A Solution to Increased Consumption of Ultra-Processed Foods in The EU and the Risk of Obesity, Type 2 Diabetes and Cardiovascular Disease

A Thesis Presented as part fulfilment for the Award of
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By

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DECLARATION

I hereby certify that the material, which I now submit for assessment on the programme of study leading to the award of M.Sc Food Business Management and Technology, is entirely my own work and has not been taken from the work of others save to the extent that such work has been cited and acknowledged within the text of my own work. No portion of work contained in this thesis has been submitted in support of an application for another degree or qualification to this or any other institution.

Signed:____ ________________ Date: 12/08/22__________

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Abstract

The objective of this research was to evaluate the association between the rise in consumption of ultra-processed foods and drinks, as defined by the NOVA classification system, and the associated risk in the development of obesity, type 2 diabetes (T2D), and cardiovascular disease (CD) in the European Union (EU). The findings from the research were then used to provide a more effective solution to reducing the risk and rate of onset of these diseases by 2030, in line with current EU strategy. The dietary habits of human beings have evolved over the past 2.5 million years, from the paleolithic hunter gatherer era to the modern-day western diets ubiquitous in highly processed foods, propelled by the industrial revolution in the 19th century. We now see an unbalanced nutritional profile, high in refined carbohydrates, saturated fats, sugars, salt, and low in fibre. Simultaneously, since the industrial revolution, there has been a global rise in non-communicable diseases such as obesity, diabetes, and cardiovascular diseases. Six highly reputable studies, investigating the relationship between consumption of ultra-processed foods and the risk of obesity, diabetes and cardiovascular diseases were analysed across 9 EU countries, including a total of 896,225 participants. All studies showed significant correlation between increased consumption of ultra-processed foods and increased risk of development of obesity, T2D and CD, with significant increase in associated risk with an increment of 10% increase in ultra-processed foods. Ultra-processed foods are ingrained in society, and this is unlikely to change. A lot of functional and clean label foods are ultra-processed pre-packaged foods. Therefore, a more impactful solution on reducing the risk and rate of onset of obesity, type 2 diabetes and cardiovascular diseases needs to come from the food industry. Food manufacturers must implement smart reformulations that considers the whole impact of a food formulation as opposed to partially focusing on specific ingredients that drive health and wellness claims to promote their foods. True to health formulations considers the nutritional composition, food matrix, processing conditions, functional ingredient mapping and the incorporation of more functional foods into more food products. All these factors can feed into the determination and use of specific deterrent marketing claims. The use of deterrent marketing will ensure that food manufacturers carry out thorough research and development into suitable ingredient substitutions and processing techniques that do not propagate further disease risk, while also ensuring consumers receive more balanced information, and are more aware of the true impact of foods, compelling more accurate food choices, reducing the risk and rate of onset of obesity, type 2 diabetes, and cardiovascular diseases by 2030.

Abbreviations

Ace-K	Acesulfame Potassium
BMI	Body mass index
CD	Cardiovascular disease
EFSA	European Food Safety Authority
EPIC	European Prospective Investigation into Cancer and Nutrition
EU	European Union
FFQ	Food Frequency Questionnaire
FPQ	Food Propensity Questionnaire
GI	Glycaemic Index
HPH	High Pressure Homogenization
HPP	High Pressure Processing
HR	Hazard ratio
MSG	Mono Sodium Glutamate
NCDs	Non communicable diseases
NTP	Non Thermal Processes
TFAs	Trans Fatty Acids
T2D	Type 2 Diabetes
UPD	Ultra-processed drinks
UPF(s)	Ultra-processed food(s)
UPFD	Ultra-processed foods and drinks
UV-LED	Ultra-Violet Light Emitting Diode
RAS	Renin-angiotensin-system
ROS	Reactive oxygen species
RR	Relative risk
SNS	Sympathetic nervous system
SUN study/project	Seguimiento Universidad de Navarra
WHO	World Health Organisation

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Chapter 1

Introduction

1.0. Overview

The objective of this thesis is to evaluate the most relevant and current research on the rise in consumption of ultra-processed foods, to include drinks (UPFs) and their contribution and effects on obesity, type 2 diabetes (T2D), and cardiovascular disease (CD) in the European Union (EU). The thesis will also categorize and define UPFs, and their commonalities and describe the state of obesity, T2D and CD in the EU. The findings from this research will be used to provide a more effective solution to reducing the rate of onset of obesity, T2D and CD, by 2030 in line with current EU strategy. Chapter 1 will discuss the global evolution of the human diet and lifestyle, define UPFs, their increased consumption, and concerns for health as it pertains to Obesity, T2D and CD.

1.1. Global Evolution of the Human Diet and Lifestyle

Humans are part of the genus Homo, that emerged over 2.5 million years ago, marking the emergence of hunting, and gathering. Our ancestors being hunter gatherers, meant they had to exert energy to hunt gather, prepare, and eat their food as it was not readily available, not easily preserved or stored. Through observation they were naturally leaner and fitter in physique, void of the various chronic health problems we see today. Increasing brain and body size, correlated with increased sophistication in hunting and gathering, marking a vital change in hominin evolution. The discovery and use of fire for cooking also marked a profound change in diet of early hunters and gatherers, at around 450,000 years ago. The act of cooking food, made it safe and more palatable for the body to digest and utilize nutrients, meaning human physiology has adapted to cooked food (Pontzer and Wood, 2021). Additionally, our ancestors thrived on a paleolithic diet high in natural resources, from plant sources to animal protein from lean meats and fish. Following on from the Paleolithic era, the Neolithic era emerged around 10,000 years ago as agricultural practices took hold, leading to the development of more starchy foods from grains and legumes as the main dietary staple and the introduction of dairy. Still this period saw considerable amounts of fibre, dairy, vegetable proteins and plant sterols (Jew, AbuMweis and Jones, 2009) all from natural agricultural practices, providing a well-rounded nutritious dietary profile. Additionally, the food process of fermentation, baking bread and making cheese also emerged, making the storage and preservation of food more important (Huebbe and Rimbach, 2020). Another major socioeconomic shift that formed the key driver into the modern-day western diets, arose in the 19th century during the industrial revolution. This era saw advancements in the generation and use of electricity, the mass production of steel which propelled the manufacturing industry away from hand manufacturing to steam machines and internal combustion engines. These advancements had a great effect on the processing of food with the introduction of steam and rolling mills for the mass production of refined flour and enhancement of food preservation techniques. The rise in urbanization, economic prosperity and working women during the 20th century gave more purpose to food processing to increase the convenience and palatability of food. The food industry consistently met the growing demands by intensifying food processing methods, as the rise for convenient and pre-processed food rose during the 20th century forming the modern day western diet (Huebbe and Rimbach, 2020).

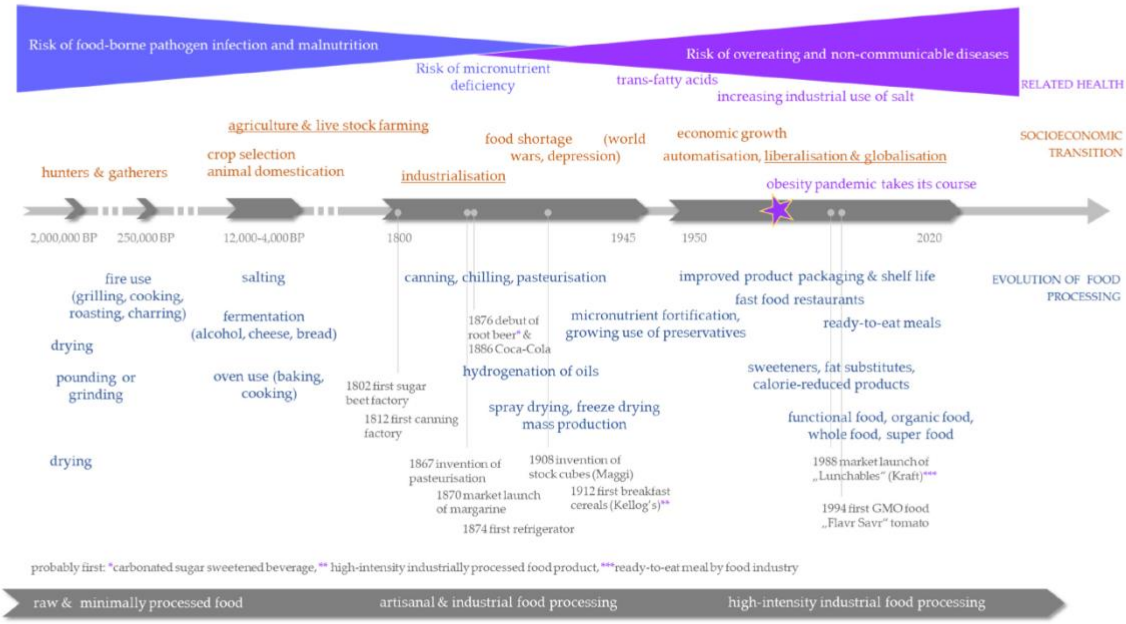

Figure 1. Time-dependent evolution of food processing associated with major transitions in human socioeconomic conditions.

Figure 1.1: Evolution timeline of the human diet (Huebbe and Rimbach, 2020).

Western diets now contain more foreign food groups that did not exist in the Paleolithic era or that were consumed in small amounts such as, cereals, refined sugars and oils, dairy, and alcohol. It now encompasses more skewed dietary portions known to be related to health, such as glycaemic load, fatty acid composition, macro and micro nutrient composition and fibre content (Jew, AbuMweis and Jones, 2009).

TABLE 2. ESTIMATED DAILY INTAKE OF MACRONUTRIENTS AND MICRONUTRIENTS FROM THE PALEOLITHIC DIET AND THE WESTERN DIET

	Paleolithic intake[a]	*Current intake*[b]
Protein (% energy)	37	14.7
Carbohydrate (% energy)	41	51.9
Fat (% energy)	22	32.7
Polyunsaturated fat:saturated fat	1.4	0.6
n-6 fatty acid:*n*-3 fatty acid	1.0:1.0[c]	9.8:1[c]
Cholesterol (mg)	480	265
Fiber (g)	104	15.2[d]
Riboflavin (mg)	6.49	2
Folate (mg)	357	361
Thiamin (mg)	3.91	1.6
Vitamin C (mg)	604	97
Vitamin A (mg of retinol equivalent)	2870	983
Vitamin E (mg)	32.8	8.8
Iron (mg)	87.4	15.2
Zinc (mg)	43.4	11.4
Calcium (mg)	1,956	863
Sodium (mg)	768	3,375
Potassium (mg)	10,500	2,628

[a]Data from Eaton *et al.*[13] unless otherwise indicated, based on 913 g of meat and 1,697 g of vegetable food/day yielding 3,000 kcal.
[b]Data from Wright *et al.*[14] and Ervin *et al.*[15–17]
[c]Data from Kris-Etherton *et al.*[18]
[d]Data from the Institute of Medicine.[19]

Table 1.1: Estimated daily intake of nutrients from the palelithic diet as compared to the modern day western diet (Jew, AbuMweis and Jones, 2009).

1.2. Ultra-Processed Foods

Ultra-processed foods (UPF) are defined by the NOVA food classification system. This system and term were developed by Carlos Monteiro, a professor at the department of Nutrition from the University of Sao Paulo in Brazil. Monteiro brought to light in his article on Nutrition and health, that the focus on food should not only consider its nutrients but its processing and extent of processing, which is often overlooked. The majority of food and drink nowadays are processed to varying degrees, and Monteiro proposed a system to divide foods into different groups based on the type and intensity of processing (Monteiro, 2009). This formed the basis for the NOVA food classification system, which is now an internationally recognised and referenced system in global health and nutrition matters. NOVA classifies all foods into 4 groups, based on the nature, extent, and purpose of processing. The four groups are: Group 1—Unprocessed or minimally processed foods, Group 2- Processed culinary ingredients, Group 3- Processed foods and Group 4- Ultra processed foods. Group 1- Unprocessed foods, are the edible part of plants or animals separated from nature, that has not undergone any form of industrial processing. Minimally processed foods are natural foods altered by industrial physical processes, such as the removal of unwanted parts, drying, powdering, crushing, boiling etc. with the intention to increase shelf life and to make them more edible. Very rarely minimally process foods contain additives. Group 2- processed culinary ingredients are group 1 substances that have undergone further industrial processes such as pressing, centrifuging, refining, extracting, or mining. They are often used as seasonings and used to prepare and cook group 1 foods. They may contain additives to prolong shelf life, protect original properties and prevent spoilage. Group 3- processed foods are the combined results of group 2 ingredients to group 1 foods using preservation methods such as canning and bottling, and non-alcoholic fermentation in the case of breads and cheeses. They may contain additives to extend shelf life, protect original properties and prevent spoilage. Group 4- Ultra- processed foods are exclusive industrial use, ingredient formulations made by a series of industrial processes requiring specialised equipment and technology. Processes can include, fractionation, chemical modification, extrusion, moulding, pre-frying etc. the use of additives are ubiquitous in these foods, at different stages of manufacture, with the aim to improve palatability. Additives include flavourings, emulsifiers, thickeners, sweeteners, colourants, preservatives etc. Table 1.2. below further describes each group (Monteiro *et al.*, 2019).

TABLE 1. THE NOVA FOOD CLASSIFICATION SYSTEM AND ITS FOUR GROUPS DEFINED ACCORDING TO THE EXTENT AND PURPOSE OF FOOD PROCESSING

NOVA GROUP	DEFINITION	EXAMPLES
|GROUP 1| Unprocessed or minimally processed foods	*Unprocessed* Edible parts of plants (fruit, seeds, leaves, stems, roots, tubers) or of or from animals (muscle, fat, offal, eggs, milk), and also fungi, algae, all after separation from nature. Spring and tap water. *Minimally processed* Unprocessed foods altered by industrial processes such as removal of inedible or unwanted parts, drying, powdering, squeezing, crushing, grinding, fractioning, steaming, poaching, boiling, roasting, and pasteurization, chilling, freezing, placing in containers, vacuum packaging, non-alcoholic fermentation, and other methods that do not add salt, sugar, oils or fats or other food substances to the original food. The main aim of these processes is to extend the life of unprocessed foods, enabling their storage for longer use, or to make them edible, and, often, to make their preparation easier or more diverse. Infrequently, minimally processed foods contain additives that prolong product duration, protect original properties or prevent proliferation of microorganisms.	Fresh, squeezed, chilled, frozen, or dried fruit and leafy and root vegetables; grains such as brown, parboiled or white rice, corn cob or kernel, wheat berry or grain; legumes such as beans, lentils, and chickpeas; starchy roots and tubers such as potatoes, sweet potatoes and cassava; fungi such as fresh or dried mushrooms; meat, poultry, fish and seafood, whole or in the form of steaks, fillets and other cuts; fresh, powdered, chilled or frozen eggs; fresh, powdered or pasteurized milk; fresh or pasteurized fruit or vegetable juices (with no added sugar, sweeteners or flavours); grits, flakes or flour made from corn, wheat, oats, or cassava; tree and ground nuts and other oily seeds (with no added salt or sugar); herbs and spices used in culinary preparations, such as thyme, oregano, mint, pepper, cloves and cinnamon, whole or powdered, fresh or dried; fresh or pasteurized plain yoghurt; tea, coffee, and drinking water. Also includes foods made up from two or more items in this group, such as dried mixed fruits, granola made from cereals, nuts and dried fruit with no added sugar, honey or oil; pasta, couscous and polenta made with flours, flakes or grits and water; and foods with vitamins and minerals added generally to replace nutrients lost during processing, such as wheat or corn flour fortified with iron and folic acid.
|GROUP 2| Processed culinary ingredients	Substances obtained directly from group 1 foods or from nature by industrial processes such as pressing, centrifuging, refining, extracting or mining. Used to prepare, season and cook group 1 foods. May contain additives that prolong product duration, protect original properties or prevent proliferation of microorganisms.	Vegetable oils crushed from seeds, nuts or fruit (notably olives); butter and lard obtained from milk and pork; sugar and molasses obtained from cane or beet; honey extracted from combs and syrup from maple trees; starches extracted from corn and other plants; vegetable oils with added anti-oxidants; salt mined or from seawater, and table salt with added drying agents. Also includes products consisting of group 2 items, such as salted butter, and group 2 items with added vitamins or minerals, such as iodised salt.

Cont.

