ULTRA-PROCESSED FOODS AND CARDIOMETABOLIC HEALTH

PhD thesis

of

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DECLARATION

This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration except where specifically indicated in the text.

It is not substantially the same as any that I have submitted, or, is being concurrently submitted for a degree or diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text.

I further state that no substantial part of my thesis has already been submitted, or, is being concurrently submitted for any such degree, diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text.

All the research presented in this dissertation was conducted at the MRC Epidemiology Unit and the Centre for Diet and Activity Research (CEDAR), under the supervision of Martin White and Jean Adams.

This dissertation does not exceed 60 000 words excluding references, tables, figures and appendixes, as prescribed by the Degree Committee of the Faculty of Clinical Medicine.

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KAI SCHULZE – ULTRA-PROCESSED FOODS AND CARDIOMETABOLIC HEALTH – PHD ABSTRACT

The overall aim of my thesis was to investigate the associations between ultra-processed food consumption (UPF) and cardiometabolic health at the individual and the population-level, while adhering to methodological principles such as incorporating and presenting a multiverse of statistical results and interpreting statistical hypothesis testing in a non-dichotomous way. I addressed these aims in three studies: a systematic review and meta-analysis of 41 prospective cohort studies, an ecological, longitudinal cross-country comparison, and a prospective analysis in the UK EPIC-Norfolk cohort. The research presented in this dissertation revealed consistent associations between UPFs and adverse cardiometabolic health.

The results of the systematic review and meta-analyses of chapter 2 provided the first systematic analysis of published nutritional epidemiology studies from the perspective of food processing. I defined UPF consumption more broadly and identified studies in which UPF consumption had been termed in several different but related ways, such as fast, convenience, or Western foods. I combined those diets and dietary pattern studies that were characterized by a higher relative intake of UPFs in non-linear and summary random-effects meta-analysis estimates. Higher intakes of UPFs were associated with both an increased risk of cardiovascular diseases (CVD) and type 2 diabetes mellitus (T2DM).

Higher sales of UPF were associated with an increased risk of adiposity and diabetes mellitus in the country-level analysis in chapter 3, using data from 76 countries across all five continents over 16 years. The panel analysis demonstrated that a strong and consistent association existed between the sales of UPFs at the food system level and adiposity and diabetes prevalence in low-to-middle-income countries (LMICs) for children, adolescent, and adult populations, as well as for both sexes separately. This finding adds value to the literature because no previous study had systematically investigated these associations in countries in which often a lack of individual data exists and had estimated associations for LMICs and high-income countries (HICs) separately. However, the analysis did not establish an association between UPF and adiposity in HICs, which was surprising, given that previous studies indicating an association at the individual level were mostly from HICs. The lack of variability in UPF data from HICs during the study period were likely a key reason for the lack of estimated associations in HICs. As a consequence of the many combinations of data processing and analytical methods and the variability of point estimates and P-values, no particular set of point estimates was emphasized, but the consistency

of findings indicate that the expansion of global adiposity and diabetes since 2000 can partially be attributed to the increased sales of UPFs, at the level of the food system or country.

The associations that were found in the meta-analysis and the panel study were replicated in prospective analyses of detailed data from over 17,000 individuals in the EPIC-Norfolk cohort, yielding associations between increased UPF intake and adiposity as well as risk of T2DM and CVD. This study demonstrated that the way UPF intake is operationalized can fundamentally influence results. Previous UPF studies had only expressed UPFs as weight or the proportion of food weight, with the justification that energy measures would not capture the non-calorific components of UPFs with potentially adverse effects on health. Guided by previous nutritional epidemiological research to adjust for total energy intake, I modelled UPF and disease risks in five different ways. The analyses revealed that these different approaches affect the statistical results, but also that they affect the results differently for different diseases. For example, the differences between measures of UPF intake based on energy and weight were much more pronounced for T2DM as an outcome than for CVD, suggesting that potentially different mechanisms relating to dietary energy and other factors common to UPFs might be responsible for different outcomes.

Chapter four was also the first research to comprehensively test the associations between UPF and three important cardiometabolic disease outcomes (adiposity, T2DM, and CVD) in a prospective cohort with a long follow-up period. The findings of an almost consistent positive association provide the strongest evidence to date that UPFs are positively associated with adverse risk of cardiometabolic health. The secondary analyses of eight different food groups and outcomes indicated that greater consumption of ultra-processed meat, fish, and eggs; fast foods; and SSBs are associated with an increased risk of T2DM and CVD, whereas consumption of ultra-processed fruits and vegetables, milk and diary, fats, and breads and cereals might not be associated with an increased risk of disease. Body weight is likely a very important mediator of the association between UPF and T2DM and CVD, while increased total energy intake through UPFs is likely the most important driver of the UPF-adiposity association.

ACKNOWLEDGEMENTS

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List of Abbreviations and Acronyms

95% CI	95 per cent confidence Intervals
$	US Dollar
%	Percentage
£	GB Pound
<	Less then
>	Greater then
≤	Less than or equal to
≥	Greater than or equal to
BMI	Body-Mass-Index
CIs	Confidence intervals
cm	centimetres
CRA	Comparative risk assessment
CVD	Cardiovascular diseases
DM	Diabetes mellitus
E.g.	Exempli gratia or “for example”
FDBGs	Food-based dietary guidelines
FI	Fumiaki Imamura
HICs	High-income countries
IDF	International Diabetes Federation
IGT	Impaired glucose tolerance
I.e.	Id est or “That is”
JA	Jean Adams
Kg	Kilogram
KS	Kai Schulze
LICs	Low-income countries
LMICs	Low-to-middle income countries

MW	Martin White
N	Number (used to indicate number of participants in a study)
NCDs	Non-communicable diseases
NCD RisC	NCD Risk Factor Collaboration database
NHS	National Health Service
NHST	Null-hypothesis significance testing
OR	Odds ratio
HR	Hazard ratio
RCT	Randomized controlled trial
SD	Standard deviation
SSBs	Sugar-sweetened beverages
T1DM	Type 1 Diabetes mellitus
T2DM	Type 2 Diabetes mellitus
UK	United Kingdom
US	United States
UPFs	Ultra-processed foods
WHO	World Health Organization
Q1	First quintile
Q5	Fifth quintile

LIST OF APPENDICES

1 BACKGROUND

'The doctor of the future will give no medicine but will instruct his patient in the care of the human frame, in diet and in the cause and prevention of disease.'

(Thomas Edison, ca. 1903)

In 2018, more than 2.5 billion adults and 400 million children - nearly 40% of the global population – were overweight or obese and therefore at risk of developing type 2 diabetes mellitus (T2DM).[1] Since 1980, global obesity prevalence has doubled, and diabetes prevalence quadrupled, while cardiovascular diseases (CVD) remain the leading cause of death worldwide.[2] The associated annual economic burden of overweight, obesity, diabetes, and CVD on global health-care systems and the wider global economy has been estimated to exceed US$3.5 trillion each year.[1,3–6] While this "slow-motion disaster" (Margaret Chan)[7] now encompasses countries at almost all stages of development, the issue is likely to intensify if the current trends continues, given that no country has been able to reverse its obesity pandemic in all age groups.[8]

Suboptimal nutrition is a leading risk factor of these three related conditions, in high-income countries and increasingly in low- to middle-income countries as well.[3,9] Despite decades of debates and nutrition recommendations, global efforts to prevent diet-related chronic diseases can reasonably be considered a failure. Nutrition did not have its own Millennium Development

Goal and is still not part of the Sustainable Development Goals in a holistic manner, as Goal number two – zero hunger – captures only one aspect of malnutrition.[10]

In the past decade, the relationship between the global food system and diet-related conditions and diseases has become better understood. Globalization and the emergence of globalized food and beverage corporations have changed the nature of food systems with mass-produced and highly- or ultra-processed foods (UPFs) beginning to predominate. When I set out the plan for my PhD in 2015, little systematic research had been undertaken about the associations between UPFs and cardiometabolic health, especially regarding T2DM and CVD. The research included in this dissertation contributes to filling these gaps in the evidence through investigating UPFs from different perspectives and in different analyses. In this introductory chapter, I will provide the background needed to meet these aims and will introduce the concepts that are used throughout the thesis.

The first part will define the three cardiometabolic health outcomes included: adiposity, T2DM, CVD, and briefly summarize their global trends and risk factors. Secondly, I will give a short history of food processing, introduce and discuss the NOVA classification that will be used throughout the PhD to classify foods according to their degree of food processing, and briefly review key evidence from previous epidemiological and public health research on food processing. Finally, I will discuss reasons for the replication crisis in science, and outline the methodological approaches taken in this PhD to address these.

1.1 Definition and epidemiology of cardiometabolic health

1.1.1 Defining and classifying adiposity, T2DM, and CVD

1.1.1.1 Classifications of body weight

Adiposity or obesity is a condition characterized by excessive body fat that can have adverse health effects and is officially recognized as a disease by the American and Canadian Medical Associations as well as by few countries such as Portugal.[11] At present, the most commonly used

measurement determines the weight relative to height as the body mass index (BMI), calculated by dividing the weight (in kilogram) by the square of the height (in meters).[12] A given adult BMI can be classified into categories ranging from underweight (BMI < 18.5) to morbidly obese (BMI >= 40). A BMI between 18.5 and 24.9 kg/m^2 corresponds to a healthy weight, a BMI between 25.0 and 29.9 kg/m^2 is considered overweight, and a BMI of ≥30.0 kg/m^2 is defined as obese. Obesity itself is again classified separately: Class 1 (or mild) obesity is considered between a BMI of 30.0 and 34.9 kg/m^2, 35.0 to 39.9 kg/m^2 is class 2 (or moderate) obesity, and ≥40.0 kg/m^2 is classified as class 3 (or severe) obesity.[13]

Different BMI cut-offs for different ethnicities have been discussed in previous research. After 20 years of following initially healthy women, the Nurses' Health Study in the United States (US) has demonstrated that, at the same BMI, Asians had a more than double risk of developing T2DM than whites, and Hispanics and Blacks had a higher risk of disease as well, albeit to a lesser extent.[14] Reasons remain a matter of scientific debate, but a likely explanation is the distribution and percentage of body fat, as well as lean body mass.

The distribution of body fat is clinically relevant and can be very variable. For example, for two individuals of the same BMI, one can be metabolically healthy obese, whereas the other could have numerous metabolic abnormalities, including insulin resistance, dyslipidaemia, hypertension, etc.[15] Higher amounts of visceral fat, for example, which surrounds the organs and is indicated by a higher waist circumference or waist-to-hip ratio, is associated with adverse cardiovascular outcomes and metabolic syndrome.[16] At the same BMI, Asians have 3 to 5 percent higher total body fat and are more likely to develop abdominal obesity, which might partially explain the higher risk of T2DM and CVD.[17] Conversely, studies have shown that at the same BMI, blacks have a lower body fat and higher lean muscle mass than whites.[18,19] Due to a lack of scientific agreement and the variability of observed risks at the same BMI within different Asian populations, alternative cut-off points for Asian populations have not been generally adopted or officially recommended by the World Health Organization (WHO).[20] However, with

the emergence of new evidence, several entities have started to use different cut-offs. For example, China and Japan define overweight and obesity as a BMI of 24 (or higher) and as a BMI of 28 (or higher), respectively.[21]

Given these debates, additional measurements such as waist circumference, fat-mass percentage, or waist-to-hip ratio are used in research to discriminate further the distribution of fat and source of adiposity. A waist circumference of >= 80 cm in European women and >= 94 in European men or >= 80 and >= 90 cm in South Asians, Chinese, and Japanese women and men, respectively, is defined as indicating an increased cardiovascular risk.[16,22,23] Further research has found waist-to-height ratio (as a measure of 'central' obesity) to be a better *single* predictor of 'early health risks' than BMI and waist-circumference.[24] However, these predictive properties were not tested in the context of multivariable modelling. Furthermore, comparisons between different measures of adiposity have displayed high correlations between BMI and other indices of body adiposity (over 0.8 in all cases)[25]. Thus, at the population-level, BMI indicates obesity well and continues to be the most commonly used measure of obesity, despite some advantages of alternative measurements at the individual level.[26]

Body weight and adiposity in children are classified using different definitions than in adults due to the variation of body composition between different age periods and sexes. Generally accepted as the reference definition for children up to the age of five years are the Child Growth Standards by the WHO, which are derived from data from children of all world regions that were born and raised under optimal conditions.[27] The WHO growth reference data complements the growth standards with data for children and adolescents of ages 5-19 years. Some countries publish and use country-specific reference estimates which are derived from historic data on the development of children in that country. In the US, for example, the Centers for Disease Control and Prevention use the WHO standards for children younger than two years but have different cut-off points for overweight and obesity expressed as percentiles of the BMI distribution in older age brackets.[28]

1.1.1.2 Classification and diagnosis of diabetes mellitus

Type 1 diabetes mellitus (T1DM) is a severe and lifelong condition where the immune system damages the cells that produce insulin, which in turn causes high blood glucose levels that can lead to various adverse health conditions and early death.[29] The sudden commencement of T1DM and, consequently, the usually fast contact with the health care system enable a correct recording of new cases. The main aetiological factors of T1DM include genetic susceptibility and environmental factors especially during the early years of life, whereas diet has only a minor role in the aetiology of T1DM.[29,30] Since diet is the main subject-matter of this PhD, T1DM will not be examined. However, due to reasons of data availability, it was not possible to differentiate between type 1 and type 2 diabetes in the analyses of chapter 3.

Type 2 diabetes mellitus is a largely preventable condition.[31] In T2DM, either the insulin producing beta cells in the pancreas do not produce enough insulin, or the cells of the muscles, fat, and liver do not react enough to insulin and cannot take up glucose from the blood, or both. The classification and diagnosis of T2DM is challenging due to its slow development and unclear starting point, a lack of definite and clear-cut metabolic signals, and an elongated pre-detection period.[32] An accurate time of onset is therefore hard to determine and a significant number of undiagnosed cases exists, the proportion varying by place, time, and population. Three test methods for detecting T2DM are common in epidemiological research - the oral glucose tolerance test, fasting plasma glucose tests, and tests for the concentration of glycated haemoglobin (HbA1c test). In 2006, WHO criteria recommended diagnosis of T2DM based on symptoms of diabetes mellitus (i.e. polyuria or polydipsia) and one of the three following criteria: a random venous plasma glucose concentration of ≥ 11.1 mmol/l, a fasting plasma glucose concentration of ≥ 7.0 mmol/l (whole blood ≥ 6.1 mmol/l), or a two-hour post-challenge glucose of ≥ 11.1 mmol/l using a 75g anhydrous glucose in an oral glucose tolerance test. The cut-off diagnostic criteria for the glycated haemoglobin (HbA1c) test as defined by the WHO are HbA1c levels of ≥ 48 mmol/mol or 6.5%.

The diagnostic accuracy of these different tests remains a matter of continuing debate. For example, a study that was presented recently at the Endocrine Society's annual meeting 2019 indicated that diabetes diagnoses defined solely by HbA1c are highly unreliable, with a strong tendency for underestimation of the prevalence of diabetes and overestimation of normal glucose tolerance.[33] Additionally, the measurement of fasting glucose alone has been found to underestimate the prevalence of diabetes by 20-25%.[34] For this and other reasons, some researchers have argued that the global and national diabetes prevalence rates that are published regularly by the International Diabetes Federation (IDF) and the WHO underestimate actual prevalence rates.[35]

1.1.1.3 Classification of cardiovascular disease

CVD is a group of disorders of the heart and blood vessels which comprise a number of sub-diseases: coronary heart disease (blockage of blood vessels supplying the heart muscle), cerebrovascular diseases (blockage of blood vessels supplying the brain), peripheral arterial disease (blockage of blood vessels supplying arms and legs), rheumatic heart disease (heart and heart valve damage from rheumatic fever), congenital heart disease (malfunction of heart structure from birth), and deep vein thrombosis and pulmonary embolism (blood clots in the leg veins that can dislodge to heart and lungs).[36,37]

The classification and diagnosis of cardiovascular disease will, depending on the suspected type, involve a series physical tests such as, blood tests, chest x-ray, electrocardiogram, Holter monitoring, echocardiogram, stress tests, cardiac catherization, cardiac computerized tomography scan, or cardiac magnetic resonance imaging. CVD outcomes investigated in the subsequent chapters are specified by ICD9 codes 401-448 or ICD10 codes I10-I79. Extensively listing over 100 disease classifications for these CVD outcomes would be beyond the scope of this introduction; however, all data on CVD incidence or mortality that is used in this PhD is based on objective diagnoses by trained medical personnel.

1.1.2 Overview of global trends in adiposity, T2DM, and CVD

Globally increasing rates of overweight, obesity and T2DM are major drivers of the pandemic of non-communicable diseases (NCDs) pandemic.[38]

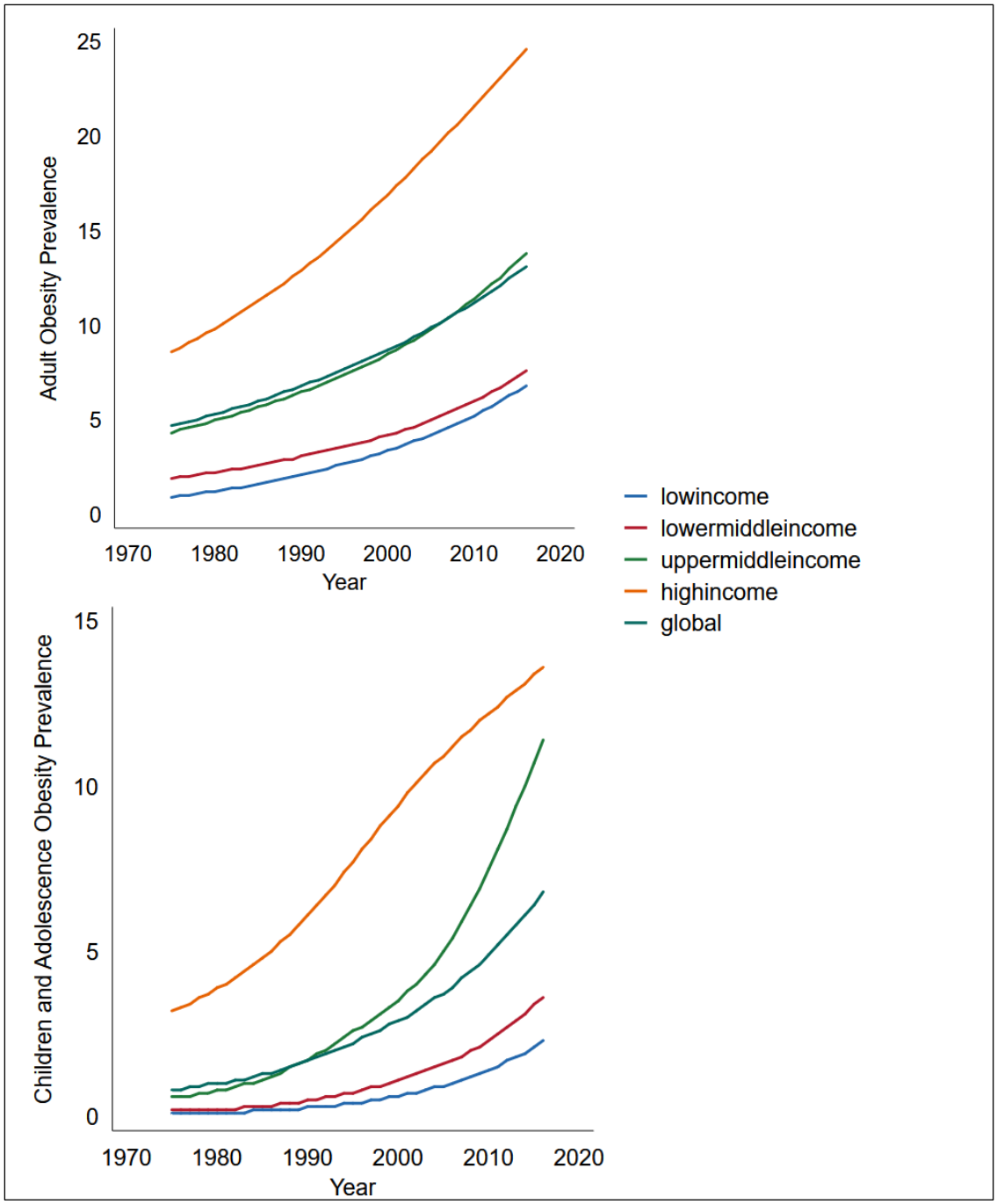

Figure 1.1 Trends in obesity prevalence
In adults (top), and children and adolescents (bottom) between 1975 and 2015, data from NCD RisC 2016 and 2017.[2,39]

The first signs of the obesity epidemic were visible in high-income countries (HICs), especially in Europe and the United States (see Figure 1.1.).[16]

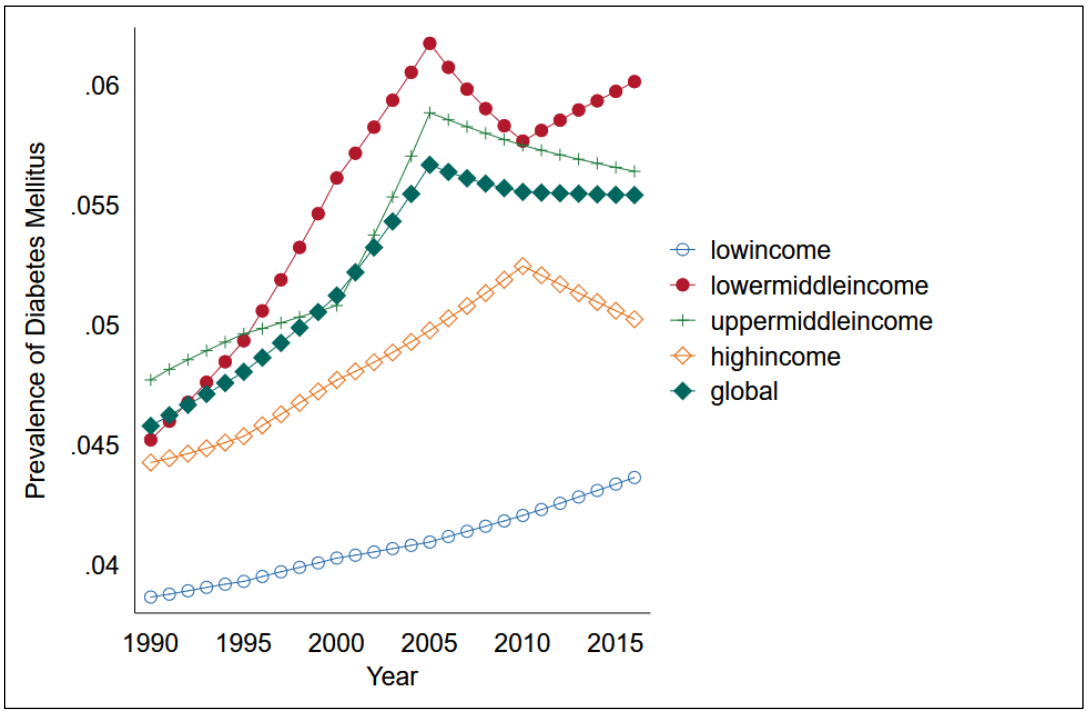

Figure 1.2 Trends in T2DM prevalence
In adults between 1990 and 2015, data from NCD RisC (2016).[2]

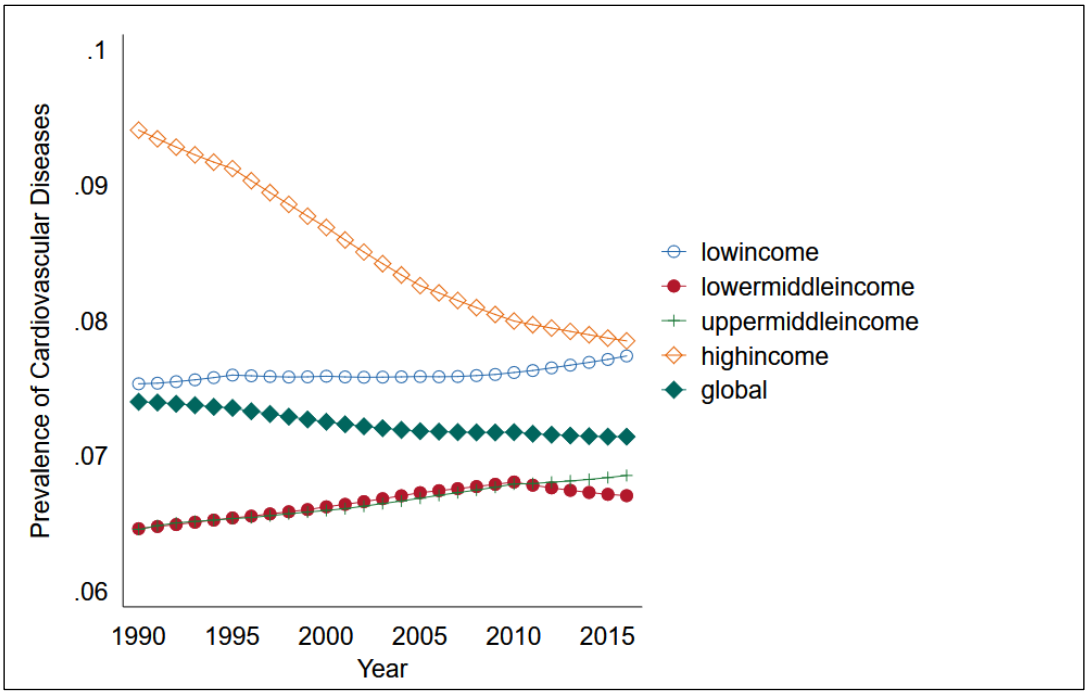

Figure 1.3 Trends in cardiovascular disease prevalence
In adults between 1990 and 2015, data from NCD RisC (2016).[2]

In 1975, the age-standardized adult obesity prevalence rates were 0.9% in low-income countries (LICs), 1.9 in low-to-middle income countries (LMICs), 4.3% in upper-middle income countries (UMICs), and 8.6% in HICs, while the global prevalence rate was 4.7%. The gap between HICs and the other regions was more pronounced in children and adolescents, where the prevalence

was 3.2% in HICs and below 0.5% elsewhere with an overall global prevalence of 0.8%. Although obesity prevalence has changed dramatically in both adult and children and adolescents in the last 40 years, changes happened with slightly different trajectories in these two populations.

Whereas the tripartite structure of HICs, UMICs, and LMICs and LICs continued in adult obesity over time, the obesity prevalence of children in UMICs has almost caught up with that of HICs. It should be noted that there is considerable disparity between sexes and the countries within income groups. For example, surveys have shown prevalence rates of 6.2% and 4.0% in French women and men (1994-1996), while in the Czech Republic (which is also a high income country) the prevalence was 32.2% for women and 30.0% for men at the same time.[40] Differences occur also between countries and sexes in the low-income setting: in Eritrea, the obesity prevalence is 2.0% in men and 7.6% in women, while Ghanaian women have 16.6% obesity prevalence, whereas 4.5% of the Ghanaian men are obese.[39]

The global increase in diabetes mellitus prevalence came to a halt in 2005 because of the declining prevalence in UMICs and LMICs, while the prevalence continued to increase in HICs until 2010 and in LICs until today (see Fig 1.2). Different from obesity, the highest prevalence rates are currently not in high-income countries. In 2016, the estimates for LICs, LMICs, UMICs, and HICs are 4.3%, 6.0%, 5.3%, and 5.0% respectively, implying that globally over 400 million individuals currently have a largely preventable condition. If impaired glucose tolerance (IGT) is considered as well, another 350 million individuals are added to the total number affected.[41] When both diabetes and IGT in adult populations are considered, the global prevalence in 2017 was estimated at 16.1% of adults aged between 20 and 79 years. Limitations in screening and diagnosis implicate uncertainty in the estimates as well as a high proportion of people living with undiagnosed diabetes, which has been estimated to be an additional 212 million people globally.[42]

In 2015, cardiovascular diseases were the prime cause of mortality – 17.7 million individuals died in 2015 (31% of all deaths globally), and 75% of those deaths took place outside of HICs. The

trends of age-standardized cardiovascular disease prevalence differ from obesity and diabetes mellitus (see Figure 1.3). Globally, the prevalence of CVD has fallen slightly from 7.4% in 1990 to 7.1% in 2016, which was mostly driven by the decline in HICs from 9.4% to 7.9%, while the prevalence in the other income groups has been slowly increasing. Out of all premature deaths (under the age of 70), a third are caused by cardiovascular diseases. Another notable difference, compared to obesity and diabetes, is the high prevalence of CVD in LICs which has almost fully converged to HIC levels with 7.7% in 2016. Rates in LMICs and UMICs do not substantially differ and have risen from both 6.5% in 1990 to 6.7% and 6.9%, respectively.

The differing trends between obesity and diabetes on the one hand and CVDs on the other hand need some further context. After a gradual increase over 60 years, the decline in age-standardized CVD prevalence and mortality rates became first apparent in the 1970s; throughout the industrialized world, for example, mortality from coronary heart disease and stroke had decreased to about one-third of their 1960s values by 2000. Modelling studies have demonstrated that this remarkable reduction was partially due to significant improvements in prevention and treatment, which included a steep fall in cigarette smoking, progress in treatment and control of hypertension, broader use of statins to decrease cholesterol levels, as well as development and use of stents and thrombolysis in coronary syndromes to limit and prevent infarctions.[43] However, the evidence does not exhaustively explain the decline, and furthermore, first signs of reversal in certain populations are emerging. Globally, the decline seems to have abated for now.

After having described global trends of the three cardiometabolic health conditions, the next section will briefly describe some of the important risk factors of these three related conditions.

1.1.3 Risk factors for adiposity, T2DM, and CVD

Risk factors for cardiometabolic health can be conceptualized along two dimensions: first, along modifiable and non-modifiable risk factors, and secondly along three broad “level-groupings” of individual, socio-economic, and environmental risk factors. Some important risk factors are

summarized in Figure 1.4. Risk factors rarely occur in isolation and often interact and cluster in individuals.[44] For example, at a fundamental level, changes in body weight result from an imbalance between calories consumed and calories spent, which is the result of individual dietary behaviours. Unhealthy individual food choices (e.g. foods with high calorific value, high palatability, but low nutrient density) might affect the calorie intake, but the individual choices themselves can partially be the result of socioeconomic factors such as income and education, or environmental risk factors such as living in an area with little access to healthy foods (so called 'food deserts') or a social environment that promotes obesogenic behaviours.[16]

Non-modifiable risk factors for obesity include age, sex, ethnicity, genetics, and family history of obesity. Modifiable risk factors include dietary factors such as total energy intake, physical activity, a sedentary lifestyle, little or too much sleep, mental health (e.g. depression or stress), or drugs. As mentioned, important socioeconomic risk factors are income and education, and in terms of environmental risk factors the geographic location (i.e. the built environment) and social networks are important. Additionally, recent research suggests that environmental pathogens such as viruses or other organisms that affect the microbiome play a role in obesity.

Global increases in T2DM are closely tied to increasing rates of obesity in adults, children and adolescents, given that obesity and overweight have been found to be the strongest predictor of T2DM in prospective epidemiological studies.[45] Studies of the European Prospective Investigation into Cancer (EPIC) have also demonstrated that the effect of weight changes on T2DM is more pronounced for younger adults than weight changes after the age of 40.[45] However, weight gain does not affect the T2DM risk of all individuals in the same way. As was introduced above regarding ethnic differences, the existence of a 'metabolically obese' phenotype has been proposed as an explanation for the disparity between obesity and T2DM in Asian populations.[46]

Higher levels of visceral fat and abdominal adiposity have been demonstrated to be independent risk factors for insulin resistance, T2DM, and other cardiovascular disease factors.[31] Yet, some

debate exists about whether non-alcoholic fatty liver disease or visceral fat is a better predictor of T2DM. It has been argued that fat accumulation in the liver determines hepatic insulin resistance and beta-cell dysfunction, and a meta-analysis of prospective cohorts has shown that non-alcoholic fatty liver was more strongly associated with insulin resistance than abdominal fat.[45,47] All the risk factors mentioned for obesity are also risk factors for T2DM. Additionally, smoking, hypertension, inflammation, age, family history of diabetes, and intrauterine environment are determinants that influence the risk of diabetes.[45,47]

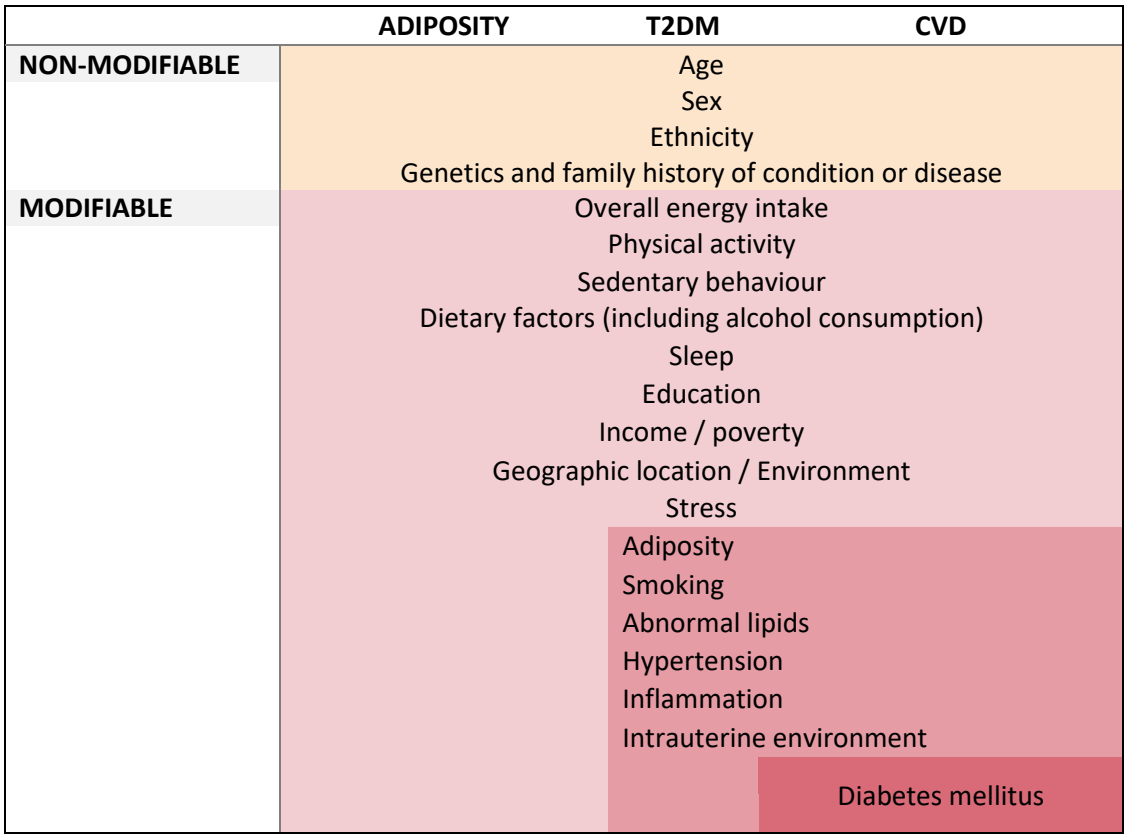

Figure 1.2 Important non-modifiable and modifiable risk factors of adiposity, T2DM, and CVD

CVD risk factors not only include all the non-modifiable and modifiable risk factors of adiposity and T2DM; the two outcomes are significant risk factors for CVD themselves. Around 70% of individuals at risk of CVD have several risk factors that interact in a synergistic manner which can increase an individual's aggregate risk from four-fold with one risk factor to 60-fold in the presence of five risk factors.[44]

Thus, adverse cardiometabolic health is the result of a complex interaction of different risk factors and conditions that have the potential to reinforce and modify each other. While it is

critical to recognize that any attempt to improve cardiometabolic health focusing on only one factor is likely to fail, it is important to understand the relative importance of each of these risk factors. In epidemiology and public health research, comparative risk assessments (CRA) provide a structured approach to estimate the relative importance of different risk factors.[9,48] The most recent and systematic efforts undertaken at the global, regional, and national level are the CRAs of the Global Burden of Disease Study (GBD) 2017. The first publication estimated levels and trends in exposure, attributable deaths, and attributable disability-adjusted life-years (DALYs) for 84 behavioural, environmental and occupational, and metabolic risks or groups of risks from 1990 to 2017.[49] Overall, dietary risks were attributable to approximately 9.1 (of the total 34) million global deaths in 2017 and led to 255 million (of the total 1.2 billion) DALYs. The large majority (approximately > 90%) of these deaths and DALYs were for cardiometabolic and related conditions. If one was to count high fasting plasma glucose and high BMI as risk factors that are closely diet-related as well, diet and diet-related risk factors are, with smoking, short gestation for birthweight and alcohol use, among the globally leading risk factors for deaths and DALYs. A second recent GBD publication has evaluated the consumption of major foods and nutrients across 195 countries and has quantified the relative impact of their suboptimal intake on NCD mortality and morbidity.[50] The main dietary risk factors were diets low in whole grains, high in sodium, low in fruits, low in nuts and seeds, and low in vegetables, fibre, and legumes. In summary, multiple risk factors influence adiposity, T2DM, and CVD in a complex manner. Adiposity is a main risk factor for T2DM itself, and both are important risk factors for CVD.

Diet is therefore a leading risk factor for all three conditions. A major component of modern diets are UPFs, and as the next section will argue, these foods combine many nutritionally advantageous properties that have previously been associated with adverse cardiometabolic health.

1.2 Ultra-processed foods: food processing, the NOVA classification, and a brief review of research

This section will briefly introduce food processing, present a classification scheme that is currently used in nutritional epidemiology and public health research to classify foods according to the degree of food processing, discuss the concept, and review some of the key literature on UPFs.

1.2.1 The four phases of food processing

Various food preparation, preservation, cooking, and processing techniques have been a central part of human evolution and have affected the development of populations and civilizations.[51,52] Overall, the progress of food processing can be divided into four phases. The first phase was characterized by a relatively slow evolution of techniques over thousands of years, moving away from the early hunter-gatherer cultures to early settlements in cities, in which food was mostly provided from surrounding areas.[52] This involved the development of basic tools with which mostly fresh foods were preserved through drying, salting, and smoking, etc. An important exception was the production of bread, which was produced based on flour that was made in water- or animal powered mills.[53]

The second phase started with the industrial revolution in the late 18th century and influenced food processing via multiple innovations and developments. Coal and steam engines and machines transformed transportation and drastically removed barriers to trade, influencing the price and the availability of food ingredients such as fats, salt, and sugars, as well as flours and spices that were previously only available in specific regions.[54] Also, the characteristics and properties of certain macronutrients (such as protein) and micronutrients (such as minerals) were discovered, and the first effort in establishing nutrition as a biochemical discipline happened, as well as advances in other scientific disciplines such as mechanical and chemical engineering.[55]

The different types of food processing invented during the 1800s until the mid-1950 have been described in great detail elsewhere.[56,57] In summary, a whole new set of industrial food technologies led to the development of new, mass-produced industrial food products that, in many ways, are the ancestors of the foods we still consume today. Confectionary, buns and cakes, breakfast cereals, soft drinks, condensed milk, and industrial breads entered the food system on a mass-scale for the first time during this period. Interestingly, given the logistical challenges to provide food for soldiers during the 2nd World War, military research formed the fundament for various new food processing developments that were the basis for a whole range of commercial products after the war.[58, i] Another key development during this period was the mass-introduction of the refrigerator for private households. This transformed food storage and safety and enabled a range of new types of processed foods based on, for example, dairy ingredients such as ice cream or desserts.

The third phase begins in the 1950s and is characterized by two main developments. First, food science and technology advanced further and food companies began to focus on the development of convenience products that were easy to prepare or almost ready-to-eat. Initially food companies targeted middle-class working wives and mothers, but later wider parts of society (and situations of daily life) were addressed. Regionally, this affected most countries of Western (and Northern) Europe and North America, partially because those were the most affluent and economically most rapidly developing regions at the time, partially because in these regions research and technological change enabled the development of food technology, but also because these were the regions in which most modern food corporations originated and the capital for expansion and investment existed. Secondly, a new type of economic globalization and trade integration began with the establishment of the Bretton-Woods system in 1946 (to prevent Economic depression and war) and the General Agreement on Tariffs and

[i] For example, the 'finger-staining dust on Cheetos' can be traced back to a dehydrated, compressed 'jungle' cheese that was invented by government scientists in 1943 in the United States.[58]

Trade (GATT, predecessor of the World Trade Organization) in 1947 to rationalize trade among nations.[59,60] In HICs, diets started to change in a way that is commonly referred to as the 'nutrition transition', which is a shift in the food system away from home and artisanal prepared foods and dishes towards ready-to-consume and pre-prepared meals and drinks.[61]

Note that some authors date the beginning of the third phase to the 1980s, in which 'a revolution that has transformed food systems and supplies and dietary patterns in most countries and settings in just over one generation' began.[62] This refers to a comprehensive global integration of international food systems and the advent of multinational food and beverage corporations as global players. However, I would argue that this is misguided for two reasons. First, it neglects the new nature of the established system post World War II that was qualitatively different from the international system before the second World War (due to GATT). Secondly, the new food processing technologies that were developed after 1945 that led to the nutrition transition in HICs warrant a separate phase. In that sense, the developments in food systems of HICs after the second World War were too different to be conceptionally combined with the second period that started with industrialization, whereas the fourth phase (comprehensive global integration of food systems) was itself different enough to be considered separately.

Thus, I argue that the fourth phase of food processing began in the 1980s. The participation of over 123 countries in the Uruguay rounds of the GATT between 1986 and 1993 was unprecedented in terms of numbers. But the effects of these negotiations were not seen until the 1990s, when the WTO was established, and the integration of most participating countries into global trade and the international financial system came into effect. This was the moment at which food and beverage corporations really became global entities, triggering the nutrition transition on all continents, often as the result of an accession into international trade and finance systems of a given country. This transformed (and is still transforming) the global food

system into a system that increasingly supplies and markets mass-produced, branded, highly- or ultra-processed food and drink products.[59,63–65]

There is a far-reaching difference between foods prepared before the nutrition transition and modern day ready-to-eat products. Dishes made at home were dominant in foods that were minimally processed and often nutrient-rich. By comparison, ready-to-eat and ultra-processed foods are mostly products of industrial components that contain few whole foods and are often characterized by a combination of unhealthy properties.[66] The next section will introduce and discuss the NOVA classification – a scheme to classify the degree of food processing which is currently used in the epidemiological and public health literature and throughout the chapters of this PhD.

1.2.2 Definition and discussion of NOVA

1.2.2.1 Introduction of the NOVA classification scheme

In 2009, Carlos Monteiro from the Center for Epidemiological Studies in Health and Nutrition at the University of Sao Paolo published a commentary criticizing the practice in nutrition and health to either focus on nutrients or on food and drinks.[67] He argued that an overlooked issue in both research and policy was food processing and suggested three groups of processed foods. This publication was the precursor of the NOVA classification, and subsequent publications further developed the definitions and extended the classification scheme by splitting the third group into 'processed' and 'ultra-processed'.[62,68]

Currently, the NOVA system classifies foods into four groups according to the nature, extent, and purpose of industrial food processing.[69,70] This PhD focuses on the fourth NOVA group 'ultra-processed foods' (UPFs), defined as predominantly industrial formulations of typically more than five ingredients.

NOVA-Group	Definition and examples
Group 1. Unprocessed or minimally processed foods	Unprocessed (or natural) foods are edible parts of plants (seeds, fruits, leaves, stems, roots) or of animals (muscle, offal, eggs, milk), and fungi, algae and water, after separation from nature. Minimally processed foods are natural foods altered by processes that include removal of inedible or unwanted parts, and drying, crushing, grinding, fractioning, filtering, roasting, boiling, non-alcoholic fermentation, pasteurization, refrigeration, chilling, freezing, placing in containers and vacuum-packaging. These processes are designed to preserve natural foods, to make them suitable for storage, or to make them safe or edible or more pleasant to consume. Many unprocessed or minimally processed foods are prepared and cooked at home or in restaurant kitchens in combination with processed culinary ingredients as dishes or meals.
Group 2. Processed culinary ingredients	Processed culinary ingredients, such as oils, butter, sugar and salt, are substances derived from Group 1 foods or from nature by processes that include pressing, refining, grinding, milling and drying. The purpose of such processes is to make durable products that are suitable for use in home and restaurant kitchens to prepare, season and cook Group 1 foods and to make with them varied and enjoyable hand-made dishes and meals, such as stews, soups and broths, salads, breads, preserves, drinks and desserts. They are not meant to be consumed by themselves and are normally used in combination with Group 1 foods to make freshly prepared drinks, dishes and meals.
Group 3. Processed foods	Processed foods, such as bottled vegetables, canned fish, fruits in syrup, cheeses and freshly made breads, are made essentially by adding salt, oil, sugar or other substances from Group 2 to Group 1 foods. Processes include various preservation or cooking methods, and, in the case of breads and cheese, non-alcoholic fermentation. Most processed foods have two or three ingredients and are recognizable as modified versions of Group 1 foods. They are edible by themselves or, more usually, in combination with other foods. The purpose of processing here is to increase the durability of Group 1 foods, or to modify or enhance their sensory qualities.
Group 4. Ultra-processed foods	Ultra-processed foods, such as soft drinks, sweet or savoury packaged snacks, reconstituted meat products and pre-prepared frozen dishes, are not modified foods but formulations made mostly or entirely from substances derived from foods and additives, with little if any intact Group 1 food. Ingredients of these formulations usually include those also used in processed foods, such as sugars, oils, fats or salt. But ultra-processed products also include other sources of energy and nutrients not normally used in culinary preparations. Some of these are directly extracted from foods, such as casein, lactose, whey and gluten. Many are derived from further processing of food constituents, such as hydrogenated or interesterified oils, hydrolysed proteins, soya protein isolate, maltodextrin, invert sugar and high-fructose corn syrup. Additives in ultra-processed foods include some also used in processed foods, such as preservatives, antioxidants and stabilizers. Classes of additives found only in ultra-processed products include those used to imitate or enhance the sensory qualities of foods or to disguise unpalatable aspects of the final product. These additives include dyes and other colours, colour stabilizers; flavours, flavour enhancers, non-sugar sweeteners; and processing aids such as carbonating, firming, bulking and anti-bulking, de-foaming, anti-caking and glazing agents, emulsifiers, sequestrants and humectants. A multitude of sequences of processes is used to combine the usually many ingredients and to create the final product (hence 'ultra-processed'). The processes include several with no domestic equivalents, such as hydrogenation and hydrolysation, extrusion and moulding, and pre-processing for frying. The overall purpose of ultra-processing is to create branded, convenient (durable, ready to consume), attractive (hyper-palatable) and highly profitable (low-cost ingredients) food products designed to displace all other food groups. Ultra-processed food products are usually packaged attractively and marketed intensively.

