificity of GHQ caseness to measure CES-D ascertained depression was lower for incident than for recurrent depression and sensitivity was higher for recurrent depression than incident depression, suggesting bias could differ by type of analysis (regarding recurrence and incidence).

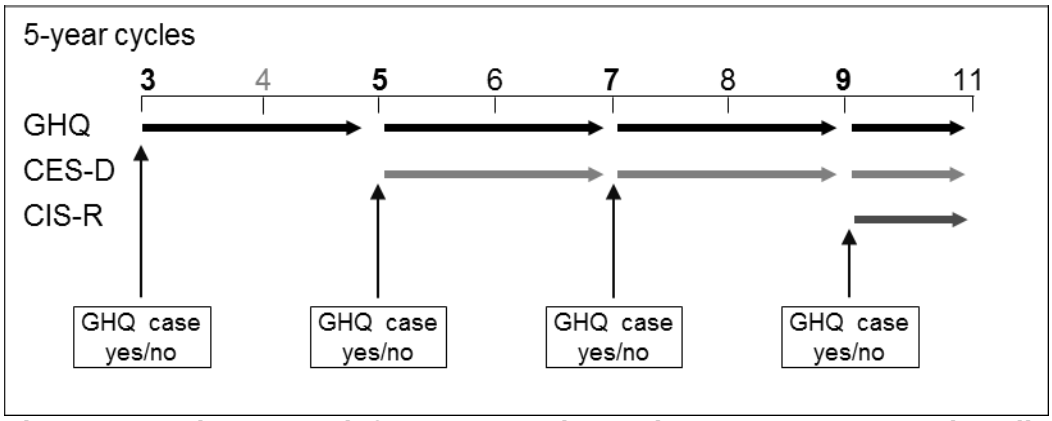



**Figure 26 Cycle approach for 5-year cycles and GHQ, CES-D, CIS-R baseline exclusion for analyses of incidence and recurrence**
Numbers indicate study phases. Phases with food frequency data are in bold; there was no data on common mental disorder available at Phase 4.
Abbreviations: GHQ, 30-item General health questionnaire; CES-D, Center for Epidemiologic Studies Depression Scale, CIS-R, revised Clinical Interview Schedule.

In sum, the misclassification in mood disorder measurements, their incidence and recurrence could have led to biased estimates in all analyses.

(3) Covariates

BMI and waist circumference were measured by trained staff at the study screening and disease status was validated with information from the clinical examination at the screening, Hospital Episode Statistics, information from general practitioners and cancer registration data increasing their accuracy (see Chapter 4: 4.3). All other covariates were measured using self-report, which is also subject to misreporting. Misclassification and measurement error in covariates can increase the chance of

residual confounding (see Chapter 8: 8.3.3) (Fewell, Davey Smith & Sterne, 2007; Davey Smith & Phillips, 1992).

### *8.4.3 Confounding*

Associations between high sugar intake from sweet food / beverages and incident CMD in men and recurrent depression in women were robust against adjustment in the final model comprising of socio-demographic factors, health behaviours and other dietary factors (attenuation <26%). The association with recurrent depression in women was attenuated by 67% by additional adjustment for baseline BMI and central obesity. This suggested that adiposity could lie on the pathway between high sugar intake from sweet food / beverages and recurrent mood disorders (explained in more detail in 8.5.1, Biological plausibility). Associations between sugar intake from sweet food / beverages and clinical depression after 10 years in men and recurrent clinical depression after 5 years in both men and women became statistically non-significant after adjustment for covariates.

Associations between high fibre intakes from sweet food / beverages and incident CMD after 5 and 10 years were little attenuated (attenuation <10%) when adjusted for socio-demographic factors, health behaviours and other dietary factors, which was considered the final model, and further adjustment for adiposity and disease did not change the results.

Interactions between fibre intake and financial insecurity in the association between financial insecurity and CMD were attenuated slightly (attenuation 30%) and interactions between fibre intake and last grade level in the association between last grade level and depression were not attenuated (attenuation <5%) upon adjustment for covariates.

The fact that main associations were just slightly affected by adjustment for confounders strengthens results. However, the risk of residual confounding remains (see Chapter 8: 8.3.3) (Fewell, Davey Smith & Sterne, 2007; Davey Smith & Phillips, 1992).

### *8.4.4 Chance*

Chance describes random error, which can be reduced by high power, repeated measurements, standardised methods but increase when running multiple tests (Rothman, Greenland & Lash, 2008; Feise, 2002). Furthermore, replication in another

cohort can inform whether chance is a driving factor in an observed association (Hill, 1965).

Statistical power depends on sample size and effect size. As shown in Chapter 8: 8.2.1 the Whitehall II study had a large sample size. REM increased the power further by investigating up to four observations per participant (see Chapter 8: 8.2.4). Unnecessary stratification was avoided by only stratifying by sex if estimates were found to be statistically different. Furthermore, exposures, outcomes and covariates were collected repeatedly using standardised and validated methods (see Chapter 8: 8.2.1).

Effect sizes for associations between free sugar, fibre intake and mood disorders have been shown to be small. Previous studies with large sample sizes (n=8 964-69 954) found effect sizes of between OR/HR 1.2-1.5 for associations between free sugar intake and incident mood disorders (see Chapter 2: 2.6.3*)* (Guo *et al.*, 2014; Gangwisch *et al.*, 2015; Sanchez-Villegas *et al.*, 2012, 2017*).* Effect size reported by the one prospective study that found an association between fibre intake and mood disorder incidence was equally small (OR 0.86) even though the sample size was large (69 954 participants) (see Chapter 2: 2.6.4) (Gangwisch *et al.*, 2015). These effect sizes suggest that to ensure statistical power, sample sizes had to be very large. In support, it could be shown that most results that were statistically significant were in the mode of the analysis with the largest number of person-observations: incident CMD after 5-years.

As shown in 8.3.4 use of multiple tests can increase the risk of a chance finding and if significance levels would have been corrected using Bonferroni correction all associations between sugar intake from sweet food / beverages and interactions between fibre intake and last grade level would have been considered non-significant. The association between fibre intake and incident CMD after 5 years would have remained significant (Feise, 2002). However it has to be noted that this is a conservative method and in contrast, repeated analyses in EPIC-Norfolk supported a positive association between sugar intake from sweet food / beverages and incident mood disorders in men (Feise, 2002). Associations with antidepressant intake showed a similar direction suggesting that the association in Whitehall II might not be entirely explained by chance.

## 8.5 Do associations meet the criteria of causality?

Observational research cannot prove causality but there are factors that make a causal explanation more likely. In the following section several steps will be taken to assess whether associations found could reflect a causal effect using Potischman & Weed's (1999) adapted Bradford Hill's criteria for causation for nutritional epidemiology. Potischman & Weed (1999) do not include specificity, coherence, experiment and analogy (Bradford Hill, 1965). Associations between diet and mood disorder are unlikely to be specific as they are known to be associated with many other health outcomes (2.2.3, 2.2.4). Bradford Hill (1965) defined coherence as a finding that is not in contrast with known facts of the history and biology of the disease and has been applied as associations with subclinical markers (Mente *et al.*, 2009). Here, coherence will refer to coherence across several mood disorders measures and sex differences within analyses. Experimental evidence will be discussed in a separate section for all objectives.

The following key criteria will be addressed:

- Coherence of association: Describing similarities and differences of associations across mood measures, and between women and men.
- Consistency of association: Describing consistency across different studies and study designs.
- Strength of association: Weaker associations are more likely to be due to bias.
- Temporality: Determining influence on onset or progression of mood disorders to reduce the chance of reverse causation.
- Dose-response manner: Presence of a gradient of greater exposure to greater incidence or recurrence.
- Biological plausibility: A plausible mechanism between cause and effect.

### *8.5.1 Objective I: Is high sugar intake from sweet food / beverages a risk factor in mood disorders?*

**Coherence**

*Differences in results by mood disorder measure*

In this thesis associations between sugar intake from sweet food / beverages and mood disorders were analysed using four measures of mood disorders. The positive associations between sugar intake from sweet food / beverage intake with incident GHQ measured CMD and incident antidepressant intake in men were not found for CES-D measured depression. A positive association between sugar intake from sweet

food / beverages and recurrent depression measured using CES-D in women was not found in GHQ measured recurrent CMD after adjustment for other dietary factors. Associations with CIS-R depression did not reach statistical significance but mostly supported associations found with either measure.

As shown in 8.3.5, these differences are difficult to disentangle. They could either suggest that associations between sugar intakes from sweet food / beverages are restricted to certain sets of symptoms, the result of a power issue or selective missingness. However, as all measures were shown to be specific measures for interviewer assessed depressive disorder (Head *et al.*, 2013) and were shown to be associated similarly with covariates (see Chapter 4: 4.6), the inconsistency of results comparing CMD and CES-D was unexpected and call associations found into question.

*Sex difference in the association between sugar intake from sweet food / beverages and mood disorders*

The difference in findings by sex for Objective I in Whitehall II and EPIC-Norfolk contrasts previous research regarding the association between free sugar intake and mood disorder. Sanchez-Villegas et al. (2017) did not find a difference by sex, Guo et al. (2014) found slightly smaller estimates in women compared to men in associations between juice intake and depression and Gangwisch et al. (2015) found associations with incident mood disorder in a women-only cohort (Ramos, 2018). Sanchez-Villegas et al. (2012) did not report any sex differences.

Earlier research on other dietary exposures and depressive symptoms in the Whitehall II study had also reported sex differences in contrast with other research which suggested that the difference by sex might be specific to Whitehall II (see Chapter 8: 8.2.5) (Akbaraly *et al.*, 2009, 2013; Molendijk *et al.*, 2018; Lai *et al.*, 2014). Whitehall II includes a low number of women which might have specific characteristics based on their employment in the Civil Service in 1985-88. In 1985 only 56.3% of women were in employment compared to 78.4% of men, suggesting that many women would not have been covered by an occupational cohort such as Whitehall II (Office for National Statistics, 2018a, 2018b). Surprisingly, the sex difference was replicated in a representative cohort in the UK, even though associations between sugar intake from sweet food / beverages and incident antidepressant intake were weaker.

One reason for not finding an association between dietary exposures and outcomes can be too little variance in dietary intake, but there was no large difference in variance of sugar intake from sweet food and beverages between women (29.0) and men (33.6) not supporting this explanation (Potischman & Weed, 1999). Two potential explanations for a sex difference in the association between sugar intake from sweet

food / beverages and mood disorders are biological sex differences and gender differences in dietary reporting.

Biological differences in the association between free sugar intake and mood disorders have not been investigated and are therefore merely speculative. However, for two of the five potential pathways in which an association between free sugar intake and mood disorder could operate, namely BDNF and dopamine, some sex differences have been reported (see Chapter 2: 2.3.1). Despite a strong hypothesis of an association between BDNF level and depression, the association between genetic variants of BDNF level and depression have only been found in men and not women (Verhagen *et al.*, 2010). This suggests that a BDNF lowering effect of free sugars would only affect mood disorders in men but not in women. Similarly, sex differences have been reported regarding dopamine release and dopamine receptors (Fattore & Melis, 2016). Thus men react with a greater dopamine release after challenged with a stimulant than women (Munro *et al.*, 2006). Therefore, men could be more vulnerable than women to addiction-like adaptations in response to high sugar intake, which in turn could increase their risk for mood disorders (Avena, Rada & Hoebel, 2008; Grant *et al.*, 2004; Dunlop & Nemeroff, 2007). Still, a biological explanation is in contrast with findings in earlier research that found similar associations between free sugar intake and depression in women (Gangwisch *et al.*, 2015; Sanchez-Villegas *et al.*, 2017; Guo *et al.*, 2014).

Another possible explanation could be gender differences in reporting of sweet food and beverage intake. These could bias estimates in women differently than in men. Women have been shown to feel distressed over eating and weight at a young age (Wardle & Beales, 1986). Women are more likely to perceive themselves as overweight than men, even when of normal weight (Yaemsiri, Slining & Agarwal, 2011; Wardle *et al.*, 2000), and women have higher rates of attempting to lose weight (Santos *et al.*, 2016). This could explain why social desirability has a stronger effect on dietary reporting in women than in men (Hebert *et al.*, 1995, 1997) and why women have been found to underreport dietary intake more in Whitehall II and EPIC-Norfolk (Stallone *et al.*, 1997; Lentjes *et al.*, 2014). The hypothesis of gender differences in misreporting of sugary foods is further supported by observations that biomarkers for sucrose intake and FFQ measured intake correlate less in women than in men (Kuhnle *et al.*, 2015; Tasevska *et al.*, 2011).

In this thesis, this could mean that women would have underreported their sweet food and beverages intake potentially more than men. As shown in 8.4.2 stark misreporting of sweet food and beverages that depended on actual intake could lead to observed associations in the opposite direction of the real effect. In minimally adjusted analyses,

there was a significant lower chance of depression in women reporting high sugar intakes from sweet food / beverages and overall estimates in women tended to be below OR 1, supporting this hypothesis.

On the other hand, I found an association between sugar intake from sweet food / beverages and recurrent depression in women and an explanation of gendered bias in reporting is also in contrast with earlier research. These contradictions could only be further explained by more accurate reporting depending on current mood which has been reported in some studies (Whited *et al.*, 2014; Yannakoulia *et al.*, 2007), country-specific differences in misreporting between the UK, U.S. and Spain, or that the finding of an association with recurrent depression was the result of bias or chance.

**Consistency**

*Across cross-sectional studies*

A cross-sectional positive association between sugar intake from sweet food / beverages and CMD was in line with previous cross-sectional research (Chamberlain, Redden & Grant, 2017; El Ansari, Adetunji & Oskrochi, 2014; Jeffery *et al.*, 2009; Shi *et al.*, 2010; Yu *et al.*, 2014).

*Across prospective studies*

The findings of a positive association between sugar intake from sweet foods and beverages with incident CMD after 5 years in men in Whitehall II and a suggestion of a positive association between sugar intake from sweet food / beverages and incident antidepressant intake in meta-analyses of Whitehall II and EPIC-Norfolk was in line with previous prospective studies that found positive associations between added sugar intake, frequent consumption of sweet food and drinks and increased chances for incident mood disorders (Sanchez-Villegas *et al.*, 2017, 2012; Gangwisch *et al.*, 2015; Guo *et al.*, 2014). The difference by sex found in this thesis contrasts the literature (see Chapter 8: 8.5.1, Coherence).

This was the first study investigating an association between a sugar-dense diet and recurrent mood disorders and the association between mood disorders and long-term change in sugar intake from sweet food / beverages.

**Strength**

Smaller associations are more likely to be explained by bias, while larger associations (OR/RR≥4) might be seen as implausible in the context of nutritional epidemiology (Potischman & Weed, 1999; Ioannidis, 2013).

The odds of developing incident CMD 5 years later was increased by 21% in men with the highest sugar intake from sweet food / beverages as compared to those with the lowest. The odds of developing recurrent depression was doubled in women with high sugar intakes compared to women with low intakes. In sum, associations between sugar intake and sweet food and beverages and incident CMD in men were modest and associations with recurrent depression in women strong.

**Temporality**

In this thesis associations were found between sugar intakes from sweet food / beverages and incident and recurrent mood disorders after 5 years. There was no association over 10 years, but it is unlikely that associations with 5 year mood disorders were the result of reverse causation as baseline cases were excluded from the models and in separate models did not support a reverse effect.

No evidence was found for the alternative hypothesis that sugar intake increased following mood disorders. This is likely due to the FFQs used in this study and the timeframes of data-collection. The hypothesis was based on potential biological explanations for how sugar intake could alleviate low mood in times of stress and the results of short-term experiments. Associations in this thesis could only be analysed long-term (Barr *et al.*, 1999; Benton & Donohoe, 1999; Dum, Gramsch & Herz, 1983; Gibson, 2006; Hajnal, Smith & Norgren, 2004; Shabbir *et al.*, 2013; Smith, 2004; Ulrich-Lai, 2016; Ventura *et al.*, 2014; Wurtman & Wurtman, 1995) (see Chapter 2: 2.4.1). The FFQ did only cover diet over the last 12 months and might not record shorter term dietary changes (see Chapter 8: 8.3.2). Changes in sugar intake from sweet food / beverages could only be calculated over 5 years. Moreover, a reverse association could depend on particular symptoms such as anhedonia or change in appetite which were not further investigated (ICD10Data.com, 2018; Rahe *et al.*, 2016).

In sum, a temporal association was found in the direction from sugar intake from sweet food / beverages to incident and recurrent mood disorders. There was no association found in the opposite direction, reflecting absence of a long-term association between mood and later change in level of free sugar intake.

**Dose-response relationship**

Associations between sugar intake from sweet food and beverages and incident CMD in men showed a dose-response manner. Associations with antidepressant intake in meta-analyses between Whitehall II and EPIC-Norfolk showed a stepwise increased chance for sugar intakes from sweet food and beverages above the lowest tertile and weak associations when intake was operationalised continuously. This could either

reflect the nature of the association or bias introduced by categorising (Flegal, Keyl & Nieto, 1991). The former is supported by a similar threshold effect reported by Sanchez et al. (2012) for the association between commercial baked goods and chances for self-reported depression diagnosis or habitual antidepressant intake. The meta-analysis for the association between sugar intake from sweet food / beverages and incident antidepressant intake in men was only significant when operationalised per tertile.

Associations between sugar intake from sweet food and beverages and recurrent depression showed a borderline dose-response relationship (trend 0.052) with a strongly increased chance in women in the highest tertile of intake as compared to the lowest.

**Biological plausibility**

Biologically the association between sugar intake from sweet food / beverages and incident CMD in men could be explained by the ability of sugar-dense diets to lower BDNF a growth factor that has been shown to be also reduced in depression and to increase low-grade inflammation in the body (Sen, Duman & Sanacora, 2008; Gainey *et al.*, 2016; Heyward *et al.*, 2012; Molteni *et al.*, 2002; Calder *et al.*, 2011; Dantzer *et al.*, 2008; Kivimäki *et al.*, 2014). Furthermore, sugar-dense diets could trigger reactive postprandial hypoglycaemia which could be either experienced as mood disorder symptoms or affect the HPA axis and thereby depressive symptoms (Belmaker & Agam, 2008; Schwartz *et al.*, 1987; Virally & Guillausseau, 1999; Stetler & Miller, 2011). Finally, the association could be mediated through the effect of sweet foods/drinks on the reward system and dopaminergic neurotransmission (Guo *et al.*, 2014; Lenoir *et al.*, 2007; Avena, Rada & Hoebel, 2008; Dunlop & Nemeroff, 2007; Grant *et al.*, 2004). There was little evidence that the associations between sugar intake from sweet food / beverages and incident CMD and antidepressant intake in men were explained through adiposity (see Chapter 2: 2.3.3).

In contrast, associations between sugar intake from sweet food / beverages and recurrent depression in women were attenuated when adjusted for baseline BMI and central obesity suggesting that adiposity might partly mediate the association between sugar intake from sweet food / beverages and recurrent depression. High sugar intake could have increased chances to gain fat which in turn could increase the chance for a relapse or reduce the chance to recover from mood disorder by adversely affecting systemic inflammation, leptin resistance or lead to weight discrimination and body image dissatisfaction (Galic, Oakhill & Steinberg, 2010; Rossetti, Halfon & Boutrel, 2014; Lu, 2007; Morenga, Mallard & Mann, 2013; Luppino *et al.*, 2010; Jackson,

Beeken & Wardle, 2015; Dantzer *et al.*, 2008; Fransson *et al.*, 2010; Kivimäki *et al.*, 2014; Eidsdottir *et al.*, 2014) (see Chapter 2: 2.3.3).

### *8.5.2 Objective II: Is high fibre intake from sweet food / beverages a protective factor in mood disorders?*

**Coherence**

*Differences in results by mood disorder measure*

Associations between fibre intake and mood disorders showed a similar direction in all three mood disorder assessment methods. Even associations with clinical depression after 5 and 10 years showed an inverse association, but depended on adjustments and sensitivity analyses. Only few associations reached statistical significance. This difference is mostly explained by differences in statistical power as shown in 8.3.5.

*Sex differences in the association between dietary fibre intake and mood disorders*

There were no sex differences in the association between fibre intake and mood disorders. One initial sex difference between dietary fibre and CIS-R depression was found to be due to an outlier with extremely high fibre intake.

**Consistency**

*Across cross-sectional studies*

Previous cross-sectional studies had found ambiguous results on the association between fibre intake and prevalent mood disorders with four studies suggesting an inverse association (Gopinath *et al.*, 2017; Woo *et al.*, 2006; Green & Pope, 2000; Xu *et al.*, 2018) and four studies not (Fang *et al.*, 2013; Miki *et al.*, 2016; Davison, Gondara & Kaplan, 2017; Davison & Kaplan, 2012). However, earlier studies had rarely adjusted for health behaviours. In analyses in this thesis an inverse association between fibre intake and mood disorders were attenuated when adjusted for other health behaviours.

*Across prospective studies*

The finding of an inverse association between fibre intake and incident CMD and depression at follow-up was in line with findings from the Women's Health Initiative that found a comparable association of a 14% reduced chance of incident depression after three years in those in the highest quintile of fibre intake compared to participants in the lowest (Gangwisch *et al.*, 2015). A study in the SUN cohort published in 2017 did not find an association (Sanchez-Villegas *et al.*, 2017). In contrast to this thesis and Gangwisch et al. (2015), Sanchez-Villegas et al. (2017) analysed data including

younger participants (18+), suggesting that fibre might only play a role in mood-disorders in middle-aged and older adults.

The finding of no associations between fibre intake and recurrent mood disorders after adjustment for covariates was in line with research from Akbaraly et al. (2013) who investigated the association between fibre intakes and recurrent depressive episodes based on CES-D and antidepressant intake over up to three data collection phases of the Whitehall II study.

The finding that mood disorders did not change fibre intake was in line with findings from a Canadian nested case-control study (Gougeon *et al.*, 2017).

**Strength**

The chance of incident CMD 5 years later was reduced by 26% in participants with the highest fibre intake compared to the lowest intake. There was a strong inverse association between fibre intake and clinical depression that could be shown after exclusion of participants with extreme intakes, unknown or known diagnosis at each baseline and after adjustment for other dietary factors (OR 0.55, p=0.042).

In sum, associations between fibre intake and incident mood disorders were moderate.

**Temporality**

In this thesis associations between fibre intake and mood disorders were stronger when analysed prospectively regarding incidence and remained over a 5-year lag period. There were no associations with recurrent mood disorders after adjustment of covariates and mood disorders were not associated with changes in fibre intake over 5 years of follow-up.

As shown in 8.5.1, Temporality issues in data collection such as the differences in timeframes could have reduced the ability to investigate the association between mood disorders and change in fibre intake. However, results are strengthened by the consistency with findings from a nested case-control study by Gougeon et al. (2017) who collected dietary data and data on mood disorders yearly.

In sum, a temporal association was found in the direction from fibre intake to incident mood disorder. There was little evidence for an association in the opposite direction.

**Dose response**

Associations found between fibre intake and incident CMD 5 and 10 years later showed a dose-response manner.

**Biological plausibility**

The association with fibre intake could be explained by its effects on the gut microbiome composition and metabolism (Claesson et al., 2012; David et al., 2014; Scott, Gratz, Sheridan, Flint, & Duncan, 2013). The gut microbiome is suggested to interact with mental health through affecting neurotransmitters, the vagus nerve and the immune system. SFAs are generated as a result of metabolising dietary fibre and have been shown to advance the pathways mentioned above (Belmaker & Agam, 2008; Dantzer *et al.*, 2008; Foster & McVey Neufeld, 2013; Sampson & Mazmanian, 2015; Wallace & Milev, 2017) (see Chapter 2: 2.3.2).

### *8.5.3 Objective III: Does sugar intake from sweet food and beverages, and dietary fibre intake, act as a moderator in the association between financial insecurity and mood disorders?*

Objectives I and II suggested a direct association between sugar intake from sweet food / beverages and fibre intake and mood disorders. Objective III addressed the question whether sugar intake from sweet food / beverages and/or fibre intake could act as moderators in the association between financial insecurity and socio-economic position and mood disorders.

**Coherence**

Interactions between fibre intake and financial insecurity, last and current grade level showed a similar direction supporting the association. Wider confidence intervals in associations with current grade level can be explained by power as the number of observations halved in these analyses due to participants leaving the civil service or retiring.

The interaction of fibre intake and financial insecurity in the association with CMD and the interaction of fibre intake and last grade level in the association with CES-D measured depression were much weaker with CES-D measured depression and CMD, respectively.

Sex-interactions with sugar intake from sweet food / beverages and fibre intake were included in all models to account for potential differences and associations between financial insecurity and grade level and mood disorders did not differ by sex.

**Consistency**

It was not possible to compare the findings of this study to previous literature as to the best of my knowledge no previous study had investigated the association of a potential

moderating role of free sugar intake or fibre intake in the association between socio-economic factors in mood disorders (Chapter 2: 2.6.5).

**Strength**

Interactions between fibre intake and financial insecurity in the association with incident GHQ measured CMD 5 years later were weak ($OR_{interaction}$ 0.88, p=0.13). Interactions between fibre intake and last grade level in the association with incident CES-D measured depression 5 years later were strong ($OR_{interaction}$ 0.54, p=0.03).

**Temporality**

The associations between financial insecurity, grade level and mood disorders were all based on prospective analyses.

**Dose response**

Interactions with sugar intake and fibre intake were modelled continuously only and a dose-response relationship was not tested further.

**Biological plausibility**

The effect of fibre intake on the gut microbiome could favourably affect dysregulations that occur in mood disorders through modulating neurotransmitters, activating the vagus nerve, the immune system and effects of SFAs (see Chapter 2: 2.3.2.) might potentially increase biological resilience against financial and psychosocial stressors.

### *8.5.4 Experimental evidence*

The findings of a positive association between sugar intakes from sweet food / beverages and inverse association between fibre intake and mood disorders are in line with findings from two randomised controlled trials (Jacka *et al.*, 2017; Breymeyer *et al.*, 2016).

Breymeyer et al. (2016) investigated the association between glycaemic load diet and depressive symptoms and Jacka et al. (2017) the effect of an overall diet recommendations on remission and depressive symptoms in participants with moderate to severe depression (see Chapter 2: 2.6.1). Breymeyer et al (2016) showed that consuming a high glycaemic load diet that included unrefined grains and added sugars over 28 days resulted in higher depressive symptoms scores compared to consuming a low glycaemic diet that was restricted in added sugars and high in wholegrain products. A randomised cross-over design and the provision of food reduced the risk of bias, confounding and non-compliance. However, the sample size

was low (82 participants) increasing the risk of a chance finding (Breymeyer *et al.*, 2016). Jacka et al. (2017) showed that dietary counselling recommending a widespread dietary change including reduced intake of sweets and sweetened beverages and increased intake of wholegrain, vegetables and legumes reduced symptoms of depression and anxiety and increased remission compared to participating in a social support intervention. The study had a low sample size (67 participants) increasing the risk of a chance finding, but the control intervention reduced the chance that changes just occurred through the involvement in an intervention (Jacka *et al.*, 2017).

Trials were not specifically set up to test the effect of low free sugar intake and high fibre intake but the effect on mood lends some support for a causal association.

## 8.6 Summaries and judgement of the observed associations

The associations reported in 8.1 will be judged based on their validity and causal criteria discussed in 8.4 and 8.5 (Grimes & Schulz, 2002). Validity was investigated regarding the risk of selection bias, information bias, confounding and chance; causal criteria were coherence of associations within studies, consistency, strength, temporality, dose-relationship and biological plausibility (see Table 57).

**Table 57 Summary of results in respect to criteria of causality (Potischman & Weed, 1999; Hill, 1965)**

| Objective | Objective I | | Objective II | Objective III |
|---|---|---|---|---|
| **Finding** | Positive association between sugar intake from sweet food / beverages and incident mood disorders in men. | Positive association between sugar intake from sweet food / beverages and recurrent mood disorders in women. | Inverse association between dietary fibre intake and incident mood disorders. | Fibre intake moderating the association between last grade level and mood disorders. |
| **Coherence** | X | X | √ | X |
| **Consistency** | √ | N/A | (√) | N/A |
| **Strength** | (√) | √ | (√) | √ |
| **Temporality** | √ | √ | √ | √ |
| **Dose-response relationship** | (√) | (√) | √ | N/A |
| **Plausibility** | √ | √ | √ | (√) |

√=criterion met; X=criterion not met; N/A=not available; Brackets mark limitations.

### *8.6.1 How likely is it that the association between high sugar intake from sweet food / beverages and mood disorder is causal?*

Based on chapters 8.4 and 8.5.1 the following judgements can be made. There was little evidence that associations observed between sugar intake from sweet food and beverages and mood disorders could be explained by selection bias as associations did not change after excluding participants with missing data in covariates. Associations between sugar intake from sweet food and beverages were only moderately attenuated when adjusted for known and measured covariates. However, sugar intake from sweet food / beverages, mood disorder measures and covariates were all measured imperfectly wherefore residual confounding could still explain associations (Fewell, Davey Smith & Sterne, 2007). The use of multiple measures and modes of analysis resulted in a considerable risk that associations could be explained by chance. In the case of an association between sugar intake from sweet food / beverages and CMD in men the association could be shown to be similar in an

independent cohort and using antidepressant intake. It is therefore unlikely that this association can be entirely explained by chance.