TABLE 1. *Cont.*

NOVA GROUP	DEFINITION	EXAMPLES
| GROUP 3 | Processed foods	Products made by adding salt, oil, sugar or other group 2 ingredients to group 1 foods, using preservation methods such as canning and bottling, and, in the case of breads and cheeses, using non-alcoholic fermentation. Processes and ingredients here are designed to increase the durability of group 1 foods and make them more enjoyable by modifying or enhancing their sensory qualities. They may contain additives that prolong product duration, protect original properties, or prevent proliferation of microorganisms.	Canned or bottled vegetables and legumes in brine; salted or sugared nuts and seeds; salted, dried, cured, or smoked meats and fish; canned fish (with or without added preservatives); fruit in syrup (with or without added anti-oxidants); freshly made unpackaged breads and cheeses.
| GROUP 4 | Ultra-processed foods	Formulations of ingredients, mostly of exclusive industrial use, made by a series of industrial processes, many requiring sophisticated equipment and technology (hence 'ultra-processed'). Processes used to make ultra-processed foods include the fractioning of whole foods into substances, chemical modifications of these substances, assembly of unmodified and modified food substances using industrial techniques such as extrusion, moulding and pre-frying; use of additives at various stages of manufacture whose functions include making the final product palatable or hyper-palatable; and sophisticated packaging, usually with plastic and other synthetic materials. Ingredients include sugar, oils or fats, or salt, generally in combination, and substances that are sources of energy and nutrients that are of no or rare culinary use such as high fructose corn syrup, hydrogenated or interesterified oils, and protein isolates; classes of additives whose function is to make the final product palatable or more appealing such as flavours, flavour enhancers, colours, emulsifiers, and sweeteners, thickeners, and anti-foaming, bulking, carbonating, foaming, gelling, and glazing agents; and additives that prolong product duration, protect original properties or prevent proliferation of microorganisms. Processes and ingredients used to manufacture ultra-processed foods are designed to create highly profitable products (low-cost ingredients, long shelf-life, emphatic branding), convenient (ready-to-consume) hyper-palatable products liable to displace freshly prepared dishes and meals made from all other NOVA food groups.	Many ready-to-consume products such as carbonated soft drinks; sweet or savoury packaged snacks; chocolate, candies (confectionery); ice-cream; mass-produced packaged breads and buns; margarines and other spreads; cookies (biscuits), pastries, cakes, and cake mixes; breakfast 'cereals', 'cereal' and 'energy' bars; 'energy' drinks; milk drinks, 'fruit' yoghurts and 'fruit' drinks; 'cocoa' drinks; 'instant' sauces. Many pre-prepared ready-to-heat products including pies and pasta and pizza dishes; poultry and fish 'nuggets' and 'sticks', sausages, burgers, hot dogs, and other reconstituted meat products; and powdered and packaged 'instant' soups, noodles and desserts. Infant formulas, follow-on milks, other baby products; 'health' and 'slimming' products such as meal replacement shakes and powders.

Adapted from Monteiro *et al*., 2017a.

Table 1.2. Four groups of the NOVA classification system (Monteiro *et al.*, 2019).

1.3. EU Consumption Trends of Ultra-Processed Foods

Consequently with the rise in urbanization and industrialization in the 20th century, which further drives the rise in more processed convenience/ ready to eat foods, we see ultimately that the consumption of UPFs globally have increased over time and have rapidly displaced traditional eating patterns framed around more minimally processed and unprocessed foods, to more convenient ready to eat UPF foods (Mertens, Colizzi and

Peñalvo, 2022). Between 1990-2010 the calorie contribution from the consumption of UPFs tripled from 11% o 32% of total daily energy intake (Rico-Campà *et al.*, 2019). Food/drink sales volumes from 80 countries worldwide showed the highest sales of UPFs in Western Europe, North America, and Australasia, with increasing consumption trends in other world regions. The EU, has seen a rapid increase in the consumption of UPFs in recent decades, with research suggesting a higher contribution of more than 50% of daily total calorie intake. In Europe UPFs on average contributed 25% of total dietary energy, with the highest contribution from the UK and Germany and lowest contributions observed in Portugal and Italy (Mertens, Colizzi and Peñalvo, 2022).

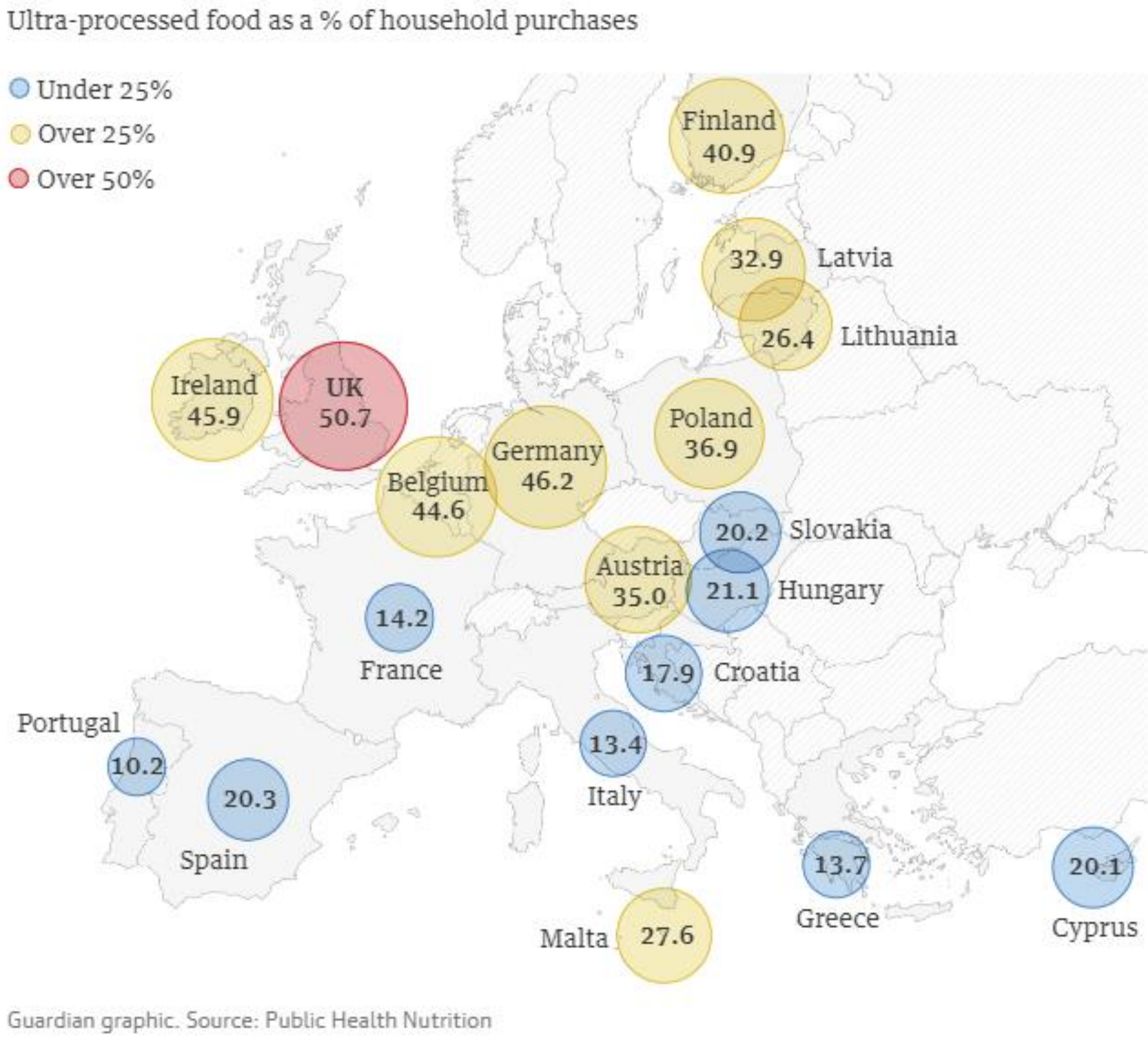

Figure 1.2: The below image illustrates the % of household purchases of UPFs across EU countries (The Guardian, 2018).

UPFs as we know are foods that go through multiple processing steps and are a combination of ingredients that have gone through multiple processing steps, with very little natural/ minimally processed ingredients in their formulation. Many different types of UPFs and products exist on the market, and the adjacent-

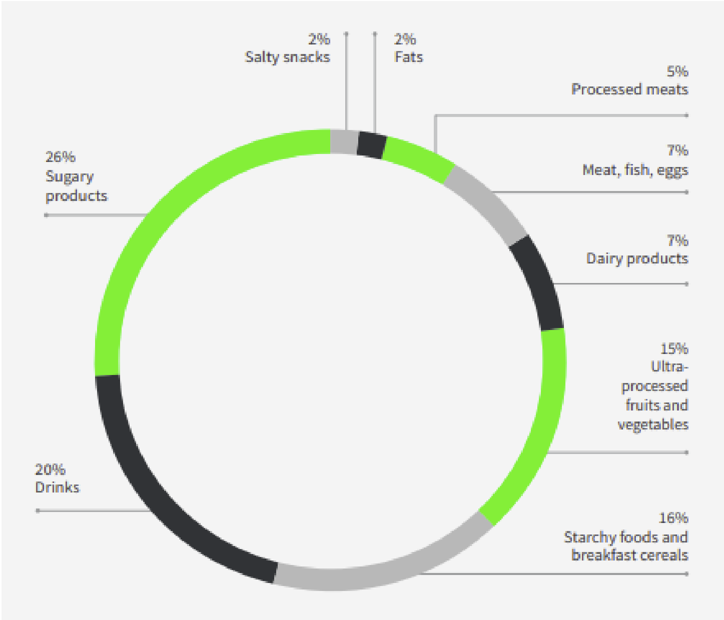

Fig 1.2.1: % Consumption of UPFs in Europe (UEG, 2020)

image shows the % consumption of UPFs in Europe. The highest being Sugary products and drinks (UEG, 2020).

1.4. Increasing Concerns Regarding Ultra-Processed Foods

UPFs typically contain 5 or more ingredients from food or food substrates, and are void of whole unprocessed foods. They commonly contain a host of additives such as emulsifiers, sweeteners, colours, preservatives, flavours and other additive ingredient to enhance the organoleptic properties, palatability, increase shelf-life, promote convenience and are cost effective. UPFs are therefore regarded to having low nutritional quality with a high energy desnsity. They are often high in saturated fats, added sugar and salt, and refined carbohydrates, with low fibre and vitamin/mineral content (Lane *et al.*, 2021). Nutrition is attributable to health outcomes and a driver for chronic diseases. Poor dietary habits increase the risk of obesity and obesity related death, as well as drive the risk of various noncommunicable diseases such as cardivascular diseases and diabetes which are among the leading cause of death globally. It is generally accepted based on vast amount of evidence that what constitutes a healthy diet consists of foods that are high in fibre, low in added sugar, salt, saturated fat and refined carbohydrates as obtained from whole/minimally processed foods plant based foods such as fruits, vegetables, nuts, seeds, pulses, wholegrains and lean protein such as oily fish. This is often referred to as the mediterreanian diet. In recent decades as the global shift away from the consumption of minimally processed foods such as home-cooked meals towards UPFs ready to eat meals and snacks have increased, so has the same era seen a rapid rise in non-communicable diseases such as obesity, type 2 diabetes (T2D) and cardiovascular diseases (CD) (Dicken and Batterham, 2022). A myriad of peer-reviewed literature including observational studies, cross sectional analysis and cohort studies have all reported a relationship with the increased consumptions and proportions of ultra-processed foods in the EU and the effects of obesity, CD and T2D. While human nutrition has evolved over the past 10,000 years, and more significantly in the last 250 years, the human genome itself has largely remained the same, resulting in a lack of biological adoption to our current nutritional environment. The human genome is still better suited to a preagricultural and paleolithic era. These significant changes in diet and lifestyle have caused metabolic distortions within the body that have resulted in increased oxidative stress and production of reactive oxygen species (ROS). ROS's, are highly unstable and reactive chemicals formed from oxygen, that can cause damage to DNA and proteins, leading to cell death. Other metabollic distortions include, hyperinsulinemia and insulin resistance, inflammation and atypical function of metabolic systems such as the renin-angiotensin-system (RAS) and sympathetic nervous system (SNS) all of which form the foundations of modern day chronic diseases such as obesity, T2D and CD (Kopp, 2019).

Chapter 2

Obesity, Type 2 Diabetes, Cardiovascular disease

2.0. Overview

Chapter 2 discusses the rise in obesity type 2 diabetes and cardiovascualar diseases, as it pertains to ultra-processed food consumption. It will also discuss the effects of these diseases and the relationship between them aswell as their global disease burden.

2.1. Obesity

Obesity is a chronic multisystem disease, as a result of excessive fat accumulation, and is associated with increased morbidity and mortality. It is defined on the basis of having a body mass index (BMI) of >30 kg/m^2. Body weight is a result of genetics and envirenmental factors combined. As BMI has increased in the global population over time at an exceeding rate, it would suggest environmental factors are the main causative drivers of obesity in recent times. Obesity rates continue to increase drastically globally, with recent global estimates reporting 712 million adults and children to be obese worldwide. Between 1970- 2015 the prevalence of obesity more than doubled in more than 70 countries, with prevalence generally higher in women than men. Once considered a problem only in westernised high income countries, obesity rates are rising in countries with a lower sociodemographic index, with a 1.7- fold increase reported since 1980 (Sarma, Sockalingam and Dash, 2021). Alarmingly, >7% of children and adolescents were obese in 2016, compared to 1% in 1975. Although, the obesity rate of increase is slowing down in most high income countries, it continues to rise in low and middle income countries. It is expected that nearly 20% of the worlds population will be obese by 2025 if current rates continue (Loos and Yeo, 2022). As a result of this worldwide obesity crisis, there has also been an increase in obesity related comorbidites (Sarma, Sockalingam and Dash, 2021). In the EU alone it is estimated that over half (52.7%) of the adult population (>18 years old) were overweight or obese i.e. had a body mass index (BMI) above 25 in 2019. Figure 2.1 and 2.1.1 below shows the variation in % of adult males and females across EU countries that were overweight (to include obese) in 2019. For overweight men and women, the distribution ranges from between 37.1% in Italy and 58.5% in Croatia for women, and between 52.9% in France and 73.2% in Croatia for men that were considered overweight in 2019. For obesity, the highest % of the adult population that were obese were recorded in Estonia (23.6 %) Latvia (25.7 %), Ireland

(26.0 %) and Malta (26.7 %), while for obese men the highest shares were found in Croatia (23.7 %), Ireland (25.7 %), Hungary (25.8 %) and Malta (30.6 %). On the other hand, the lowest % of men and women considered obese were observed in in Italy (10.7 %), Romania (10.8 %), Bulgaria (11.9 %) and Cyprus (14.1 %) for women and Romania (11.1 %), Italy (12.9 %), the Netherlands (13.2 %) and France (14.3 %) for men.

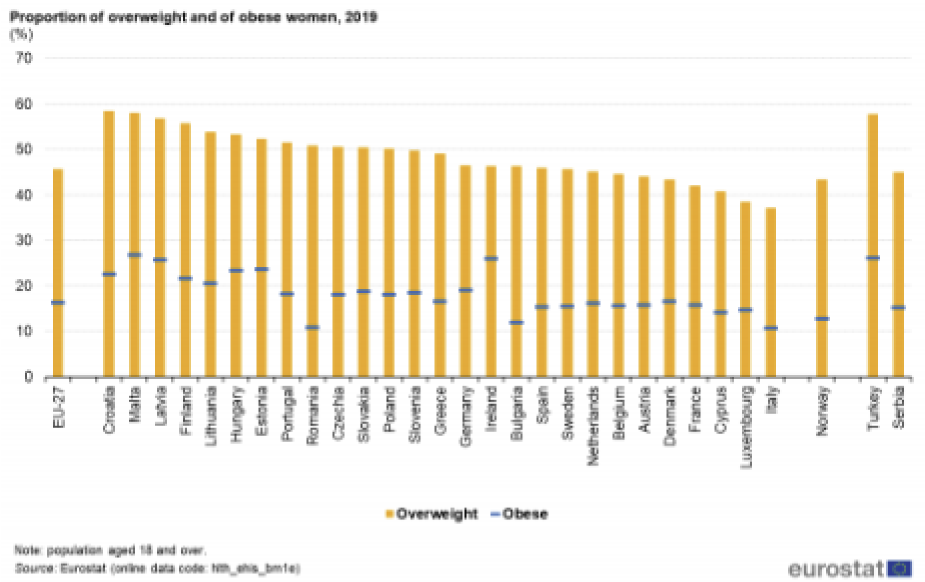

Figure 1: Proportion of overweight and obese women, 2019 (%)

Source: Eurostat (hlth_ehis_bm1e)

Fig 2.1: Shows the proportion of overweight and obese women combined in EU member states (Eurostat, 2021).

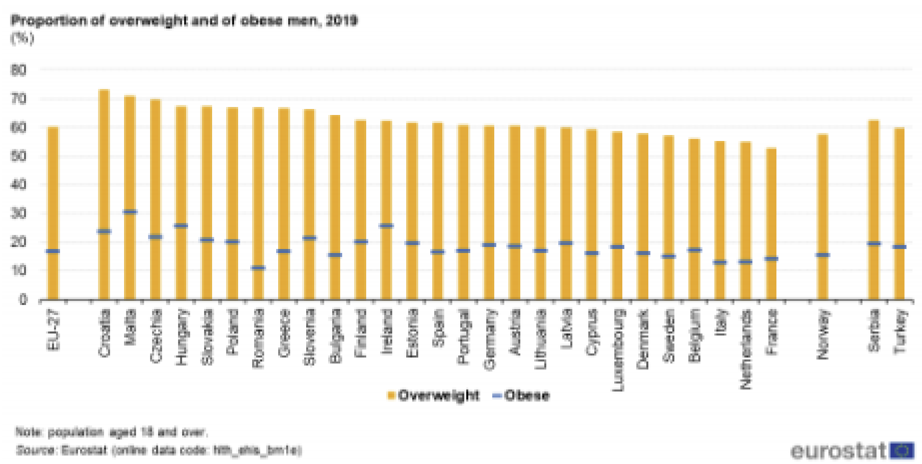

Figure 2: Proportion of overweight and obese men, 2019

(%)

Source: Eurostat (hlth_ehis_bm1e)

Fig 2.1.1: Shows the proportion of overweight and obese men combined in EU member states (Eurostat, 2021).