Table 1.1 NOVA-classification

Taken from Monteiro CA, Cannon G, Moubarac JC, Levy RB, Louzada MLC, Jaime PC. The UN Decade of Nutrition, the NOVA food classification and the trouble with ultra-processing. Public Health Nutr. 2018;21(1):5-17.

These include, for example, industrially produced ice cream, candy, confectionery, desserts, biscuits and cookies; sodas and sweetened drinks; instant packaged noodles and soups; sweet or savoury packaged snacks; sugary milk and fruit drinks; energy drinks; ready-to-eat meals; and sausages, burgers, hot dogs, meat balls, poultry, nuggets or other transformed meat products with added preservatives other than salt (such as nitrites). Foods that are predominantly made from conventional culinary ingredients (such as fats, oils, and sugars) in combination with uncommon ingredients such as "hydrogenated or interesterified oils, hydrolysed proteins, soy protein isolate, maltodextrin, invert sugar and high fructose corn syrup, artificial colours, colour stabilisers, flavours, flavour enhancers, or non-sugar sweeteners" are also ultra-processed.[70]

According to NOVA, UPFs are classified in contrast to the other three groups. The first group includes "un- or minimally processed foods" that are fresh or processed without any additional ingredients such as salts, sugars, oils, or fats, and fruits and vegetables, grains, nuts, seeds, fresh and pasteurized milk, natural yogurt with no added sugar or artificial sweeteners, pulses, pasta, rice, eggs. The second group encompasses "processed culinary ingredients" derived from the first group or from nature and can include additives to conserve the original properties (salt, sugar, vegetable oils, butter, and other substances to convert group one foods into culinary preparations). The third group are "processed foods" – relatively simple foods which are often made by adding sugar, salt or other group 2 ingredients to un- or minimally processed foods (canned or bottled vegetables; fruits in syrup; legumes; salted or sugared nuts and seeds; cheeses; freshly made breads). There are various potential characteristics and pathways by which greater consumption of UPFs could cause adverse cardiometabolic health outcomes. The next section reviews the main characteristics of UPFs and how these could adversely affect cardiometabolic health.

1.2.2.2 Putting NOVA in context

The NOVA classification was not the first to look at the processing of foods. At least four other food classification systems that incorporate food processing have been published and

empirically applied. One, developed by the International Agency for Research on Cancer, classified foods into one of three levels of processing ('non-processed', 'modestly or moderately processed', 'processed'), and was applied in two publications using data from the European Prospective Investigation into Cancer and Nutrition (EPIC) study.[71,72] The first estimated the contribution of highly industrially processed foods to nutrient intakes and patterns, finding that highly industrially processed foods dominate diets and nutrient patterns in Nordic and central European countries, while the second publication found associations between highly processed food intake and plasma elaidic acid levels, which is biomarker of industrial trans fatty acids in diets.[73] Another classification has been formulated by a 'joint task force' of the US Academy of Nutrition and Dietetics, the American Society for Nutrition, the Institute of Food Technologists, and the International Food Information Council in the US, categorizing foods into five categories ('minimally processed'; 'foods processed for preservation'; 'mixtures of combined ingredients'; 'ready-to-eat processed foods'; and 'prepared foods/meals'). It was applied once in a paper using data from the US National Health and Nutrition Examination Survey to determine the energy and nutrient contributions from processed foods, finding that minimally processed foods contributed high levels of nutrients but little energy, while 'ready-to-eat' foods provided a lot of energy but little fibre.[74]

A classification system by the Mexican National Institute of Public Health divided foods and products into three categories ('modern industrialized', 'industrialized traditional', and 'non-industrialized').[75] It has been used to estimate the relative energy contribution of the three groups in 1-4 year olds (more than 39% of total energy was provided by both categories of industrialized foods together) and to determine factor that predict higher intake of industrialized foods (higher income, urban residence, monetary support from government).[75,76] Another classification using three categories ('unprocessed', 'primary or partially processed', 'highly processed') has been devised by the International Food Policy Research Institute in Guatemala and has been applied to examine the contribution of processed food products to

prevalence of overweight and obesity, finding that a that increases of household expenditures on 'partially processed foods' by 10% increased the BMI of members of the household by almost 4%. An increase in highly processed foods increased the BMI slightly more, by 4.25%.[77]

These four classifications as well as the NOVA classification have been qualitatively evaluated in a systematic review of food classification systems, and to my knowledge, this is the only publication that has attempted to compare and rate food processing classification systems in the context of Epidemiology and Public Health.[62] The quality of all five systems was evaluated using the five criteria specificity, coherence, clarity, comprehensiveness, and workability, and rated each criterion and how well it was met with zero (not at all) to three points (completely). The US system was rated worst (5 points), followed by the Guatemalan (7), European (9), and Mexican (10) classification systems. NOVA received 13 points and was considered strongest in terms of quality.

There are two points worthy of note regarding this publication. First, two of the co-authors were involved in the development of the NOVA system, which questions the neutrality and unbiasedness of the review. Secondly, the methods and how the assessments were derived and undertaken is unclear. Because of a possible conviction of the superiority of NOVA at the design phase of the study by the authors, it is possible that the criteria to assess the classifications were defined in a way that would ensure a higher rating for the NOVA classification. This is particularly likely with regards to the criterion 'specificity', which demands a strong differentiation between industrial and home-made methods of processing in the classification, a distinction that has been an emphasis of the proponents of NOVA. The other criteria seem less specific to NOVA. For example, whether the system covers all types of foods, whether it can be applied to data from household or population-based nutrition surveys, whether it is clearly defined, or whether the food groups are related to one another logically (internal coherence) are sensible questions designed to capture internal validity aspects. Nevertheless, it is still possible that assessments were undertaken to favour the NOVA classification.

While there is no way of knowing whether this was the case, my own assessment of the five classifications comes to a similar conclusion. I will focus on one or two key aspects of each classification that to me demonstrate their inferiority. The Guatemalan and European classifications lack differentiation due to having only three groups. Combining foods such as vegetable oils, rice, pasta, crisps, pizza in one 'processed food' category seriously limits applicability as these are hardly comparable foods with very different nutritional characteristics. The Guatemalan classification also lacks proper explanations of the first and second food groups. The US classification is simply difficult to apply, as many foods could easily be placed into multiple categories. A frozen pizza, for example, could be classified into the 'ready-to-eat processed' group just as well as into the 'prepared foods/meals' group, and I would argue that this would apply to many foods. Finally, the Mexican classification that was ranked second highest in the review has issues in terms of its generalisability – the distinction between 'modern industrialized', 'non-industrialized', 'industrialized traditional', and 'locally made traditional foods' might make sense in the context of Mexico, but are, in my view, very difficult to apply in countries such as the UK, Germany, France or the US, in which the nutrition transition has been mostly completed and in which traditional foods that are locally made would be difficult to identify. In sum, despite questionable methods in the review of food classification systems, I agree with the general conclusion of the paper and judge the NOVA classification to be the superior food processing classification for the application in nutrition studies, from those that I have reviewed.

Apart from explicit food classifications, food processing has also implicitly been a part of previous nutrition research, in the context of dietary pattern studies. The epidemiological literature on modern dietary patterns sometimes refers to food processing. For example, a report on obesity and cancer prevention has referred to 'Western dietary patterns' that are 'energy-dense, and increasingly made up from processed foods', including 'fatty or sugary foods such as processed meats, pastries, baked goods, confectionery, sugared and often also alcoholic

drinks'[62,78] Studies of this type of dietary pattern have been undertaken in many countries and have associated these dietary patterns with obesity, T2DM, and CVD outcomes, as well as mortality.[79–84] These diets are usually defined by a higher relative intake of processed meats, refined grains, savoury snacks, chocolates and sweets. They also sometimes include unprocessed or little processed foods of animal origin such as milk, meat, and eggs. Other similar dietary patterns that have a different name but mean fundamentally the similar type of diet are fast food, convenience, and ready-to-eat dietary patterns.[85–88] All these studies were *a posteriori* approaches in which the name of the dietary pattern was determined after the pattern was empirically derived from the data, and this type of study has been found to be internally valid.[89] Thus, several previous nutrition studies have dealt with the issue of food processing implicitly, and hence carry some information about the relationship between food processing and disease risks that have previously not been explored. This observation is the basis for the systematic review and meta-analysis that will follow in chapter 2.

1.2.2.3 Characteristics of UPFs and UPF-cardiometabolic health pathways

UPFs could affect cardiometabolic health in multiple ways, and this section briefly summarizes how different characteristics of UPFs can negatively affect adiposity, T2DM, and CVD outcomes.

Obesity is a disorder of the energy homeostasis system which is influenced by diet through multiple pathways, including brain reward, satiety, glucose-insulin responses, and energy intake and expenditure.[3,90,91] Previous research has shown that diets high in refined carbohydrates and fats lead to rapid and pronounced weight gain.[92,93] UPFs are often characterized by a combination of high levels of refined carbohydrates and fats, are often highly energy-dense and usually contain flavours and food additives that affect reward and satiety systems along the gut-brain axis; a causal link with obesity is thus plausible.[3,91] Consequently, in the first conducted randomized controlled trial (RCT) of *ad libitum* UPF versus unprocessed food consumption, participants in the UPF group consumed on average about 500 calories more than participants in the unprocessed group, and this was due to increased fat and carbohydrate but not protein

intake.[94] Participants in the UPF group also gained 0.8 kg body weight over a two-week period, while participants in the unprocessed group lost 1.1 kg ($P < 0.001$). One systematic review has investigated the association between UPF intake and body fat in children and adolescents previously.[95] It reported small but positive associations, mostly based on cross-sectional designs, but found a lack of comparability of the studies included.

In studies from different countries, UPFs have been found to contain higher levels of sugar, sodium, unhealthy fats (saturated and trans fats from partially hydrogenated oils), energy, and less content of fibre and various micronutrients.[96–103] UPFs have also been found to be less satiating and have a higher glycaemic load than minimally or unprocessed foods.[104] Current research indicates that high intakes of sugar and unhealthy fats, low intakes of dietary fibre, and high intake of foods with a high glycaemic index negatively affect the development of insulin resistance and T2DM.[105–109]

Multiple additional pathways might associate increased CVD risk with UPFs. Diets high in UPFs tend to contain lower levels of fruits, vegetables, nuts and seeds, whole grains, and higher levels of fats and dietary sodium.[97,110–112] These characteristics have previously been associated with increased risk of CVD.[3,113] While recent research on dietary fats has de-emphasized the role of saturated fats,[114–118] trans fats have been associated with increased CVD risk, especially total CHD and CHD mortality risk.[119,120] Furthermore, recent research has shown how toxic lipid peroxidation products (such as α,β,4-hydroxy-2-trans-nonenal [4-HNE]) are produced during the heating process of polyunsaturated frying oils that are used to produce fast foods and other UPFs.[121,122] These toxic aldehydes are implicated in the pathogenesis of various cardiovascular (and neurodegenerative) diseases via multiple cell processes such as oxidative stress signalling, cell proliferation, transformation or cell death.[122–126] CVD has a more complex aetiology in which, depending on disease subtype, non-nutritional risk factors may play a relatively more important role than in the aetiology of T2DM. Regarding both CVD and T2DM, an additional pathway explaining diet-disease associations could be the relationship between diets and the gut

microbiome. A large body of research supports the hypothesis that Western diets and UPFs affect changes in the gut microbiome which are associated with obesity and metabolic diseases, possibly through the pathways of gut dysbiosis (microbial imbalance or maladaptation) and inflammation.[127]

1.2.2.4 A brief overview of the literature on UPFs using the NOVA system

Studies on UPFs usually investigate one or more of the following three aspects: firstly, estimating the nutritional content and the dietary quality of diets high in UPFs; secondly, measuring the level and geographic distribution of UPFs in regions, countries, or specific food locations (i.e. supermarkets); and thirdly estimating UPF-disease associations.

Most studies that estimate the level of UPF consumption use data from epidemiological studies and household surveys. Data from these study types suggests that UPFs contribute to between 30% and 60% of total energy intake. For example, UPFs represent 30% of total energy intake in Brazil, about 60% in Canada, 58% in the US, 59% in Norway, 57% in the UK, 55% in Sweden, 30% in Chile, 60% in New Zealand, 59% in Belgium, and 52% in Spain.[98,101,103,110,128–132] Some studies estimate consumption and consumption trends based on food purchasing or sales data (as far as I know, exclusively based on data from the Euromonitor Passport Global Market Information Database). Here, UPFs are usually expressed as weight in kilograms per capita per year. Some publications have anecdotally shown the development of sales of certain food groups.[133–135] One publication has displayed the trends in UPFs sales in Latin America, while another very recent study has shown how UPF sales have developed since 2002 in 80 countries.[136,137]

Prior to 2016, a number of small cross-sectional studies had associated UPF intake with body fat, adiposity, and metabolic syndrome.[128,130,138,139] Beginning in 2016, the first longitudinal studies on UPFs and diseases appeared. UPFs were associated with obesity and overweight, then with hypertension, lipid profile in children, and T1DM and celiac disease.[140–143]

In 2018, the first UPF study on cancer risk was published, demonstrating small but positive associations, and in 2019, one prospective cohort on cardiovascular diseases and two

publications on UPFs and overall mortality followed.[98,144–146] Finally, in 2019, the first randomized-controlled trial on *ad libitum* UPFs intake and weight change followed, demonstrating a strong increase both in energy intake as well as a drastic weight change.[147]

There are three shortcomings of the literature that I have addressed in this thesis and were notably more prevalent and visible at the start of my PhD than they are now, due to the significant growth of interest in this area over the past 3 years. First, as outlined above in the section on the context of NOVA, there is value and information in previous dietary pattern studies about the disease risk of diets that are high in UPFs. No systematic review regarding cardio-metabolic health had been undertaken nor was any information synthesized in a meta-analysis. A second shortcoming is the almost complete lack of information from regions which have recently gone through a nutrition transition or are still in a phase of transitioning. Except a few studies from Brazil, little was known empirically about UPFs in LMICs, but those are the regions that have recently been most exposed to UPFs and are the main drivers behind the global adiposity and diabetes crises. Thirdly, no study on UPFs has so far investigated whether there is a difference in estimated disease risk when UPFs are operationalized in different ways. For example, all studies that estimate the share of UPFs in overall diet measure UPFs as energy. However, all the studies that estimate disease association use weight-based measures of UPF intake, and it is unclear whether results would differ or not using different metrics. Finally, no study has estimated the risks between UPF intake and T2DM in a prospective cohort.

1.3 Methodological considerations

Since I started my PhD in 2015, discussions about the 'replication crisis', chance, *P*-values, and significance testing have become central to scientific debates, in part triggered by papers that reported alarmingly low reproducibility rates in diverse fields such as Psychology, Experimental Economics, and Cancer Biology.[148–151] In 2016, a survey among 1,500 researchers across the globe found that 52% of researchers believe that there is a significant reproducibility crisis, while 38% believed that there is a slight crisis.[150] A number of reasons at structural and individual levels

have been suggested, including incentives in research to 'publish or perish', as well as individuals' and research groups' failure to adhere to good scientific practices.[151–153] In this context, some authors have challenged study methods and approaches in nutritional epidemiology, questioning whether the discipline in the current state should inform dietary guidelines and policy.[154–157] Most critical points relate to the difficulty to properly account for confounding among the different nutrients, clinical outcomes, and other variables; the limitations of dietary assessment tools and challenge to measure diets accurately; suboptimal and potentially selective research reporting; and the difficulty to detect small effect sizes reliably for nutritional risk factors and nutrition-related interventions. The proposed solution by some authors has been to largely replace nonrandomized studies and use randomized studies in human nutrition research going forward. From my perspective, most of these issues have been at the core of methodological debates in epidemiology and nutritional science. Statistical and conceptual solutions are available and are already implemented to varying degrees, which is part of the reason why I disagree with the overall conclusion to fundamentally deemphasize nonrandomized studies. I will touch on some of the main points in the final discussion. Two aspects that influence reproducibility and can be addressed by individual researchers, however, are less frequently discussed about in the field of nutrition – the concepts 'researcher degrees of freedom', and *P*-values and 'null-hypothesis significance testing'.

1.3.1 Researcher degrees of freedom

A key observation from the statistical literature is that results can be dependent on so-called 'researcher degrees of freedom' – or the data processing and analytical choices that individual researchers can make – even in the absence of selection on statistical significance and in the presence of pre-specification of analysis plans.[158–161] To demonstrate this, 29 teams independently prespecified 29 analyses of the same dataset for the same research question, yielding 21 unique combinations of covariates and a wide range of results.[162] In a similar manner, a replication study identified key data processing steps for which equivalent choices existed to

construct alternative datasets and apply the same data analysis as the original article, yielding fundamentally different results.[163] Wicherts et al. (2016) have systematised this and have presented a list of 34 types of researcher degrees of freedom across the main study phases hypothesizing, design, collection, analyses, and reporting. If multiple defendable and reasonable combinations of data generating, processing, and analytical choices exist, researchers can increase transparency by a) making these choices explicit and b) displaying the results of combinations of equally defendable choices of data processing and data analysis in what has been termed a 'multiverse analysis'.[153,161,163]

1.3.2 *P*-values and null-hypothesis significance testing

A second problem that has fundamentally contributed to the reproducibility crisis is the erroneous interpretation of *P*-values and 'null-hypothesis significance testing' (NHST) which has led to the misleading practice of dichotomizing *P*-values below 0.05 as significant and above 0.05 as not significant. There are two aspects of NHST that demonstrate that this narrow interpretation is wrong. First, it has been repeatedly demonstrated that 'the difference of between "significant" and "not significant" is not significant itself'.[160,161,163–165] Even apparently different *P*-values such as 0.03 and 0.1 can, in many situations, simply be explained by sampling variability and do not necessarily represent real features of the underlying parameters. Focusing on confidence intervals as they are commonly applied does not necessarily help – a lower confidence interval (CI) (of, i.e. a hazard ratio (HR)) of 0.97 with a *P*-value of 0.07 (at the 95% level) is statistically indistinguishable from a lower CI of 1.04 with a *P*-value of 0.04, yet, the latter case would be reported as an association whereas the former would often not.

The second problematic aspect of *P*-values and statistical significance is the focus on null hypotheses, treating all other assumptions that are used to calculate the *P*-value to be correct.[166] The *P*-value tests *all* the assumptions about how the data were generated, including the entire statistical model, and not only the hypothesis of interest. However, these assumptions usually encompass more than is usually understood and presented as modelling assumptions. For

example, one assumption is that intermediate results from analysis were not used to determine which results and which analyses would be presented, or that no contingencies in the data processing exist in the construction of the data. An (in my opinion) accurate definition has been provided by Greenland et al. (2016): '[…] the *P*-value is seen as a continuous measure of the compatibility between the data and the entire model used to compute it, ranging from 0 for complete incompatibility to 1 for perfect compatibility, and in this sense may be viewed as measuring the fit of the model to the data.'[167] Thus, a low *P*-value does not necessarily imply a low possibility of a chance finding, if considered in isolation, and the value of a narrow dichotomous focus on NHST can be misleading.

1.3.3 Approach taken in my PhD

On the basis of this discussion and the published literature, besides the specific analytical approaches of each chapter, I oriented the work in this PhD according to three overarching methodological principles:

- Incorporation of potentially equivalent data processing and analytical choices in the planning, conduct, and reporting of the study. Reporting of multiple combinations of equivalent choices if these combinations are likely to influence the results (i.e. multiverse analysis).
- A continuous rather than dichotomous interpretation of *P*-values in the context of the totality of model assumptions. No 'selection on statistical significance'.
- Maximization of transparency on data processing and data analysis, as well as enabling replicability as much as possible through publication of complete Stata analysis code as well as dataset used (where possible).

My thinking about these methodological issues and the decision to use these principles was neither linear nor finished before I began executing my empirical analyses. Rather, at different points during my PhD, both the scientific field and I were at different stages of these scientific discussions (for example, I discovered the above definition of *P*-values only in late 2018). The implications for the approaches taken throughout the PhD is that the three main chapters adhere to these principles in slightly different ways. Additionally, this difference is also the result of two other factors: firstly, what type of statistical method was needed to perform the analyses

partially determined how researcher degrees of freedom and NHST were approached; secondly, and importantly, the established methodological conventions and reporting standards of scientific journals also influenced my reporting and writing. I had certain target journals in mind while conducting and writing the different chapters, and thus had to balance my thinking with the methods and reporting practices of journals. In the overall discussion at the end of the PhD, I will summarize and critically discuss the approaches used in the overarching context of this thesis.

1.4 Aims and research questions

To improve cardiometabolic health and decrease adiposity and risk of T2DM and CVD, a better understanding of UPF-disease associations is needed, as well as an expansion of knowledge on 'what it is about UPFs' that explains potentially increased risks of disease. In addition, greater knowledge about the global distribution, trends, and disease associations, as well as how research on UPFs connects to previous nutrition research is needed. Furthermore, I will attempt to demonstrate some principles or 'best practices' that can make research more reproducible and transparent.

Given these identified gaps in the evidence, this PhD investigates the associations between UPFs and cardiometabolic health. Chapter 2 investigates previous nutrition studies from an UPF perspective by systematically searching the literature, identifying prospective cohort studies that estimate disease risks of diets or dietary pattern defined by higher relative intakes of UPFs, and estimating associations between UPFs and adiposity, T2DM, and CVD in meta-analyses.

The third chapter explores trends of sales of UPFs at the country level for 76 countries between 2001 and 2016 and estimates the associations between UPF sales and adiposity and diabetes for children and adolescents and adults, as well as for females and males and low-to-middle income and high-income countries separately.

The fourth chapter examines associations between UPFs and the three outcomes in the prospective cohort study of EPIC-Norfolk. Its starting point is the fact that consumption of UPFs, as defined by the NOVA classification, can be operationalized in several ways. In these analyses I estimate disease risks and associations for five different ways of operationalizing the NOVA classification.

The specific research questions across the three chapters are outlined below:

Chapter 2 – Assessing associations between UPFs and cardiometabolic health in previous nutrition studies:

- Is increased UPF intake associated with increased risk of adiposity, T2DM, and CVD?
- Are these associations linear or do they follow a non-linear form?

Chapter 3 – Displaying global trends in UPFs and assessing country-level associations between UPFs and adiposity and diabetes mellitus in 76 countries:

- What are the global trends in UPFs between 2001 and 2016?
- Are increased sales of UPFs associated with adiposity and diabetes mellitus?
- Is there a difference between LMICs and HICs?

Chapter 4 – Assessing associations between UPFs and cardiometabolic health in EPIC-Norfolk:

- Are UPFs associated with T2DM, CVD, and adiposity in *EPIC-Norfolk*?
- Are estimated UPF-outcome associations different when UPFs are measured as weight compared to UPFs measured as energy?
- What are the relative contributions of ultra-processed food groups to UPF measurements as weight and energy?

2 ASSOCIATIONS BETWEEN ULTRA-PROCESSED FOOD INTAKE AND CARDIOMETABOLIC HEALTH

A SYSTEMATIC REVIEW AND META-ANALYSIS

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A summarized version of this chapter is currently in preparation for submission.

2.1 Introduction

To my knowledge, no systematic review of the associations between UPFs and cardiometabolic health outcomes exists. Despite this paucity of research on UPFs defined according to NOVA, substantial other research has been conducted on highly- or ultra-processed foods, albeit under different definitions, as was described in chapter 1. Analyses of fast, convenience, junk, or western foods differ in terminology, but capture fundamentally similar types of readily consumable and highly palatable foods with nutritionally disadvantageous profiles that in most cases would be classified as ultra-processed according to the NOVA classification. The aim of this systematic review was to identify prospective diet and dietary pattern cohort studies characterized by higher relative intakes of UPFs as reflected by NOVA and that reported cardiometabolic health risk estimates. I then aimed to synthesize those estimates in a non-linear dose-response and summary meta-analysis.

2.2 Contributions

Kai Schulze (KS), Jean Adams (JA), and Martin White (MW) designed the study with inputs from Fumiaki Imamura (FI). KS, Katrine Eijlerskov (KE), Rebecca Love (RL), Tarra Penney (TP), Hannah Forde (HF), Eleanor Winpenny (EW), MW, and JA performed the search, screen, review, selection, and data extraction process. KS performed the analysis and FI gave feedback and input on the analytical approach. KS drafted the manuscript. JA, MW, and FI contributed to the interpretation of the results and critically reviewed the chapter.

2.3 Methods

2.3.1 Search strategy

I followed the MOOSE guidelines for conducting and reporting of systematic reviews and meta-analyses of observational studies.[168,169] I performed a systematic search using PubMed, Embase, CINAHL, and Cochrane Library up to October 2018, using a wide range of search terms (Table 2.1). The search strategy was independently reviewed by an experienced medical librarian at

the University of Cambridge (Isla Kuhn). Furthermore, I searched the reference lists of relevant reviews.[95,113,170–174]

2.3.2 Study selection

I included prospective cohort studies of the association between diets defined by a higher absolute or relative intake of UPFs and risk of three health outcomes (obesity, incident type two diabetes mellitus, and incidence of any cardiovascular event) published in English and excluded abstract only publications and grey literature. To be included, the dietary exposure had to be defined by at least three ultra-processed foods or food groups according to group four of the NOVA classification (Table 1.1).[69,70] Studies that used data-driven (*a posteriori*) approaches to derive dietary patterns had to be defined by at least three ultra-processed foods or food groups with factor loadings of ≥ .2 to be included. This number was informed by a qualitative review of previous literature and chosen for reasons of practicality – including every study with two or less UPFs would have implied including a large number of studies with diets that were most definitely not characterized by UPFs, whereas only including studies with four, five, or more UPFs would have excluded studies with little detailed dietary information which, for example, were explicitly defined by three UPF food groups as a proxy for a diet high in UPFs. Adjusted estimates of hazard, odds, or risk ratios for two or more non-referent categories or a continuous range of the exposure had to be available for non-linear analyses, either with 95% confidence intervals or information available to calculate them.

Search terms 1 (dietary exposure – processed / ultra-processed foods):

a) ("processed" or "ultraprocessed" or "ultra-processed" or "convenience" or "snack" or "fast" or "junk" or "packaged" or "chilled" or "frozen" or "refined" or "canned" or "industrial*" or (ready#prepared) or (ready#eat) or "ready-to-eat" or "energy-dense" or "western*")
b) ("food" or "foods" or "product" or "products" or "meal*" or "food product*" or "foodstuff*" or "diet" or "diets")
c) Search: a) adjacent by maximum of four words with b)
d) ("snack*" or "ready#meal*" or "confectionary" or "bread*" or "baked good*" or "pizza*" or "ice#cream*" or "biscuit*" or "breakfast cereal*" or "cake*" or "cookie*" or "pie*")
e) Search: c) or d)

Search terms 2 (association, relationship, link):

("relation*" or "related" or "association*" or "associated" or correlation*" or "correlated" or "connection*" or "connected" or "links" or "link" or "linked")

Search terms 3 (obesity):

("obes*" or "overweight" or "overweight" or "BMI" or "body mass" or "body fat" or "body composition" or "body weight" or "body shape" or "waist circumference" or "abdominal fat" or "adiposity" or "waist circumference" or "skinfold" or "skin fold" or "waist to hip ratio" or "waist-hip ratio" or "waist to height ratio" or "waist-height ratio" or "weight adj2 gain" or "weight adj2 loss" or "weight adj2 loss" or "weight adj2 change")

Search terms 4 (diabetes):

a) ("diabetes") AND ("type 2" or "type two" or "type ii" or "type II" or "non-insulin dependent")
b) ("T2DM" or "prediabet*" or "pre-diabetes" or "prediabetic state" or "pre-diabetic" or "glucose intolerance" or "glucose intolerant" or "IGT" or "IFG")
c) ("impaired fasting") AND ("glucose" or "glycaemi*" or "glycemi*" or "bloodglucose" or "blood glucose")
d) Search: a) or b) or c)
e)

Search terms 5 (cardiovascular diseases):

a) ("cardiovascular disease*" or "CVD" or "coronary heart disease*" or "CHD" or "coronary disease*" or "cerebrovascular disease* or "heart disease*" or "myocardial infarction" or "myocardial ischemia" or "acute coronary syndrome" or "stroke" or "haemorrhagic stroke" or "ischemic stroke" or "ischemic heart disease" or "ischaemic heart disease" or "blood pressure" or "hypertension" or "cholesterol" or "triglycerides" or "carotid intima media thickness" or "C- reactive protein")

Search terms 6 (Exclusion of animal and in vitro studies):

a) ("animals" or "rat" or "rats" or "mouse" or "mice" or "animal study" or "animal studies" or "in vitro")
b) ("human") [i.e. MeSh terms for "human studies"]
c) Search: [a) not [a) and b)]]

Search strategy:

a) (1 AND 2 AND (3 OR 4 OR 5)) NOT 6

Table 2.1 Search terms (adapted for each database)

MeSH or Emtree or "Exploding terms" are not included here but were included as appropriate for the respective databases.

Studies that reported relative risks with a referent category that was not comparable were excluded (for example a different dietary pattern such as 'healthy' instead of the lowest intake of the UPF dietary pattern); only studies with populations that were free of the outcome of interest at baseline (i.e. no T2DM for studies with T2DM as outcome, etc.) were included. If more than one relevant publication from the same cohort existed, the study that included the largest number of adverse cardiometabolic events was included. Reference lists of included publications were examined for additional relevant studies. The selection process for each article was independently performed by the first author (KS) and one co-author (JA, KE, HF, RL, TP, EW).

2.3.3 Data extraction and study quality

Using a standardized extraction form, I extracted information on: author and publication, cohort, included participants, dietary assessment method, dietary pattern method, relevant UPFs included, outcome and ascertainment, and risk estimates. The full list of the 24 items that were extracted for each study is provided in Table 2.2.

When risk estimates were extracted, statistical models that had the greatest degree of control for potential confounding were preferred. An exception to this rule was made with the adjustment of potential intermediate variables such as, for example, components of metabolic syndrome when T2DM risk was estimated, or hypertension and serum cholesterol levels when CVD endpoints such as incident CHD or CVD were estimated. If the alternative model was adjusted only for age while the multivariable model included other confounders as well, the multivariable model with intermediates was chosen. Stratified estimates were extracted whenever possible. The data extraction process was independently performed by the first author (KS) and one co-author (JA, KE, HF, RL, TP, EW, MW). Discrepancies were discussed and resolved by consensus. If all the information was not available in an identified publication, related publications were searched and examined. If the desired information could not be retrieved, data were requested from authors through a standardized form. The quality of each

study was assessed according to the Newcastle-Ottawa scale[175], independently by the first author (KS) and one co-author (JA, MW).

1) author names;
2) year and country of publication;
3) study cohort name;
4) recruitment and follow-up period (range and/or mean/median years);
5) cohort definition (inclusion / exclusion criteria; selection process;
6) inclusion / exclusion criteria of study population (details / n);
7) number of participants;
8) sex of participants;
9) age range of study population;
10) ethnicity of study population (% of each if multiple);
11) dietary assessment method (including number of items);
12) dietary pattern method (*a priori*, *a posteriori*, reduced-rank, etc.);
13) name of dietary pattern;
14) list of UPF items with loadings >= .2 (or number of UPF items defining the diet);
15) total number of food items / groups with loadings of >= .2 (if a posteriori);
16) type of outcome;
17) outcome ascertainment method;
18) total number of cases;
19) total person-time or total number of participants at risk at baseline;
20) percentile ranges (exposure categories);
21) midpoint-value for each percentile range (dose);
22) category-specific number of cases;
23) category-specific number of non-cases (for case-control studies), person-years (for incidence rate data), and number of participants at risk at baseline (for cumulative incidence data);
24) category-specific risk estimates including upper and lower uncertainty intervals.

Table 2.2 List of data extracted from each study

2.3.4 Statistical analysis

Outcomes evaluated in the quantitative analysis included incidence of T2DM and incidence of and mortality from any CVD event. Adiposity outcomes were narratively synthesised due to the lack of comparability of risk estimates. For dose-response analyses, the risk estimates of each non-referent exposure category were assumed to represent the midpoint dose of the category percentile ranges, expressed in percentiles of the exposure distribution. For example, the risk estimates of the second quintile relative to the first quintile represented the 30th versus 10th percentile range, the estimate from the third quintile relative to the first represented the 50th versus 10th percentile range, and so on.

Two-stage random-effects dose-response meta-analyses were performed to examine linear and non-linear relationships between UPF exposure and cardiometabolic health risks. In the first stage, the generalized-least-squares method reported by Greenland and Orsini was used to calculate study-specific coefficients based on risk estimates, confidence intervals, cases, and person-time of all referent and non-referent exposure categories.[176–178] In the second stage, non-linear associations were estimated using multivariate random-effects meta-analysis with restricted cubic splines of three knots at 10th, 50th, and 90th percentiles of the intake distribution, according to recommended percentiles by Harrell (2001).[178–180] *P*-values for overall association and non-linear association were generated accordingly.

As a secondary analysis, random-effects models were used to calculate summary relative risks for highest versus lowest categories of exposure.[181] The random-effects models additionally included those studies which met the inclusion criteria but for which I was unable to obtain risk estimates other than the highest versus lowest exposure category. Heterogeneity was assessed using the Q-test and the I^2 statistic, with the heterogeneity estimate being calculated from the inverse-variance fixed-effect model.[182] I^2 values of ≤25%, ≤50%, ≤75%, and >75% were interpreted as indicating no, little, moderate, and significant heterogeneity respectively. Small study effects, such as publication bias, were assessed by inspection of funnel plots for asymmetry and Egger's test and Begg's test.[183,184] A sensitivity analysis by exclusion of one study at a time was performed to assess the stability of results. To assess the evidence of heterogeneity of associations by length of follow-up, number of participants, or study quality, meta-regression was performed.

95% confidence intervals were calculated for the relative risk estimates in the dose-response and summary meta-analyses. *P*-values were reported for the Q-test, Egger's test, Begg's test, meta-regression, overall association, and tests of non-linearity. As outlined in chapter 1, I recognize that the choice of any particular threshold to determine statistical significance is arbitrary.[165,185] To guide interpretation, however, I interpret p-values ≤ 0.005 as strong

evidence[185,186], p-values > 0.005 & ≤ 0.05 as moderate evidence, p-values > 0.05 and ≤ 0.1 as weak evidence, and p-values > 0.1 as no evidence against the null-hypothesis. All analyses were performed in Stata, version 15.1 (StataCorp LLC, College Station, Texas, USA). The full extracted data, the dataset for the meta-analysis, the MOOSE checklist, and the Stata code for all analyses are available at https://github.com/kai-schulze/upf_slrma.

2.4 Results

2.4.1 Search results and study and diet characteristics

The process of identification and study selection is summarized in Figure 2.1. From a total of 14,495 records identified I screened the full text of 157 articles, of which 116 were excluded. A list of the excluded studies and reasons for the exclusion is provided in Appendix Table 1. Four additional studies that met the inclusion criteria were identified by hand searching the reference lists of the articles that were full-text reviewed. I included a total of 41 publications from 30 cohorts comprising over 33,220 cardiometabolic health events among 1,054,475 participants.[79–83,85,86,88,140,141,143,187–217]

Table 2.3 summarizes some key characteristics of studies included in the review and analysis, and Appendix Table 2 shows the main characteristics for each included publication. Twenty studies were conducted in Europe, fifteen in North America, five were from Asia, and one was from South America. The study sizes ranged from 427 to 129,501 participants and had a mean follow-up of 9.18 years. Out of nine possible points, the average study quality of the studies was 5.4, nine studies had a high study quality (> 6 points), 24 studies were of moderate study quality (4-6 points), and eight studies were judged to be of low quality (see appendix table 3 for details).

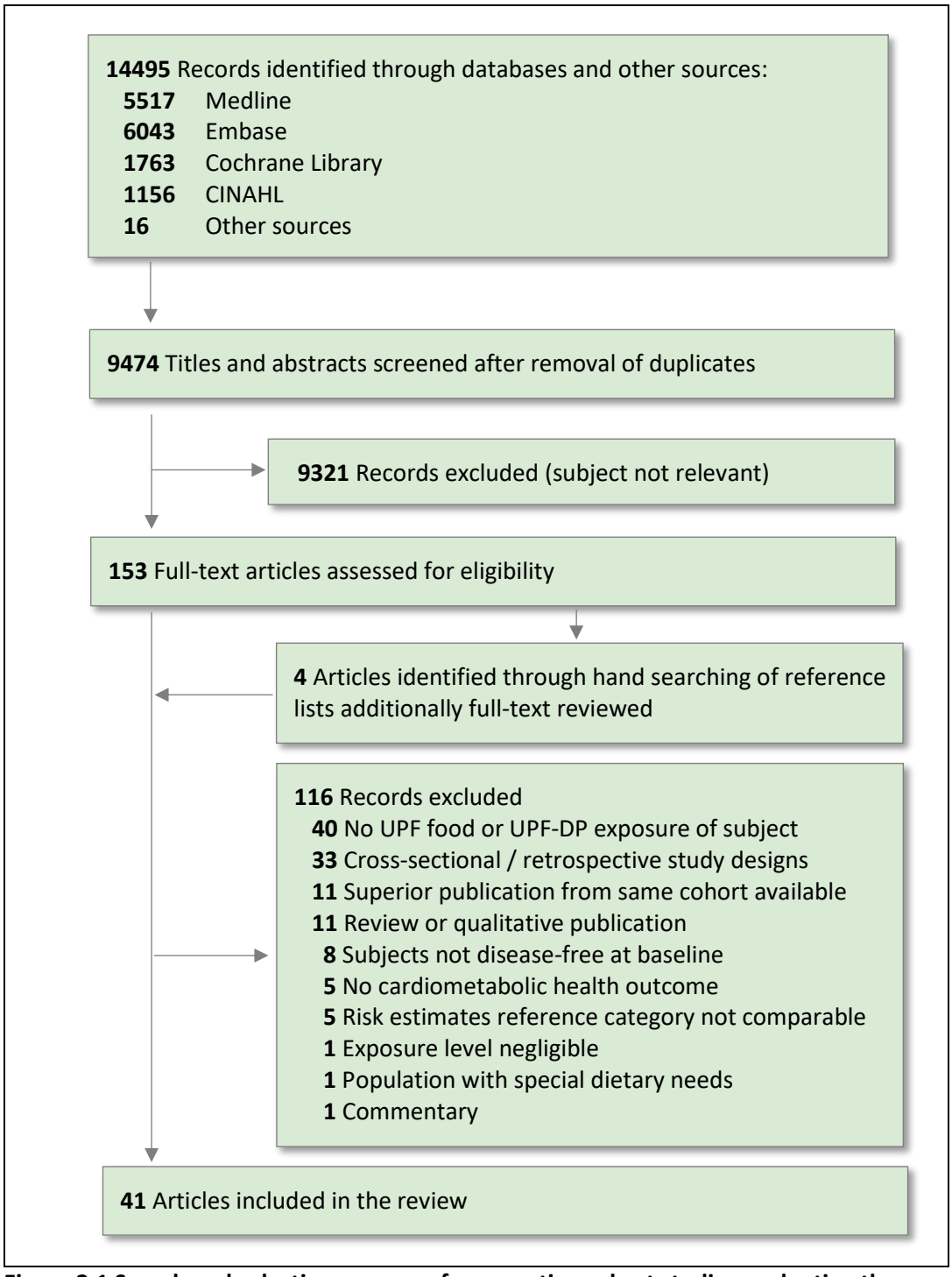


Figure 2.1 Search and selection process of prospective cohort studies evaluating the associations between UPF intake and cardiometabolic health outcomes

Characteristic		All outcomes
Studies (risk estimates), n:		41 (51)
CVD events, n:		16763
T2DM events, n:		9620
Adiposity events, n:		>6837*
Participants, n:		1,054,475
Studies by geographical location, n:		
	Europe	20
	North America	15
	Asia	5
	South America	1
Studies by study size, n:		
	>= 100.000	2
	10000-<100.000	15
	1000-<10000	21
	<1000	3
Study size:		
	Mean (n)	25718
	Range (min-max)	427-129501
Duration of follow-up:		
	Mean (years)	9.18
	Range of follow-up (years)	2-28.5
Names of diets or dietary patterns:		
	Western	15
	Sweet	7
	Fast-foods	5
	Ultra-processed foods according to NOVA	2
	Unnamed	4
	Energy-dense	2
	Fats & processed Meats	2
	Junk and convenience	1
	Other	3
Average number of UPFs in dietary patterns (min-max):		7.63 (3-33)
Approaches to derive dietary pattern:		
	Number of *a posteriori* dietary patterns	35
	Number of *a priori* dietary patterns	6
Average loading† of UPFs in *a posteriori* dietary patterns (min-max):		0.39 (0.21-0.63)
Average % of UPFs with a loading of > 0.2 of total number of food groups / items with loadings of > 0.2 (min-max):		46.7% (21.7%-87.5%)
Categorization of exposures:		
	Quartiles	15
	Quintiles	12
	Continuous	9
	Tertiles	5
Average study quality of maximum 9 (min-max):		5.4 (3-8)

* Some adiposity studies reported aggregated estimates from which no information on singular events could be derived

† Factor loadings in factor analyses or component coefficients in principal component analyses express the correlation between the original variables (i.e. food groups) and the underlying factors (i.e. Western dietary pattern).

Table 2.3 Key characteristics of included studies and diets and dietary patterns

The main sources of heterogeneity between studies related to representativeness of exposed cohorts (some were restricted to specific populations such as civil servants); adjustment for confounding factors such as socio-economic status, health-related behaviours, and family history; the degree to which the exposure represented all ultra-processed foods; and the comparability of measures of adiposity outcomes (e.g. BMI, fat-free-mass, fat-mass-index, etc.).

2.4.2 Ultra-processed food intake and cardiovascular disease risk

I included 18 risk estimates from 16 publications in the non-linear dose-response analysis and an additional five risk estimates from four publications in the summary random-effects meta-analysis of highest versus lowest UPF intake or UPF dietary patterns score category and CVD risk, with 16,763 CVD events among 595,288 participants.[79–81,83,88,140,188–191,196–198,201,202,204,206,208,214,218]

In the non-linear analyses, the lowest reference category was the 10th percentile of the UPF intake or UPF dietary pattern score distribution. There was weak evidence of non-linearity (*P*=0.068) and a slightly convex non-linear relationship between UPF intake or UPF dietary patterns score category and CVD risk was observed (Figure 2.2, top). Table 2.4 shows the relative risk estimates and confidence intervals from the non-linear dose-response analysis for selected dose values. The summary relative risk for the highest versus lowest UPF intake or UPF dietary pattern score category was 1.18 (95% CI, 1.09-1.27; *P*-value for overall association <0.001; I^2 =42.3%, $P_{Heterogeneity}$=0.018; Figure 2.2, bottom). There was no evidence of publication bias with Egger's test (*P*=0.597) and Begg's test (*P*=0.285), and the funnel-plot exhibited symmetry (Appendix Figure 1, top).