It was shown that the associations in men were consistent with earlier research that found positive associations between free sugar, sweet food and drink intake and mood disorders. Association were in a temporal direction from baseline to follow-up, showed a dose-response relationship in Whitehall II and could be plausible. However, associations were not very strong and most importantly were not coherent throughout analysis (see Table 57). There was no similar association found when mood disorders were assessed using the CES-D questionnaire and the sex difference was in contrast with earlier research and could not be unequivocally explained.

The association between sugar intake from sweet food / beverages and recurrent depression in women was also not coherent. Associations in men showed a similar direction suggesting the sex difference might be the result of power and the association could not be replicated with the GHQ. In regard to this finding, no earlier research was available and due to too little cases, associations could not be repeated in EPIC-Norfolk. Still, the association was strong, in the direction of diet to recurrent depression, nearly showed a dose-response relationship and could be plausible (Table 57).

A causal link between a diet low in sugar is additionally supported by two trials that found that diets with low free sugar intake lead to decreased depressive symptoms and increase the chance of recovery in participants with depression at the start of the intervention.

In sum, the associations between sugar intake from sweet food / beverages and incident CMD in men may reflect a causal association, whereas the association between sugar intake from sweet food / beverages and recurrent depression in women might be the result of chance. More research will be needed to ascertain the role of chance and explain differences in measures and sex (see Chapter 8: 8.7).

### *8.6.2 How likely is it that the association between fibre intake and mood disorder is causal?*

Based on chapters 8.4 and 8.5.2 the following judgements can be made. There was little evidence that associations observed between fibre and mood disorders could be explained by selection bias as associations did not change after excluding participants with missing data in covariates. Associations were robust against the adjustment of confounders. Still, as for Objective I the risk of residual confounding explaining associations cannot be entirely ruled out as measurement of fibre intake, mood

disorders and covariates was imperfect. There was little evidence that the inverse association between fibre intake and incident CMD was the result of chance.

The inverse association between fibre intake and incident mood disorder could be shown in all mood disorder measures and did not differ by sex. Findings of this objective were in line with findings from one of two other studies on prospective associations between fibre intake and incident mood disorders. Associations were moderate, in the direction of fibre intake to follow-up mood disorder, in a dose-response manner and could be considered plausible. Finally, a causal association is supported by a trial that found a diet high in complex carbohydrates to reduce depressive symptoms as compared to a diet high in simple carbohydrates.

In sum, the inverse association between fibre intake and incident psychiatric morbidity could be causal. Further research will be needed to confirm findings from this study (see Chapter 8: 8.7).

### *8.6.3 How likely is it that sugar intake from sweet food and beverages and fibre intake are moderators in the association between financial insecurity and mood disorders?*

There was no evidence for a moderating role of sugar intake from sweet food / beverage wherefore this section will focus on dietary fibre intake. Judgements are made based on chapters 8.4 and 8.5.3. There was strong evidence that interactions (<0.2) between fibre intake and financial insecurity in the associations between financial insecurity and CMD were the results of selection bias as the interaction appeared after exclusion of participants with missing data in covariates (see Chapter 8: 8.4.1). Furthermore, there was considerable risk of a chance finding due to the large number of modes of analyses, which could potentially explain the interaction with fibre intake in the association between last grade level and incident depression.

However, the interaction between fibre intake in the association between last grade level was strong and from fibre intake and grade level to future incident depression. It can be speculated that fibre intake could potentially increase the biological resilience to mood disorders. No earlier research can confirm the findings found in this study.

In sum, there is no sufficient evidence that fibre intake moderates an association between financial insecurity and last grade level with mood disorders. However, due to the strength of the interaction between fibre intake and last grade level in this study and the public health importance of this question future research should replicate analyses

regarding the potential role of fibre as a moderator in the association between socio-economic position and mood disorder.

## 8.7 Future research

Only few prospective studies had investigated the association between sugar dense diets, fibre intake and mood disorders. This thesis suggests an association between free sugar intake, fibre intake and mood disorders. Further studies are needed to come to a conclusion whether the associations could be causal.

### *8.7.1 Methodological considerations for future observational research*

In this thesis several methodological approaches could have led to bias, confounding and chance. Future studies could improve data-collection and design to avoid some of these limitations.

One key limitation was the assessment of dietary intake. Misreporting has been found to be evident in all dietary assessment methods, such as FFQ, 24-h recall and diet diary (Livingstone & Black, 2003; Macdiarmid & Blundell, 1998, 1997). Misreporting could be monitored or reduced by adding biomarkers or photo-assisted recording to traditional methods (Gemming, Utter & Ni Mhurchu, 2015; Kuhnle, 2012). Impressively, a study in EPIC-Norfolk found that using a biomarker for sugar intake could explain an inverse association found between reported total sugar intake and adiposity to a positive between biomarker measured sugar intake and adiposity (Kuhnle *et al.*, 2015). Adding wearable camera systems to 24-h recalls has been found to help identify unreported items in diet data collection (Gemming *et al.*, 2013; Gemming, Utter & Ni Mhurchu, 2015). Both areas need further innovation, as many biomarkers are unable to identify the actual food source and photo and camera assisted nutrition recording can lead to diet changes in response and raise issues of privacy and ethics (Kuhnle, 2012; Gemming, Utter & Ni Mhurchu, 2015; Hassannejad *et al.*, 2017). Adding additional methods to dietary data collection could improve validity of future studies.

Residual confounding is a key limitation in nutritional epidemiology and regarding the research question of links between diet and mood disorders (Ioannidis, 2013; Davey Smith & Phillips, 1992; Davey Smith *et al.*, 2007). Most previous prospective studies on the association between free sugar, fibre intake and mood disorders had only included self-reported covariates and only few covariates were assessed objectively in analyses in this thesis. Increasing the validity of covariates by using objectively measured data such as measured weight could reduce risk of residual confounding slightly. However, the most effective way to reduce the risk of residual confounding would be by conducting a RCT (discussed in more detail in 8.7.3).

An important limitation in analyses in this thesis and in some previous research was the insufficient handling of multiple testing (Sanchez-Villegas *et al.*, 2017; Guo *et al.*, 2014; Akbaraly *et al.*, 2013). Future studies should set out methods such as Bonferroni correction or false discovery rate a priori (Feise, 2002; Bland & Altman, 1995; Curran-Everett, 2000).

### *8.7.2 Related research questions*

Several questions were outside of the scope of this thesis but could add further insight in the role of diet in mood disorders.

In this thesis it was hypothesised that an association between mood disorders and diet changes could be explained by changes in diet related health behaviour such as grocery-shopping and cooking. In future research I would like to investigate cooking behaviour and mood disorders in Whitehall II.

The role of social context of eating was ignored in analyses in this thesis as social support and network variables had not been available at all phases included. Social support and networks could provide a potential alternative pathway in the association between dietary intake and mood disorders, as they have been found to be associated with dietary intake (Henriksen, Torsheim & Thuen, 2014). In future work I would like to investigate the role of social relationships and dietary intake in Whitehall II.

Biological explanations for an association were based on a vast number of potential connections. More research is needed regarding biological links between free sugar, sweet food / beverage and fibre intake and mood disorders. For example, cohort studies including inflammatory markers could investigate the link through inflammation as reported for dietary indices (Akbaraly *et al.*, 2016) and cohort studies including stool samples could investigate a link between dietary fibre intake and mood disorders through gut microbiota. Interventional studies could produce even more powerful evidence.

### *8.7.3 Interventional studies*

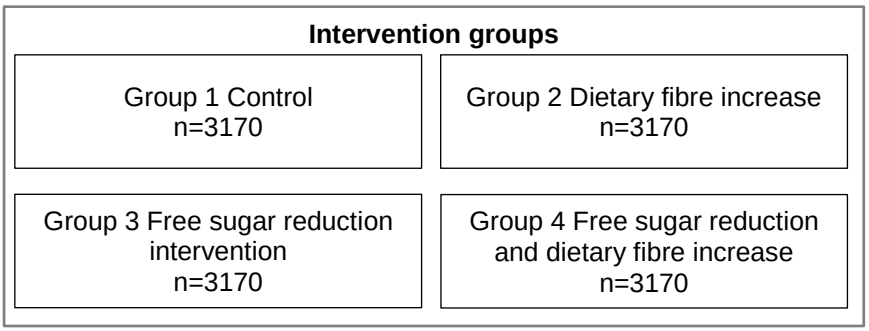
A definitive answer to whether there is a causal association between free sugar, fibre intake and mood disorders can only come from a well-conducted randomised controlled trial. Testing the effect of high sugar intake with a trial would be unethical but the effect of a diet low in free sugars and high in fibre as compared to no dietary intervention could be investigated with a trial. Only two small RCTs of high quality have

investigated the association between dietary intake including limited intake of free sugars and increased intake of fibre-rich foods such as wholegrain products, fruits and vegetables. Other trials were of low quality, included only diseased patients or dietary supplements in interventions making it difficult to distinguish effects (Parletta *et al.*, 2017; Opie *et al.*, 2014).

RCTs reduce the risk of confounding. However, RCTs in nutrition have specific difficulties such as blinding and compliance. A dietary intervention cannot be blinded as the participant will either be aware what food they are provided with or what they are recommended to eat. This awareness could bias the results due to a placebo effect, misreporting of dietary intake by participants in the intervention group in follow-up screenings or because participants might change their behaviour in other ways due to their awareness of the intervention. Compliance of participants to nutritional recommendations has been found to be low and is difficult to assess due to misreporting of dietary intake. Low compliance has been suggested to underline the unsuccessfulness of some trials on diet and health associations (Willett, 2010; Li *et al.*, 2014). Some considerations for a potential trial are presented in Box 1.

**Box 1 Initial consideration for a randomised controlled trial on dietary intervention to improve fibre intake and reduce free sugar intake for the prevention of common mental disorder**

**Design:** 2x2 factorial design, randomised controlled trial




**Follow-up time:** 12 months

**Outcome:** CMD based on questionnaire

**Intervention:** Dietary recommendations and support for behaviour change towards a diet high in fibre and reduced in free sugars, potentially including smartphone applications;
Target: reaching the recommended levels of fibre intake (30g/day) and staying below the recommended level of free sugar intake (30g/day or 5% of total energy intake.

**Control:** If meetings were involved in intervention the control groups should be engaged in some sort of meeting parallel to meetings with intervention group (as in Jacka et al. 2017)

**Compliance assessment:** 24-h dietary recall and 24-h urine samples

**Secondary outcomes/mediators:** Single symptoms, weight, waist circumference, stool samples

For a 2x2 factorial design sample sizes are calculated independently and then the higher sample size is chosen (Montgomery, Peters & Little, 2003). Table 58 shows sample sizes at different levels of power and drop-put rates. Mean attrition rate of behaviour change trials has been found to be 17% (Crutzen *et al.*, 2015). Incidence was set as the point prevalence of common mental disorders 15.7% (Stansfeld *et al.*, 2016). Recruitment of participants just below threshold could potentially increase the incidence and reduce the samples size.

**Table 58 Sample size per intervention group at different power and drop-out levels**

| | | Drop out | | |
|---|---|---|---|---|
| | | **15%** | **20%** | **25%** |
| **Power** | **Fibre intake** | | | |
| | 0.80 | 1714 | 1788 | 1863 |
| | 0.85 | 1952 | 2036 | 2121 |
| | 0.90 | 2272 | 2371 | 2470 |
| | 0.95 | 2796 | 2917 | 3039 |
| | **Free sugar intake** | | | |
| | 0.80 | 3557 | 3712 | 3866 |
| | 0.85 | 4057 | 4234 | 4410 |
| | 0.90 | 4733 | 4939 | 5145 |
| | 0.95 | 5833 | 6086 | 6340 |

Aim of the intervention would be reaching the recommendation of 30g dietary fibre per day and a reduction of sugar intake to 30g per day. New technology such as smartphone apps could increase the feasibility of a trial as they are of low cost and offer support in self-monitoring of dietary choices (Taylor *et al.*, 2013; Coughlin *et al.*, 2015).

Jacka et al. (2017) used a control intervention which could be mirrored in a new trial in the form that some sort of meeting or other type of control-intervention is provided for those in group 1. Apart from it reducing the risk of measuring the effect of engagement in a trial rather than the actual intervention it would furthermore support comparison with this earlier study. Compliance to the intervention could be assessed using a dietary recall and total excretion of sucrose and fructose via 24h urine samples to control for misreporting (Kuhnle *et al.*, 2015; Tasevska *et al.*, 2011).

Several of the related research questions raised above such as a potential mediation by adiposity or biological pathways could also be investigated in a trial as well for example by measuring weight and waist circumference or collecting stool samples to assess gut microbiome changes. While such a large trial would require massive funding, it would offer important evidence whether public health action should be taken to prevent mood disorders by diet.

## 8.8 Policy implications

### *8.8.1 Adding to the list of reasons for reducing free sugar intake and increasing fibre intake*

In recent years, a number of countries have implemented policies to reduce free sugar intakes in particular sugar-sweetened beverages in response to its adverse health effects such as obesity (Popkin & Hawkes, 2016). In the UK, a sugar levy of 18 and 24 pence per litre for drinks of 5 and 8 grams or more sugar per 100ml took effect in April 2018 (HM Revenue & Customs, 2016). However, the topic remains controversial. A number of societies and committees responsible for setting nutritionally guidelines have rejected to change their guidelines towards recommending lower levels of free sugar intake due to the small effect sizes and lack of trial evidence (Kaiser *et al.*, 2013). Adding evidence from mental health might be an important motivation as the costs of a dietary interventions are small compared to the high healthcare and societal costs of poor mental health (Centre for Mental Health, 2010; McManus *et al.*, 2009; NHS England, 2015; Steel *et al.*, 2014; Brunner, Cohen & Toon, 2001).

The findings from this thesis do not offer a strong case for a causal association between free sugar and fibre intake in the prevention of mood disorders but suggest a potential association. From a population perspective, a small effect could still have an important impact. Currently only 9% of British adults reach the recommendation of fibre intake and free sugar intake is on average double the recommended level (Public Health England, 2018). Therefore, this research and future research could add a mental health component to the evidence of adverse effects of high free sugar intake and low fibre intake on physical health outcomes and could support the implementation of policy action (Stephen *et al.*, 2017; Morenga, Mallard & Mann, 2013; Sheiham & James, 2014; Yang *et al.*, 2014; Hu & Malik, 2010; Malik *et al.*, 2010; Hartley *et al.*, 2016; Threapleton *et al.*, 2013b, 2013a; Liu *et al.*, 2015).

There are several ways how diet can be improved on a population level. Some such as media and education campaigns, food labelling and information can support individual behaviours changes. Others target structural changes such as interventions set in schools and workplaces, restricting marketing and offering economic incentives (Mozaffarian *et al.*, 2012). Studies have found that interventions on an individual level can be effective in increasing fibre intake whereas those targeting structural changes are more effective to reduce free sugar intake (Bhattarai *et al.*, 2013; Cabrera Escobar *et al.*, 2013; Maderuelo-Fernandez *et al.*, 2015; Rees *et al.*, 2013; Vargas-Garcia *et al.*, 2017).

### *8.8.2 Dietary interventions and mental health inequalities*

Several researchers have made strong claims regarding the role of diet in mental health based on the links found between dietary patterns and depression. Sarris et al. (2015) described diet and nutrition as *'central determinants [...] of mental health'* and Dawson, Dash & Jacka (2016) called for *'Public health approaches and messages should now focus on the importance of diet for mental as well as physical health, while clinicians should promote the benefits of dietary improvement and facilitate access to dietary support for their patients.'* (Dawson, Dash & Jacka, 2016:p.338; Sarris *et al.*, 2015).

Navarro warned in 1976 that the focus on health behaviours could redirect the question of health differences to the individual and thereby undermine the role of distribution of wealth and political power in health inequalities (Navarro, 1976). In this thesis it was shown that associations with financial insecurity were stronger and more consistent than those with sugar intake from sweet food / beverages and dietary fibre intake. Furthermore, results of this thesis did not find evidence that interventions reducing sugar intake and increasing fibre intake could buffer associations between socio-economic stressors and mood disorders. These results stress that mental health inequalities remain an important public health issue that cannot be moderated by dietary interventions (Allen *et al.*, 2014). Yet, tackling inequalities could improve diets as free sugar intake and fibre intake show a socio-demographic gradient with higher sugar intake and lower fibre intake in more deprived groups (James *et al.*, 1997; Maguire & Monsivais, 2015; Pechey *et al.*, 2013; Giskes *et al.*, 2010; Barrett *et al.*, 2017) (see Chapter 2: 2.5.4).

In sum, findings from this study support public health interventions targeting structural changes in free sugar availability and promoting individual change to higher fibre intakes. Public health interventions aiming at the prevention of mental health problems should however independently tackle health inequalities upstream as these might improve both diets *and* mental health.

## 8.9 Conclusion

This thesis aimed to investigate the role of sugar intake from sweet food / beverages and fibre intake as predictors of mood disorders and as moderators of an association between financial insecurity, socio-economic position and mood disorders.

Men without current mood disorders with high sugar intake from sweet food / beverages had 21% increased odds of developing CMD as compared to those with low intakes. This association was not seen in women, although free sugar intake was linked with recurrent mood disorder. The sex difference in this association could not be explained by specifics of the Whitehall II cohort as a similar sex difference was found when investigating the association in an independent sample. That there was no association between sugar intake from sweet food / beverages and incident mood disorders in women might be due to biological differences in operating pathways or gender differences in misreporting, but future research will be needed to test these hypotheses.

Women with current mood disorders and high sugar had double the odds to experience depression again, 5 years later. Associations were significantly weaker in men but showed a similar direction. These findings were novel, but it cannot be ruled out that they could be a chance finding.

Men and women without current mood disorders and high dietary fibre intake had 26% lower odds of developing CMD 5 years later than those with low intakes. Associations were similar after 10 years and across different mood disorder measures. There was no association between fibre intake and recurrent mood disorders.

Mood disorders were not associated with long-term changes in sugar intake from sweet food / beverages and fibre intake.

There was no evidence that sugar intake from sweet food / beverages could amplify and fibre intake could weaken the association between financial insecurity and mood disorders. However, participants who had been in the lowest grade level in civil service and high fibre intakes had a reduced chance to develop incident depression than participants with lower fibre intakes, but it cannot be ruled out that this was a chance finding.

As dietary intake and mood disorders as well as covariates were not measured without error, residual confounding remains a potential alternative explanation for all observed associations and future research will be needed to clarify whether associations reflect causality.

Mood disorders present a major public health concern. Diets low in fibre and high in free sugars may play an important role in occurrence at population level. If the thesis findings are confirmed, a mental health dimension would be added to the adverse health effects of diets high in free sugars and low in fibre.

## Appendices

## Appendices relating to Chapter 2

### Appendix 1 Food composition tables and change of food intake

The use of food composition tables to derive especially micronutrient intakes can be flawed if they are not updated frequently as food ingredients change over time might (Willett & Sampson, 2012). Table A 1 shows that while the added sugar intake in sweet food and beverages has remained relatively stable changes were much greater in cereal and savoury foods.

**Table A 1 Total sugar per 100g for different food items based on *'McCance and Widdowson's composition of foods'* (1991; 2002; 2015)**

| **Sweet food and beverages** | **5th edition 1991** | **6th edition 2002** | **7th edition 2015** |
|---|---|---|---|
| | Total sugar g/100g | Total sugar g/100g (% change to 5th Edition) | |
| sweet biscuits | 26.6 | 27.5 (3.4) | 26 (-2.3) |
| buns or pastries | 21.4 | 21.3 (-0.5) | 21 (-1.9) |
| Cakes | 36.5 | 36.5 (0.0) | 36.5 (0.0) |
| chocolates or chocolate bars | 53.7 | 47.5 (-11.5) | 50.4 (-6.1) |
| fruit pies, tarts or crumbles | 16.1 | 16.3 (1.2) | 16.3 (1.2) |
| ice cream | 22.1 | 18.7 (-15.4) | 23.5 (6.3) |
| jam, marmalade or honey | 69.0 | 69 (0.0) | 69 (0.0) |
| milk puddings | 10.7 | 10.4 (-2.8) | 10.2 (-4.7) |
| sponge puddings | 18.9 | 18.5 (-2.1) | 18.5 (-2.1) |
| added sugar | 105 | 105 (0.0) | 105 (0.0) |
| sweets, toffees or mints | 86.9 | 86.7 (-0.2) | 86.7 (-0.2) |
| fizzy soft beverages | 5.6 | 5.8 (3.6) | 5.8 (3.6) |
| fruit squash or cordial | 4.9 | 4.9 (0.0) | 4.9 (0.0) |
| fruit juice | 9.9 | 9.9 (0.0) | 9.7 (-2.0) |
| cocoa or hot chocolate | 6.8 | N/A | 6.5 (-4.4) |
| malted milk beverages, such as Horlicks | 10.2 | N/A | 8.5 (-16.7) |
| | | | |
| Frozen Pizza | 6.9 | 2.0 (-71.0) | 3.9 (-43.5) |
| Savoury meat pie | 22.9 | 27.5 (20.1) | 27.5 (20.1) |
| Ketchup | 2.3 | 1.5 (-34.8) | 0.9 (-60.9) |
| Sugar puffs (cereal) | 56.5 | 51.5 (-8.8) | 36.8 (-34.9) |
| Shreddies (cereal) | 10.2 | 15.4 (51.0) | 20.3 (99.0) |

**Appendix 2 Search terms free sugar, sweet food / beverages and mood disorders**

Search terms used were: *"mood"* or *"mood disorder"* or *"mood disorders"* or *"affective"* or *"depressive"* or *"depression"* or *"depressions"* or *"anxiety"* or *"mood disorders"* or *"anxiety disorder"* or *"anxiety disorders"* or *"depressive disorders"* or *"depressive disorder"* combined with *"diet"* or *"dietary"* or *"nutritional"* or*" food"* or *"Diets"* or *"foods"* or *"nutrition"* and *"sugars"* or *"sugar"* or *"saccharose"* or *"sweetened"* or *"sucrose"* or *"glucose"* or *"sweet"* or *"fructose"*. In PubMED the Medical Subject Headings *"Depressive Disorders"*, *"Anxiety Disorders"*, *"Mood Disorder"* and *"Diet"* were added to the search.

**Appendix 3 Search terms dietary fibre intake and mood disorders:**

Search terms used were: *"mood"* or *"mood dis*or*der"* or *"mood dis*or*ders"* or *"affective"* or *"depressive"* or *"depression"* or *"depressions"* or *"anxiety"* or *"mood disorders"* or *"anxiety disorder"* or *"anxiety disorders"* or *"depressive disorders"* or *"depressive disorder"* combined with *"diet"* or *"dietary"* or *"nutritional"* or*" food"* or *"Diets"* or *"foods"* or *nutrition* and *"fibre"* or *"fiber"* or *"fibres"* or *"fibers"*. In PubMED the Medical Subject Headings "Depressive Disorders", "Anxiety Disorders", "Mood Disorder", "Diet" and *"Dietary Fiber"* were added to the search.

**Appendix 4 Detailed study descriptions: Cross-sectional evidence on associations between free sugar, sweet food and beverages and mood disorders**

Chamberlain et al. (2017) recruited 225 U.S. students that gambled at least 5 times in the previous year, based on the hypothesis that these might have more impulsive behaviour than the general population. While higher free sugar intake was not associated with impulsivity it was associated with higher depressive and anxiety symptom scores.

Appleton et al. (2007) found no association between cake intake and depressive symptoms in a sample of Northern Irish and French men. An inverse association in Northern Irish men was attenuated after adjustment for socio-demographic factors and there was no association in men in France before and after adjustment.

Two studies in university students followed similar designs but found opposing results. Mikolajczyk et al. (2009) and El Ansari et al. (2014) analysed the association between food groups and depressive symptoms in students from central European and UK universities, respectively. Mikolajczyk et al. (2009) found no significant association between sweet food and soft beverages intake and depressive symptoms, but El Ansari et al. (2014) found a positive correlation between sweet food intake and

depressive symptoms in the UK sample. The difference in results between these similar studies might have been due to differences in the student populations that were not adjusted for.

Jeffery et al (2009) investigated the association between *'high-calorie sweet'* food intake grouping FFQ-food items such as cake, sweetened soda and fruit beverages, chocolate and cornbread. They found a positive association in the sample of middle-aged women. A Finnish study took a similar approach of defining a *'sweet energy dense food'* group and found a similar association that was attenuated by adjustment for emotional eating (Konttinen *et al.*, 2010). Still, this must not mean that emotional eating is a confounder in this association. Emotional eating could potentially lie on a pathway between depressive symptoms and *'sweet energy dense'* and the cross-sectional nature does not allow drawing a conclusion.

Finally, two studies investigated the role of soft drink consumption and found increased soft drink consumption to be associated with a higher prevalence of doctor-diagnosis of depression, psychological distress and depressive symptoms (Shi *et al.*, 2010; Yu *et al.*, 2014).

Two studies included measures of anxiety of which one found an association with free sugar intake and the other did not (Shi *et al.*, 2010; Chamberlain, Redden & Grant, 2017).

**Appendix 5 Detailed study descriptions: Prospective evidence on associations between free sugar, sweet food and beverage intake and mood disorders**

Gangwisch et al. (2015) analysed data from the U.S. Women's' Health Study including middle-aged and elderly women that were followed up over three years. The association was attenuated after adjustment of socio-demographic factors, health behaviour social support, life events and fatty acids and minimally adjusted when further adjusted for healthy dietary factors, but remained statistically significant. The researchers additionally analysed associations with total sugars, glucose, sucrose, lactose and fructose and other dietary factors. Except for a reduced chance of depression in those with high lactose intake, none of the other sugar measures were associated with depressive symptoms (Gangwisch *et al.*, 2015). This finding underscores a special role of free sugars as compared to total sugar intake.

Sanchez-Villegas et al. (2017) analysed data from the SUN cohort a study of university graduates from Seguimiento Universidad de Navarra in Spain. Associations with added sugar intake were hardly changed after adjustment for confounders beyond energy intake, age and sex and remained statistically significant in analyses of continuous

intakes. Added sugar intake was defined as sugar content from sweet foods and beverages. The study additionally analysed the association with sweetened beverages only, but this associations did not reach significance. 10-year average added sugar intake was associated with depressive symptoms at follow-up in both analyses of continuous intake and quartiles and was not associated with sweetened beverages intake (Sanchez-Villegas *et al.*, 2017). The results suggest that the association between free sugar intake and mood disorders could not be explained sweet beverage intake, only.

In an earlier study using SUN cohort data Sanchez-Villegas et al. (2012) found that '*commercial baked goods'* intake was associated with an increased risk of incident depression after six years in a non-linear manner.

Guo et al. (2014) studied associations between non-alcoholic beverage intakes and depression diagnosis in over 250,000 U.S. middle-aged and older adults. One can of sugar-sweetened soft drink per day was associated with 26%, four or more cans of fruit beverages was associated with 38% increased odds for incident depression diagnosis 5 years later compared to consuming none (Guo *et al.*, 2014). Associations with sugar-sweetened soft beverages did not differ by sex but associations with fruit beverages were stronger in men. Guo et al. (2014) investigated differences between regular and diet beverages and found a similar positive association for diet soft drinks, fruit drinks and ice tea suggesting that sweetness could facilitate the association rather than sugar.

**Appendix 6 Detailed study descriptions: Cross-sectional evidence on associations between dietary fibre intake and mood disorders**

Davison & Kaplan (2012) investigated the association between fibre intake and depressive symptoms in a small sample of adults with diagnosed mood disorders and found no association. In another Canadian but healthy population study Davison et al. (2017) found that men between 31 and 50 years and women between 51 and 70 years with poor mental health and food insecurity had significantly lower fibre intakes than those without food insecurity and good mental health before adjustment for potential confounders. In a small study of 225 young women an inverse association between fibre intake and depressive symptoms was attenuated after adjustment for socio-demographic factors, diseases, medication and energy intake (Fang *et al.*, 2013).

Gopinath et al. (2017) analysed data from middle-aged Australian women and found lower prevalence of depressive symptoms in those with higher bread and cereal fibre intake and some non-linear inverse association with total and vegetable fibre intake. Estimates showed significantly lower chances when comparing the 2$^{nd}$ to the 1$^{st}$ tertile

but not when comparing the highest to the lowest tertile. Gopinath et al. (2017) did not report whether tertiles were calculated from energy-adjusted or unadjusted intakes which can affect the grouping and could explain the non-linear results. A person that underreported their energy intake might be grouped in the lowest tertile even though their relative fibre intake might have been higher than in others (Brown *et al.*, 1994). The researchers found no significant association when depressive symptoms were assessed using the Mental health index scale (Gopinath *et al.*, 2017).

In a study of employees of a manufacturing company fibre intake from vegetables and fruit was associated with reduced chances of having depressive symptoms. An association with total fibre intake was attenuated after adjustment for socio-demographic factors, health behaviours, sleep duration, BMI, energy and micronutrient intake (Miki *et al.*, 2016).

A study in 3394 Chinese elderly found high fibre intake to be associated with lower geriatric depression symptoms in models adjusted for cognitive function, socio-demographic factors and medical diseases (Woo *et al.*, 2006).

Xu et al. (2018) analysed data from the U.S. National Health and Nutrition Examination Survey and found a strong inverse association between total fibre intake and fibre intake from fruits and vegetables with symptoms of depression in models adjusted for socio-demographic factors, health behaviours, BMI, energy intake, hypertension and diabetes.

Green & Pope (2000) investigated the association between history of depressive symptoms based on recall and current dietary behaviour. They found that those with a history of depressive symptoms or diagnosis were more likely to report attempting to consume more fibre.