Obesity is a serious global concern, and is largely responsible for the other main global non-communciable diseases, Type 2 Diabetes (T2D), Cardiovascular disease (CD), hypertension and certain cancers. The physical effects of obesity also impact quality of life, with sufferers experiencing limited mobility, osteoartharitis and sleep apnea (Loos and Yeo, 2022). It also presents a huge public health concern as the effects of obesity have a significant direct and indirect cost that strains the health care system and social resources. By the 21st century, infectious diseases, that were the main cause of death in the 20th century, were replaced by non-infectious diseases such as T2D, CD and cancer, which have now become the major cause of death in the 21st century. In contrast, obesity and these chronic diseases were rarely seen or absent in hunter-gatherer and non-westernized populations (Kopp, 2019). Given the association between excess adiposity and many comorbidities, the reverse is true in that weight loss can reduce or prevent some of these comorbidities. Clinical trials showed that a 5-10% weight loss can prevent T2D in those individuals at risk with recent meta-analysis also suggesting a reduction in incidence of T2D by 38%. Obesity itself is linked to insulin resistance, which is a precursor to the devlopment of T2D. Metabolic syndrome, is a group of conditions that occur together, including high blood pressure, high blood sugar, insulin resistance, excess abdominal fat and abnormal cholesterol and triglyceride levels, that increase the risk of T2D and CD. This syndrome has risen in parallel with the rise in obesity and prevalence is between 25-30% in western countries. Cardivioscular disease is the main cause of death of obese patients, accounting for approximately 60% of deaths. Epidemiological data and mechanistic animal studies, show that obesity increases the risk of atleast 13 different cancers, and worsen outcomes in malignant cases (Sarma, Sockalingam and Dash, 2021).

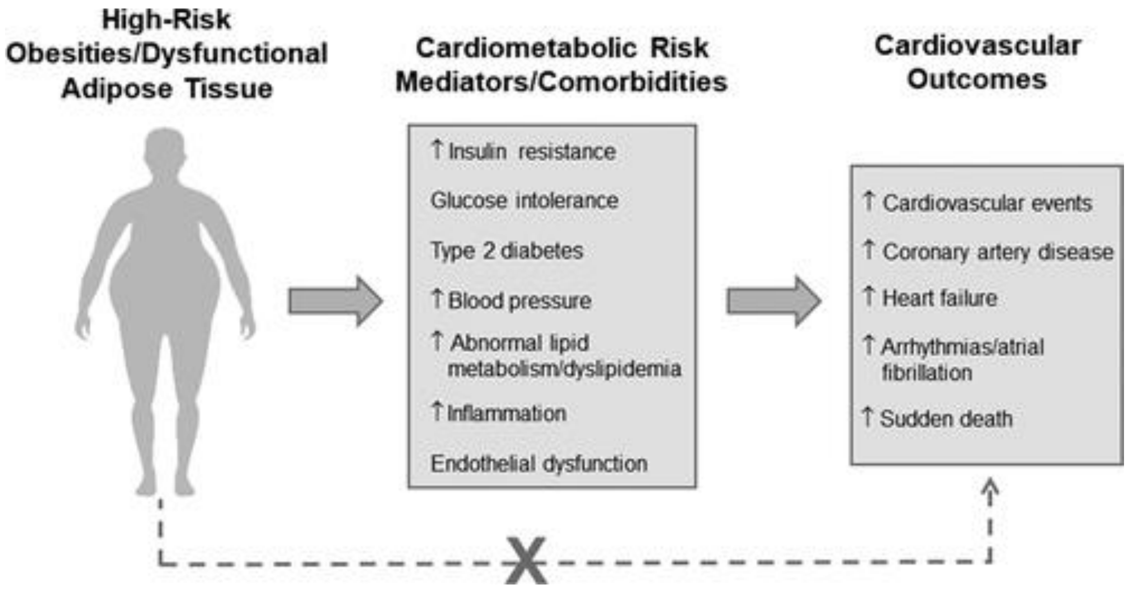

Figure 2.1.2: Shows the increased risk of cardiometabolic factors and cardiovascular outcomes as a result of obesity/dysfunctional adipose tissue (Piché, Tchernof and Després, 2020).

2.2. Type 2 Diabetes

Type 2 Diabetes (T2D) is one of the most prevalent metabolic disorders globally. It is caused by either a compromised secretion of insulin from pancreatic beta-cells and/or the insensitivity to insulin by isulin-sensitive tissues in the body. Blood glucose levels are regulated by pancreatic hormones, insulin, and glucagon through a negative feedback loop, so the molecular mechanisms in the synthesis, release and response to insulin are tightly controlled. This means any disruption to these mechanisms will create a metabolic imbalance resulting in the disease. T2D is characterised by chronic elevated blood glucose levels (hyperglycaemia), as insulin secretion is unable to maintain glucose homeostatis. If left untreated, over time can cause damage to nerves, the heart, eyes, kidneys and blood vessels. Over 90% of diabetes mellitus cases are T2D. It is influenced by both genetics and the environment, with genetic factors usually being switched on when exposed to environmental factors, such as sedentary lifestyle habits and high calorie intake. Obesity is the strongest risk factor, with patients with T2D predominantly obese, having a higher body fat percentage, particularly around the abdominal region. Adipose tissue around the abdomen propogates insulin resistance through various inflammatory mechanisms, such as increased free fatty acid and adipokine deregulation (Galicia-Garcia *et al.*, 2020). T2D is a global public health concern with 425Mn people affected worldwide in 2017, and expected to rise to 629Mn cases by 2045 (Srour *et al.*, 2020). In 2019 463Mn adults between 20-79 years old suffered with diabetes, causing 4.2Mn deaths worldwide. People with T2D have a 15% increased risk of all cause mortality, with cardiovascular diseases (CD) as the greatest cause of morbidity and mortality associated with Diabetes (Galicia-Garcia *et al.*, 2020). Ultra processed foods (UPFs) as discussed are of a poorer nutritional quality, and are naturally higher in calories, contributing disproportionate amounts of excess added sugars, salt, unhealthy saturated fats and trans fats as well as highly refined carbohydrates. They also often contain contaminants formed during high temperature processsing as well as industrial additives. UPFs currently account for over 50% of calories in some EU countries and on average 25% of calories across EU countries (Mertens, Colizzi and Peñalvo, 2022). These high- caloric foods promote the production of reactive oxygen species (ROS) which further propagates the generation of inflammatory molecules, further inducing oxidative stress. The steady increase of ROS species contributes significantly to the pathogenesis of T2D, disrupting key metabolic pathways and sustaining inflammation (Galicia-Garcia *et al.*, 2020).

2.3. Cardiovascular Disease

Cardiovascular disease (CD) is the leading cause of death worldwide, making up a third of deaths globally (Srour *et al.*, 2019). Cardiovascular disease covers a host of conditions affecting the cardiovascular system, including ischemic heart disease, stroke, heart failure, peripheral arterial disease and a number of other cardiac and vascular conditions. Global cases of CD continue to rise, with prevalent cases nearly doubling from 271Mn in 1990 to 523Mn in 2019. Global deaths from CD have also increased from 12.1Mn in 1990 to 18.6Mn in 2019. Ischemic heart disease, a term referring to heart problems as a result of narrowed heart arteries made up nearly 50% of all CD deaths in 2019 (Mensah, Roth and Fuster, 2019).

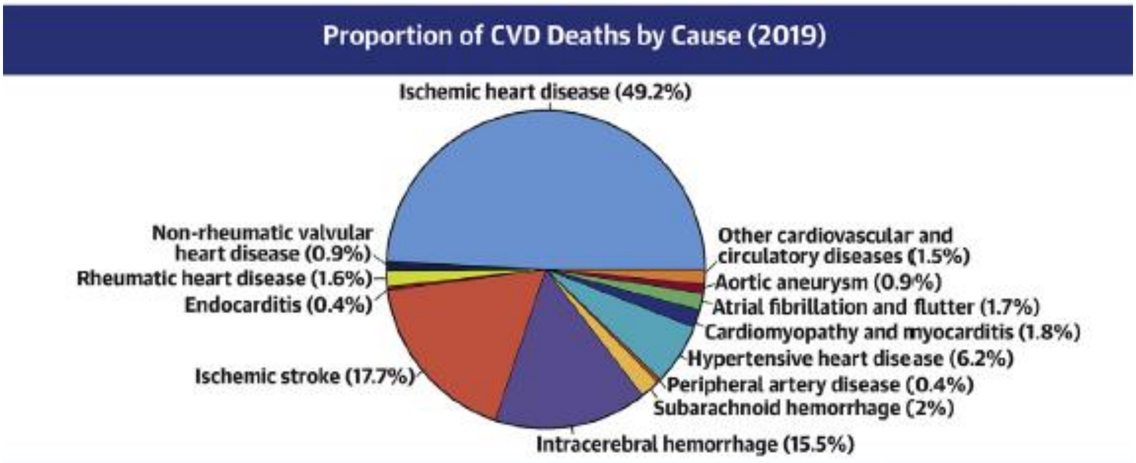

Figure 2.3. % of CD deaths by cause in 2019 (Mensah, Roth and Fuster, 2019).

Diet is the main contributing factor to CD mortality. In 2015, across the EU, 56% of deaths in men and 48% of deaths in women were attributed to dietary factors. According to the World Health Organisation (WHO), European and American guidelines, primary and secondary preventative factors of CD include a balanced and diverse diet, regular physical exercise and eliminating excessive alchohol consumption (Srour *et al.*, 2019). UPFs being of low dietary quality, having a higher content of fat, saturated fat and trans fat, would have a direct effect and increase risk on CD. As we see in figure 2.3. Ischemic heart disease made up 49.2% of CD deaths in 2019, attributed to narrowing of arteries. Narrowing of arteries are often caused by fatty deposits in the arteries from trans fat and saturated fatty foods. Furthermore current research suggests that the contaminant acrylamide, which is formed by high heat industrial processing of foods, as a result of the malliard reaction is associated with an increase risk of CD. Acrolein, another compound formed during the industrial heating of fats may also be associated with an increased risk of CD (Srour *et al.*, 2019). As discussed, the consumption of energy dense, UPFs coupled with a sedentary lifestyle lead to high-risk obesity, where cardiovascular and metabolic consequences lead to increased risk of severe cardiovascular outcomes. Individuals who are obese are liklier to develop several cardiovascular diseseases, to include coronary heart disease, atrial fibrillation, angina, heart failure, myocardial infarction and sudden cardiac death. The distribution of excess fat viscerally, as opose to subcutaneous adiposity is more directly asscoiated with elevated risk of CD and mortality, as oppose to BMI (Piché, Tchernof and Després, 2020).

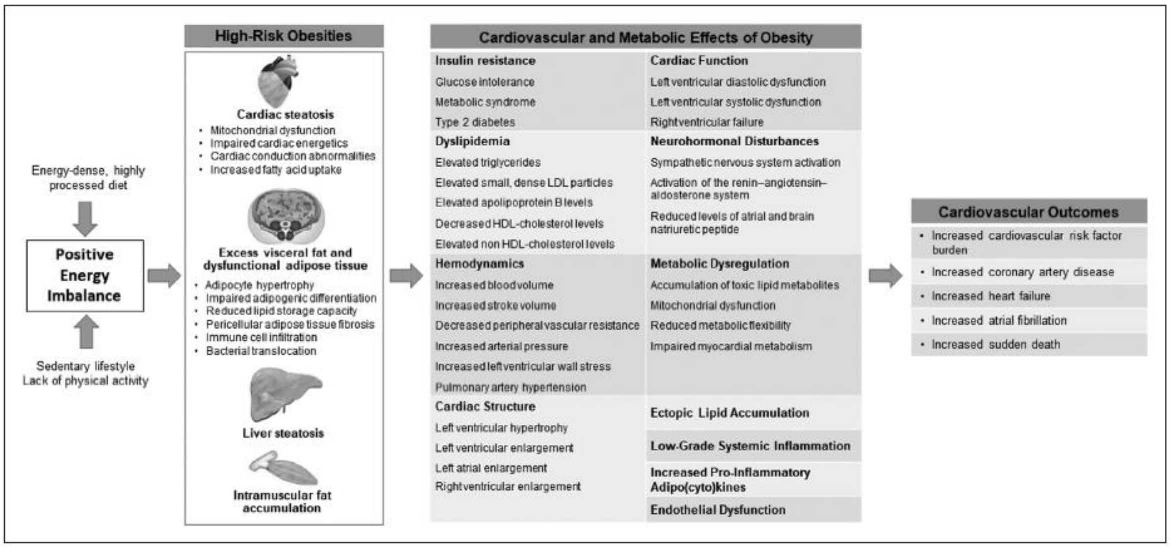

Figure 2.3.1. Shows the effects and outcomes of obesity as it pertains to Cardiovascular disease.

2.4. Thesis Outline

This introduction has discussed and set out how the the evolution of the human diet and the rise in urbanisation and industrilisation has led to a rise in the ultra processing of foods. This change in dietary habits has also led to a change in nutrient profile, with an increase in cumsumption in high energy nutrient imbalanced and deficient foods with more added non nutritive processed additives and ingredients (Mertens, Colizzi and Peñalvo, 2022). Similarly in the same time frame we see a rise in non communicable diseases, such as obesity, type 2 diabetes and cardiovascular diseases. With focus on the EU, we are facing a public health crisis, on the disease burden of these 3 diseases. Current measures that have been put in place have yet to be impactful. This thesis aims to analyse reputable and highly cited research on the effects of consumption of UPFs in the EU and the risk of obesity, T2D and CD. Based on the outcome, a more impactful solution will be proposed on how the food industry can best address the effects of UPFs, with the aim to see a decline in the risk and rate of these diseases by 2030, in line with current EU strategy.

Chapter 3

Materials and Methods

3.1. Scope

The aim was to search for the most recent studies on ultra proceessed foods and the risk it has on obesity, type 2 diabetes (T2D), and cardiovascular diseases (CD). The focus were based on studies conducted in countries within the European Union population and published from 2019 onwards to ensure the most recent and up to date data. The studies also had to be highly regarded in industry, which would mean it would have to be proportionately cited, with regard to published date (>8 citations) and pusblished in reputable, highly regarded and established journals. The research studies had to be a mixture of longitudinal and analytical studies to obtain a well rounded overview in the area.

3.2. Search Methodology & Selection Criteria

The primary search methodology used was google scholar. Search terms used were a combination of key words such as ultra-processed foods, diabetes, cardiovascular disease, obesity, risk, and mortality. This was enough to bring up research articles on the topic. Various EU countries and the term EU itself were inputed as search terms in order to bring up relevant studies. To best filter and select the most appropriate research papers the following inclusion criteria were considered: A large sample size representative of the population of the country as best as possible; EU based participants; adult population (>18 years), observational studies such as cohort studies, cross-sectional and/or meta-analysis reviews. The selection of papers would have also had to have presented substantial and accurate data with identified cofactors to present an association of risk between UPFs, obesity, T2D and CD in the form of hazard ratios (HR) and relative risk (RR). Figure 3.2. summarises the methodology and selection of the research papers to be discussed in this thesis, and Table 3.2. summarises the research papers selected.

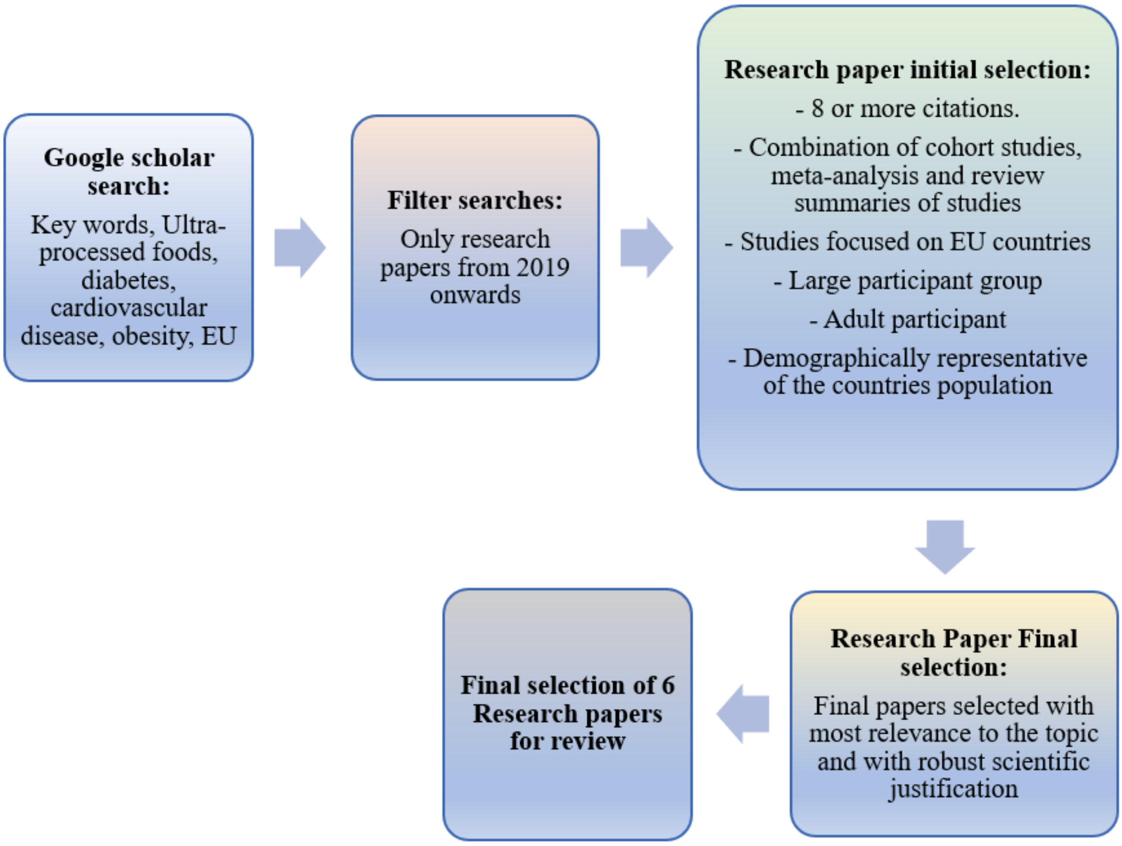

Figure 3.2. Summary of the methodology of selection of appropriate and relevant research papers

Disease focus	Paper Title	Authors	Type of Study	Country	Participants	No of citations (Google scholar)
Obesity	Ultra-processed food intake in association with BMI change and risk of overweight and obesity: A prospective analysis of the French NutriNet-Santé cohort	Beslay et al., 2020	Prospective Analysis	France	110,260 adult participants	87

Obesity	Consumption of ultra-processed foods associated with weight gain and obesity in adults: A multi-national cohort study	Cordova et al., 2021	Cohort Study	9 EU countries	348,748 adults aged 25- 70 years	11
Diabetes	Ultra-processed foods and type-2 diabetes risk in the SUN project: A prospective cohort study	Llavero-Valero *et al.*, 2021	Cohort Study	Spain	20,060 adult participants from SUN project	15
Diabetes	Ultraprocessed food consumption and risk of type 2 diabetes among Participants of the NutriNet-Santé Prospective Cohort	Srour *et al.*, 2020	Cohort Study	France	104,707 adult participants	201
Cardiovascular Disease	Ultra-processed food intake and risk of cardiovascular disease: prospective cohort study (NutriNet-Santé)	Srour *et al.*, 2019	Cohort Study	France	105,159 adult participants	434
All cause mortality/ cardiovascular disease	Ultra-Processed Food Consumption and Adult Mortality Risk: A Systematic Review and Dose–Response Meta-Analysis of 207,291 Participants	Suksatan *et al.*, 2022	Meta-analysis	Spain, Italy, France, USA	207,291 adult participants	8

Table 3.2. Summarises the research papers selected for the purpose of this thesis.