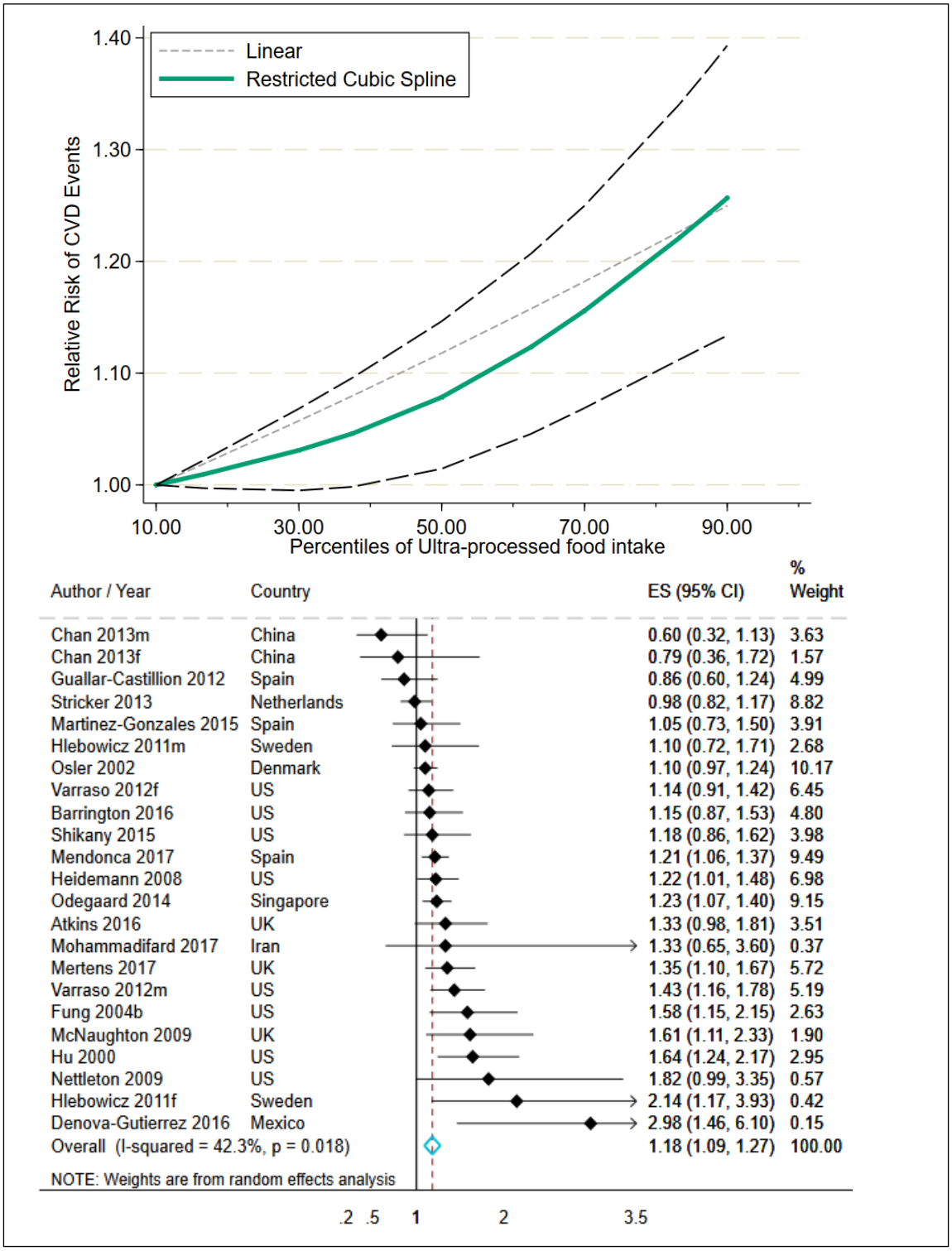


Figure 2.2 Ultra-processed food intake and cardiovascular disease risk

Top: Non-linear dose-response random-effects meta-analysis modelled with restricted cubic splines with lowest measured intake (10%) as reference intake. 95% confidence intervals (dashed lines) and linear dose-response point estimates as dotted lines. Bottom: Random-effects meta-analysis of highest versus lowest UPF intake or UPF dietary patterns score category and CVD risk.

Ultra-processed food intake percentile	Relative risks (95% CI)	
	CVD	T2DM
10	1.00	1.00
12.5	1.01 (1.00-1.01)	1.01 (1.01-1.02)
30	1.06 (1.00-1.07)	1.10 (1.07-1.19)
50	1.12 (1.01-1.15)	1.21 (1.15-1.37)
70	1.18 (1.07-1.25)	1.34 (1.23-1.53)
87.5	1.24 (1.13-1.37)	1.46 (1.28-1.67)
90	1.25 (1.13-1.39)	1.48 (1.28-1.71)

Table 2.4 Ultra-processed food intake and CVD and T2DM Risk
Non-linear dose-response meta-analysis of CVD and T2DM associated with intake of UPFs for selected intake percentiles.

2.4.3 Ultra-processed food intake and risk of type 2 diabetes mellitus

I included nine risk estimates from eight publications in the non-linear dose-response analysis and one additional estimate in the summary random-effects meta-analysis of highest versus lowest UPF intake or UPF dietary patterns score category and incident T2DM risk, with a combined 9,620 T2DM events among 368,579 participants.[82,193,195,203,210,212,217,219,220] There was no evidence of non-linearity (*P*=0.313), and the summary relative risk for the highest versus lowest UPF intake or UPF dietary patterns score category was 1.46 (95% CI, 1.23-1.68; *P*-value for overall association <0.001; I^2 =77.2%, $P_{Heterogeneity}$ <0.001; Figure 2.3, bottom). There was no evidence of publication bias with Egger's test (*P*=0.569) and Begg's test (*P*=0.371), and the funnel-plot exhibited slight asymmetry (Appendix Figure 1, bottom).

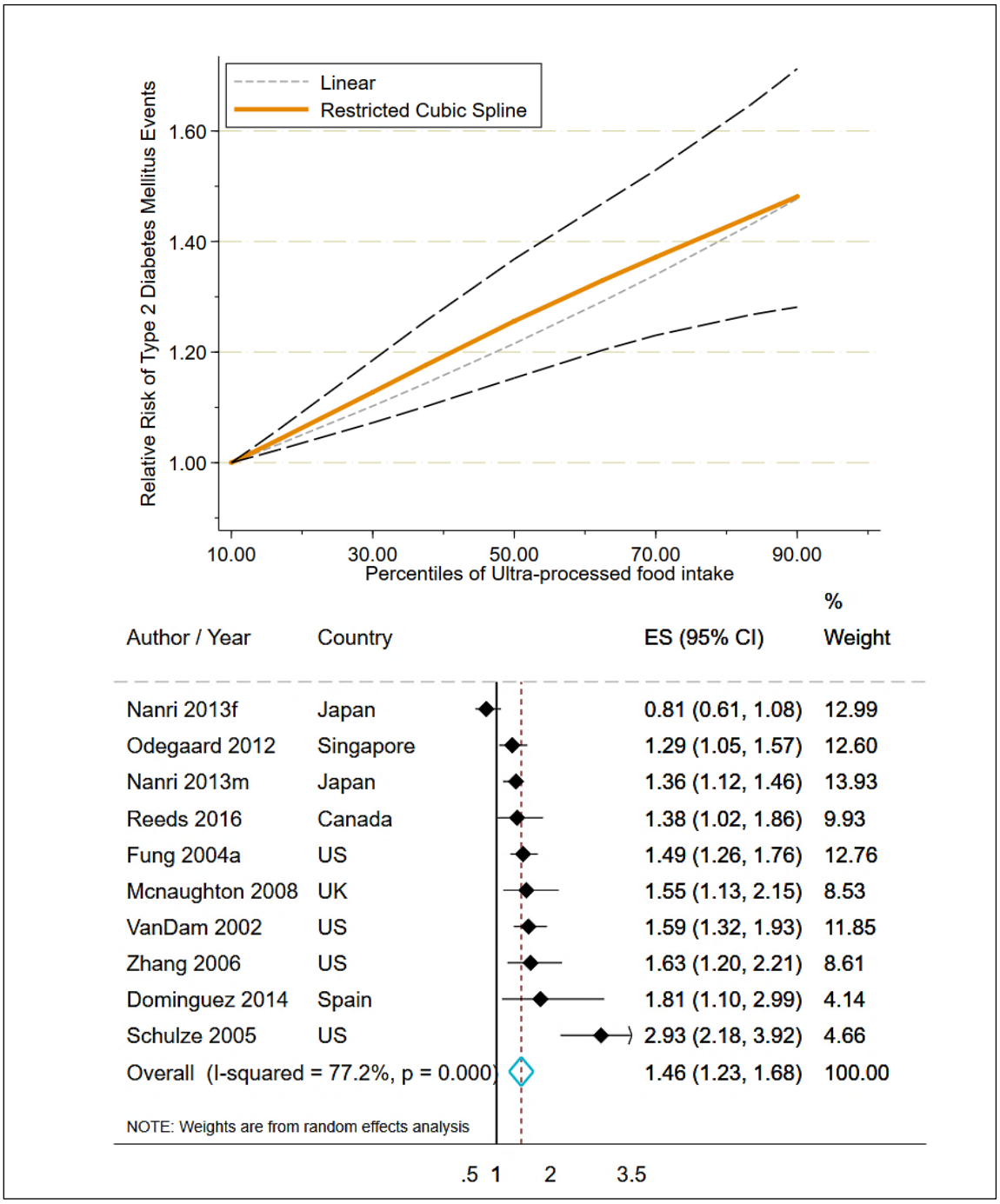


Figure 2.3 Ultra-processed food intake and Type 2 diabetes mellitus risk
Top: Non-linear dose-response random-effects meta-analysis modelled with restricted cubic splines with lowest measured intake (10%) as reference intake. 95% confidence intervals (dashed lines) and linear dose-response point estimates dotted lines. Bottom: Random-effects meta-analysis of highest versus lowest UPF intake or UPF dietary patterns score category and T2DM risk.

2.4.4 Ultra-processed food consumption and adiposity

I included twelve studies with 90,608 participants in the narrative synthesis of the association between UPF intake and adiposity.[84–86,141,187,192,194,207,209,211,215,216] Five studies reported coefficients from linear regressions, five from odds and hazard ratios, and two from mean changes of adiposity outcomes (Table 2.5). These inconsistencies regarding the types of

estimates of association precluded any quantitative summary of evidence. Half of the studies reported small risk estimates with wide uncertainty intervals that included the null;[86,194,207,209,215,216] the remainder reported that increased intake of UPFs was associated with increased risk of adiposity.

Publication	Population	Exposure	Type of estimate	Estimate (CI / SE*)
Ambrosini, 2012	Children	Energy-dense foods DP†	Lin. regression beta-coefficient of: SD¥ increase in DP (z-score) and fat mass index (z-score)	0.06 (0.03; 0.10)
Oellingrath, 2011	Children	Junk / convenience food DP	Lin. regression beta-coefficient of: change in DP-score and change in BMI categories (normal to overweight/obese)	-0.15 (-0.5; 0.19)
Voortmann, 2016	Children	Western DP	Lin. regression beta-coefficient of: FMI and DP-score; Q4 vs. Q1	-0.01 (-0.11; 0.09)
Diethelm, 2014	Children	Convenience food DP	Lin. regression beta-coefficient of: DP-score and change in BMI; Q3 vs. Q1	2.25 (2.01; 2.49)
Durao, 2017	Girls	Energy-dense foods DP	Lin. regression beta-coefficient of: DP-score and change in BMI (z-score);	0.075 (0.009; 0.14)
	Boys			-0.014 (-0.093; 0.0065)
Cutler, 2012	Old girls	Sweet and salty foods DP	OR of: DP-score and weight status (BMI >= 85th percentile)	0.97 (0.83; 1.14)
	Old boys			0.86 (0.72; 1.03)
	Young girls			0.92 (0 .71; 1.19)
	Young boys			0.99 (0.74; 1.34)
Bes-Rastrollo, 2006	Adults	Consumption of hamburgers, pizzas, and sausages (HPS)	OR of: consumption of HPS and any weight gain; Q5 vs. Q1	1.21 (1.03; 1.42)
Pala, 2013	Children	Sweet and fat DP	OR of: DP-score and overweight / obesity; Q3 vs. Q1	0.97 (0.77; 1.22)
Togo, 2004	Females	Sweet DP	OR of: BMI > 30 & DP-score	3.8 (0.97; 14.94)
	Males			1.63 (0.45; 5.87)
Mendonca, 2016	Adults	Consumption of UPF (NOVA)	HR for UPF consumption and incident overweight & obesity; Q4 vs. Q1	1.26 (1.10; 1.45)
Ritchie, 2007	Black girls	Sweet and cheese DP	Mean change in BMI during follow-up (10 years)	9.04 (1.03 (SE))
	White girls	Fast food DP		6.24 (0.32 (SE))
Schulze, 2006	Adults	Western DP	Mean weight change during follow up (8 years)	7.45 (0.12 (SE)

Table 2.5 Summary of estimates of association of adiposity studies
* SE = standard error; † DP = dietary pattern; ¥ SD = standard deviation.

Three of the four studies with adult populations reported positive association, while only three of eight studies with children populations did. Six of the eight adiposity studies with a sample size of under 5,000 participants reported large uncertainty and no association, while three of the four largest studies did find an association.

2.4.5 Meta-regression and sensitivity analyses

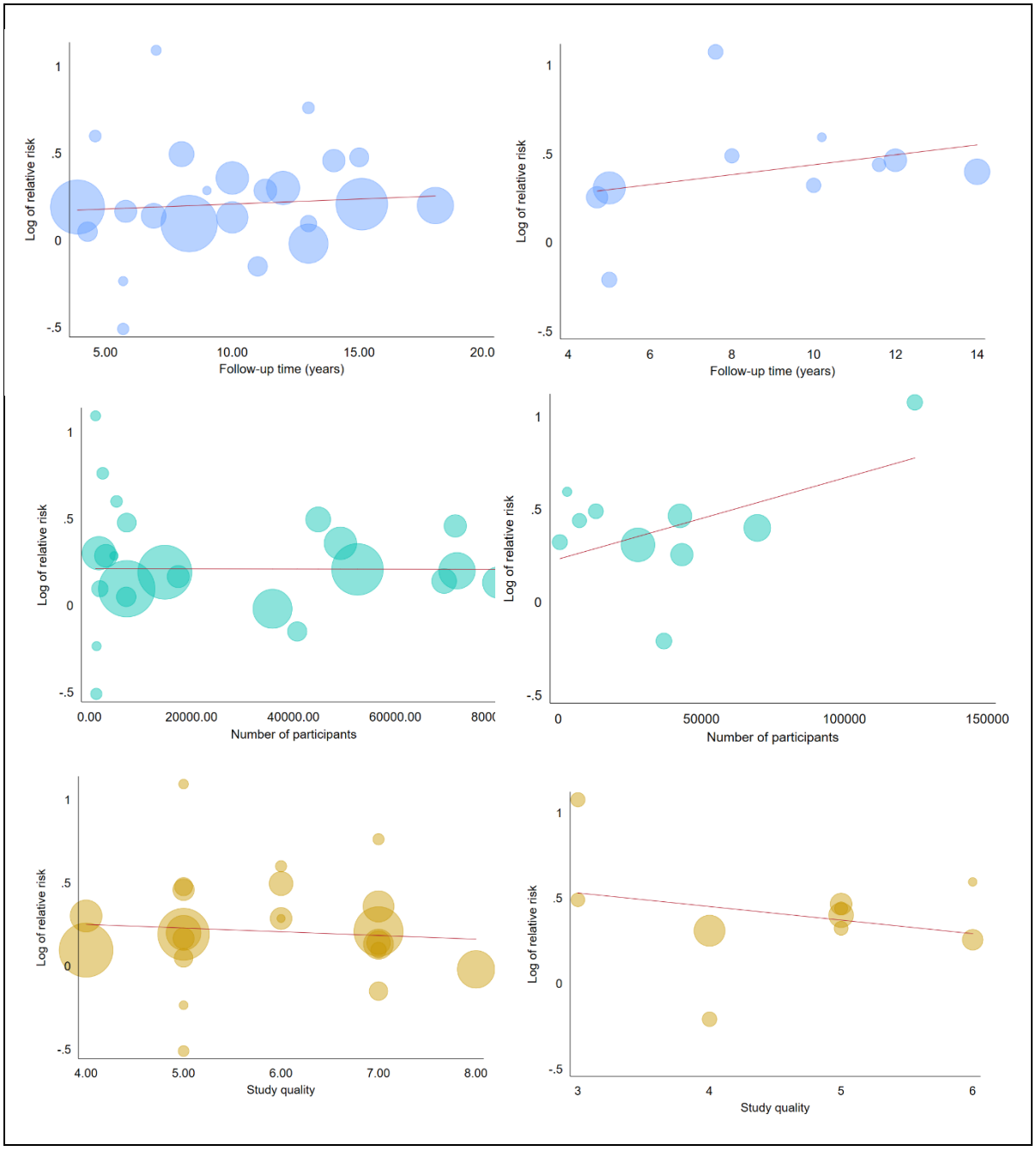


Figure 2.4 Meta-regression analyses of CVD and T2DM risks
Meta-regression of follow-up time, number of participants, and study quality on log relative risk estimates of studies. Left panels: CVD risk; right panels: T2DM risk. Solid lines represent the meta-regression slope of the change in log relative risk estimates for increasing levels of stratification variables. Size of the data markers is proportional to the weight in the meta-regression.

I examined potential heterogeneity by length of follow-up time, number of participants, and study quality performing a meta-regression of the log of relative risks (Figure 2.4). Regarding CVD, I found no evidence for heterogeneity by follow-up time (*P*=0.622), number of participants (*P*=0.981), or study quality (*P*=0.552). Regarding T2DM, there was also no evidence to suggest heterogeneity by follow-up time (*P*=0.394), number of participants (*P*=0.130), or study quality (*P*=0.459).

When each study was excluded from the summary meta-analysis of CVD, no study changed the overall summary relative risk estimate by more than ±0.02 (i.e. from 1.18 to 1.20), and only one study changed the I^2 by more than ± 5% (Chan 2013m, -11%, Table 2.6). In the summary meta-analysis of UPF and T2DM risk, the exclusion of the study with the highest risk estimate[212] resulted in the largest reduction in the summary risk estimate, from 1.46 (95% CI, 1.23 to 1.68) to 1.37 (95% CI, 1.18 to 1.57) (Table 2.7). The exclusion of the study with the lowest risk estimates (Nanri 2013, RR for females 0.81 [95% CI, 0.61-1.08]) resulted in the largest increase in the summary risk estimate from 1.46 to 1.51 (95% CI, 1.34-1.68). Notably, excluding this study also reduced the heterogeneity from I^2 = 77.2% (significant heterogeneity) to I^2 = 49.5% (little heterogeneity), indicating this study as the source of the high heterogeneity of the overall summary risk estimate for T2DM.

Excluded study	Estimates
Fung 2004b	1.17 (95% confidence interval 1.08 to 1.26; *P*-value for overall association <0.001; I^2 =40.7%, $P_{Heterogeneity}$=0.025)
Hu 2000	1.17 (95% confidence interval 1.08 to 1.25; *P*-value for overall association <0.001; I^2 =38.3%, $P_{Heterogeneity}$=0.036)
McNaughton 2009	1.17 (95% confidence interval 1.08 to 1.26; *P*-value for overall association <0.001; I^2 =41.8%, $P_{Heterogeneity}$=0.022)
Mertens 2017	1.17 (95% confidence interval 1.08 to 1.27; *P*-value for overall association <0.001; I^2 =42.3%, $P_{Heterogeneity}$=0.020)
Varraso 2012m	1.17 (95% confidence interval 1.08 to 1.26; *P*-value for overall association <0.001; I^2 =40.3%, $P_{Heterogeneity}$=0.027)
Atkins 2016	1.18 (95% confidence interval 1.08 to 1.27; *P*-value for overall association <0.001; I^2 = 44.0%, $P_{Heterogeneity}$= 0.015)
Barrington 2016	1.18 (95% confidence interval 1.09 to 1.28; *P*-value for overall association <0.001; I^2 = 44.9%, $P_{Heterogeneity}$= 0.018)
Denova-Gutierrez 2016	1.18 (95% confidence interval 1.09 to 1.27; *P*-value for overall association <0.001; I^2 = 41.3%, $P_{Heterogeneity}$= 0.023)
Heidemann 2008	1.18 (95% confidence interval 1.08 to 1.28; *P*-value for overall association <0.001; I^2 =44.6%, $P_{Heterogeneity}$=0.019)
Hlebowicz 2011f	1.18 (95% confidence interval 1.09 to 1.27; *P*-value for overall association <0.001; I^2 =42.0%, $P_{Heterogeneity}$=0.021)
Hlebowicz 2011m	1.18 (95% confidence interval 1.09 to 1.28; *P*-value for overall association <0.001; I^2 =44.8%, $P_{Heterogeneity}$=0.013)
Mendonca 2017	1.18 (95% confidence interval 1.08 to 1.28; *P*-value for overall association <0.001; I^2 =44.3%, $P_{Heterogeneity}$=0.014)
Mohammadifard 2017	1.18 (95% confidence interval 1.09 to 1.27; *P*-value for overall association <0.001; I^2 =44.9%, $P_{Heterogeneity}$=0.013)
Nettleton 2009	1.18 (95% confidence interval 1.09 to 1.27; *P*-value for overall association <0.001; I^2 =43.2%, $P_{Heterogeneity}$=0.017)
Odegaard 2014	1.18 (95% confidence interval 1.08 to 1.28; *P*-value for overall association <0.001; I^2 =43.9%, $P_{Heterogeneity}$=0.015)
Shikany 2015	1.18 (95% confidence interval 1.09 to 1.28; *P*-value for overall association <0.001; I^2 =44.9%, $P_{Heterogeneity}$=0.012)
Chan 2013f	1.19 (95% confidence interval 1.10 to 1.28; *P*-value for overall association <0.001; I^2 = 43.2%, $P_{Heterogeneity}$= 0.017)
Martinez-Gonzales 2015	1.19 (95% confidence interval 1.09 to 1.28; *P*-value for overall association <0.001; I^2 =44.4%, $P_{Heterogeneity}$=0.014)
Osler 2002	1.19 (95% confidence interval 1.09 to 1.29; *P*-value for overall association <0.001; I^2 =43.4%, $P_{Heterogeneity}$=0.016)
Varraso 2012f	1.19 (95% confidence interval 1.09 to 1.28; *P*-value for overall association <0.001; I^2 =44.9%, $P_{Heterogeneity}$=0.013)
Chan 2013m	1.20 (95% confidence interval 1.11 to 1.28; *P*-value for overall association <0.001; I^2 = 31.3%, $P_{Heterogeneity}$= 0.081)
Guallar-Castillion 2012	1.20 (95% confidence interval 1.11 to 1.29; *P*-value for overall association <0.001; I^2 =39.3%, $P_{Heterogeneity}$=0.031)
Stricker 2013	1.20 (95% confidence interval 1.11 to 1.29; *P*-value for overall association <0.001; I^2 =37.1%, $P_{Heterogeneity}$=0.042)

Table 2.6 Summary meta-analyses of UPF and CVD risk with exclusion of each study at a time

Excluded study	Estimates
Schulze 2005	1.37 (95% confidence interval 1.18 to 1.57; *P*-value for overall association <0.001; I^2 = 69.8%, $P_{Heterogeneity}$ = 0.001)
Dominguez 2014	1.44 (95% confidence interval 1.21 to 1.67; *P*-value for overall association <0.001; I^2 = 79.2%, $P_{Heterogeneity}$ < 0.001)
Odegaard 2012	1.44 (95% confidence interval 1.23 to 1.76; *P*-value for overall association <0.001; I^2 = 79.6%, $P_{Heterogeneity}$ < 0.001)
VanDam 2002	1.44 (95% confidence interval 1.20 to 1.69; *P*-value for overall association <0.001; I^2 = 78.2%, $P_{Heterogeneity}$ < 0.001)
Zhang 2006	1.44 (95% confidence interval 1.20 to 1.68; *P*-value for overall association <0.001; I^2 = 79.0%, $P_{Heterogeneity}$ < 0.001)
Mcnaughton 2008	1.45 (95% confidence interval 1.21 to 1.69; *P*-value for overall association <0.001; I^2 = 79.4%, $P_{Heterogeneity}$ < 0.001)
Fung 2004a	1.46 (95% confidence interval 1.21 to 1.72; *P*-value for overall association <0.001; I^2 = 78.9%, $P_{Heterogeneity}$ < 0.001)
Reeds 2016	1.47 (95% confidence interval 1.22 to 1.72; *P*-value for overall association <0.001; I^2 = 79.7%, $P_{Heterogeneity}$ < 0.001)
Nanri 2013m	1.50 (95% confidence interval 1.21 to 1.78; *P*-value for overall association <0.001; I^2 = 79.7%, $P_{Heterogeneity}$ < 0.001)
Hlebowicz 2011f	1.51 (95% confidence interval 1.34 to 1.68; *P*-value for overall association <0.001; I^2 = 49.5%, $P_{Heterogeneity}$ < 0.045)
Hlebowicz 2011m	1.37 (95% confidence interval 1.18 to 1.57; *P*-value for overall association <0.001; I^2 = 69.8%, $P_{Heterogeneity}$ = 0.001)

Table 2.7 Summary meta-analyses of UPF and T2DM Risk with exclusion of each study at a time

2.5 Discussion

Diets and dietary patterns characterized by higher relative intake of UPFs compared with lower intake were associated with an increased risk of CVD and T2DM. There was weak evidence of a non-linear relationship between UPF consumption and CVD risk. No evidence for publication bias was found, and there was no evidence for heterogeneity by length of follow-up, number of participants or study quality for either outcome. The overall risk estimates regarding CVD and T2DM were robust to the exclusion of single studies, and the high heterogeneity in the T2DM risk estimates was driven by one study with a very low risk estimate. While inconsistencies in the estimates of association of the adiposity studies precluded a quantitative synthesis of the findings, the narrative review revealed mixed findings with half of the studies showing a positive

association, while the other half did not find an association, and those were studies of children populations.

2.5.1 Interpretation and comparison with other studies

To my knowledge, this is the first study that has systematically investigated prospective diet and dietary pattern cohort studies from an UPF perspective and summarized those in non-linear dose-response and summary random-effects meta-analyses. One previous prospective cohort has found a positive association with hypertension,[140] and one very recent study has demonstrated a small but positive association with cardiovascular diseases.[144] The hypothesis and pathways that were introduced in the first chapter all apply here and can be briefly repeated: UPFs have been found to contain higher levels of sugar, sodium, unhealthy fats (saturated and trans fats) (from partially hydrogenated oils), energy, and less fibre and various micronutrients.[96–103] UPFs have also been found to be less satiating and have a higher glycaemic load than minimally or unprocessed foods.[104] Current research indicates that high intakes of sugar, unhealthy fats, little dietary fibre, and foods with a high glycaemic index negatively affect the development of insulin resistance and T2DM.[105–109] If the observed greater risk of T2DM with increasing intakes of UPFs is a causal association, it is likely the result of the combination of these nutritional risk factors.

Regarding CVD, the diets included in this review that were high in UPFs contained lower levels of fruits, vegetables, nuts and seeds, whole grains, and higher levels of fats and dietary sodium.[97,110–112] These characteristics have previously been associated with increased risk of CVD.[3,113] Also, trans fats were a still a widely used ingredient during the study period of most of the cohorts (1990's and 2000's). Trans fats have been associated with increased CVD risk, especially total CHD and CHD mortality risk.[119,120] CVD has a more complex aetiology in which, depending on disease subtype, non-nutritional risk factors may play a relatively more important role than in the aetiology of T2DM.

This could explain why the estimated relative risks between UPFs and CVD were smaller and possibly have a slightly different functional form than in the association between UPFs and T2DM. Regarding both CVD and T2DM, one pathway explaining diet-disease associations could be the relationship between diets and the gut microbiome. A large body of research supports the hypothesis that Western diets and UPFs affect changes in the gut microbiome which are associated with obesity and metabolic diseases, possibly through the pathways of gut dysbiosis (microbial imbalance or maladaptation) and inflammation.[127]

Current research indicates a positive association between UPFs and adiposity, as outlined in the background chapter. One systematic review has investigated the association between UPF intake and body fat in children and adolescents previously.[95] It reported small but positive associations, mostly based on cross-sectional designs, and found a lack of comparability of the studies included, which was repeated in my findings. The positive associations found in the study of adults confirms previous research from an RCT of *ad libitum* UPF versus unprocessed food consumption showing a strong positive causal effect of UPF intake on adiposity.[94]

2.5.2 Limitations

Most of the studies included in the analyses did not specifically investigate the degree of processing of foods. Hence, the extent to which the dietary exposure captured UPF consumption as defined by NOVA differed between the studies. While some studies classified dietary data according to *a priori* classifications, most included studies investigated dietary patterns empirically derived by factor analysis or similar methods.[89,221,222] A major limitation of these data-driven studies was that they did not contain information about the average consumption of included food groups. Hence, on an absolute scale, exact conclusions about the comparability of the exposures of the studies included are limited and statements about absolute levels of UPF consumption and associated risks are not possible in this study. However, studies of overall diets or dietary patterns have been found to be reproducible and internally valid.[223–226] Since individual dietary pattern scores are based on actual intakes in data-driven *a posteriori* studies,

individuals with higher dietary pattern scores truly have higher relative intakes of the foods that a given dietary pattern is defined by. Most included studies used *a posteriori* dietary patterns defined by higher intakes of UPFs (or were *a priori* studies of the NOVA classification). Hence, the relative exposure (of higher versus lower intakes of UPF) between included studies is comparable, despite the variability of absolute UPF consumption levels between studies, which, however, is likely low given that most studies were high-income populations with broadly comparable levels of UPF consumption patterns in the population. Moreover, in comparison to nutrition studies of single food groups or nutrients, dietary pattern studies reduce the risk of nutritional confounding from other unhealthy or healthy non-UPF food items, although some risk for confounding remains.

Residual confounding could have influenced the results. Although all included studies adjusted for confounding and risk estimates that were adjusted according to predefined criteria were extracted, violations of the 'ignorability' assumption (a lack of overlap or lack of balance in covariate structure between more and less exposed participants) are plausible and can imply erroneous covariate-adjusted estimates and confidence intervals.[227–229] When relative risks are small at high levels of exposure – as is the case here regarding CVD – residual confounding is likely to bias the estimates upwards, and confidence intervals do not adequately reflect the uncertainty around the estimates.

Measurement error in the assessment of diet and covariates also could have influenced the results. If there was measurement error in the exposure, the relative risks in the published studies may have been influenced by regression dilution bias, which attenuates the estimated disease risk association.[230] However, given that there might have been measurement error in the covariates as well, it is unclear in which direction the observed association could have been biased.

2.5.3 Implications for policy and future research

Although one RCT on UPFs and adiposity exists,[147] further RCTs are needed to test the effects of overall diets high in UPFs on short-term outcomes, particularly cardiometabolic biomarkers, as long-term RCTs will not be feasible. More prospective cohort studies on UPFs and CVD and T2DM should be undertaken to solidify and broaden the evidence base. Future studies should also always report the range of intake of UPFs to enable comparisons across studies. Further research should also be undertaken especially in the context of low-to-middle income and emerging countries. To increase comparability between studies of adiposity, less common measures such as fat-mass-indices or mean weight changes between should be avoided; usage of common metrics such as age-dependent and potentially ethnicity-specific BMI or z-score of BMI would be preferable. Odds and hazard ratios (and their updates[231]) should be used to measure strengths of associations instead of measures such as linear regressions. Interventions to reduce consumption of UPFs may offer promising strategies to reduce the risk of T2DM and CVD. Such interventions would have wider reach, greater impact and equity if delivered at population-level.[232] Chapter 4 as well as the overall discussion will discuss the implications of the findings for research and policy in much greater detail.

2.6 Conclusion

In these meta-analyses, any intake compared with the lowest intake of UPFs was consistently associated with a greater risk of T2DM and high levels of UPF intake compared with the lowest intake were associated with an increased risk of CVD. UPF consumption was associated in most studies of adult populations but only in a few studies of children's populations.

3 ULTRA-PROCESSED FOODS AND ADIPOSITY AND DIABETES MELLITUS

A PANEL ANALYSIS OF 76 COUNTRIES BETWEEN 2001 AND 2016

Co-Authors: JA and MW.

A summarized version of this chapter is currently under review at *The Lancet Public Health.*

3.1 Introduction

The findings of the previous chapter have indicated that overall, UPFs are likely associated with T2DM and CVD. These studies with individual-level data are less susceptible to measurement error and other biases than those using aggregate data. However, individual-level data cannot quantify associations between changes in the overall food system and population-level trends of adiposity and diabetes on a global scale.[233] Furthermore, in regions in which the most rapid transitions of food systems are taking place (currently mostly low-to-middle income countries), individual-level data is often unavailable or inadequate to quantify the effects of changing diets on health.[234] Accordingly, only few studies in the last chapter were performed in the context of low-to-middle income countries.

A recent systematic review concluded that food sales and purchase data have become a valuable tool for public health research in areas in which traditional methods of dietary assessments are limited, such as consistently measuring shifts in the food supply.[235] Changes in sales of UPFs at the country-level are anecdotally associated with health-outcomes.[135] One previous study reported trends in sales of UPF food groups, finding positive associations with adult adiposity. However, it only analysed one population and outcome combination (adult adiposity), did not present trends of UPFs for each country, did not investigate diabetes, did not estimate associations for children and adolescent populations which are increasingly at risk of diabetes and adiposity, or reported findings by income category.[137] Performing analyses by classes of income separately might be insightful given that countries of different levels of income are at different stages of the nutrition transition – performing aggregate analyses for all countries at the same time could potentially conceal differences in association for a given period of time.

The aim of the research reported in this chapter was thus to estimate the longitudinal associations between sales of UPF products and the prevalence of adiposity and diabetes mellitus in 76 countries for the years 2001 to 2016 for both sexes of adult, children and adolescent populations, and present results for all countries and LMICs and HICs separately.

In studying the relationship between UFPs and adiposity or diabetes at population level, multiple choices regarding outcome selection, analytical strategy, or exposure definition are possible. As outlined in chapter 1, a key observation of research on the 'replication challenge' in the biomedical and social sciences[149,236,237] is that results can be highly dependent on so-called 'researcher degrees of freedom' - or the data processing and analytical choices that individual researchers make - even when analyses are pre-specified and selection on statistical significance is absent.[158–161] Since multiple plausible combinations of outcomes, exposure definitions, covariates, and modelling strategies exist to address the study aims, I conducted a 'multiverse analysis'. I first describe global levels of UPF sales, graphically explore unadjusted bivariate associations between UPFs and adiposity and diabetes mellitus, and finally estimate associations between UPF and adiposity and diabetes mellitus prevalence in multivariable regression models.

3.2 Contributions

KS conceived and designed the study. JA and MW contributed to the study design. KS compiled and analyzed the data. KS, JA, and MW interpreted the data. KS wrote the manuscript, and MW and JA revised the manuscript. All authors approve the final version of the manuscript.

3.3 Methods

3.3.1 Data sources and food classification according to the level of processing

I identified country-level time-series data available in officially published sources for 40 high-income countries (HICs) and 36 low-to-middle income countries (LMICs) between 2001 and 2016. Details of variable definitions, data sources, income classification, and included countries are provided in Tables 3.1 and 3.2.

Variables	Definition	Data Source
	Outcomes	
Mean BMI of adults and children and adolescents	Age-standardized mean BMI, by sex	NCD-RisC[238]
Prevalence of overweight in adults and children and adolescents	Age-standardized population prevalence of overweight (more than 1 SD to 2 SD above the median BMI), by sex	NCD-RisC[238]
Prevalence of obesity in adults and children and adolescents	Age-standardized population prevalence of overweight (more than 2 SD above the median BMI), by sex	NCD-RisC[238]
Prevalence of diabetes mellitus	Age-standardized population prevalence of diabetes mellitus, by sex.	
	Dietary exposures (all g/capita/day)	
Unprocessed or minimally processed foods (NOVA 1)	Combined sales of the following foods: Fruits, vegetables, starchy roots, pulses, nuts, rice, pasta and noodles, fish and seafood, eggs	Euromonitor Global Passport[239]
Processed culinary ingredients (NOVA 2)	Combined sales of the following foods: Oils and fats, butter and margarine, sugars and sweeteners.	Euromonitor Global Passport[239]
Processed foods (NOVA 3)	Combined sales of the following foods: Frozen yoghurt, processed meat and seafood, yoghurt products, sour milk products, processed / canned fruits and vegetables, cheese, other dairy.	Euromonitor Global Passport[239]
Ultra-processed foods (NOVA 4)	Combined sales of the following foods: Breakfast cereals, sweet and savoury snacks (Chips/crisps, corn chips, pretzels, sweet snacks, salted nuts), confectionery (chocolates, sweets, pastilles, jellies), sugar confectionary, ice creams, frozen desserts, biscuit and snack bars, baked goods (packaged), frozen products (pizza, ready meals, others), soups, ready meals, sauces, dressings and condiments, spreads, carbonates (carbonates drinks), sweetened juices, sports and energy drinks	Euromonitor Global Passport[239]
	Covariates	
Urban population (% of total)	Urban population refers to people living in urban areas as defined by national statistical offices. It is expressed as the % of the total population.[240]	World Bank[240]
Dietary energy consumption (kcal per capita)	Dietary energy consumption per capita refers to the amount of food, expressed in kilocalories (kcal) per day, available for each individual in the total population during the reference period.	FAO Statistical Division[241]
Alcohol consumption (litres per capita)	Pure litres of alcohol consumed per adult aged 15 years or older, per capita	Global Burden of Disease Study / IHME[242]
Cigarette consumption (litres per capita)	Amount cigarettes consumed, per capita	Global Burden of Disease Study / IHME[242]
Insufficient physical activity	Sex-specific age-standardized prevalence of insufficient physical activity among adults for the year 2016 from the WHO, which was defined as the percentage of the population attaining less than 150 minutes moderate-intensity physical activity. Data was based on standardized self-reported questionnaires (GPAQ and IPAQ, see references)	World Health Organisation[243,244]
GDP per capita	Gross domestic product as purchasing power parity	World Bank[240]
Income classification	Countries with a gross national income of over US$ 12,476 per capita were classified as high-income and countries with a gross national income of over US$ 1025 and under US$ 12,476 per capita in 2001 were classified as low-to-middle-income.[245] All countries in the sample fell in one of these categories.	World Bank[240]

Table 3.1 Variable definitions and data sources

Briefly, I obtained data on age-standardised body-mass index (BMI) and overweight and obesity population prevalences (in children, adolescents, and adults), as well as age-standardised sex-specific adult diabetes mellitus prevalence data from the NCD Risk Factor Collaboration database (NCD-RisC).[2,39] Food sales data were taken from the Passport Global Market Information Database by Euromonitor International, an independent provider of strategic market research that estimates annual country-level sales of fresh and packaged foods in retail environments (e.g. supermarkets, grocery shops) and foodservices locations (i.e. full service and take-out restaurants) based on local and regional statistics from trade sources, national statistics, and company reports.[239] Data on the sales of 42 different food groups were classified into four categories of food processing according to the NOVA classification, see Table 1.1 for the NOVA classification and Table 3.1 for the classification of Euromonitor data according to NOVA. For the descriptive analyses, the NOVA variables were converted into grams or litres per day (for solids and liquids respectively) per person using annual population data from the World Bank.[240]

There could be a lag period between changes in UPFs at the food system level and changes in the outcomes studied here because population-level adiposity and DM in a given year is not only affected by the food that was sold and consumed in that specific year, but also of the foods that were consumed in the previous years. Lagged dependent variables would have reduced the observations available for analysis substantially; to be able to take lag periods into account, I created additional UPF exposure variables with moving averages.[246,247] The first variable contained the two-year moving average values of the years t and t_{-1}, and the second variable included the three-year moving average value of the years and t, t_{-1}, and t_{-2}, and so on. Since the lag period between changes in the food system and type two diabetes onset are expected to be longer, I created an additional four-year moving average for analyses of diabetes outcomes.

Name
Algeria, Argentina, Australia, Austria, Azerbaijan, Belarus, Bolivia, Bosnia-Herzegovina, Brazil, Bulgaria, Cameroon, Canada, Chile, China, Colombia, Costa Rica, Croatia, Czech Republic, Denmark, Dominican Republic, Ecuador, Egypt, Estonia, Finland, France, Georgia, Germany, Greece, Guatemala, Hungary, India, Indonesia, Iran, Ireland, Israel, Italy, Japan, Kazakhstan, Latvia, Lithuania, Macedonia, Malaysia, Mexico, Morocco, Netherlands, New Zealand, Nigeria, Norway, Pakistan, Peru, Philippines, Poland, Portugal, Romania, Russia, Saudi Arabia, Serbia, Slovakia, Slovenia, South Africa, South Korea, Spain, Sweden, Switzerland, Taiwan, Thailand, Tunisia, Turkey, United States, Ukraine, United Arab Emirates, United Kingdom, Uruguay, Uzbekistan, Venezuela

Table 3.2 List of included countries

Covariate data was derived from multiple sources. The domestic supply of alcohol per adult age 15 years and over was taken from the Global Burden of Disease Study 2016 Covariates[248] and overall dietary energy availability (kilocalories (kcal) per person per day) from food balance sheets of the Food and Agriculture Organization Statistical Division.[241] As a cross-country indicator of physical activity, I used sex-specific age-standardized prevalence of insufficient physical activity[243,244], and GDP per capita as well as the percentage of population living in urban areas were retrieved from the World Bank.[240] The final dataset included all countries for which food exposure data was available for the entire period; four countries were excluded. There were no missing values for other variables except for insufficient physical activity for three countries (3.9%), and I imputed those values to the median value of the country-group (LMIC or HIC) to which the country belonged.

3.3.2 Empirical strategy

Previous studies found that UPF sales have plateaued or even decreased in some HICs, while sales continue to increase in LMICs in Asia and Latin America; I thus planned to explore and estimate associations for HICs and LMICs separately.[249,250] To explore unadjusted longitudinal bivariate associations and identify specific countries with strong associations, I calculated relative changes in the UPF sales per capita per day and outcome variables for each country between 2001 and 2016, with the reference values for each variable set at '100' for the year 2001. I explored country-level changes in bivariate plots and added a quadratic prediction of the outcome variable using linear regressions. The data for analyses were hierarchically structured country-level panel data with 16 annual observations for each country. This type of data

structure is a special case of multi-level data in which country-years (lower level-1) data are nested or clustered within countries (higher level-2) over time.

To guide the modelling specifications, I performed a series of econometric tests to assess the statistical properties of the dataset. Woolridge's test[251] indicated the presence of autocorrelation within countries; Greene's test[252] suggested heteroscedastic residuals after a fixed-effects regression; findings from Pesaran's test[253] implied cross-sectional dependence of the errors; while Frees'[254] and Friedman's tests[255] did not; and both the Levin-Lin-Chu and the Im-Pesaran-Shin tests[256] suggested the absence of a unit-root of the panel dataset.

As the first estimation strategy, I performed a fixed-effects regression that accounted for heteroscedastic, auto-correlated (or clustered), and cross-sectionally dependent standard errors,[257] using the following equation, shown in its demeaned form:[258]

$$(y_{it} - \overline{y}_i) = \beta_W(x_{it} - \overline{\mathrm{x}}_i) + (\epsilon_{it} - \overline{\epsilon}_{it})$$

The subscript i indicates level 2 (country) and t denotes level 1 (years). y_{it} is the outcome that varies between and within countries and $\overline{y}_i$ is the country-mean of the outcome. x_{it} is a covariate that varies between and within countries, $\overline{\mathrm{x}}_i$ the country-mean of that variable, and ϵ_{it} is the error on level 1 and $\overline{\epsilon}_{it}$ its mean. By subtracting the country-means, this approach models only the variation within the countries during the study period, and β_W thus represents the 'within' coefficient estimate for the variables of interest.[259] This is a conservative strategy that minimizes the risk of bias from unobserved confounding between countries, but it excludes time-invariant variables from the estimation, as well as all the variation that exists between the countries in the dataset.[259,260] To use both within- and between-variation I used a second modelling strategy, a two-level hierarchical linear mixed model which allows for both intercepts and slopes to vary across groups.[261,262] I specified the standard errors to account for autocorrelation and heteroscedasticity and used the following equation:

$$y_{it} = \alpha_{t[i]} + \beta_{t[i]}x_i + \varepsilon_i$$

where $\alpha_{t[i]}$ is the varying intercept of the value of *t* assigned to the country i, $\beta_{t[i]}$ is the varying slope (or coefficient) of covariate x for country i, and ε_i is the country-specific error term.

In the multivariable analyses, the first model included only UPF sales; to account for the possibility of confounding by unprocessed foods, physical inactivity, or income, model two included these variables as covariates; model three additionally adjusted for alcohol consumption (not in children and adolescent populations) and total energy intake; and model four additionally adjusted for the proportion of the population living in urban areas. As a known risk factor of type 2 diabetes mellitus, I additionally included smoking in model three. To construct the multiverse, associations were estimated for combinations of each of the outcomes, sexes, populations, exposure averages, models, and estimation strategies, yielding 288 and 64 combinations in total in the case of adiposity and diabetes, respectively. The summary of all combinations of the model dimensions are shown in Table 3.3.

As discussed in the introductory chapter, I recognize that the statistical practice to dichotomize statistical findings into 'not significant' and 'significant' at *P*-value of 0.05 is arbitrary.[166] Proposed solutions range from completely abandoning statistical significance[164,263] to redefining it at *P*=0.005.[148,164–166,185,263] Here, I follow Greenland et al.[166] and interpret estimated *P*-values as a continuous measure of the compatibility between the observed data and what would be predicted or expected if the entire statistical model and all its assumptions (such as the null hypothesis) that were used to compute the *P*-value were correct, ranging from no compatibility (*P*=0) to complete compatibility (*P*=1). With this approach, the *P*-value can be viewed as measuring the fit of the model to the data, but a low *P*-value does not indicate which of the model assumptions is incorrect. I report *P*-values down to 0.0001 and *P*-values smaller than 0.0001 as 0.0000. The analysis protocol, Stata code, and data (except data from Euromonitor, which requires a paid subscription) are available at https://github.com/kai-schulze/upf_panel. All analyses were performed in Stata, version 15.1 (StataCorp LLC, College Station, Texas, USA).

Dimension	Specification	Number of specifications
	Adiposity	
Outcomes	BMI Overweight Obesity	3
Population	Adults Children & adolescents	2
Sex	Female Male	2
Exposure averages	Annual Two-year average Three-year average	3
Number of models	M1: Ultra-processed foods M2: M1 + unprocessed foods, insufficient physical activity, GDP M3: M2 + Total energy intake, alcohol consumption (for adults) M4: M3 + proportion of population in urban areas	4
Statistical approaches	1. Fixed effects regression with SE adjusted for heteroscedasticity, autocorrelation, and cross-sectional dependence 2. Two-level hierarchical linear mixed model with varying intercepts and coefficient with SE adjusted for autocorrelation and heteroscedasticity	2
	Total number of estimates (product)	**288**
Diabetes		
Outcome	Diabetes	1
Population	Adults	1
Sex	Female Male	2
Exposure averages	Annual Two-year average Three-year average Four-year average	4
Number of models	M1: Ultra-processed foods M2: M1 + unprocessed foods, insufficient physical activity, GDP M3: M2 + Total energy intake, alcohol consumption, smoking M4: M3 + proportion of population in urban areas	4
Statistical approaches	1. Fixed effects regression with SE adjusted for heteroscedasticity, autocorrelation, and cross-sectional dependence 2. Two-level hierarchical linear mixed model with varying intercepts and coefficient with SE adjusted for autocorrelation and heteroscedasticity	2
	Total number of estimates (product):	**64**

Table 3.3 Multiverse model dimensions for analyses of adiposity and diabetes

3.4 Results

I included data from 76 countries over 16 years, giving 1216 observations in total and representing a population of 5.9 billion individuals or 79% of the global population in 2016. Table 3.4 shows descriptive statistics for all countries in years 2001 and 2016. The prevalence of adiposity and diabetes outcomes increased considerably during the study period, for both sexes, as well as for adults and children. Unprocessed food sales, urban population, GDP per capita, and total available energy grew during the study period, whereas per capita alcohol consumption changed little.