**Appendix 7 Detailed study descriptions: Prospective evidence on associations between dietary fibre intake and mood disorders**

Gangwisch et al. (2015) analysed data from a large cohort of women in the US. The researchers found an inverse association between dietary fibre intake and depressive symptoms. Associations were attenuated after adjustment for confounders such as health behaviours, BMI, diseases and social support but remained statistically significant.

Sanchez-Villegas et al. (2017) investigated the association between fibre intake and self-reported diagnosed depression in a cohort of university graduates. The research group found no association between fibre intake at baseline and depression at follow-

up independent of adjustments. There was also no association between average fibre intake over 10 years and depression diagnosis over 16 years.

Other studies are presented in main text.

## Appendices relating to Chapter 4

### Appendix 8 Food Frequency Questionnaire

# STRESS & HEALTH STUDY

## FOOD QUESTIONNAIRE

For each food, please block in the red rectangle in the column to indicate how often, on **average,** you have eaten the specified amount **during the past year.** The amount of each food is given in the heading of each section or after the individual food. Amounts are either a "medium serving" or a common household unit such as a slice or pint.

Please note that you do not need to be too precise when blocking in the rectangles - a single bold stroke over the length of the rectangle will do. Use either a black or blue pen, or an HB pencil. Please do not mark like this: 

**EXAMPLES:**
For white bread the amount is one slice, so if you eat 4 or 5 slices a day, you should block in the rectangle in the column headed "4 - 5 per day".

| ***FOODS AND AMOUNTS*** | ***AVERAGE USE LAST YEAR*** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **BREAD AND SAVOURY BISCUITS (one slice or biscuit)** | Never or less than once/mth | 1 - 3 per mth | Once a week | 2 - 4 per week | 5 - 6 per week | Once a day | 2 - 3 per day | 4 - 5 per day | 6 + per day |
| White bread and rolls | | | | | | | | | |

For chips, the amount is a "medium serving", so if you have a helping of chips twice a week you should block in the rectangle in the column headed "2 - 4 per week".

| **POTATOES, RICE AND PASTA (medium serving)** | Never or less than once/mth | 1 - 3 per mth | Once a week | 2 - 4 per week | 5 - 6 per week | Once a day | 2 - 3 per day | 4 - 5 per day | 6 + per day |
|---|---|---|---|---|---|---|---|---|---|
| Chips or french fries | | | | | | | | | |

For full cream milk (silver top), the amount is a pint, so if you take about half a pint a day, you should block in the rectangle in the column headed "2 - 4 per week", because you are drinking about 3 pints each week.

| **DAIRY PRODUCTS AND FATS** | Never or less than once/mth | 1 - 3 per mth | Once a week | 2 - 4 per week | 5 - 6 per week | Once a day | 2 - 3 per day | 4 - 5 per day | 6 + per day |
|---|---|---|---|---|---|---|---|---|---|
| Full cream milk - silver top (pint) | | | | | | | | | |

For very seasonal fruits such as strawberries and raspberries you should estimate your average use when the fruits are in season, so it you eat strawberries or raspberries about once a week when they are in season you should block in the rectangle in the column headed "once a week".

| **FRUIT (1 fruit or medium serving)** | Never or less than once/mth | 1 - 3 per mth | Once a week | 2 - 4 per week | 5 - 6 per week | Once a day | 2 - 3 per day | 4 - 5 per day | 6 + per day |
|---|---|---|---|---|---|---|---|---|---|
| Strawberries, raspberries | | | | | | | | | |

Please estimate your average food use as best you can, and please answer every question - **DO NOT LEAVE ANY LINES BLANK.**

| FOODS AND AMOUNTS | | AVERAGE USE LAST YEAR | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **MEAT AND FISH (medium serving)** | | Never or less than once/mth | 1 - 3 per mth | Once a week | 2 - 4 per week | 5 - 6 per week | Once a day | 2 - 3 per day | 4 - 5 per day | 6 + per day |
| Beef: roast, steak, mince, stew or casserole | XBEEF | | | | | | | | | |
| Beefburgers | XBEEFBU | | | | | | | | | |
| Pork: roast, chops or stew | XPORK | | | | | | | | | |
| Lamb: roast, chops or stew | XLAMB | | | | | | | | | |
| Chicken or other poultry | XCHICK | | | | | | | | | |
| Bacon | XBACON | | | | | | | | | |
| Ham | XHAM | | | | | | | | | |
| Corned beef, Spam, luncheon meats | XCORNBF | | | | | | | | | |
| Sausages | XSAUSAG | | | | | | | | | |
| Savoury pies, eg meat pie, pork pie, pasties, steak & kidney pie | XSAVPIE | | | | | | | | | |
| Liver, liver pate, liver sausage | XLIVER | | | | | | | | | |
| Fried fish in batter, as in fish and chips | XBATFIS | | | | | | | | | |
| Fish fingers, fish cakes | XFISHFIN | | | | | | | | | |
| Other white fish, fresh or frozen, eg cod, haddock plaice, sole, halibut | XWHIFISH | | | | | | | | | |
| Oily fish, fresh or canned, eg mackerel, kippers, tuna, salmon, sardines, herring | XOILFISH | | | | | | | | | |
| Shellfish, eg crab, prawns, mussels | XSHEFISH | | | | | | | | | |
| | | Never or less than once/mth | 1 - 3 per mth | Once a week | 2 - 4 per week | 5 - 6 per week | Once a day | 2 - 3 per day | 4 - 5 per day | 6 + per day |

Please answer every question - **DO NOT LEAVE ANY LINES BLANK.**

| ***FOODS AND AMOUNTS*** | | ***AVERAGE USE LAST YEAR*** | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **BREAD & SAVOURY BISCUITS (one slice or one biscuit)** | Never or less than once/mth | 1 - 3 per mth | Once a week | 2 - 4 per week | 5 - 6 per week | Once a day | 2 - 3 per day | 4 - 5 per day | 6+ per day |
| White bread and rolls **XWHIBRD** | | | | | | | | | |
| Brown bread and rolls **XBROBRD** | | | | | | | | | |
| Wholemeal bread and rolls **XWHOLBRD** | | | | | | | | | |
| Cream crackers, cheese bisc. **XCRACKER** | | | | | | | | | |
| Crispbread, eg Ryvita **XCRISBRD** | | | | | | | | | |
| **CEREALS (one bowl)** | | | | | | | | | |
| Frosties, Ricicles, Sugar Puffs, Coco Pops **XFROS** | | | | | | | | | |
| Corn Flakes, Rice Krispies, Special K **XCFLAK** | | | | | | | | | |
| Shredded Wheat, Weetabix, Wheat Flakes, Puffed Wheat, Shreddies, Grape Nuts **XSHRED** | | | | | | | | | |
| Muesli, Fruit 'n' Fibre, Country Store, Weetos, Start **XMUES** | | | | | | | | | |
| All-Bran, Bran Flakes, Bran Buds, Sultana Bran **XBRAN** | | | | | | | | | |
| Porridge, Readybrek **XPORRI** | | | | | | | | | |
| **POTATOES, RICE AND PASTA (medium serving)** | | | | | | | | | |
| Boiled, mashed, instant or jacket potatoes **XBOILPOT** | | | | | | | | | |
| Chips or french fries **XCHIPS** | | | | | | | | | |
| Roast potatoes **XROASPOT** | | | | | | | | | |
| Potato salad **XPOTSAL** | | | | | | | | | |
| White rice **XWRICE** | | | | | | | | | |
| Brown rice **XBRICE** | | | | | | | | | |
| White or green pasta, eg spaghetti, macaroni, noodles **XPASTA** | | | | | | | | | |
| Wholemeal pasta **XWHPAST** | | | | | | | | | |
| Lasagne **XLASAGNE** | | | | | | | | | |
| Pizza **XPIZZA** | | | | | | | | | |
| | Never or less than once/mth | 1 - 3 per mth | Once a week | 2 - 4 per week | 5 - 6 per week | Once a day | 2 - 3 per day | 4 - 5 per day | 6+ per day |

Please answer every question - **DO NOT LEAVE ANY LINES BLANK.**

| ***FOODS AND AMOUNTS*** | | ***AVERAGE USE LAST YEAR*** | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **DAIRY PRODUCTS & FATS** | Never or less than once/mth | 1 - 3 per mth | Once a week | 2 - 4 per week | 5 - 6 per week | Once a day | 2 - 3 per day | 4 - 5 per day | 6 + per day |
| Full cream milk - silver top (pint) | XFCMILK | | | | | | | | |
| Semi-skimmed milk - red striped top (pint) | XSSMILK | | | | | | | | |
| Skimmed milk - blue striped top (pint) | XSKMILK | | | | | | | | |
| Channel Islands milk - gold top (pint) | XCIMILK | | | | | | | | |
| Sterilized milk - metal cap (pint) | XSTMILK | | | | | | | | |
| Dried milk (teaspoon) | XDRMILK | | | | | | | | |
| Soya milk (pint) | XSOYMLK | | | | | | | | |
| Coffee whitener, eg Coffe-mate (teaspoon) | XCOFFWH | | | | | | | | |
| Single cream (tablespoon) | XSCREAM | | | | | | | | |
| Double or clotted cream (tablespoon) | XDCREAM | | | | | | | | |
| Yoghurt (5 oz. carton) | XYOGHURT | | | | | | | | |
| Cheese, eg Cheddar, Brie, Edam (medium serving) | XCHEESE | | | | | | | | |
| Cottage cheese, low fat soft cheese (medium serving) | XCOTCHE | | | | | | | | |
| Eggs as boiled, fried, scrambled, etc (one) | XEGGS | | | | | | | | |
| Quiche (medium serving) | XQUICHE | | | | | | | | |
| Salad cream, mayonnaise (tablespoon) | XMAYO | | | | | | | | |
| French dressing/vinaigrette (tablespoon) | XVINAIGR | | | | | | | | |
| **The following on bread, vegetables, etc:** | | | | | | | | | |
| Butter (teaspoon) | XBUTTER | | | | | | | | |
| Hard margarine in wrapper, eg Stork, Krona (teaspoon) | XHARDMAR | | | | | | | | |
| Polyunsaturated margarine, eg Flora, sunflower (tsp) | XPOLYUNS | | | | | | | | |
| Other soft margarine in tub, eg Blue Band, Stork S.B. (tsp) | XSOFTMAR | | | | | | | | |
| Low fat spread, eg Outline, Gold (teaspoon) | XLFSPREA | | | | | | | | |
| | Never or less than once/mth | 1 - 3 per mth | Once a week | 2 - 4 per week | 5 - 6 per week | Once a day | 2 - 3 per day | 4 - 5 per day | 6 + per day |

Please answer every question - **DO NOT LEAVE ANY LINES BLANK.**

| ***FOODS AND AMOUNTS*** | | ***AVERAGE USE LAST YEAR*** | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **SWEETS & SNACKS (medium serving)** | Never or less than once/mth | 1 - 3 per mth | Once a week | 2 - 4 per week | 5 - 6 per week | Once a day | 2 - 3 per day | 4 - 5 per day | 6 + per day |
| Sweet biscuits, eg Nice, digestive, chocolate (one) | XBISCUIT | | | | | | | | |
| Cakes | XCAKES | | | | | | | | |
| Buns & pastries | XBUNS | | | | | | | | |
| Fruit pies, tarts, crumbles | XTARTS | | | | | | | | |
| Milk puddings, eg rice, semolina, tapioca | XMILKPUD | | | | | | | | |
| Sponge puddings | XSPONGE | | | | | | | | |
| Ice cream, choc ices | XICECREA | | | | | | | | |
| Chocolates, chocolate bars, eg Mars, Crunchy | XCHOC | | | | | | | | |
| Sweets, toffees, mints | XSWEETS | | | | | | | | |
| Sugar added to tea, coffee, cereal (teaspoon) | XSUGAR | | | | | | | | |
| Crisps or other packet snacks, eg Wotsits | XCRISPS | | | | | | | | |
| Peanuts or other nuts | XNUTS | | | | | | | | |
| **SOUPS, SAUCES AND SPREADS** | | | | | | | | | |
| Vegetable soups (bowl) | XVEGSOU | | | | | | | | |
| Meat soups (bowl) | XMEATSO | | | | | | | | |
| Sauces, eg white sauce, cheese sauce, gravy (tablespoon) | XSAUCE | | | | | | | | |
| Tomato ketchup (tablespoon) | XKETCHU | | | | | | | | |
| Pickles, chutney (tablespoon) | XPICKLES | | | | | | | | |
| Marmite, Bovril (teaspoon) | XMARMITE | | | | | | | | |
| Jam, marmalade, honey (teaspoon) | XJAM | | | | | | | | |
| Peanut butter (teaspoon) | XPEANUB | | | | | | | | |
| | Never or less than once/mth | 1 - 3 per mth | Once a week | 2 - 4 per week | 5 - 6 per week | Once a day | 2 - 3 per day | 4 - 5 per day | 6 + per day |

**STRESS & HEALTH STUDY**

Please answer every question - **DO NOT LEAVE ANY LINES BLANK.**

| ***FOODS AND AMOUNTS*** | ***AVERAGE USE LAST YEAR*** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **DRINKS** | Never or less than once/mth | 1 - 3 per mth | Once a week | 2 - 4 per week | 5 - 6 per week | Once a day | 2 - 3 per day | 4 - 5 per day | 6 + per day |
| Tea (cup) **XTEA** | | | | | | | | | |
| Coffee, regular (cup) **XCOFFEE** | | | | | | | | | |
| Coffee, decaffeinated (cup) **XDECAFF** | | | | | | | | | |
| Cocoa, hot chocolate (cup) **XCOCOA** | | | | | | | | | |
| Horlicks, Ovaltine (cup) **XHORLI** | | | | | | | | | |
| Wine (glass) **XWINE** | | | | | | | | | |
| Beer, lager or cider (half pint) **XBEER** | | | | | | | | | |
| Port, sherry, vermouth (glass) **XPORT** | | | | | | | | | |
| Liqueurs eg Baileys (glass) **XLIQU** | | | | | | | | | |
| Spirits, eg gin, brandy whisky, vodka (single) **XSPIRITS** | | | | | | | | | |
| Fizzy soft drinks, eg Coca Cola, lemonade (glass) **XFIZZY** | | | | | | | | | |
| Low calorie or diet fizzy soft drinks (glass) **XLOWCAL** | | | | | | | | | |
| Real fruit juice (100%) eg orange, apple juice (glass) **XFJUICE** | | | | | | | | | |
| Fruit squash or cordial (glass) **XSQUASH** | | | | | | | | | |
| **FRUIT (1 fruit or medium serving) For very seasonal fruits such as strawberries, please estimate your average use when the fruit is in season** | | | | | | | | | |
| Apples **XAPPLES** | | | | | | | | | |
| Pears **XPEARS** | | | | | | | | | |
| Oranges, satsumas, mandarins **XORANGES** | | | | | | | | | |
| Grapefruit **XGRAPEFR** | | | | | | | | | |
| Bananas **XBANANAS** | | | | | | | | | |
| Grapes **XGRAPES** | | | | | | | | | |
| Melon **XMELON** | | | | | | | | | |
| Peaches, plums, apricots **XPEACHES** | | | | | | | | | |
| Strawberries, raspberries **XSTRAWB** | | | | | | | | | |
| Tinned fruit **XTINFRUI** | | | | | | | | | |
| Dried fruit, eg raisins, prunes **XDRIEDFR** | | | | | | | | | |
| | Never or less than once/mth | 1 - 3 per mth | Once a week | 2 - 4 per week | 5 - 6 per week | Once a day | 2 - 3 per day | 4 - 5 per day | 6 + per day |

Please answer every question - **DO NOT LEAVE ANY LINES BLANK.**

| ***FOODS AND AMOUNTS*** | ***AVERAGE USE LAST YEAR*** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **VEGETABLES–FRESH, FROZEN OR TINNED (medium serving)** | Never or less than once/mth | 1 - 3 per mth | Once a week | 2 - 4 per week | 5 - 6 per week | Once a day | 2 - 3 per day | 4 - 5 per day | 6+ per day |
| Carrots **XCARROTS** | | | | | | | | | |
| Spinach **XSPINACH** | | | | | | | | | |
| Brocolli **XBROCCOL** | | | | | | | | | |
| Spring greens, kale **XGREENS** | | | | | | | | | |
| Brussels sprouts **XSPROUT** | | | | | | | | | |
| Cabbage **XCABBAGE** | | | | | | | | | |
| Peas **XPEAS** | | | | | | | | | |
| Green beans, broad beans runner beans **XBEANS** | | | | | | | | | |
| Marrow, courgettes **XMARROW** | | | | | | | | | |
| Cauliflower **XCAULIFL** | | | | | | | | | |
| Parsnips, turnips, swedes **XPARSNIP** | | | | | | | | | |
| Leeks **XLEEKS** | | | | | | | | | |
| Onions **XONIONS** | | | | | | | | | |
| Garlic **XGARLIC** | | | | | | | | | |
| Mushrooms **XMUSHROO** | | | | | | | | | |
| Sweet peppers **XPEPPERS** | | | | | | | | | |
| Green salad **XSALAD** | | | | | | | | | |
| Tomatoes **XTOMATO** | | | | | | | | | |
| Coleslaw **XCOLESL** | | | | | | | | | |
| Baked beans **XBAKEDB** | | | | | | | | | |
| Dried lentils, beans, peas **XLENTILS** | | | | | | | | | |
| Tofu or soya bean curd **XTOFU** | | | | | | | | | |
| Soya meat, TVP, Vegeburger **XTVP** | | | | | | | | | |
| | Never or less than once/mth | 1 - 3 per mth | Once a week | 2 - 4 per week | 5 - 6 per week | Once a day | 2 - 3 per day | 4 - 5 per day | 6+ per day |

**2** Are the foods listed on the previous pages representative of the foods that you usually eat or drink? Yes ☐ No ☐

**3** What kind of fat do you usually use for frying? **Select one only** **XFRYFAT**

Butter ☐ Solid vegetable fat ☐
Lard/dripping ☐ Margarine ☐ **XFFTYPE**
Liquid vegetable oil ☐ None ☐

Which brand do you usually use? **XFFBRAND** .....

**4** What kind of fat do you usually use for baking? **Select one only** **XBAKEFAT**

Butter ☐ Solid vegetable fat ☐
Lard/dripping ☐ Margarine ☐ **XBFTYPE**
Liquid vegetable oil ☐ ☐
**XBFBRAND**

Which brand do you usually use? .....

**5** How often do you eat food that is fried at home? **Select one only**

IE

Less than once a week ☐ 4 - 6 times a week ☐
1 - 3 times a week ☐ Daily ☐

**6** How often do you eat food that is fried away from home? **Select one only** XFRYAWAY

| | | | |
|---|---|---|---|
| Less than once a week | ☐ | 4 - 6 times a week | ☐ |
| 1 - 3 times a week | ☐ | Daily | ☐ |

**7** What do you do with the visible fat on your meat? **Select one only** XMEATFAT

| | | | |
|---|---|---|---|
| Don't eat meat | ☐ | Eat some of the fat | ☐ |
| Eat as little as possible | ☐ | Eat most of the fat | ☐ |

**8** How often do you eat grilled or roast meat? **Select one only** XOFTNGR

| | | | | | |
|---|---|---|---|---|---|
| Never | ☐ | Once a week | ☐ | 5+ times per week | ☐ |
| Less than once per week | ☐ | 2-4 times per week | ☐ | | |

**9** If you eat grilled or roast meat, do you usually have it - **Select one only** XHOWGRI

| | | | | | |
|---|---|---|---|---|---|
| Lightly cooked | ☐ | Medium | ☐ | Well done/dark brown | ☐ |

**10** How often do you add salt to food while cooking? **Select one only** XSALTCK

| | | | | | |
|---|---|---|---|---|---|
| Never | ☐ | Sometimes | ☐ | Always | ☐ |
| Rarely | ☐ | Usually | ☐ | | |

**11** How often do you add salt to any food at the table **before** tasting it? **Select one only** XPRESAL

| | | | | | |
|---|---|---|---|---|---|
| Never | ☐ | Sometimes | ☐ | Always | ☐ |
| Rarely | ☐ | Usually | ☐ | | |

**12** How often do you add salt to any food at the table **after** tasting it? **Select one only** XPOSTSA

| | | | | | |
|---|---|---|---|---|---|
| Never | ☐ | Sometimes | ☐ | Always | ☐ |
| Rarely | ☐ | Usually | ☐ | | |

**13** Do you regularly use a salt substitute (e.g. LoSalt)? Yes ☐ No ☐ XSALTSUB

If **yes**, which brand ..... XSALTBR

**14** Over the last five years have you regularly taken any vitamin, mineral, cod-liver oil, etc. supplements?

If **yes**, which brand? XVITAMIN Yes ☐ No ☐

| Brand Name | Daily amount | Years taken in last 5 years |
|---|---|---|
| XVITBR1 | XVITDO1 | XVITTY1 |
| XVITBR2 | XVITDO2 | XVITTY2 |
| XVITBR3 | XVITDO3 | XVITTY3 |

**FOR OFFICE USE ONLY**
**STUDY NUMBER**

## Appendix 9 General Health Questionnaire

**GENERAL HEALTH QUESTIONS**

**Please read this carefully:**

We should like to know if you have had any medical complaints, and how your health has been in general, **over the past few weeks.** Please answer **ALL** the questions on the following pages simply by circling the answer which you think most nearly applies to you. Remember that we want to know about present and recent complaints, not those that you had in the past.

It is important that you try to answer **ALL** the questions.

**HAVE YOU RECENTLY:—**

| | | | | | | |
|---|---|---|---|---|---|---|
| GHQ01 | 80. | — been able to concentrate on whatever you're doing? | Better than usual 1 | Same as usual 2 | Less than usual 3 | Much less than usual 4 |
| GHQ02 | 81. | — lost much sleep over worry? | Not at all 1 | No more than usual 2 | Rather more than usual 3 | Much more than usual 4 |
| GHQ03 | 82. | — been having restless, disturbed nights? | Not at all 1 | No more than usual 2 | Rather more than usual 3 | Much more than usual 4 |
| GHQ04 | 83. | — been managing to keep yourself busy and occupied? | More so than usual 1 | Same as usual 2 | Rather less than usual 3 | Much less than usual 4 |
| GHQ05 | 84. | — been getting out of the house as much as usual? | More so than usual 1 | Same as usual 2 | Less than usual 3 | Much less than usual 4 |
| GHQ06 | 85. | — been managing as well as most people would in your shoes? | Better than most 1 | About the same 2 | Rather less well 3 | Much less well 4 |
| GHQ07 | 86. | — felt on the whole you were doing things well? | Better than usual 1 | About the same 2 | Less well than usual 3 | Much less well 4 |
| GHQ08 | 87. | — been satisfied with the way you've carried out your task? | More satisfied 1 | About same as usual 2 | Less satisfied than usual 3 | Much less satisfied 4 |
| GHQ09 | 88. | — been able to feel warmth and affection for those near to you? | Better than usual 1 | About same as usual 2 | Less well than usual 3 | Much less well 4 |
| GHQ10 | 89. | — been finding it easy to get on with other people? | Better than usual 1 | About same as usual 2 | Less well than usual 3 | Much less well 4 |
| GHQ11 | 90. | — spent much time chatting with people | More time than usual 1 | About same as usual 2 | Less time than usual 3 | Much less than usual 4 |
| GHQ12 | 91. | — felt that you are playing a useful part in things? | More so than usual 1 | Same as usual 2 | Less useful than usual 3 | Much less useful 4 |

**HAVE YOU RECENTLY:—**

| | | | | | | |
|---|---|---|---|---|---|---|
| GHQ13 | 92. | — felt capable of making decisions about things? | More so than usual 1 | Same as usual 2 | Less so than usual 3 | Much less capable 4 |
| GHQ14 | 93. | — felt constantly under strain? | Not at all 1 | No more than usual 2 | Rather more than usual 3 | Much more than usual 4 |
| GHQ15 | 94. | — felt you couldn't overcome your difficulties? | Not at all 1 | No more than usual 2 | Rather more than usual 3 | Much more than usual 4 |
| GHQ16 | 95. | — been finding life a struggle all the time? | Not at all 1 | No more than usual 2 | Rather more than usual 3 | Much more than usual 4 |
| GHQ17 | 96. | — been able to enjoy your normal day-to-day activities? | More so than usual 1 | Same as usual 2 | Less so than usual 3 | Much less than usual 4 |
| GHQ18 | 97. | — been taking things hard? | Not at all 1 | No more than usual 2 | Rather more than usual 3 | Much more than usual 4 |
| GHQ19 | 98. | — been getting scared or panicky for no good reason | Not at all 1 | No more than usual 2 | Rather more than usual 3 | Much more than usual 4 |
| GHQ20 | 99. | — been able to face up to your problems? | More so than usual 1 | Same as usual 2 | Less able than usual 3 | Much less able 4 |
| GHQ21 | 100. | — found everything getting on top of you? | Not at all 1 | No more than usual 2 | Rather more than usual 3 | Much more than usual 4 |
| GHQ22 | 101. | — been feeling unhappy and depressed | Not at all 1 | No more than usual 2 | Rather more than usual 3 | Much more than usual 4 |
| GHQ23 | 102. | — been losing confidence in yourself? | Not at all 1 | No more than usual 2 | Rather more than usual 3 | Much more than usual 4 |
| GHQ24 | 103. | — been thinking of yourself as a worthless person? | Not at all 1 | No more than usual 2 | Rather more than usual 3 | Much more than usual 4 |
| GHQ25 | 104. | — felt that life is entirely hopeless? | Not at all 1 | No more than usual 2 | Rather more than usual 3 | Much more than usual 4 |
| GHQ26 | 105. | — been feeling hopeful about your own future? | More so than usual | About same as usual | Less so than usual | Much less hopeful |
| GHQ27 | 106. | — been feeling reasonably happy, all things considered? | More so than usual 1 | About same as usual 2 | Less so than usual 3 | Much less than usual 4 |
| GHQ28 | 107. | — been feeling nervous and strung-up all the time? | Not at all 1 | No more than usual 2 | Rather more than usual 3 | Much more than usual 4 |
| GHQ29 | 108. | — felt that life isn't worth living? | Not at all 1 | No more than usual 2 | Rather more than usual 3 | Much more than usual 4 |
| GHQ30 | 109. | — found at times you couldn't do anything because your nerves were too bad? | Not at all 1 | No more than usual 2 | Rather more than usual 3 | Much more than usual 4 |

## Appendix 10 Center for Epidemiological Studies Depression questionnaire

The sentences that follow concern your feelings and behaviour over the **past week**. Please read the statements carefully and circle the score (0, 1, 2 or 3) for each statement that best describes how often you felt this way during the **past week.**

| | Rarely or none of the time (less than 1 day) | Some or a little of the time (1-2 days) | Occasionally or moderate amount of time (3-4 days) | Most or all of the time (5-7 days) |
|---|---|---|---|---|
| 1. I was bothered by things that usually don't bother me. **MDPN01** | 0 | 1 | 2 | 3 |
| 2. I did not feel like eating, my appetite was poor. **MDPN02** | 0 | 1 | 2 | 3 |
| 3. I felt that I could not shake off the blues even with help from my family and friends. **MDPN03** | 0 | 1 | 2 | 3 |
| 4. I felt that I was just as good as other people. **MDPN04** | 0 | 1 | 2 | 3 |
| 5. I had trouble keeping my mind on what I was doing. **MDPN05** | 0 | 1 | 2 | 3 |
| 6. I felt depressed. **MDPN06** | | 1 | 2 | 3 |
| 7. I felt that everything I did was an effort. **MDPN07** | 0 | 1 | 2 | 3 |
| 8. I felt hopeful about the future. **MDPN08** | 0 | 1 | 2 | 3 |
| 9. I thought my life had been a failure. **MDPN09** | 0 | 1 | 2 | 3 |
| 10. I felt fearful. **MDPN10** | 0 | 1 | 2 | 3 |
| 11. My sleep was restless. **MDPN11** | 0 | 1 | 2 | 3 |
| 12. I was happy. **MDPN12** | 0 | 1 | 2 | 3 |
| 13. I talked less than usual. **MDPN13** | 0 | 1 | 2 | 3 |
| 14. I felt lonely. **MDPN14** | 0 | 1 | 2 | 3 |
| 15. People were unfriendly. **MDPN15** | 0 | 1 | 2 | 3 |
| 16. I enjoyed life. **MDPN16** | 0 | 1 | 2 | 3 |
| 17. I had crying spells. **MDPN17** | 0 | 1 | 2 | 3 |
| 18. I felt sad. **MDPN18** | 0 | 1 | 2 | 3 |
| 19. I felt that people disliked me. **MDPN19** | 0 | 1 | 2 | 3 |
| 20. I could not get going. **MDPN20** | 0 | 1 | 2 | 3 |

**Table A 2 Missing data and covariates at phase 5 and 9**

| | Phase 5 | | | Phase 9 | | |
|---|---|---|---|---|---|---|
| Covariates | n | % Missing | p | N | % Missing | p |
| GHQ | | | <.001 | | | <.001 |
| No | 5503 | 30.7 | | 5570 | 22.6 | |
| Yes | 1533 | 35.4 | | 1005 | 31.4 | |
| Sex | | | <.001 | | | <.001 |
| Men | 5473 | 36.8 | | 4759 | 24.2 | |
| Women | 2397 | 43.9 | | 2002 | 30.5 | |
| Age | | | .38 | | | .21 |
| <50 years | 3790 | 38.1 | | 3336 | 25.3 | |
| ≥50 years | 4039 | 39.1 | | 3419 | 26.6 | |
| Ethnic Group | | | <.001 | | | <.001 |
| White | 7186 | 36.9 | | 6218 | 24.3 | |
| South Asian | 390 | 53.6 | | 311 | 40.2 | |
| Black | 228 | 59.2 | | 169 | 37.9 | |
| Marital Status | | | .083 | | | .003 |
| Married/cohabiting | 5425 | 32.3 | | 4999 | 24.8 | |
| Single | 818 | 33.0 | | 751 | 28.0 | |
| Divorced/widowed | 678 | 36.6 | | 896 | 29.8 | |
| Last grade level in Civil service | | | <.001 | | | <.001 |
| Highest | 3231 | 32.6 | | 3033 | 21.6 | |
| Intermediate | 3426 | 39.8 | | 2875 | 27.4 | |
| Lowest | 1213 | 53.5 | | 853 | 37.5 | |
| Smoking | | | <.001 | | | <.001 |
| Never Smoker | 3527 | 32.3 | | 3100 | 23.5 | |
| Ex-Smoker | 2904 | 31.9 | | 3065 | 23.7 | |
| Current Smoker | 767 | 45.0 | | 386 | 35.5 | |
| Physical activity | | | <.001 | | | <.001 |
| Non/mild | 2926 | 38.3 | | 2313 | 28.1 | |
| Moderate | 3272 | 29.1 | | 3516 | 22.8 | |
| Vigorous | 928 | 26.6 | | 780 | 20.1 | |
| Alcohol consumption | | | <.001 | | | <.001 |
| None | 1330 | 39.8 | | 1492 | 32.0 | |
| Moderate | 3370 | 31.8 | | 3360 | 21.9 | |
| Heavy | 2382 | 29.7 | | 1669 | 21.7 | |
| Sleep duration | | | .002 | | | <.001 |
| less than 7 h/day | 2928 | 34.9 | | 2509 | 27.5 | |
| ≥ 7 h/day | 4179 | | | 4085 | 22.3 | |
| BMI | | | <.001 | | | <.001 |
| Normal, <25kg/$m^2$ | 2401 | 24.7 | | 2317 | 17.7 | |
| Overweight | 2469 | 25.5 | | 2660 | 19.1 | |
| Obese. ≥30kg/$m^2$ | 812 | 34.4 | | 1216 | 23.8 | |
| Central obesity (W / M) | | | <.001 | | | <.001 |
| No | 4204 | 25.5 | | 4432 | 18.2 | |
| Yes (Waist ≥88/ 102cm) | 936 | 32.3 | | 1763 | 22.6 | |
| Diabetes | | | .15 | | | <.001 |
| No | 7471 | 38.8 | | 5935 | 25.3 | |
| Yes | 399 | 42.4 | | 826 | 31.1 | |
| CVD | | | <.001 | | | .13 |
| No | 7297 | 38.3 | | 5791 | 25.6 | |
| Yes | 573 | 46.8 | | 953 | 27.9 | |
| Cancer | | | .082 | | | .27 |
| No | 7635 | 38.8 | | 6167 | 26.3 | |
| Yes | 227 | 44.5 | | 588 | 24.1 | |

Abbreviations: BMI, Body mass index; CVD, cardiovascular disease; GHQ, General Health Questionnaire; M, men; W, women.