3.3. Summary of Study Methodology Used in Chosen Research Papers

All chosen research papers utilised similar methods to gather information for analysis. out of the six selected papers, four of them were cohort studies and two were analytical studies (meta and prospective). The three studies by, Beslay *et al*., and Srour *et al*., were based of the French Nutrinet Sante cohort study. This study is the largest ongoing nutrition study of its kind globally. It was launched in 2009 in France and is an on-going cohort study aimed at studying the relationship between nutrition and health. It consistently recruits adults (>18 years old) among the general french population that are followed via a dedicated online platform. By the beginning of 2021, data was being collected from 171,000 people. The process involves the completion by participants of 5 questionaires at baseline, each capturing sociodemographic, lifestyle characteristics, anthropometry, health status, physical activity and dietary intake. The study is registered at clinical trials.gov as NCT03335644 (Beslay *et al.*, 2020). The Cohort study by Llavero-Valero *et al*., is based of another well renowned cohort study known as the SUN project. The SUN project, is a large cohort study, started in 1999 and ended in 2018. The primary aim of the study was to evaluate the impact of diet and lifestyle on the prevention of various non-communicable disease outcomes, such as cardiovascular diseases, type II diabetes, cancer, amongst others. It also aims to demonstrate the benefit of a Mediterranean diet on overall health and reduction in all cause mortality. the Mediterranean diet is characterized by a high consumption of olive oil (as the main fat source), vegetables, fruits, legumes, unrefined cereals, a high consumption of fish (as the main protein source) with a moderate consumption of dairy (mostly cheese and yoghurt), a reduced intake of wine as well as reduced consumption of meat products other than fish. The cohort study takes place in Spain, in a Mediterranean setting, and the study participants are purposely selected to be university students at the starting point (>20 years), primarily from the University of Navarra and other Spanish universities. The aim of this selection criteria is to have highly educated participants to restrict for cofounding by socioeconomic status. The study involves the collection of data with regards to diet, eating patterns, lifestyle, sociodemographics, anthropometrics, medications and preventative measures (Carlos *et al.*, 2018). The cohort study by Cordova et al., is a multi-national study across 9 EU countries conducted in accordance with the well renowned EPIC study. The European Prospective Investigation into Cancer and Nutrition (EPIC) study, is a an ongoing cohort study across 23 centres in 10 Europeans countries

(UK, France, Germany, The Netherlands, Italy, Norway, Spain, Greece, Sweden, Denmark) (Cordova *et al.*, 2021). Its primary purpose is to investigate the association between nutrition and cancer, with the potential of studying other diseases also (Riboli *et al.*, 2002). Finally, the Study by Suksatan *et al*., is a meta-analysis, whereby data was extracted from seven cohort studies, across 4 countries, The selected studies were prospective cohort studies. The assessment method of all studies utilised either a food frequency questionnaire (FFQ) or 24-h recall questionnaire. Random-effect models were used to determine association and outcomes (Suksatan *et al*., 2022). All six studies grouped food and drink according to the NOVA classification system.

Chapter 4

Results

4.0. Thesis Outline

With focus on the EU, there is a global rise in non communciable diseases, obesity, cardiovascular disease (CD) and type 2 Diabetes (T2D), creating an EU wide disease burden and public health crisis. Current measures that have been put in place have yet to be impactful. This results section will analyse the six selected studies on the effects of consumption of UPFs in the EU and the risk of obesity, T2D and CD. These results will provide insight into measurable and impactful solutions that will be proposed on how the food industry can best address the effects of UPFs, with the aim to see a decline in the rate of these diseases by 2030.

4.1. Ultra-Processed Foods and Obesity

UPF consumption has drastically increased in the EU and worldwide, representing 50-60% of total energy intake in some high income countries In the same time frame the prevalence of overweight and obesity has also drastically risen over the last century and continues to rise (Beslay *et al.*, 2020). The following two studies, one being a cohort study from the French Nutrinet Sante study and the other a multi-national cohort study, from the European Prospective Investigation into Cancer and Nutrition (EPIC) study both explore the correlations between the consumption of UPF and overweight and obesity (Beslay *et al.*, 2020), (Cordova *et al.*, 2021).

4.1.1. Beslay et al., 2020

Marie Besley et al., investigated the associations with UPF consumption as it pertains to the risk of being overweight and obese, including change in BMI, in a large french cohort. A total of 110,260 adult participants (>18 years old) from the french NutriNet-Sante´ cohort were included between 2009-2019. Dietary intakes were collected at baseline using 24-h dietary records, with recorded food items grouped according to the NOVA classification system, based on the degree of food processing. The associations between the change in proportion of UPF and BMI were analysed by linear mixed models and the associations of risk of overweight and obesity were assessed using Cox proportional hazard models. Particpants that were not overweight or obese at baseline, that completed atleast two 24-hour dietary records, who were followed up for atleast six months and had no missing anthropometric data at baseleine were included in the study (Beslay *et al.*, 2020).

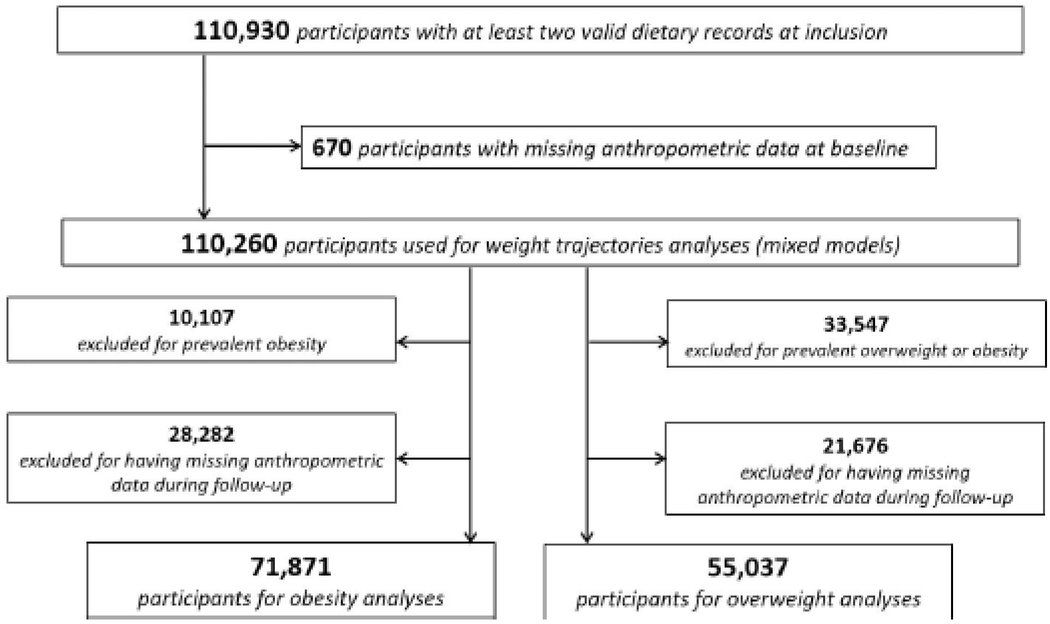

Figure 4.1.1. Flowchart for study population (Beslay *et al.*, 2020).

Table 4.1.1. sumarises the baseline characteristics of the participants, showing a significantly higher intake of UPF in the fourth quartile (32.4%) compared to the first quartile (7.5%). Particpiants in the fourth quarter were younger, more likely to smoke, higher educated and were less physiclaly active than those in the first quartile. The participants in the fourth quarter also had a higher saturated fatty acid, sodium, sugar, and energy intake, with a lower intake of dietary fibre and alcohol (Beslay *et al.*, 2020).

	All participants	Quartile[b] 1	Quartile[b] 2	Quartile[b] 3	Quartile[b] 4
		(n = 27,609)	(n = 27,576)	(n = 27,556)	(n = 27,519)
UPF (%)	17.1 (10.3)	7.5 (2.1)	13.2 (1.8)	18.7 (2.2)	32.4 (9.6)
Age, years	43.1 (14.6)	47.7 (13.7)	44.9 (14.3)	42.4 (14.6)	37.5 (14.1)
Sex, women, *n* (%)	86,253 (78.2)	21,601 (78.2)	21,574 (78.2)	21,553 (78.2)	21,525 (78.2)
Educational level, *n* (%)					
<High school degree	20,013 (18.1)	5,212 (18.9)	4,941 (17.9)	4,873 (17.7)	4,987 (18.1)
<2 years after high school	19,061 (17.3)	4,145 (15.0)	4,300 (15.6)	4,764 (17.3)	5,852 (21.3)
≥2 years after high school	71,186 (64.6)	18,252 (66.1)	18,335 (66.5)	17,919 (65.0)	16,680 (60.6)
Marital status, *n* (%)					
Single (living alone)	32,532 (29.5)	7,380 (26.7)	7,383 (26.8)	7,990 (29.0)	9,779 (35.5)
In couple	77,728 (70.5)	20,229 (73.3)	20,193 (73.2)	19,566 (71.0)	17,740 (64.5)
BMI, kg/m^2	23.8 (4.6)	23.8 ± 4.4	23.8 ± 4.3	23.8 ± 4.5	23.9 ± 5.0
Smoking status, *n* (%)					
Current	18,731 (17.0)	4,181 (15.1)	4,319 (15.7)	4,526 (16.4)	5,705 (20.7)
Former	36,243 (32.9)	10,564 (38.3)	9,373 (34.0)	8,852 (32.1)	7,454 (27.1)
Never	55,286 (50.1)	12,864 (46.6)	13,884 (50.3)	14,178 (51.4)	14,360 (52.2)
IPAQ physical activity level, *n* (%)[c]					
High	31,638 (33.2)	9,152 (38.0)	8,222 (34.0)	7,671 (32.2)	6,593 (28.3)
Moderate	40,825 (42.8)	10,171 (42.2)	10,516 (43.6)	10,251 (43.0)	9,887 (42.4)
Low	22,881 (24.0)	4,748 (19.7)	5,391 (22.3)	5,918 (24.8)	6,824 (29.3)
Energy intake, kcal/d	1,893.2 (503.9)	1,816.2 (473.8)	1,896.5 (489.0)	1,925.5 (507.8)	1,934.70 (534.5)
Alcohol intake, g/d	7.9 (12.7)	8.8 (13.5)	8.7 (13.0)	7.8 (12.4)	6.2 (11.7)
Sodium intake, mg/d	2,683.9 (954.6)	2,536.2 (919.5)	2,696.7 (931.5)	2,762.0 (962.1)	2,741.0 (987.4)
SFA, g/d	32.8 (13.2)	29.7 (12.2)	32.7 (12.7)	33.9 (13.2)	34.74 (13.9)
Dietary fibre, g/d	19.6 (7.6)	21.0 (8.1)	20.0 (7.4)	19.7 (7.3)	17.7 (7.4)
Sugar, g/d	92.2 (35.4)	85.3 (33.9)	90.9 (32.7)	93.7 (34.0)	99.1 (39.1)

[a]Values are means (SDs) or *n* (%).

[b]Sex-specific quartiles of the proportion of UPF intake in the total quantity of food consumed. Cut-offs for quartiles were 10.2, 15.5, and 22.5 for men and 9.9, 15.2, and 22.1 for women, respectively.

[c]Available for 95,344 participants. Participants were categorized into the "high," "moderate," and "low" categories according to IPAQ guidelines [52] (Method C in S1 Appendix).

Abbreviations: BMI, body mass index; IPAQ, International Physical Activity Questionnaire; SFA, saturated fatty acid; UPF, ultra-processed food

Table 4.1.1. Baseline characteristics of participants according to sex specific quartiles, N= 110,260 (2009-19) (Beslay *et al.*, 2020).

Figure 4.1.1.1. Below shows a change over time in BMI based on quartiles of UPF consumption over 9 follow up years. Participants in the fourth quarter had a higher baseline BMI than the other 3 quartiles. A significant increase in BMI, was observed over the 9 follow up years, with the highest increase in BMI observed in the fourth quartile with lowering increases of BMI in the third, second and lowest observed in the first quartile (Beslay *et al.*, 2020).

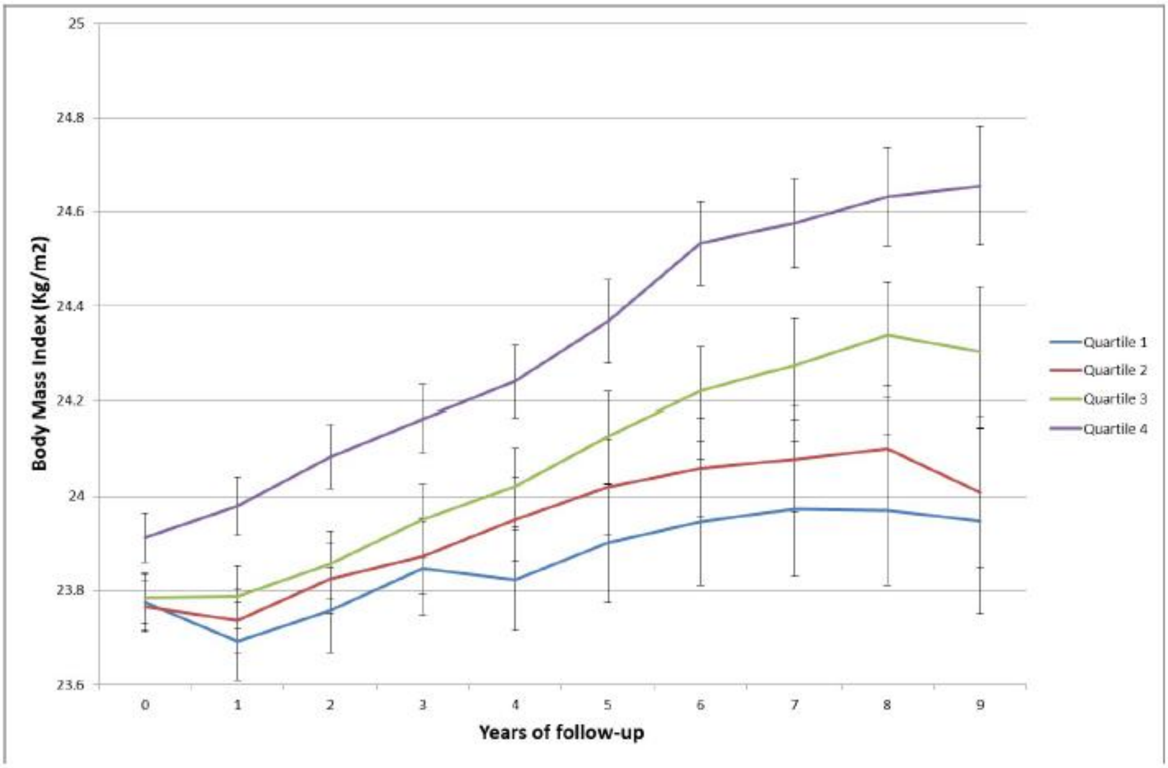

Figure 4.1.1.1. BMI change over time accroding to four quartiles of proportion of UPF in the diet (Beslay *et al.*, 2020).

Analysis to identify the risk of overweight and obesity were conducted on 55,037 participants that were not overweight at baseline and 71,871 participants that were not obese at baseline. During follow up (a mean of 4.1 years) 7,063 participants became overweight and during a median follow up time of 5 years, 3,066 participants became obese. These results demonstrated that participants with a higher proportion of UPF in their diet were at a higher risk of overweight (hazard ratio (HR) for an absolute increment of 10 in % of UPF in the diet = 1.11 [1.08–1.14], $P < 0.001$), and obesity (hazard ratio (HR) for an absolute increment of 10 in % of UPF in the diet = 1.09 [1.05–1.13], $P < 0.001$). These trends were statistically significant from the third quartile, and strongest in the fourth quartile, remaining unaffected by adjustments of cofactors across all models (Beslay *et al.*, 2020).