	2001	2016	
	Median (IQR)	**Median (IQR)**	**p-value***
Population (n=76 countries)	5.2 billion	5.9 billion	
BMI (adult female) [kgm^{-1}]	25.7 (25.0-26.3)	26.7 (25.3-27.4)	<0.001
BMI (adult male) [kgm^{-1}]	25.8 (24.5-26.4)	26.8 (25.8-27.5)	<0.001
BMI (female) [kgm^{-1}]	19.2 (18.7-19.9)	19.6 (19.1-20.2)	<0.001
BMI (boys) [kgm^{-1}]	19.1 (18.6-19.6)	19.8 (19.4-20.2)	0.008
Overweight prevalence (females) [%]	30.0 (28.5-31.3)	30.4 (29.3-31.3)	0.20
Overweight prevalence (males) [%]	38.3 (34.1-42.2)	40.6 (37.8-42.5)	0.061
Overweight prevalence (girls) [%]	19.4 (13.0-24.7)	23.9 (19.2-30.6)	<0.001
Overweight prevalence (boys) [%]	18.9 (15.8-25.9)	29.6 (24.1-33.2)	<0.001
Obesity prevalence (females) [%]	19.0 (15.6-23.7)	25.2 (20.6-29.7)	<0.001
Obesity prevalence (males) [%]	15.3 (10.4-17.3)	22.1 (17.1-25.0)	<0.001
Obesity prevalence (girls) [%]	4.0 (2.6-6.0)	7.3 (4.8-10.3)	<0.001
Obesity prevalence (boys) [%]	5.6 (4.2-8.6)	10.8 (8.6-14.0)	<0.001
Diabetes prevalence (female) [%]	6.7 (6.1-7.6)	7.1 (5.9-10.4)	<0.001
Diabetes prevalence (male) [%]	6.5 (5.6-8.0)	8.4 (7.4-10.0)	0.037
Ultra-Processed Foods [g per capita/d]	405 (249-598)	458 (323-632)	0.061
Unprocessed Foods [g per capita/d]	731 (557-852)	821 (639-993)	<0.001
Urban Population [%]	66 (55-78)	70 (58-82)	0.10
Alcohol consumption [litres per capita]	9.1 (6.0-12.2)	9.3 (6.7-11.6)	0.87
Total Energy Supply [100 kcal/d]	3012.1 (2738.0-3327.4)	3158.1 (2911.7-3417.8)	0.02
GDP per capita (PPP)	9905.0 (6105.0-25265.0)	22780.0 (13800.0-37825.0)	<0.001

Table 3.4 Descriptive statistics at 2001 and 2016

*p-value for Wilcoxon-rank sum test of equal medians. N=76 countries in both years.

Globally, absolute sales of UPFs in 2016 ranged from 32 g per capita per day in India to 899 g per capita per day in the United States (Figure 3.1, top panel; Table 3.4). Change in the sales of UPFs between the years 2001 and 2016 was different for countries at different levels of development (Figure 3.1, bottom panel). While sales decreased slightly from 572 to 558 grams per day on average in HICs, sales in LMICs increased on average by almost 30% from 261 to 335 grams per day. Countries with increases of over 50% were China (299%), India (267%), Indonesia (216%), Pakistan (213%), Peru (181%), Thailand (172%), Nigeria (170%), and Chile (150%). Data for each country are provided in Appendix Table 4.

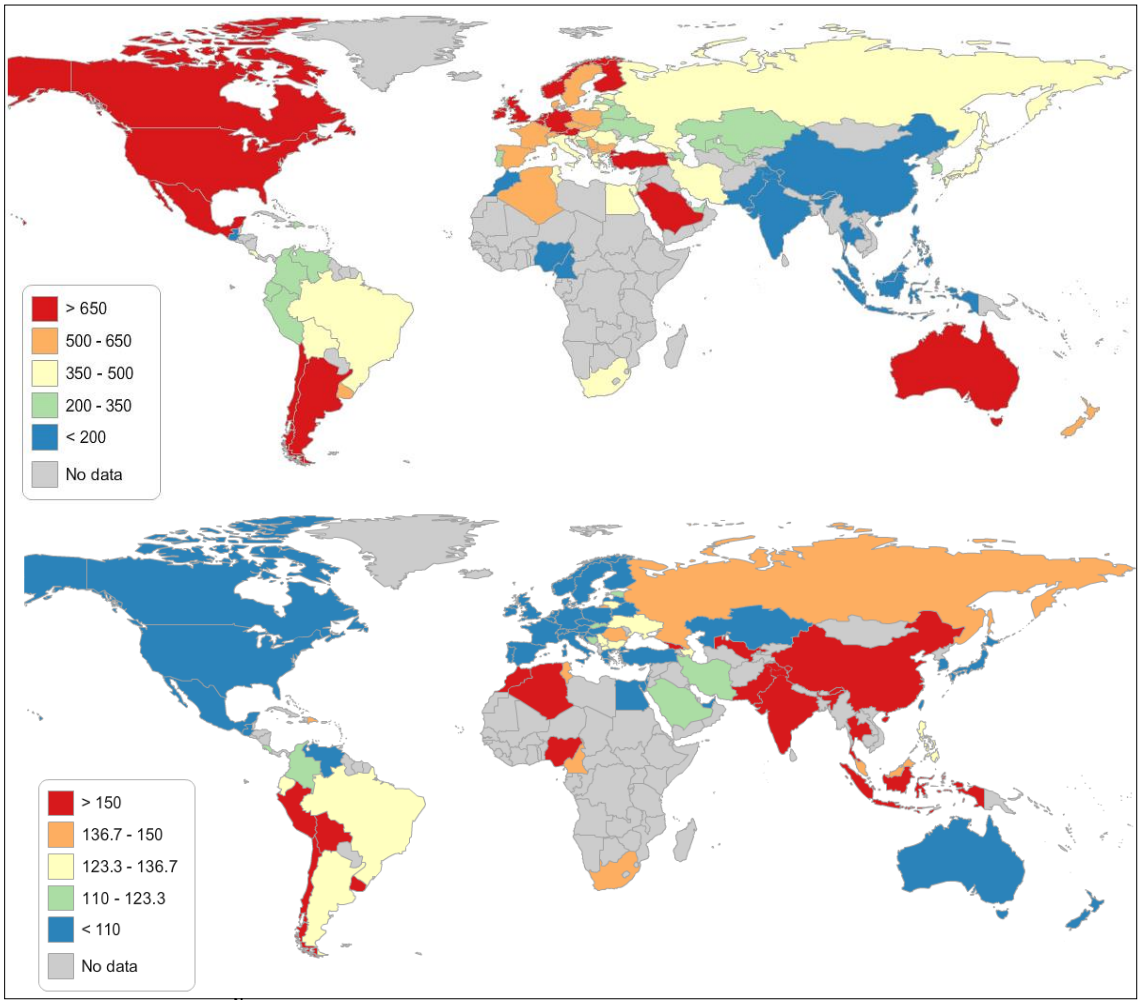


Figure 3.1 Levels of ultra-processed food sales
In g per capita per day in 2016 (top panel) and changes in ultra-processed food sales from 2001 to 2016 (bottom panel, in %, 2001=100%).

I plotted changes in UPF sales against changes in adiposity and diabetes outcomes, for women, men, girls, and boys, and for all countries combined and for LMICs and HICs separately. Figures

3.2 and 3.3 illustrate results for BMI, obesity, and diabetes. The associations between changes in UPF sales and changes in BMI were consistently positive, regardless of sex, age, or country income level. Associations between changes in UPF sales and changes in overweight or obesity were positive when all countries were considered but were flatter in the HICs subsample. Some countries had consistently large positive associations between changes in UPF sales and all adiposity outcomes, notably China, India, Nigeria, Pakistan, South Africa, and Thailand. Bivariate associations between UPF and diabetes prevalence were positive in the whole sample but were more consistent in males when LMICs and HICs were considered separately.

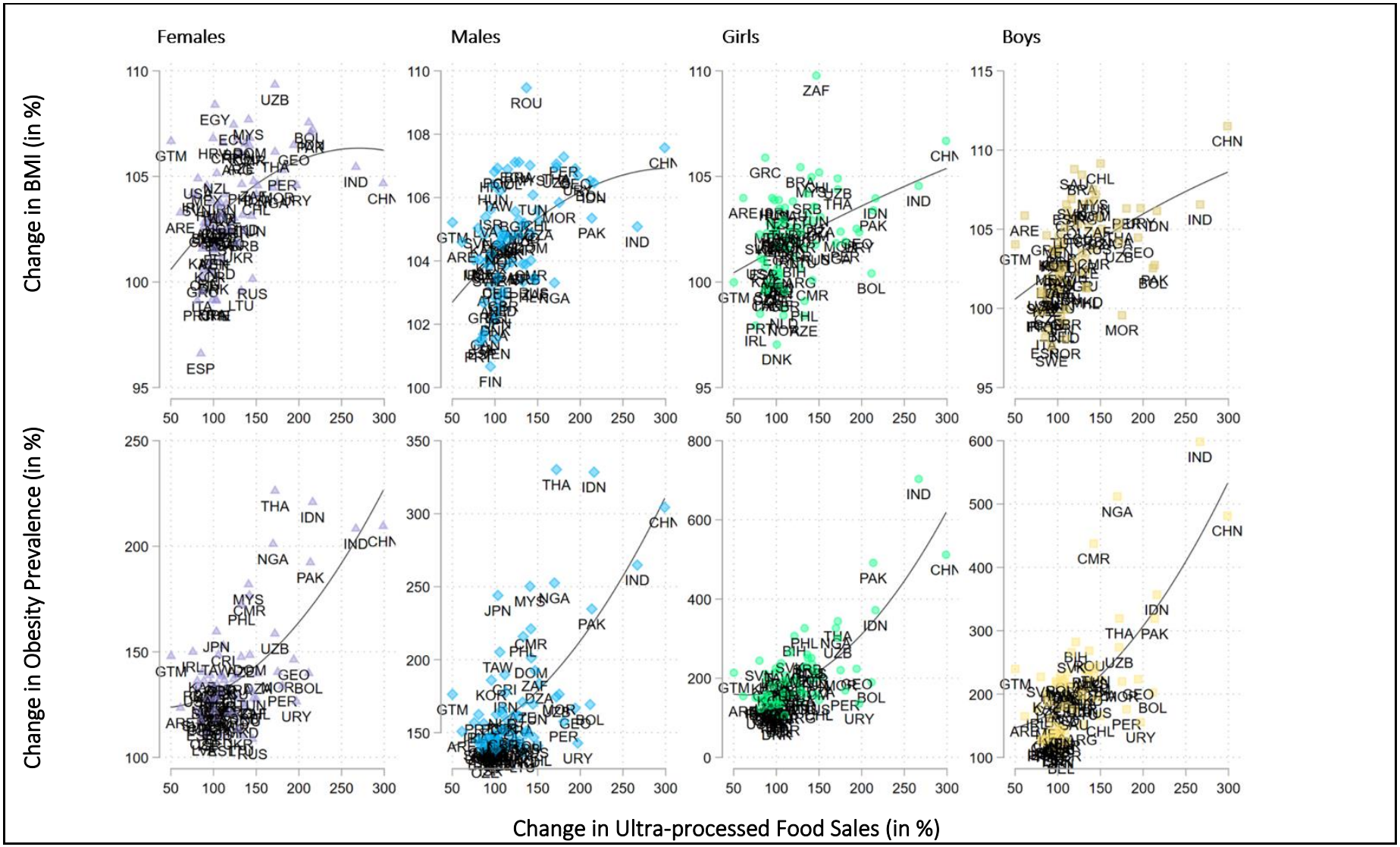


Figure 3.2 Bivariate association between changes in ultra-processed food sales and BMI (top row) and obesity prevalence (bottom row)
Changes between 2001 and 2016, in %, 2001 = 100. Quadratic predictions from linear regressions between the two change variables as solid lines.

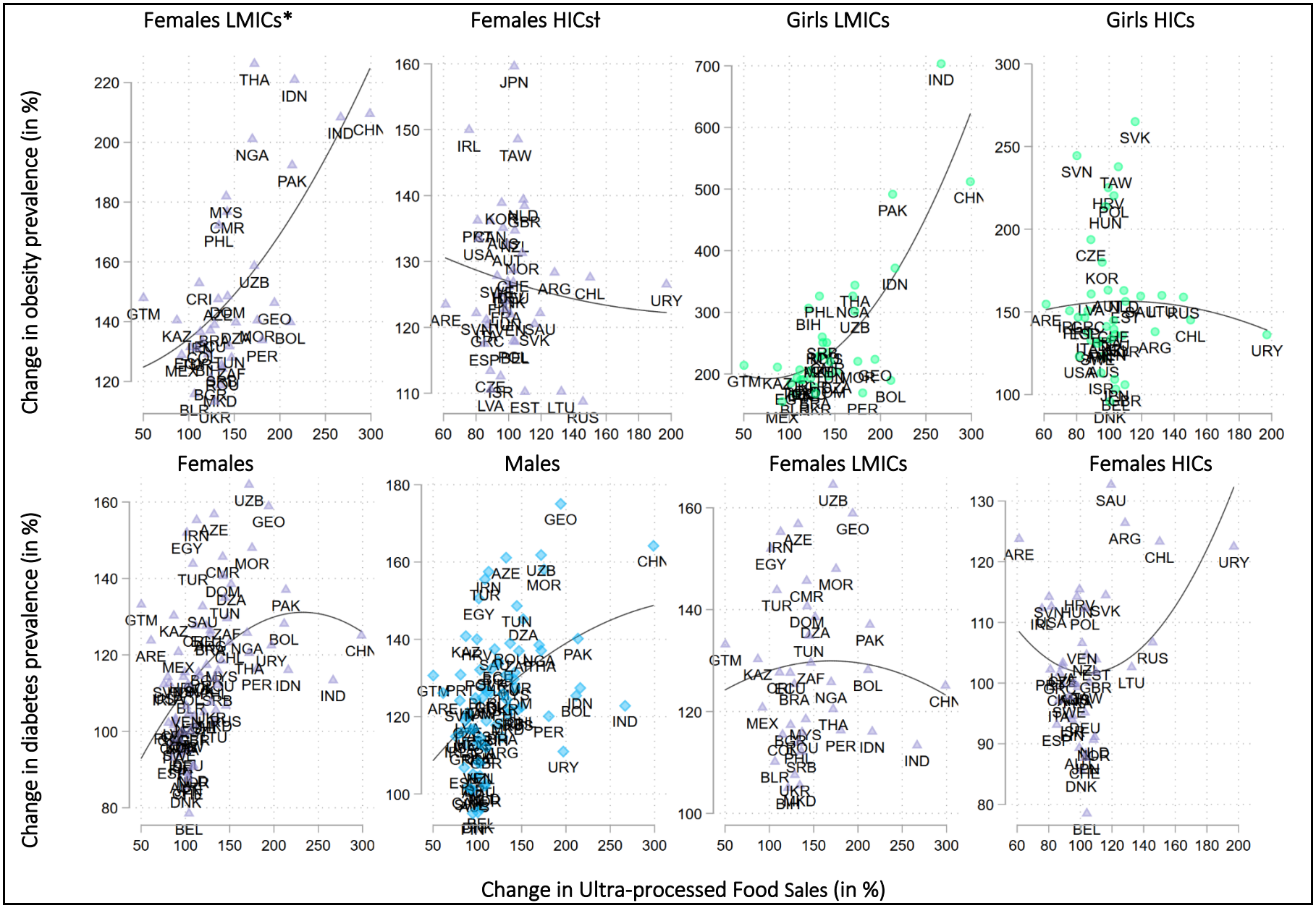
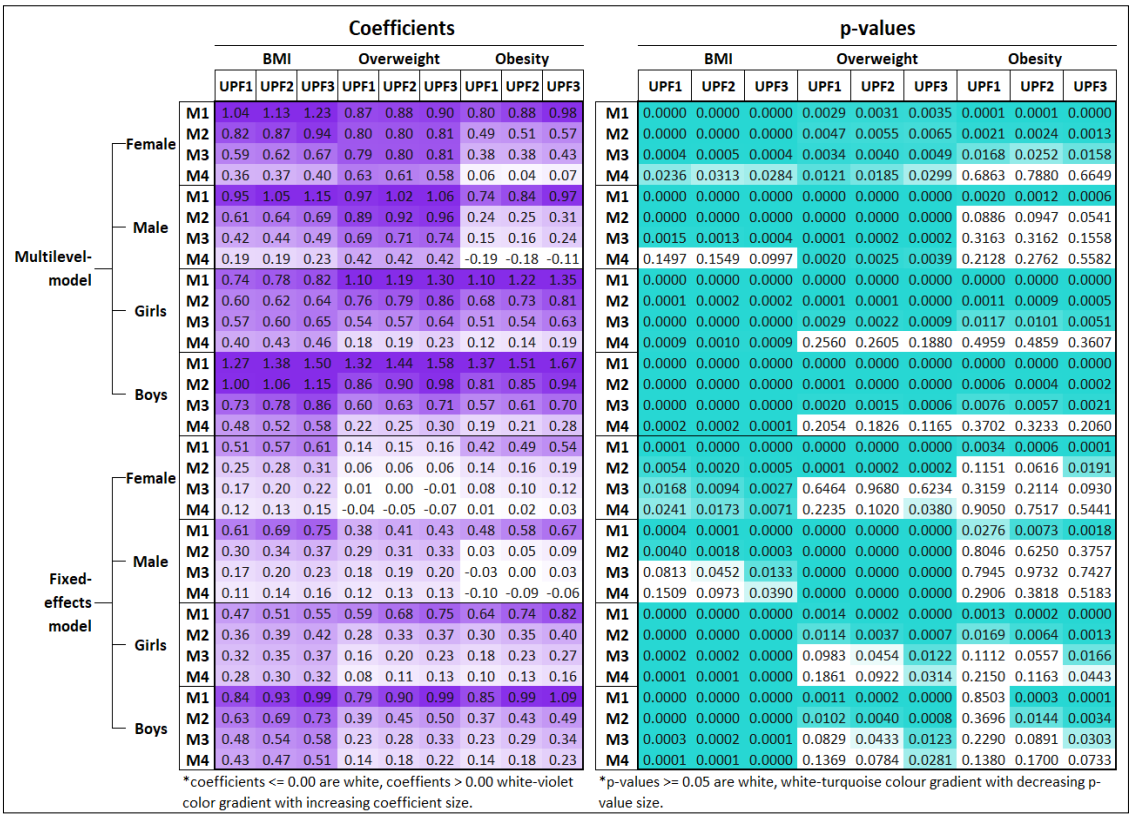


Figure 3.3 Bivariate association between changes in ultra-processed food sales and obesity prevalence (top row) and diabetes prevalence (bottom row)
Changes between 2001 and 2016, in %, 2001 = 100. Quadratic predictions from linear regressions between the two change variables as solid lines. *LMICs = Low- and middle-income countries; †HICs= High-income countries.

In the multiverse analysis of adiposity, 279 of 288 coefficient estimates of the association between UPFs and adiposity were positive (Figure 3.4). The magnitude of associations was generally larger between UPFs and BMI than for overweight and obesity and increased with the length of rolling average of UPF sales. 176 (61.1%) of *P*-values were below 0.005 (median *P*-value 0.0013).



Coefficients

		BMI			Overweight			Obesity		
		UPF1	UPF2	UPF3	UPF1	UPF2	UPF3	UPF1	UPF2	UPF3
Multilevel-model	Female	M1	1.04	1.13	1.23	0.87	0.88	0.90	0.80	0.88	0.98
		M2	0.82	0.87	0.94	0.80	0.80	0.81	0.49	0.51	0.57
		M3	0.59	0.62	0.67	0.79	0.80	0.81	0.38	0.38	0.43
		M4	0.36	0.37	0.40	0.63	0.61	0.58	0.06	0.04	0.07
	Male	M1	0.95	1.05	1.15	0.97	1.02	1.06	0.74	0.84	0.97
		M2	0.61	0.64	0.69	0.89	0.92	0.96	0.24	0.25	0.31
		M3	0.42	0.44	0.49	0.69	0.71	0.74	0.15	0.16	0.24
		M4	0.19	0.19	0.23	0.42	0.42	0.42	-0.19	-0.18	-0.11
	Girls	M1	0.74	0.78	0.82	1.10	1.19	1.30	1.10	1.22	1.35
		M2	0.60	0.62	0.64	0.76	0.79	0.86	0.68	0.73	0.81
		M3	0.57	0.60	0.65	0.54	0.57	0.64	0.51	0.54	0.63
		M4	0.40	0.43	0.46	0.18	0.19	0.23	0.12	0.14	0.19
	Boys	M1	1.27	1.38	1.50	1.32	1.44	1.58	1.37	1.51	1.67
		M2	1.00	1.06	1.15	0.86	0.90	0.98	0.81	0.85	0.94
		M3	0.73	0.78	0.86	0.60	0.63	0.71	0.57	0.61	0.70
		M4	0.48	0.52	0.58	0.22	0.25	0.30	0.19	0.21	0.28
Fixed-effects model	Female	M1	0.51	0.57	0.61	0.14	0.15	0.16	0.42	0.49	0.54
		M2	0.25	0.28	0.31	0.06	0.06	0.06	0.14	0.16	0.19
		M3	0.17	0.20	0.22	0.01	0.00	-0.01	0.08	0.10	0.12
		M4	0.12	0.13	0.15	-0.04	-0.05	-0.07	0.01	0.02	0.03
	Male	M1	0.61	0.69	0.75	0.38	0.41	0.43	0.48	0.58	0.67
		M2	0.30	0.34	0.37	0.29	0.31	0.33	0.03	0.05	0.09
		M3	0.17	0.20	0.23	0.18	0.19	0.20	-0.03	0.00	0.03
		M4	0.11	0.14	0.16	0.12	0.13	0.13	-0.10	-0.09	-0.06
	Girls	M1	0.47	0.51	0.55	0.59	0.68	0.75	0.64	0.74	0.82
		M2	0.36	0.39	0.42	0.28	0.33	0.37	0.30	0.35	0.40
		M3	0.32	0.35	0.37	0.16	0.20	0.23	0.18	0.23	0.27
		M4	0.28	0.30	0.32	0.08	0.11	0.13	0.10	0.13	0.16
	Boys	M1	0.84	0.93	0.99	0.79	0.90	0.99	0.85	0.99	1.09
		M2	0.63	0.69	0.73	0.39	0.45	0.50	0.37	0.43	0.49
		M3	0.48	0.54	0.58	0.23	0.28	0.33	0.23	0.29	0.34
		M4	0.43	0.47	0.51	0.14	0.18	0.22	0.14	0.18	0.23

*coefficients <= 0.00 are white, coeffients > 0.00 white-violet color gradient with increasing coefficient size.

p-values

	BMI			Overweight			Obesity		
	UPF1	UPF2	UPF3	UPF1	UPF2	UPF3	UPF1	UPF2	UPF3
M1	0.0000	0.0000	0.0000	0.0029	0.0031	0.0035	0.0001	0.0001	0.0000
M2	0.0000	0.0000	0.0000	0.0047	0.0055	0.0065	0.0021	0.0024	0.0013
M3	0.0004	0.0005	0.0004	0.0034	0.0040	0.0049	0.0168	0.0252	0.0158
M4	0.0236	0.0313	0.0284	0.0121	0.0185	0.0299	0.6863	0.7880	0.6649
M1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0020	0.0012	0.0006
M2	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0886	0.0947	0.0541
M3	0.0015	0.0013	0.0004	0.0001	0.0002	0.0002	0.3163	0.3162	0.1558
M4	0.1497	0.1549	0.0997	0.0020	0.0025	0.0039	0.2128	0.2762	0.5582
M1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
M2	0.0001	0.0002	0.0002	0.0001	0.0001	0.0000	0.0011	0.0009	0.0005
M3	0.0000	0.0000	0.0000	0.0029	0.0022	0.0009	0.0117	0.0101	0.0051
M4	0.0009	0.0010	0.0009	0.2560	0.2605	0.1880	0.4959	0.4859	0.3607
M1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
M2	0.0000	0.0000	0.0000	0.0001	0.0000	0.0000	0.0006	0.0004	0.0002
M3	0.0000	0.0000	0.0000	0.0020	0.0015	0.0006	0.0076	0.0057	0.0021
M4	0.0002	0.0002	0.0001	0.2054	0.1826	0.1165	0.3702	0.3233	0.2060
M1	0.0001	0.0000	0.0000	0.0000	0.0000	0.0000	0.0034	0.0006	0.0001
M2	0.0054	0.0020	0.0005	0.0001	0.0002	0.0002	0.1151	0.0616	0.0191
M3	0.0168	0.0094	0.0027	0.6464	0.9680	0.6234	0.3159	0.2114	0.0930
M4	0.0241	0.0173	0.0071	0.2235	0.1020	0.0380	0.9050	0.7517	0.5441
M1	0.0004	0.0001	0.0000	0.0000	0.0000	0.0000	0.0276	0.0073	0.0018
M2	0.0040	0.0018	0.0003	0.0000	0.0000	0.0000	0.8046	0.6250	0.3757
M3	0.0813	0.0452	0.0133	0.0000	0.0000	0.0000	0.7945	0.9732	0.7427
M4	0.1509	0.0973	0.0390	0.0000	0.0000	0.0000	0.2906	0.3818	0.5183
M1	0.0000	0.0000	0.0000	0.0014	0.0002	0.0000	0.0013	0.0002	0.0000
M2	0.0000	0.0000	0.0000	0.0114	0.0037	0.0007	0.0169	0.0064	0.0013
M3	0.0002	0.0002	0.0000	0.0983	0.0454	0.0122	0.1112	0.0557	0.0166
M4	0.0001	0.0001	0.0000	0.1861	0.0922	0.0314	0.2150	0.1163	0.0443
M1	0.0000	0.0000	0.0000	0.0011	0.0002	0.0000	0.8503	0.0003	0.0001
M2	0.0000	0.0000	0.0000	0.0102	0.0040	0.0008	0.3696	0.0144	0.0034
M3	0.0003	0.0002	0.0001	0.0829	0.0433	0.0123	0.2290	0.0891	0.0303
M4	0.0001	0.0001	0.0000	0.1369	0.0784	0.0281	0.1380	0.1700	0.0733

*p-values >= 0.05 are white, white-turquoise colour gradient with decreasing p-value size.

Figure 3.4 Associations between UPFs and adiposity for 76 countries between 2001 and 2016
Left panel: coefficients denote the change in the outcome variables for a one SD increase in UPFs. Right panel: p-values for the UPF coefficient estimations. UPF1-3: one-year, two-year, and three-year rolling averages of UPFs. M1: UPFs (unadjusted); M2: M1 + unprocessed foods, insufficient physical activity, GDP per capita (PPP); M3: M2 + total available energy, alcohol consumption; M4: M3 + urbanization.

Coefficients were larger for children and adolescent populations, and the estimated associations of the multilevel-models were generally higher than those of the fixed-effects regressions. No clear pattern was observed between the sexes in adult populations, but the associations between UPFs and adiposity were stronger for boys than for girls. Analysing countries from LMICs and HICs separately yielded clear differences in the magnitude and *P*-values of the estimated associations (Figure 3.5). In LMICs, the coefficients of the association between UPFs

and adiposity were large, mostly positive, and with low *P*-values (78.8% of *P*-values <0.005; median 0.0001).

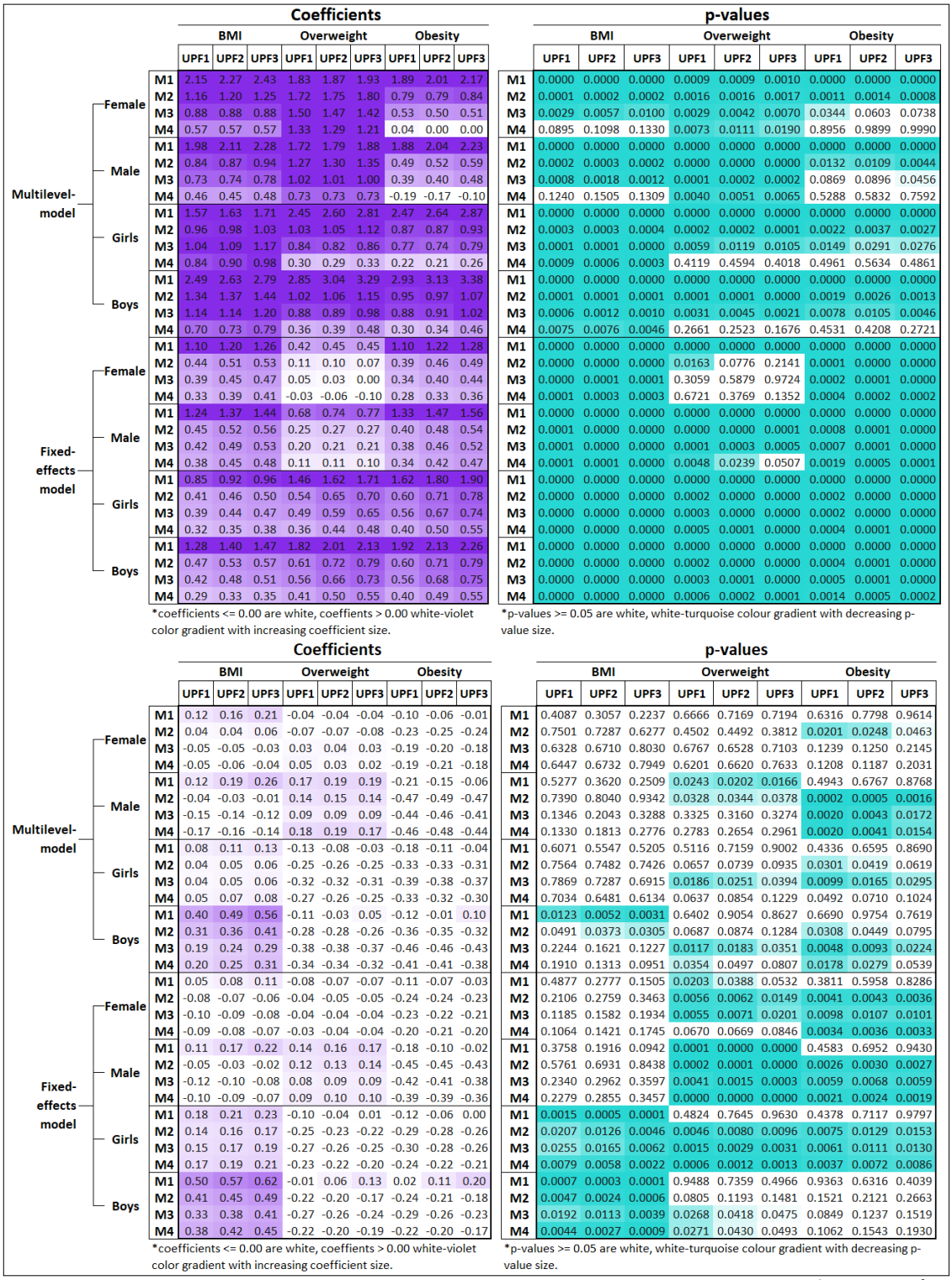


Figure 3.5*:* Associations between UPFs and adiposity between 2001 and 2016, for LMICs (top panels) and HICs (bottom panels)

Left panels: coefficients denote the change in the outcome variables for a one SD increase in UPFs. Right panel: p-values for the UPF coefficient estimations. UPF1-3: one-year, two-year, and three-year rolling averages of UPFs. M1: UPFs (unadjusted); M2: M1 + unprocessed foods, insufficient physical activity, GDP per capita (PPP); M3: M2 + total available energy, alcohol consumption; M4: M3 + urbanization.

In HICs, this pattern was inverted; coefficients were small and sometimes negative while *P*-values were large (19.4% of *P*-values <0.005; median 0.0827).

In the multiverse analysis of diabetes, all coefficient estimates of the association between UPFs and diabetes prevalence were positive (Figure 3.6). The associations were generally larger for men, and the successive addition of confounding factors reduced the magnitude of the association. 75.0% of the *P*-values were below 0.005 (median 0.0001). When I analysed LMICs and HICs separately, the pattern was broadly similar to that for adiposity. The magnitude of the coefficient estimates was higher in LMICs, and 62.5% of the *P*-values were below 0.005 (median 0.0001). However, the *P*-values in the multi-level models 3 and 4 were higher compared to those in the fixed-effects models. In HICs, some coefficients were negative, and 1.6% of the *P*-values were below 0.005, and the median *P*-value was 0.4402.

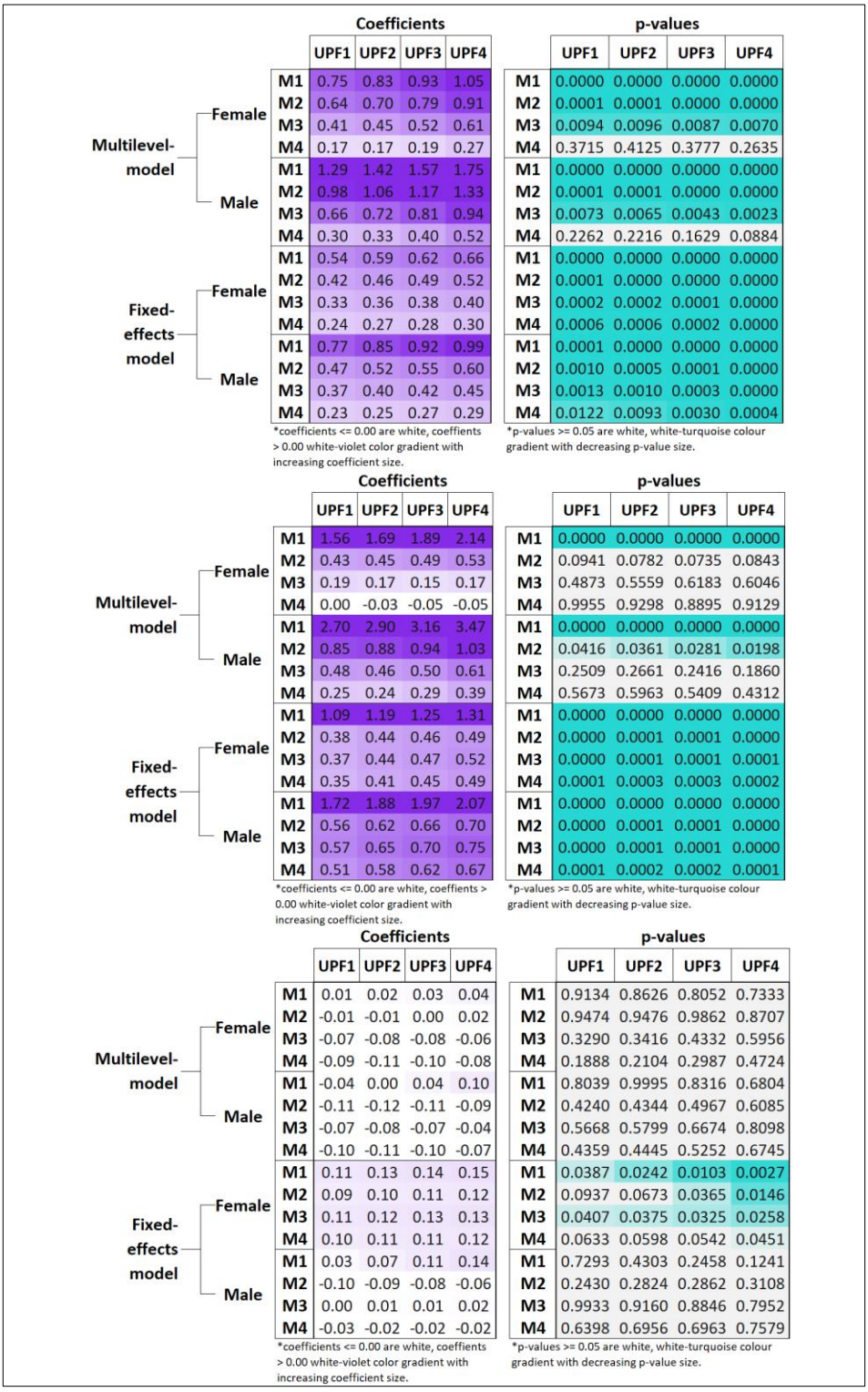


Figure 3.6 Associations between UPFs and diabetes between 2001 and 2016, for all countries (top panels), LMICs (middle panels), and HICs (bottom panels)

Left panels: coefficients denote the change in the outcome variables for a one SD increase in UPFs. Right panel: p-values for the UPF coefficient estimations. UPF1-4: one year- to four year rolling averages of UPFs. M1: UPFs (unadjusted); M2: M1 + unprocessed foods, insufficient physical activity, GDP per capita (PPP); M3: M2 + total available energy, alcohol consumption, cigarette consumption; M4: M3 + urbanization.

3.5 Discussion

In this study, I compiled a database of annual country-level panel data of UPF sales and adiposity and diabetes outcomes for 76 countries between the years 2001 and 2016. The results show that sales of UPFs varied greatly between countries and have increased substantially in LMICs during the study period, while sales of UPFs stagnated in many HICs. Unadjusted bivariate associations were particularly strong in Chile, China, India, Indonesia, Pakistan, South Africa, and Thailand. Adiposity was positively associated with UPF sales across almost all combinations in the multiverse analyses, including important socioeconomic and nutritional factors such as income, total energy intake, sales of unprocessed foods, physical activity, and urbanization, with very low *P*-values indicating strong evidence for violations of the model assumptions. In HICs, both the magnitude and the sign of the associations varied, and *P*-values were often large. Between the sexes, associations were larger overall for boys than for girls, but no clear pattern was observed in adult populations. These patterns of results were broadly replicated for diabetes, although the findings were less consistent for LMICs compared to adiposity.

3.5.1 Comparison with other studies and interpretation

One previous country-level panel study used similar data reported a positive association between soft drinks sales and adiposity and diabetes outcomes.[264] Several other studies have shown that the sales of packaged and some processed foods have increased in LMICs from Asia and Latin America and have plateaued in HICs. [135,137,249,250,265–267] However, I am not aware of previous studies that systematically classified all available food groups according to their degree of food processing and performed multivariable analyses on associations with diabetes and adiposity outcomes on a large sample of countries in both adult and children and adolescent population or reported such analyses for HICs and LMICs separately. Also, for each variable, I aimed to select the best data available from leading sources that had been published in peer-reviewed journals, such as, for example, NCD-RisC, Global Burden of Disease Studies, or the WHO. Using the multiverse-analysis approach, I was able to demonstrate that the observed

patterns did not result from specific combinations of outcomes, covariates, populations, or estimation strategies, and were robust in multiple equivalent analyses.

Several hypotheses that were explained in chapters 1 and 2 shall be briefly repeated here to explain the findings. In studies from different countries, UPFs have been found to contain higher levels of sugar, sodium, trans fats (from complete or partially hydrogenated oils), energy, and less fibre and various micronutrients.[96–98,110,111,134,268–270] UPFs have also been found to be less satiating and have a higher glycaemic load than minimally or unprocessed foods.[104] High intakes of sugar and unhealthy fats, low intakes of dietary fibre, and high intake of foods with a high glycaemic index negatively affect the development of insulin resistance and type two diabetes mellitus, which accounts for approximately 90-95% of all diabetes mellitus cases.[105–109] Obesity is a disorder of the energy homeostasis system which is influenced by diet through multiple pathways, including brain rewards, satiety, glucose-insulin responses, and energy intake and expenditure.[3,90,91] Studies have shown that diets high in refined carbohydrates and fats lead to rapid and pronounced weight gain.[93,271] Since UPFs are often characterized by a combination of high levels of refined carbohydrates and fats, are often highly energy-dense and usually contain flavours and food additives that affect reward and satiety systems along the gut-brain axis, a causal link with obesity is plausible.[3,91] Accordingly, the results that UPFs are associated with adiposity are consistent with biological mechanisms and evidence from individual-level studies.[94,132]

Although individual-level evidence of an association between UPFs and adiposity is based on studies from HICs[94,141], I did not observe an association in HICs at the population-level. This result is likely to be related to differences in the variation of the exposure between these two study types. While there is much variation in UPF consumption between participants in cohort studies, this is not the case when sales of UPFs are measured on the aggregate level in HICs. In HICs, the main phase of the nutrition transition happened during the 1980s and 1990s, and levels of UPFs were already high and relatively evenly distributed in 2001.[65,272,273] With greater awareness of

nutritional risks, eating culture has shifted in some HICs, and small noticeable trends towards better dietary quality have been reported over the study period.[274] This was not the case for many LMICs, of which some had just entered a nutrition transition in the early 2000s, or were in the midst of it, and there was much variation within and between those countries in the sample.[272,273] Once the analyses were run separately in HICs, there was little variation in the UPF sales exposure and hence no 'signal' which could have been picked up by the different analyses. This does not mean that there is no association in HICs, but that the rapid increases in LMICs in both exposures and outcomes over the study period allow associations to be identified more clearly in LMICs. UPFs are likely associated with outcomes in HICs as well, as is indicated by individual-level evidence, but the combination of data, methods, and time period used here are not suitable to capture this association.

3.5.2 Strengths and limitations

This is the first study that provides evidence on the associations between UPFs and adiposity and diabetes in regions that traditionally lack data, estimates associations separately for LMICs and HICs, and uses a multiverse approach to make the data processing and analytical approaches transparent. The study also has several limitations. First, its ecological nature means that the analysis is based on aggregate-level data that does not allow inferences to be made at an individual-level. Second, measurement error and limitations in the data quality could have influenced the results. Euromonitor applies the same methodology to collect and measure data in all countries; however, systematic differences in data accessibility, coverage, and precision might exist between countries at different stages of development. However, it is not certain in which direction the results would be biased by this variability. Also, I used sales data on UPFs as a proxy for consumption. Per capita food waste tends to be higher in HICs than in LMICs.[275] This might have attenuated the estimated association in HICs to some extent, but it is unlikely that accounting for differences in food waste would have fundamentally changed observed patterns, as this would have required substantial food waste of UPFs, which are by definition shelf-stable

and have a lower risk of waste than other food groups. Additionally, food waste also would have to be differential according to outcomes, which is unlikely. Another limitation was that data on insufficient physical activity was only available for the year 2016. However, a recent analyses of the trends in insufficient physical activity between 2001 and 2016 (for which the individual country data are unpublished) show no changes in overall insufficient physical activity levels globally, but a minor increase in HICs, Latin America, and the Caribbean, and a decrease of insufficient physical activity levels in East and southeast Asia.[243] Using this data would have possibly strengthened the observed overall pattern of results.

Third, residual confounding could have influenced the results. I included the main factors that could have potentially confounded the country-level associations between UPFs and adiposity and diabetes outcomes. However, violations of the 'ignorability' assumption (a lack of overlap or lack of balance in covariate structure between more and less exposed countries) are plausible and can imply erroneous covariate-adjusted estimates and *P*-values.[228,261]

Given these limitations, I consider the emphasis on any specific point estimate including any specific *P*-value inappropriate for the context of this study. However, I evaluate that none of the limitations alone, or a combination thereof, would have substantially altered the patterns I observed. The results provide evidence that greater sales (and likely consumption) of UPFs in LMICs are consistently associated with increases in obesity and diabetes, and that likely associations in HICs are not captured due to a lack of variation in sales of UPF in HICs.

3.5.3 Implications for research and policy

Further research is needed to investigate the associations in LMICs in prospective cohort studies. Further analysis is also needed to geographically decompose aggregate findings so as to identify regional variations in outcomes and UPF exposure within countries, for example rural versus urban areas. Adiposity and diabetes are amongst the most pressing global health issues of our time, with worrying trends in low-to-middle income countries.[276] Actions at the food system level to decrease sales of UPFs likely offer promising strategies to reduce population-level

adiposity and diabetes. Such interventions would have a wider reach, greater impact, and equity if delivered at the population-level, than to individuals at high risk.[232] Further details of research and policy recommendations are provided in the overall discussion of this thesis.

4 A PROSPECTIVE COHORT ANALYSIS IN *EPIC-NORFOLK*

Co-authors: FI, MW, JA, and Marleen Lentjes.

A summary of this work is in preparation as a manuscript for submission to *Circulation*.

4.1 Introduction

This is the final chapter that explores associations between UPF intake and cardiometabolic health. The first two chapters established that previous nutrition studies viewed from an UPF perspective demonstrated associations between dietary patterns characterized by higher relative intake of UPFs and T2DM and CVD, and that associations between sales of UPFs and diabetes and adiposity at the country-level exist in LMICs. However, given the methodological limitations of both chapters and the limited explicit evidence on UPFs and cardiometabolic health from prospective cohorts, the research reported in this chapter aimed to estimate the associations of higher UPF intakes and risk of adverse cardiometabolic health outcomes and assess the dose-response relationships in the prospective *EPIC-Norfolk* cohort.