**Table A 3 Sample characteristics of complete case sample, without missing data in covariates and missing data sample including those missing covariates**

| Covariates at phase 3 | Non-missing (incl. covariates) | | Missing (incl. covariates) | | |
|---|---|---|---|---|---|
| | n | | n | | p |
| GHQ caseness | | | | | .89 |
| no | 5768 | 78.0 | 392 | 78.2 | |
| yes (≥5 symptoms) | 1629 | 22.0 | 109 | 21.8 | |
| Sex | | | | | .057 |
| Men | 5157 | 69.7 | 329 | 65.7 | |
| Women | 2240 | 30.3 | 172 | 34.3 | |
| Age | | | | | .001 |
| <50 years | 3857 | 52.1 | 298 | 59.5 | |
| ≥50 years | 3540 | 47.9 | 203 | 40.5 | |
| Ethnic Group | | | | | <.001 |
| White | 6877 | 93.0 | 417 | 83.2 | |
| South Asian | 320 | 4.33 | 45 | 8.98 | |
| Black | 200 | 2.70 | 39 | 7.78 | |
| Marital Status | | | | | .91 |
| Married/cohabiting | 5687 | 76.9 | 376 | 76.4 | |
| Single | 1062 | 14.4 | 74 | 15.0 | |
| Divorced/widowed | 648 | 8.76 | 42 | 8.54 | |
| Last grade level in Civil service | | | | | <.001 |
| Highest | 2882 | 39.0 | 182 | 36.3 | |
| Intermediate | 3356 | 45.4 | 192 | 38.3 | |
| Lowest | 1159 | 15.7 | 127 | 25.3 | |
| Smoking | | | | | .27 |
| Never Smoker | 3423 | 46.3 | 15 | 53.6 | |
| Ex-Smoker | 2894 | 39.1 | 7 | 25.0 | |
| Current Smoker | 1080 | 14.6 | 6 | 21.4 | |
| Physical activity | | | | | .008 |
| Non/mild | 2732 | 36.9 | 216 | 43.1 | |
| Moderate | 3292 | 44.5 | 213 | 42.5 | |
| Vigorous | 1373 | 18.6 | 72 | 14.4 | |
| Alcohol consumption | | | | | .002 |
| None | 1713 | 23.2 | 139 | 28.2 | |
| Moderate | 3874 | 52.4 | 264 | 53.5 | |
| Heavy | 1810 | 24.5 | 90 | 18.3 | |
| Sleep duration | | | | | .008 |
| less than 7 h/day | 1850 | 25.0 | 149 | 30.3 | |
| ≥ 7 h/day | 5547 | 75.0 | 342 | 69.7 | |
| BMI | | | | | .28 |
| Normal, <25kg/$m^2$ | 3728 | 52.8 | 225 | 49.0 | |
| Overweight | 2659 | 37.68 | 188 | 40.96 | |
| Obese. ≥30kg/$m^2$ | 669 | 9.48 | 46 | 10.02 | |
| Central obesity | | | | | .58 |
| No | 6364 | 91.1 | 420 | 91.9 | |
| Yes (Waist ≥102/≥88 cm) | 619 | 8.9 | 37 | 8.1 | |
| Diabetes | | | | | .004 |
| No | 7203 | 97.4 | 477 | 95.2 | |
| Yes | 194 | 2.62 | 24 | 4.79 | |
| CVD | | | | | .44 |
| No | 7143 | 96.6 | 487 | 97.2 | |
| Yes | 254 | 3.43 | 14 | 2.79 | |
| Cancer | | | | | .78 |
| No | 7296 | 98.7 | 493 | 98.6 | |
| Yes | 93 | 1.26 | 7 | 1.40 | |

Abbreviations: BMI, Body mass index; CVD, cardiovascular disease; GHQ, General Health Questionnaire; M, men; W, women.

**Table A 4 Sensitivity and specificity for GHQ caseness with CES-D ascertained depression caseness as the criterion at collection phase 9 by sex**

| | n | cases | Sensitivity (95%-CI) | Specificity (95%-CI) | +PV | -PV | +LR | -LR | AUC (95%-CI) |
|---|---|---|---|---|---|---|---|---|---|
| **GHQ caseness** | | | | | | | | | |
| **Prevalence** | | | | | | | | | |
| Men | 4505 | 455 | 65.1 (60.5; 69.4) | 92.1 (91.3; 93.0) | 0.48 | -0.96 | 8.29 | 0.38 | 0.79 (0.76; 0.81) |
| Women | 1767 | 338 | 60.4 (54.9; 65.6) | 92.2 (90.6; 93.5) | 0.65 | -0.91 | 7.70 | 0.43 | 0.76 (0.74; 0.79) |
| **Incidence**[a] | | | | | | | | | |
| Men | 3416 | 205 | 51.7 (44.6; 58.7) | 94.1 (93.2; 94.8) | 0.36 | 0.97 | 8.69 | 0.51 | 0.73; (0.69; 0.76) |
| Women | 1207 | 140 | 49.3 (40.7; 57.9) | 94.0 (92.4; 95.4) | 0.52 | 0.93 | 8.22 | 0.54 | 0.72 (0.67; 0.76) |
| **Recurrence**[b] | | | | | | | | | |
| Men | 740 | 211 | 75.4 (69.0; 81.0) | 80.5 (76.9; 83.8) | 0.61 | 0.89 | 3.87 | 0.31 | 0.78 (0.77; 0.81) |
| Women | 391 | 158 | 71.5 (63.8; 78.4) | 82.4 (76.9; 87.1) | 0.73 | 0.66 | 4.06 | 0.35 | 0.77 (0.73; 0.81) |

Abbreviations: +PV, positive predictive value; -PV, negative predictive value; +LR, positive likelihood ratio; -LR, negative likelihood ratio; AUC, area under the receiver operating characteristic (ROC) curve.
[a] Among participants with no GHQ caseness at phase 7.
[b] Among participants with GHQ caseness at phase 7.

**Table A 5 Odds ratios for having missing values by GHQ and CES-D caseness by phase, adjusted for age, sex their interaction, ethnicity and last grade level in civil service**

| | Outcome: CES-D/GHQ missingness | | |
|---|---|---|---|
| **Exposure** | n / missing | OR (95%-CI) | p |
| **GHQ** | | | |
| Phase 7 | 6667 / 824 | 1.27 (1.06; 1.51) | 0.008 |
| Phase 9 | 6516 / 298 | 1.69 (1.27; 2.24) | <.001 |
| Phase 11 | 6102 / 337 | 1.77 (1.37; 2.28) | <.001 |
| **CES-D** | | | |
| Phase 7 | 5935 / 92 | 1.74 (1.07; 2.84) | 0.027 |
| Phase 9 | 6249 / 31 | 3.02 (1.35; 6.74) | 0.007 |
| Phase 11 | 5808 / 43 | 2.97 (1.54; 5.71) | 0.001 |

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; GHQ, General Health Questionnaire.

**Table A 6 Crude association of GHQ caseness with covariates at phases 3 and 5**

| Covariates at phase | GHQ caseness Phase 3 | | | GHQ caseness Phase 5 | | |
|---|---|---|---|---|---|---|
| | n | % | p | n | % | p |
| Sex | | | <.001 | | | <.001 |
| Men | 5486 | 20.5 | | 3461 | 18.8 | |
| Women | 2412 | 25.5 | | 1344 | 25.2 | |
| Age | | | <.001 | | | <.001 |
| < median | 4155 | 25.1 | | 2345 | 26.2 | |
| > median | 3743 | 18.6 | | 2460 | 15.2 | |
| Ethnic Group in Whitehall II | | | .018 | | | .13 |
| White | 7294 | 22.2 | | 4531 | 20.4 | |
| South Asian | 365 | 23.3 | | 181 | 26.5 | |
| Black | 239 | 14.6 | | 93 | 20.4 | |
| Marital Status | | | <.001 | | | <.001 |
| Married/cohabiting | 6063 | 20.5 | | 3672 | 19.4 | |
| Single | 1136 | 25.3 | | 548 | 23.7 | |
| Divorced/widowed | 690 | 29.6 | | 430 | 27.4 | |
| Last grade level in Civil service | | | .15 | | | .045 |
| Highest | 3171 | 21.8 | | 2179 | 19.0 | |
| Intermediate | 3741 | 22.9 | | 2062 | 21.7 | |
| Lowest | 1395 | 20.5 | | 564 | 22.7 | |
| Smoking | | | .006 | | | .95 |
| Never Smoker | 3438 | 20.8 | | 2388 | 20.6 | |
| Ex-Smoker | 2901 | 22.1 | | 1978 | 20.5 | |
| Current Smoker | 1086 | 25.4 | | 422 | 19.9 | |
| Physical activity | | | <.001 | | | <.001 |
| Non/mild | 2948 | 25.1 | | 1805 | 25.6 | |
| Moderate | 3505 | 20.9 | | 2319 | 18.5 | |
| Vigorous | 1445 | 18.5 | | 681 | 14.4 | |
| Alcohol consumption | | | .99 | | | .10 |
| None | 1852 | 22.0 | | 801 | 23.0 | |
| Moderate | 4138 | 22.0 | | 2299 | 19.5 | |
| Heavy | 1900 | 22.2 | | 1674 | 21.0 | |
| Sleep duration | | | <.001 | | | <.001 |
| less than 7 h/day | 1999 | 26.8 | | 1906 | 28.0 | |
| ≥ 7 h/day | 5889 | 20.4 | | 2869 | 15.5 | |
| Energy intake (kcal) | | | .030 | | | .042 |
| < median | 3899 | 21.0 | | 2371 | 19.4 | |
| > median | 3999 | 23.0 | | 2434 | 21.8 | |
| Modified DASH diet score | | | .94 | | | .50 |
| < median | 4447 | 22.0 | | 2627 | 21.0 | |
| > median | 3447 | 22.0 | | 2136 | 20.2 | |
| Fish intake | | | .41 | | | .47 |
| < median | 4486 | 21.7 | | 2525 | 21.0 | |
| > median | 3412 | 22.5 | | 2278 | 20.1 | |
| Tea / coffee | | | .94 | | | .65 |
| ≤ 1 cup of either/day | 690 | 21.9 | | 154 | 22.1 | |
| > 1 cup of either/day | 7208 | 22.0 | | 4651 | 20.6 | |
| BMI (M) | | | .059 | | | .009 |
| Normal, <25kg/m$^2$ | 2781 | 20.4 | | 1256 | 18.8 | |
| Overweight, 25-29.9kg/m$^2$ | 2093 | 19.3 | | 1408 | 17.7 | |
| Obese. ≥30kg/m$^2$ | 370 | 24.6 | | 314 | 25.2 | |
| BMI (W) | | | .025 | | | .76 |
| Normal, <25kg/m$^2$ | 1172 | 27.6 | | 553 | 26.2 | |
| Overweight, 25-29.9kg/m$^2$ | 754 | 22.4 | | 431 | 25.1 | |
| Obese. ≥30kg/m$^2$ | 345 | 23.5 | | 219 | 23.7 | |
| Central obesity (M) | | | .28 | | | .065 |
| No | 4821 | 20.1 | | 2285 | 18.5 | |
| Yes (Waist ≥102cm) | 360 | 22.5 | | 354 | 22.6 | |
| Central obesity (W) | | | .21 | | | .33 |
| No | 1963 | 25.7 | | 848 | 26.9 | |
| Yes (Waist ≥88cm) | 296 | 22.3 | | 280 | 23.9 | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Diabetes | | | .10 | | | .79 |
| No | 7680 | 22.0 | | 4575 | 20.6 | |
| Yes | 218 | 22.0 | | 230 | 21.3 | |
| CVD | | | .035 | | | .18 |
| No | 7630 | 21.8 | | 4500 | 20.4 | |
| Yes | 268 | 27.2 | | 305 | 23.6 | |
| Cancer | | | .47 | | | .38 |
| No | 7789 | 22.0 | | 4674 | 20.7 | |
| Yes | 100 | 19.0 | | 126 | 17.5 | |

Abbreviations: BMI, Body mass index; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension; GHQ, General Health Questionnaire; M, men; W, women.

**Table A 7 Crude association of GHQ, CES-D and depression caseness with covariates at phase 11**

| Covariates at phase 11 | **GHQ caseness** | | | **CES-D caseness** | | | **CIS-R Depression caseness** | | |
|---|---|---|---|---|---|---|---|---|---|
| | n | % | p | n | % | p | n | % | p |
| Sex | | | <.001 | | | <.001 | | | <.001 |
| Men | 4344 | 15.4 | | 4149 | 10.0 | | 3899 | 2.80 | |
| Women | 1758 | 21.2 | | 1616 | 17.6 | | 1475 | 5.76 | |
| Age | | | <.001 | | | .22 | | | .14 |
| <50 years | 3427 | 15.5 | | 3299 | 11.7 | | 3129 | 3.29 | |
| ≥50 years | 2675 | 19.1 | | 2466 | 12.7 | | 2245 | 4.05 | |
| Ethnic Group in Whitehall II | | | <.001 | | | <.001 | | | .005 |
| White | 5707 | 16.6 | | 5441 | 11.5 | | 5034 | 3.40 | |
| South Asian | 261 | 26.8 | | 221 | 24.4 | | 224 | 7.14 | |
| Black | 134 | 17.2 | | 103 | 16.5 | | 116 | 6.03 | |
| Marital Status | | | <.001 | | | <.001 | | | <.001 |
| Married/cohabiting | 4517 | 15.4 | | 4302 | 9.5 | | 4011 | 2.84 | |
| Single | 663 | 21.6 | | 623 | 18.8 | | 600 | 4.33 | |
| Divorced/widowed | 869 | 22.7 | | 788 | 20.7 | | 713 | 7.57 | |
| Last grade level in Civil service | | | <.001 | | | <.001 | | | <.001 |
| Highest | 2839 | 14.8 | | 2738 | 9.0 | | 2569 | 2.65 | |
| Intermediate | 2573 | 18.0 | | 2430 | 13.5 | | 2257 | 4.03 | |
| Lowest | 690 | 23.2 | | 597 | 20.9 | | 548 | 6.39 | |
| Smoking | | | 0.113 | | | .005 | | | .70 |
| Never Smoker | 2611 | 16.3 | | 2468 | 11.5 | | 2372 | 3.33 | |
| Ex-Smoker | 2950 | 17.6 | | 2805 | 12.1 | | 2574 | 3.73 | |
| Current Smoker | 216 | 21.3 | | 203 | 19.2 | | 172 | 4.07 | |
| Physical activity | | | <.001 | | | <.001 | | | <.001 |
| Non/mild | 2176 | 22.7 | | 2022 | 17.2 | | 1840 | 5.82 | |
| Moderate | 3229 | 14.9 | | 3080 | 10.2 | | 2911 | 2.78 | |
| Vigorous | 682 | 9.7 | | 653 | 5.2 | | 610 | 0.98 | |
| Alcohol consumption | | | <.001 | | | <.001 | | | <.001 |
| None | 1450 | 22.4 | | 1315 | 17.3 | | 1195 | 6.44 | |
| Moderate | 3191 | 15.4 | | 3048 | 10.9 | | 2871 | 2.86 | |
| Heavy | 1384 | 15.5 | | 1333 | 9.9 | | 1244 | 2.65 | |
| Sleep duration | | | <.001 | | | <.001 | | | <.001 |
| less than 7 h/day | 2374 | 23.6 | | 2217 | 18.1 | | 2070 | 6.33 | |
| ≥ 7 h/day | 3711 | 13.0 | | 3535 | 8.4 | | 3291 | 1.88 | |
| BMI (M) | | | .35 | | | .60 | | | .63 |
| Normal, <25kg/m$^2$ | 1470 | 15.6 | | 1404 | 9.1 | | 1441 | 2.57 | |
| Overweight | 1839 | 14.0 | | 1760 | 9.7 | | 1800 | 2.67 | |
| Obese. ≥30kg/m$^2$ | 649 | 15.7 | | 623 | 10.4 | | 637 | 3.30 | |
| BMI (W) | | | .72 | | | .41 | | | .75 |
| Normal, <25kg/m$^2$ | 601 | 19.6 | | 561 | 16.2 | | 581 | 5.51 | |
| Overweight | 496 | 21.2 | | 463 | 18.6 | | 486 | 6.38 | |
| Obese. ≥30kg/m$^2$ | 413 | 21.5 | | 367 | 15.3 | | 397 | 5.29 | |
| Central obesity (M) | | | .40 | | | .21 | | | .15 |
| No | 2735 | 14.7 | | 2613 | 9.2 | | 2681 | 2.50 | |
| Yes (Waist ≥102 cm) | 1229 | 15.7 | | 1180 | 10.5 | | 1202 | 3.33 | |
| Central obesity (W) | | | .35 | | | .14 | | | .91 |
| No | 830 | 19.8 | | 775 | 15.5 | | 809 | 5.69 | |
| Yes (Waist ≥88 cm) | 677 | 21.7 | | 611 | 18.5 | | 653 | 5.82 | |

Abbreviations: BMI, Body mass index; CES-D, Center for Epidemiologic Studies Depression Scale; CIS-R, Revised Clinical Interview Schedule; CVD, cardiovascular disease; GHQ, General Health Questionnaire; M, men; W, women.

## Appendices relating to Chapter 5

### Table A 8 Crude association of sugar intake from sweet food / beverages with covariates at phase 5, 7 and 9

| Covariates | Sugar intake from sweet food / beverages, grams | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Phase 5 | | | Phase 7 | | | Phase 9 | | |
| | n | Mean ± SD | p | n | Mean ± SD | p | n | Mean ± SD | p |
| Sex | | | <.001 | | | <.001 | | | <.001 |
| Men | 3461 | 57.1 ± 34.5 | | 3643 | 52.7 ± 33.1 | | 3608 | 51.3 ± 31.8 | |
| Women | 1344 | 43.1 ± 27.7 | | 1347 | 42.4 ± 29.0 | | 1392 | 40.4 ± 27.4 | |
| Age[a] | | | .35 | | | .39 | | | .11 |
| < mean | 2345 | 52.7 ± 32.2 | | 2392 | 49.5 ± 32.3 | | 2492 | 47.6 ± 30.2 | |
| ≥ mean | 2460 | 53.6 ± 34.4 | | 2598 | 50.3 ± 32.4 | | 2508 | 49.0 ± 31.8 | |
| Ethnic Group | | | <.001 | | | <.001 | | | <.001 |
| White | 4531 | 53.7 ± 33.5 | | 4714 | 50.6 ± 32.4 | | 4709 | 49.1 ± 31.1 | |
| South Asian | 181 | 43.8 ± 29.4 | | 186 | 37.4 ± 28.7 | | 186 | 35.3 ± 26.5 | |
| Black | 93 | 42.3 ± 24.6 | | 90 | 39.5 ± 29.0 | | 105 | 35.9 ± 26.9 | |
| Marital Status | | | <.001 | | | .001 | | | <.001 |
| Married/cohabiting | 3672 | 53.7 ± 33.5 | | 3834 | 49.8 ± 31.7 | | 3757 | 48.2 ± 30.4 | |
| Single | 548 | 53.5 ± 32.4 | | 603 | 53.7 ± 37.4 | | 541 | 52.3 ± 33.5 | |
| Divorced/widowed | 430 | 47.0 ± 31.9 | | 545 | 46.5 ± 30.4 | | 629 | 45.3 ± 32.0 | |
| Last grade level in Civil service | | | <.001 | | | <.001 | | | <.001 |
| Highest | 2179 | 55.2 ± 33.0 | | 2337 | 51.3 ± 31.4 | | 2379 | 50.1 ± 30.5 | |
| Intermediate | 2062 | 52.9 ± 34.3 | | 2130 | 49.6 ± 33.1 | | 2088 | 48.0 ± 31.4 | |
| Lowest | 564 | 46.0 ± 30.1 | | 523 | 45.0 ± 33.3 | | 533 | 41.4 ± 30.7 | |
| Smoking | | | <.001 | | | <.001 | | | <.001 |
| Never Smoker | 2388 | 55.4 ± 33.9 | | 2406 | 52.1 ± 33.6 | | 2373 | 49.9 ± 31.6 | |
| Ex-Smoker | 1978 | 51.0 ± 32.5 | | 2209 | 47.6 ± 30.7 | | 2339 | 46.4 ± 30.0 | |
| Current Smoker | 422 | 50.4 ± 33.3 | | 360 | 49.7 ± 33.2 | | 249 | 49.9 ± 34.5 | |
| Physical activity | | | <.001 | | | .060 | | | <.001 |
| Non/mild | 1805 | 50.0 ± 31.7 | | 1638 | 48.4 ± 33.5 | | 1663 | 45.5 ± 30.7 | |
| Moderate | 2319 | 54.9 ± 34.0 | | 2805 | 50.6 ± 31.6 | | 2714 | 49.8 ± 31.2 | |
| Vigorous | 681 | 55.4 ± 34.7 | | 547 | 51.1 ± 32.8 | | 623 | 49.3 ± 30.8 | |
| Alcohol consumption | | | <.001 | | | <.001 | | | <.001 |
| None | 801 | 57.0 ± 36.0 | | 875 | 53.2 ± 36.7 | | 1014 | 52.2 ± 36.4 | |
| Moderate | 2299 | 55.0 ± 33.7 | | 2525 | 51.7 ± 31.9 | | 2623 | 49.0 ± 30.0 | |
| Heavy | 1674 | 48.9 ± 31.0 | | 1566 | 45.2 ± 23.0 | | 1306 | 43.8 ± 27.8 | |
| Sleep duration | | | .59 | | | .82 | | | .85 |
| less than 7 h/day | 1906 | 52.8 ± 33.3 | | 1978 | 50.0 ± 32.8 | | 1820 | 48.4 ± 31.8 | |
| ≥ 7 h/day | 2869 | 53.3 ± 33.3 | | 3006 | 49.8 ± 32.1 | | 3174 | 48.2 ± 30.6 | |
| Energy intake from other diet | | | <.001 | | | <.001 | | | <.001 |
| < median | 2395 | 37.2 ± 21.2 | | 2494 | 34.8 ± 20.5 | | 2496 | 33.7 ± 19.9 | |
| > median | 2410 | 69.0 ± 35.6 | | 2496 | 65.0 ± 34.9 | | 2504 | 62.9 ± 33.2 | |
| modified DASH diet score | | | <.001 | | | <.001 | | | <.001 |
| < median | 2627 | 55.8 ± 34.7 | | 2476 | 53.3 ± 33.9 | | 2868 | 49.9 ± 32.5 | |
| > median | 2136 | 50.1 ± 31.3 | | 2422 | 46.6 ± 30.4 | | 2106 | 46.2 ± 28.8 | |
| Fish intake | | | .45 | | | .38 | | | .76 |
| < median | 2525 | 53.5 ± 33.4 | | 2608 | 50.3 ± 32.6 | | 2664 | 48.4 ± 31.2 | |
| > median | 2278 | 52.8 ± 33.2 | | 2374 | 49.5 ± 32.1 | | 2334 | 48.2 ± 30.8 | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Tea / coffee | | | .30 | | | <.001 | | | <.001 |
| ≤ 1 cup of either/day | 154 | 50.4 ± 34.9 | | 200 | 41.8 ± 33.0 | | 227 | 39.0 ± 32.3 | |
| > 1 cup of either/day | 4651 | 53.2 ± 33.3 | | 4790 | 50.2 ± 32.3 | | 4773 | 48.7 ± 30.9 | |
| Fibre intake | | | <.001 | | | <.001 | | | <.001 |
| 1st Tertile | 1321 | 43.0 ± 26.7 | | 1278 | 40.2 ± 25.8 | | 1452 | 38.5 ± 25.5 | |
| 2nd Tertile | 1831 | 52.2 ± 30.6 | | 2021 | 48.7 ± 30.5 | | 1989 | 49.8 ± 30.5 | |
| 3rd Tertile | 1653 | 62.2 ± 38.2 | | 1691 | 58.6 ± 36.4 | | 1559 | 55.5 ± 33.9 | |
| BMI (M) | | | <.001 | | | <.001 | | | <.001 |
| Normal, <25kg/m$^2$ | 1256 | 61.3 ± 35.6 | | 1327 | 56.4 ± 33.7 | | 1352 | 54.9 ± 32.1 | |
| Overweight | 1408 | 55.4 ± 33.8 | | 1748 | 51.8 ± 33.0 | | 1692 | 50.1 ± 31.8 | |
| Obese. ≥30kg/m$^2$ | 314 | 46.7 ± 29.0 | | 556 | 46.6 ± 30.9 | | 555 | 46.3 ± 29.8 | |
| BMI (W) | | | .78 | | | .52 | | | .75 |
| Normal, <25kg/m$^2$ | 553 | 44.1 ± 27.2 | | 541 | 43.3 ± 29.7 | | 556 | 40.9 ± 27.0 | |
| Overweight | 431 | 42.9 ± 27.9 | | 471 | 41.3 ± 27.2 | | 459 | 39.6 ± 27.9 | |
| Obese. ≥30kg/m$^2$ | 219 | 43.6 ± 28.2 | | 328 | 42.9 ± 30.4 | | 371 | 40.4 ± 27.3 | |
| Central obesity (M) | | | .001 | | | <.001 | | | <.001 |
| No | 2285 | 57.7 ± 34.7 | | 2915 | 53.8 ± 33.4 | | 2754 | 52.5 ± 31.8 | |
| Yes (Waist ≥102 cm) | 354 | 51.4 ± 35.3 | | 720 | 48.1 ± 31.8 | | 849 | 47.7 ± 31.4 | |
| Central obesity (W) | | | .19 | | | .48 | | | .45 |
| No | 848 | 44.2 ± 28.1 | | 905 | 42.9 ± 29.0 | | 872 | 40.8 ± 27.3 | |
| Yes (Waist ≥88 cm) | 280 | 41.7 ± 27.1 | | 438 | 41.7 ± 29.0 | | 515 | 39.7 ± 27.6 | |
| Diabetes | | | <.001 | | | <.001 | | | <.001 |
| No | 4575 | 53.6 ± 33.3 | | 4623 | 50.8 ± 32.4 | | 4431 | 49.3 ± 30.7 | |
| Yes | 230 | 43.6 ± 32.6 | | 367 | 39.0 ± 30.1 | | 569 | 40.6 ± 32.3 | |
| CVD | | | .73 | | | .18 | | | .32 |
| No | 4500 | 53.1 ± 33.1 | | 4512 | 50.1 ± 32.5 | | 4308 | 48.1 ± 30.8 | |
| Yes | 305 | 53.8 ± 36.6 | | 478 | 48.0 ± 31.3 | | 687 | 49.4 ± 32.5 | |
| Cancer | | | .36 | | | .64 | | | .021 |
| No | 4674 | 53.2 ± 33.4 | | 4724 | 50.0 ± 32.5 | | 4548 | 48.0 ± 31.0 | |
| Yes | 126 | 50.5 ± 31.2 | | 261 | 49.0 ± 30.4 | | 446 | 51.5 ± 31.4 | |

Abbreviations: BMI, Body mass index; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension; M, men; W, women.