	Proportion of UPF in the diet[a]						
Overweight	**Q1**	**Q2**	**Q3**	**Q4**		**Continuous[b]**	
	HR	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	P_{trend}	**HR (95% CI)**	P
***N* cases/non-cases**	1,666/12,092	1,706/12,054	1,830/11,930	1,861/11,898		7,063/47,974	
Model 1	1	1.06 (1.00–1.14)	1.19 (1.11–1.28)	1.26 (1.18–1.35)	<0.001	1.11 (1.08–1.14)	<0.001
Model 2	1	1.07 (1.00–1.14)	1.19 (1.12–1.28)	1.30 (1.21–1.39)	<0.001	1.11 (1.08–1.14)	<0.001
Model 3	1	1.06 (0.99–1.13)	1.18 (1.10–1.26)	1.24 (1.16–1.33)	<0.001	1.10 (1.08–1.13)	<0.001
Model 4	1	1.05 (0.98–1.13)	1.17 (1.09–1.25)	1.22 (1.14–1.31)	<0.001	1.10 (1.07–1.13)	<0.001
Model 5	1	1.05 (0.98–1.13)	1.17 (1.09–1.25)	1.22 (1.13–1.31)	<0.001	1.10 (1.07–1.13)	<0.001
Obesity	**Q1**	**Q2**	**Q3**	**Q4**		**Continuous**	
	HR	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	P_{trend}	**HR (95% CI)**	P
***N* cases/non-cases**	687/17,280	723/17,245	803/17,166	853/17,114		3,066/68,805	
Model 1	1	1.05 (0.94–1.16)	1.10 (1.00–1.22)	1.15 (1.04–1.28)	0.005	1.09 (1.05–1.13)	<0.001
Model 2	1	1.09 (0.98–1.21)	1.26 (1.13–1.39)	1.41 (1.27–1.57)	<0.001	1.19 (1.15–1.23)	<0.001
Model 3	1	1.05 (0.95–1.17)	1.11 (1.00–1.23)	1.16 (1.05–1.30)	0.003	1.10 (1.06–1.14)	<0.001
Model 4	1	1.06 (0.95–1.18)	1.12 (1.01–1.24)	1.20 (1.08–1.33)	<0.001	1.11 (1.07–1.15)	<0.001
Model 5	1	1.05 (0.95–1.17)	1.11 (1.00–1.23)	1.15 (1.03–1.28)	0.009	1.10 (1.05–1.14)	<0.001

Qi [i = 1–4] = Quartile, n = 55,307 for overweight analyses and 71,871 for obesity analyses. Model 1 was a multi-adjusted Cox proportional hazard model adjusted for age (timescale), sex, educational level (<high school, <2 years after school, ≥2 years after high school), marital status (living alone or not), baseline BMI (continuous), physical activity (high, moderate, low), smoking status (never, former, current), alcohol intake (continuous), number of 24-hour dietary records (continuous), and energy intake (continuous); model 2 = model 1 unadjusted for baseline BMI; model 3 = model 1 + intakes of sodium, sugar, SFAs, and dietary fibre (continuous); model 4 = model 1 + healthy and Western dietary patterns (continuous); model 5 = model 1 + consumption of fruit and vegetables, and sugary drinks (continuous).

[a]Cut-offs for quartiles were 9.9, 14.9, and 21.5 for men and 9.6, 14.5, and 21.1 for women in the overweight analyses; and 9.8, 14.8, and 21.2 for men and 9.6, 14.5, and 21.1 for women in the obesity analyses.

[b]HR for an absolute increment of 10 in the percentage of UPF in the diet.

Abbreviations: BMI, body mass index; HR, hazard ratio; SFA, saturated fatty acid; UPF, ultra-processed food

Table 4.1.1.1. Shows the associations between UPF intake and risk of overweight and obesity from Cox proportional hazard models (Beslay *et al.*, 2020).

4.1.2. Cordova et al., 2021

Cordova et al., examined the relationship between UPF consumption, weight gain and risk of obesity. It included 348,748 men and women between the ages of 25- 70 years old, recruited between 1992-2000 from 9 european countries. Dietary questionnaires were used to assess food and drink consumption with classification according to the NOVA classification system based on the degree of processing (Cordova *et al.*, 2021). Multilevel mixed linear regression models were used to evaluate the association between UPF consumption and change in body weight in kg, over 5 years. To estimate the risk of overweight and obesity after 5 years, Poisson regression models were used stratified according to baseline BMI (Cordova *et al.*, 2021). The following table 4.1.2. shows the characteristics of the study population, split into quintiles of UPF consumption, with Q5 having the highest UPF daily consumption in g/day and Q1 having the lowest daily consumption. Habitual consumption of UPF, was modelled on a continuous scale per 1 standard deviation (SD)/g equivalent to approximately 250g/day, and divided into quintiles, with the lowest quintile (Q1) used as the reference. Particpants in the highest quintile (Q5) gained the most weight, were younger, and consumed more sugar/confectionary, cakes, biscuits, more soft drinks and less alcohol than the lowest quintile (Q1). Within 5 years there was a mean weight increase of 2.1kg, with large variation amongst participants (Cordova *et al.*, 2021).

Main characteristics of the study population according to quintiles (Q) of baseline ultra-processed foods[a] consumption in g/day of 348 748 men and women in the EPIC-PANACEA study.

	Q1	Q2	Q3	Q4	Q5
Ultra-processed food intake (g/day)	176 ± 102	221 ± 117	270 ± 129	364 ± 133	686 ± 303
Follow-up time (years)	5·2 ± 2·4	5·2 ± 2·5	5·0 ± 2·4	5·0 ± 2·2	5·2 ± 2·0
Weight change (kg/5years)[b]	1·9 ± 4·8	1·9 ± 4·9	2·1 ± 4·9	2·2 ± 5·0	2·3 ± 5·4
Women (%)	60	79	82	78	68
Age (years)	52·5 ± 8·0	52·1 ± 8·0	52·2 ± 8·3	51·7 ± 9·4	50·0 ± 11·2
BMI at inclusion (kg/m^2)	25·6 ± 4·0	25·1 ± 4·1	24·8 ± 4·0	24·7 ± 4·0	25·4 ± 4·3
BMI categories (%)					
< 25 kg/m^2	48	56	59	59	52
25 < 30 kg/m^2	38	33	31	31	35
≥ 30 kg/m^2	14	12	10	10	13
University degree (%)	23	24	26	27	25
Missing	0·8	1·1	1·6	1·8	1·8
Physically inactive (%)	20	19	18	18	18
Missing	0·5	1·1	1·5	2·1	2·7
Smoking status at baseline (%)					
Never	45	51	53	53	50
Former	28	26	26	28	29
Current	26	21	18	17	19
Missing	1·1	1·9	2·4	2·2	1·6
Previous illness (%)[c]	7	7	8	8	8
Missing	6·3	5·8	6·1	10·4	15·8
EPIC dietary intake					
Total energy intake (kcal/day)	2314 ± 648	1976 ± 552	1935 ± 540	1973 ± 551	2181 ± 630
Vegetables (g/day)	99 ± 64	102 ± 67	106 ± 71	107 ± 70	99 ± 67
Fruits (g/day)	122 ± 94	123 ± 93	120 ± 88	113 ± 83	104 ± 80
Legumes (g/day)	9 ± 14	7 ± 11	6 ± 10	6 ± 9	7 ± 11
Meat/meat products (g/day)	51 ± 23	52 ± 24	51 ± 25	47 ± 26	43 ± 27
Dairy (g/day)	155 ± 114	156 ± 106	160 ± 106	177 ± 107	179 ± 115
Fish (g/day)	23 ± 21	23 ± 21	20 ± 20	18 ± 17	15 ± 16
Egg/egg products (g/day)	10 ± 9	10 ± 8	10 ± 8	9 ± 8	8 ± 7
Potatoes (g/day)	51 ± 39	48 ± 36	44 ± 32	44 ± 30	46 ± 29
Cereals/cereal products (g/day)	107 ± 42	106 ± 38	103 ± 39	101 ± 41	100 ± 45
Sugar/confectionary (g/day)	15 ± 12	18 ± 14	19 ± 16	21 ± 17	25 ± 28
Cakes/biscuits (g/day)	14 ± 14	18 ± 16	21 ± 18	24 ± 19	24 ± 20
Added fat (g/day)	14 ± 7	13 ± 7	12 ± 7	12 ± 7	12 ± 7
Non-alcoholic beverages (g/day)	451 ± 434	555 ± 442	610 ± 425	640 ± 384	669 ± 366
Soft drinks (g/day)	4 ± 9	9 ± 17	15 ± 25	27 ± 38	115 ± 140
Coffee (g/day)	181 ± 199	211 ± 209	209 ± 196	215 ± 195	209 ± 194
Alcoholic beverages (g/day)	115 ± 145	80 ± 110	70 ± 100	65 ± 93	64 ± 97
mrMED score units/day	9 ± 3	9 ± 3	9 ± 3	8 ± 3	8 ± 3

Data are expressed as arithmetic mean ± standard deviation (SD) if not stated otherwise.
First quintile corresponds to the lowest and quintile five to the highest intake of ultra-processed foods.
BMI body mass index (calculated as weight in kilograms divided by height in meters squared).
mrMED modified relative Mediterranean diet score (range 0–18; higher score characterizing a Mediterranean diet).
[a] Energy-adjusted baseline ultra-processed food consumption (g/day) using the residual method. Standardized residuals were computed by linear regression of baseline ultra-processed foods (g/day) regressed on energy intake and center.
[b] Calculated as weight at follow-up minus weight at baseline divided by the follow-up time in years and multiplied by 5 years.
[c] Type 2 diabetes, cardiovascular disease, cancer.

Table 4.1.2. Characteristics of the study population according to quintiles of baseline UPF consumption in g/day (N= 348,748) (Cordova *et al.*, 2021).

Table 4.1.2.1 Shows the change in body weight over 5 years, based on energy-adjusted baseline UPF consumption. Higher consumption of UPF was asscociated with a greater weight gain over 5 years after adjusting for cofounders (0.12 kg per 1 SD increment/5years, 95% CI 0.087 to 0.152). After further adjustment to account for a medditerreanean diet, associations remained unchanged (Cordova *et al.*, 2021).

Difference in body weight gain (kg) over 5 years according to baseline ultra-processed food[a] consumption (g/day) in 348 748 men and women.

		Model 1	Model 2	Model 3
Beta (95%CI) per 1 SD/day		0·135 (0·097, 0·174)	0·120 (0·087, 0·152)	0·118 (0·085, 0·151)
Quintiles of UPF intake	UPF (g/day) mean intake ± standard deviation (SD)			
Lowest	176 (±102)	Reference	Reference	Reference
Q2	221 (±117)	0·002 (−0·093, 0·098)	−0·008 (−0·092, 0·076)	−0·009 (−0·095, 0·076)
Q3	270 (±129)	0·118 (0·003, 0·234)	0·104 (0·002, 0·205)	0·101 (−0·002, 0·205)
Q4	364 (±133)	0·219 (0·115, 0·324)	0·197 (0·111, 0·282)	0·193 (0·105, 0·282)
Q5	686 (±303)	0·401 (0·292, 0·510)	0·357 (0·272, 0·442)	0·352 (0·262, 0·442)
P trend (linear)		<0·001	<0·001	<0·001

Multilevel linear mixed models with random effect on the intercept and slope according to center.
Overall mean 5- year weight gain corresponded to 2·1 kg (SD 5·0) and positive beta values indicate more weight gain (kg) over the same period.
Standardized residuals were computed by a linear regression of baseline ultra-processed foods (g/day) regressed on energy intake and center.
Model 1 was adjusted for age, sex, and BMI at baseline.
Model 2 was further adjusted for educational level, levels of physical activity, alcohol intake at baseline, smoking status at baseline, and plausibility of dietary energy reporting.
Model 3 was further adjusted for modified relative Mediterranean diet score.
[a] Energy-adjusted baseline ultra-processed food consumption (UPF) (g/day) using the residual method (1 standard deviation, SD = 250g).

Table 4.1.2.1. Change in Body weight (kg) over 5 years, according to baseline UPF consumption (g/day) (N= 348,748) (Cordova *et al.*, 2021).

The following spline graph (figure 4.1.2) showed a linear dose response correlation between consumption of UPF (per 1 SD/day) and weight gain. Over 5 years, a mean 5-year weight gain corresponded to 2.1 kg (SD 5.0) (Cordova *et al.*, 2021).

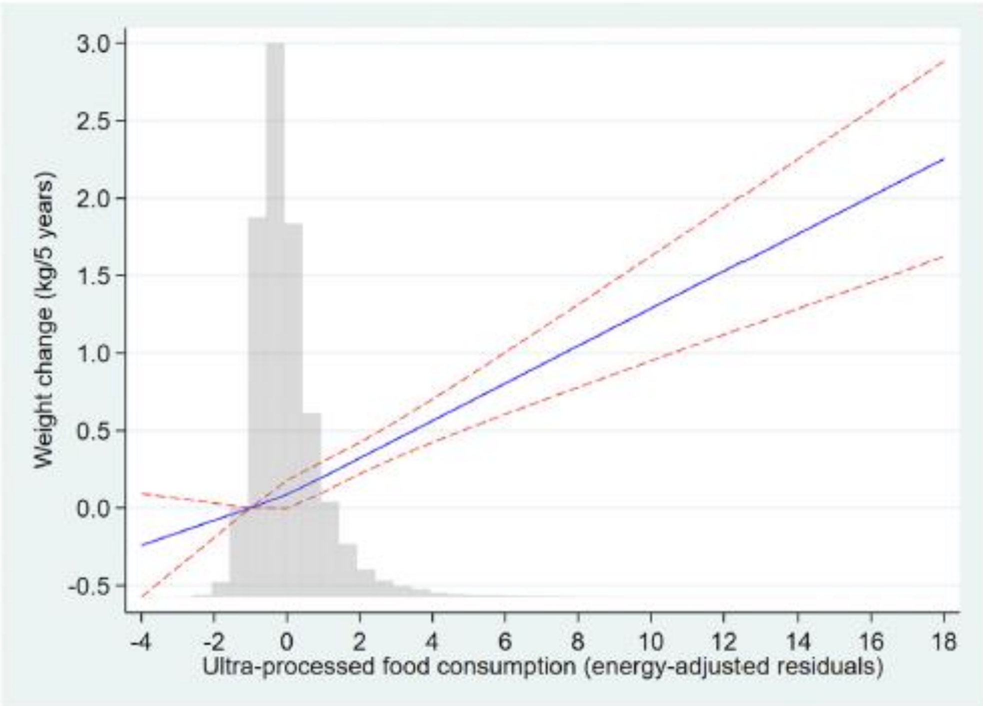

Figure 4.1.2. Three knot spline graph showing the association of UPF consumptions (per 1 SD/day) and weight gain (Cordova *et al.*, 2021).

The adjusted relative risk (RR) based on 95% confidence interval (CI) of becoming overweight or obese after 5 years, based on the continuous consumption of UPF and baseline BMI were calculated. The 191,255 participants who had a BMI in the normal range (<25kg/m^2) at baseline, when compared between the highest vs lowest quintile of UPF consumption, had a 15% higher risk (95% CI 1.11 to 1.19) of becoming overweight or obese after 5 years (P trend <0.001). Similarly, the 103,259 participants who were overweight (>25kg/m^2) at baseline had a 16% risk (95% CI 1.09 to 1.23) of becoming obese (P trend <0.001) after 5 years, when comparing the UPF consumption between the highest and lowest quintile (Cordova *et al.*, 2021).

Adjusted relative risks (RR) [95% CI] of becoming overweight or obese over 5 years according to baseline ultra-processed food[a] consumption (g/day) and baseline BMI in men and women.

	BMI <25 kg/m^2 at baseline (n = 191 255)			BMI ≥25 to <30 kg/m^2 at baseline (n = 103 259)[b]		
	N (%)	N overweight or obese (%)	RR of becoming overweight or obese (95% CI)	N (%)	N obese (%)	RR of becoming obese (95% CI)
ultra-processed food consumption (per 1 SD/day)	191 255 (100)	29 094 (15)	1·05 (1·04, 1·06)	103 259 (100)	12 708 (12)	1·05 (1.03, 1.07)
Quintiles of ultra-processed food consumption						
lowest			Reference			
Q2	38 251 (20)	5513 (14)	1·00 (0·97, 1·03)	20 532 (20)	2285 (11)	0·95 (0·90, 1·01)
Q3	38 251 (20)	5456 (14)	1·04 (1·01, 1·07)	20 662 (20)	2663 (13)	1·08 (1·02, 1·14)
Q4	38 251 (20)	6665 (15)	1·06 (1·02, 1·09)	20 738 (20)	2682 (13)	1·07 (1·01, 1·13)
Q5	38 251 (20)	6664 (17)	1·15 (1·11, 1·19)	20 726 (20)	3031 (15)	1·16 (1·09, 1·23)
P trend (linear)			<0·001			<0·001

A modified Poisson regression approach was used to calculate the RR and 95% CI. Analyses were stratified by initial body mass index (BMI) categories (<25 kg/m^2: normal weight, ≥ 25 to < 30 kg/m^2: overweight; and ≥30 kg/m^2: obese).
Adjusted for age, sex, country/center, BMI at baseline, follow-up time in years, educational level, levels of physical activity, alcohol intake at baseline, smoking status at follow-up, and plausibility of dietary energy reporting, and for the modified relative Mediterranean diet score.
[a] Energy-adjusted baseline ultra-processed food consumption (g/day) using the residual method (1 standard deviation, SD = 250g). Standardized residuals were computed by a linear regression of baseline ultra-processed foods (g/day) regressed on energy intake and center.
[b] Number of overweight participants at baseline who become obese.

Table 4.1.2.2. Adjusted relative risk (RR) of overweight or obesity over 5 years according to baseline UPF consumption (g/day) and baseline BMI (Cordova *et al.*, 2021).

4.1.3. Obesity Results Summary

Both Cohort studies demonstrated an increased risk of overweight and obesity associated with the consumption of UPFs. The NutriNet-Sante´ cohort study by Beslay et al., demonstrated that participants with a higher proportion of UPF in their diet were at a higher risk of overweight and obesity (HR for an absolute increment of 10 in % of UPF in the diet) (Beslay *et al.*, 2020). The EPIC cohort study conducted amongst 9 EU countries, demonstrated that higher consumption of UPF corresponded to significantly higher body weight gain over 5 years, with an additional 15% higher risk of overweight and obese amongst participants of normal weight at baseline, when compared with the highest and lowest quintile of UPF consmption (Cordova *et al.*, 2021).