Two high quality epidemiology studies have previously investigated the relationship between UPFs and adiposity. In the first randomized controlled trial of *ad libitum* UPF versus unprocessed food consumption, participants in the UPF group consumed on average about 500 calories more than participants in the unprocessed group.[94] Participants in the UPF group also gained 0.8 kg body weight, while participants in the unprocessed food group lost 1.1 kg over a period of two weeks. In the Spanish University of Navarra Follow-Up *SUN* cohort, UPF intake was prospectively associated with an increased risk of overweight and obesity (HR: 1.26; 95% CI: 1.10, 1.45). Regarding CVD as an outcome, UPF intake was prospectively associated with an increased risk of CVD in the French *NutriNet-Santé* cohort (HR: 1.12; 95% CI: 1.05, 1.20).[144] Both studies, however, have their shortcomings. First, the *SUN* cohort consists of a special population (university students), while *NutriNet-Santé* is a web-based cohort with a comparatively short follow-up (7.4 years median) for CVD. Furthermore, to my knowledge, no evidence from prospective cohorts on the associations between UPFs and T2DM exists, and no study has compared different ways of operationalizing UPF intake.

4.2 Contributions

KS, JA, and MW designed the study with inputs from FI and Stephen Sharp. Marleen Lentjes coordinated the generation of the dataset and provided input into the operationalization of the UPF variables and ultra-processed food groups. KS conducted the analyses and drafted the manuscript. All authors contributed to the interpretation of the results and critically reviewed the chapter. I would also like to express gratitude to the *EPIC-Norfolk* data team for preparing the dataset and making it accessible.

4.3 Methods

4.3.1 Study population and setting

EPIC-Norfolk is an ongoing prospective cohort that is part of the Europe-wide multi-centre European Prospective Investigation into Cancer (EPIC) study located in 23 centres in 10 countries.[277] The goal of the full EPIC study was to follow individuals to estimate incidence of cancer and cause-specific mortality; however the aim of EPIC-Norfolk further included causes of disability and death in middle and later life, as well as investigating psychosocial factors, physical activity, and a broader set of aspects of lifestyle.[278] 30,445 community-dwelling women and men were recruited from thirty-five General Practitioners' surgeries in Norfolk county, United Kingdom (39% response rate). After giving informed consent, 25,639 participants (99.6% British) aged 39-79 years attended a baseline health examination (HE1) between 1993 and 1997 and, of these, 15,786 (61%) attended a second health examination (HE2) between 1997 and 2000.[279] At both health checks, participants completed a health and lifestyle questionnaire and a semi-quantitative food frequency questionnaire (FFQ) and trained personnel took anthropometric measurements as well as blood samples, which were then processed for various assays at the Department of Clinical Biochemistry, University of Cambridge, or stored for later analysis at -80 °C. Participants were followed-up by March 2016 for incidence and mortality outcomes. The detailed recruitment method and study protocol of EPIC-Norfolk have been described previously.[278]

Since the National Health Service is the point of entry for health-care services in the UK, the General Practitioners' registers almost completely matched with the official population statistics estimates during the recruitment years. General practice age and sex registers therefore operated as a population sampling frame, and except having had a lower percentage of current smokers, the EPIC-Norfolk cohort corresponded to the overall UK population regarding many characteristics, such age, sex, and anthropometry measurements.[279] The study was approved by the Norfolk District Health Authority Ethics Committee, conducted according to the Declaration of Helsinki, and participants gave informed consent.

4.3.2 Dietary assessment and degree of processing

A semi-quantitative 130-items food-frequency questionnaire (FFQ) that asked participants about the average intake of food items over the past year was used to assess habitual diet. The validity of this FFQ was evaluated and compared against 16-day weighted dietary records, 24-hour dietary recall and selected biomarkers.[278,280] The open-source cross-platform program FETA (FFQ EPIC Tool for Analysis) was used to derive macro- and micronutrient content of the FFQ data.[279] To classify all FFQ items according to their degree of food processing I used the NOVA system, a food classification scheme that classifies foods into four groups according to the nature, extent, and purpose of industrial food processing, described in Table 1.1.[66,70] Two authors (KS and ML) independently classified all foods in the EPIC-Norfolk FFQ according to NOVA and disagreements were resolved by consensus.

4.3.3 Outcome ascertainment at baseline and follow-up

At the two health examinations weight, height, and waist and hip circumference were measured (to the nearest 0.1 kg and cm, respectively), while participants wore light clothing and no shoes. BMI was calculated by dividing an individuals' weight by its height in metres squared. Baseline diabetes status was determined by self-reported diabetes medication, diabetes medication shown at the baseline examination, participants changing their diet in the past twelve months due to diabetes; or participants stating compliance to a diabetic diet. Funding for measuring

HbA1c was available from 1995 onward, therefore around 50% of all participants' HbA1c measurements were taken at baseline. HbA1c was measured on fresh EDTA blood samples using high-performance liquid chromatography (Diamat Automated Glycated Haemoglobin Analyzer; Bio-Rad Laboratories Ltd., Hemel Hemstead, U.K.), which was standardized to the Diabetes Control and Complications Trial (DCCT) assay. Identical measurements were taken at HE2. During follow-up, incident diabetes was identified if: participants reported physician-diagnosed diabetes or diabetes medication or presented diabetes medication to the assessment at HE2; a clinical diagnosis appeared on medical records, diabetes registers, or death certificates; or they had an HbA1c of ≥ 6.5% at HE2.

Participants admitted to a hospital with a diabetes-related condition were identified by their National Health Service number. Hospitals were linked to the East Norfolk Health Authority database, which identifies all hospital contacts throughout England and Wales for Norfolk residents. Vital status for all EPIC-Norfolk participants was obtained through death certification at the Office for National Statistics, and death certification with coding for diabetes was identified. Previous validation studies in this cohort using capture–recapture analysis indicated that the use of multiple sources of ascertainment information for diabetes detected 99% of incident cases when comparing with diagnostic information from a comprehensive review of medical records.

Incident CVD included any first ever case of fatal and non-fatal event as a result of ischaemic heart disease, ischaemic stroke, haemorrhagic stroke, heart failure, peripheral vascular disease, or other cardiovascular outcomes as specified by the relevant ICD codes (ICD9 401-448 or ICD10 I10-I79).[281] Again, the East Norfolk Health Authority database in conjunction with the National Health Service number was utilized to ascertain cause-specific hospital admissions. Cardiovascular mortality was determined through death certificates with ICD codes held at the UK Office for National Statistics. Cardiovascular incidence and mortality as well as type 2 diabetes incidence were ascertained until March 31, 2016.

4.3.4 Assessment of other covariates

Participant information on demographic, lifestyle, and health characteristics were evaluated at HE1 and HE2 via a self-administered questionnaire. Four levels of physical activity (inactive, moderately inactive, moderately active, active) were determined from the validated EPIC short physical activity questionnaire that was developed to assess both leisure and work activity.[282] Levels of education (no education, O-level, A-level, higher education degree), social class (non-skilled, semi-skilled, skilled manual, skilled non-manual, manager, professional), smoking status (current, former, or never smoker) and marital status (single, widowed, separated, divorced, married) and Townsend deprivation (continuous). Non-fasting blood samples were taken from which blood lipids and cholesterols were assayed.

4.3.5 Participant exclusions and missing values

To address potentially invalid dietary assessments, I identified improbable energy reporting by calculating the basal metabolic rate from the Henry equations and derived the Goldberg cut-offs to determine and exclude improbable energy reporting according to the methods suggested by Black.[283–285] I then excluded all the participants with missing dietary information for which no UPF exposure could be derived. After exclusion of participants based on improbable energy reporting and missing dietary information, I observed less than 0.8% of missing values of the covariates included in the analysis, except for social class (2.1%) and information on further education (1.2%). These values were imputed to the modal value (for categorical variables) or to the median (for continuous variables). Participants with T2DM and participants with self-reported cardiovascular diseases at baseline were excluded for the analyses of T2DM and CVD, respectively.

4.3.6 Ultra-processed food variables, energy adjustment, and repeated measurements

In previous prospective cohort analyses UPF consumption has been expressed as total weight or proportion of total food weight.[96,98,140,141] This has been justified based on the assumption that

a measure of UPF consumption based on total or proportion of energy would not take into account the properties of UPFs that do not contribute any calorific value such as added factors that result from the processing of foods (i.e. additives, alterations, contaminants, etc.).[98,141] This assumption has so far remained theoretical as no direct comparisons of associations between UPF consumption and health outcomes between weight- and energy-measures of UPFs have been performed. However, the decision to use certain ways to define the exposure can affect the results of statistical analyses in fundamental ways.[158–161] Since I could not justify one specific way of measuring or operationalizing UPFs, I combined the UPF weight and energy variables with common nutritional epidemiological approaches to define exposures and adjust for total energy intake, in order to reduce confounding by total dietary intake and enable an assessment of dietary quality independent of dietary quantity.[286–288] The approaches are based on suggestions for adjustments for total energy by Willett et al. (1997).

Modelling approach	UPF intake expressed as:	Relation expressed	Residual method
Weight (absolute)	Absolute weight (g per day)	Disease risk = UPF + total energy + covariates	Yes (weight and energy)
Weight (proportion)	Proportion of UPF intake as weight (in % of total food weight per day)	Disease risk = UPF + total energy + covariates	Yes (weight and energy)
Energy (absolute)	Absolute energy (in kcal per day)	Disease risk = UPF + total energy + covariates	Yes (energy)
Energy (proportion)	Proportion of UPF intake as energy (in % of total energy from foods per day)	Disease risk = UPF + total energy + covariates	No
Energy (partition)	Absolute energy (in kcal per day)	Disease risk = UPF + energy from non-UPF sources + covariates	No

Table 4.1 Summary of approaches to measure UPF exposures, adjust for total energy intake, and model exposure disease relations

Five ways of operationalizing the UPF exposure were created: first, absolute weight of UPFs consumed per capita per day in grams (adjusted for total energy and total weight by the residual method); second, proportion of UPF intake of total food weight intake in percent (adjusted for

total energy and total weight by residual method); third, absolute intake of energy consumed from UPFs per capita per day in kcal (adjusted for total energy by residual method); forth, absolute intake of energy consumed from UPFs per capita per day in kcal (not adjusted for total energy as required for energy-partition models); and proportion of energy consumed from UPFs of total energy intake in per cent (not adjusted for total energy, as required for energy-density models). The approaches to model the UPF exposure and adjustments for total energy intake are summarized below in table 4.1.

In the longitudinal analyses of T2DM and CVD, repeated exposure and covariate information were included through the cumulative average method for the participants for which the incidence of disease occurred after the second health examination.[289,290] In other words, if the date of the disease incidence was after the second health examination, an average of the two measurements at HE 1 and HE 2 was calculated for the exposure and covariate variables to be used in the analyses. If the date of the disease incidence was before the second health examination, only exposure and covariate values from the first health examination were used.

To understand which food groups contribute most to UPF intake and how those potentially differ for the weight and energy measures, all FFQ food items that were characterized as ultra-processed according to NOVA were aggregated into eight ultra-processed food groups (ultra-processed: drinks; starchy foods and cereals; confectionary, sweets, and sugary products; fats; fast foods and savoury snacks; milk and dairy; meat, fish, and eggs).

4.3.7 Statistical analysis

To evaluate the association between consumption of UPFs and incidence of T2DM or any CVD event I used Cox proportional hazard models with the Efron approximation method to handle tied events (events with exactly the same survival time) that can potentially cause minor issues in Cox-regressions if not accounted for.[291,292] The underlying time variable was age from the first available FFQ to age at diagnosis of T2DM, CVD (or death for CVD-mortality), or the date of administrative censoring, whichever occurred first. Each of the five approaches to express UPF

exposure were modelled continuously increasing from the 10th to 90th percentile and categorically as quintiles with approximately equal numbers of participants in each group. In the analyses of quintiles, the hazard ratios were modelled with the lowest quintile as the reference category. The proportional hazard assumption was confirmed by examining Schoenfeld residuals. I assessed the risk of being obese at HE1 and HE2 cross-sectionally by estimating logistic regression models with robust Huber and White standard errors.

I estimated five models that were incrementally adjusted to account for known or potential risk and confounding factors. Model one was minimally adjusted for sex and age (as the underlying timescale in the analyses of T2DM and CVD). Model two included main socio-economic and health-related confounders: physical activity, marital status, smoking status, alcohol intake (g/d, continuous), educational level, social class, Townsend area deprivation index, and BMI. In the analyses of T2DM, model two was additionally adjusted for family history of diabetes. In the analyses of adiposity, models were not adjusted for BMI. To assess associations independent of the potential influences of the nutritional quality of the diets and individual's total energy intakes, I adjusted for unprocessed food consumption (g/d, continuous) and total energy intake (kcal/d, continuous) in model three.

Based on known nutritional risk factors,[3,293–296] I added nutritional confounders to models four and five for each of the three outcomes. In the analyses of CVD, model four included sodium intake (mg/d, continuous) and saturated fat intake (g/d, continuous), and model five additionally adjusted for fibre intake (non-starch polysaccharides, g/d, continuous). In the analyses of T2DM, model four adjusted for sugar intake (g/d, continuous) and model five additionally for fibre intake. In the analyses of adiposity, model four adjusted for overall carbohydrate intake (g/d, continuous) and model five additionally for overall fat intake (g/d, continuous).

The shapes of the associations were modelled by using restricted cubic splines with four knots at the 5th, 35th, 65th, and 95th percentiles UPF exposure, as recommended by Harrell.[180] The hazard ratios and confidence intervals in those analyses were estimated against the 10th

percentile of intake, and in each case reported for all UPF intake values between the 1st and 99th percentile.[180]

As secondary analyses, I estimated the associations between each of the eight UPF groups and risk of T2DM and CVD as well as odds ratio of adiposity.

I conducted four sensitivity analyses by (1) excluding incident cases during the first two years of follow-up, (2) estimating associations based on a complete case analysis, (3) excluding participants with improbable energy reporting based on a simpler exclusion rule (<800 kcal or >4200 kcal per day in men and <500 or >3500 kcal per day in women)[297], and (4) combined unprocessed foods with processed culinary ingredients (NOVA 2) for use as a covariate, as those two groups are frequently consumed together.

In line with the previous chapters, I recognize that the choice of any particular threshold to determine statistical significance is arbitrary, and that *P*-values and 95% confidence intervals of hypothesis tests often do not adequately reflect the strength of the evidence against null hypotheses.[148,164,165,185] However, as is common in studies of nutritional epidemiology, provide tables with 95% confidence intervals for all main analyses. For the secondary analyses, *P*-values are presented as a continuous measure of the compatibility of the model with the data and I report *P*-values until 0.0001 and *P*-values smaller than 0.0001 as 0.0000.[165,185] All analyses were performed in Stata, version 15.1 (StataCorp LLC, College Station, Texas, USA). The analysis protocol and Stata code are available at https://github.com/kai-schulze/upf_epic.

4.4 Results

4.4.1 Participant selection, cohort characteristics, and UPF food groups

After exclusion of participants with no dietary information (n=891) and improbable energy-intake based on Henry and Goldberg equations (n=7,190), a total of 17,558 participants were generally eligible for analysis, with a median follow-up of 19.45 years (IQR 17.63-20.89; mean

17.85). Of 17,204 participants eligible for the analysis of T2DM, 1,262 developed the disease over 302,184 person-years (17.57 years of follow-up on average).

A total of 8,333 participants developed primary incident CVD (non-fatal or fatal) over 242,224 person-years (15.05 years of follow-up on average). Figure 4.1 shows the process for selecting and excluding participants and creating three datasets for the analysis of the three conditions.

Figure 4.2 shows the relative contribution of the eight aggregated ultra-processed food groups to the overall UPF intake as energy and weight. When UPF intake was expressed as energy, the three food groups ultra-processed confectionary, sweets, and sugary products; breads, starchy foods, and cereals; and fats were the three largest contributors to UPF intake with 27, 24, and 22 percent of total UPF energy intake. When UPFs were measured as weight, ultra-processed breads, starchy foods, and cereals; drinks and SSBs; and confectionary, sweets, and sugary products were the three main contributing groups with 22, 19, and 17 percent of total UPF intake measured as weight. The main difference between weight and energy measures were the almost four-fold difference of UPF drinks (5 vs. 19%), an over two-fold difference of UPF fats (9 vs. 22%), a higher share of confectionary, sweets, and sugar products in the UPF energy measure (17 vs. 27%), and a higher share of UPF fruits and vegetables when UPF is expressed as weight measures (5 vs. 13%).

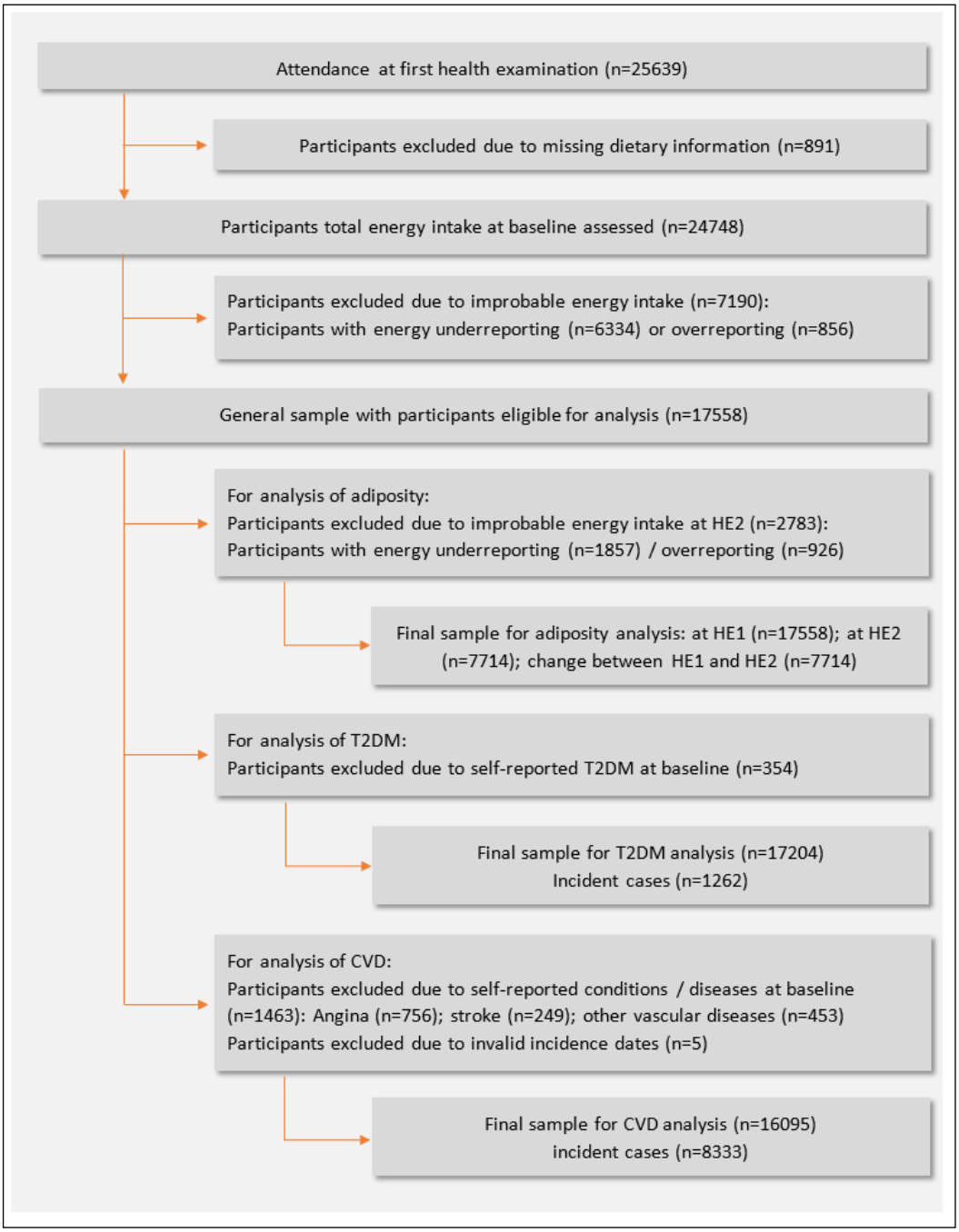


Figure 4.1 Flowchart of participants

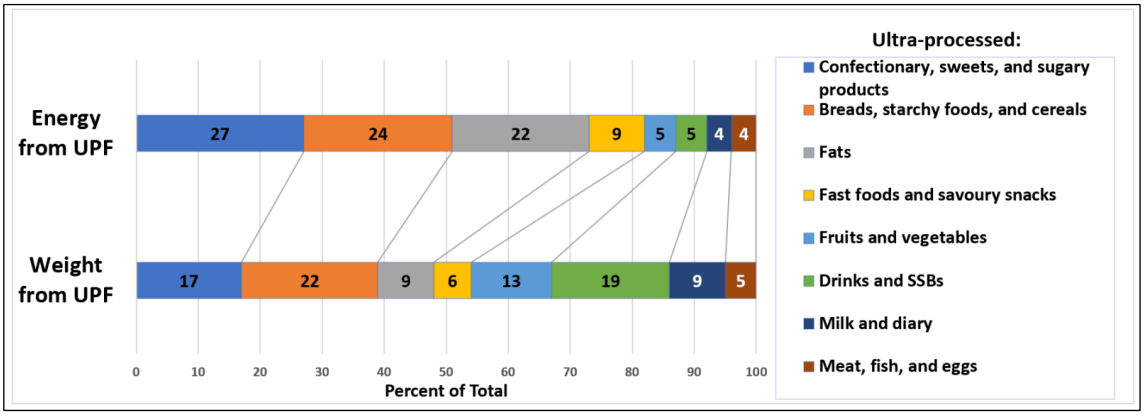


Figure 4.2 Relative contribution of aggregated ultra-processed food groups to UPF weight and energy variables

All food items in the aggregated groups are ultra-processed according to NOVA 4.

Table 4.2 shows the main baseline characteristics of participants according to the lowest and highest UPF intake quintiles of the four UPF approaches to measure UPF intake.[b] Participants at baseline had a mean age of 59.7 years, were 57.9% female, had an average BMI of 26, and about 60% of the sample were inactive or moderately inactive. Across the four UPF variables, individuals in the fifth quintile (Q5) were slightly younger and were much less likely to be female. For example, while in the first quintile (Q1) of UPF intake measured as weight 80.3% of individuals were female, only 32.9% were female in Q5. Participants in Q5 of the UPF variables had less formal education and slightly below average levels of higher education. High consumers of UPFs worked more in skilled manual jobs and were more active in comparison to the sample average. They smoked less than those consuming few UPFs, and the difference was particularly strong when UPF intake was expressed as weight or proportion of weight.

[b] Note: I present participant characteristics using the four unadjusted UPF variables weight, proportion of weight, energy, and proportion of energy. In statistical analyses, however, I used those four variables residually adjusted, and additionally energy unadjusted in the energy partition models. Hence the difference between five approaches in the statistical analyses and the four variables in the descriptive.

	All participants	Quintiles 1 and 5 of ultra-processed food consumption variables							
		Weight		Proportion of Weight		Energy		Proportion of Energy	
		Q1	Q5	Q1	Q5	Q1	Q5	Q1	Q5
Age (years)	59.7 (9.4)	60.6 (9.3)	58.2 (9.3)	60.3 (9.2)	58.8 (9.6)	60.3 (9.3)	58.5 (9.4)	60.2 (9.3)	59.1 (9.5)
Sex									
Female (%)	10,158 (57.9%)	2,589 (73.7%)	1,592 (45.3%)	2,336 (66.5%)	1,816 (51.7%)	2,821 (80.3%)	1,155 (32.9%)	2,325 (66.2%)	1,675 (47.7%)
Social class									
professional	1,203 (6.9%)	238 (6.8%)	203 (5.8%)	252 (7.2%)	204 (5.8%)	274 (7.8%)	195 (5.6%)	299 (8.5%)	188 (5.4%)
manager	6,634 (37.8%)	1,395 (39.7%)	1,310 (37.3%)	1,430 (40.7%)	1,241 (35.3%)	1,449 (41.3%)	1,203 (34.3%)	1,502 (42.8%)	1,125 (32.0%)
skilled non-manual	2,959 (16.9%)	657 (18.7%)	550 (15.7%)	624 (17.8%)	570 (16.2%)	619 (17.6%)	532 (15.2%)	559 (15.9%)	583 (16.6%)
skilled manual	3,934 (22.4%)	674 (19.2%)	842 (24.0%)	697 (19.8%)	850 (24.2%)	668 (19.0%)	924 (26.3%)	675 (19.2%)	899 (25.6%)
semi-skilled	2,245 (12.8%)	435 (12.4%)	474 (13.5%)	401 (11.4%)	496 (14.1%)	404 (11.5%)	520 (14.8%)	374 (10.6%)	545 (15.5%)
non-skilled	583 (3.3%)	113 (3.2%)	132 (3.8%)	108 (3.1%)	150 (4.3%)	98 (2.8%)	137 (3.9%)	103 (2.9%)	171 (4.9%)
Marital Status									
Single, Widowed, Separated, Divorced	3,182 (18.1%)	755 (21.5%)	601 (17.1%)	695 (19.8%)	661 (18.8%)	759 (21.6%)	569 (16.2%)	673 (19.2%)	668 (19.0%)
Married	14,376 (81.9%)	2,757 (78.5%)	2,910 (82.9%)	2,817 (80.2%)	2,850 (81.2%)	2,753 (78.4%)	2,942 (83.8%)	2,839 (80.8%)	2,843 (81.0%)
Education									
No formal education	6,444 (36.7%)	1,329 (37.8%)	1,245 (35.5%)	1,280 (36.4%)	1,366 (38.9%)	1,244 (35.4%)	1,308 (37.3%)	1,152 (32.8%)	1,467 (41.8%)
School until age 16	1,848 (10.5%)	381 (10.8%)	384 (10.9%)	367 (10.4%)	391 (11.1%)	385 (11.0%)	335 (9.5%)	362 (10.3%)	342 (9.7%)
School until age 18	7,034 (40.1%)	1,352 (38.5%)	1,470 (41.9%)	1,401 (39.9%)	1,376 (39.2%)	1,404 (40.0%)	1,469 (41.8%)	1,481 (42.2%)	1,346 (38.3%)
Bachelor's degree or above	2,232 (12.7%)	450 (12.8%)	412 (11.7%)	464 (13.2%)	378 (10.8%)	479 (13.6%)	399 (11.4%)	517 (14.7%)	356 (10.1%)

Table 4.2 Baseline characteristics of study population

For quintiles one and five of UPF consumption variables, EPIC-Norfolk cohort (n=17558), United Kingdom, 1993-2016. Values are numbers (percentages / SD).

		Quintiles 1 and 5 of ultra-processed food consumption variables							
		Weight		Proportion of Weight		Energy		Proportion of Energy	
	All participants	Q1	Q5	Q1	Q5	Q1	Q5	Q1	Q5
Physical activity									
Inactive	5,538 (31.5%)	1,338 (38.1%)	951 (27.1%)	1,214 (34.6%)	1,089 (31.0%)	1,323 (37.7%)	892 (25.4%)	1,126 (32.1%)	1,116 (31.8%)
Moderately inactive	4,998 (28.5%)	1,006 (28.6%)	952 (27.1%)	1,008 (28.7%)	960 (27.3%)	1,062 (30.2%)	900 (25.6%)	1,014 (28.9%)	963 (27.4%)
Moderately active	4,053 (23.1%)	766 (21.8%)	821 (23.4%)	791 (22.5%)	797 (22.7%)	730 (20.8%)	855 (24.4%)	809 (23.0%)	812 (23.1%)
Active	2,969 (16.9%)	402 (11.4%)	787 (22.4%)	499 (14.2%)	665 (18.9%)	397 (11.3%)	864 (24.6%)	563 (16.0%)	620 (17.7%)
BMI	26.0 (3.7)	25.2 (3.5)	27.1 (4.0)	25.5 (3.5)	26.7 (4.1)	25.4 (3.5)	26.5 (3.7)	25.6 (3.6)	26.3 (3.9)
Smoking status									
Current Smoker	1,943 (11.1%)	497 (14.2%)	351 (10.0%)	510 (14.5%)	348 (9.9%)	453 (12.9%)	424 (12.1%)	463 (13.2%)	453 (12.9%)
Former Smoker	7,178 (40.9%)	1,283 (36.5%)	1,591 (45.3%)	1,390 (39.6%)	1,513 (43.1%)	1,267 (36.1%)	1,602 (45.6%)	1,390 (39.6%)	1,500 (42.7%)
Never Smoked	8,437 (48.1%)	1,732 (49.3%)	1,569 (44.7%)	1,612 (45.9%)	1,650 (47.0%)	1,792 (51.0%)	1,485 (42.3%)	1,659 (47.2%)	1,558 (44.4%)
Family history of Diabetes									
Yes	2,257 (12.9%)	435 (12.4%)	482 (13.7%)	429 (12.2%)	485 (13.8%)	459 (13.1%)	463 (13.2%)	443 (12.6%)	469 (13.4%)
No	15,283 (87.1%)	3,074 (87.6%)	3,027 (86.3%)	3,080 (87.8%)	3,022 (86.2%)	3,052 (86.9%)	3,046 (86.8%)	3,066 (87.4%)	3,038 (86.6%)

Table 4.2 (continued) Baseline characteristics of study population

For quintiles one and five of UPF consumption variables, EPIC-Norfolk cohort (n=17558), United Kingdom, 1993-2016. Values are numbers (percentages / SD)

	All participants	Quintiles 1 and 5 of ultra-processed food consumption variables							
		Weight		Proportion of Weight		Energy		Proportion of Energy	
		Q1	Q5	Q1	Q5	Q1	Q5	Q1	Q5
UPF intake									
Weight (g/day)	426.7 (193.8)	227.3 (42.5)	715.7 (213.0)	247.0 (65.0)	674.0 (242.5)	278.3 (130.3)	613.0 (209.6)	293.3 (130.6)	570.8 (222.9)
Proportion of weight (%)	14.4 (5.9)	8.6 (2.3)	22.0 (6.6)	7.9 (1.5)	23.3 (5.7)	10.0 (4.5)	19.2 (6.2)	9.6 (3.8)	19.7 (6.6)
Energy (kcal/d)	922.9 (342.9)	578.5 (150.8)	1276.3 (386.5)	613.2 (184.7)	1205.4 (392.4)	512.3 (93.6)	1449.4 (248.8)	562.2 (154.5)	1329.8 (330.7)
Proportion of energy	41.2 (9.8)	31.7 (7.7)	48.6 (9.0)	30.9 (7.0)	49.7 (8.9)	29.4 (6.1)	52.1 (7.0)	27.6 (4.4)	55.0 (4.8)
Total energy intake									
Kcal/d	2194.1 (483.7)	1826.3 (309.8)	2591.5 (548.0)	1973.3 (398.0)	2383.0 (545.4)	1759.8 (284.0)	2786.2 (430.3)	2021.5 (431.2)	2394.4 (525.7)
Nutrients									
Carbohydrates (g/day)	276.7 (69.0)	220.8 (43.6)	335.7 (78.0)	239.0 (55.3)	309.1 (78.8)	215.5 (42.8)	359.2 (63.6)	242.8 (58.8)	314.6 (75.9)
Sugars (g/day)	144.4 (45.8)	116.9 (32.7)	177.5 (53.7)	128.3 (39.1)	161.8 (53.7)	116.3 (33.1)	186.7 (52.1)	131.2 (39.9)	162.3 (56.6)
Fats (g/day)	82.9 (25.8)	68.9 (19.1)	97.4 (30.3)	72.7 (21.7)	90.9 (28.7)	62.7 (17.6)	110.0 (25.6)	74.4 (24.7)	92.7 (27.1)
Saturated fats (g/day)	31.9 (11.7)	27.7 (9.9)	36.6 (12.9)	29.0 (10.9)	34.3 (12.2)	25.1 (9.6)	41.6 (11.7)	30.4 (12.6)	34.2 (11.1)
Alcohol (g/day)	8.8 (13.3)	9.6 (14.9)	9.4 (13.7)	12.6 (18.0)	7.3 (10.9)	9.9 (14.8)	8.5 (12.7)	12.8 (17.7)	6.0 (9.5)
Sodium (mg/day)	3056.2 (790.1)	2400.7 (476.8)	3717.6 (913.5)	2599.9 (612.2)	3404.0 (899.5)	2418.9 (514.7)	3816.3 (819.4)	2700.6 (705.8)	3365.7 (843.2)
Fibre (g/day)	19.7 (6.2)	17.1 (5.4)	22.3 (6.9)	18.9 (6.3)	19.9 (6.3)	18.1 (6.0)	21.7 (6.4)	19.7 (6.9)	19.2 (5.9)

Table 4.3 UPF and nutrient intakes of study population

For quintiles one and five of UPF consumption variables, EPIC-Norfolk cohort (n=17558), United Kingdom, 1993-2016. Values are numbers (percentages / SD).

At baseline, the mean intake of UPFs expressed as weight was 426.7 grams per day and the mean proportion of UPFs of total food weight consumed was 14.4% (Table 4.3). On average, 922.9 kcals per day were consumed when UPFs were measured as energy, and this amounted to an average of 42.1% of total energy consumed. Comparing UPF intake between individuals with the highest and lowest consumption revealed important findings. First, average UPF intakes between Q1 and Q5 roughly increased between two- to threefold. This was the case when UPF intake was measured as absolute weight, proportion of weight, and absolute energy; the increase was slightly lower on average when UPF intake was expressed as the proportion of energy (roughly between a 50 to 100% increase). Secondly, a higher proportion or relative intake of UPFs in the diet also implied a higher absolute consumption of UPFs in the overall diet. For example, the average consumption of UPFs measured as absolute weight was on average 247 g/day for individuals with the lowest proportion of weight of UPF, compared to 674 g/day for those in Q5 of the proportion of weight from UPFs. Thirdly, the changes between in UPF intake between Q1 and Q5 were more pronounced when UPF intake was measured as weight – regarding the weight measures, the average increase for all eight possible comparisons between Q1 and Q5 was 144%, while the average increase for all eight comparisons of the energy measures was 103% (calculations not shown). The total energy intake was higher for those in the Q5 of UPF consumption, but the increase was less strong for the two variables measuring the proportion of UPF intake.

Regarding nutrient intakes, the carbohydrate and sugar intake increased relatively more than the fat and saturated fat intake between Q1 and Q5 for all UPF measures, while alcohol consumption was lower in Q5 of UPF intake, except when measured as weight. Finally, sodium intake was much higher for those in the fifth quintiles of UPF intake, while fibre consumption was similar between Q1 and Q5, except, again, when measured as weight (here, it was higher).

4.4.2 Associations between ultra-processed food intake and adiposity, type 2 diabetes mellitus, and cardiovascular diseases

4.4.2.1 Ultra-processed food intake and incident type 2 diabetes mellitus

Table 4.4 displays the estimated associations between UPF intake and risk of T2DM. The number of incident type 2 diabetes cases increased with increasing quintiles of UPF intake expressed as weight or proportion of weight (from 209 to 334 and 200 to 329, quintiles one to five). This was also the case in the three models in which participants were classified according to quintiles of energy from UPF, although the difference of incident cases between the first and the second quintile was much more pronounced compared to the weight-based measures, and the trend appeared less linear than in the case of the weight measures.

In the Cox-models, higher intake of UPFs expressed as weight was associated with a higher risk of type T2DM, after multivariable adjustment for covariates. For a continuous increase from the 10^{th} to the 90^{th} percentile of UPF intake the HRs ranged from 1.63 (95% CI: 1.47 to 1.81, UPF weight as proportion, unadjusted model 1) to 1.28 (95% CI: 1.15 to 1.42; UPF as absolute weight; model 5). When risks were estimated for being in the highest vs. lowest quintile of UPF intake, HRs ranged from 1.90 (95% CI: 1.59 to 2.25; UPF as absolute weight; unadjusted model 1) to 1.49 (95% CI: 1.23 to 1.81; UPF weight as proportion; model 5). The confidence intervals consistently excluded 1.00, and the HRs slightly increased once sugar and fibre consumption were adjusted for in model 4. Once waist circumference and BMI were included (model 5), HRs decreased substantially. Overall, the estimated risk of T2DM of the UPF approaches expressed as energy were less pronounced and had more uncertainty compared to UPFs expressed as weight. The HRs for the continuous case ranged from 1.47 (95% CI: 1.23 to 1.77; UPF energy-partition; model 4) to 1.08 (95% CI: 0.93 to 1.25; UPF as absolute energy; model 5). HRs for individuals in the fifth quintile relative to those in the first quintile varied between 1.49 (95% CI 1.25 to 1.79; UPF as proportion of energy; model 1) to 1.04 (95% CI: 0.83 to 1.31; UPF energy-partition; model 5). Here, the confidence intervals did not always exclude 1.00.

		Quintiles				
	Continuous ¥	1	2 vs. 1	3 vs. 1	4 vs. 1	5 vs. 1
	HR (95% CI)	HR	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Weight (absolute)*						
Cases/non-cases	*1,262/15,942*	*209/3,236*	*219/3,209*	*244/3,171*	*256/3,064*	*334/3,064*
Model 1	1.51 (1.38 to 1.64)	1	1.08 (0.89 to 1.30)	1.20 (0.99 to 1.44)	1.30 (1.08 to 1.56)	1.90 (1.59 to 2.25)
Model 2	1.50 (1.37 to 1.63)	1	1.08 (0.89 to 1.31)	1.22 (1.01 to 1.47)	1.31 (1.09 to 1.57)	1.87 (1.57 to 2.23)
Model 3	1.50 (1.36 to 1.65)	1	1.07 (0.89 to 1.30)	1.20 (1.00 to 1.45)	1.28 (1.06 to 1.54)	1.82 (1.51 to 2.18)
Model 4	1.55 (1.41 to 1.72)	1	1.08 (0.89 to 1.30)	1.23 (1.02 to 1.48)	1.31 (1.09 to 1.58)	1.90 (1.58 to 2.29)
Model 5	1.28 (1.15 to 1.42)	1	1.06 (0.87 to 1.28)	1.18 (0.98 to 1.43)	1.22 (1.01 to 1.47)	1.53 (1.27 to 1.84)
Weight (proportion)*						
Cases/non-cases	*1,262/15,942*	*200/3,258*	*221/3,221*	*229/3,218*	*283/3,158*	*329/3,087*
Model 1	1.63 (1.47 to 1.81)	1	1.10 (0.91 to 1.33)	1.15 (0.95 to 1.39)	1.45 (1.21 to 1.74)	1.85 (1.56 to 2.21)
Model 2	1.59 (1.43 to 1.76)	1	1.11 (0.91 to 1.34)	1.13 (0.93 to 1.36)	1.47 (1.22 to 1.77)	1.75 (1.47 to 2.10)
Model 3	1.61 (1.42 to 1.83)	1	1.10 (0.91 to 1.34)	1.11 (0.92 to 1.35)	1.45 (1.20 to 1.74)	1.69 (1.40 to 2.05)
Model 4	1.64 (1.44 to 1.87)	1	1.09 (0.90 to 1.32)	1.11 (0.92 to 1.35)	1.45 (1.20 to 1.74)	1.71 (1.41 to 2.07)
Model 5	1.41 (1.24 to 1.61)	1	1.09 (0.90 to 1.33)	1.09 (0.90 to 1.32)	1.40 (1.16 to 1.68)	1.49 (1.23 to 1.81)
Energy (absolute)*						
Cases/non-cases	*1,262/15,942*	*205/3,242*	*259/3,188*	*250/3,177*	*264/3,177*	*284/3,158*
Model 1	1.30 (1.13 to 1.50)	1	1.26 (1.05 to 1.51)	1.23 (1.02 to 1.48)	1.28 (1.06 to 1.53)	1.43 (1.19 to 1.71)
Model 2	1.17 (1.01 to 1.35)	1	1.23 (1.02 to 1.47)	1.18 (0.98 to 1.43)	1.20 (1.00 to 1.44)	1.27 (1.05 to 1.52)
Model 3	1.15 (1.00 to 1.34)	1	1.21 (1.01 to 1.46)	1.16 (0.96 to 1.40)	1.18 (0.98 to 1.41)	1.24 (1.03 to 1.50)
Model 4	1.14 (0.98 to 1.32)	1	1.21 (1.01 to 1.46)	1.16 (0.96 to 1.39)	1.17 (0.97 to 1.41)	1.23 (1.02 to 1.48)
Model 5	1.08 (0.93 to 1.25)	1	1.20 (0.99 to 1.44)	1.14 (0.95 to 1.38)	1.18 (0.98 to 1.42)	1.15 (0.95 to 1.39)
Energy (proportion)ł						
Cases/non-cases	*1,262/15,942*	*198/3,250*	*247/3,185*	*256/3,176*	*269/3,176*	*292/3,153*
Model 1	1.41 (1.22 to 1.63)	1	1.25 (1.04 to 1.51)	1.27 (1.05 to 1.52)	1.35 (1.12 to 1.62)	1.49 (1.25 to 1.79)
Model 2	1.30 (1.12 to 1.50)	1	1.27 (1.05 to 1.53)	1.23 (1.02 to 1.49)	1.32 (1.09 to 1.59)	1.37 (1.13 to 1.64)
Model 3	1.25 (1.07 to 1.46)	1	1.26 (1.04 to 1.52)	1.21 (1.00 to 1.46)	1.28 (1.06 to 1.55)	1.30 (1.07 to 1.58)
Model 4	1.26 (1.08 to 1.48)	1	1.26 (1.04 to 1.52)	1.21 (1.00 to 1.46)	1.28 (1.06 to 1.55)	1.32 (1.08 to 1.60)
Model 5	1.16 (0.99 to 1.36)	1	1.18 (0.98 to 1.43)	1.15 (0.95 to 1.39)	1.21 (1.00 to 1.47)	1.18 (0.97 to 1.44)
Energy (partition)ł						
Cases/non-cases	*1,262/15,942*	*207/3,234*	*251/3,180*	*239/3,191*	*290/3,153*	*275/3,184*
Model 1	1.31 (1.14 to 1.51)	1	1.20 (1.00 to 1.44)	1.11 (0.92 to 1.33)	1.34 (1.12 to 1.61)	1.32 (1.09 to 1.60)
Model 2	1.27 (1.10 to 1.47)	1	1.20 (1.00 to 1.45)	1.10 (0.91 to 1.33)	1.32 (1.10 to 1.59)	1.29 (1.06 to 1.57)
Model 3	1.27 (1.10 to 1.47)	1	1.20 (1.00 to 1.45)	1.10 (0.91 to 1.33)	1.32 (1.10 to 1.59)	1.29 (1.06 to 1.57)
Model 4	1.47 (1.23 to 1.77)	1	1.23 (1.02 to 1.48)	1.14 (0.94 to 1.39)	1.40 (1.15 to 1.70)	1.43 (1.15 to 1.79)
Model 5	1.11 (0.92 to 1.33)	1	1.09 (0.90 to 1.31)	0.94 (0.78 to 1.14)	1.09 (0.90 to 1.33)	1.04 (0.83 to 1.31)

Table 4.4 Associations between ultra-processed food intake and risk of type 2 diabetes mellitus, from multivariable Cox proportional hazard models, EPIC-Norfolk cohort, United Kingdom, 1993-2016 (n=17,204)

¥ Continuous HR: Hazard ratio for an increase in consumption from the 10th to 90th percentile for each of the ultra-processed foods variables.

* Ultra-processed food exposure variables 1-3 (absolute weight, proportion of weight, and absolute energy) were adjusted with the residual method. Model 1: adjusted for age (as timescale) and sex; Model 2: model 1 + physical activity, social class, education, smoking status, marital status, Townsend deprivation index, alcohol consumption, height, family history of diabetes. Model 3: model 2 + unprocessed food intake, and total energy intake; Model 4: model 3 + sugar and fibre consumption; Model 5: Model 4 + waist circumference and BMI.

ł Variables in the energy-partition and proportion of energy (or density) models were not adjusted via residual method. Models 1-5 of the energy-partition approach were like the above except that instead of total energy intake a variable with the energy from non-UPF sources was included, derived by subtracting the energy from UPFs from total energy consumed for each participant.