[a]At phase 5 mean age was approximately 55 years, at phase 7 60 years and at phase 9 65 years.

**Table A 9 Crude association of tertiles of sugar intake from sweet food / beverages with covariates in Whitehall II by gender**

| Covariates at phase 3 | Sugar intake from sweet food / beverages, Men | | | | | Women | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Tertile | Tertile | Tertile | | | Tertile | Tertile | Tertile | |
| | n | 1 | 2 | 3 | p | n | 1 | 2 | 3 | p |
| Age | | | | | .63 | | | | | .90 |
| <50 years | 3023 | 55.8 | 54.2 | 55.3 | | 1132 | 47.0 | 47.5 | 46.4 | |
| ≥50 years | 2463 | 44.2 | 45.8 | 44.7 | | 1280 | 53.0 | 52.5 | 53.6 | |
| Ethnic Group | | | | | <.001 | | | | | .21 |
| White | 5172 | 91.6 | 94.3 | 96.9 | | 2122 | 86.8 | 87.2 | 89.9 | |
| South Asian | 227 | 6.4 | 4.0 | 2.1 | | 138 | 6.36 | 6.60 | 4.26 | |
| Black | 87 | 2.0 | 1.7 | 1.0 | | 152 | 6.86 | 6.22 | 5.84 | |
| Marital Status | | | | | <.001 | | | | | .001 |
| Married/cohabiting | 4536 | 80.5 | 84.3 | 83.4 | | 1527 | 65.7 | 66.4 | 58.3 | |
| Single | 643 | 11.9 | 10.7 | 12.7 | | 493 | 18.7 | 17.4 | 25.1 | |
| Divorced/widowed | 302 | 7.6 | 5.0 | 4.0 | | 388 | 15.61 | 16.16 | 16.57 | |
| Last grade level in Civil service | | | | | <.001 | | | | | .38 |
| Highest | 2684 | 45.4 | 50.3 | 51.0 | | 380 | 16.8 | 16.5 | 14.0 | |
| Intermediate | 2454 | 46.6 | 43.6 | 44.0 | | 1094 | 43.5 | 44.9 | 47.6 | |
| Lowest | 348 | 7.9 | 6.2 | 5.0 | | 938 | 39.7 | 38.6 | 38.4 | |
| Smoking | | | | | .002 | | | | | .014 |
| Never Smoker | 2297 | 40.7 | 45.1 | 47.3 | | 1141 | 46.1 | 52.7 | 53.2 | |
| Ex-Smoker | 2198 | 45.4 | 41.3 | 40.6 | | 703 | 34.5 | 31.4 | 28.0 | |
| Current Smoker | 681 | 13.8 | 13.6 | 12.1 | | 405 | 19.4 | 15.9 | 18.73 | |
| Physical activity | | | | | .018 | | | | | .30 |
| Non/mild | 1715 | 34.1 | 30.8 | 28.9 | | 1233 | 53.4 | 50.4 | 49.6 | |
| Moderate | 2553 | 44.3 | 47.2 | 48.1 | | 952 | 36.8 | 41.2 | 40.4 | |
| Vigorous active | 1218 | 21.6 | 22.0 | 23.0 | | 227 | 9.9 | 8.4 | 10.0 | |
| Alcohol consumption | | | | | <.001 | | | | | .017 |
| None | 954 | 14.4 | 15.1 | 22.6 | | 898 | 33.9 | 37.8 | 40.0 | |
| Moderate | 2846 | 46.3 | 54.2 | 55.2 | | 1292 | 54.6 | 54.3 | 52.0 | |
| Heavy | 1680 | 39.3 | 30.7 | 22.1 | | 220 | 11.5 | 7.9 | 8.0 | |
| Sleep duration | | | | | .45 | | | | | .49 |
| less than 7 h/day | 1339 | 25.4 | 23.7 | 24.2 | | 660 | 28.9 | 26.3 | 27.0 | |
| ≥ 7 h/day | 4142 | 74.6 | 76.3 | 75.8 | | 1747 | 71.1 | 73.7 | 73.0 | |
| Energy intake from other diet | | | | | <.001 | | | | | <.001 |
| < median | 2382 | 70.2 | 46.6 | 14.1 | | 1563 | 85.3 | 70.6 | 39.3 | |
| > median | 3104 | 29.8 | 53.4 | 85.9 | | 849 | 14.7 | 29.4 | 60.7 | |
| Modified DASH diet score | | | | | <.001 | | | | | <.001 |
| < median | 3093 | 50.6 | 57.2 | 61.4 | | 1354 | 85.3 | 70.6 | 39.3 | |
| > median | 2390 | 49.4 | 42.8 | 38.6 | | 1057 | 14.7 | 29.4 | 60.7 | |
| Fish intake | | | | | .002 | | | | | <.001 |
| < median | 3235 | 57.2 | 62.4 | 57.4 | | 1251 | 85.3 | 70.6 | 39.3 | |
| > median | 2251 | 42.8 | 37.6 | 42.6 | | 1161 | 14.7 | 29.4 | 60.7 | |
| Tea / Coffee | | | | | <.001 | | | | | .002 |
| ≤ 1 cup of either/day | 409 | 9.8 | 6.3 | 6.3 | | 281 | 13.34 | 13.32 | 8.39 | |
| > 1 cup of either/day | 5077 | 90.2 | 93.7 | 93.7 | | 2131 | 86.7 | 86.7 | 91.6 | |
| Fibre intake | | | | | <.001 | | | | | <.001 |
| 1st Tertile | 1611 | 38.2 | 31.4 | 18.7 | | 864 | 45.5 | 32.7 | 29.3 | |
| 2nd Tertile | 1983 | 35.8 | 37.3 | 35.4 | | 838 | 29.4 | 40.6 | 34.3 | |
| 3rd Tertile | 1892 | 26.0 | 31.4 | 45.9 | | 710 | 25.1 | 26.6 | 36.4 | |
| BMI | | | | | <.001 | | | | | .74 |
| Normal, <25kg/m$^2$ | 2781 | 46.2 | 52.4 | 60.3 | | 1172 | 51.8 | 51.3 | 51.7 | |
| Overweight | 2093 | 44.7 | 40.9 | 34.3 | | 754 | 31.81 | 34.49 | 33.29 | |
| Obese. ≥30kg/m$^2$ | 370 | 9.2 | 6.7 | 5.3 | | 345 | 16.38 | 14.25 | 14.97 | |
| Central obesity | | | | | .001 | | | | | .40 |
| No | 4821 | 91.4 | 93.1 | 94.6 | | 1963 | 88.2 | 86.7 | 85.8 | |
| Yes (Waist ≥102/≥88 cm) | 360 | 8.6 | 6.9 | 5.4 | | 296 | 11.8 | 13.3 | 14.2 | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Diabetes | | | | | <.001 | | | | .39 |
| No | 5331 | 95.8 | 97.4 | 98.3 | | 2349 | 96.8 | 97.7 | 97.7 |
| Yes | 155 | 4.2 | 2.6 | 1.7 | | 63 | 3.24 | 2.28 | 2.31 |
| CVD | | | | | .001 | | | | .042 |
| No | 5287 | 95.0 | 97.0 | 97.1 | | 2343 | 97.5 | 95.9 | 97.9 |
| Yes | 199 | 5.0 | 3.0 | 2.9 | | 69 | 2.49 | 4.06 | 2.07 |
| Cancer | | | | | .34 | | | | .13 |
| No | 5431 | 99.3 | 99.0 | 98.8 | | 2358 | 97.5 | 98.9 | 97.8 |
| Yes | 53 | 0.7 | 1.0 | 1.2 | | 47 | 2.50 | 1.15 | 2.20 |

Abbreviations: BMI, Body mass index; CVD, cardiovascular disease; GHQ, General Health Questionnaire; M, men; W, women.

**Table A 10 Association of sugar intake from sweet food and beverages with incident mood disorders by sex**

| | Per 30g of sugar intake from sweet food and beverages /day | | |
|---|---|---|---|
| | events / person observations | Model adjusted for age, sex and ethnicity, OR (95% CI) | p |
| Incident CMD | | | |
| **after 2 years** | | | |
| Both men & women | | 1.03 (0.95, 1.11) | .53 |
| men | 609 / 5361 | 1.08 (0.98, 1.19) | .10 |
| women | 299 / 1880 | 0.89 (0.77, 1.03) | .13 |
| **after 5 years** | | | |
| Both men & women | | 1.07 (1.01, 1.13) | .014 |
| men | 1381 / 11875 | 1.10 (1.04, 1.17) | .001 |
| women | 663 / 4283 | 0.96 (0.86, 1.07) | .49 |
| **after 10 years** | | | |
| Both men & women | | 1.04 (0.97, 1.12) | .23 |
| men | 962 / 8492 | 1.06 (0.98, 1.15) | .17 |
| women | 459 / 3038 | 0.99 (0.85, 1.15) | .91 |
| Incident depression | | | |
| **after 5 years** | | | |
| Both men & women | | 0.96 (0.87, 1.07) | .45 |
| men | 487 / 7915 | 1.02 (0.90, 1.15) | .74 |
| women | 310 / 2691 | 0.81 (0.66, 1.00) | .048 |
| **after 10 years** | | | |
| Both men & women | | 1.08 (0.98, 1.19) | .13 |
| men | 587 / 8072 | 1.11 (0.99, 1.24) | .088 |
| women | 360 / 2772 | 1.01 (0.84, 1.22) | .91 |
| Incident clinical depression | | | |
| **after 5 years** | | | |
| Both men & women | | 1.03 (0.79, 1.34) | .81 |
| men | 27 / 2778 | 1.16 (0.82, 1.64) | .40 |
| women | 33 / 977 | 0.90 (0.60, 1.36) | .62 |
| **after 10 years** | | | |
| Both men & women | | 1.15 (0.90, 1.46) | .26 |
| men | 30 / 2423 | 1.45 (1.12, 1.90) | .006 |
| women | 23 / 771 | 0.61 (0.34, 1.08) | .092 |

**Table A 11 Prospective association of sugar intake from sweet food / beverages and incident CMD after 5 years in men excluding participants with unknown or self-reported doctor diagnosed depression at each baseline[a]**

| | | Incident CMD after 5 years, OR (95% CI) | | |
|---|---|---|---|---|
| | events / person observations | Model 0[b] | Model 1[c] | Model 2[d] |
| Sugar intake from sweet food / beverages | | | | |
| Lowest Tertile | 436 / 4176 | 1 (reference) | 1 (reference) | 1 (reference) |
| Middle Tertile | 413 / 3714 | 1.06 (0.90, 1.25) | 1.08 (0.91, 1.27) | 1.06 (0.89, 1.25) |
| Highest Tertile | 439 / 3327 | 1.32** (1.12, 1.56) | 1.32** (1.12, 1.57) | 1.26* (1.05, 1.51) |
| p for trend | | .001 | .002 | .014 |
| Continuous (30g/day increment) | 1288 / 11220 | 1.12*** (1.05, 1.19) | 1.12*** (1.05, 1.19) | 1.10** (1.02, 1.17) |

* p<.05, **p<.005, *** p<.001.
[a]Prospective association across phases 3, 5, 7, 9 for 5-year incident CMD.
[b]Model 0 (1346 events / 11667 person observations): adjusted for age, ethnicity.
[c]Model 1: additionally adjusted for marital status, last grade level in civil service, smoking, alcohol intake, physical activity, sleep duration.
[d]Model 2: additionally adjusted for energy intake from other foods, modified DASH diet score, fish, coffee, tea and fibre intake.

**Table A 12 Prospective association of sugar intake from sweet food / beverages and incident depression after 5 years in women[a]**

| | Incident depression after 5 years, OR (95% CI) | | | |
|---|---|---|---|---|
| | events / person observations | Model 0[b] | Model 1[c] | Model 2[d] |
| Sugar intake from sweet food / beverages | | | | |
| Lowest Tertile | 127 / 996 | 1 (reference) | 1 (reference) | 1 (reference) |
| Middle Tertile | 88 / 829 | 0.82 (0.55, 1.22) | 0.86 (0.58, 1.28) | 0.86 (0.58, 1.28) |
| Highest Tertile | 81 / 751 | 0.72 (0.47, 1.12) | 0.84 (0.55, 1.28) | 0.85 (0.55, 1.32) |
| p for trend | | .14 | .39 | .93 |
| Continuous (30g/day increment) | 296 / 2576 | 0.81* (0.66, 1.00) | 0.87 (0.71, 1.06) | 0.87 (0.71, 1.07) |

* p<.05, **p<.005, *** p<.001.
[a]Prospective association across phases 5, 7, 9 for 5-year incident depression.
[b]Model 0 (310 events / 2691 person observations): adjusted for age, ethnicity.
[c]Model 1: additionally adjusted for marital status, last grade level in civil service, smoking, alcohol intake, physical activity, sleep duration.
[d]Model 2: additionally adjusted for energy intake from other foods, modified DASH diet score, fish, coffee, tea and fibre intake.

**Table A 13 Association of sugar intake from sweet food and beverages with recurrent mood disorders by sex**

| Outcome | Per 30g of sugar intake from sweet food and beverages /day<br>events / person observations | Model adjusted for age, sex and ethnicity, OR (95% CI) | p |
|---|---|---|---|
| Recurrent CMD | | | |
| **after 2 years** | | | |
| Both men & women | | 1.03 (0.91, 1.16) | .66 |
| Men | 478 / 1167 | 1.01 (0.87, 1.16) | .92 |
| women | 281 / 583 | 1.09 (0.86, 1.37) | .48 |
| **after 5 years** | | | |
| Both men & women | | 1.09 (1.00, 1.19) | .062 |
| Men | 1025 / 2520 | 1.07 (0.96, 1.19) | .22 |
| women | 560 / 1266 | 1.14 (0.98, 1.32) | .095 |
| **after 10 years** | | | |
| Both men & women | | 1.03 (0.92, 1.14) | .65 |
| Men | 708 / 2050 | 0.99 (0.87, 1.14) | .93 |
| women | 386 / 1008 | 1.11 (0.92, 1.35) | .28 |
| Recurrent depression | | | |
| **after 5 years** | | | |
| Both men & women | | 1.27 (1.09, 1.48) | .002 |
| Men | 462 / 1523 | 1.16 (0.97, 1.39) | .11 |
| women | 262 / 723 | 1.62 (1.20, 2.17) | .002 |
| **after 10 years** | | | |
| Both men & women | | 1.04 (0.90, 1.20) | .59 |
| Men | 488 / 1934 | 1.03 (0.86, 1.23) | .75 |
| women | 277 / 925 | 1.09 (0.83, 1.42) | .54 |
| Recurrent clinical depression | | | |
| **after 5 years** | | | |
| Both men & women | | 1.23 (1.02, 1.47) | .029 |
| Men | 57 / 397 | 1.16 (0.94, 1.43) | .18 |
| women | 31 / 192 | 1.53 (1.03, 2.27) | .035 |
| **after 10 years** | | | |
| Both men & women | | 1.00 (0.80, 1.25) | .98 |
| Men | 50 / 542 | 0.93 (0.71, 1.21) | .60 |
| women | 23 / 238 | 1.17 (0.78, 1.75) | .46 |

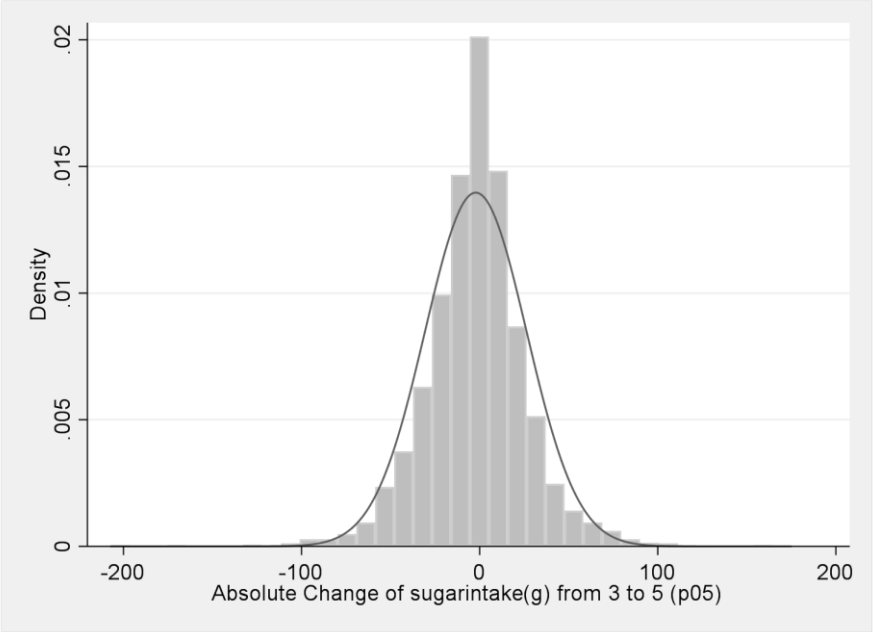



**Figure A 1 Distribution of change in sugar intake from sweet food / beverages from phase 3 to 5**

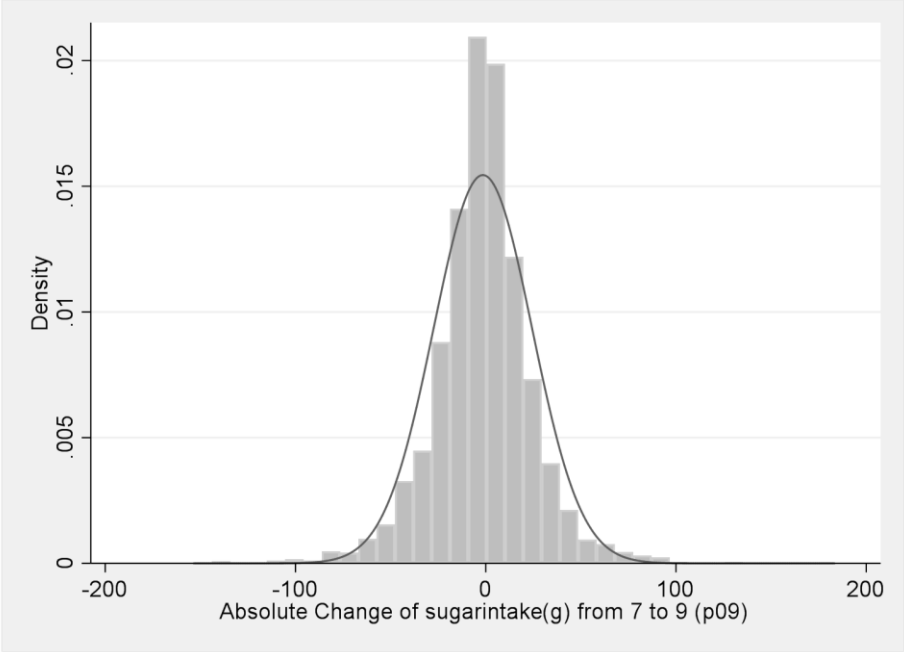



**Figure A 2 Distribution of change in sugar intake from sweet food / beverages from phase 5 to 7**

**Table A 14 Association of CMD and depression with subsequent 5-year change in sugar intake from sweet food / beverages after exclusion of participants with extreme sugar intake (>7SD)**

| | 5-year change in intake from sweet food / beverages | | | |
|---|---|---|---|---|
| | Events | Participants | OR (95% CI) *β-Coefficient*[a] *(95% CI)* | p |
| **CMD** | | | | |
| **At phase 3 – Sugar intake change from sweet food / beverages: phase 3 to 5** | | | | |
| Reduction | 235 | 1087 | 1 (reference) | |
| No change | 541 | 2629 | 0.96 (0.81, 1.14) | 0.64 |
| Increase | 177 | 880 | 0.93 (0.74, 1.16) | 0.50 |
| Continuous change in grams per day | 953 | 4596 | *-0.01 (-2.01, 1.99)* | 1.00 |
| | 235 | 1087 | 1 (reference) | |
| **At phase 5 – Sugar intake change from sweet food / beverages: phase 5 to 7** | | | | |
| Reduction | 173 | 866 | 1 (reference) | |
| No change | 398 | 2104 | 0.94 (0.76, 1.15) | 0.52 |
| Increase | 148 | 616 | 1.26 (0.98, 1.62) | 0.08 |
| Continuous change in grams per day | 719 | 3586 | *1.61 (-0.67, 3.90)* | 0.17 |
| **At phase 7 – Sugar intake change from sweet food / beverages: phase 7 to 9** | | | | |
| Reduction | 176 | 818 | 1 (reference) | |
| No change | 431 | 2369 | 0.83 (0.68, 1.01) | 0.08 |
| Increase | 129 | 731 | 0.81 (0.62, 1.04) | 0.10 |
| Continuous change in grams per day | 736 | 3918 | *-1.39 (-3.42, 0.64)* | 0.18 |
| **Depression** | | | | |
| **At phase 7 – Sugar intake change from sweet food / beverages: phase 7 to 9** | | | | |
| Reduction | 104 | 764 | 1 (reference) | |
| No change | 287 | 2253 | 0.96 (0.75, 1.23) | 0.76 |
| Increase | 80 | 683 | 0.88 (0.64, 1.21) | 0.42 |
| Continuous change in grams per day | 471 | 3700 | *0.14 (-2.31, 2.60)* | 0.90 |

[a]Change in sugar intake in cases compared with non-cases, adjusted for age, sex and ethnicity.

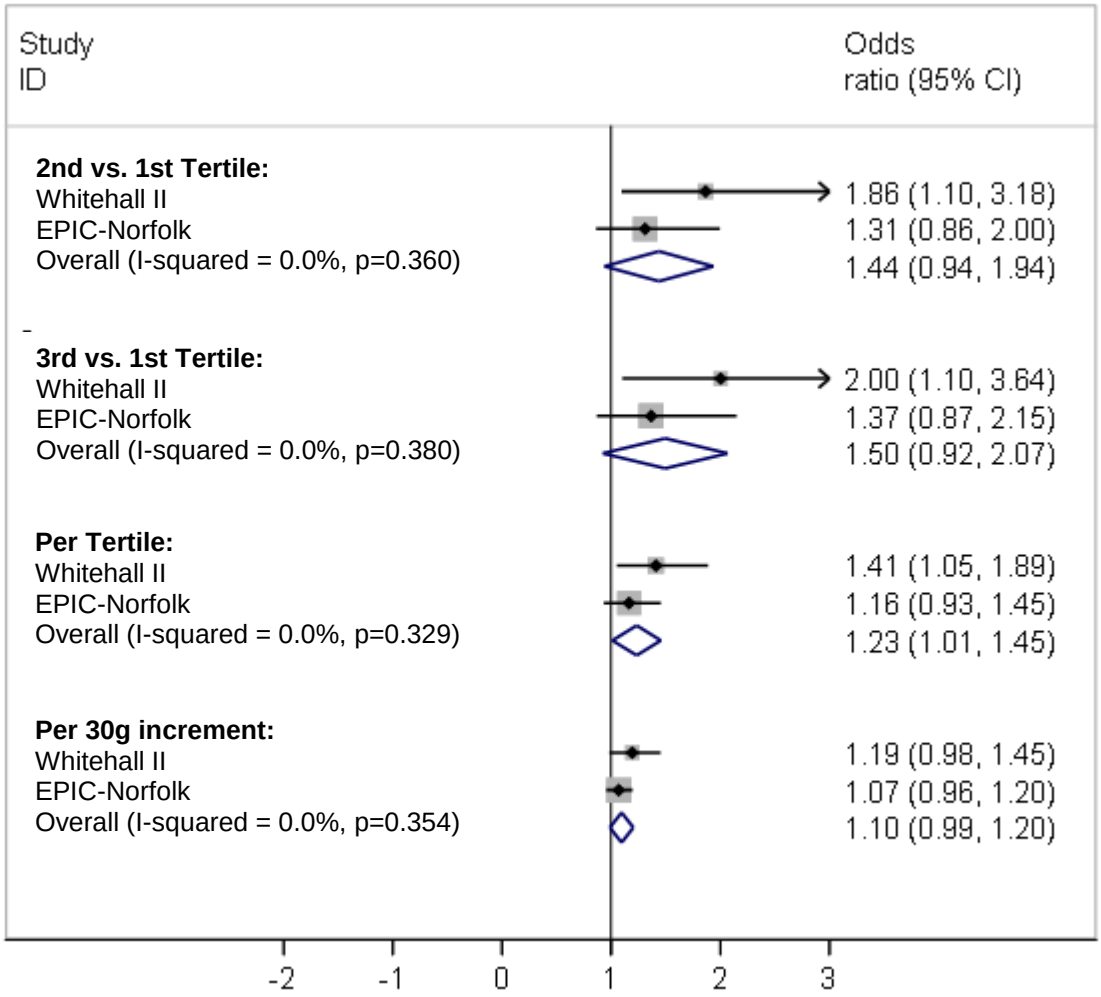



**Figure A 3 Association of sugar intake from sweet food / beverages with incident antidepressant intake in men in fully adjusted models**

$2^{nd}$ vs $1^{st}$, $3^{rd}$ vs $1^{st}$, Tertile trend, adjusted for age, ethnicity (in Whitehall II), socio-demographic factors, health behaviours and diet-related factors, BMI, central obesity, diabetes, CVD and cancer.