4.2. Ultra-processed foods and Type 2 Diabetes

UPF consumption are ubiquitous in western diets, with many studies linking the consumption of UPFs to increased risk of all cause mortality and chronic diseases, however data regarding the risk of T2D is in its infancy, these two prospective cohort studies by Llavero-Valero et al., and Srour et al., analyse the associations between the consumption of UPF and risk of Type 2 Diabetes (T2D) (Llavero-Valero *et al.*, 2021), (Srour *et al.*, 2020).

4.2.1. Llavero-Valero et al., 2021

Llavero-Valero *et al.*, conducted a cohort study published in 2021 to evaluate the association between UPF consumption and the risk of T2D. The cohort study utilised 20,060 participants from the SUN project, that were followed up every 2 years, with a median follow up of 12 years. A 136 item food frequency questionaire (FFQ) was used to evaluate consmption. Food was also grouped according to the NOVA classification system and participants grouped into tertiles according to the intake of UPF as a proportion of total energy intake (Llavero-Valero *et al.*, 2021). Figure 4.2.1. shows the inclusion criteria in the form of a flowchart of participants.

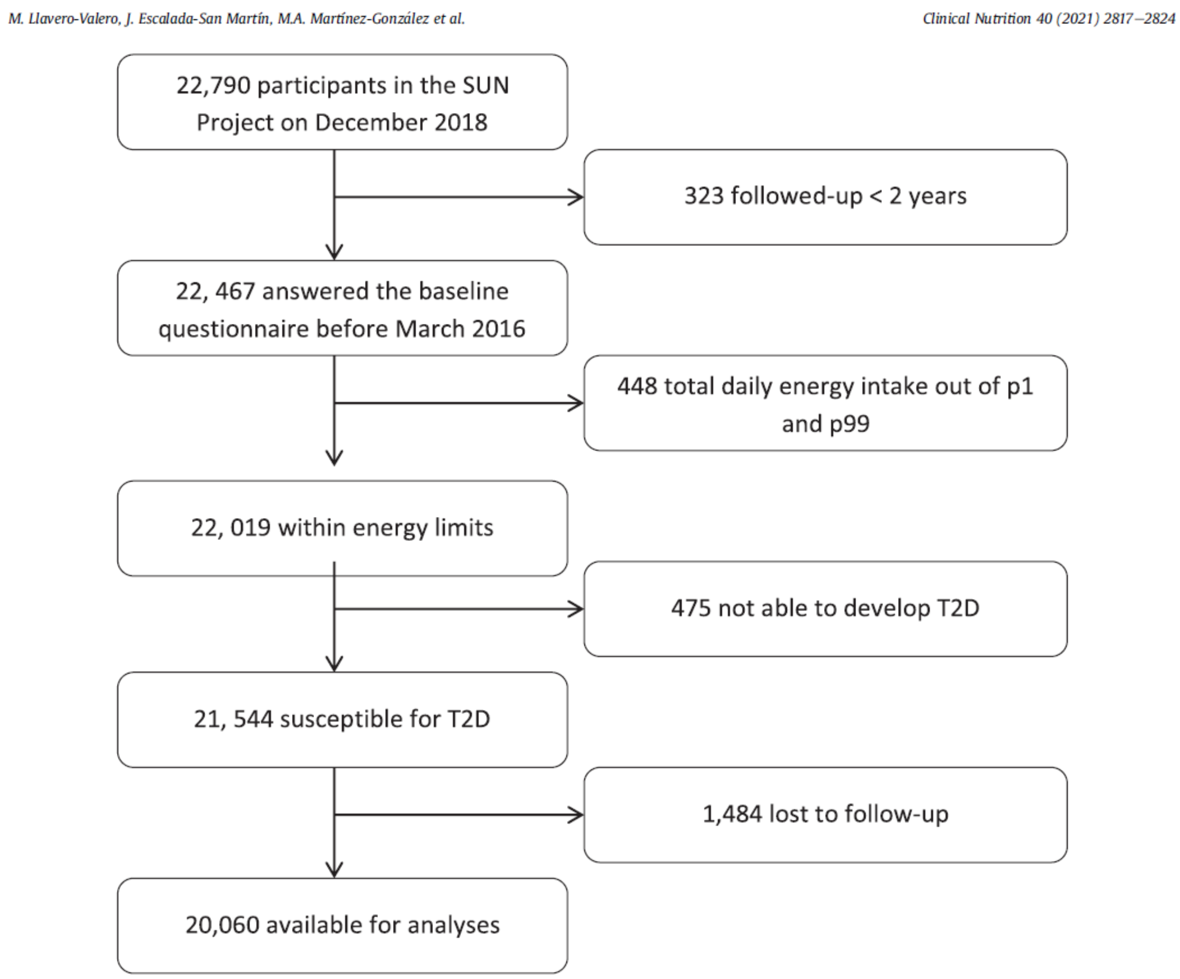

Figure 4.2.1. Shows the flow chart of partipants (Llavero-Valero *et al.*, 2021).

Table 4.2.1. shows the initial baseline characteristics of participants at the start of the study, grouped accoding to tertiles of UPF consumption. A pearson correlation coefficient was calculated between a mediterranean diet and UPF consumption, with p values less than 0.05 considered statistically significant. participants at the highest tertile of UPF consumption, UPF-3, had a higher average BMI than participants in the lowest tertile UPF-1. Other cofactors at baseline meant that partipants at the highest tertile UPF-3 were more likely to be current smokers, more hypertension, depression, cancer and caridiovascular diseases at baseline compared to the UPF-1. Although UPF-3 participants were more likley to have a higher level of univeristy education (Llavero-Valero *et al.*, 2021).

Age and sex-adjusted[a] characteristics of the SUN participants according to tertiles of ultra-processed consumption.

	TERTILES OF UPF			
	UPF1 <214.6 g/d	UPF 2 214.6 g/d – 323.3 g/d	UPF 3 >323.3 g/d	p value[b]
N	6687	6687	6686	
Age[c] (years) (SD)	37.3 (11.8)	37.3 (12.2)	38.2 (13.5)	0.024
Women[c] (%)	59.9	61.0	60.6	0.52
BMI (kg/m^2) (SD)	23.2 (3.3)	23.4 (3.4)	23.7 (3.8)	<0.001
Smoking status (%)				<0.001
Never	50.5	48.2	48.0	
Current	19.1	22.9	24.5	
Former	30.5	28.9	27.5	
Education level (%)				<0.001
Graduate	74.3	73.0	70.5	
Postgraduate	6.6	7.5	8.0	
Doctorate	8.8	10.2	11.3	
Family History of T2D (%)	14.3	14.3	14.5	0.63
Prevalent Hypertension (%)	17.9	19.0	20.8	<0.001
Prevalent cancer (%)	3.2	3.2	3.6	0.61
CVD at baseline (%)	1.4	1.2	1.9	0.004
Hypercholesterolemia (%)	16.6	16.3	16.7	0.09
Prevalent depression (%)	10.3	10.9	12.9	<0.001
Trichopoulou's 9-point score (SD)	4.9 (1.7)	4.0 (1.7)	3.7 (1.7)	<0.001
Energy intake (kcal/day)	2711.0 (756.3)	2309.5 (722.6)	2540.3 (818.2)	<0.001
Physical activity (METs-h/wk) (SD)	26.1 (25.1)	21.8 (20.7)	21.5 (21.4)	<0.001
Snacking (%)	31.1	34.4	38.9	<0.001
Soft drinks (portions/day) (SD)	0.1 (0.1)	0.1 (0.2)	0.4 (0.7)	<0.001
TV hours/day (SD)	1.6 (1.2)	1.6 (1.1)	1.7 (1.2)	<0.001
Protein intake (% of E) (SD)	18.1 (3.3)	18.3 (3.2)	17.5 (3.2)	<0.001
Carbohydrate intake (% of E) (SD)	44.3 (7.8)	42.8 (7.1)	43.5 (7.1)	<0.001
Fat intake (% of E) (SD)	35.7 (7.1)	37.0 (6.2)	37.1 (6.2)	<0.001
SFAs (% of E) (SD)	11.7 (3.3)	12.7 (3.0)	13.1 (3.2)	<0.001
PUFAs (% of E) (SD)	4.9 (1.5)	5.3 (1.5)	5.4 (1.6)	<0.001
MUFAs (% of E) (SD)	15.7 (4.0)	15.8 (3.5)	15.6 (3.4)	0.035

Continuous variables are expressed as means and (standard deviation) and categorical variables as percentages.
E: energy, MUFAs: Monounsaturated fatty acids, PUFAs: Polyunsaturated fatty acids, SFAs: Saturated fatty acids.
[a] Adjusted through inverse probability weighting.
[b] Through ANOVA and Chi-squared test weighted by the inverse probability weighting method.
[c] Not adjusted.

Table 4.2.1. Shows the characteristics of participants according to tertiles of UPF consumption (Llavero-Valero *et al.*, 2021).

Cox proportional hazard models, were created with input of updated food consumption data over the 10 years follow up period. Table 4.2.1.1 shows participants at that highest tertile (3) had a 53% relatively higher hazard of developing T2D, compared to those participants in the lowest tertile (1) (Llavero-Valero *et al.*, 2021).

Cox proportional HRs and 95% CI for incident T2D according to baseline consumption of ultra-processed foods.

	TERTILES			
	1	2	3	P trend
Incident TD2	66	53	56	
Person-years	72 121	72 078	70 950	
Age and sex adjusted	1.00 (reference)	1.09 (0.76–1.57)	1.66 (1.15–2.41)	0.007
Multivariable adjusted[a]	1.00 (reference)	0.99 (0.69–1.43)	1.53 (1.06–2.22)	0.024
Repeated dietary measurements¶				
Age and sex-adjusted	1.00 (reference)	1.14 (0.79–1.64)	1.70 (1.18–2.47)	0.005
Multivariable adjusted[b]	1.00 (reference)	1.07 (0.74–1.54)	1.65 (1.14–2.38)	0.023

[a] Adjusted for sex, age, tertiles of body mass index, educational status, family history of diabetes, smoking status, snacking between meals, 8-item active + sedentary lifestyle score, and following a special diet at baseline. Stratified by decades of age and recruitment period.
[b] Model with repeated measures (updated data at 10 years of follow-up).

Table 4.2.1.1. Shows Cox proportional hazard ratios (HR) and 95% confidence interval (CI) at baseline consumpion of UPF for incident T2D (Llavero-Valero *et al.*, 2021).

The Nelson Aalen curve in figure 4.2.1.1. shows the cumulative hazard for the development of T2D over time across the tertiles of UPF consumption, with the highest tertile UPF-3 associated with a higher incidence of development of T2D.

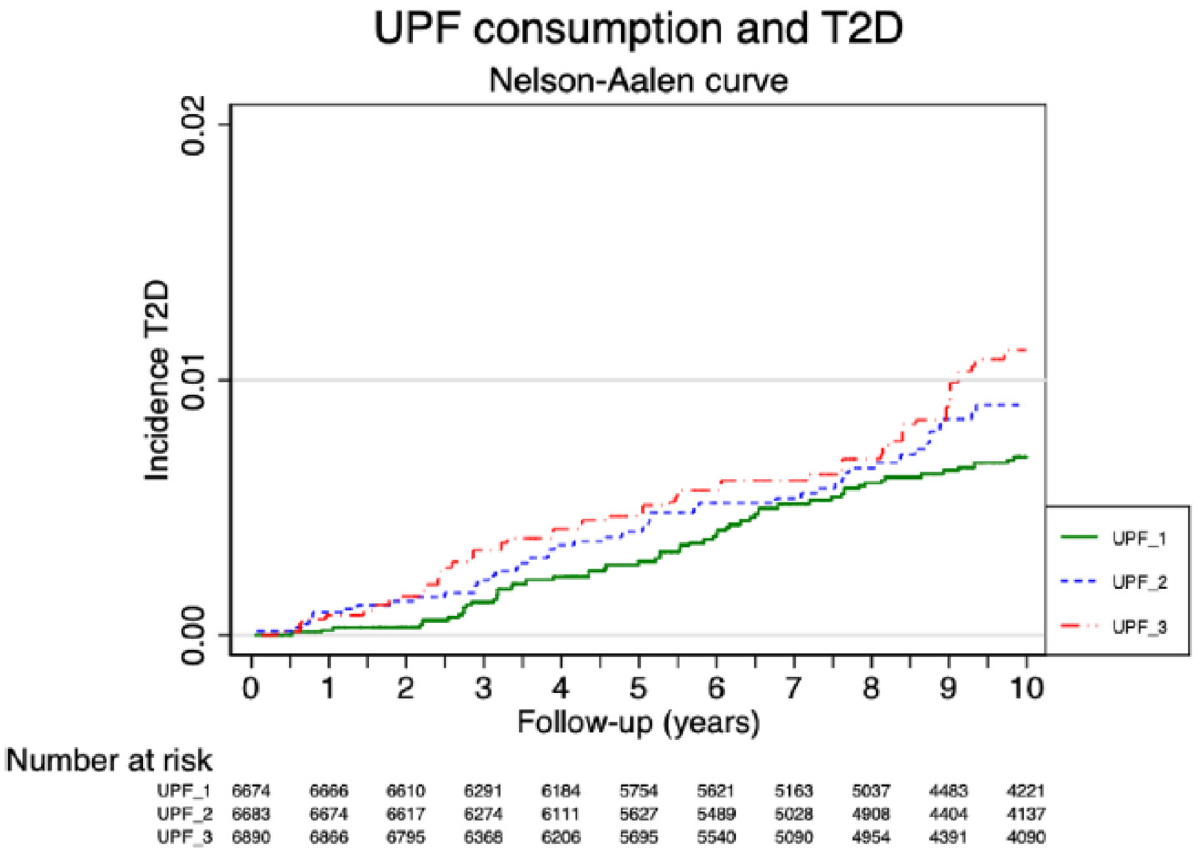

Figure 4.2.1.1. Nelson-Aalen estimate of incidence of T2D according to tertiles of UPF consumption (Llavero-Valero *et al.*, 2021).

The sensitivity analysis in table 4.2.1.2 showed that results remained relatively unchanged between the first and third tertile, when accounting for variable scenarios. Only a slight negative relationship was associated between a Mediterranean diet and UPF consumption (r ¼ _0.16, p ¼ <0.001)., even after adjusting to adherence to a Mediterranean diet (Llavero-Valero *et al.*, 2021).

Sensitivity analysis for incident T2D according to baseline consumption of ultraprocessed food (third tertile versus first tertile).

VARIABLE	N	Incident T2D	HR (95% CI)
Overall[a]	20 060	175	1.53 (1.06–2.22)
Including only women	12 344	43	1.32 (0.59–2.94)
Including only men	7716	132	1.59 (1.03–2.43)
Excluding participants with family history of T2D	17 029	107	1.32 (0.82–2.13)
Willett's energy limits (<800 kcal/d or >4000 kcal/d in men and <500 kcal/d or >3500 kcal/d in women)	18 382	166	1.59 (1.08–2.33)
Energy limits: percentiles 5–95	18 039	159	1.64 (1.11–2.43)
Excluding participants with prevalent hypertension	16 286	66	1.60 (0.88–2.90)
Excluding participants with prevalent cancer	19 414	164	1.67 (1.13–2.46)
Excluding participants with prevalent cardiovascular disease	19 776	163	1.57 (1.06–2.31)
Additionally adjusting for Mediterranean diet	20 060	175	1.50 (1.02–2.21)
Additionally adjusting for difference sugar added intake during the follow-up and daily saccharin intake	2060	175	1.52 (1.05–2.21)
Additionally adjusted for total energy intake	2060	175	1.52 (1.05–2.22)

[a] Adjusted for sex, age, tertiles of body mass index, educational status, family history of diabetes, smoking status, snacking between meals, 8-item active + sedentary lifestyle score, and following a special diet at baseline. Stratified by decades of age and recruitment period.

Table 4.2.1.2. Sensititivity analysis for incident of T2D at baseline consumption of UPF-third tertile vs first tertile (Llavero-Valero *et al.*, 2021).

4.2.2. Srour et al., 2020

The Nutrinet Sante study by Srour et al, involved the completion by participants of 5 questionaires at baseline, each capturing sociodemographic, lifestyle characteristics, anthropometry, health status, physical activity and dietary intake. Furthermore fasting blood samples were also taken at baseline for 19,772 participants. As part of the dietary intake data collection, particpants completed 3 consecutive web based 24-h dietary records at baseline and every 6 weeks, randomly assigned over a 2 week period to include weekdays and weekends. All consumed food and beverage items were grouped according to the NOVA classification system, with primary focus on category 4- Ultra processed foods. For this cohort study, a final population of 104,707 participants were selected from the NutriNet-Santé cohort from 2009-2019. Various inclusion/exclusion criteria were applied to ensure the appropriate cohort group as described in figure 4.2.2. (Srour *et al.*, 2020).