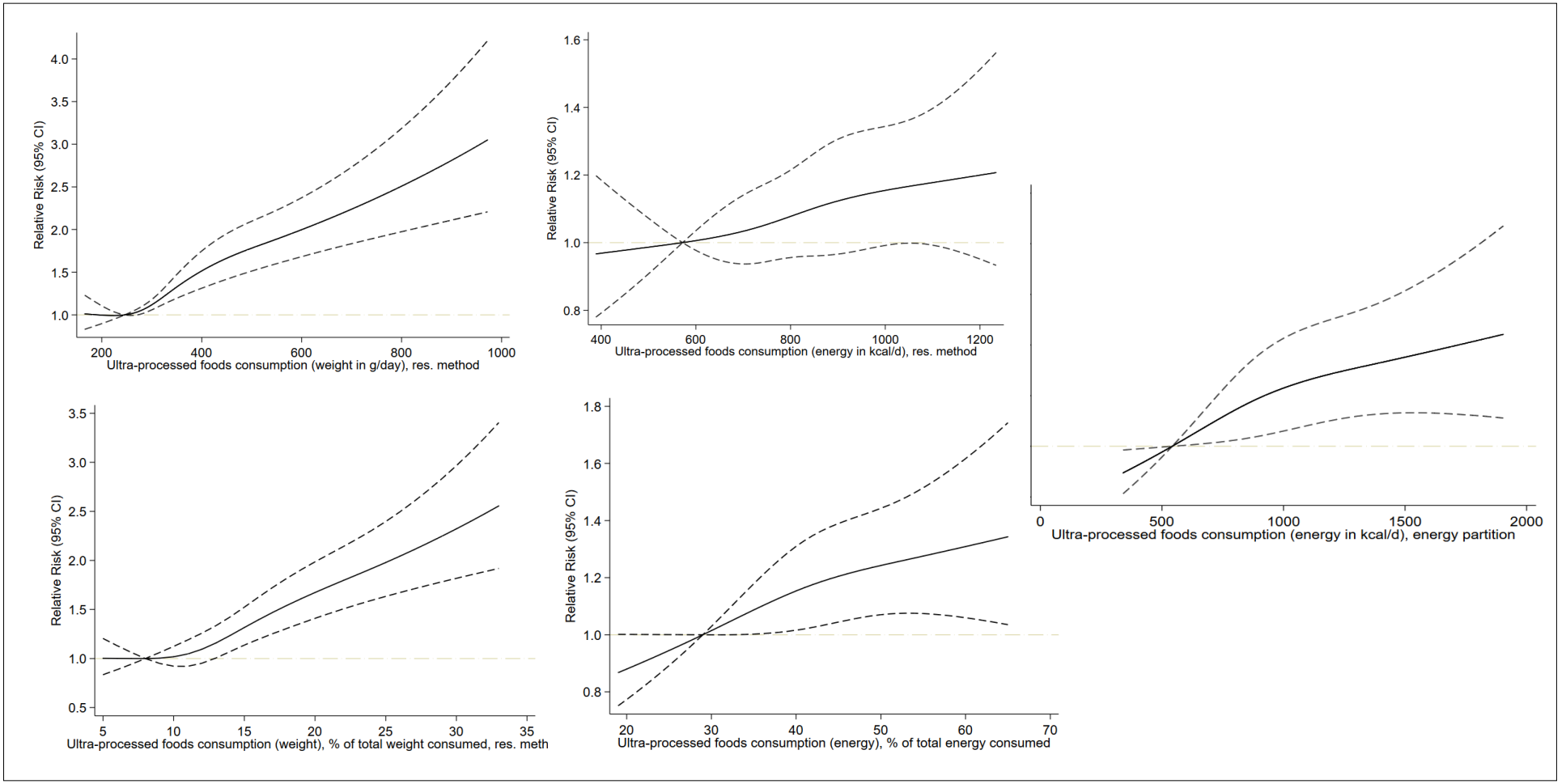


Figure 4.3 Associations between ultra-processed food intake and risk of type 2 diabetes mellitus, from multivariable Cox proportional hazard models, modelled with restricted cubic splines, EPIC-Norfolk cohort, United Kingdom, 1993-2016 (n=17,204)

UPF intake as absolute weight (left column, top), proportion of weight (left column, bottom), and absolute energy (middle column, top) were adjusted with the residual method. UPF intake as proportion of energy (middle column, bottom) and energy-partition (right column) were not adjusted via residual method. All estimates were adjusted for age (as timescale) and sex, physical activity, social class, education, smoking status, marital status, Townsend deprivation index, alcohol consumption, height, family history of diabetes, unprocessed food intake, and total energy intake. The energy-partition approach was like the above except that instead of total energy intake a variable with the energy from non-UPF sources was included, derived by subtracting the energy from UPFs from total energy consumed for each participant.

All estimates of the energy models that included BMI and waist circumference (model 5) did include 1.00, as well as four other estimates (model 3 and 4, see Table 4.4). Similar to the UPF weight measure, the HRs increased once sugar and fibre consumption were adjusted for in model 4 and decreased once waist circumference and BMI were included in model 5. The results of the estimated shapes of the associations between UPF and T2DM, shown graphically in Figure 4.3, reflect these findings. The difference in the range of HRs between the weight and the energy models is visible, as well as the overall general trend of a continuously increased risk with higher UPF intake. In the weight measures, up to approximately 250g of UPFs per day, or about 10% share of UPF intake of overall intake, no change of risk is visible; the slopes then increase while the confidence intervals widen slightly at higher levels of UPF consumption. The shapes for the UPF energy approaches also show positive trends, but, as above, with generally lower values of relative risks and wider confidence intervals than in the estimates of the UPF weight measures. Also, the lower confidence interval is either below or remains close to 1.00 for the energy-residual and energy-density models across much of the range of UPF intake.

	Continuous ¥	Quintiles				
		1	2 vs. 1	3 vs. 1	4 vs. 1	5 vs. 1
	HR (95% CI)	HR	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Weight (absolute)*						
Cases/non-cases	8,333/7,762	1,688/1,556	1,601/1,633	1,693/1,547	1,659/1,542	1,692/1,484
Model 1	1.15 (1.10 to 1.20)	1	0.96 (0.89 to 1.03)	1.04 (0.98 to 1.12)	1.08 (1.01 to 1.15)	1.20 (1.12 to 1.29)
Model 2	1.14 (1.10 to 1.19)	1	0.96 (0.89 to 1.03)	1.05 (0.98 to 1.12)	1.07 (1.01 to 1.16)	1.20 (1.12 to 1.28)
Model 3	1.13 (1.08 to 1.18)	1	0.95 (0.89 to 1.02)	1.04 (0.97 to 1.11)	1.07 (1.00 to 1.15)	1.17 (1.09 to 1.26)
Model 4	1.11 (1.06 to 1.17)	1	0.95 (0.88 to 1.01)	1.02 (0.95 to 1.10)	1.05 (0.98 to 1.13)	1.15 (1.06 to 1.24)
Model 5	1.07 (1.02 to 1.12)	1	0.94 (0.88 to 1.01)	1.01 (0.95 to 1.09)	1.03 (0.96 to 1.11)	1.09 (1.01 to 1.18)
Weight (proportion)*						
Cases/non-cases	8,333/7,762	1,661/1,593	1,595/1,638	1,664/1,549	1,677/1,537	1,736/1,445
Model 1	1.18 (1.13 to 1.24)	1	0.94 (0.88 to 1.01)	1.04 (0.97 to 1.11)	1.05 (0.98 to 1.13)	1.23 (1.15 to 1.32)
Model 2	1.16 (1.11 to 1.22)	1	0.94 (0.87 to 1.00)	1.03 (0.96 to 1.10)	1.05 (0.98 to 1.12)	1.20 (1.13 to 1.29)
Model 3	1.14 (1.08 to 1.21)	1	0.93 (0.87 to 1.00)	1.02 (0.96 to 1.10)	1.04 (0.97 to 1.11)	1.18 (1.10 to 1.27)
Model 4	1.13 (1.07 to 1.19)	1	0.93 (0.87 to 1.00)	1.01 (0.95 to 1.09)	1.02 (0.95 to 1.10)	1.16 (1.08 to 1.25)
Model 5	1.10 (1.05 to 1.17)	1	0.93 (0.87 to 1.00)	1.02 (0.95 to 1.09)	1.02 (0.95 to 1.10)	1.14 (1.06 to 1.23)
Energy (absolute)*						
Cases/non-cases	8,333/7,762	1,586/1,654	1,673/1,573	1,681/1,534	1,717/1,495	1,676/1,506
Model 1	1.15 (1.09 to 1.22)	1	1.07 (1.00 to 1.15)	1.11 (1.03 to 1.19)	1.14 (1.07 to 1.22)	1.17 (1.09 to 1.25)
Model 2	1.11 (1.05 to 1.17)	1	1.07 (1.00 to 1.14)	1.09 (1.01 to 1.17)	1.12 (1.05 to 1.20)	1.12 (1.04 to 1.20)
Model 3	1.10 (1.04 to 1.17)	1	1.06 (0.99 to 1.14)	1.08 (1.01 to 1.16)	1.11 (1.04 to 1.19)	1.11 (1.04 to 1.20)
Model 4	1.08 (1.02 to 1.15)	1	1.06 (0.99 to 1.13)	1.07 (0.99 to 1.14)	1.10 (1.02 to 1.18)	1.09 (1.02 to 1.18)
Model 5	1.08 (1.02 to 1.15)	1	1.05 (0.98 to 1.13)	1.07 (1.00 to 1.14)	1.10 (1.03 to 1.18)	1.09 (1.01 to 1.17)
Energy (proportion)ł						
Cases/non-cases	8,333/7,762	1,595/1,654	1,619/1,603	1,747/1,491	1,685/1,529	1,687/1,485
Model 1	1.18 (1.12 to 1.25)	1	1.05 (0.98 to 1.13)	1.14 (1.06 to 1.21)	1.13 (1.06 to 1.21)	1.18 (1.10 to 1.27)
Model 2	1.16 (1.09 to 1.23)	1	1.06 (0.99 to 1.14)	1.14 (1.06 to 1.21)	1.13 (1.05 to 1.21)	1.15 (1.08 to 1.24)
Model 3	1.14 (1.07 to 1.21)	1	1.06 (0.98 to 1.13)	1.12 (1.05 to 1.20)	1.11 (1.04 to 1.20)	1.13 (1.05 to 1.22)
Model 4	1.11 (1.04 to 1.18)	1	1.05 (0.97 to 1.12)	1.10 (1.03 to 1.17)	1.09 (1.01 to 1.17)	1.10 (1.02 to 1.18)
Model 5	1.10 (1.03 to 1.17)	1	1.05 (0.98 to 1.12)	1.10 (1.02 to 1.27)	1.09 (1.02 to 1.17)	1.09 (1.01 to 1.18)
Energy (partition)ł						
Cases/non-cases	8,333/7,762	1,580/1,654	1,645/1,570	1,703/1,519	1,708/1,512	1,697/1,507
Model 1	1.19 (1.12 to 1.26)	1	1.07 (1.00 to 1.14)	1.09 (1.02 to 1.17)	1.12 (1.04 to 1.20)	1.22 (1.14 to 1.32)
Model 2	1.18 (1.11 to 1.25)	1	1.08 (1.00 to 1.15)	1.09 (1.02 to 1.17)	1.13 (1.05 to 1.21)	1.22 (1.13 to 1.31)
Model 3	1.18 (1.12 to 1.25)	1	1.08 (1.00 to 1.15)	1.09 (1.02 to 1.17)	1.13 (1.05 to 1.21)	1.22 (1.13 to 1.31)
Model 4	1.17 (1.10 to 1.24)	1	1.07 (1.00 to 1.12)	1.08 (1.01 to 1.16)	1.11 (1.04 to 1.19)	1.20 (1.11 to 1.29)
Model 5	1.10 (1.04 to 1.17)	1	1.04 (0.97 to 1.12)	1.05 (0.98 to 1.13)	1.06 (0.99 to 1.14)	1.12 (1.04 to 1.21)

Table 4.5 Associations between ultra-processed food intake and risk of cardiovascular diseases, from multivariable Cox proportional hazard models, EPIC-Norfolk cohort, United Kingdom, 1993-2016 (n=16,095)

¥ Continuous HR: Hazard ratio for an increase in consumption from the 10th to 90th percentile for each of the ultra-processed foods variables.

* Ultra-processed food exposure variables 1-3 (absolute weight, proportion of weight, and absolute energy) were adjusted with the residual method. Model 1: adjusted for age (as timescale) and sex; Model 2: model 1 + physical activity, social class, education, smoking status, marital status, Townsend deprivation index, alcohol consumption, height, family history of diabetes. Model 3: model 2 + consumption of unprocessed food consumption and total energy intake; Model 4: model 3 + salt and saturated fat intake; Model 5: Model 4 + waist circumference and BMI.

ł Variables in the energy-partition and proportion of energy (or density) models were not adjusted via residual method. Models 1-5 of the energy-partition approach were like the above except that instead of total energy intake a variable with the energy from non-UPF sources was included, derived by subtracting the energy from UPFs from total energy consumed for each participant.

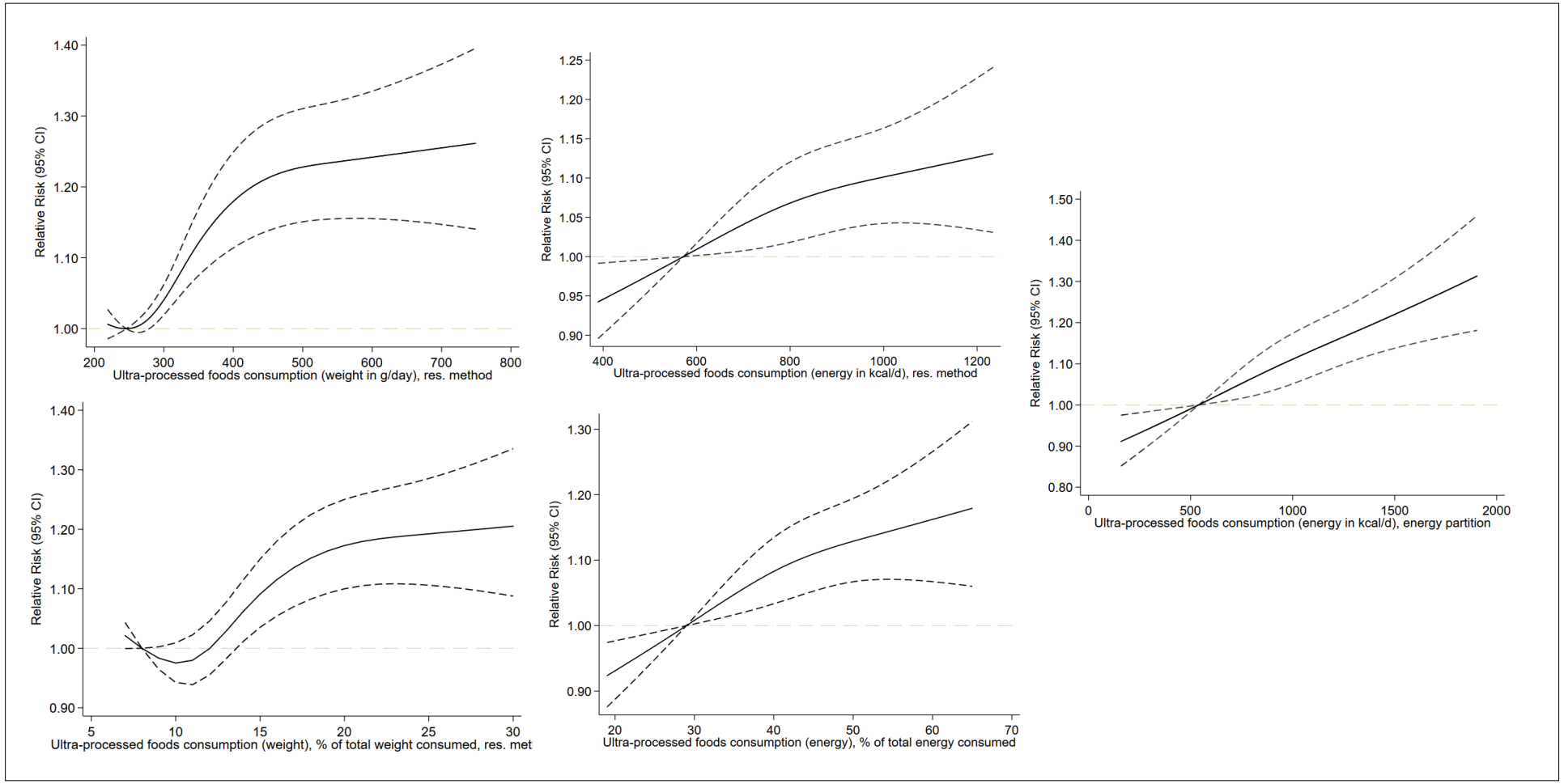


Figure 4.4 Associations between ultra-processed food intake and risk of cardiovascular diseases, from multivariable Cox proportional hazard models, modelled with restricted cubic splines, EPIC-Norfolk cohort, United Kingdom, 1993-2016 (n=16,095)

UPF intake as absolute weight (left column, top), proportion of weight (left column, bottom), and absolute energy (middle column, top) were adjusted with the residual method. UPF intake as proportion of energy (middle column, bottom) and energy-partition (right column) were not adjusted via residual method. All estimates were adjusted for age (as timescale) and sex, physical activity, social class, education, smoking status, marital status, Townsend deprivation index, alcohol consumption, height, family history of diabetes, unprocessed food intake, and total energy intake. The energy-partition approach was like the above except that instead of total energy intake a variable with the energy from non-UPF sources was included, derived by subtracting the energy from UPFs from total energy consumed for each participant.

4.4.2.2 Ultra-processed food intake and incident cardiovascular diseases

Table 4.5 and Figure 4.4 present the estimated associations between UPF intake and risk of any incident cardiovascular disease event. The number of incident CVD cases first decreased between the first and the second quintile of UPF intake expressed as absolute weight or proportion of weight, and then increased continuously between quintiles three to five. When UPF intake was expressed as energy, this was not the case – here incident cases increased between the first and second quintile but then remained at an approximately similar level.

In the Cox-models, higher intake of UPFs was associated with an increased risk of CVD across both weight and energy measures. The HRs were smaller than in the case of T2DM, but more consistent across all five approaches to expressing and modelling UPF intake. HRs for an increase UPF intake from the 10^{th} to the 90^{th} percentile ranged from 1.19 (95% CI: 1.12 to 1.26; UPF energy-partition; model 1) to, 1.07 ([i.e.] 95% CI: 1.02 to 1.12; UPF as absolute weight; model 5). In all continuous cases, the confidence intervals excluded 1.00. HRs for being in the highest vs. lowest quintile of UPF intake ranged from 1.23 (95% CI: 1.15 to 1.33; UPF as proportion of weight; model 1) to 1.09 ([i.e.] 95% CI: 1.01 to 1.18; UPF as proportion of energy, model 5). In none of the continuous or the Q5 vs. Q1 estimates was 1.00 included in the confidence intervals. However, the lower confidence intervals were often close to 1.00, mostly for models 4 and 5, and especially in the energy models (absolute and as a proportion). In comparison with T2DM, the inclusion of salt and saturated fats did not affect risk estimates as much as sugar and fibre, and the inclusion of waist circumference resulted in decreased HRs, but not as much as it did in the case of T2DM.

Estimating the risks across the ranges of UPF intakes indicated a different functional relationship between UPF energy and weight approaches that was not as clearly visible in the previous results (Figure 4.4). In the weight measures, estimated risks followed some sort of sigmoid curve (first a small decrease in risk, followed by an increase, and flattening of the curve towards the higher intakes). In the energy measures, the shapes appeared positively linear.

4.4.2.3 Ultra-processed food intake and adiposity

	Health Check 1		Health Check 2	
	Continuous ¥	Q5 vs. Q1	Continuous ¥	Q5 vs. Q1
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Weight (absolute)*				
Model 1	1.79 (1.66 to 1.93)	2.50 (2.16 to 2.89)	1.68 (1.51 to 1.87)	2.20 (1.81 to 2.68)
Model 2	1.71 (1.58 to 1.85)	2.33 (2.01 to 2.70)	1.64 (1.47 to 1.83)	2.08 (1.70 to 2.54)
Model 3	1.66 (1.52 to 1.83)	2.13 (1.82 to 2.49)	1.60 (1.41 to 1.81)	1.91 (1.54 to 2.36)
Model 4	1.71 (1.57 to 1.87)	2.20 (1.88 to 2.57)	1.63 (1.43 to 1.85)	1.95 (1.57 to 2.41)
Weight (proportion)*				
Model 1	1.74 (1.60 to 1.90)	2.03 (1.76 to 2.34)	1.57 (1.40 to 1.76)	1.92 (1.58 to 2.34)
Model 2	1.61 (1.47 to 1.76)	1.82 (1.57 to 2.10)	1.49 (1.32 to 1.69)	1.77 (1.44 to 2.17)
Model 3	1.46 (1.31 to 1.62)	1.60 (1.37 to 1.87)	1.36 (1.17 to 1.58)	1.54 (1.24 to 1.92)
Model 4	1.49 (1.34 to 1.66)	1.62 (1.39 to 1.90)	1.37 (1.18 to 1.59)	1.55 (1.24 to 1.93)
Energy (absolute)*				
Model 1	1.35 (1.20 to 1.51)	1.37 (1.19 to 1.58)	1.25 (1.07 to 1.45)	1.34 (1.10 to 1.64)
Model 2	1.16 (1.03 to 1.30)	1.16 (1.00 to 1.34)	1.08 (0.92 to 1.27)	1.16 (0.95 to 1.43)
Model 3	1.13 (1.00 to 1.28)	1.12 (0.97 to 1.31)	1.05 (0.89 to 1.24)	1.13 (0.91 to 1.39)
Model 4	1.14 (1.01 to 1.29)	1.13 (0.97 to 1.32)	1.05 (0.89 to 1.24)	1.13 (0.92 to 1.39)
Energy (proportion)ǂ				
Model 1	1.60 (1.42 to 1.80)	1.57 (1.36 to 1.82)	1.36 (1.16 to 1.60)	1.41 (1.16 to 1.71)
Model 2	1.54 (1.36 to 1.74)	1.49 (1.28 to 1.73)	1.26 (1.07 to 1.49)	1.28 (1.04 to 1.57)
Model 3	1.30 (1.14 to 1.48)	1.23 (1.05 to 1.44)	1.19 (0.99 to 1.43)	1.19 (0.96 to 1.49)
Model 4	1.32 (1.16 to 1.51)	1.25 (1.06 to 1.47)	1.20 (1.00 to 1.44)	1.20 (0.97 to 1.50)
Energy (partition)ǂ				
Model 1	1.99 (1.78 to 2.22)	2.17 (1.86 to 2.53)	1.37 (1.18 to 1.59)	1.60 (1.31 to 1.97)
Model 2	2.20 (1.96 to 2.47)	2.45 (2.09 to 2.86)	1.46 (1.24 to 1.71)	1.63 (1.32 to 2.02)
Model 3	2.20 (1.96 to 2.46)	2.44 (2.09 to 2.85)	1.41 (1.19 to 1.67)	1.57 (1.26 to 1.95)
Model 4	2.49 (2.15 to 2.88)	2.51 (2.10 to 3.00)	1.55 (1.25 to 1.93)	1.63 (1.26 to 2.11)

Table 4.6 Associations between ultra-processed food intake and adiposity, from multivariable logistic regression models, EPIC-Norfolk cohort, United Kingdom, 1993-2016 (n=17,558)

¥ Continuous OR: Odds ratio for an increase in consumption from the 10th to 90th percentile for each of the ultra-processed foods variables.

* Ultra-processed food exposure variables 1-3 (absolute weight, proportion of weight, and absolute energy) were adjusted with the residual method. Model 1: adjusted for age (as timescale) and sex; Model 2: model 1 + physical activity, social class, education, smoking status, marital status, Townsend deprivation index, alcohol consumption, height. Model 3: model 2 + unprocessed food intake, and total energy intake; Model 4: model 3 + sugar intake.

ǂ Variables in the energy-partition and proportion of energy (or density) models were not adjusted via residual method. Models 1-4 of the energy-partition approach were like the above except that instead of total energy intake a variable with the energy from non-UPF sources was included, derived by subtracting the energy from UPFs from total energy consumed for each participant.

Table 4.6 and Figure 4.5 present the associations between UPF intake and adiposity. In cross-sectional logistic models, odds ratios (ORs) for an increase in UPF intake from the 10th to the 90th percentile ranged from 2.49 (95% CI: 2.15 to 2.88; UPF energy-partition; HE1; model 4) to 1.08 (95% CI: 0.89 to 1.24; UPF as absolute energy; HE2; model 3). When individuals of the fifth quintile were compared to the first quintile of UPF intakes, ORs ranged from 2.51 (95% CI: 2.10 to 3.00; UPF energy-partition; HE1; model 4) to 1.12 (95% CI: 0.97 to 1.31; UPF as absolute energy; HE1; model 3). Overall, estimates at the second health examination were slightly lower than at the first. The lower CIs of the approaches using absolute energy from UPFs and proportion of energy from UPFs included 1.00 or were very close to including 1.00 when the models were adjusted for confounders. This was not the case for the two weight approaches and the energy-partition models, the latter of which had the highest estimates of all five approaches.

Estimating the risks across the ranges of UPF intakes non-linearly indicated similar positive functional relationships between UPF energy and weight approaches (Figure 4.5). Reflecting the results from Table 4.6, the weight approaches as well as the energy-partition approach showed positive associations, large estimates, and narrow CIs. While UPF as absolute energy at both health examinations and UPF expressed as proportion of total energy consumed at HE2 indicate no clear association, UPF expressed as proportion of total energy consumed at HE1 shows a small but positive association.

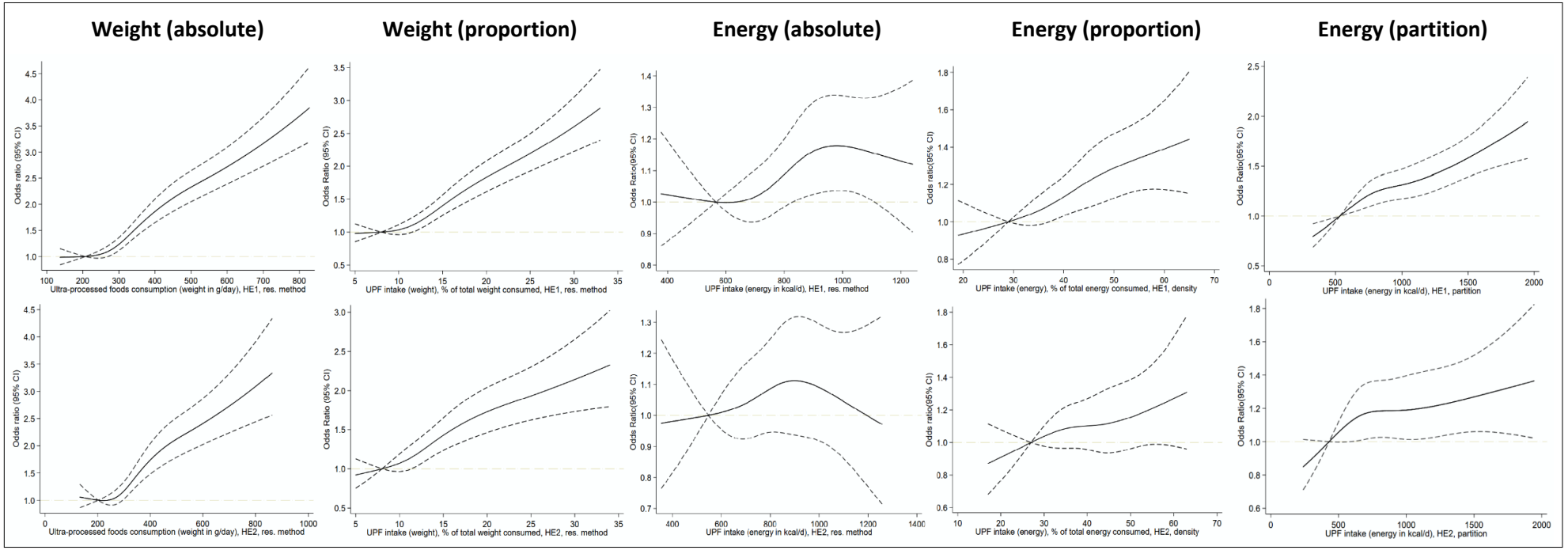


Figure 4.5 Associations between ultra-processed food intake and obesity, from multivariable logistic models, modelled with restricted cubic splines, EPIC-Norfolk cohort, United Kingdom, 1993-2016 (n=17,588)

Associations were estimated at the first health examination (top row) and second health examination (bottom row). UPF intake as absolute weight (first column), proportion of weight (second column), and absolute energy (third column) were adjusted with the residual method. UPF intake as proportion of energy (forth column) and energy-partition (fifth column) were not adjusted via residual method. Estimates were adjusted for age (as timescale) and sex, physical activity, social class, education, smoking status, marital status, Townsend deprivation index, alcohol consumption, height, unprocessed food intake, total energy intake, and sugar intake. The energy-partition approach was like the above except that instead of total energy intake a variable with the energy from non-UPF sources was included, derived by subtracting the energy from UPFs from total energy consumed for each participant.

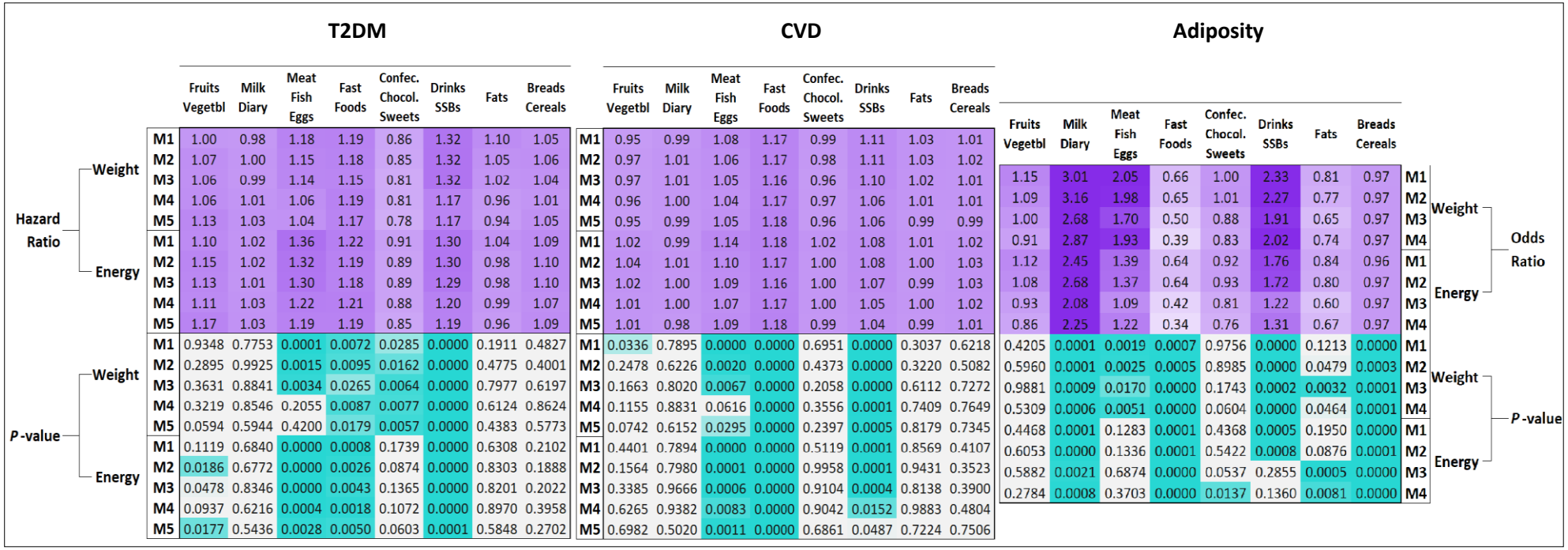


Figure 4.6 Associations between ultra-processed food groups intake and obesity, from multivariable logistic models, modelled with restricted cubic splines, EPIC-Norfolk cohort, United Kingdom, 1993-2016 (n=17,588)

Associations between eight ultra-processed food groups and T2DM, CVD, and adiposity were estimated in multivariable Cox-regressions (T2DM and CVD) and logistic regressions (adiposity). For each outcome, the models were identical to those used in the analyses above. HRs and ORs were estimated for an increase in consumption of each ultra-processed food group from the 10th to 90th percentile. The cells in the upper half represent the estimated HRs or ORs; the darker the colour, the higher the estimate of association. The cells in the bottom half represent the *P*-value of the point estimates; the darker the colour, the smaller the *P*-value.

4.4.2.4 Ultra-processed food groups and cardiometabolic health

UPF intake was decomposed into eight ultra-processed food groups to estimate associations of individual food groups with T2DM and CVD risk, as well as adiposity (Figure 4.6). Intake from each ultra-processed food group was expressed as weight and energy (both absolute), in changes from the 10th to the 90th intake percentiles. In the analyses of T2DM and CVD risk, a similar pattern emerged. The three ultra-processed food groups meat, fish, and eggs; fast foods; and drinks and SSBs were consistently associated with increased risk of T2DM and CVD. For example, the HR for an increased intake of fast foods from the 10th to 90th percentile was 1.18 (*P*-value < 0.0001; fast food as weight or energy; model 5). The HRs of the estimated T2DM risk were larger than those of CVD risk, and regarding T2DM, confectionary, chocolates, and sweets were only associated when they were expressed as weight, while they were not associated regarding CVD. Ultra-processed fruits and vegetables; milk and dairy; fats; and breads and cereals were not associated with an increased risk of disease for neither of the two diseases.

In the analyses with adiposity as an outcome, the pattern was different. Ultra-processed drinks and SSBs were strongly positively associated, as were ultra-processed milk and dairy foods, while meat, fish, and eggs, were associated only in the weight measures. Surprisingly, fast foods were negatively associated here – an increased consumption of fast foods from the 10th to the 90th percentile was associated with an OR of 0.34 (*P*-value < 0.0001; fast food as weight or energy; model 4). Breads and cereals were also negatively associated with adiposity, although only marginally, and meat, fish, and eggs were positively associated with adiposity, but only when expressed as weight.

4.4.2.5 Sensitivity analyses

Excluding incident T2DM and CVD during the first years of follow-up and estimating associations based on complete cases did not change the estimated associations and their functional forms. Excluding participants with improbable energy reporting based on a simpler exclusion rule (<800 kcal or >4200 kcal per day in men and <500 or >3500 kcal per day in women) and combining

unprocessed foods with processed culinary ingredients for use as a covariate instead of only NOVA also did not change the results across the three analyses.

4.5 Discussion

4.5.1 Summary of main findings

In this prospective cohort study, two main ways to measure UPF intake according to NOVA were used – UPF intake as absolute weight and energy. When the two variables were disaggregated into eight ultra-processed food groups, the three groups ultra-processed confectionary, sweets, and sugary products; breads, starchy foods, and cereals; and fats contributed most to energy intake from UPFs. When UPF intake was measured as weight, ultra-processed drinks and SSBs instead of fats were among the top three food groups. Higher intake of UPFs was associated with an increased risk of T2DM in four of the five approaches to measure UPFs and adjust for total energy intake, and the risks were more pronounced when UPF intake was measured as weight compared to energy. Furthermore, the addition of BMI and waist circumference reduced the risk estimates substantially. UPF intake was also associated with an increased risk of CVD. The estimated HRs were lower than in the case of T2DM but were more consistent across the five ways of expressing UPF and adjusting for total energy intake. UPF intake was associated with obesity for both weight measures and the energy partition models, but when UPF intake was expressed as energy, ORs as well as the CIs decreased once the confounders including total energy were adjusted for. Estimating associations between each ultra-processed food group and risk of T2DM and CVD showed a similar pattern, with ultra-processed meat, fish, and eggs; drinks and SSBs; and fast foods being associated with an increased risk of diseases. The associations between the ultra-processed food groups and adiposity were somewhat surprising – while drinks, SSBs, milk, and dairy were strongly associated with adiposity, fast foods were associated with reduced odds of obesity.

4.5.2 Comparison with other studies and interpretation

Two previous studies have estimated the proportion of energy from ultra-processed foods in the United Kingdom based on the National Diet and Nutrition Survey to be 53 and 56.8%, respectively.[131,298] In this study, the average energy from UPFs was 41%, which is likely due to the fact that the dietary assessments at HE1 and HE2 happened in the mid to late 1990s – 20-25 years ago – when dietary habits and the range of UPFs available was somewhat different. While no research on the long term trends of food groups defined as 'ultra-processed' is available for the UK, previous studies have shown that the consumption of sugary drinks has doubled between 1975 and 2007 and ready-meals and convenience meat products have increased by 480% between 1974 and 2011, while fresh fruits and vegetables, cereals, and milk have remained constant over time.[299–301] In Sweden (which arguably has experienced a comparable transformation of its food system), UPF consumption increased by 134% between 1960 and 2010, mostly driven by large increases in sodas as well as snack foods such as crisps and candies.[302] Thus, the somewhat lower overall energy from UPFs in *EPIC-Norfolk* is in line with previous research and is likely to be partially driven by less consumption of UPF drinks, ready-meals, and convenience products in the 90's. Outside the UK, the largest share of energy intake in many countries come from UPFs – figures from Brazil, Canada, France, Germany, Netherlands, Norway, Spain, and Sweden suggest a range of energy intake from 40% to 65% in population diets.[97,98,170,268,303] These figures demonstrate the important role of UPFs in the U.K., high-income, but increasingly also low-to-middle-income countries.[133]

A few studies have previously suggested that UPFs contribute to increasing risk of adverse cardiometabolic health, such as obesity[141,142], hypertension[140], and dyslipideamia[143] – but no previous prospective epidemiological study has evaluated the association between the degree of food processing specifically and T2DM, which is why the systematic review and meta-analyses was performed in chapter 2. In chapter 2, the summary relative risk estimate for the highest versus lowest UPF intake or dietary pattern score was 1.46 (95% CI: 1.23 to 1.68). Even though the UPF exposure was not identical with the more precise exposure data used here, the

estimated HRs in *EPIC-Norfolk* were roughly comparable when UPF was expressed as weight, and lower when UPF was expressed as energy.

One study from the French *Nutrinet-Santé* has specifically estimated associations between UPF intake according to NOVA and CVD, finding a small but positive association of 1.12 (HR; 95% CI: 1.06 to 1.21; model 5) for a 10 percent increase in the proportion of UPF intake expressed as weight of total food intake.[144] When the highest quarter was compared to the lowest quarter of UPF intake, the estimated HR was 1.26 (HR; 95% CI: 1.07 to 1.48; model 5). The HRs in *Nutrinet-Santé* were more consistent across the different model specifications; the models adjusted for only age and sex were even identical to the fully adjusted models. In *EPIC-Norfolk*, adjusting for nutritional and non-nutritional confounders changed the estimated risks. However, the study in *Nutrinet-Santé* was internally less consistent: while the HR for a continuous increase of 10% was 1.12, an increase from the highest versus lowest quarter (which would amount to an average increase of 75%) of UPF intake was 1.26, less than what would be expected from the continuous HR estimates. In the present study, the continuous and the categorical estimates were supposed to estimate similar intake differences, and the estimated risks were comparable. Furthermore, Srour et al. also applied Black's method to use the basal metabolic rate and the Goldberg cut-offs to identify and exclude energy underreporting. 20% of the *Nutrinet-Santé* cohort were excluded. Here, 26% of the sample were excluded based on energy underreporting, and the small difference is likely due to the higher validity of the dietary assessment method in the *Nutrinet-Santé* cohort (24h dietary records with measurements every 6 months).

Several hypotheses could explain the associations between UPF and T2DM and CVD. The nutritional hypotheses introduced in the first chapter are also relevant here and will be discussed briefly: UPFs have been found to contain higher levels of sugar, sodium, energy, and less fibre, nuts, seeds, whole grains, and various micronutrients.[96–103] UPFs have also been found to be less satiating and have a higher glycaemic load than minimally or unprocessed foods.[104] High intakes of sugar, little dietary fibre, nuts, seeds, grains, and consumption of foods with a

high glycaemic index negatively affect the development of insulin resistance and T2DM.[105–109] Ultra-processed drinks and SSBs had the highest estimated HRs in the analyses of food groups, followed by fast foods and ultra-processed meats, fish and eggs. The associations between UPFs and T2DM can thus be partially explained by ultra-processed food groups with previously established disease associations.[304–309]

Additionally regarding CVD, diets high in UPFs contained lower levels of fruits and vegetables and higher levels of dietary sodium.[97,110–112] These characteristics have previously been associated with increased risk of CVD.[3,113] Also, trans fats from partially hydrogenated oils were a still a widely used ingredient during the period during which the data was collected at HE1 and HE2 (1990 and 2000). Trans fats have been associated with increased CVD risk, especially total CHD and CHD mortality risk.[119,120]

The associations between UPF intake and higher risk of CVD and T2DM might be due to the lower consumption of un- and minimally processed foods in individuals with higher intakes of UPFs.[c] This is difficult to disentangle because individuals with higher consumption of UPFs consumed relatively less non-UPFs. However, associations remained similar after adjusting for the intake of non-UPFs, indicating that less intake of non-UPFs could not be a major source of the associations. Furthermore, adjustments for saturated fats, sugar, fibre, sodium, and total energy also did not alter the associations substantially, suggesting that the nutritional composition of UPFs is not the only factor that explains estimated associations and other components of UPFs might contribute to an increased disease risk.

Thus, a second set of mechanisms that might potentially explain UPF-CVD associations do not relate to common nutritional factors but to food additives and newly formed compounds that result from the food processing process. In principle, safety regulations determine upper limits of artificial food additives to guard consumers from potentially harmful effects of specific

[c] In *EPIC-Norfolk*, the correlation between UPFs and un- and minimally processed foods (expressed as proportion of weight) was -0.5.

compounds, but how multiple substances from multiple consumed foods may add up and interact with each other is mostly unknown.[144] For some of the additives allowed in the European Union, several negative health effects have been suggested in animal and *in vitro* studies. I will list evidence for some of the commonly used food additives here, summaries of greater detail can be found elsewhere.[144,310–312]

High amounts of sulphur-based compounds (such as sulphites) used in ready-to-eat dressings have been shown to negatively impact heart health in rats.[313] Monosodium glutamates found in sauces, dressings, and other convenience products have been demonstrated to induce oxidative stress through lipid peroxidation in mice and thus may harm coronary arteries and increase risk of CVD.[314] Monosodium glutamate also has the potential to disrupt endocrine hormone regulation which might play a role in the pathogenesis of obesity by impairing secretion of glucagon-like peptide-1, related satiety responses, and glucose-stimulated insulin release.[315] Emulsifiers commonly used in UPFs can affect low grade inflammation and obesity in mice.[316] Animal and *in vitro* models of thickening agents such as carrageenan have also shown an increased risk of impaired fasting glucose and insulin resistance, as well as distortion of insulin signals.[317] Furthermore, prolonged exposure to zero-calorie artificial sweeteners in cellular models suggest potential adverse effects on heart health, while an RCT with adipose women has found that sucralose elevated blood sugar and insulin levels.[318,319] However, studies of regular consumers of sucralose did not have this effect.[320–322]

The high temperatures of food processing techniques produce newly formed contaminants such as acrylamide, bisphenol A, polycyclic aromatic hydrocarbons, or glycidyl fatty acid esters from palm oils and fats. Acrylamide is found in chips, biscuits, fries, certain preparation based on cereals, or breads, and has been found to increase the risk of CVDs in two cohorts in the US.[323,324] Animal studies have shown associations between prenatal exposures of bisphenol A and increased body weight and prevalence of obesity, impaired glucose tolerance, and lipid metabolism in mice, as well as higher concentrations of plasma triglycerides.[325] While the carcinogenic properties of glycidyl fatty acid esters have been repeatedly demonstrated, high

dosages of one type (2-MCPD) have caused cardiac arrests and other adverse heart events in experimental studies of rodents.[312]

In summary, a large range of potentially harmful compounds that are produced and added during the processing of foods might be related to health. In their study, Srour et al. hypothesized that 'cocktail effects' of food additives and substances due to food processing may explain the estimated associations, because associations between UPF and CVD risk remained after adjusting for nutritional and non-nutritional confounders. This interpretation of the *Nutrinet-Santé* study is flawed for two reasons. First, none of the models included in the paper estimated the association between UPF intake and CVD while adjusting for un- and minimally processed foods as well as other potentially adverse nutritional factors such as sugar and sodium intake at the same time. Hence none of the study results represented an attempt to simultaneously adjust for all nutritional factors other than the 'cocktail' of additives and other food related substances. Secondly, even if all confounders would be accounted for, individuals that consume little UPFs are substantially different from those consuming a lot of UPFs – they smoke less, are more active, have a higher education, and have an overall healthier diet. It is questionable that multivariable regression adjustment methods can really account for these differences and provide adequate control in a way that allows the type of *ceteris paribus* interpretation as described above. This point will be discussed further in the limitation section below, but it is mainly for this reason that the results presented in this chapter also do not allow for any inferences regarding potential effects of additives and other compounds, even though I have adjusted for a large range of potential nutritional confounders simultaneously and associations remained. The estimated associations for CVD could simply be the result of the generally poorer nutritional quality of diets that are high in UPFs combined with the effects of other health-related characteristics and non-nutritional confounders. In the context of a non-randomized observational cohort study, it is untestable and, unfortunately, a matter of beliefs whether the interaction of food additives and other compounds play a role in the disease pathogeneses or not. However, a well-established mechanism regarding food additives is the

increased food and excess energy intake due to formulations that are designed to hit a 'bliss point' or state of satiety, pleasure, and 'hedonia' during consumption.[326] The influences that food additives such as flavour enhancers can have on interactions of neurotransmitter, receptors, appetite, satiety, conditioned preferences, as well as the brain reward system have been established previously, and it is likely that increased energy intake and a sustained positive energy balance is one of the central mechanisms through which food additives in UPFs affect cardiometabolic health.[327]

Regarding both CVD and T2DM, another potential pathway explaining diet-disease associations could be the relationship between diets and the gut microbiome. A large body of research supports the hypothesis UPFs and Western diets (that are often characterized by higher relative intakes of UPFs, as shown in chapter 2) affect changes in the gut microbiome which are associated with obesity and metabolic diseases, possibly through the pathways of gut dysbiosis (microbial imbalance or maladaptation) and inflammation.[127]

More generally, CVD has a more complex aetiology in which, depending on disease subtype, non-nutritional risk factors may play a relatively more important role than in the aetiology of T2DM. This could explain why the estimated relative risks between UPFs and CVD were smaller and possibly have a slightly different functional form than in the association between UPFs and T2DM.

In line with current research, positive associations between UPF intake and adiposity were found in the analyses. In the previously mentioned RCT of *ad libitum* UPF versus unprocessed food consumption, participants in the UPF group consumed on average about 500 calories more than participants in the unprocessed group, and this was due to increased fat and carbohydrate but not protein intake.[94] Participants in the UPF group also gained 0.8 kg body weight over a two-week period, while participants in the unprocessed group lost 1.1 kg ($P < 0.001$).