## Appendices relating to Chapter 6

### Table A 15 Crude association of energy adjusted fibre intake with covariates at phase 5, 7 and 9

| Covariates | Energy adj. Fibre intake[a], grams | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Phase 5 | | | Phase 7 | | | Phase 9 | | |
| | n | Mean ± SD | p | n | Mean ± SD | p | n | Mean ± SD | p |
| Sex | | | .006 | | | <.001 | | | <.001 |
| Men | 3465 | 25.6 ± 7.6 | | 3644 | 26.2 ± 7.4 | | 3611 | 25.8 ± 7.3 | |
| Women | 1346 | 24.9 ± 7.6 | | 1347 | 24.9 ± 7.5 | | 1392 | 24.4 ± 7.4 | |
| Age[a] | | | .016 | | | .34 | | | .19 |
| < mean | 2346 | 25.1 ± 7.8 | | 2392 | 25.7 ± 7.5 | | 2493 | 25.3 ± 7.5 | |
| ≥ mean | 2465 | 25.6 ± 7.5 | | 2599 | 26.0 ± 7.5 | | 2510 | 25.6 ± 7.2 | |
| Ethnic Group | | | .002 | | | <.001 | | | <.001 |
| White | 4533 | 25.3 ± 7.6 | | 4714 | 25.7 ± 7.4 | | 4712 | 25.3 ± 7.3 | |
| South Asian | 183 | 27.2 ± 8.7 | | 187 | 28.1 ± 8.2 | | 186 | 28.2 ± 7.6 | |
| Black | 95 | 26.1 ± 7.0 | | 90 | 27.7 ± 8.5 | | 105 | 26.8 ± 9.0 | |
| Marital Status | | | .56 | | | .002 | | | .001 |
| Married/ cohabiting | 3677 | 25.5 ± 7.6 | | 3835 | 26.0 ± 7.3 | | 3759 | 25.7 ± 7.1 | |
| Single | 548 | 25.2 ± 8.0 | | 603 | 25.1 ± 8.3 | | 542 | 24.9 ± 8.2 | |
| Divorced/ widowed | 431 | 25.2 ± 7.3 | | 545 | 25.3 ± 7.8 | | 629 | 24.6 ± 7.7 | |
| Last grade level in Civil service | | | .37 | | | .001 | | | .97 |
| Highest | 2179 | 25.4 ± 7.2 | | 2337 | 26.1 ± 7.2 | | 2379 | 25.5 ± 6.9 | |
| Intermediate | 2066 | 25.5 ± 8.0 | | 2131 | 25.9 ± 7.7 | | 2090 | 25.4 ± 7.5 | |
| Lowest | 566 | 25.0 ± 7.9 | | 523 | 24.7 ± 8.0 | | 534 | 25.5 ± 8.6 | |
| Smoking | | | <.001 | | | <.001 | | | <.001 |
| Never Smoker | 2389 | 25.9 ± 7.4 | | 2406 | 26.2 ± 7.3 | | 2374 | 25.8 ± 7.2 | |
| Ex-Smoker | 1979 | 25.5 ± 7.6 | | 2210 | 26.0 ± 7.5 | | 2341 | 25.4 ± 7.4 | |
| Current Smoker | 425 | 22.4 ± 8.2 | | 360 | 22.9 ± 8.2 | | 249 | 23.3 ± 7.7 | |
| Physical activity | | | <.001 | | | <.001 | | | <.001 |
| Non/mild | 1808 | 24.8 ± 7.3 | | 1638 | 25.3 ± 7.6 | | 1664 | 24.9 ± 7.3 | |
| Moderate | 2322 | 25.6 ± 7.7 | | 2806 | 26.0 ± 7.3 | | 2716 | 25.6 ± 7.3 | |
| Vigorous | 681 | 26.2 ± 7.9 | | 547 | 26.8 ± 7.6 | | 623 | 26.5 ± 7.6 | |
| Alcohol consumption | | | <.001 | | | <.001 | | | <.001 |
| None | 802 | 26.4 ± 8.7 | | 875 | 27.0 ± 8.7 | | 1015 | 26.5 ± 8.5 | |
| Moderate | 2303 | 25.9 ± 7.5 | | 2526 | 26.4 ± 7.3 | | 2623 | 25.8 ± 7.0 | |
| Heavy | 1675 | 24.1 ± 7.1 | | 1566 | 24.3 ± 6.8 | | 1308 | 23.8 ± 6.7 | |
| Sleep duration | | | .58 | | | .60 | | | .013 |
| less than 7 h/day | 1906 | 25.3 ± 7.8 | | 1978 | 25.9 ± 7.6 | | 1823 | 25.1 ± 7.2 | |
| ≥ 7 h/day | 2875 | 25.4 ± 7.5 | | 3007 | 25.8 ± 7.4 | | 3174 | 25.6 ± 7.4 | |
| Energy intake | | | .004 | | | .037 | | | .015 |
| < median | 2375 | 25.1 ± 6.1 | | 2443 | 25.6 ± 6.2 | | 2469 | 25.2 ± 6.0 | |
| > median | 2436 | 25.7 ± 8.8 | | 2548 | 26.1 ± 8.5 | | 2534 | 25.7 ± 8.5 | |
| modified DASH diet score | | | <.001 | | | <.001 | | | <.001 |
| < median | 2627 | 22.1 ± 6.0 | | 2476 | 22.4 ± 5.9 | | 2868 | 22.5 ± 6.0 | |
| > median | 2136 | 29.4 ± 7.4 | | 2422 | 29.5 ± 7.3 | | 2106 | 29.5 ± 7.1 | |
| Fish intake | | | <.001 | | | <.001 | | | <.001 |
| < median | 2529 | 24.9 ± 7.2 | | 2609 | 25.5 ± 7.4 | | 2665 | 24.9 ± 7.0 | |
| > median | 2279 | 25.9 ± 8.0 | | 2374 | 26.3 ± 7.5 | | 2336 | 26.0 ± 7.7 | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Tea / coffee | | | .93 | | | <.001 | | | .005 |
| ≤ 1 cup of either/day | 154 | 25.3 ± 7.4 | | 200 | 28.4 ± 8.8 | | 227 | 26.8 ± 7.5 | |
| > 1 cup of either/day | 4657 | 25.4 ± 7.6 | | 4791 | 25.7 ± 7.4 | | 4776 | 25.4 ± 7.3 | |
| Sugar intake from sweet food beverages | | | <.001 | | | <.001 | | | <.001 |
| 1st Tertile | 1667 | 27.0 ± 7.5 | | 1982 | 27.4 ± 7.5 | | 2075 | 26.6 ± 7.0 | |
| 2nd Tertile | 1603 | 25.5 ± 7.1 | | 1624 | 25.7 ± 6.8 | | 1595 | 25.5 ± 6.9 | |
| 3rd Tertile | 1535 | 23.4 ± 7.8 | | 1384 | 23.8 ± 7.7 | | 1330 | 23.5 ± 8.0 | |
| BMI (M) | | | <.001 | | | .052 | | | <.001 |
| Normal, <25kg/m$^2$ | 1257 | 26.2 ± 8.1 | | 1257 | 26.5 ± 7.6 | | 1257 | 26.6 ± 7.6 | |
| Overweight | 1411 | 25.0 ± 7.3 | | 1411 | 26.1 ± 7.1 | | 1411 | 25.3 ± 7.1 | |
| Obese. ≥30kg/m$^2$ | 314 | 25.5 ± 7.9 | | 314 | 25.7 ± 8.2 | | 314 | 25.5 ± 7.2 | |
| BMI (W) | | | 0.95 | | | .21 | | | .12 |
| Normal, <25kg/m$^2$ | 553 | 24.8 ± 7.6 | | 553 | 25.3 ± 7.4 | | 553 | 24.4 ± 7.2 | |
| Overweight | 433 | 25.0 ± 8.1 | | 433 | 24.9 ± 7.4 | | 433 | 25.0 ± 7.2 | |
| Obese. ≥30kg/m$^2$ | 219 | 24.9 ± 7.6 | | 219 | 24.4 ± 8.0 | | 219 | 24.0 ± 7.9 | |
| Central obesity (M) | | | 0.25 | | | .019 | | | .004 |
| No | 2289 | 25.5 ± 7.7 | | 2289 | 26.3 ± 7.4 | | 2289 | 26.0 ± 7.3 | |
| Yes (Waist ≥102 cm) | 354 | 25.0 ± 8.1 | | 354 | 25.6 ± 7.7 | | 354 | 25.2 ± 7.1 | |
| Central obesity (W) | | | 0.85 | | | .13 | | | .33 |
| No | 849 | 24.7 ± 7.7 | | 849 | 25.2 ± 7.4 | | 849 | 24.6 ± 7.2 | |
| Yes (Waist ≥88 cm) | 281 | 24.8 ± 7.9 | | 281 | 24.5 ± 7.8 | | 281 | 24.2 ± 7.7 | |
| Diabetes | | | .003 | | | .016 | | | .003 |
| No | 4580 | 25.3 ± 7.5 | | 4624 | 25.8 ± 7.4 | | 4434 | 25.3 ± 7.4 | |
| Yes | 231 | 26.9 ± 8.9 | | 367 | 26.8 ± 7.9 | | 569 | 26.3 ± 7.0 | |
| CVD | | | .27 | | | .18 | | | .036 |
| No | 4505 | 25.3 ± 7.6 | | 4513 | 25.8 ± 7.5 | | 4311 | 25.4 ± 7.4 | |
| Yes | 306 | 25.8 ± 7.6 | | 478 | 26.3 ± 7.1 | | 687 | 26.0 ± 7.3 | |
| Cancer | | | .96 | | | .13 | | | .15 |
| No | 4680 | 25.4 ± 7.6 | | 4725 | 25.8 ± 7.4 | | 4551 | 25.5 ± 7.4 | |
| Yes | 126 | 25.4 ± 7.2 | | 261 | 26.5 ± 8.2 | | 446 | 25.0 ± 6.9 | |

Abbreviations: BMI, Body mass index; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension; M, men; W, women.

[a]At phase 5 mean age was approximately 55 years, at phase 7 60 years and at phase 9 65 years.

**Table A 16 Crude association of tertiles of energy adjusted fibre intake with covariates in Whitehall II by gender**

| | Fibre intake, % | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Covariates at phase 3 | Men | | | | | Women | | | | |
| | | Tertile | Tertile | Tertile | | | Tertile | Tertile | Tertile | |
| | n | 1 | 2 | 3 | p | n | 1 | 2 | 3 | p |
| Age | | | | | .001 | | | | | .90 |
| <50 years | 3023 | 57.4 | 56.5 | 51.7 | | 1132 | 47.2 | 46.3 | 47.4 | |
| ≥50 years | 2463 | 42.6 | 43.5 | 48.3 | | 1280 | 52.8 | 53.7 | 52.6 | |
| Ethnic Group | | | | | .003 | | | | | .22 |
| White | 5172 | 96.0 | 93.5 | 93.5 | | 2122 | 89.2 | 86.6 | 87.9 | |
| South Asian | 227 | 2.78 | 5.02 | 4.52 | | 138 | 4.39 | 7.07 | 5.99 | |
| Black | 87 | 1.22 | 1.53 | 1.98 | | 152 | 6.43 | 6.30 | 6.13 | |
| Marital Status | | | | | <.001 | | | | | .028 |
| Married/cohabiting | 4536 | 79.1 | 83.7 | 85.1 | | 1527 | 64.0 | 65.9 | 59.9 | |
| Single | 643 | 14.4 | 11.3 | 9.8 | | 493 | 19.9 | 17.6 | 24.4 | |
| Divorced/widowed | 302 | 6.55 | 4.96 | 5.09 | | 388 | 16.11 | 16.47 | 15.71 | |
| Last grade level in Civil service | | | | | .19 | | | | | .12 |
| Highest | 2684 | 47.0 | 48.5 | 51.0 | | 380 | 14.9 | 16.2 | 16.4 | |
| Intermediate | 2454 | 46.6 | 44.9 | 42.9 | | 1094 | 43.9 | 44.1 | 48.6 | |
| Lowest | 348 | 6.4 | 6.6 | 6.1 | | 938 | 41.2 | 39.7 | 35.0 | |
| Smoking | | | | | <.001 | | | | | <.001 |
| Never Smoker | 2297 | 38.9 | 44.5 | 49.1 | | 1141 | 45.7 | 51.7 | 56.5 | |
| Ex-Smoker | 2198 | 41.0 | 43.5 | 42.9 | | 703 | 28.5 | 32.7 | 33.3 | |
| Current Smoker | 681 | 20.1 | 12.0 | 8.01 | | 405 | 25.8 | 15.5 | 10.22 | |
| Physical activity | | | | | <.001 | | | | | .054 |
| Non/mild | 1715 | 35.2 | 29.3 | 29.6 | | 1233 | 54.4 | 50.3 | 47.6 | |
| Moderate | 2553 | 45.8 | 47.7 | 46.0 | | 952 | 37.4 | 40.4 | 41.2 | |
| Vigorous active | 1218 | 19.0 | 23.0 | 24.3 | | 227 | 8.1 | 9.4 | 11.1 | |
| Alcohol consumption | | | | | <.001 | | | | | <.001 |
| None | 954 | 13.3 | 17.5 | 21.1 | | 898 | 35.0 | 36.8 | 40.8 | |
| Moderate | 2846 | 44.2 | 53.4 | 57.5 | | 1292 | 52.5 | 55.0 | 53.5 | |
| Heavy | 1680 | 42.5 | 29.2 | 21.4 | | 220 | 12.5 | 8.2 | 5.7 | |
| Sleep duration | | | | | .012 | | | | | .44 |
| less than 7 h/day | 1339 | 26.6 | 24.6 | 22.3 | | 660 | 26.5 | 26.9 | 29.2 | |
| ≥ 7 h/day | 4142 | 73.4 | 75.4 | 77.7 | | 1747 | 73.5 | 73.1 | 70.8 | |
| Energy intake from other diet | | | | | <.001 | | | | | <.001 |
| < median | 2351 | 39.8 | 49.5 | 39.3 | | 1548 | 65.3 | 69.4 | 56.9 | |
| > median | 3135 | 60.2 | 50.5 | 60.7 | | 864 | 34.7 | 30.6 | 43.1 | |
| Modified DASH diet score | | | | | <.001 | | | | | <.001 |
| < median | 3093 | 86.9 | 55.9 | 29.5 | | 1354 | 85.9 | 47.7 | 26.0 | |
| > median | 2390 | 13.1 | 44.1 | 70.5 | | 1057 | 14.1 | 52.3 | 74.0 | |
| Fish intake | | | | | <.001 | | | | | <.001 |
| < median | 3235 | 61.6 | 60.1 | 55.5 | | 1251 | 57.4 | 52.6 | 43.7 | |
| > median | 2251 | 38.4 | 39.9 | 44.5 | | 1161 | 42.6 | 47.4 | 56.3 | |
| Tea / Coffee | | | | | .30 | | | | | .064 |
| ≤ 1 cup of either/day | 409 | 6.71 | 7.52 | 8.06 | | 281 | 9.86 | 12.08 | 13.55 | |
| > 1 cup of either/day | 5077 | 93.3 | 92.5 | 91.9 | | 2131 | 90.1 | 87.9 | 86.4 | |
| Sugar intake | | | | | <.001 | | | | | <.001 |
| 1st Tertile | 1816 | 24.2 | 34.6 | 39.7 | | 802 | 26.9 | 34.7 | 40.1 | |
| 2nd Tertile | 1820 | 32.1 | 34.9 | 32.5 | | 788 | 28.1 | 38.2 | 32.7 | |
| 3rd Tertile | 1850 | 43.7 | 30.5 | 27.8 | | 822 | 45.0 | 27.1 | 27.2 | |
| BMI | | | | | .007 | | | | | .028 |
| Normal, <25kg/m$^2$ | 2781 | 50.9 | 51.9 | 56.1 | | 1172 | 49.0 | 50.1 | 56.7 | |
| Overweight | 2093 | 41.44 | 40.29 | 38.19 | | 754 | 35.38 | 34.71 | 28.66 | |
| Obese. ≥30kg/m$^2$ | 370 | 7.66 | 7.85 | 5.76 | | 345 | 15.59 | 15.23 | 14.63 | |
| Central obesity | | | | | .39 | | | | | .49 |
| No | 4821 | 92.4 | 93.0 | 93.6 | | 1963 | 85.8 | 87.7 | 87.4 | |
| Yes (Waist ≥102/≥88 cm) | 360 | 7.6 | 7.0 | 6.4 | | 296 | 14.2 | 12.3 | 12.6 | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Diabetes | | | | | .13 | | | | | .41 |
| No | 5331 | 97.4 | 97.6 | 96.6 | | 2349 | 97.7 | 97.6 | 96.7 | |
| Yes | 155 | 2.60 | 2.40 | 3.43 | | 63 | 2.25 | 2.44 | 3.28 | |
| CVD | | | | | .005 | | | | | .34 |
| No | 5287 | 97.4 | 96.5 | 95.4 | | 2343 | 97.7 | 96.9 | 96.6 | |
| Yes | 199 | 2.60 | 3.54 | 4.63 | | 69 | 2.25 | 3.08 | 3.42 | |
| Cancer | | | | | .78 | | | | | .93 |
| No | 5431 | 98.9 | 99.1 | 99.1 | | 2358 | 98.2 | 97.9 | 98.0 | |
| Yes | 53 | 1.10 | 0.87 | 0.94 | | 47 | 1.82 | 2.07 | 2.00 | |

Abbreviations: BMI, Body mass index; CVD, cardiovascular disease; GHQ, General Health Questionnaire; M, men; W, women.

**Table A 17 Association of energy adjusted fibre intake with incident mood disorders by sex**

| | | Per 10g of fibre intake/day increment | |
|---|---|---|---|
| Outcome | events / person observations | Model adjusted for age, sex and ethnicity, OR (95% CI) | p |
| Incident CMD | | | |
| **after 2 years** | | | |
| Both men & women | | 0.95 (0.85, 1.07) | .38 |
| Men | 610 / 5364 | 0.95 (0.82, 1.10) | .51 |
| women | 300 / 1882 | 0.94 (0.79, 1.12) | .49 |
| **after 5 years** | | | |
| Both men & women | | 0.87 (0.81, 0.94) | .001 |
| Men | 1381 / 11880 | 0.89 (0.81, 0.98) | .019 |
| women | 664 / 4285 | 0.84 (0.73, 0.96) | .011 |
| **after 10 years** | | | |
| Both men & women | | 0.85 (0.77, 0.95) | .003 |
| Men | 962 / 8495 | 0.86 (0.76, 0.97) | .013 |
| women | 459 / 3039 | 0.85 (0.70, 1.03) | .099 |
| Incident depression | | | |
| **after 5 years** | | | |
| Both men & women | | 0.87 (0.75, 1.01) | .061 |
| Men | 487 / 7432 | 0.84 (0.70, 1.01) | .058 |
| women | 311 / 2692 | 0.94 (0.74, 1.18) | .59 |
| **after 10 years** | | | |
| Both men & women | | 0.78 (0.68, 0.91) | .001 |
| Men | 587 / 8075 | 0.73 (0.61, 0.87) | .001 |
| women | 361 / 2773 | 0.89 (0.70, 1.12) | .33 |
| Incident clinical depression | | | |
| **after 5 years** | | | |
| Both men & women | | 0.99 (0.70, 1.41) | .96 |
| Men | 27 / 2778 | 1.50 (1.00, 2.25) | .053 |
| women | 33 / 977 | 0.61 (0.35, 1.06) | .078 |
| **after 10 years** | | | |
| Both men & women | | 0.72 (0.48, 1.08) | .12 |
| Men | 30 / 2423 | 0.73 (0.42, 1.26) | .26 |
| women | 23 / 771 | 0.71 (0.38, 1.32) | .28 |

**Table A 18 Prospective association of energy adjusted fibre intake and incident depression after 5 and 10 years[a]**

| | | Incident depression | | | | |
|---|---|---|---|---|---|---|
| | events / person observations | Model 0[b] | Model 1[c] | Model 2[d] | Model 3[e] | Model 4[f] |
| **After 5 years** | | | | | | |
| Fibre intake | | | | | | |
| Lowest Tertile | 259 / 3007 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| Middle Tertile | 246 / 3459 | 0.77* (0.61, 0.98) | 0.81 (0.63, 1.04) | 0.79 (0.60, 1.04) | 0.79 (0.60, 1.04) | 0.78 (0.60, 1.04) |
| Highest Tertile | 201 / 3047 | 0.69* (0.53, 0.90) | 0.77 (0.58, 1.01) | 0.70* (0.50, 0.98) | 0.70* (0.50, 0.98) | 0.70* (0.50, 0.98) |
| p for trend | | .006 | .052 | .036 | .038 | .038 |
| Continuous (10g/day increment) | 706 / 9513 | 0.87 (0.76, 1.01) | 0.92 (0.80, 1.07) | 0.90 (0.75, 1.08) | 0.90 (0.75, 1.08) | 0.90 (0.75, 1.09) |
| **After 10 years** | | | | | | |
| Fibre intake | | | | | | |
| Lowest Tertile | 301 / 3045 | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| Middle Tertile | 279 / 3252 | 0.88 (0.69, 1.11) | 0.90 (0.69, 1.16) | 0.90 (0.68, 1.19) | 0.90 (0.68, 1.19) | 0.90 (0.68, 1.19) |
| Highest Tertile | 241 / 3176 | 0.69** (0.53, 0.89) | 0.76* (0.57, 1.00) | 0.73 (0.52, 1.03) | 0.74 (0.53, 1.03) | 0.73 (0.52, 1.03) |
| p for trend | | .005 | .049 | .070 | .071 | .070 |
| Continuous (10g/day increment) | 821 / 9473 | 0.78*** (0.68, 0.91) | 0.81** (0.70, 0.95) | 0.77* (0.63, 0.93) | 0.77* (0.63, 0.93) | 0.77** (0.63, 0.93) |

* p<.05, **p<.005, *** p<.001.

[a]Prospective association across phases 5, 7, 9 for 5 yearsand 3, 5, 7 for 10 year depression.

[b]Model 0 for incident depression after 5 years (797 events / 10606 person observations); after 10 years (947 events / 10844 person observations); adjusted for age, sex and their interaction and ethnicity.

[c]Model 1: additionally adjusted for marital status, last grade level in civil service, smoking, alcohol intake, physical activity, sleep duration.

[d]Model 2: additionally adjusted fish, total calorie intake, modified DASH diet score, sugar intake from sweet food / beverages*sex, coffee and tea intake

[e]Model 3: additionally adjusted for BMI and central adiposity.

[f]Model 4: additionally adjusted for baseline CVD, diabetes and cancer.

**Table A 19 Prospective association of energy adjusted fibre intake and recurrent depression after 10 years[a]**

| | | Recurrent depression | | |
|---|---|---|---|---|
| | events / person observations | Model 0[b] | Model 1[c] | Model 2[d] |
| **After 10 years** | | | | |
| Fibre intake | | | | |
| Lowest Tertile | 256 / 936 | 1 (reference) | 1 (reference) | 1 (reference) |
| Middle Tertile | 249 / 911 | 0.89 (0.62, 1.27) | 1.03 (0.71, 1.49) | 1.08 (0.73, 1.61) |
| Highest Tertile | 214 / 874 | 0.77 (0.53, 1.12) | 0.82 (0.56, 1.22) | 0.92 (0.57, 1.47) |
| p for trend | | .18 | .35 | .72 |
| Continuous (10g/day increment) | 719 / 2721 | 0.81* (0.66, 0.99) | 0.85 (0.69, 1.06) | 0.88 (0.67, 1.15) |

*p<.05, **p<.005, *** p<.001.
[a]Prospective association across phases 3, 5, 7 for 10-year recurrent depression.
[b]Depression model 0:(5-year cycles: 7654 events / 2859 person observations); adjusted for age, sex and their interaction and ethnicity.
[c]Model 1: additionally adjusted for marital status, last grade level in civil service, smoking, alcohol intake, physical activity, sleep duration.
[d]Model 2: additionally adjusted fish, total calorie intake, modified DASH diet score, sugar intake from sweet food / beverages*sex, coffee and tea intake.

**Table A 20 Association of energy adjusted fibre intake with recurrent mood disorders by sex**

| | Per 10g of fibre intake/day increment | | |
|---|---|---|---|
| | events / person observations | Model adjusted for age, sex and ethnicity, OR (95% CI) | p |
| Recurrent CMD | | | |
| **after 2 years** | | | |
| Both men & women | | 0.90 (0.76, 1.06) | .21 |
| men | 478 / 1167 | 0.99 (0.80, 1.22) | .92 |
| women | 281 / 583 | 0.76 (0.56, 1.03) | .075 |
| **after 5 years** | | | |
| Both men & women | | 1.03 (0.91, 1.17) | .62 |
| men | 1025 / 2520 | 1.06 (0.90, 1.23) | .49 |
| women | 560 / 1266 | 1.00 (0.82, 1.21) | .98 |
| **after 10 years** | | | |
| Both men & women | | 0.92 (0.78, 1.07) | .26 |
| men | 708 / 2050 | 0.90 (0.74, 1.11) | .33 |
| women | 386 / 1008 | 0.93 (0.73, 1.18) | .54 |
| Recurrent depression | | | |
| **after 5 years** | | | |
| Both men & women | | 0.92 (0.74, 1.14) | .44 |
| men | 462 / 1523 | 0.91 (0.68, 1.20) | .50 |
| women | 262 / 723 | 0.92 (0.65, 1.31) | .65 |
| **after 10 years** | | | |
| Both men & women | | 0.81 (0.66, 0.99) | .042 |
| men | 488 / 1934 | 0.87 (0.67, 1.12) | .28 |
| women | 277 / 925 | 0.70 (0.48, 1.00) | .052 |
| Recurrent clinical depression | | | |
| **after 5 years** | | | |
| Both men & women | | 0.86 (0.62, 1.19) | .37 |
| men | 57 / 397 | 0.92 (0.62, 1.37) | .68 |
| women | 31 / 192 | 0.77 (0.44, 1.35) | .36 |
| **after 10 years** | | | |
| Both men & women | | 1.09 (0.80, 1.50) | .58 |
| men | 50 / 542 | 1.21 (0.80, 1.84) | .36 |
| women | 25 / 238 | 0.94 (0.55, 1.59) | .81 |

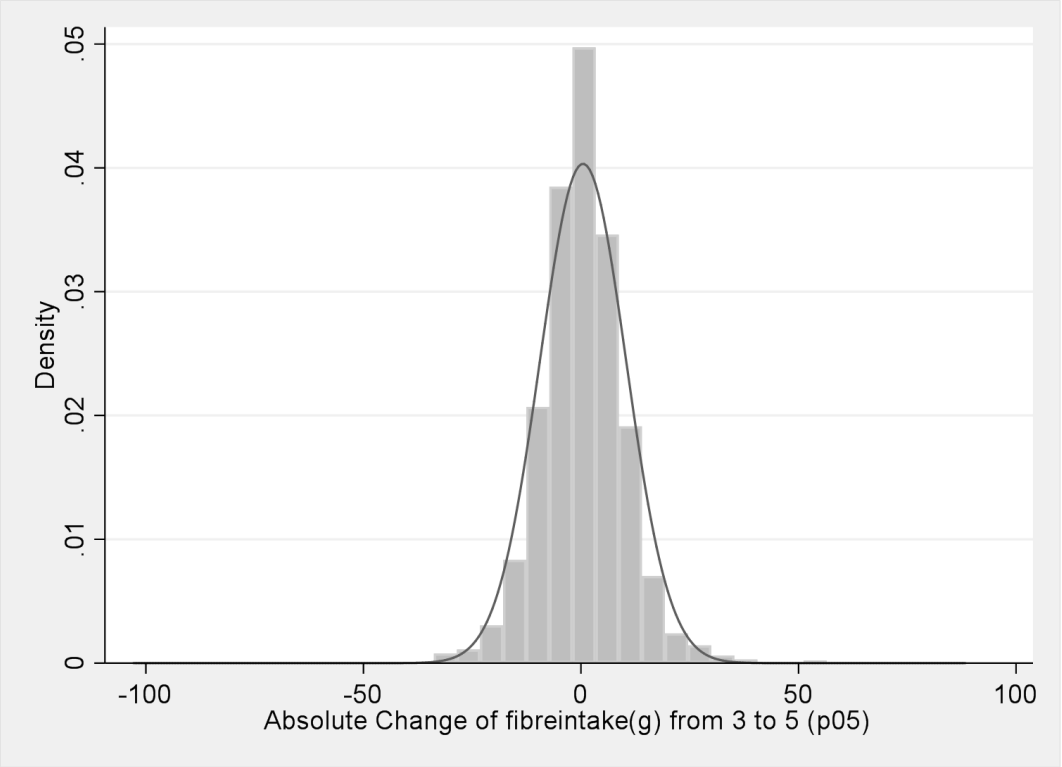



**Figure A 4 Distribution of change in dietary fibre intake from phase 3 to 5**

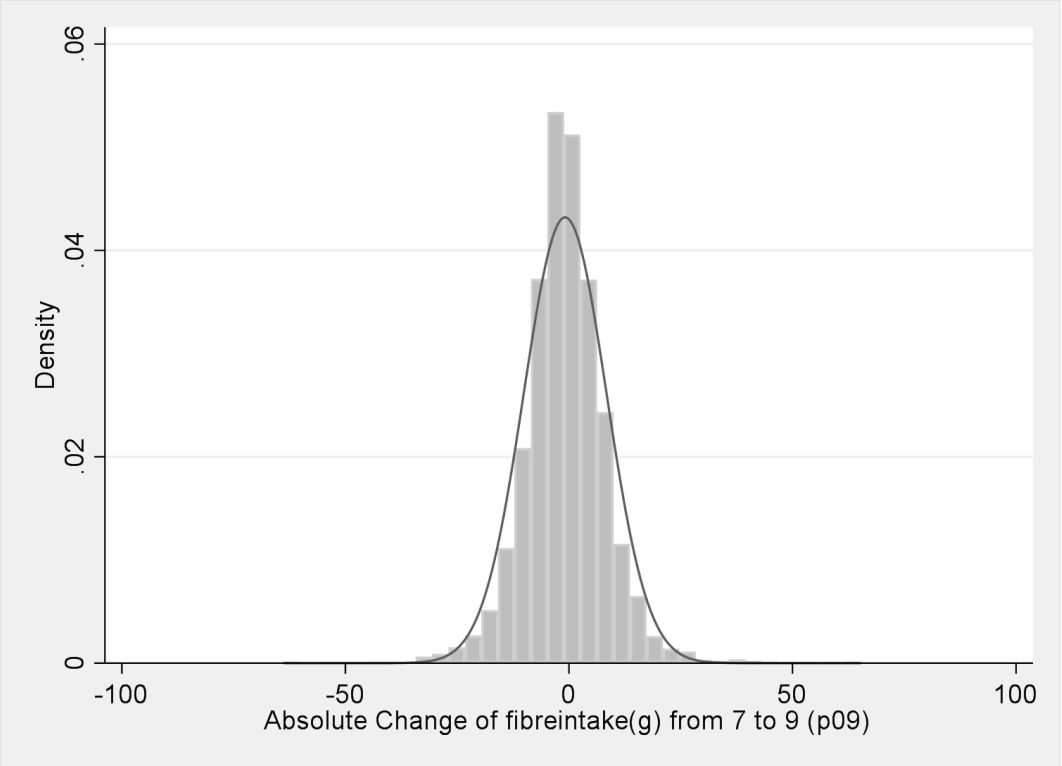



**Figure A 5 Distribution of change in dietary fibre intake from phase 7 to 9**

**Table A 21 Association of CMD and depression with subsequent 5-year change in fibre intake after exclusion of extreme fibre intakes (>7 SD)**

| | 5-year change in fibre intake | | | | | |
|---|---|---|---|---|---|---|
| | Not adjusted for energy intake | | | Energy adjusted | | |
| | events / participants | OR (95% CI) *β-coefficient*[a] *(95% CI)* | p | events / participants | OR (95% CI) *β-coefficient*[a] *(95% CI)* | p |
| **CMD** | | | | | | |
| **At phase 3 – Fibre intake change: phase 3 to 5** | | | | | | |
| Reduction | 231 / 1087 | 1.06 (0.90, 1.28) | .46 | 259 / 1227 | 1.03 (0.87, 1.23) | .70 |
| No change | 487 / 2399 | 1 (reference) | | 495 / 2408 | 1 (reference) | |
| Increase | 235 / 1123 | 1.03 (0.86, 1.23) | .74 | 199 / 974 | 1.00 (0.83, 1.20) | .97 |
| Continuous change in grams per day | 953/ 4609 | *0.07 (-0.60, 0.73)* | .84 | 974 / 4609 | *0.05 (-0.46, 0.56* | .86 |
| **At phase 5 – Fibre intake change: phase 5 to 7** | | | | | | |
| Reduction | 136 / 786 | 0.79* (0.63, 0.98) | .034 | 150 / 736 | 1.04 (0.84, 1.29) | .74 |
| No change | 403 / 1985 | 1 (reference) | | 380 / 1946 | 1 (reference) | |
| Increase | 180 / 824 | 1.08 (0.88, 1.33) | .40 | 189 / 913 | 1.02 (0.83, 1.24) | .86 |
| Continuous change in grams per day | 719 / 3595 | *1.00* (0.28, 1.71)* | .006 | 719 / 3595 | *0.28 (-0.27, 0.83)* | .31 |
| **At phase 7 – Fibre intake change: phase 7 to 9** | | | | | | |
| Reduction | 182 / 986 | 0.88 (0.73, 1.07) | .22 | 200 / 968 | 1.15 (0.95, 1.40) | .15 |
| No change | 431 / 2182 | 1 (reference) | | 402 / 2163 | 1 (reference) | |
| Increase | 126 / 758 | 0.79* (0.63, 0.99) | .037 | 137 / 795 | 0.94 (0.76, 1.16) | .56 |
| Continuous change in grams per day | 740 / 3926 | *-0.48 (-1.19 0.23)* | .18 | 739 / 3926 | *-0.45 (-0.99, 0.08)* | .10 |
| **Depression** | | | | | | |
| **At phase 7 – Fibre intake change: phase 7 to 9** | | | | | | |
| Reduction | 100 / 933 | 0.70** (0.55, 0.90) | .005 | 111 / 917 | 0.94 (0.74, 1.19) | .61 |
| No change | 290 / 2061 | 1 (reference) | | 266 / 2036 | 1 (reference) | |
| Increase | 84 / 713 | 0.78 (0.60, 1.02) | .064 | 97 / 754 | 1.02 (0.79, 1.31) | .90 |
| Continuous change in grams per day | 474 / 3707 | *-0.11 (-0.95, 0.73)* | .80 | 474 / 3707 | *-0.14 (-0.78,0.50* | .66 |

*p<.05, **p<.005, *** p<.001.