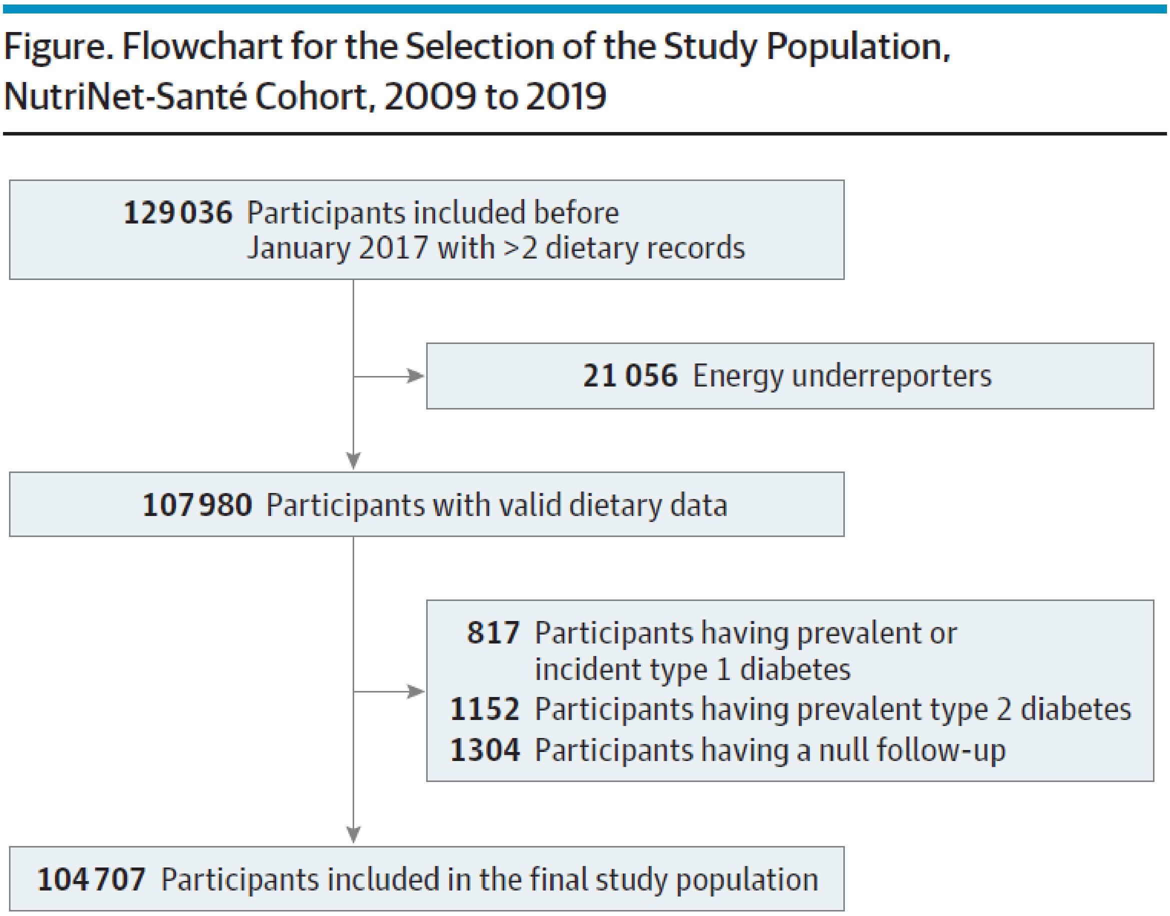

Figure 4.2.2. Flowchart showing selection of study population from 2009-2019 (Srour *et al.*, 2020).

Table 4.2.2 illustrates various characterisitics of participants, showing that overall, the % of UPF were higher in younger participants, obese individuals, current smokers and those with lower activity levels (Srour *et al.*, 2020).

Characteristic	No. (%)	Ultraprocessed Food in the Diet, %	
		Mean (SD)	*P* Value[a]
All	104 707 (100.0)	17.29 (9.81)	
Age at baseline, y (n = 104 707)			
18-44	59 247 (56.58)	19.42 (10.65)	<.001
45-59	28 930 (27.62)	14.77 (8.06)	
≥60	16 530 (15.79)	14.04 (7.20)	
Sex (n = 104 707)			
Men	21 800 (20.82)	17.58 (9.99)	<.001
Women	82 907 (79.18)	17.21 (9.77)	
Educational level (n = 98 024)			
<High school degree	17 952 (17.14)	17.25 (10.34)	<.001
<2 y after high school	17 882 (17.08)	18.96 (10.94)	
≥2 y after high school	62 190 (59.39)	16.97 (9.34)	
Smoking status (n = 104 633)			
Current	17 892 (17.09)	18.95 (11.39)	<.001
Former	34 217 (32.68)	16.00 (8.92)	
Never	52 524 (50.16)	17.56 (9.68)	
IPAQ physical activity level (n = 90 146)			
High	29 382 (28.06)	16.09 (9.30)	<.001
Moderate	38 788 (37.04)	17.06 (9.43)	
Low	21 976 (20.99)	18.69 (10.37)	
Body mass index[b] (n = 101 823)			
<25	72 357 (69.10)	17.14 (9.68)	<.001
25-29.9	21 209 (20.25)	17.02 (9.64)	
≥30	8257 (7.88)	18.86 (11.13)	

Table 4.2.2. Shows the proportion in weight of UPFs in the diet of participants (2009-19) (Srour *et al.*, 2020).

A higher FSAm-NPS DI score, which refers to the food standards agency nutrient profiling system dietary index, was associated with a higher consmption of UPF. A higher FSAm-NPS DI score reflects poorer nutritional quality, meaning higher intakes of energy, saturated fatty acids, sodium, sugary drinks, red and processed meats, coupled with lower consumption of fibre, whole grains, nuts, fruits and vegetables. The P values were obtained from linear regression models adjusted for sex, age, and energy intake. (Srour *et al.*, 2020).

Nutritional Factor	Mean (SD)	Proportion of Ultraprocessed Food in the Diet	
		Change in Nutritional Factor, β (SE)[a]	P Value[b]
FSAm-NPS dietary index	6.59 (2.46)	0.62 (0.01)	<.001
Energy intake without alcohol, Kcal/d	1847.14 (450.86)	29.95 (1.36)	<.001
Alcohol intake, g/1000 kcal/d	3.91 (5.53)	−0.50 (0.02)	<.001
Sodium intake, mg/1000 kcal/d	1479.10 (369.21)	6.97 (1.20)	<.001
Saturated fatty acids, g/1000 kcal/d	17.78 (4.02)	0.31 (0.01)	<.001
Fiber, g/1000 kcal/d	10.72 (3.57)	-0.78 (0.01)	<.001
Sugar, g/1000 kcal/d	50.39 (13.45)	1.32 (0.04)	<.001
Whole grains, g/1000 kcal/d	18.96 (24.36)	-3.14 (0.08)	<.001
Yogurt, g/1000 kcal/d	33.68 (42.75)	-2.58 (0.14)	<.001
Sugary drinks, g/1000 kcal/d	24.94 (53.64)	25.22 (0.15)	<.001
Red and processed meat, g/1000 kcal/d	40.01 (27.34)	1.68 (0.09)	<.001
Nuts, g/1000 kcal/d	2.52 (5.40)	-0.49 (0.02)	<.001
Fruits and vegetables, g/1000 kcal/d	228.93 (129.04)	-37.54 (0.37)	<.001

Table 4.2.2.1. Shows the associations between % of UPF in the diet and nutritional factors (2009-19) (Srour *et al.*, 2020).

Cause specific multiadjusted Cox proportional hazard models were used to analyse the associations between the weight proportion of UPF consumption and the risk of T2D in the 104,707 patients from 2009-19. Model 1 represents a cause specific Cox proportonal hazard model, adjusted for age, sex, educational level, baseline BMI, physical activity, smoking status, alcohol intake, number of 24-h dietary records, energy/calorie intake, FSAm-NPS DI score, and family history of T2D. Model 2- represents model 1 unadjusted for FSAm-NPS DI but adjusted for saturated fatty acid, sodium, sugar, and dietary fibre intake. Model 3 represents model 1 unadjusted for FSAm-NPS DI but adjusted for sugary dirnks, red and processed meat, whole grains, nuts, yoghurt and fruit and vegetables. Model 4 represents model 1 with the addition of baseline dyslipidemia and hypertension including treatment for both, and lastly model 5 was model 1 with the addition of % weight change among particpants with available anthropometric data. Development of T2D or death were treated as competing events for puprose of analysis, and the continuous participant follow up ended at the date of last questionaire completions (January 9th 2019), date of T2D diagnosis or death, whichever occurred first. All tests were two sided and a P value of <0.05 was considered statistically significant . UPF intake was associated with an increased risk of T2D (Model 1: HR for a 10-point increment in % of UPF, 1.15; 95% CI, 1.06-1.25; *P* = .001) with associations remaining significant after further adjustments of for model 2,3,4, and 5. (Srour *et al.*, 2020).

Variable	Absolute Increment of 10% of UPF in the Diet, HR (95% CI)	P Value
No. of cases/total	821/104 707	
Model 1	1.15 (1.06-1.25)	.001
Model 2	1.19 (1.09-1.30)	<.001
Model 3	1.14 (1.04-1.25)	.005
Model 4	1.13 (1.03-1.23)	.006
Model 5[b]	1.13 (1.01-1.27)	.04

Table 4.2.2.2. Shows the associations between the proportion in weight of UPF and the risk of T2D (2009-19) (Srour *et al.*, 2020).

4.2.3. Type 2 Diabetes Results Summary

Both Cohort studies demonstrated an increased risk of T2D associated with the consumption of UPFs. Llavero-Valero *et al.*, demonstrated that a higher consumption of UPFs in a highly educated, mediterranean cohort group, with a low initial risk of T2D, was associated with increased risk of new onset of T2D, even after adjusting for potential cofactors (Llavero-Valero *et al.*, 2021). Srour *et al.*, showed that UPF intake was associated with an increased risk of T2D accounting for a 10 point increment in % of UPF consumption. Risk remained significant after adjustments of covariables (Srour *et al.*, 2020).

4.3. Ultra-Processed Foods and Cardiovascular Disease

With the increased consumption of UPF globally, cardiovascular diseases (CD) have also increased, and are now the main cause of death worldwide, representing a third of all deaths globally. dietary factors are the largest contributing factor to CD mortality in Europe (Srour *et al.*, 2019). Both observational studies, assess the risk of CD in association with UPF consumption.

4.3.1. Srour et al., 2019

The Nutrinet Sante study has been used as part of a prospective cohort study to investigate the associations between consumption of UPF and overall risk of cardiovascular diseases. Dietary intakes of 105,159 adult (>18 years old) participants were collected using 24-h dietary records. The process involves the completion by participants of 5 questionaires at baseline, each capturing sociodemographic, lifestyle characteristics, anthropometry, health status, physical activity and dietary intake. All recorded food items were categorised according to the four food groups of the NOVA classification system, with primary focus on category 4- Ultra processed foods. Multivariable Cox proportional hazard models, adjusted for known cofounders are used to assess outcome. For this cohort study, a final population of 105,159 participants were selected from the NutriNet-Santé cohort from 2009-2018. Various inclusion/exclusion criteria were applied to ensure the appropriate cohort group as described in figure 4.3.1 (Srour *et al.*, 2019).

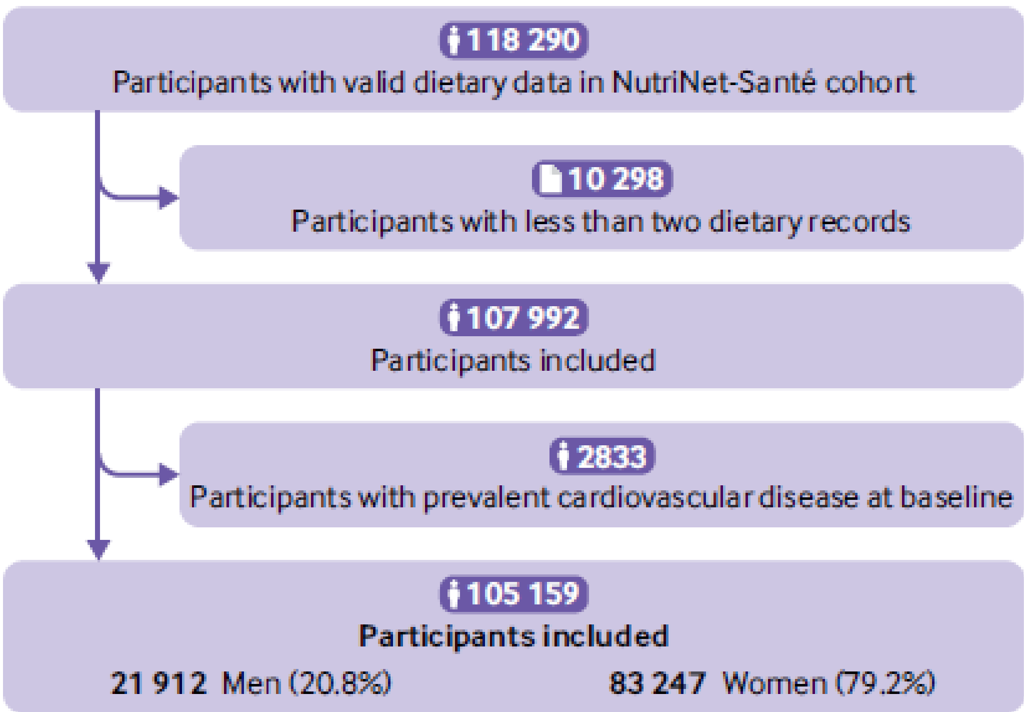

Figure 4.3.1. Flowchart showing selection of study population from 2009-2018 (Srour *et al.*, 2019).

According to the baseline characteristics, participants at the highest quarter, hence highest intake of UPF, were younger, current smokers, less highly educated, less physical activity levels and had less family history of CD. This group also had a higher BMI and higher intakes of energy, carbohydrates, lipids and sodium, with lower intakes of dietary fibre, fruit & vegetables, alcohol, and lower prevalence of metabolic disease. (Srour *et al.*, 2019).

Characteristics	All participants	Quarters of ultra-processed food consumption†				P value‡
		First (n=26 396) (low intake)	Second (n=26 418)	Third (n=26 326)	Fourth (n=26 019) (high intake)	
Mean (SD) age (years)	42.7 (14.5)	47.6 (13.6)	44.8 (14.1)	41.8 (14.4)	36.4 (13.5)	<0.001
Sex:						
Women	83 247 (79.2)	20 890 (79.1)	20 905 (79.1)	20 845 (79.2)	20 607 (79.2)	
Men	21 912 (20.8)	5506 (20.9)	5513 (20.9)	5481 (20.8)	5412 (20.8)	
Mean (SD) body mass index	23.6 (4.4)	23.6 (4.2)	23.6 (4.2)	23.6 (4.4)	23.8 (4.8)	<0.001
Family history of CVD§	28 000 (26.6)	8431 (31.9)	7548 (28.6)	6655 (25.3)	5366 (20.6)	<0.001
Educational level:						<0.001
<High school degree	18 152 (17.3)	4797 (18.2)	4596 (17.4)	4380 (16.6)	4379 (16.8)	
<2 years after high school	17 971 (17.1)	3896 (14.8)	4006 (15.2)	4527 (17.2)	5542 (21.3)	
≥2 years after high school	69 036 (65.6)	17 703 (67.1)	17 816 (67.4)	17 419 (66.2)	16 098 (61.9)	
Smoking status:						<0.001
Current	17 946 (17.1)	4039 (15.3)	4077 (15.4)	4346 (16.5)	5484 (21.1)	
Former	34 421 (32.7)	10 022 (38.0)	9131 (34.6)	8321 (31.6)	6947 (26.7)	
Never	52792 (50.2)	12 335 (46.7)	13 210 (50.0)	13 659 (51.9)	13 588 (52.2)	
Physical activity level¶:						<0.001
High	29 443 (28.0)	8776 (33.2)	7555 (28.6)	7146 (27.1)	5966 (22.9)	
Moderate	38 926 (37.0)	9695 (36.7)	10 167 (38.5)	9817 (37.3)	9247 (35.5)	
Low	22 150 (21.1)	4468 (16.9)	5302 (20.1)	5804 (22.0)	6576 (25.3)	
Mean (SD) intakes:						
Energy (kJ/day)	7949.9 (1959.2)	7679.5 (1871.0)	7970.0 (1877.2)	8076.6 (1953.7)	8075.3 (2100.4)	<0.001
Alcohol (g/day)	7.8 (11.8)	9.0 (13.1)	8.5 (11.9)	7.5 (11.1)	5.9 (10.7)	<0.001
Total lipid (g/day)	81.6 (25.3)	77.2 (24.1)	81.4 (24.0)	83.3 (25.0)	84.4 (27.3)	<0.001
Carbohydrate (g/day)	198.1 (57.5)	188.6 (57.4)	197.4 (54.6)	201.9 (56.3)	204.7 (60.2)	<0.001
Sodium (mg/day)	2717.2 (885.6)	2601.1 (867.6)	2749.9 (862.6)	2782.7 (876.9)	2735.3 (923.7)	<0.001
Fruit and vegetables (g/day)	407.1 (221.6)	505.2 (249.9)	434.1 (201.1)	385.2 (192.3)	302.3 (186.5)	<0.001
Total dietary fibre (g/day)	19.5 (7.2)	21.0 (7.7)	20.1 (6.9)	19.3 (6.8)	17.4 (6.9)	<0.001
Ultra-processed food (%)	17.4 (9.9)	7.5 (2.3)	13.0 (1.4)	18.3 (1.8)	30.8 (9.1)	-
Prevalent morbidity:						
Type 2 diabetes	1384 (1.3)	462 (1.7)	366 (1.4)	320 (1.2)	236 (0.9)	<0.001
Hypertension	8279 (7.9)	2613 (9.9)	2277 (8.6)	1993 (7.6)	1396 (5.4)	<0.001
Dyslipidemia	8038 (7.6)	2391 (9.1)	2193 (8.3)	1984 (7.5)	1470 (5.6)	<0.001
Hypertriglyceridemia	1441 (1.4)	384 (1.4)	380 (1.4)	355 (1.3)	322 (1.2)	0.1

IPAQ=International Physical Activity Questionnaire.
*For all covariates except physical activity, a low proportion of values were missing (0-5%); the latter were replaced by the modal value among the population study: ≥2 years of higher education for educational level and 22.9 for body mass index.
†Quarters of proportion of ultra-processed food intake in total quantity of food consumed. Sex specific cut-offs for quarters of ultra-processed proportions were 0.108, 0.156, and 0.220 in men and 0.106, 0.154, and 0.218 in women.
‡Analysis of variance or χ^2 test where appropriate.
§Among first degree relatives.
¶Available for 90 519 participants. They were categorised into the high, moderate, and low categories according to IPAQ guidelines.[48]

Table 4.3.1. Shows the baseline characteristics of the study participants grouped according to quarters of UPF consumption (Srour *et al.*, 2019).