Physically, all weight gain is the result of a positive energy balance: if an individual consumes more than she expends, she gains weight, but if there are no excess calories, there is no weight

gain. This would imply, however, that once total energy intake (i.e. the quantity of food) is accounted for, no positive association should be observed. In the analysis presented here, this was only the case for the UPF-energy and UPF as proportion of energy measures. This might indicate that some ways of adjusting for total energy intake perform better than others. For example, when the energy-based measure of UPFs was used in conjunction with the residual method and total energy consumed as a model covariate, little association between UPFs and adiposity remained. This, however, also indicates that the inclusion of confounders (such as total energy intake) in multivariable regressions might not always provide adequate control for the confounder of interest. It might also mean that associations based on weight-based measurements overestimate exposure-disease relationships, because even after adjusting and controlling for energy intake, UPF consumption expressed as absolute or proportion of weight was strongly associated with increased odds of adiposity. This should not have been the case if adjusting for energy intake provides adequate control of the influence of the quantity of the foods consumed. Furthermore, the estimated associations between UPF intake and CVD risk were broadly similar for the weight and energy measures but varied considerably when associations between UPF intake and T2DM and adiposity were estimated. The way exposures are expressed might therefore affect estimates of different exposure-disease associations to varying degrees, possibly as a result of underlying mechanisms.

The comparison of the food groups that contribute most to UPF consumption as either weight or energy measure might offer a potential explanation of the different associations with risks of disease. Participants with the highest consumption of energy from UPF consumed over 50% of this energy through ultra-processed breads, starchy foods, cereals, fats, and fruits and vegetables. Thus, a large part of the main contributing food groups to energy from UPFs according to NOVA in *EPIC-Norfolk* were therefore foods that do not have an unequivocally disadvantageous nutritional profile. In comparison, almost a fifth of the UPFs measured as weight were ultra-processed drinks and SSBs alone, and another 17 percent were confectionary,

sweets, and sugary products. Thus, the stronger association of UPF intake expressed as weight or proportion of weight and T2DM might therefore be explained by different relative shares of ultra-processed food groups to the overall composition of the weight and energy measures.[308,328] Additionally, the increase in the consumption of UPFs between the lowest and highest quintiles of UPF consumption was on average 40% higher when UPF was measured as weight in comparison to UPF measured as energy. These two findings are related – the larger increases of UPF intake measured as weight was driven by the higher share of UPF drinks and SSBs, which weigh a lot but are not as energy dense as other UPFs (due to the high water content). Thus, differences in the contribution of food groups and related larger increases in measured UPF intake likely account for the differences in the estimates of the UPF weight and energy measures.

The findings that fast foods were negatively associated with adiposity is puzzling. One potential explanation might be reversed causality, because overweight and obese people could have been eating fewer of these foods to avoid further weight gain or to lose weight. During the 1990s, when public knowledge and attitudes to food were somewhat different, to lose weight people tended to cut out fatty foods, whereas now they are more likely to cut out sugary and carbohydrate-rich foods. In *EPIC-Norfolk*, the correlation between proportion of fast foods as a share of overall food intake and BMI was -0.05, implying that individuals with higher BMI and higher energy intakes consumed almost the same relative or slightly fewer relative amounts of fast foods than people with low BMI and lower energy intakes. Individuals thus consumed more energy through ultra-processed food groups other than fast foods, and this higher relative amount of other food groups and similar or even less amount of fast foods has potentially led to the estimation of the negative association between fast foods and adiposity.

4.5.3 Strengths and limitations of study

Strengths of this study include the prospective design with a large sample size and a long follow-up time of over 17 years which is well suited to assess risks of chronic diseases with long pathogeneses. Since outcome ascertainment in *EPIC-Norfolk* was externally linked to medical

records, potential bias from loss to follow-up is minimized. Furthermore, this is the first study to assess and compare different ways of expressing UPFs, and the first study to provide a comprehensive analysis of the associations between UPF intake and three cardiometabolic health outcomes in one cohort study. It is also the first study to explicitly estimate associations between UPFs and risk of T2DM.

This study has also several limitations. First, dietary intakes were measured between over 25 (at HE1) to 15 years ago (at HE2). As discussed above, this explains why a little over 40% of overall energy was consumed through UPFs, which is 15-20% less intake compared to what has been estimated for today.[131,298] The overall summary relative risks estimated in *EPIC-Norfolk* might therefore be lower as what would have been observed with average exposure levels of today. Furthermore, measurement error from self-reported dietary exposures may have influenced the relative risks by regression dilution bias, which attenuates the estimated disease risk association.[230] However, given that there might have been measurement error in the covariates as well, it is unclear in which direction the observed association could have been biased. Also, changes in the diet over the study could not be fully accounted for, although some of the error was accounted for by using repeated measurements of diet as well as of covariates.

Residual confounding from unmeasured confounders and imprecise measurements of potential confounders could also have influenced the results. I attempted to adjust as well as possible for confounders. However, the 'ignorability' assumption holds that conditional on the confounding covariates, the probability that a participant is exposed to high or low levels of UPFs should be equal, or in other words, all confounding variables are controlled for. Even if this was the case, differences in the distributions of the confounder covariates between more and less exposed participants (or a lack of overlap and lack of balance in technical terms) are plausible and can imply erroneous covariate-adjusted estimates and confidence intervals.[227–229] Accordingly, a review reported that the coefficient estimates from confounder adjusted multivariable logistic and Cox-regression were larger than estimates using propensity score methods (to adjust for confounders) in over 50% of the cases (50 of 96 studies).[329] Differences in the distributions of

important confounders such as un- and minimally processed foods, sex, smoking, physical activity, or education level between individuals with high and low intakes of UPFs exist in *EPIC-Norfolk.* Residual confounding from differences in distributions of those variables might therefore explain some of the estimated associations.

Furthermore, BMI and waist circumference were considered as confounders in the analyses of the risk of CVD and T2DM. Yet, recent evidence has suggested BMI as a mediator in the association between diet and T2DM and CVD.[281,330–332] This might explain the decreases in risk estimates once BMI was accounted for in the models 5 of the analyses presented here, which might underestimate UPF-disease associations. Additionally, generalisability is limited due to a potential healthy cohort bias and the inclusion of mostly Caucasian Europids in the UK in the sample.[278]

4.5.4 Conclusions and implications for research and policy

In this prospective cohort study, higher intakes of UPFs were associated with adiposity and increased risk of T2DM and CVD. While different approaches to measure UPF intakes and to adjust for total energy intake yielded different estimated associations between UPF and adiposity and T2DM risk, this was not the case for CVD. The stronger associations between UPF intake measured as weight and T2DM were possibly due to higher relative contribution of ultra-processed drinks and SSBs and larger increases in UPF intake between Q1 and Q5 of UPF intake measured as weight (compared to increases when UPF intake was measured as energy). Generally, associations between UPF and CVD and T2DM were likely driven by a combination of unhealthy nutritional profiles of UPFs, less relative intakes of un- and minimally processed foods, and at least to some extent from potential residual confounding from adjusted nutritional and non-nutritional confounders. Whether food additives and newly formed substances from food processing processes contribute to the CVD pathogeneses is, currently, subject to speculation. It is, however, likely that the ingredients used in UPFs to increase consumption therefore lead to an overconsumption of food and energy. Although inference from cross-sectional analyses

are limited, the estimated associations between UPF and adiposity at both health examinations, as well as the decreases of the estimated associations after adjustment for BMI and waist circumference in the prospective analyses, point towards a substantial mediating effect of body weight on the UPF-disease pathway.

Despite the limitations, the findings imply that the processing of *some* but not all ultra-processed food groups does affect health adversely through various ways, most likely the overall nutritional composition and a production that is designed to hit the 'bliss point' to increase consumption. However, not all UPFs seem to be created equal. A modified hypothesis on UPFs could be that not all UPFs are unhealthy, but most food groups that are associated with increased risk of disease are ultra-processed. It is likely that much of the food processing that is currently used does something to the foods that make it unhealthy, whether it is the nutritional composition, a hyper-palatability through additives, or potential interaction effects of compounds resulting from the food processing itself.

These findings have some implications for future research. The UPF disease association should be tested in other large cohorts. To provide further insights, associations between the entire UPF group as well as disaggregated ultra-processed food groups and disease should be estimated. In this context, it should also be tested whether associations between the entire UPF group and diseases remain once some of the major ultra-processed food groups such as ultra-processed drinks and SSBs or confectionary and sugary products are removed from the aggregated UPF group. If this was not the case, it would call an undifferentiated negative assessment of all foods ultra-processed further into question.

Additionally, as the analyses presented here have shown, different ways of measuring UPF intake and adjusting for total energy affect the results. Future research efforts should be guided towards developing theory and testing of the implications of these data processing choices for different diseases by reporting the results for different combinations of measuring UPF intake, as well as adjusting for total energy intake. Furthermore, adjusting for confounding in

multivariable regression models has limitations and can potentially lead to biased associations. In this context, non-randomized observational studies should compare different methods to adjust for confounders, such as using Cox-regression in propensity score matched samples and samples without propensity score matching.[333,334] Reporting the results for different adjustment methods can help to make transparent whether residual confounding from adjusted confounders exists and whether the findings are similar for different methods.

Regarding food additives and compounds generated during food processing, it is unlikely that further research from cohort studies without brand and product-specific dietary assessment methods will provide insights into the question of whether potential interaction or 'cocktail' effects of these substances exist. Newer cohorts that have exact brand and product information may be better suited to assess these associations.

Yet, regardless of whether these substances or mixtures thereof play a role or not, or whether certain ultra-processed food groups are more important than others, in light of previous evidence and the findings presented in this chapter, the evidence of an association between higher intakes of UPFs and adverse cardiometabolic health is broadening.[132,140,143–145] Consumers should therefore be informed about these associations. France and Brazil have already introduced recommendations to promote the consumption of unprocessed or minimally processed foods in their national dietary guidelines.[335,336] The field of food science and technology could potentially contribute to a product reformulation by developing products that may still have 'bliss point' and are as enjoyable as UPFs, but with better nutritional profiles, fresher and less refined ingredients, more fibre, and less calories. While the evidence on the positive impact of diet-related fiscal measures on the consumption of unhealthy (and often ultra-processed) foods has accumulated, the effect of fiscal policies on population-level body weight and health has been ambiguous.[337–340] The combination of food taxes and subsidies combined with information may be a good starting point but is likely not enough to have the transformative effect that would be needed to halt the global cardiometabolic health crisis.

Other, more drastic regulatory and fiscal solutions are potentially needed. Further discussion on the implications of the findings for research and policy are provided in the next chapter, the overall discussion.

5 Overall Discussion

5.1 Introduction

In this thesis, my overall aims were to investigate the associations between ultra-processed food consumption and cardiometabolic health, both at the individual and the population-level, while following methodological principles such as incorporating and presenting the multiverse of statistical results as well as approaching statistical hypothesis testing in a non-dichotomous way. I addressed these aims with three studies: a systematic review and meta-analysis, an ecological, cross-country comparison, and a prospective cohort analysis. Each chapter includes an interpretation of the results, a contextualisation within the existing literature, a section outlining the strengths and limitations of the study and a discussion of the implications for policy and future research.

In chapter two (systematic review) I discussed the reasons for the limited comparability of the exposure across the studies included in the meta-analysis, the risk of confounding from unobserved and observed variables, as well as measurement errors in exposures and covariates. In chapter three (ecological study), I discussed the challenges of undertaking studies at the population-level, the limitations of comparability of food system data across different countries, and the difficulties in estimating associations when little or no variability in the data exists, even though a 'true' association is likely. In chapter four (cohort study), I discussed the influence that

different ways of operationalizing UPF exposure had on statistical results in the prospective cohort analysis and the residual confounding that can stem from imbalances in the covariate structure. In this chapter I summarize the main findings of these three epidemiological analyses, discuss the overall methodological strengths and weaknesses of the methods used, and give an overview of the implications for public health policy, alongside recommendations for future research.

5.2 Summary of findings

The research presented in this dissertation reveals consistent associations between UPFs and adverse cardiometabolic health. My analyses are the first to review previous dietary patterns studies from a food processing perspective and meta-analyse associations between diets and dietary patterns high in UPFs and risk of T2DM and CVD. Individual-level data is not always available in countries with less resources and analyses of country-level data can identify global trends and associations. By systematically investigating country-level associations between UPF sales and adiposity and diabetes in both LMICs and HICs over a prolonged period, chapter 3 adds insights about the global nature of UPFs and their associations with the cardiometabolic health of populations. The research in chapter 4 advances provides insights regarding an important aspect of nutritional epidemiological research through comparing different ways of operationalizing measurement of UPFs in a prospective cohort study. This work is the first to establish an association between a higher share of UPFs in diets (as defined by NOVA) and risk of T2DM, in a prospective cohort study.

The results of the systematic review and meta-analyses contribute to research on UPFs, and nutrition in general, by providing the first systematic analysis of published nutrition and dietary pattern studies from the perspective of UPFs according to the NOVA classification. By including studies that have previously not been considered in the assessment of the relevance of UPFs for health outcomes, this research makes a significant contribution to the field by showing that the evidence-base on UPFs and cardiometabolic health risk is not limited to studies of the NOVA

classification. In my study, I uniquely defined UPF consumption more broadly, identifying studies in which UPF consumption had been assessed in a range of ways under several different names, and combining those that were characterized by a higher relative intake of UPFs into one summary estimate.

The result that higher sales of UPF are associated with an increased risk of adiposity and DM at the country-level was demonstrated in the panel analysis in chapter 3, using data from 76 countries across all five continents. The panel analysis revealed that a strong and consistent association exists between the sales of UPFs at the food system level and adiposity and diabetes prevalence in LMICs for children, adolescent, and adult populations, as well as for both sexes separately. This finding adds value to the literature as no previous study had conclusively investigated these associations in countries for which a lack of data existed and had estimated associations for LMICs and HICs separately. However, the analysis did not establish an association between UPF and adiposity in HICs, which was surprising, given that the previous studies indicating an association at the individual level were mostly from HICs. This result must be interpreted cautiously. It seems likely that the lack of variability in UPF data from HICs during the study period were a key reason for the lack of estimated associations in HICs. Given the biological plausibility, previous evidence on the nutrition transition in LMICs, and the impact that food system transformations have on the health of those populations, as well as convincing evidence from an RCT and prospective cohort studies, it is very possible that the estimated associations in LMIC represent true associations but proving causality will require further prospective studies of individuals in LMICs. Because of the many combinations of data processing, analytical methods and the resulting variability of point estimates and *P*-values, emphasizing any particular set of point estimates would not have made sense in this case. However, the consistency of findings indicates that the expansion of global adiposity and diabetes since 2000 can partially be attributed to the increased sales of UPFs.

The associations that were found in the meta-analysis and the panel study were replicated in prospective analyses of detailed data from over 17,000 individuals in the *EPIC-Norfolk* cohort. This study added to the literature showing that the way exposures are measured or operationalized can fundamentally influence results.[161,163] Previous UPF studies have only expressed UPFs as weight or the proportion of food weight, with the justification that energy measures would not capture the non-calorific components of UPFs with potentially adverse effects on health. As outlined in chapter four, this argument is somewhat misguided given that many of the components without calorific value also have very little weight and secondly, the assumption that those potential effects would disappear just because UPFs are measured in terms of energy instead of weight seems unrealistic. Since it is very common to express nutritional exposure or risk factors in terms of energy, and no comparison of different ways of expressing UPFs had been made previously, I conducted the first study (chapter 4) on UPFs that estimated disease risks using a range of different methods for operationalizing UPF intake. Based on previous nutritional epidemiological research to adjust for total energy intake, I modelled UPF and associated diseases risks in five different ways. The analyses revealed that these different approaches affect the statistical results, but also that they affect the results differently for different diseases. For example, the differences between measures of UPF intake based on energy and weight were much more pronounced for T2DM as an outcome than for CVD, for example, suggesting that potentially different mechanisms relating to dietary energy and other factors common to UPFs might be responsible for different outcomes.

Chapter 4 was also the first analysis to comprehensively test the associations between UPF and three important cardiometabolic disease outcomes (adiposity, T2DM, and CVD) in a prospective cohort with a long follow-up period. The findings of an almost consistent positive association provide the strongest evidence to date that UPFs are positively associated with adverse risk of cardiometabolic health. The secondary analyses of eight different food groups and outcomes indicate that greater consumption of ultra-processed meat, fish, and eggs; fast foods; and SSBs

are associated with an increased risk of T2DM and CVD, whereas consumption of ultra-processed fruits and vegetables, milk and dairy, fats, and breads and cereals might not be associated with an increased risk of disease. Body weight is likely a very important mediator of the association between UPF and T2DM and CVD, while increased total energy intake through UPFs is likely the most important driver of the UPF-adiposity association.

The remaining sections will examine additional methodological considerations for each chapter that put the findings in context across the entire thesis, sum up the findings in light of those considerations, and describe the implications of the findings for research and policy.

5.3 Methodological considerations

In this section, I provide an overview of the methodological issues that are relevant for the thesis as a whole. I have structured the methodological discussions according to their implications for internal and external validity and will address each methodological topic for each chapter. In short, internal validity refers to the degree to which the results are attributable to the explanatory variable of interest and not some other competing explanation.[341] The factors that influence internal validity in this thesis are study design, confounding, exposures, outcomes, and chance and bias. External validity refers to the question of whether the estimated associations and potential causal relationships can be generalized to different measures, persons, settings, and times. Influences on external validity discussed in this section are selection and attrition biases, and generalisability.

5.3.1 Internal validity

5.3.1.1 Study design

Studies of long-term health outcomes and their determinants are often of a non-randomized, observational nature.[342,343] 'Manipulation' or 'experimentation' is not possible for some factors (i.e. genes) or not ethical or feasible for long term outcomes due to problems of adherence and costs. In nutritional epidemiological studies of long-term outcomes such as CVD or T2DM, these

problems apply (e.g. randomizing a dietary pattern and then following up for decades is practically impossible).[341] Thus, in this context, research relies on non-randomized observational data, in which, ideally, the characteristics and exposures of interest are measured at multiple points in time. The most powerful of these study designs is the prospective cohort study, in which participants are followed over a long period of time; and this was the study type of the analyses in EPIC-Norfolk. In principle – and in contrast to cross-sectional studies – cohort studies can better assess causality due to the longitudinal nature of the study design (the exposure or risk factor precedes the outcome) and specificity (a change in risk factor is associated with a change in the outcome). However, a number of assumptions have to be met, such as: alternative explanations are either controlled for or ruled out, very little loss-to follow-up exists or is at least non-differential, and there is no bias in the exposure and outcome assessment.[344,345] In chapter 4 I have controlled for as many alternative explanations as possible by including a wide range of nutritional and non-nutritional confounding factors, there was very little loss-to-follow up regarding the outcome, and bias in exposure assessment was minimized through exclusion of participants with improbable energy intakes as well as the use of repeated measurements. Additionally, although two repeated measurements were used, no additional information which was collected after 2003 could be used, which leaves uncertainty about whether the exposure and covariate information measured at HE1 and HE2 can be assumed to be valid for the remainder of the follow-up period.

Chapter 2 was designed as a systematic review and meta-analysis of prospective cohort studies. How well a meta-analysis can draw unbiased conclusions about an effect of interest is dependent on the validity of the studies and risk estimates that are used to derive a pooled estimate. I limited the inclusion criteria to only prospective cohort studies, which is the highest quality of study types available for long-term dietary studies of T2DM and CVD. All included studies fulfilled several pre-specified inclusion criteria (prospective cohort study with more than a duration of one year, objectively measured outcomes, use of a validated dietary assessment

method and a set of important confounding variables in statistical models). I also assessed the study quality across nine domains nested in three main areas: the selection of the study groups, the comparability of the groups, and the ascertainment of either the exposure or outcome of interest.[175] Higher ratings of the domains represent a higher internal validity, and meta-regressions demonstrated that the quality ratings did not change estimated associations. The main limitation of study design of the meta-analysis was the lack of ability to influence the exposure measurement. Because the starting point of the study was to combine different diets and dietary patterns, no unified definition such as NOVA to define the dietary exposure existed, and I had no information on the absolute values of UPF intake between the different studies. However, as discussed in chapter 2, the main information was derived from the relative comparison of diets high and low in UPFs, and the similarities between the results in the meta-analyses and *EPIC-Norfolk* indicate that high versus low intakes were indeed captured. Another key limitation was the variability of the measures of associations of studies investigating adiposity, which precluded a quantitative synthesis of the data, although this had technically less to do with the nature of the meta-analysis but with the variation of the measures to operationalize adiposity and body weight.

Experimentation or randomization in the context of nutrition and NCDs are seldom done due to ethics and practicalities, and this becomes impossible in the context of the nation state or at the food system level. Yet, social scientists attempt to undertake causal inference at the country-level to study factors that affect entire countries or larger multiple regions, such as policies, or global streams of trade and investment. Arguably, trends and associations that transcend the individual and local levels are relevant to public health and epidemiology as well, to identify and quantify health-relevant factors, such as global trends in the food system and sales of UPFs. Many threats to internal validity exist in those studies, and I attempted to reduce those by using repeated longitudinal data which allows for including information of changes in exposures, confounders, and outcomes. I considered undertaking a quasi-experimental study in chapter 3

but concluded that this was not possible because the data did not fulfil the requirements for those analyses. For example, one of the assumptions of the instrumental-variable approach would have required a variable that predicts the exposure, but conditional on the exposure shows no independent association with the outcome and affects the outcome solely through the effect on the exposure. Neither variable of the dataset nor publicly available data would have fulfilled this criterion. The difference-in-difference approach would have required some sort of treatment at a specific point in time and pre- and post-treatment data, which also is not possible for the type of data used. Thus, when other causal inference methods are not applicable, longitudinal panel data analysis is considered the 'gold standard' in country-level analyses, which is what was used in chapter 3.[259,346,347]

5.3.1.2 Confounding

Confounding or omitted variable bias is a main danger for internal validity in statistical analyses. A confounding factor is both associated with the outcome and the exposure, but not on the causal path between the two, and can conceal or wrongly lead to an association if the factor is unaccounted for.[348] In each chapter, I attempted to account as well as possible for confounding by adjusting for identified confounding variables in multivariable statistical models. I did not perform any stepwise selection model selection algorithms (such as forward selection or backward elimination) in which variables are included or excluded based on observed changes in estimates. I also did not use 'tests' to guide the model selection (such as coefficient estimates, *P*-values, F- or Chi-squared). Harrell (2001) provides an extensive explanation as to why this is problematic for most regressions, including upwards biased parameter estimates and R-squared values, downwards biased *P*-values, or exacerbated collinearity problems.[180] Instead, in each chapter, confounding factors were identified through a review of relevant literature.

Across all analyses, I attempted to adjust as well as possible for basic demographics such as age and sex, socio-economic variables such as income, education and social class, and additional relevant variables including physical activity, history of disease, smoking, alcohol consumption,

and a proxy for geographic location. Importantly, when studying dietary risk factors in nutrition studies, other aspects of diet could be associated with the exposure and outcomes. To capture this possibility, the *EPIC-Norfolk* analyses and the country-level study included variables of the consumption or sales of unprocessed foods, which combines many healthy food groups such as un- or minimally processed fruits, vegetables, nuts, legumes, or seeds; as well as total energy. In the meta-analysis, most studies adjusted for at least some proxy variables of healthy foods such as fruits and vegetables.

But as is the case in analyses that are based on the evaluation of secondary data, the adjustment variables were bound to what data was available. In the ecological study, for example, I was able to only use a cross-sectional indicator for the level of physical activity in countries because no longitudinal information was available. In the meta-analyses, because no control over the inclusion of confounders existed, first only studies with a prespecified degree of confounder adjustment were selected (i.e. there had to be some form of adjustment for socio-economic position). Secondly, I elicited the risk estimates that provided the best adjustment for confounding (again as prespecified), which would not necessarily imply the greatest degree of adjustment or the models with most included variables. For example, I did not use risk estimates of models that included potential mediators which would lie on the causal pathway, because risk estimates including those would have likely biased the estimates downwards.

Additionally, as was described in each chapter and in more detail in chapter 4, the ability of multivariable regressions to adequately control for confounding by including confounding variables as adjustment variables can be limited. Across the studies, it is likely that some residual confounding from adjusted variables remains. Especially in the case of CVD the remaining true associations could be small if residual confounding from adjusted confounders existed. I have not tested for this possibility and hence do not know how strong this issue really is across the studies.

5.3.1.3 Chance

To briefly refer back to the methodological background, common definitions of *P*-values and statistical significance focus on null hypotheses, treating all other assumptions that are used to calculate the *P*-value as correct.[166] The *P*-value tests *all* the assumptions about how the data were generated, including the entire model, and not only the hypothesis of interest. However, these assumptions usually encompass a number of assumptions, such as that no intermediate results from analysis were used to determine which results and which analyses would be presented, or that no contingencies in the data processing existed in the construction of the data. Thus, a low *P*-value does not imply a low possibility of a chance finding, if considered in isolation.

I have attempted to use this type of thinking on *P*-values and confidence intervals to guide interpreting and dealing with chance throughout my PhD. Although I started each chapter with this intention in mind, I took slightly different approaches in the three chapters as a reflection of both my own methodological development throughout my PhD as well as my attempt to mitigate the partially contrasting goals of up-to-date statistical definition and following reporting practices of journals.

For example, a systematic review and meta-analysis must follow a certain protocol to be considered by most general medical journals. Statistically, most statistical packages compute and report summary risk estimates and their 95% CIs in forest plots that are mandatory. I have reported *P*-values wherever possible, but in most published meta-analyses the focus remains on whether the CIs include 1.00 or not. In the country-level panel analysis, I came as close as possible to my ideal of reporting by presenting a multiverse of statistical results and displaying and interpreting *P*-values in a continuous manner. In the EPIC analysis, I again attempted to adhere to established reporting practices (i.e. having a large table reporting the estimates and confidence intervals across quintiles and continuously) in the main analysis but presented continuous *P*-values in the secondary analyses.

Overall, across the chapters, *P*-values were very small, especially regarding T2DM, where they were often below 0.001 or even 0.0001. A very clean interpretation would suggest a strong incompatibility of the data with model assumptions. For each chapter, I can exclude the possibility that the assumption of no selection on statistical significance was violated. Secondly, assumptions of the statistical models underlying the analyses of each chapter were fulfilled. Random-effects meta-analyses have no assumption about a common effect and assumes no specific distributional form.[349] I am not aware of an assumption that could have affected the standard error estimates in the meta-analyses. In the panel analyses, the series of Econometric tests guided model specifications mostly regarding the calculation of standard error. Violations of statistical models such as autocorrelation, heteroscedastic residuals, or the presence of unit-roots were either accounted for in the model specifications or could be excluded. The multiverse analyses also made transparent that data dependent estimation of the models was unlikely. In *EPIC-Norfolk*, the examination of Schoenfeld residuals as well as a complete presentation of the results across different ways of operationalizing the exposure, and a wide range of both unadjusted and adjusted models, indicate that a chance finding is unlikely. Thus, I judge it to be unlikely that the results presented in my PhD are due to chance. In addition to this statistical discussion of chance, the biological plausibility and consistency of the findings across all three chapters make it additionally unlikely that the main findings in this thesis resulted from chance.

5.3.1.4 Error and bias in measurement

To validly assess associations between UPF consumption and cardiometabolic health, the exposure and the outcomes need to be accurately defined and quantified. In all three studies, I have used the NOVA classification as the basis to classify foods according to the degree of food processing. Overall, it is relatively straightforward to classify existing foods and food groups according to the NOVA classification. However, in a few instances, it is not – additional information about the preparation process of the foods and their exact composition is needed for accurate classification. In population studies that use standardized dietary assessment

methods, this information is often not available. In each chapter, foods were classified independently by at least, me and another co-author, and in each case, agreements of the applied classifications were very high, and disagreements were resolved by consensus. Thus, in the chapters that included data from prospective cohort studies, the validity of the UPF measure was mostly dependent on the validity of the dietary assessment tool, and both the review chapter as well as the *EPIC*-cohort included only validated dietary assessment tools.

However, misreporting of energy is a well-known and serious issue. As discussed in chapter 3, the validity of food sales is somewhat difficult to assess, but it is unlikely that the measurement error in the data provided by Euromonitor would work in way that biases the exposure-disease association in a systematic way. *In EPIC-Norfolk*, the FFQs have been validated and calibrated against weighed food diaries, 24h-recall instruments, as well biomarkers. In addition, I identified improbable energy reporting by using Henry equations and Goldberg cut-offs to determine and exclude improbable energy reporting. Yet, the potential for measurement error regarding the exposure across the different studies remains. However, for this to be a serious issue, the UPF intake of individuals or countries with a higher risk or prevalence of disease would have to be systematically overestimated, or the UPF intake of individuals or countries with a lower risk or prevalence of disease would have to be systematically underestimated, or both. I judge this possibility to be unlikely to have happened in this manner across each of the three different analyses.

The chapters that included individual-level analysis used objective and validated measurements of the outcomes. The use of objective outcome data offers reductions in measurement error and removes recall, interviewer, or responder bias. In the meta-analyses of T2DM and CVD, 20 of the 24 included publications used outcome ascertainment methods that were considered as objective according to the assessments of study quality of the Newcastle-Ottawa scale. In the panel study, I used only high-quality publicly available data on national prevalence from the Institute of Health Metrics and the NCD-RisC factor collaboration. These data represent the best

available assessments of country-level prevalence of diseases, which have maximized the use of objective outcome data in each country with validated methods to estimate outcomes in cases in regions with sparse objective data.[2,39] In *EPIC-Norfolk*, as described, cases are ascertained based on objective measures.

5.3.2 External validity

Selection bias and Generalisability

Selection bias can substantially alter the accuracy of the findings and impact how applicable study findings are. Selection bias in epidemiology and public health research occurs when systematic differences between the study population and the wider population exist (affecting generalisability).[350] Selection bias in cohorts can be introduced due to a number of reasons, the most prominent being loss-to-follow up or attrition bias. In *EPIC-Norfolk*, general practice registers operated as a population sampling frame, thus *EPIC-Norfolk* was representative of the overall UK population at the onset of the study. It is possible however that some groups of the population were systematically absent from the GP registers in the early 90's. The study population was followed-up for vital status though the Office of National Statistics and for disease incidence through local health authority databases. Given the almost complete coverage through the NHS, the loss-to-follow up for T2DM and CVD events is negligible. Yet, as is common in cohort studies, the representativeness of the *EPIC-Norfolk* cohort for exposure and covariate information at subsequent (health) examinations was affected by participant attrition. This affected the repeated measurement of participant characteristics, implying that for approximately half of the sample only information on exposure and covariates from the first health examination could be used. The consumption of UPFs decreased a small amount between the first and the second health examination, suggesting a differential loss-to-follow up between the first and the second health examination. This has likely influenced the cross-sectional estimates regarding adiposity at the second health examination, which were lower than those at the first. Regarding the prospective associations, this would have biased the results if those

that were not included in the second health examination had changed their diets during follow-up in a systematically different manner than those who continued to participate in the study, and additionally, in a way that would have influenced their disease risk. Specifically, those that were not followed up between HE1 and HE2 were participants with higher intakes of UPFs. The results would have overestimated the prospective UPF-disease association if those with higher UPFs that were not interviewed at HE2 decreased their UPF consumption during the late 90s and 2000s. To the best of my knowledge, I am not aware of any evidence of a reduction of UPF consumption in general or among high consumers of UPFs in the UK during this period. It thus seems unlikely that there was an overestimation of effects due to differential loss-to-follow up between HE1 and HE2. As outlined, no such loss to follow-up occurred regarding the CVD and T2DM outcomes.

Additionally, while the long follow-up period in *EPIC-Norfolk* is positive for assessing long-term outcomes such as T2DM and CVD, the age of the study and dietary assessment somewhat limits the generalisability and relevance for the present day. As discussed in chapter 4, the UPFs sold during the 90s and early 2000s were likely slightly different from those available today, and the relative contribution of the UPF food groups might have been different as well.

The cohorts that were pooled in the meta-analysis were mostly large population-based cohorts such as *EPIC*-Spain or *EPIC*-Netherlands, the *Malmoe Diet and Cancer Study*, or the *REGARDS* study. However, some included cohorts were occupational, and thus not necessarily representative of the underlying population. Also, given that all included studies were cohorts, some attrition bias is likely. In over 70% of the cohorts, the follow-up was judged to be adequate according to the Newcastle-Ottawa scale criterion. In the analysis of the panel data, data for all 76 countries were available for the period under study, hence there was full follow-up and an overall a low risk of selection bias (as here defined), except for four countries for which sufficient exposure data was not available for the year 2001.

The wider generalisability of the epidemiological findings was strengthened by the replication of associations across three independent analyses. The inclusion of 41 prospective cohort studies from three different continents and the *EPIC-Norfolk* analysis from the UK provide a basis for the generalisability across the developed world. The analysis that includes data from countries with a combined population of about 6 billion individuals further extends the generalisability to the context of countries with lower income. However, as *EPIC-Norfolk* is a cohort from the UK and only six out of 41 studies in the systematic review were from countries outside of the EU and North America, the generalisability of the findings from prospective cohorts in particular are somewhat limited to developed contexts.

5.4 Conclusion of the evidence

Thus, my thesis and each of its chapters have important strengths and limitations. Despite the limitations, there was consistency of the estimated associations across different individual- and population-level datasets, as well as similarities of the meta-analyses and *EPIC-Norfolk* analyses regarding the CVD and T2DM risk estimates. Also, previous research has established causal associations between UPFs and adiposity, as well as solid evidence of an association with CVD and hypertension.[140,141,144,351] These findings from previous research and the research in my thesis indicate that UPFs are adversely associated with cardiometabolic health. The strength of the estimated associations is stronger for T2DM than for CVD. The estimated associations also depended on the way UPF intake is expressed and total energy intake is accounted for, and this affects risk of T2DM and adiposity more than CVD, most likely due to the different relative contributions of ultra-processed foods groups to the two measures, such as SSBs. Although individuals who consume more UPFs consume less healthy foods, this does not explain the findings because associations remained after the consumption of un- and minimally processed foods (fruits and vegetables, seeds, nuts, etc.) were accounted for.

The estimated associations are likely to be attributable to a combination of unhealthy macro- and micronutrient profiles of UPFs, increased energy intake due to the hyper palatability of UPFs

which result from specifically designed nutrient combinations (e.g. salt, sugar, fat) in combination with food additives, and potentially further negative effects from food additives and newformed compounds. These properties of UPFs are intrinsically related to the processing processes because those have been specifically designed to give UPFs exactly those properties. Thus, some of the current food processing technologies create foods that are associated with an increased risk of adverse cardiometabolic health.

However, not all UPFs might be equally associated with diseases. As the analyses of the ultra-processed food groups revealed, some food groups were associated with the outcomes while some were not. An updated hypothesis regarding UPFs might thus be that not all UPFs are unhealthy, but most unhealthy food groups are ultra-processed. The next sections address the implication of my findings for dietary public health policy and research.

5.5 Recommendations for research

This section outlines overarching and cross-cutting recommendations for future studies that emerged from the research I conducted in this thesis.

My analyses have shown that many distinctly named unhealthy dietary patterns are broadly comparable in that they are defined by higher relative intakes UPFs. Many of the dietary patterns defined as unhealthy are often characterized by high intakes of UPFs and low intakes of minimally processed foods. Rather than finding new names for dietary patterns (i.e. junk, fast food, convenience, etc.) that are specific to the cohort in which they are tested, I would suggest narrowing the focus on a few key concepts of unhealthy diets (such as those high in UPFs) that are extensively tested until all aspects have been exhaustively understood. While much of the research on healthy dietary patterns is currently concerned with a few key diets such Mediterranean and DASH diets, a similar focus could happen regarding unhealthy diets. Additionally, the relationship between other established ways of categorising unhealthy foods such as the UK Nutrient Profiling Model or the Nutri-Score should be tested to identify potential similarities and differences, as well as their predictive powers for disease. In a similar manner,

relationships between UPFs and healthy dietary patterns such as the Mediterranean diet, DASH diet, or Healthy Eating Indices should be investigated to see how the distributions of those scores, or index values correlate with intakes of UPF.

Almost every study that had investigated the share of UPFs in diets or looked at dietary quality, used energy from UPFs as the measure to operationalize UPFs. Yet, oddly, almost every prospective cohort study that estimated disease associations measured UPFs as weight. One possible interpretation of this could be that those measures were consciously or unconsciously chosen due to the very fact that they produce the strongest disease associations. In the analyses of *EPIC-Norfolk* (chapter 4) I used a full range of possible approaches to operationalize measurement of UPFs. The weight measures consistently produced stronger associations than the energy measures. Future research should develop theory and investigate empirically what each of the two main approaches are measuring and which should be used for which outcome and why. If for example, the relative contributions of ultra-processed food groups are different for weight and energy measures in different cohorts, then using the same measure might yield different results even though the underlying association is the same. Theoretical and empirical work should use such a range of approaches and, based on this, argue for and against the selection of one or the other measure in each specific context as well as in general.

The investigation of ultra-processed food groups and their relation to the overall aggregate group of UPFs should be of main future importance. In this thesis, a likely reason for the different findings using different measurement metrics, were differences in contributing food groups. If it repeatedly turns out to be the case that certain UPF food groups produce lower disease associations (e.g. UPF breads), than this has implications for the concept of UPFs itself. One line of investigation could estimate the associations of the unprocessed and ultra-processed versions of the same food groups to test whether there are any differences between the two to disentangle whether it is the processing or the food groups themselves that are associated with health outcome. This is, of course, only possible for those food groups for which unprocessed

and ultra-processed versions exist. This could potentially shed light on the hypothesis that not all UPFs are unhealthy but most unhealthy food groups are ultra-processed. This would contribute to an improved and more differentiated concept of UPFs.

Regarding nutritional epidemiological methods, a central issue is residual confounding from adjusted confounders. If people who eat more UPFs (or have an unhealthy diet in general), smoke more, drink more alcohol, do less physical activity, or live in deprived areas, can we *fully* adjust for these differences in multivariable Cox-regressions, and can the residual confounding from this be quantified? Future nutritional epidemiology research needs to test and compare different methods to adjust for imbalances in the covariate structure. One possible way would be to use propensity-scores to match individuals with similar values on the confounding variables but differences in the exposure variable. Especially if sample sizes are large, matching could enable estimation of 'treatment effects' in survival analysis, for example in the context of the counterfactual or potential outcomes framework as, for example, suggested by Rubin and Imbens (2015).[228,352,353] In brief, the potential outcomes framework provides a way to quantify causal effects by attempting to approximate the ideal situation of a randomized experiment in non-randomized observational data. The causal effect is defined for a hypothetical intervention as the difference between the outcomes that would be observed for participants (or study subjects) that were exposed versus those that were not exposed.[354] VanderWeele (2017) argues that in non-randomized observational epidemiology, the potential outcomes framework is able to provide the conceptual and mathematical link between data and causal effect estimates in the context of non-randomized observational epidemiology and that very few (if any) satisfactory alternatives to do so exist.[354]

Another issue that has repeatedly come up throughout this thesis is the influence that researcher degrees of freedom can exert on the results. In some of my analyses, estimates of different equivalent choice combinations led to two- or even three-fold differences in the magnitude of the coefficient estimates and sometimes even a different sign. This might not be

a coincidence. In one large scale replication study, over 25% of 100 replicated effect sizes that were previously positive were negative in the replication.[355] If this is what data processing and analytical choices can do to statistical results, researchers should embrace the messiness surrounding empirical analyses that involve a lot of equivalent choices and to display the range of results, rather than presenting only selected results that give a sense of precision which may not necessarily reflect the true underlying uncertainties. Displaying results in a multiverse or a similar way can contribute to transparency on the possible range of results while also increasing replicability and reproducibility of research, because the focus on very specific 'significant' point estimates would be reduced.

As outlined in the introduction, calls for a radical reform of nutritional epidemiology have suggested to largely replace nonrandomized with randomized studies. To me, the conclusion of this criticism is out of touch with the progress that researchers have made on the topic of causal inference from nonrandomized data in the past decade. Issues like confounding, selective results, and selective reporting can be addressed by choosing the right methodological, conceptual, and statistical approaches, by testing whether all the assumptions necessary are met, as well as being transparent about the potential multiverse of results and a commitment to not select favourable results. In that sense, I agree with the idea of reforming certain aspects of the field, but rather than abandoning nonrandomized evidence altogether, my suggestions is to make the causal question central to nonrandomized nutrition research from the outset. Nutrition research should not give up on the wealth of epidemiological data that has been generated in the past decades to narrowly focus on randomized approaches that cannot address important research question that require lifelong study. Instead, reforming should mean embracing the advances from the causal inference literature that stem from the intersection of computer science and statistics. As has been proposed by authors such as Imbens, Robins, Hernan, Gelman, and others, we should be doubling down on the task to elicit the best causal estimate from nonrandomized data as possible.[227,342,353]

Additionally, previous research has argued that the concept of highly or UPFs is easier to understand for the public and might therefore improve the communication of dietary guidelines.[66,356] This might make sense intuitively due to the simplicity of the concept, but further research needs to test whether this is true. Furthermore, the meta-analysis in chapter 2 has demonstrated a strong variability of the association measures of adiposity and body weight. Future research should reach a consensus regarding which measures should be used as a best practice and how associations can be quantified. Finally, the impact of dietary public health recommendations, including those in the next section, should be subject of research to determine whether the proposed policies and already implemented measures have their desired effects.

5.6 Implications for dietary public health policy

Given rising prevalence rates globally, adiposity and T2DM continue to be major public health concerns.[357,358] Governments, international and national health agencies, civil society organisations, and other key stakeholders are prioritizing the promotion of healthy nutrition and actions to tackle diet-related NCDs.[359–361] For example, in April 2016, the United Nations General Assembly agreed on a resolution proclaiming the UN Decade of Action on Nutrition, calling on the WHO and FAO to lead the implementation in collaboration with other agencies such as the World Food Programme.[362] The findings presented in this thesis have multiple implications for the field of dietary public health and public health policy.

The trends of sales of UPFs and their associations with adiposity and diabetes in LMICs suggest that a stronger focus on unhealthy nutrition and UPFs should be prioritized in those countries. While additional research is needed to establish further associations, my findings suggest that UPFs might be one of the key drivers behind the current obesity and T2DM crises, and thus deserve more attention in the future. The associations between UPFs and T2DM demonstrated in all three chapters, alongside the previously established evidence on adiposity, CVD, and mortality, provide additional motivation for strategies to reduce consumption of UPFs. To

suggest potential policies, it is helpful to identify individual and other influences on diet and health.

There are various ways to conceptualize the factors affecting what people eat. The 'ecological approach', for example, suggests three levels that affect individual diets.[363] First, intrapersonal factors include attitudes, beliefs, and perceptions that individuals have regarding dietary behaviours. Secondly, social and cultural environments include the interactions that people have with their families, their friends, their colleagues, the institutions and organizations in which they spend their professional and leisure time (e.g. workplaces, schools and universities, sport facilities, etc.), as well as government, laws, and policy. Thirdly, the physical environment concerns the availability of different types of foods at home, in the neighbourhood, and more generally the characteristics of the physical infrastructure that affects what foods are consumed. More recently, the recognition of the importance of systems dynamics and different feedback mechanisms that influence diets have led to various complex multi-level representations and modelling studies of food systems and the food environment.[364]

Figure 5.1 depicts a more generally accepted attempt to capture those dynamics in an integrated framework of food systems. It has been adopted by multiple international organizations and committees, such as the Committee on World Food Security, the High Panel of Experts on Food Security and Nutrition, and the Global Panel on Agriculture and Food Systems for Nutrition.[364,365]

According to the framework, diet quality is influenced by an individual's income, time, purchasing power, knowledge, and preferences.