[a]Change in fibre intake in cases compared with non-cases, adjusted for age, age, sex and their interaction and ethnicity.

## Appendices relating to Chapter 7

**Table A 22 Crude association of financial insecurity with covariates at phases 5, 7 and 9**

| Covariates | Any financial insecurity | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Phase 5 | | | Phase 7 | | | Phase 9 | | |
| | n | % | p | n | % | p | n | % | p |
| GHQ | | | <.001 | | | <.001 | | | <.001 |
| no | 3769 | 35.4 | | 3977 | 26.3 | | 4262 | 22.1 | |
| yes | 974 | 49.0 | | 960 | 42.5 | | 682 | 37.0 | |
| Sex | | | .005 | | | <.001 | | | <.001 |
| Men | 3425 | 37.0 | | 3604 | 27.0 | | 3573 | 21.0 | |
| Women | 1318 | 41.4 | | 1333 | 35.9 | | 1371 | 32.4 | |
| Age | | | <.001 | | | .065 | | | .061 |
| < median | 2319 | 42.5 | | 2375 | 30.7 | | 2471 | 25.3 | |
| > median | 2424 | 34.2 | | 2562 | 28.3 | | 2473 | 23.0 | |
| Ethnic Group | | | <.001 | | | <.001 | | | <.001 |
| White | 4479 | 36.9 | | 4666 | 27.9 | | 4661 | 22.8 | |
| South Asian | 174 | 59.8 | | 182 | 52.7 | | 183 | 38.3 | |
| Black | 90 | 62.2 | | 89 | 61.8 | | 100 | 62.0 | |
| Marital Status | | | <.001 | | | <.001 | | | <.001 |
| Married/cohabiting | 3632 | 37.1 | | 3801 | 27.5 | | 3719 | 22.0 | |
| Single | 539 | 37.8 | | 594 | 31.1 | | 534 | 26.4 | |
| Divorced/widowed | 420 | 50.0 | | 535 | 40.7 | | 622 | 33.9 | |
| Last grade level in Civil service | | | <.001 | | | <.001 | | | <.001 |
| Highest | 2161 | 26.0 | | 2322 | 19.6 | | 2361 | 15.7 | |
| Intermediate | 2035 | 46.4 | | 2100 | 34.2 | | 2069 | 28.0 | |
| Lowest | 547 | 56.3 | | 515 | 54.0 | | 514 | 47.5 | |
| Smoking | | | <.001 | | | <.001 | | | .004 |
| Never Smoker | 2350 | 34.7 | | 2381 | 28.0 | | 2347 | 23.0 | |
| Ex-Smoker | 1962 | 39.0 | | 2188 | 29.3 | | 2312 | 24.1 | |
| Current Smoker | 415 | 53.5 | | 354 | 38.7 | | 249 | 32.5 | |
| Physical activity | | | <.001 | | | <.001 | | | .089 |
| Non/mild | 1783 | 43.3 | | 1617 | 34.0 | | 1641 | 25.9 | |
| Moderate | 2285 | 36.8 | | 2779 | 27.6 | | 2688 | 23.6 | |
| Vigorous | 675 | 29.8 | | 541 | 24.8 | | 615 | 22.0 | |
| Alcohol consumption | | | <.001 | | | <.001 | | | <.001 |
| None | 786 | 44.1 | | 861 | 38.3 | | 994 | 32.8 | |
| Moderate | 2268 | 38.5 | | 2495 | 28.1 | | 2596 | 22.7 | |
| Heavy | 1661 | 34.9 | | 1558 | 26.3 | | 1299 | 19.6 | |
| Sleep duration | | | <.001 | | | <.001 | | | <.001 |
| less than 7 h/day | 1880 | 44.1 | | 1958 | 35.4 | | 1796 | 28.4 | |
| ≥ 7 h/day | 2834 | 34.3 | | 2973 | 25.4 | | 3142 | 21.7 | |
| BMI | | | <.001 | | | <.001 | | | <.001 |
| Normal, <25kg/$m^2$ | 1781 | 35.4 | | 1847 | 25.8 | | 1887 | 21.1 | |
| Overweight | 1816 | 39.4 | | 2197 | 29.7 | | 2129 | 24.7 | |
| Obese. ≥30kg/$m^2$ | 527 | 45.2 | | 874 | 36.5 | | 913 | 29.0 | |
| Central obesity (W / M) | | | <.001 | | | <.001 | | | .002 |
| No | 3088 | 37.7 | | 3779 | 27.8 | | 3590 | 22.9 | |
| Yes (Waist ≥88/ 102 cm) | 624 | 46.5 | | 1146 | 34.9 | | 1344 | 27.2 | |
| Diabetes | | | .005 | | | .001 | | | .004 |
| No | 4516 | 37.8 | | 4574 | 28.8 | | 4387 | 23.5 | |
| Yes | 227 | 47.1 | | 363 | 37.2 | | 557 | 29.1 | |
| CVD | | | .16 | | | .25 | | | .061 |
| No | 4443 | 38.0 | | 4464 | 29.2 | | 4261 | 23.7 | |
| Yes | 300 | 42.0 | | 473 | 31.7 | | 678 | 27.0 | |
| Cancer | | | .52 | | | .25 | | | .81 |
| No | 4614 | 38.3 | | 4673 | 29.6 | | 4495 | 24.2 | |
| Yes | 124 | 35.5 | | 259 | 26.3 | | 443 | 23.7 | |

Abbreviations: BMI, Body mass index; CVD, cardiovascular disease; GHQ, General Health Questionnaire; M, men; W, women.

**Table A 23 Crude association of financial insecurity with diet at phases 5, 7 and 9**

| Covariates | Any financial insecurity | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Phase 5 | | | Phase 7 | | | Phase 9 | | |
| | n | % | p | n | % | p | n | % | p. |
| Energy intake (kcal) | | | .001 | | | .001 | | | .30 |
| < median | 2371 | 40.7 | | 2469 | 31.6 | | 2469 | 24.8 | |
| > median | 2372 | 35.8 | | 2468 | 27.2 | | 2475 | 23.5 | |
| Modified DASH diet score | | | .028 | | | .011 | | | .10 |
| < median | 2599 | 39.6 | | 2456 | 30.9 | | 2835 | 24.9 | |
| > median | 2104 | 36.5 | | 2389 | 27.6 | | 2083 | 22.9 | |
| Fish intake | | | .48 | | | .89 | | | .74 |
| < median | 2497 | 37.8 | | 2579 | 29.3 | | 2639 | 23.9 | |
| > median | 2244 | 38.8 | | 2350 | 29.5 | | 2303 | 24.4 | |
| Coffee and tea | | | .93 | | | .010 | | | <.001 |
| ≤ 1 cup of either/day | 153 | 38.6 | | 197 | 37.6 | | 226 | 35.0 | |
| > 1 cup of either/day | 4590 | 38.2 | | 4740 | 29.1 | | 4718 | 23.6 | |
| Sugar intake from sweet food / beverages M) | | | .004 | | | .063 | | | .25 |
| < median | 1528 | 39.7 | | 1666 | 28.5 | | 1630 | 21.8 | |
| > median | 1897 | 34.8 | | 1938 | 25.7 | | 1943 | 20.3 | |
| Sugar intake from sweet food / beverages (W) | | | .71 | | | .65 | | | .75 |
| < median | 843 | 41.0 | | 803 | 35.4 | | 841 | 32.7 | |
| > median | 475 | 42.1 | | 530 | 36.6 | | 530 | 31.9 | |
| Fibre intake (energy adj.) (M) | | | .35 | | | .008 | | | .34 |
| < median | 1689 | 37.8 | | 1724 | 29.1 | | 1707 | 21.7 | |
| > median | 1736 | 36.2 | | 1880 | 25.2 | | 1866 | 20.4 | |
| Fibre intake (energy adj.) (W) | | | .38 | | | .19 | | | .75 |
| < median | 693 | 42.6 | | 760 | 37.4 | | 768 | 32.0 | |
| > median | 625 | 40.2 | | 573 | 33.9 | | 603 | 32.8 | |

Abbreviations: DASH, Dietary Approaches to Stop Hypertension; M, men; W, women.

## Appendices relating to Chapter 8

### Appendix 11 Number of tests to assess Bonferroni correction

Number of tests for association between sugar intake from sweet food / beverage and mood disorders: estimates for both sexes: cross-sectional*2 measures, prospective incidence 5y*2 measure, prospective incidence 10y*2 measures, prospective recurrence 2y*1 measure, prospective recurrence 5y*2 measures, prospective recurrence 10y*3 measures; for men and women separately: prospective incidence 2y*1 measure, prospective incidence 5y*1 measures, prospective incidence 10y*1 measure, prospective recurrence 5y*1 measure.

Number of tests for association between fibre intake and mood disorders: estimates for both sexes: cross-sectional*2 measures, prospective incidence 5y*2 measure, prospective incidence 10y*3 measures, prospective recurrence 2y*1 measure, prospective recurrence 5y*3 measures, prospective recurrence 10y*3 measures; for men and women separately: prospective incidence 5y*1 measures.

Number of tests for interactions of dietary intake in the association between financial insecurity, grade level and mood disorders: For each financial insecurity, last and current grade level one association per mood disorder measure, and two interactions one with sugar intake from sweet food / beverages and one with fibre intake

## Published paper of the thesis

Title: Sugar intake from sweet food and beverages, common mental disorder and depression: prospective findings from the Whitehall II study

Authors: Anika Knüppel, Martin J. Shipley, Clare H. Llewellyn & Eric J. Brunner

Journal: Scientific Reports

Date: 27 July 2017

Link: https://www.nature.com/articles/s41598 017 05649 7



Differences between publication and this thesis

To ensure comparability across objectives analyses presented in this thesis were slightly different than in the publication. Analyses in this paper were based on more participants than analyses of objective I. In the publication participants were included even if they had reported their diet to be not representative of their dietary intake. Also, analyses were not adjusted for fibre intake and sex interactions were tested in tertile analyses instead of continuously operationalised sugar intakes from sweet food / beverages. These differences lead to slightly different results: Associations between sugar intake from sweet food / beverages and recurrent depression showed no sex differences and were not stratified and attenuated after adjustment for other dietary factors. Apart from that difference conclusions from the paper are in line with those of this thesis.

SCIENTIFIC REPORTS

OPEN

# Sugar intake from sweet food and beverages, common mental disorder and depression: prospective findings from the Whitehall II study

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Anika Knüppel, Martin J. Shipley, Clare H. Llewellyn & Eric J. Brunner

**Intake of sweet food, beverages and added sugars has been linked with depressive symptoms in several populations. Aim of this study was to investigate systematically cross-sectional and prospective associations between sweet food/beverage intake, common mental disorder (CMD) and depression and to examine the role of reverse causation (influence of mood on intake) as potential explanation for the observed linkage. We analysed repeated measures (23,245 person-observations) from the Whitehall II study using random effects regression. Diet was assessed using food frequency questionnaires, mood using validated questionnaires. Cross-sectional analyses showed positive associations. In prospective analyses, men in the highest tertile of sugar intake from sweet food/beverages had a 23% increased odds of incident CMD after 5 years (95% CI: 1.02, 1.48) independent of health behaviours, socio-demographic and diet-related factors, adiposity and other diseases. The odds of recurrent depression were increased in the highest tertile for both sexes, but not statistically significant when diet-related factors were included in the model (OR 1.47; 95% CI: 0.98, 2.22). Neither CMD nor depression predicted intake changes. Our research confirms an adverse effect of sugar intake from sweet food/beverage on long-term psychological health and suggests that lower intake of sugar may be associated with better psychological health.**

Sugar consumption is increasingly discussed as an intervention target to reduce prevalence of obesity, diabetes and other non-communicable diseases[1,2]. In Britain, adults consume approximately double, and in the U.S. triple, the recommended level of added sugar for additional health benefits (5% of energy intake), with sweet foods and drinks contributing three-quarters of the intake[1,3,4]. Meanwhile, major depression is predicted to become the leading cause of disability in high income countries by 2030[5].

Higher sugar consumption was linked to higher depression prevalence in several ecological and cross-sectional studies[6–8]. To date, few studies have investigated the prospective association of sweet food and beverage intake with depression[9–12]. Although all studies found an increased risk of depression with higher baseline consumption of added sugars, soft drinks, juices and pastries; none examined the role of 'reverse causation' in producing the observed association. Reverse causation refers, in this context, to the possibility that a mood disorder may lead to higher sugar intake, so that the diet-mental health association is wholly or partly the result of poor mental health rather than of high sugar intake[13–15]. A prospective study with repeat measures of food intake and mental health provides the opportunity to examine the bidirectional nature of the association, and to contribute novel evidence on the effect of sugar dense diet on depression in the general population.

There are several plausible biological explanations for an association of habitual sugar intake and subsequent risk of depression, in the long-term. Firstly, low levels of the growth factor brain derived neurotrophic factor (BDNF) have been discussed as facilitating neurogenesis and hippocampal atrophy in depression[16]. Rodents fed high-fat high-sugar diets, but not high-fat diets only, show a decrease in BDNF level[17–19], which could be a mechanistic link between diets high in sugar and depression. Secondly, carbohydrate consumption has been

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associated with increased circulating inflammatory markers, which may depress mood[20,21]. Thirdly, high sugar diets could induce hypoglycaemia through an exaggerated insulin response and thereby influence hormone levels and potentially mood states[22]. Fourthly, addiction-like effects of sugar suggest dopaminergic neurotransmission mechanisms might connect frequent sugar intake with depression[23–25]. Lastly, obesity could be a mediating factor between a sugar-dense diet and depression[26,27] not only via inflammatory but also psychosocial factors like weight discrimination[28].

The aim of this study is to investigate whether sugar intake from sweet food/beverages is positively associated with the risk of both incident and recurrent mood disorders, and to establish the role of the reverse effect in the Whitehall II cohort, using prospective, repeat measures data collected over a 22 year period.

## Methods

**Study cohort.** The Whitehall Study II consists of non-industrial civil servants, who were recruited in London at age 35 to 55 years during 1985–1988 (phase 1). The initial sample size was 10,308 individuals (33.1% female and 66.9% male). The participants were followed up via questionnaire in 1989–1990 (phase 2), 1991–1993 (phase 3), 1995–1996 (phase 4), 1997–1999 (phase 5), 2001 (phase 6), 2003–2004 (phase 7), 2006 (phase 8), 2008–2009 (phase 9) and 2012–2013 (phase 11). In phases 1, 3, 5, 7, 9 and 11 they were additionally invited for screening in a research clinic[29]. Phase 10 (2011) consisted of a smaller sample of participants used for a pilot study. The study was approved by the Joint UCL/UCLH Committee on the Ethics of Human Research and carried out in accordance with the ethical principles set out in the Declaration of Helsinki. Further all participants have been asked for informed consent at every follow-up.

**Ascertainment of sugar intake from sweet food/beverages.** Diet was assessed at phases 3, 5, 7 and 9 using a 127-item machine-readable semi-quantitative food frequency questionnaire (FFQ) which originates from the tool used in the US Nurses' Health Study, a self-administered questionnaire on habitual diet over the past 12 months[30,31]. In order to reflect most diets in the UK it has been modified and anglicized[32]. This FFQ has been validated against a 7 day diet diary in a stratified random sample of 865 participants in the Whitehall Study II at collection phase 3[30]. Sweet food and beverage intake was measured with 15 items such as cakes, biscuits, added sugar to coffee or tea, and fizzy soft drinks (see Supplementary Table S1). Sugar intake was calculated by multiplying sweet food/beverage consumption frequencies per day by their sugar content and portion size based on *McCance and Widdowson's The Composition of Foods, 5th edition*[33].

**Depressive symptom assessment.** The 30-item General Health Questionnaire (GHQ) measures depressive and somatic symptoms over the past two weeks[34]. Caseness was defined as reporting $\geq$5 symptoms and is referred to as common mental disorder (CMD). This measure was included in follow-up questionnaires at all phases apart from phase 4. In addition, the 20-item Center of Epidemiologic Studies Depression Scale (CES-D), a self-report measure of depressive symptoms in the general population over the past week[35], was administered at phases 7, 9 and 11. Individuals scoring $\geq$16 were considered cases of depression[36]. Lastly, a clinical interview using the Revised Clinical Interview Schedule (CIS-R) was administered at phase 11 with participants assessed according to International Classification of Diseases (ICD-10) F32 criteria. The computerized self-completion version of the CIS-R included questions on depressive symptoms that were present for at least 2 weeks[37–39]. The GHQ and CES-D have been validated against the CIS-R in this cohort and showed high sensitivity and specificity in measuring depressive episodes[39].

**Covariates.** Potential confounders were chosen based on review of the literature and restricted to variables available at all phases used in the analyses. All estimates were initially adjusted for age, ethnicity (White/ South Asian/ Black) and sex, with an interaction of sex and age where both sexes included. Socio-demographic variables consisted of marital status (married/cohabiting, single or divorced/widowed) and last employment grade level within the civil service, (high, intermediate, low). Health behaviours included smoking (never, former, current), alcohol intake (none: $\leq$1 unit/weeks, moderate, heavy: $\geq$14 units/week) self-reported physical activity (vigorous, moderate and non/mild)[40] and duration of sleep (5 categories from $\leq$5 hours to $\geq$9 hours/day). Diet-related factors comprised energy intake, diet quality, fish, coffee and tea intake based on FFQ data. Energy intake was used to ascertain dietary misreporting. Misreporting was considered where the log ratio of energy intake to estimated energy expenditure was outside of 3 SD of the log mean. This definition was adopted by Mosdol *et al*. 2007 and based on basal metabolic rate equations of the Department of Health[41–43]. Since sugar intake from sweet food/beverages was strongly correlated with energy intake ($r = 0.61$, $P < 0.001$), energy intake was adjusted for with the partition method by using energy intake from other foods[44]. Diet quality was assessed using the Dietary Approaches to Stop Hypertension (DASH) diet score modified by excluding a measure for sweet drinks[45]. DASH diet score, coffee and tea intake were analysed as continuous variables, fish intake per day as quintiles and all dichotomized for descriptive analyses. Body mass index (BMI) (kg/m$^2$) and central obesity (in women waist circumference $\geq$88 cm and in men $\geq$102 cm) were both measured by trained staff[46]. Physical health was defined as diabetes and cardiovascular disease (coronary heart disease and stroke, CVD) based on self-reports which were validated using the study clinical examination, Hospital Episode Statistics data, and by contacting general practitioners for confirmation when no other external source existed. Cancer was based on cancer registration data[29]. Finally, doctor diagnosis of depression was based on self-report at phases 1 to 4 and on self-reported antidepressant intake at all phases after phase 4.

**Statistical analysis.** At each phase, participants were included if they had answered at least 8 of the FFQ sweet food and beverage items[47] (less than 5% of eligible sample had one missing item and about 1% two or more), their ethnicity was known to be either White, Black or South Asian, and participants were not energy misreporters (see above). In addition, participants were also excluded from analyses if they had incomplete data

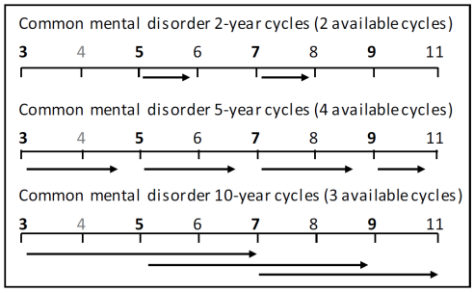


**Figure 1.** Modes of analysis using cycle approach for common mental disorder[a]. Numbers indicate study phases. Phases with food frequency data in bold; no data on common mental disorder available at Phase 4. [a]Common mental disorder measured using the 30-item General Health Questionnaire.

on GHQ-, CES-D- or CIS-R caseness for outcome-specific analyses, respectively. Supplementary Fig. S1 shows how the included sample was reached (see Online).

Three binary outcomes were analysed, GHQ caseness, CES-D caseness and CIS-R caseness. Daily sweet food and beverage intake was modelled as sex-specific tertiles of sugar intake from sweet food/beverages based on the distribution at phase 3 (in men $<39.5$, $\geq 39.5$ to $<67.0$ and $\geq 67.0$ g/day; in women $<30.0$, $\geq 30.0$ to $<51.0$ and $\geq 51.0$ g/day). To describe the sample at phase 3, GHQ cases, non-cases and tertiles of sugar intake by covariate were compared. To examine the prospective association of sugar intake from sweet food and beverages, a random effects logistic regression model (REM) was performed using the STATA command *xtlogit*[48], with exposures at phases 3, 5, 7 and 9 for GHQ caseness, and at phases 7 and 9 for CES-D caseness. The applicability of the REM was tested by introducing study phase-interactions and likelihood ratio tests (LRT). The prospective effect of sugar intake from sweet food/beverages on incident and recurrent CMD and depression was examined using REMs in 2, 5 and 10-year cycles[49]. Figure 1 shows the included phases for analyses using GHQ caseness as the outcome. For example, the association between sugar intake and GHQ status 2 years later was conducted by combining the associations between sugar intake at Phase 5 and incident GHQ caseness at Phase 6, and between sugar intake at Phase 7 and incident GHQ caseness at Phase 8. For all depression outcomes, incidence was assumed if no CMD was apparent at each baseline, and recurrence if CMD was apparent at each baseline. For the analyses of depression, two 5-year cycles (to Phase 9 and 11) and three 10 year cycles (to Phases 7, 9 and 11) were used. For clinical depression, one 5-year cycle and one 10-year cycle were used.

To check for reverse causation, that depressive symptoms may affect subsequent sugar intake from sweet food/beverages, linear regression models of 5-year change and multinomial logistic regression for change groups were fitted for each cycle, from phases 3 to 5, 5 to 7 and 7 to 9, with CMD at phases 3, 5, 7 respectively, and for change from phase 7 to 9 with depression at phase 7. Normal distribution of change in sugar intake from sweet food/beverages was verified using a histogram. Change groups were created by subtracting tertiles of sugar intake at baseline (t) from sugar intake from sweet food/beverages at follow-up ($t+5$ y) and coding $-2/-1$ as decrease, 0 as no change and $+1/+2$ as increase in sugar intake from sweet food/beverages.

All analyses were performed using Stata 14[50]. Interactions of CMD and depression with sex in the initial model (Model 0 per sex-specific tertile trend: adjusted for age and ethnicity) were tested using LRT since sex-differences have been reported in a prior study on the association of diet and depression in the Whitehall II cohort[51]. Further adjustments were grouped into four hierarchical models: baseline socio-demographic factors and health behaviours (Model 1), diet-related factors (Model 2), BMI and central obesity (Model 3), and physical health (Model 4). In sensitivity analyses, main analyses were repeated by: (a) excluding participants with unknown or reported doctor diagnosis of depression at each baseline (at phases 3/5/7/9: 166/156/193/209 individuals) and: (b) excluding participants with extreme values of sugar intake (>7 SD) at phases 3/5/7/9: 5/3/4/4 individuals.

## Results

Table 1 shows the prevalence of CMD and tertiles of reported sugar consumption from sweet food/beverages according to covariates at phase 3. CMD was more prevalent in women: under 50-years old, divorced/widowed, physically inactive, current smokers and those with fewer hours of sleep. Women with CMD were more likely to be in a lower grade level in civil service ($P<0.001$; not depicted). Sugar consumption was associated with socio-demographic factors, health behaviours, physical health and diet-related factors (Table 1). Unexpectedly, participants in the highest tertile of sweet food/beverage intake had the highest prevalence of normal weight and lowest prevalence of overweight and obesity as well as the lowest prevalence of abdominal obesity in men (both $P=0.002$; not depicted).

Incidence of CMD was around 9 to 15%, highest in the first cycle but did not differ greatly by cycle length. Depression and clinical depression incidence were approximately 8% and 2%, respectively. About 44% of participants who were CMD cases at baseline of each cycle remained recurrent CMD cases, 47% became recurrent depression cases and 58% recurrent clinical depression cases.

| Covariates at phase 3 | n | Common mental disorder cases[a] | | Sugar intake from sweet food/beverages | | | |
|---|---|---|---|---|---|---|---|
| | | | | Tertile 1 | Tertile 2 | Tertile3 | |
| | | % | *P* | % | % | % | *P* |
| Sex | | | <0.001 | | | | 0.84 |
| Men | 5,603 | 20.7 | | 69.0 | 69.7 | 69.1 | |
| Women | 2,484 | 25.7 | | 31.0 | 30.3 | 30.9 | |
| Age | | | <0.001 | | | | 0.87 |
| <50 years | 4,264 | 25.3 | | 53.1 | 52.5 | 52.6 | |
| ≥50 years | 3,823 | 18.9 | | 46.9 | 47.5 | 47.4 | |
| Ethnic Group | | | 0.03 | | | | |
| White | 7,423 | 22.4 | | 89.3 | 91.5 | 94.6 | <0.001 |
| South Asian | 410 | 23.7 | | 7.07 | 5.20 | 2.95 | |
| Black | 254 | 15.7 | | 3.63 | 3.33 | 2.47 | |
| Marital Status | | | <0.001 | | | | <0.001 |
| Married/cohabiting | 6,197 | 20.7 | | 75.9 | 78.8 | 75.5 | |
| Single | 1,145 | 25.8 | | 14.1 | 12.9 | 16.7 | |
| Divorced/widowed | 705 | 29.9 | | 10.0 | 8.36 | 7.82 | |
| Last grade level in Civil service | | | 0.19 | | | | 0.03 |
| Highest | 3,119 | 21.8 | | 36.3 | 39.7 | 39.7 | |
| Intermediate | 3,639 | 23.1 | | 46.0 | 44.2 | 44.8 | |
| Lowest | 1,329 | 20.8 | | 17.7 | 16.1 | 15.5 | |
| Smoking | | | 0.006 | | | | <0.001 |
| Never Smoker | 3,540 | 21.0 | | 42.7 | 47.6 | 49.4 | |
| Ex-Smoker | 2,957 | 22.4 | | 41.9 | 38.3 | 36.5 | |
| Current Smoker | 1,108 | 25.5 | | 15.4 | 14.2 | 14.2 | |
| Physical activity | | | <0.001 | | | | 0.002 |
| Non/mild | 3,027 | 25.4 | | 40.3 | 36.6 | 35.4 | |
| Vigorous | 1,475 | 19.1 | | 17.9 | 17.8 | 19.0 | |
| Alcohol consumption | | | 0.94 | | | | <0.001 |
| None | 1,916 | 22.4 | | 20.8 | 22.3 | 28.0 | |
| Moderate | 4,208 | 22.1 | | 48.3 | 53.8 | 54.1 | |
| Heavy | 1,955 | 22.4 | | 30.9 | 23.9 | 17.9 | |
| Sleep duration | | | <0.001 | | | | 0.33 |
| less than 7 h/day | 2,055 | 27.3 | | 26.4 | 24.6 | 25.4 | |
| ≥7 h/day | 6,022 | 20.5 | | 73.6 | 75.4 | 74.6 | |
| Energy intake from other diet | | | 0.03 | | | | <0.001 |
| <median (1339 kcal) | 4,042 | 21.2 | | 61.8 | 52.6 | 35.7 | |
| >median (2107 kcal) | 4,045 | 23.3 | | 38.2 | 47.4 | 64.3 | |
| Modified DASH diet score | | | 0.71 | | | | <0.001 |
| <median (17.7) | 4,522 | 22.1 | | 50.6 | 55.6 | 61.7 | |
| >median (24.8) | 3,559 | 22.4 | | 49.4 | 44.4 | 38.3 | |
| Fish intake ( | | | 0.38 | | | | 0.02 |
| <median (1 portion/week) | 4,597 | 21.9 | | 56.6 | 58.9 | 55.1 | |
| >median (4 portions/week) | 3,489 | 22.7 | | 43.4 | 41.1 | 44.9 | |
| Coffee and tea | | | 0.91 | | | | <0.001 |
| ≤1 cup of either/day | 714 | 22.4 | | 11.0 | 8.54 | 6.96 | |
| >1 cup of either/day | 7,373 | 22.2 | | 89.0 | 91.5 | 93.0 | |
| Body mass (BMI) | | | 0.02 | | | | <0.001 |
| Normal weight (<25 kg/m$^2$) | 4,052 | 22.7 | | 48.2 | 52.0 | 57.7 | |
| Overweight (25–29.9 kg/m$^2$) | 2,905 | 20.4 | | 40.4 | 38.9 | 34.0 | |
| Obese (≥30 kg/m2) | 737 | 24.3 | | 11.4 | 9.04 | 8.33 | |
| Central obesity | | | 0.59 | | | | 0.21 |
| No | 6,938 | 21.9 | | 90.4 | 91.1 | 91.8 | |
| Yes (Waist ≥88 (F)/102 (M)) | 679 | 22.8 | | 9.61 | 8.94 | 8.20 | |
| Diabetes | | | 0.90 | | | | <0001 |
| No | 7,861 | 22.2 | | 96.1 | 97.4 | 98.1 | |
| Yes | 226 | 22.6 | | 3.92 | 2.58 | 1.88 | |
| CVD | | | 0.03 | | | | 0.007 |

Continued

| Covariates at phase 3 | n | Common mental disorder cases[a] | | Sugar intake from sweet food/beverages | | | |
|---|---|---|---|---|---|---|---|
| | | | | Tertile 1 | Tertile 2 | Tertile3 | |
| | | % | *P* | % | % | % | *P* |
| No | 7,817 | 22.1 | | 95.8 | 96.7 | 97.3 | |
| Yes | 273 | 27.5 | | 4.18 | 3.29 | 2.65 | |
| Cancer | | | 0.58 | | | | 0.32 |
| No | 7.973 | 22.3 | | 98.7 | 99.0 | 98.5 | |
| Yes | 105 | 20.0 | | 1.33 | 1.05 | 1.51 | |

**Table 1.** Crude association of common mental disorder and sugar intake from sweet food/beverages with covariates at phase 3. Abbreviations: SD = Standard Deviation, CVD = cardiovascular disease, DASH = Dietary Approaches to Stop Hypertension. *P* for difference or heterogeneity, derived from t-test, chi-square test, ANOVA or Kruskal-Wallis test. [a]Common mental disorder measured using the 30-item General Health Questionnaire.

| | Prevalent common mental disorder[b], OR (95% CI) | | | |
|---|---|---|---|---|
| | events/person observations | Model 0[c] | Model 1[d] | Model 2[e] |
| Sugar intake from sweet food/beverages | | | | |
| Lowest Tertile | 1540/8402 | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| Middle Tertile | 1417/7439 | 1.08 (0.97, 1.20) | 1.10 (0.99, 1.22) | 1.07 (0.96, 1.19) |
| Highest Tertile | 1435/6872 | 1.22 (1.09, 1.36) | 1.25 (1.11, 1.41) | 1.17 (1.04, 1.32) |
| Total | 4392/22713 | | | |
| *P* for trend | | 0.001 | <0.001 | 0.011 |
| | Prevalent depression[f], OR (95% CI) | | | |
| | events/person observations | Model 0[g] | Model 1[d] | Model 2[e] |
| Lowest Tertile | 498/4025 | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| Middle Tertile | 360/3186 | 1.04 (0.83, 1.30) | 0.97 (0.77, 1.21) | 0.90 (0.72, 1.14) |
| Highest Tertile | 371/2684 | 1.36 (1.07, 1.73) | 1.25 (0.98, 1.59) | 1.08 (0.84, 1.39) |
| Total | 1229/9895 | | | |
| *P* for trend | | 0.016 | 0.098 | 0.643 |

**Table 2.** Cross-sectional association of sugar intake from sweet food/beverages and prevalent common mental disorder and depression in men and women[a]. Abbreviations: OR = Odds ratio, CI = Confidence interval, DASH = Dietary Approaches to Stop Hypertension. [a]Cross-sectional association across phases 3, 5, 7, 9 for common mental disorder and 7, 9 for depression. [b]Common mental disorder measured using the 30-item General Health Questionnaire.; [c]CMD model 0 (4675 events/23954 person observations): adjusted for age*sex, ethnicity. [d]Model 1: additionally adjusted for marital status, last grade level in civil service, smoking, alcohol intake, physical activity, sleep duration. [e]Model 2: additionally adjusted for energy intake from other foods, modified DASH diet score, fish, coffee and tea intake. [f]Depression measured using 20-item the Centre of Epidemiologic Studies Depression Scale. [g]Depression model 0 (1313 events/10269 person observations): adjusted for age*sex, ethnicity.

**Cross-sectional results.** Cross-sectional analyses showed strong positive associations between sugar intake from sweet food/beverages and common mental disorder from the GHQ, as well as CES-D caseness, when adjusted for age, sex and ethnicity (Table 2). There was no evidence for any interaction with sex ($P = 0.8$ for GHQ and $P = 0.7$ for CES-D). The association with CMD was robust whereas for depression it was removed on adjustment for socio-demographic factors, health behaviours and diet-related factors (Table 2). Further adjustments for central obesity and physical health (not shown), exclusion of 709 person-observations (377 in CES-D analysis) with reported doctor diagnosis of depression and person-observations with extreme values of sugar intake at baseline did not change the results.

**Prospective results.** Prospective analyses regarding incident CMD were stratified by sex, since interactions with sex were observed in the 5 years later model (LR test for sex interaction: GHQ 2 years later, $P = 0.26$: GHQ 5 years later, $P = 0.05$). In women, no associations were found for incident CMD with tertiles of sugar intake from sweet food/beverages (after 2 years, highest vs. lowest tertile OR: 0.98; 95% CI 0.72, 1.34; *P* for tertile trend = 0.90; after 5 years, highest vs. lowest tertile OR: 0.94; 95% CI 0.74, 1.19; *P* for tertile trend = 0.59). In men, after adjustment for age and ethnicity, sugar intake was associated with incident CMD 2 and 5 years later (Table 3). In further models, the association with 2-year incidence attenuated but the association with 5-year incidence remained (Table 3) and further adjustments for BMI, central obesity and physical health (not shown) resulted in an OR for highest vs. lowest tertile of: 1.23, 95% CI: 1.02, 1.48, *P* for trend = 0.03. Excluding participants who reported a doctor diagnosis of depression at each baseline strengthened the association (Model 4 for CMD after 5 years, Person observations = 10944; highest vs. lowest tertile OR; 1.25; 95% CI 1.03, 1.50; *P* for trend = 0.02,

| | Incident common mental disorder[b] after 2 years, OR (95% CI) | | | |
|---|---|---|---|---|
| | events/person observations | Model 0[c] | Model 1[d] | Model 2[e] |
| Sugar intake from sweet food/beverages | | | | |
| Lowest Tertile | 220/2090 | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| Middle Tertile | 205/1836 | 1.08 (0.85, 1.38) | 1.08 (0.85, 1.38) | 1.04 (0.81, 1.33) |
| Highest Tertile | 202/1615 | 1.31 (1.02, 1.68) | 1.30 (1.01, 1.67) | 1.18 (0.90, 1.55) |
| Total | 627/5541 | | | |
| *P* for trend | | 0.039 | 0.047 | 0.233 |
| | Incident common mental disorder[b] after 5 years, OR (95% CI) | | | |
| | events/person observations | Model 0[f] | Model 1[d] | Model 2[e] |
| Lowest Tertile | 477/4451 | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| Middle Tertile | 446/3958 | 1.05 (0.90, 1.23) | 1.07 (0.91, 1.25) | 1.04 (0.88, 1.22) |
| Highest Tertile | 463/3532 | 1.26 (1.07, 1.48) | 1.28 (1.08, 1.51) | 1.20 (1.01, 1.43) |
| Total | 1386/11941 | | | |
| *P* for trend | | 0.006 | 0.005 | 0.047 |

**Table 3.** Prospective association of sugar intake from sweet food/beverages and incident common mental disorder after 2 and 5 years in men[a]. Abbreviations: OR = Odds ratio, CI = Confidence interval, DASH = Dietary Approaches to Stop Hypertension. [a]Prospective association across phases 3, 5 for 2-year and 3, 5, 7, 9 for 5-year incident common mental disorder. [b]Common mental disorder measured using the 30-item General Health Questionnaire. [c]2-year model 0 (655 events/5767 person observations): adjusted for age and ethnicity. [d]Model 1: additionally adjusted for marital status, last grade level in civil service, smoking, alcohol intake, physical activity, sleep duration. [e]Model 2: additionally adjusted for energy intake from other foods, modified DASH diet score, fish, coffee and tea intake. [f]5-year model 0 (1448 events/12445 person observations): adjusted for age and ethnicity.

Supplementary Table S2) and exclusion of person observations with extremely high sugar intakes did not affect the results. In men and women, no association between sugar intake from sweet food/beverages and incident depression or clinical depression 5 years later was observed (Model 0, highest vs. lowest tertile OR, depression 0.92; 95% CI: 0.71, 1.18; *P* for tertile trend = 0.44; clinical depression: 0.95; 95% CI: 0.51, 1.75; *P* for trend = 0.84). The same exposure contrast was not associated with incident CMD or depression caseness after 10 years (Model 0, highest vs. lowest tertile OR: 1.10; 95% CI: 0.92, 1.31; *P* for tertile trend = 0.31; and 1.17; 95% CI: 0.91, 1.50, *P* for tertile trend = 0.25, respectively). However, sugar intake was positively associated with incident clinical depression after 10 years in men (Model 2 Person observations = 2572, cases = 35; *P* for tertile trend = 0.67), but negatively in women (Person observations = 848, cases = 28; *P* for tertile trend = 0.02).

Prospective analyses regarding the associations of sugar intake from sweet food/beverages and recurrent mood disorders showed no evidence for sex interaction for CMD, CES-D depression or clinical depression 5 years later. Sugar intake from sweet food/beverages was positively associated with recurrent depression after 5 years (Model 0, highest vs. lowest tertile OR: 1.81; 95% CI: 1.23, 2.66; *P* for tertile trend = 0.003, Table 4). The association was attenuated when adjusted for other diet-related factors. Moreover, there was some evidence that sugar intake from sweet food/beverages was associated with recurrent clinical depression in both sexes combined (highest vs. lowest tertile OR: 1.66; 95% CI: 0.96, 2.87 and *P* for tertile trend = 0.07) when adjusted for age, sex and ethnicity (Supplementary Table S3). This association attenuated when further factors were introduced to the model. No statistically significant association was found for sugar intake from sweet food/beverages and recurrent GHQ caseness after 2 and 5 years (Model 0 for CMD after 2 years, highest vs. lowest tertile OR: 1.05; 95% CI 0.76, 1.45; *P* for tertile trend = 0.83; for CMD after 5 years: 1.16; 95% CI 0.93, 1.46; *P* for tertile trend = 0.20).

Analyses of recurrent CMD, depression and recurrent clinical depression after 10 years showed no associations with sugar intake from sweet food/beverages.

Sensitivity analyses excluding extreme values of sugar intake and excluding person-observations with self-reported doctor diagnosis at baseline attenuated the association of sugar intake from sweet food/beverages and recurrent depression slightly (before *P* for tertile trend 0.003 after 0.022 and 0.010, respectively). Similarly, associations with clinical depression weakened when participants with depression diagnosis at baseline were excluded (Model 0, Person observations = 573; cases = 78; *P* for tertile trend = 0.17).

**Analysis of reverse causation.** Sugar intake from sweet food/beverages decreased by 2.00 (SD 28.8; 95% CI 1.20, 2.79) grams per day from phase 3 to 5, by 3.44 (SD 28.0; 95% CI 2.59, 4.30) grams from phase 5 to 7 and by 1.57 (SD 26.0; 95% CI 0.91, 2.33) grams from phase 7 to 9, and was normally distributed. Mean 5-year change was approximately 31 g sugar from sweet food/beverages per day in the decrease group, −0.7 g in the stable intake group and 29 g in the increase group. Neither CMD, nor depression predicted 5-year changes in sugar intake (Table 5).

## Discussion

The present long-term prospective study is the first to investigate the association of sugar consumption from sweet food/beverages with prevalent, incident and recurrent mood disorders, while also examining the effect

| | Recurrent depression after 5 years, OR (95% CI)[b] | | | |
|---|---|---|---|---|
| | events/person observations | Model 0[c] | Model 1[d] | Model 2[e] |
| Sugar intake from sweet food/beverages | | | | |
| Lowest Tertile | 258/848 | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| Middle Tertile | 220/737 | 1.19 (0.83, 1.73) | 1.10 (0.76, 1.60) | 1.05 (0.72, 1.53) |
| Highest Tertile | 263/719 | 1.81 (1.23, 2.66) | 1.60 (1.08, 2.37) | 1.47 (0.98, 2.22) |
| Total | 741/2304 | | | |
| *P* for trend | | 0.003 | 0.017 | 0.071 |

**Table 4.** Prospective association of sugar intake from sweet food/beverages and recurrent depression after 5 years[a]. Abbreviations: OR = Odds ratio, CI = Confidence interval, DASH = Dietary Approaches to Stop Hypertension, CVD = cardiovascular disease. [a]Prospective association across phases 7, 9 for recurrent depression. [b]Depression measured using 20-item the Centre of Epidemiologic Studies Depression Scale. [c]Model 0 (792 events/2435 person observations): adjusted for age*sex, ethnicity. [d]Model 1: additionally adjusted for marital status, last grade level in civil service, smoking, alcohol intake, physical activity, sleep duration. [e]Model 2: additionally adjusted for energy intake from other foods, modified DASH diet score, fish, coffee and tea intake.

these disorders might have on subsequent habitual sugar intake. We found an adverse effect of higher sugar intake on mental health cross-sectionally and 5 years later in a study based on 23,245 repeated measures in men and women aged between 39 and 83. Further, we found an increased likelihood for incident CMD in men and some evidence of recurrent depression in both sexes with higher intakes of sugar from sweet food/beverages. These associations with incident CMD could not be explained by socio-demo graphic factors, other diet-related factors, adiposity and other diseases although the association with recurrent depression was explained by other diet-related factors.

In our study we were able to exclude potential 'reverse causation' as the reason for the observed link between high sugar intake and low mood. Over years and decades, it could be that those susceptible to depression tend to increase their sugar intake. This group may tend to report higher consumption at study baseline even in the absence of depression at the time of the questionnaire, while having an increased risk of future depression compared to other participants[14,15]. However, there was no support for this alternative hypothesis, since the observed associations in our analysis were not the result of secondary changes in consumption of sugary food and drinks. Our study findings are consistent with the hypothesis that high sugar intake plays a causal role in the risks of both incident and recurrent depression and CMD.

Higher sugar intake from sweet food/beverages was associated with increased likelihood of incident CMD after 5 years in men. The association in men was in line with results from previous prospective studies in American and Spanish cohorts[9–11]. There are several potential explanations for the observed sex differences. First, the associations in men for incident CMD show a stronger effect with a bigger sample (comparing analysis of 2-year CMD with 5-year CMD), suggesting the lower number of female participants in our sample could have impaired the power of the analysis. Second, the results might reflect differences in pathways of depression by sex and type of depressive symptomatology[52–54]. Third, differences could be due to limitations of the study or to chance.

As described in the Introduction there are four potential mechanisms for an association of habitual sugar intake and subsequent depression risk. Sugar intake could increase depression risk over its potential influence on BDNF levels[16] and inflammation[20] which are both discussed as potential biological explanations for depression[17,21]. Furthermore postprandial hypoglycaemia[22] and addiction-like effects of sugar influencing neurotransmitters[23–25] could link sugar intake with low mood. The pathway of postprandial hypoglycaemia is also relevant in the context of Glycaemic index, which has been shown to be associated with depression prevalence and incidence[55,56]. However, it is a complex issue to tease apart the effects of a single nutrient in epidemiological studies since foods represent a mix of macro- and micronutrients. In this study associations were attenuated when adjusted for diet-related factors providing evidence of confounding and suggesting that the effect of sugar intake from sweet food/beverages could be partly explained by other components of the diet. Also, given that we analysed sugar intake from aggregated sweet foods and beverages we cannot rule out that certain types of foods and their particular components such as saturated fat content may have affected our findings. In our analysis, the association of sugar intake and recurrent depression was attenuated by measures of body fatness in participants without doctor diagnosis of depression at baseline supporting the hypothesis of an indirect effect mediated by adiposity[26–28] driving the association of sugar intake and recurrent depression.

Meanwhile, there are several sources of possible error. Our study was based on an occupational cohort but sugar intakes from sweet food/beverages were close to those reported previously in a representative cohort in the UK (approximately 40 grams), and Batty *et al.* showed that effects found in Whitehall II were comparable to those observed in population-representative cohorts[3,57]. A major limitation was the use of FFQ to derive diet data. FFQ data is subject to misreporting and underreporting, which have been found to differ by food group, depressive mood and BMI[58–60]. As reported previously in Whitehall, we showed a clear trend of lower sugar intake with higher BMI in men[60]. Nutrient content was based on food composition tables from 1991 and has to be considered

| | 5-year change in sugar intake | | | |
|---|---|---|---|---|
| | No. of events | Participants | OR (95% CI) *β-Coefficient*[a] *(95% CI)* | *P* |
| Common mental disorder[b] | | | | |
| At phase 3 – Sugar intake change: phase 3 to 5 | | | | |
| Reduction | 268 | 1201 | 1.0 (reference) | |
| No change | 584 | 2860 | 0.91 (0.77, 1.08) | 0.27 |
| Increase | 198 | 961 | 0.91 (0.74, 1.12) | 0.39 |
| Continuous change in grams per day | 1050 | 5022 | *0.08 (−1.89, 2.05)* | 0.94 |
| At phase 5 – Sugar intake change: phase 5 to 7 | | | | |
| Reduction | 210 | 1025 | 1.0 (reference) | |
| No change | 464 | 2410 | 0.93 (0.77, 1.11) | 0.41 |
| Increase | 176 | 734 | 1.21 (0.96, 1.53) | 0.10 |
| Continuous change in grams per day | 850 | 4169 | *1.18 (−0.97, 3.33)* | 0.28 |
| At phase 7 – Sugar intake change: phase 7 to 9 | | | | |
| Reduction | 200 | 744 | 1.0 (reference) | |
| No change | 505 | 2206 | 0.87 (0.73, 1.05) | 0.15 |
| I ncrease | 150 | 692 | 0.84 (0.66, 1.06) | 0.14 |
| Continuous change in grams per day | 855 | 4497 | *−1.14 (−3.09, 0.82)* | 0.26 |
| Depression[c] | | | | |
| At phase 7 – Sugar intake change: phase 7 to 9 | | | | |
| Reduction | 116 | 764 | 1.0 (reference) | |
| No change | 340 | 2233 | 1.05 (0.83, 1.32) | 0.70 |
| Increase | 97 | 688 | 0.98 (0.73, 1.32) | 0.90 |
| Continuous change in grams per day | 533 | 4238 | *1.01 (−1.35, 3.36)* | 0.40 |

**Table 5.** Association of common mental disorder and depression with subsequent 5-year change in sugar intake from sweet food/beverages. Abbreviations: No. = number, CI = confidence interval. [a]Change in sugar intake in cases compared with non-cases, adjusted for age, sex and ethnicity. [b]Common mental disorder measured using the 30-item General Health Questionnaire. [c]Depression measured using 20-item the Centre of Epidemiologic Studies Depression Scale.

as a source of error, since food composition especially of highly processed food is likely to change over the course of 18 years. In this long-term follow-up study, sugar intake from sweet food/beverages, which are consistently high in sugar content, has been used as the exposure measure. Compared to a measure of intake that includes processed foods[61], this method may involve less information bias. Furthermore, this FFQ is meant to reflect habitual diet over the course of a year and therefore might not pick up short-term diet changes or occasional binge eating[30]. Although we adjusted for a number of potential confounders, we cannot rule out residual confounding through unknown or unmeasured factors. Finally, not all depression measures were obtained in all phases and selective dropout due to depressive symptoms might have influenced case numbers[62].

In conclusion, our study provides evidence that sugar intake from sweet food/beverages increases the chance of incident mood disorders in men and limited evidence regarding recurrent mood disorders in both sexes. With a high prevalence of mood disorders, and sugar intake commonly two to three times the level recommended, our findings indicate that policies promoting the reduction of sugar intake could additionally support primary and secondary prevention of depression. To elucidate the association further, especially regarding observed sex differences our study should be replicated in representative prospective cohorts.

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## Author Contributions
E.J.B., A.K. and M.J.S. designed research; A.K. analysed the data; A.K., E.J.B., M.J.S., C.H.L. wrote the paper; E.B. had primary responsibility for final content. All authors read and approved the final manuscript.

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**Sugar intake from sweet food and beverages, common mental disorder and depression: prospective findings from the Whitehall II study**

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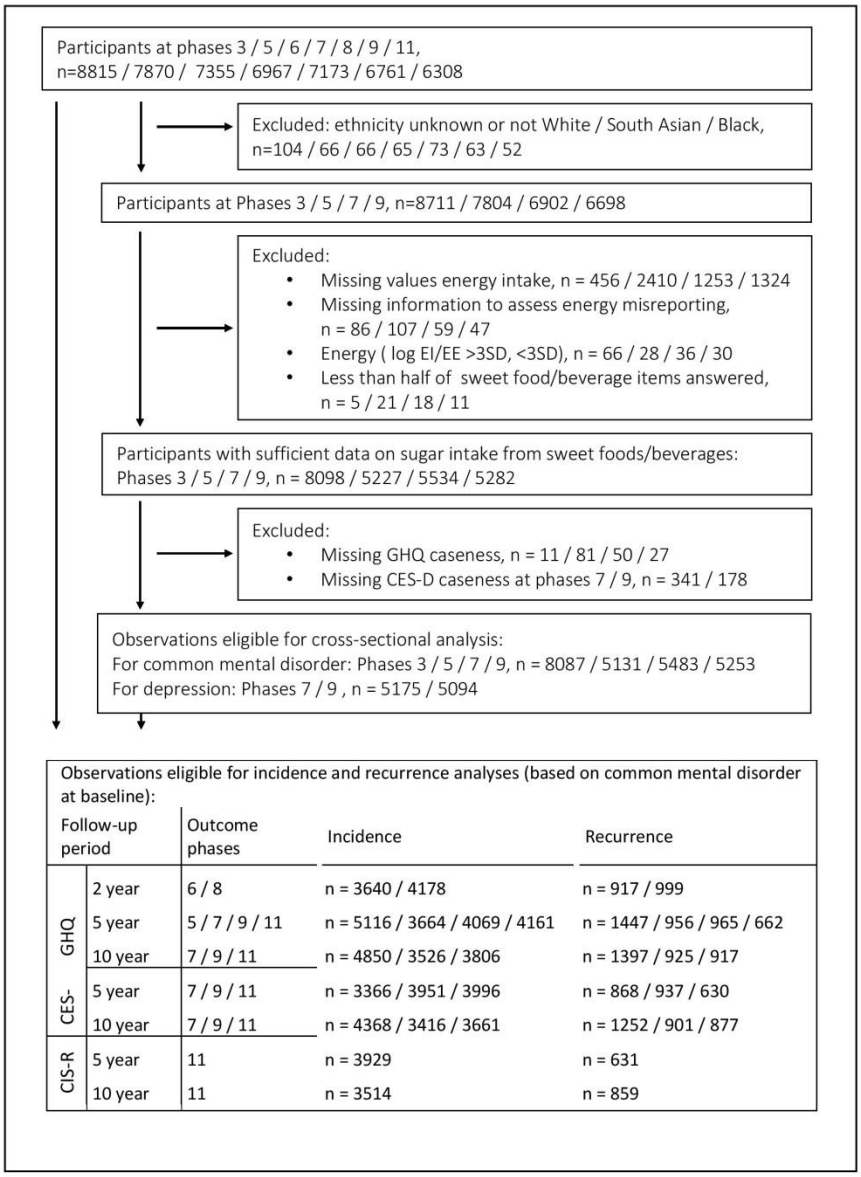


Observations eligible for incidence and recurrence analyses (based on common mental disorder at baseline):

| | Follow-up period | Outcome phases | Incidence | Recurrence |
|---|---|---|---|---|
| GHQ | 2 year | 6 / 8 | n = 3640 / 4178 | n = 917 / 999 |
| | 5 year | 5 / 7 / 9 / 11 | n = 5116 / 3664 / 4069 / 4161 | n = 1447 / 956 / 965 / 662 |
| | 10 year | 7 / 9 / 11 | n = 4850 / 3526 / 3806 | n = 1397 / 925 / 917 |
| CES- | 5 year | 7 / 9 / 11 | n = 3366 / 3951 / 3996 | n = 868 / 937 / 630 |
| | 10 year | 7 / 9 / 11 | n = 4368 / 3416 / 3661 | n = 1252 / 901 / 877 |
| CIS-R | 5 year | 11 | n = 3929 | n = 631 |
| | 10 year | 11 | n = 3514 | n = 859 |

**Figure S1 Inclusion of person observations by phase**
Abbreviations: GHQ = General Health Questionnaire, CES-D = Centre of Epidemiologic Studies Depression Scale, CIS-R = revised Clinical Interview Schedule.

| Sweet food | Beverages |
|---|---|
| sweet biscuits | fizzy soft drinks |
| buns or pastries | fruit squash or cordial |
| Cakes | fruit juice |
| chocolates or chocolate bars | malted milk drinks, such as Horlicks |
| fruit pies, tarts or crumbles | cocoa or hot chocolate |
| ice cream | |
| jam, marmalade or honey | |
| milk puddings, sponge puddings | |
| added sugar | |
| sweets, toffees or mints | |
| | |

**Table S1 Sources of sugar intake from sweet food/ beverages**

| | Incident common mental disorder[b] after 2 years, OR (95% CI) | | | |
|---|---|---|---|---|
| | events / person observations | Model 0[c] | Model 1[d] | Model 2[e] |
| Sugar intake from sweet food/beverages | | | | |
| Lowest Tertile | 214 / 2059 | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| MiddleTertile | 194 / 1799 | 1.05 (0.82 ,1.34) | 1.05 (0.82 ,1.34) | 1.00 (0.78 ,1.29) |
| Highest Tertile | 196 / 1581 | 1.33 (1.03 ,1.71) | 1.31 (1.01 ,1.70) | 1.19 (0.90 ,1.56) |
| Total | 604 / 5439 | | | |
| *P* for trend | | 0.032 | 0.045 | 0.234 |
| | | | | |
| | Incident common mental disorder[b] after 5 years, OR (95% CI) | | | |
| | events / person observations | Model 0[f] | Model 1[d] | Model 2[e] |
| Sugar intake from sweet food/beverages | | | | |
| Lowest Tertile | 463 / 4391 | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| MiddleTertile | 434 / 3886 | 1.06 (0.90 ,1.24) | 1.08 (0.92 ,1.27) | 1.05 (0.89 ,1.24) |
| Highest Tertile | 456 / 3467 | 1.30 (1.10 ,1.54) | 1.32 (1.11 ,1.56) | 1.24 (1.04 ,1.48) |
| Total | 1353 / 11744 | | | |
| *P* for trend | | 0.002 | 0.002 | 0.019 |
| | | | | |

**Table S2 Prospective association of sugar intake from sweet food/beverages and incident common mental disorder after 2 and 5 years in men excluding participants with self-reported doctor diagnosed depression at each baseline[a]**

Abbreviations: OR = Odds ratio, CI = Confidence interval, DASH = Dietary Approaches to Stop Hypertension.

[a]Prospective association across phases 3, 5 for 2-year and 3, 5, 7, 9 for 5-year incident common mental disorder.

[b]Common mental disorder measured using the 30-item General Health Questionnaire.

[c]2-year model 0 (631events / 5661 person observations): adjusted for age, ethnicity.

[d]Model 1: additionally adjusted for marital status, last grade level in civil service, smoking, alcohol intake, physical activity, sleep duration.

[e]Model 2: additionally adjusted for energy intake from other foods, modified DASH diet score, fish, coffee and tea intake.

[f]5-year model 0 (1413 events / 12238 person observations): adjusted for age, ethnicity.

| | Recurrent clinical depression after 5 years[b], OR (95% CI) | | | |
|---|---|---|---|---|
| | | Model 0[c] | Model 1[d] | Model 2[e] |
| Sugar intake from sweet food/beverages | | | | |
| Lowest Tertile | 27 / 236 | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| MiddleTertile | 26 / 182 | 1.37 (0.79, 2.40) | 1.23 (0.68, 2.24) | 1.11 (0.60, 2.05) |
| Highest Tertile | 29 / 172 | 1.65 (0.96, 2.87) | 1.58 (0.87, 2.86) | 1.24 (0.67, 2.31) |
| Total | 82 / 590 | | | |
| *P* for trend | | 0.07 | 0.13 | 0.50 |
| | | | | |

**Table S3 Prospective association of sugar intake from sweet food/beverages and recurrent clinical depression after 5 years[a]**

Abbreviations: OR = Odds ratio, CI = Confidence interval, DASH = Dietary Approaches to Stop Hypertension.

[a]Prospective association across phase 9 to 11.

[b]Clinical depression measured using the revised Clinical Interview Schedule.

[c]Clinical depression model 0 (92 events / 631 participants): adjusted for age*sex, ethnicity.

[d]Model 1: additionally adjusted for marital status, last grade level in civil service, smoking, alcohol intake, physical activity, sleep duration.

[e]Model 2: additionally adjusted for energy intake from other foods, modified DASH diet score, fish, coffee and tea intake.

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