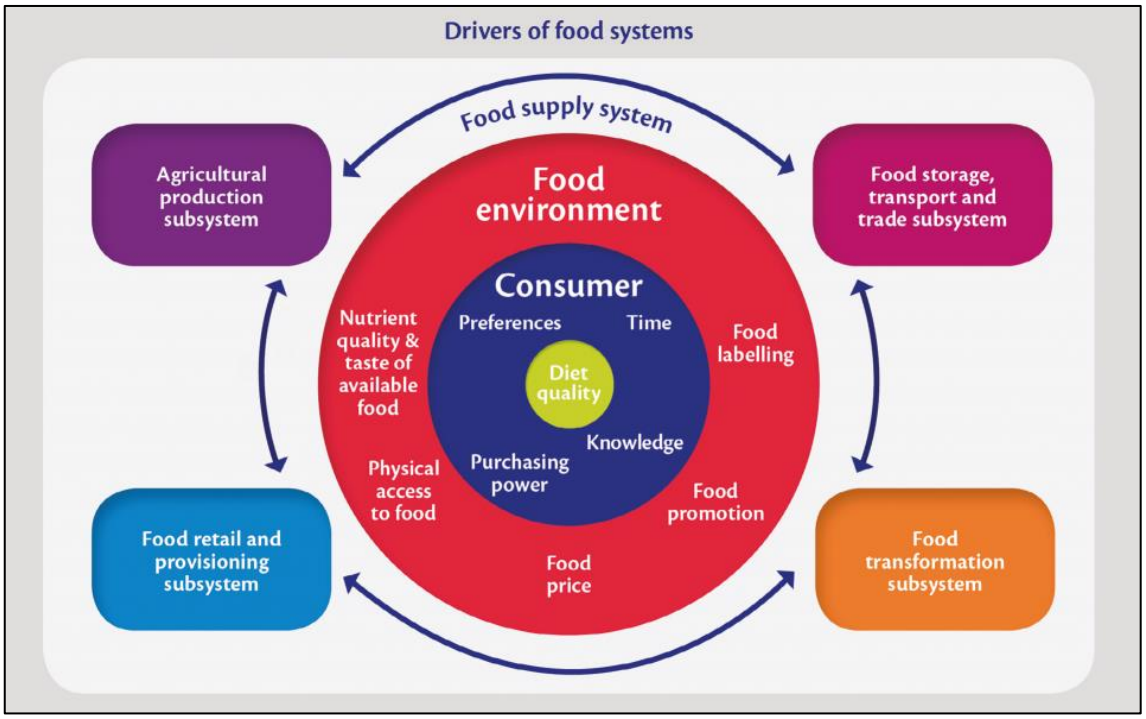


Figure 5.1 Linkages between food systems, food environment and diet quality
Taken from: Global Panel on Agriculture and Food Systems for Nutrition. Food Systems and Diets: Facing the Challenges of the 21st Century. London, UK; 2016.[365]

The way that money is spent and knowledge and preference form and express themselves are in turn influenced by the food environment, which affects and interacts with these individual factors through food prices, food promotion, food labelling, the physical access to food, and the nutrient quality and taste of the foods available. Hence, the food environment can be seen as the space in which consumers interact with the food system to decide what foods to buy, prepare, and consume, and it directly influences individuals' dietary choices and their nutritional status.[366] The food environment itself is influenced by broader food systems: agricultural production; food storage, transport, and trade; food transformation; food retail and provisioning. UPFs, for example, are easier to purchase, cost less, and are more widely available than more healthy foods as a result of developments in technology and trade.[356,367] Taking a food systems approach to improving diets at the population-level is potentially advantageous over individual-oriented approaches for reasons of leverage and sustainability.[3,361,368] A higher

leverage means that more people are affected due to the greater scale and extent of the policy. As an extreme example, a ban on trans fats at the food systems-level sets their availability in a given context effectively to zero, under the assumption of full compliance by food producers. This result would have been almost impossible to reach with individual-level intervention (e.g. 'avoid foods that contain trans fats'), due to a range of variables including differential distributions of knowledge, motivation, and resources in the population. Addressing diets at the food systems-level also increases sustainability of the desired change. A ban on trans fats eliminates consumption until the ban is reversed, while an individual-level approach in contrast might change individuals' preferences and behaviours only for a short period of time. This is partially because preferences are generally 'time-inconsistent'. As Hoch and Loewenstein argued in their seminal paper "Time-inconsistent Preferences and Consumer Self-Control", almost 30 years ago, consumers often override their long-term preferences as a result of sudden increases for desires and products.[369] Moreover, a change in circumstances such as location, income, or social networks might additionally endanger established or newly formed preferences and behaviours. The following recommendations for dietary public health policy to reduce UPF intake will therefore focus on policies addressing the food environment via the four food systems levels but also include suggestions that address individual-level factors.

Since agricultural products provide the basic inputs and ingredients to the food processing process, the agricultural production subsystem provides some, but limited opportunities, to reduce the consumption of UPFs in a given food environment. The suggestions in this area thus focus on maximizing the nutrient-density of fruits, vegetables, and legumes. Improving the nutritional quality and 'richness' of little or unprocessed agricultural products might indirectly affect UPF intake by increasing the opportunity costs for eating UPFs in comparison to consuming fresh produce. Reducing or limiting agricultural produce that is predominantly destined for further food processing might also increase the relative prices of such inputs while reducing the prices for products not entering a more complex food processing chain. Maximizing

nutrient-density could be achieved by, for example, introducing productivity metrics that evaluate production in terms of kg of nutrients produced per unit of land or labour.[365]

The food storage, transport, and trade subsystem offers additional opportunities to influence the food environment and the consumption of UPFs. Non-tariff trade barriers and increased tariffs on UPFs could decrease the amount of UPFs that are imported, reducing the availability of UPFs.[370,371] This might be especially useful for small or island countries with low or negligible domestic UPF production. Countries with a lot of domestic production of UPFs could increase barriers for crucial ingredients of UPFs, such as sugars, already refined ingredients, or food additives that are produced elsewhere and imported for the production process. Additionally, increasing food composition trading standards could improve the nutrient quality of specific imported foods or ingredients. More generally, dietary quality aspects need to be included in trade negotiations, and existing trade mechanisms could be used to put in place standards that reduce trade in UPFs and increase trade in nutrient-rich foods.[366]

The food transformation subsystem carries the most potential to reducing the consumption of UPFs and changing the overall food supply through various measures such as food reformulation, food taxes, restriction on advertising, nutrition labelling, or the development of new processing technologies. Previous research on policies that aim to promote the reformulation of foods has demonstrated considerable potential impact in comparison to policies aimed at changing individual behaviour.[372,373] A recent systematic review on food reformulation and modelling strategies has shown stronger effects on nutrient intake and health for sodium reformulation strategies compared to sugar and fats.[372] Although cross-study comparability was limited, the results showed a consistent relationship between percentages reformulated and reductions in consumption, as well as for health outcomes and quality of life measures. As shown in this thesis, the unhealthy nutritional profile of UPFs, high energy content, and increased total energy intake through UPFs are important mechanisms and characteristics that potentially drive exposure-disease associations. A core reformulation aim should be to

substantially reduce the energy content of UPFs. If everyone followed the suggested portion sizes (e.g. 30g of crisps per serving or three-five cans of SSBs per week), individuals that regularly consume these products would likely not be at particular risk. However, many consumers overconsume UPFs in multiple amounts of the suggested serving sizes.[374–376] Substantial reduction of the energy-density of UPFs could therefore potentially reduce the effects on body weight. Furthermore, reducing the fat, salt, and sugar content in food products has been a part of national strategies in countries such as the UK and Germany.[5,377] However, the German plan only contains voluntary measures and targets, while the UK's Childhood Obesity Strategy restricts marketing to children but not to the general population. While voluntary measures have been partially successful in reducing sodium content, these measures would be unlikely to reduce the consumption UPFs in general population. As experiences from food safety have shown, obligatory reformulations are more likely to produce the desired results compared to simple voluntary approaches.[378] A previously unexplored avenue of reformulation could be addressing the 'bliss point' of UPFs. Food scientists have argued that by using highly refined ingredients in the process of making UPFs, the full and natural 'hedonic' properties of the ingredients are lost.[326] Thus, by using raw sugars, sea salt, and other more natural ingredients, bliss points could potentially be achieved at lower concentrations of these ingredients. Additionally, new primary food processing techniques could also help to design foods with similar hedonic properties but based on mixtures of fruits, vegetables, and whole grains, resulting in better overall nutritional qualities. Additional investment and funding possibilities for research and start-ups that develop healthier forms of processing and processed foods could also encourage change in the food environment.

There are more policy options with the potential to improving food environments that can be implemented in the food transformations subsystem. Fiscal measures such as food taxes have received widespread attention in recent years. By 2018, taxes on SSBs; foods high in salt, fat, and/or sugar; or subsidies to improve diets and health had been adopted across 29 countries.[340]

Thus, taxes on certain UPFs subgroups have already been implemented, although not with the explicit aim to limit UPFs. Applying food taxes to UPFs is, however, not straightforward. UPFs consists of a number of diverse foods which makes the development of metrics to determine when and how taxes should be applied to the overall group of UPFs impractical. Also, if the hypothesis posited above is true (not all UPFs are unhealthy but most unhealthy foods that are unhealthy are ultra-processed), taxing all UPFs may not be necessary. There are two main ways in which food taxes on UPFs could be set-up. A simplistic approach would be to classify all ultra-processed foods and food groups and add an excise tax of, for example, £1 or 1€ per unit of weight or energy. The energy approach would have the advantage of disincentivizing the consumption of UPFs that weigh little (like chocolate or crisps) but have a very high energy density. To make the tax more acceptable in the population, the revenue should exclusively be used for programs that prevent and address diet-related disease problems in both children and adults. A second way would be to identify the main UPF food groups with clear disease associations such as SSBs or fast foods and tax those. When designing potential taxes on UPFs, some general lessons from previous experiences with food taxes should be considered. The tax (or the taxes) should be applied to a geographical unit as large as possible; an excise tax applied to volume, weight, or energy should be used; the tax should be motivated by health and not revenue reasons; the revenue of the tax should be used for health-related expenditures; the implementation of the tax should be assigned to the health ministry and not the agricultural ministry; and an understanding of the political and corporate environment when designing the tax should be considered.[340,361,379,380]

Another already used approach that could be extended are restrictions on advertising and marketing. In the UK, marketing restriction to children exist for foods that are high in salt, fat, and sugars (which are mostly ultra-processed).[381] This was aimed at reducing the appeal to children and potentially incentivize industry to reformulate their products. A government report from March 2019 has concluded, however, that, despite restrictions, children see significant

level of adverts through the media they engage with (e.g. online media), influencing their preferences, food choices, and their health status.[382] Advertising restrictions should therefore be improved by expanding to online media. Furthermore, spending on food advertising is, in general, very high. In the UK, for example, spending on junk foods (or UPFs) has been found to be 30 times of what is being spent by the UK government on promoting healthy eating.[383] Food companies spend on marketing because it works, otherwise, they would not do it. The high societal costs of diet-related NCDs provide a strong rationale for more drastic and widespread curtailing of marketing, and this should not be restricted to only children. Sports-related marketing of UPFs, large-scale advertisements in cities, and online and TV ads could be prohibited or massively reduced, by increasing the price or limiting the licensing to a fraction of available advertising spaces. Given the available evidence on SSBs and emerging evidence on UPFs, as well as an established scientific consensus on dietary risk factors contributing to the global burden of diseases, a strong narrative can potentially be created which might enable the implementation of these more drastic measures.

Suggestions regarding the retail and provisioning subsystem have often been concerned with the promotion of local foods or the promotion of healthy foods in retail environments.[384] However, sales of UPFs could be reduced by restricting or prohibiting special advertising and price promotions in retail environments. Also, previous experiments of the choice architecture have demonstrated that redesigning the layout and positioning of foods in retail such as supermarkets can increase the sales of healthy foods and decrease the consumption of unhealthy foods.[385–387] Positioning UPFs in locations in which they are less likely to be bought could reduce the sales of these products. Lastly, changing licensing laws to limit the density of food outlets such as takeaways in sensible locations such as in proximity to schools could further reduce the availability of UPFs in the food environment.

Consumption of UPFs could also be reduced through approaches that do not directly change the food environment but aim at changing the preferences and knowledge of consumers through

dietary guidelines and public awareness and media campaigns. The concepts of food processing and the comparison of minimally processed foods with foods that are highly processed are likely easy to understand and can be communicated effectively. In terms of nutritional guidelines, dietary recommendations communicated around the concepts of UPFs might therefore be easier to understand due to the simplicity of having to make decisions along only one dimension – the degree of food processing. A recent (2019) review and comparison of 90 food-based dietary guidelines (FBDGs) found almost universal inclusion of certain aspects of diets, e.g. to consume a greater variety of foods and to consume some foods in a higher proportion than others; to eat more fruits, vegetables, and legumes; and to limit sugar, fat, and salt.[359] About 25% of the FBDGs included recommendations to reduce the consumption of UPFs or related junk foods. The guidance is more common in newer dietary guidelines, for example Brazil, Uruguay, or Canada, which specifically advise consumers to limit the intake of UPFs.[336,359] Countries can generally adopt guidelines to limit the intake of UPFs or certain groups of UPFs. Targeted public awareness campaigns via conventional and social media could also contribute to shifting the social perception of UPFs, like it has happened with smoking and tobacco in many countries.[388–390]

None of the above suggested measures are likely to work in isolation. To be effective, combinations of multiple approaches should be used to increase the likelihood of success.

5.7 Final conclusion

Overall this dissertation revealed consistent associations between the consumption and the sales of ultra-processed foods and cardiometabolic health, showing evidence that data processing and analytical choices affect the strength of those associations. Although there was no explicitly formulated goal to establish causality in this thesis, it is likely that estimated associations in this thesis are at least partially causal. This judgement derives from evidence from previous research, biological plausibility, the nature of the findings throughout this thesis (consistency, strength, dose-response relationships, temporality), and the fact that alternative

explanations are unlikely to account for the estimated associations across the entire thesis, despite the methodological limitations discussed above. Regarding the initial aim of the thesis to find out 'what it is about UPFs', one conclusion is yes, it is highly probable that food processing changes unprocessed foods and ingredients into something that poses a health risk – regardless of whether the underlying mechanisms are adverse nutritional quality, the 'bliss-point' design of UPFs which, coupled with high energy content of UPFs, leads to overeating and excess energy consumption, or the effects of newly formed compounds. However, it is also true that food groups matter. The combination of foods, ingredients, and food processing technology seem to influence whether an UPF is unhealthy, neutral, or maybe even healthy. In this context, it would be logical that certain ultra-processed food groups such as SSBs, fast foods, or savoury ultra-processed snacks are likely to have a stronger influence on health than, for example, ultra-processed fruits and vegetables or breads and cereals. Not all UPFs are created equal, and future research would enable this concept to be unpacked and improve our understanding. Until then, societies are well advised to treat UPFs as an independent risk factor of cardiometabolic health.

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7 APPENDICES

APPENDIX TABLE 1. LIST OF EXCLUDED STUDIES AND REASON FOR EXCLUSION

Reason for exclusion	Reference
No UPF food or DP exposure of subjects	1-40
Cross-sectional / retrospective study design	41-73
Superior publication from same cohort available	74-84
Review or qualitative publication	85-95
Subjects not disease-free at baseline	96-103
Risk estimate reference category not comparable	104-108
No cardiometabolic health outcome	109-113
Exposure level negligible	114
Population with special dietary needs	115
Commentary	116

References of Appendix Table 1

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APPENDIX TABLE 2. MAIN CHARACTERISTICS OF INCLUDED STUDIES

Main Characteristics of Included Studies

Publication	Outcome	Country	Follow-up Period (Years)	Number of Partici-pants	Dietary Assessment Method	Name of Dietary Pattern	Approach to Derive Dietary Pattern	Number and List of UPF Items (loadings >·2) / UPF intakes across exposure categories	Type of Risk Measure	Exposure Categories	Risk Estimate	Adjustment Variables	Study Quality
Ambrosini, 2012	Adiposity	UK	8	2626	3-day food diary	Energy-dense, high-fat, low-fibre	A posteriori (RRR*)	Chocolate/confectionery (0·22); cakes/biscuits (0·2); crisps (0·2)	SD increase in DP† z-score	Continuous	0·06 (0·03 to 0·1)	Age, dietary misreporting, sex, physical activity, maternal education, pre-pregnancy	6
Atkins, 2016	CVD incidence	UK	11·3	3226	FFQ† (86 items)	High-sugar	A posteriori (PCA*)	Biscuits and pudding (0·46); chocolate and sweets (0·41); sweet spreads (0·36); breakfast cereal (0·28)	Hazard ratio	Quartiles	1·33 (0·98 to 1·81)	Age, energy intake, smoking status, alcohol intake, physical activity, social class, BMI	6
Barrington, 2016	CVD mortality	US	6·9	69582	FFQ (120 items)	Fast food items	A priori	Hotdogs, hamburgers, fried chicken, fried fish, fish sandwiches, pizza, French fries; UPF intakes not reported	Hazard ratio	Quartiles	1·15 (0·87 to 1·53)	Age, sex, energy intake, race/ethnicity, marital status, income, BMI at age 45, self-rated health, current use of disease-relevant medication, history of CVD, family history of heart attack, physical activity, smoking status, alcohol intake, mammogram in past 2 years, servings of fruits and vegetables	7
Bes-Rastrollo, 2006	Adiposity	Spain	28·5	7194	FFQ (136 items)	HPS	A priori	Hamburgers, pizza, sausages; Q1 <3·3 g/d, Q2 3·3-13·2 g/d, Q3 13·3-23·2, Q4 23·3-34·7 g/d, Q5 ≥ 34·8 g/d	Odds ratio	Quintiles	1·21 (1·03 to 1·42)	Age, sex, total energy intake from non-fast-food sources, fiber intake, alcohol intake, leisure-time physical activity, smoking status, snacking, television watching, baseline weight, and weight gain in the past 5 y	4
Chan, 2013	Stroke incidence	China	5·7	2735	FFQ (280 items)	Snack-drinks-milk products	A posteriori (PCA)	Condiments (0·52); fast food (0·36); sweets and desserts (0·33); French fries and potato chips (0·29); cakes, cookies, pies and biscuits (0·24);	Hazard ratio	Quartiles	Male: 0·6 (0·32 to 1·13) Female: 0·79 (0·36 to 1·72)	Age, physical activity, energy intake, education level, community ladder, smoking status and alcohol use, BMI and hypertension history	5
Cutler, 2013	Adiposity	US	5	3572	FFQ (152 items)	Sweet/salty snack food pattern	A posteriori (PCA)	Only used loadings for young boys (similar for girls): Chocolate bars (0·46);	Odds ratio	Quartiles	Older girls: 0·97 (0·83 to 1·14)	Race/ethnicity, SES, physical activity, and time 1 weight status	4

								other candy bars (0·53); candy with chocolate (0·45); brownies (0·55); cake (0·50); pie (0·41); sweet rolls (0·47); snack cakes (0·43); donuts (0·42); ice cream (0·42); chocolate chip cookies (0·34); popsicles (0·37); and 8 more			Older boys: 0·86 (0·72 to 1·03) Young girls: 0·92 (0·71 to 1·19) Young boys: 0·99 (0·74 to 1·34)		
Denova-Gutierrez, 2016	CVD risk	Mexico	7	1196	FFQ (116 items)	Refined foods	A posteriori (FA*)	Corn tortilla (0·6); pastries (0·19); soft drinks (0·22)	Relative risk	Quintiles	2·98 (1·46 to 6·1)	Age, sex, time, energy intake, smoking, multivitamin use, parental history of myocardial infarction, history of hypertension, physical activity, BMI, and postmenopausal hormone use	5
Diethelm, 2014	Adiposity	Germany	5	371	3-d weighed dietary records	Changes in CF / pancakes	A posteriori (PCA)	Pancakes / convenience foods (an aggregated food group based on multiple convenience foods)	b, mean change	Tertiles	2·25 (2·01 to 2·49)	Baseline BMI, sex, maternal overweight, high paternal education, gestational age, birth weight category and ever fully breast-fed	5
Dominguez, 2014	T2DM incidence	Spain	10·2	3048	FFQ (136 items)	HPS	A priori	Hamburgers, pizza, sausages; Q1 0-3 servings/month, Q2 > 3 & < two servings/week, Q3 ≥ 2 servings/week	Odds ratio	Tertiles	1·81 (1·1 to 2·99)	Age, energy intake, smoking, physical activity, family history of diabetes, cardiovascular disease/hypertension at baseline, parity, adherence to Mediterranean dietary pattern score, alcohol intake, fiber intake, and sugar-sweetened soft drinks consumption, baseline BMI	6
Durao, 2017	Adiposity	Portugal	3	1533	FFQ (35 items)	Energy Dense Foods	A posteriori (PCA)	Processed meats, crisps, pizza/burger, sweets, soft drinks, salty pastries	b	Continuous	Girls: 0·075 (0·009 to 0·14) Boys: -0·014 (-0·093 to 0·0065)	Maternal (education, BMI) and child (any breast-feeding, physical exercise, screen time, exact age and each adiposity measure at 4 years) characteristics	7
Fung, 2004a	T2DM incidence	US	14	69554	FFQ (116 item)	Western	A posteriori (PCA)	Processed meat (0·59); sweets/desserts (0·47); French fries (0·46); SSBs¥ (0·38); snacks (0·37);	Relative risk	Quintiles	1·49 (1·26 to 1·76)	Age, family history of diabetes, history of	5

								condiments (0·36); margarine (0·34); loadings from Hu 2000, may differ from this study!				hypercholesterolemia, smoking, menopausal status, calories, history of hypertension, physical activity, alcohol intake, BMI, and missing food frequency questionnaire	
Fung, 2004b	Stroke incidence	US	14	71768	FFQ (116 item)	Western	A posteriori (PCA)	SSBs (0·47), refined grains (0·46), diet soft drinks (0·26), processed meats (0·39)	Relative risk	Quintiles	1·58 (1·15 to 2·15)	Age, smoking status, BMI, menopausal status, aspirin use, energy intake, alcohol intake, and hours of moderate and vigorous physical activity	5
Guallar-Castillion, 2012	CHD incidence	Spain	11	40757	Dietary History	Westernized	A posteriori (PCA)	Fried potatoes (0·66); processed red meat (0·48); sauces and Mayonnaise (0·4); sugar, chocolate, and ice-cream (0·19);	Hazard ratio	Quintiles	0·86 (0·61 to 1·24)	BMI, waist circumference, education, smoking, physical activity at work, physical activity at home, physical activity during leisure time, diabetes, hypertension, hypercholesterolemia, cancer, oral contraceptives, menopausal status, hormone replacement therapy, total energy intake, and stratified by age at recruitment, sex, and center location	7
Heidemann, 2008	CVD mortality	US	18	72113	FFQ (116 items)	Western	A posteriori (PCA)	1984 dietary pattern: processed meat (0·57); French Fries (0·47); condiments (0·45); sweets and desserts (0·43); pizza (0·35); mayonnaise (0·34); SSBs (0·32)	Relative risk	Quintiles	1·22 (1·01 to 1·48)	Age, follow-up period, body mass index, physical activity, smoking, hormone replacement therapy, history of hypertension, use of multivitamin supplements, missing FFQ during follow-up, and total energy intake	5

Hlebowicz, 2011	CVD incidence	Sweden	13	4999	7-day menu book + diet history questionnaire	Sweets and Cakes	A posteriori (CA)	Sweets, cakes, pastry	Hazard ratio	Continuous	1·1 (0·72 to 1·71)	Age, total energy, season of data collection, body fat percentage, waist to hip ratio, smoking and history of CVD	7
Hu, 2000	CHD incidence	US	8	44875	FFQ (131 items)	Western	A posteriori (PCA)	Processed meat (0·59); sweets/desserts (0·47); French fries (0·46); SSBs (0·38); snacks (0·37); condiments (0·36); margarine (0·34)	Relative risk	Quintiles	1·64 (1·24 to 2·17)	Age, time-period, smoking, parental history of myocardial infarction before age 60 y, multivitamin and vitamin E supplement use, alcohol consumption, history of hypertension, physical activity, total energy intake, and profession	6
Martinez-Gonzales, 2015	CVD incidence	Spain	4·3	7216	FFQ (137 items)	Western	A posteriori (PCA)	High-fat processed meats (0·55); processed meals (0·32); commercial bakery (0·29); chocolates 0·29)	Hazard ratio	Quartiles	1·05 (0·73 to 1·5)	Sex, age, recruitment center, interventional group, smoking status, baseline body mass index, physical activity during leisure time, self-reported hypertension, self-reported depression, self-reported diabetes, self-reported hypercholesterolemia and education level	5
McNaughton, 2008	T2DM incidence	UK	11·6	7339	FFQ (127 items)	Dietary pattern	A posteriori (RRR)	SSB (0·23); burgers and sausages (0·22); crisps/packaged snacks (0·22);	Hazard ratio	Quartiles	1·55 (1·13 to 2·15)	Age, sex, energy misreporting, ethnicity, employment grade, smoking, alcohol, physical activity, BMI	5
McNaughton, 2009	CHD incidence	UK	15	7314	FFQ (127 item)	Dietary pattern	A posteriori (RRR)	White bread (0·27); fried potatoes (0·26); burgers & sausages (0·22); SSBs (0·22)	Hazard ratio	Quartiles	1·61 (1·11 to 2·33)	Age, sex, energy misreporting, ethnicity, employment grade, smoking, alcohol, physical activity, BMI	5
Mendonca, 2016	Adiposity	Spain	8·9	8451	FFQ (136 items)	Ultra-processed foods (NOVA)	A priori (NOVA)	Q1 1·5 servings/d, Q2 2·7 s/d, Q3 3·8 s/d, Q4 6·1 s/d	Hazard ratio	Quartiles	1·26 (1·1 to 1·45)	Sex, age, marital status, educational status, physical activity, television watching, siesta sleep, smoking	5

												status, snacking between meals, following a special diet at baseline, baseline BMI, and consumption of fruit and vegetables	
Mendonca, 2017	Hypertension incidence	Spain	3·9	14790	FFQ (136 items)	Ultra-processed foods (NOVA)	A priori (NOVA)	Q1 2·1 servings/d, Q2 3·1 s/d, Q3 5·0 s/d	Hazard ratio	Tertiles	1·21 (1·06 to 1·37)	Sex, age, physical activity, hours of TV watching, baseline body mass index, smoking status, use of analgesics, following a special diet at baseline, family history of hypertension, hypercholesterolemia, alcohol consumption, total energy intake, olive oil intake, and consumption of fruits and vegetables	5
Mertens, 2017	CVD incidence	UK	12	1838	FFQ (50 items)	Dietary pattern 1	A posteriori (PCA)	White bread (0·37); chips (0·30); SSBs (0·26); processed meat (0·20)	Hazard ratio	Tertiles	1·35 (1·1 to 1·67)	Age, smoking habits, social class, leisure time physical activity, total energy intake and usual alcohol consumption	4
Mohammadifard, 2017	CVD mortality	Iran	9	4834	FFQ (48 items)	Fast food	A posteriori (PCA)	Hamburger (0·67); pizza (0·47); sweets (0·46); SSBs (0·42)	Relative risk	Quartiles	1·33 (0·65 to 3·6)	Age and sex, education, residency, smoking status, daily physical activity, family history of cardiovascular disease, diabetes mellitus, hypertension, hypercholesterolemia, aspirin use and postmenopause in women, BMI	6
Nanri, 2013	T2DM incidence	Japan	5	64705	FFQ (147 items)	Westernized	A posteriori (PCA)	Women: processed meats (0·45); confectionaries (0·30); mayonnaise (0·38); SSBs (0·35); dressing (0·53) Men: processed meats (0·51); confectionaries (0·35), SSBs (0·43); sauce	Odds ratio	Quartiles	Female: 0·81 (0·61 to 1·08) Male:	Age, study area (11 areas), smoking status, family history of diabetes mellitus, total physical activity, history of hypertension and total energy intake, BMI	4

								(0·47); mayonnaise (0·43); dressing (0·52)			1·15 (0·9 to 1·46)		
Nettleton, 2009	CVD incidence	US	4·6	5316	FFQ (120 items)	Fats and Processed Meat	A posteriori (PCA)	Processed meats (0·64); fried potatoes (0·60); salty snacks (0·50); desserts (0·48); pizza (0·42); sweet breads (0·41), ice cream (0·40), SSB's (0·36); sweets (0·36)	Hazard ratio	Quintiles	1·82 (0·99 to 3·35)	Study center, age, sex, race-ethnicity, and energy intake, education, physical activity, smoking status, pack-years, and weekly dietary supplement use	6
Odegaard, 2012	T2DM incidence	Singapore	4·7	43176	FFQ (165 item)	Western-style fast food	A priori	Hamburgers/cheeseburgers; French fries; pizza; other sandwiches; deep-fried chicken; and hot dogs; Q1 no intake, Q2 1-3 times/month, Q3 once/week, Q4 ≥ twice week	Hazard ratio	Quartiles	1·29 (1·05 to 1·57)	Age, sex, year of interview, dialect, education, smoking, alcohol, sleep, and physical activity, nutritional factors (intake of soft drinks, juice, Eastern snacks and dim sum, vegetables, fruit, soy, rice, noodles, other pork and red meat, and total energy)	6
Odegaard, 2014	CVD mortality	Singapore	15·1	52584	FFQ (165 items)	Dim sum and meat rich	A posteriori (PCA)	Many, i.e.: Siew mai (0·44); Otar Otar (0·4); Steamed meat bao (0·38); Bakes buns with meat(0·2), flavored rice porridge (0·2)m balachan (0·2), hot dogs (0·21), hamburgers (0·21), western cakes (0·22), ice cream (0·23), French fries (0·25), salted fish (0·25), soft drinks(0·29), deep-fried snacks (0·32), pork belly (0·32), dry noodle dish (0·33), deep fried chicken (0·34)	Hazard ratio	Quartiles	1·23 (1·07 to 1·4)	Age, sex, dialect, education, and year of interview, smoking, moderate and vigorous activity, sleep, BMI, history of hypertension, and energy intake	7
Oellingrath, 2011	Adiposity	Norway	3	427	FFQ (64 items)	Junk/ convenience	A posteriori (PCA)	(4th grade only): French fries restaurant (0·6), hamburger/kebab (0·56), French fries dinner (0·49), biscuits etc· (0·51), sausages/hot dogs (0·44), processed pizza (0·41), waffles (0·47), sweets (0·32), salty snacks (0·32), white bread (0·34), ice cream (0·44), processed	Beta-coefficient	Continuous	-0·15 (-0·5 to 0·19)	Age, study area (11 areas), smoking status, family history of diabetes mellitus, total physical activity, history of hypertension and total energy intake, BMI	4

							meat for dinner (0·26), pancakes (0·45), biscuits etc· between meals (0·34), ice-cream between meals (0·25), SSB (0·34), sugar cereals (0·33), chocolate spread (0·28)					
Osler, 2002	CHD mortality	Denmark	8·3	7316	FFQ (26 items)	Western	A posteriori (PCA)	White bread (0·51); cakes and biscuits (0·43); candy/chocolate (0·44); ice-cream (0·43); margarine (0·24)	Hazard ratio	Continuous	1·1 (0·97 to 1·24)	Smoking, exercise, education, BMI and alcohol intake	4
Pala, 2013	Adiposity	Multiple	2	8223	Children's Eating Habits Questionnaire (43 items)	Sweet and fat	A posteriori (PCA)	Chocolate spreads on bread (0·38); cakes, pudding, cookies (0·35); candy/sweets (0·33); fried meat (0·28); SSBs (0·24); mayonnaise (0·24); cured meat and sausages (0·21)	Odds ratio	Tertiles	0·97 (0·77 to 1·22)	Adjusted by age, sex, country (as the grouping variable), baseline BMI (continuous), physical activity and income	5
Reeds, 2016	T2DM incidence	Canada	10	492	FFQ (34 items)	Beef and processed food pattern	A posteriori (PCA)	(Approx· loadings) SSB's (0·43), klik (0·44), cookies/cakes/pastries (0·42), chocolate/candy (0·4), fries (0·33), margarine (0·22)	Odds ratio	Continuous	1·38 (1·02 to 1·86)	Age, sex, WC, IL-6 and adiponectin	5
Ritchie, 2007	Adiposity	US	10	2371	3-day food records	Black girls: Sweet and cheese; White Girls: Fast Food	A posteriori (FA)	Black girls: SSBs (469g); flavored Milk (82g); cereals (77g); processed meat and sandwiches (54g); ice cream (53g); pizza (23g); fried Potatoes (27g); baked desserts (30g); other desserts (29g); White girls: SSBs (396g); flavored milk (90g); cereal (80g); ice Cream (57g); processed meats and sandwiches (40g); fried potatoes (32g); baked dessert (26g);	Mean change in BMI	Continuous	Black girls: 9·04 (1·03 (SE)) White girls: 6·24 (0·32 (SE))	Age of menarche, pregnancy, parental education, physical activity, and TV/video watching	7
Schulze, 2005	T2DM incidence	US	7·6	124651	FFQ (55 items)	Not named	A posteriori (RRR)	SSBs (0·47); refined grains (0·46); diet soft drinks	Relative risk	Quintiles	2·93	Age, BMI, physical activity, family history of diabetes, smoking,	3

							(0·26); processed meats (0·39)			(2·18 to 3·92)	postmenopausal hormone use, and energy intake	
Schulze, 2006	Adiposity	US	8	51,670	FFQ (133 items)	Western pattern	A posteriori (PCA)	(1991-values): processed meats (0·58); French fries (0·50); sweets and desserts (0·42); snacks (0·39); margarine (0·36); pizza (0·34); mayonnaise (0·34); SSBs (0·30);	Mean change	Continuous	7·45 (0·12 to (SE))	Age, baseline alcohol intake, physical activity, smoking, postmenopausal hormone use, oral contraceptive use, cereal fiber intake, total fat intake, and BMI, changes in confounders between time periods	6
Shikany, 2015	CHD incidence	US	5·8	17418	FFQ (110 items)	Sweets	A posteriori (FA)	Candy (0·40); chocolate (0·46); desserts (0·53); margarine (0·37); pizza (0·20); fried potatoes (0·28); salty snacks (0·30); sweet breakfast foods (0·39)·	Hazard ratio	Quartiles	1·18 (0·86 to 1·62)	Age, sex, race, and age-race interaction, education, household income, and region, total energy intake, smoking, physical activity, body mass index, waist circumference, and history of hypertension, dyslipidemia, and diabetes	5
Stricker, 2013	CHD incidence	Netherlands	13	35910	FFQ (79 items)	Western	A posteriori (PCA)	Processed meat (0·25); SSBs (0·52); cereals (0·43); French fries (0·70); fast food (0·65)	Hazard ratio	Quartiles	0·98 (0·82 to 1·17)	Age, gender, physical activity, smoking status, education, systolic- and diastolic blood pressure and energy intake	8
Togo, 2004	Adiposity	Denmark	11	2190	FFQ (26 items, no portions sizes, relative frequency of intake used)	Men: Sweet and traditional; Female: Sweet-traditional	A posteriori (FA)	Men, sweet dietary pattern: cake, biscuits, other baked goods (0·70); candy/chocolate (0·66); SSB's or ice-cream (0·42); jam or honey (0·48); Female, sweet-traditional: candy/chocolate (0·61); cake, biscuits, other baked goods (0·58); white bread (0·40), SSBs or ice-cream (0·41)	Odds ratio	Continuous	Female: 3·8 (0·97 to 14·94) Male: 1·63 (0·45 to 5·87)	Age, education, smoking, BMI, physical activity in leisure time, smoking cessation	5
Vandam, 2002	T2DM incidence	US	12	42504	FFQ (131-items)	Western pattern	A posteriori (PCA)	Processed meat (0·61); French fries (0·48); sweets and desserts (0·42);	Relative risk	Quintiles	1·59	Age, BMI, PA, total energy, smoking, alcohol, ancestry,	5

								condiments (0·41); SSBs (0·36); snacks (0·36); mayonnaise (0·34); pizza (0·29); margarine (0·29)			(1·32 to 1·93)	hypercholesterolemia, hypertension (yes or no), and family history of type 2 diabetes mellitus	
Varraso, 2012	VTE incidence	US	10	129501	FFQ (126 & 131 items)	Western	A posteriori (PCA)	Desserts, sweets, French fries (>0·3)	Hazard ratio	Quintiles	Female: 1·14 (0·91 to 1·42) Male: 1·43 (1·16 to 1·78)	Age, total physical activity level, physical inactivity level, body mass index, total caloric intake, smoking, pack-years of smoking, race/ethnicity, spouse's educational attainment, parity, menopausal status, non-aspirin nonsteroidal anti-inflammatory drug use, warfarin use, multivitamin supplement use, hypertension, coronary heart disease, and rheumatologic disease	7
Voortman, 2016	Adiposity	Netherlands	5	1980	FFQ (211 items)	Western-like	A posteriori (PCA & RRR)	Savory snacks (0·59); confections (0·72); SSBs (0·59)	Beta-coefficient	Quartiles	-0·01 (-0·11 to 0·09)	Age, BMI at enrollment, parity, folic acid supplement use, smoking and alcohol use during pregnancy; paternal smoking and education; household income; and child sex, breastfeeding in the first 4 months of life, timing of introduction of complementary feeding, age at dietary measurement, total energy, intake at 1 year, and television watching at age 2 years	7
Zhang, 2006	T2DM incidence	US	8	13110	FFQ (133 items)	Western	A posteriori (PCA)	Not clear, processed meat, sweets and deserts; French fries and pizza	Relative risk	Quintiles	1·63 (1·2 to 2·21)	Age, parity, BMI, race/ethnicity, cigarette smoking status, family history of diabetes in a first-degree relative, alcohol intake, physical activity and total energy	3

APPENDIX TABLE 3. STUDY QUALITY

Due to word limits of the thesis, the table with the study quality assessment of the studies included in the systematic review and meta-analysis in chapter 2 can be found at https://github.com/kai-schulze/PhD-online-appendix.

Publication	Representative-ness of the Exposed Cohort	Selection of the Non-exposed cohort	Ascertainment of Exposure	Demonstration that Outcome Was not Present at Start of Study	Comparability of Cohorts based on the Design or Analysis (for Age, Sex, a Marker of Socioeconomic Position [Education/Income/Occupation/Area -based Marker] (all of these)	Comparability of Cohorts Based on the Design or Analysis (other Health-related Behaviours, Race/Ethnicity, Family History of Disease)*	Ascertain ment of Outcome	Follow-up Long Enough for Outcomes to Occur	Adequacy of Follow-up of Cohorts	Total Score
Ambrosini, 2012	1	1	1	0	1	0	1	1	0	**6**
Atkins, 2016	1	1	0	1	1	0	1	1	0	**6**
Barrington, 2016	0	1	0	1	1	1	1	1	1	**7**
Bes-Rastrollo, 2006	0	1	0	1	0	0	0	1	1	**4**
Chan, 2013	0	1	0	1	1	0	1	1	0	**5**
Cutler, 2013	1	1	0	1	1	0	0	0	0	**4**
Denova-Gutierrez, 2016	0	1	0	1	0	0	1	1	1	**5**
Diethelm, 2014	0	1	1	1	0	0	1	1	0	**5**
Dominguez, 2014	0	1	0	1	1	1	0	1	1	**6**
Durao, 2017	1	1	0	1	1	0	1	1	1	**7**
Fung, 2004a	0	1	0	1	0	1	0	1	1	**5**
Fung, 2004b	0	1	0	1	0	0	1	1	1	**5**
Guallar-Castillion, 2012	0	1	1	1	1	0	1	1	1	**7**
Heidemann, 2008	0	1	0	1	0	0	1	1	1	**5**
Hlebowicz, 2011	1	1	1	1	0	0	1	1	1	**7**

Hu, 2000	0	1	0	1	1	1	0	1	1	**6**
Martinez-Gonzales, 2015	0	1	0	0	1	0	1	1	1	**5**
McNaughton, 2008	0	1	0	1	1	0	0	1	1	**5**
McNaughton, 2009	0	1	0	1	1	0	1	1	0	**5**
Mendonca, 2016	0	1	0	1	1	0	0	1	1	**5**
Mendonca, 2017	0	1	0	1	1	0	0	1	1	**5**
Mertens, 2017	0	1	0	0	1	0	1	1	0	**4**
Mohammadifard, 2017	1	1	0	1	1	0	1	1	0	**6**
Nanri, 2013	0	1	0	1	0	0	0	1	1	**4**
Nettleton, 2009	0	1	0	1	1	0	1	1	1	**6**
Odegaard, 2012	1	1	0	1	0	0	1	1	1	**6**
Odegaard, 2014	1	1	0	1	0	1	1	1	1	**7**
Oellingrath, 2011	0	1	0	1	1	0	1	0	0	**4**
Osler, 2002	0	1	0	1	1	0	0	0	1	**4**
Pala, 2013	1	1	0	1	0	0	1	1	0	**5**
Reeds, 2016	1	1	0	1	0	0	0	1	1	**5**
Ritchie, 2007	0	1	1	1	1	1	1	1	0	**7**

Schulze, 2005	0	1	0	1	0	0	0	1	0	**3**
Schulze, 2006	0	1	1	1	0	0	1	1	1	**6**
Shikany, 2015	0	1	0	1	1	1	0	1	0	**5**
Stricker, 2013	1	1	0	1	1	1	1	1	1	**8**
Togo, 2004	0	1	0	1	1	0	1	1	0	**5**
Vandam, 2002	0	1	0	1	0	1	0	1	1	**5**
Varraso, 2012	0	1	0	1	1	1	1	1	1	**7**
Voortman, 2016	0	1	1	1	1	1	1	1	0	**7**
Zhang, 2006	0	1	0	1	0	1	0	0	0	**3**

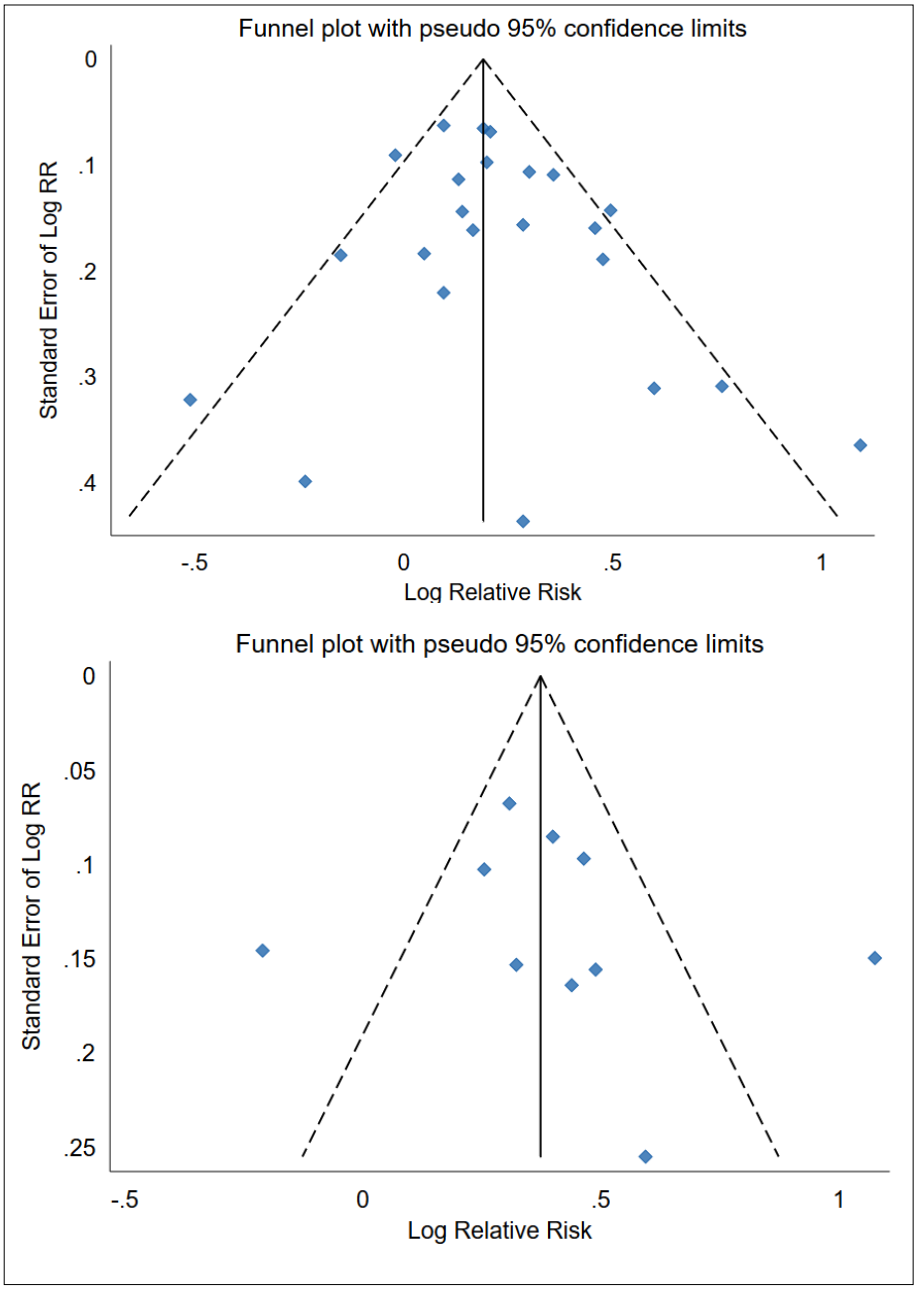
* To get a point in this category, a study **must** include: Smoking (if adult population), alcohol (if adult population), and physical activity as health-related behaviours; and family history of disease (all of these)

APPENDIX TABLE 4. COUNTRY DATA OF SALES OF ULTRA-PROCESSED FOODS

Country	UPF sales in 2016 (g/day/capita)	Change in UPF sales between 2001 and 2016 (in %)
Algeria	550	152
Argentina	716	128
Australia	682	97
Austria	664	99
Azerbaijan	322	132
Belarus	341	106
Belgium	831	104
Bolivia	391	211
Bosnia-Herzegovina	287	121
Brazil	421	128
Bulgaria	629	124
Cameroon	61	142
Canada	694	89
Chile	899	150
China	140	299
Colombia	325	115
Costa Rica	394	111
Croatia	475	99
Czech Republic	512	89
Denmark	602	101
Dominican Republic	348	143
Ecuador	314	124
Egypt	430	102
Estonia	451	110
Finland	656	95
France	570	98
Georgia	402	194
Germany	845	103
Greece	425	87
Guatemala	199	50
Hungary	462	98
India	32	267
Indonesia	64	216
Iran	470	113
Ireland	650	76
Israel	491	95
Italy	490	86
Japan	412	103
Kazakhstan	261	87
Latvia	332	89
Lithuania	369	132

Macedonia	558	134
Malaysia	165	141
Mexico	886	92
Morocco	186	175
Netherlands	746	109
New Zealand	621	104
Nigeria	64	170
Norway	726	108
Pakistan	42	213
Peru	330	181
Philippines	185	133
Poland	528	103
Portugal	340	81
Romania	477	137
Russia	378	146
Saudi Arabia	749	119
Serbia	572	136
Slovakia	546	116
Slovenia	360	80
South Africa	403	147
South Korea	208	96
Spain	548	85
Sweden	600	93
Switzerland	630	103
Taiwan	180	106
Thailand	194	172
Tunisia	442	145
Turkey	690	108
USA	899	82
Ukraine	345	129
United Arab Emirates	333	61
United Kingdom	799	110
Uruguay	623	197
Uzbekistan	211	172
Venezuela	289	101

Appendix Figure 1. Funnel Plots of Summary Meta-analysis of UPF and CVD and UPF and T2DM



Funnel plots of summary random-effects meta-analysis of highest versus lowest UPF intake or UPF dietary patterns score category and CVD risk (top) and T2DM risk (bottom)