The mean % contribution of UPFs in the overall diet was 17.6% and 17.3% for men and women respectively. The main food groups that contributed to the UPF intake were sugary products (ice-cream, confectionaries, pastries, sweetened dairy desserts), followed by UPF fruit and vegetables (instant powder vegetable soups and broths, vegetable nuggets, fruit based desserts) and beverages (carbonated beverages and artificially sweetened

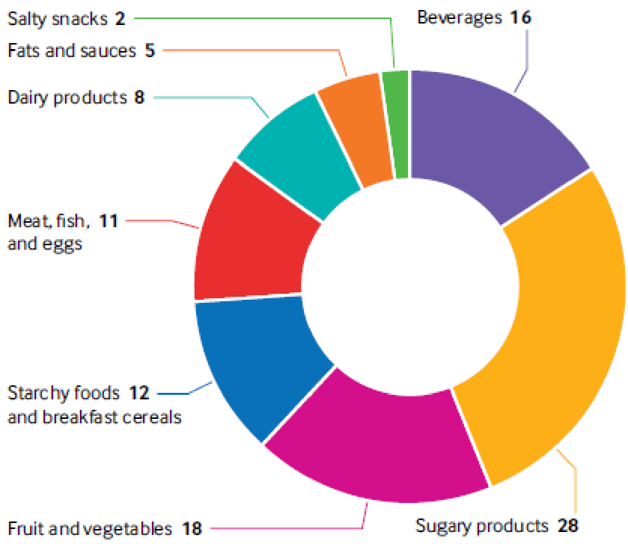

Figure 4.3.1.1. % contribution of each food group of UPF (Srour *et al.*, 2019).

non carbonated beverages), starchy foods and breakfast cereals (pre-packaged bread, industrial dough, ready to eat pasta and potato dishes) and processed meat and fish. Ultra processed beverages, fats, sauces, and meat were associatied with an increase in risk of coronary heart diseases, while ultra-processed beverages, sugary products, and salty snacks increased the risk of cerebrovascular disease. Contrastingly, no significant correlation was found with these food groups in their un-processed form and an increase in risk for CD, with the exception of salty snacks. (Srour *et al.*, 2019).

Multivariable Cox proportional hazard models were used to analyse the associations between the consumption of UPF and the risk of CD in the 105,159 patients in the NutriNet-Santé cohort, from 2009-18. Model 0 is a Cox proportional hazard model adjusted for age and sex. Model 1 is a multivariable Cox proportional hazard model adjusted for age, sex, energy/calorie intake, educational level, baseline BMI, physical activity, smoking status, alcohol intake, number of 24-h dietary records, and family history of CD. A median follow up of 5.2 years, showed an increased risk of overall CD, coronary heart diseases and cerebrovascular diseases. Model 2 represents model 1 in addition to saturated fatty acid, sodium and sugar intake. Model 3 represents model 1 plus a healthy dietary pattern (calculated by factor analysis). Model 4 represents model 1 including intakes of sugary products, red and processed meat, salty snacks, beverages, fats and sauces. Model 5 represents model 1 unadjusted for BMI, and lastly model 6 represents model 1, including baseline T2D, dyslipidemia, hypertension and hypertriglyceridemia including treatment for the conditions. These further adjustment to model 1 to account for several inidcators and nutritional quality of the diet, didn't significantly affect findings, and still supported the increased risk of cardiovascular diseases with consumption of ultra-processed foods and beverages. Furthermore, secondary analyses were performed to analyse the associations between minimally processed foods in the diet and the risk of CD. This was carried out using the multivariate Cox models, adjusted for model 1 covariates. All tests were 2 sided with a P value of <0.05 considered statistically significant. Results consistently showed that unprocessed/minimally processed foods were linked to lower risks of overall CD, 0.91 (0.86 to 0.97); P<0.001 for overall CD, hazard ratio 0.91 (95% confidence interval 0.84 to 0.99); P=0.04 for coronary heart diseases and 0.91 (0.84 to 0.98); P=0.02 for cerebrovascular diseases), (Srour *et al.*, 2019).

Models by disease type	Quarters of ultra-processed food consumption†						
	First (low intake)	Second	Third	Four (high intake)	P trend	Continuous‡	P value
All cardiovascular diseases							
No of cases/non-cases	446/25 950	410/26 008	330/25 996	223/25796		1409/103750	
Model 0	1	1.06 (0.93 to 1.22)	1.08 (0.93 to 1.24)	1.25 (1.06 to 1.47)	0.01	1.13 (1.06 to 1.21)	<0.001
Model 1	1	1.04 (0.91 to 1.19)	1.07 (0.93 to 1.23)	1.23 (1.04 to 1.45)	0.02	1.12 (1.05 to 1.20)	<0.001
Model 2	1	.05 (0.92 to 1.20)	1.08 (0.93 to 1.25)	1.25 (1.05 to 1.47)	0.02	1.13 (1.05 to 1.20)	<0.001
Model 3	1	1.03 (0.90 to 1.18)	1.05 (0.91 to 1.22)	1.20 (1.01 to 1.42)	0.05	1.11 (1.03 to 1.19)	0.003
Model 4	1	1.03 (0.90 to 1.18)	1.06 (0.90 to 1.23)	1.21 (1.02 to 1.45)	0.05	1.12 (1.04 to 1.20)	0.002
Model 5	1	1.05 (0.92 to 1.20)	1.08 (0.93 to 1.24)	1.26 (1.07 to 1.48)	0.01	1.13 (1.06 to 1.21)	<0.001
Model 6	1	1.04 (0.91 to 1.19)	1.06 (0.92 to 1.23)	1.23 (1.04 to 1.45)	0.03	1.12 (1.05 to 1.20)	0.001
Coronary heart diseases§							
No of cases/non-cases	208/26 188	194/26 224	166/26 160	97/25 922		665/104 494	
Model 0	1	1.08 (0.89 to 1.31)	1.19 (0.97 to 1.46)	1.23 (0.96 to 1.57)	0.04	1.15 (1.04 to 1.26)	0.006
Model 1	1	1.07 (0.87 to 1.30)	1.19 (0.97 to 1.46)	1 20 (0.93 to 1.53)	0.07	1.13 (1.02 to 1.24)	0.02
Model 2	1	1.07 (0.87 to 1.30)	1.20 (0.97 to 1.47)	1.22 (0.95 to 1.56)	0.05	1.14 (1.03 to 1.26)	0.01
Model 3	1	1.05 (0.86 to 1.28)	1.17 (0.95 to 1.44)	1.16 (0.90 to 1.49)	0.1	1.11 (1.00 to 1.23)	0.04
Model 4	1	1.05 (0.86 to 1.28)	1.17 (0.95 to 1.46)	1.18 (0.91 to 1.53)	0.1	1.12 (1.01 to 1.24)	0.03
Model 5	1	1.07 (0.88 to 1.31)	1.20 (0.97 to 1.47)	1.22 (0.96 to 1.57)	0.05	1.14 (1.03 to 1.26)	0.009
Model 6	1	1.06 (0.87 to 1.29)	1.18 (0.96 to 1.45)	1.18 (0.93 to 1.52)	0.08	1.12 (1.02 to 1.24)	0.02
Cerebrovascular diseases¶							
No of cases/non-cases	267/26 129	238/26 180	188/26 138	136/25 883		829/104 330	
Model 0	1	1.03 (0.87 to 1.23)	1.01 (0.84 to 1.22)	1.24 (1.00 to 1.53)	0.1	1.11 (1.02 to 1.21)	0.02
Model 1	1	1.01 (0.85 to 1.21)	0.99 (0.82 to 1.20)	1.24 (1.00 to 1.53)	0.1	1.11 (1.01 to 1.21)	0.02
Model 2	1	1.02 (0.86 to 1.22)	1.01 (0.84 to 1.22)	1.25 (1.01 to 1.55)	0.1	1.12 (1.02 to 1.22)	0.02
Model 3	1	1.00 (0.84 to 1.20)	0.99 (0.81 to 1.19)	1.21 (0.98 to 1.51)	0.2	1.10 (1.00 to 1.20)	0.04
Model 4	1	1.01 (0.84 to 1.21)	1.00 (0.82 to 1.21)	1.23 (0.98 to 1.54)	0.2	1.11 (1.01 to 1.22)	0.03
Model 5	1	1.02 (0.85 to 1.21)	1.00 (0.83 to 1.21)	1.26 (1.01 to 1.55)	0.1	1.11 (1.02 to 1.22)	0.01
Model 6	1	1.01 (0.85 to 1.21)	0.99 (0.82 to 1.20)	1.23 (1.00 to 1.53)	0.1	1.11 (1.01 to 1.21)	0.02

Mean follow-up times for overall cardiovascular, coronary heart, and cerebrovascular diseases were all equal to 5.2 years. Person years were, respectively, 518 208, 520 319, and 520023.
*Model 0 is an age (timescale) and sex-adjusted Cox proportional hazard model.
Model 1 is a multivariable Cox proportional hazard model adjusted for age (timescale), sex, energy intake, number of 24 hour dietary records, smoking status, educational level, physical activity, body mass index, alcohol intake, and family history of cardiovascular disease. Model 2=model 1+saturated fatty acid intake, sodium intake, sugar intake. Model 3=model 1+healthy dietary pattern (derived by factor analysis). Model 4=model 1+intakes of sugary products, red and processed meat, salty snacks, beverages, and fats and sauces. Model 5=model 1 without adjustment for body mass index. Model 6=model 1+baseline prevalent type 2 diabetes, dyslipidemia, hypertension, and hypertriglyceridemia (yes or no) as well as treatments for these conditions (yes or no).
†Sex specific cut-offs for quarters of ultra-processed proportions were 0.108, 0.156, and 0.220 in men and 0.106, 0.154, and 0.218 in women.
‡Hazard ratio for an absolute increment of 10 in percentage of ultra-processed foods in diet.
§Includes myocardial infarctions, angioplasties, and acute coronary syndromes.
¶Includes strokes and transient ischaemic attacks.

Table 4.3.1.1. Shows the associations between intake of UPF and overall cardiovascular, coronary and cerebrovacular diseases (2009-18) (Srour *et al.*, 2019).

The Cox proportional hazard models, used age as a primary timescale to evaluate the proportion of UPF in the diet and incidence of CD. 95% confidence intervals (CI) and Hazard ratios were computed, corresponding to a ratio of instantaneous risks for an absolute increment of 10 in the percentage of UPF in the diet. For models based on quarters of the % of UPF in the diet, P values for linear trends were obtained by coding quarters of UPF as and ordinal variable (1,2,3,4). The assumption of linearity between consumption of UPF and risk of CD were verified using restricted cubic spline functions (Figure 4.3.1.2.). Participants contributed person time, until diaganosis of CD, date of last completed questionaire, 11 January 2018, or date of death, whichever came first. Statistically significant associations were observed for overall risk of CD with intake of UPF (Srour *et al.*, 2019).

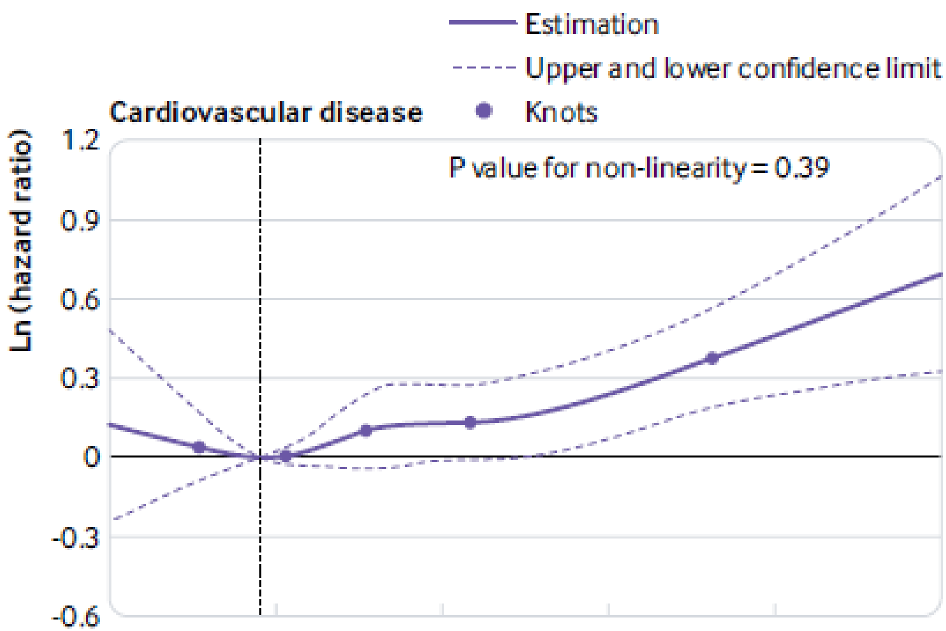

Figure 4.3.1.2. Shows a spline plot for linearity assumption of relationship between proportion of UPF and risk of overall cardiovascular disease (Srour *et al.*, 2019).

4.3.2. Suksatan et al., 2022

Suksatan et al., performed a systematic review and dose- response meta-analysis of observational cohort studies to assess the association between UPF consumption and adult mortality risk, to include cardiovascular diseases. For this assessment the focus will lie on the association of UPF consumption on cardiovascular risk for EU based studies. 12,137 studies were identified through searches via database, with the removal of duplicates yielded 10,092 studies. With the application of the inclusion criteria 7 cohort studies from 4 countries (207,291 participants) were systematically reviewed for the purposes of the dose response meta-analysis (Figure 4.3.2.) (Suksatan et al., 2022).

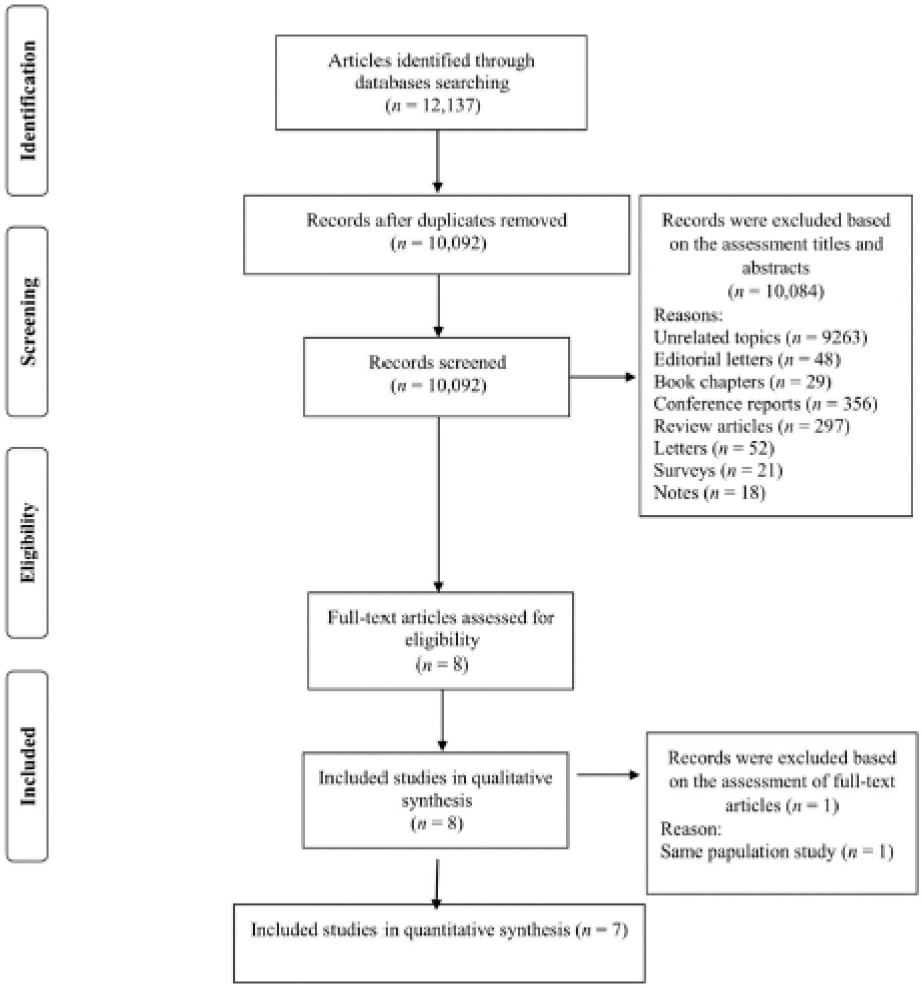

Figure 4.3.2. Flowchart of study selection (Suksatan et al., 2022).

The method used to assess the consumption of UPF, was either by proportion of total energy, total weight, or frequency of UPF intake. All studies adjusted for various variable, such as age, sex, BMI, alcohol intake, smoking status education level, and various existing/ historical/ comorbidities such as cancer, T2D, CD as seen in table 4.3.2. (Suksatan et al., 2022).

Author (Year, Location)	Study Design/Follow-Up (Years)/Source of Data/Health Status	Population/Age/BMI/(Women/Men)	Ultra-Processed Food Assessment Method	Outcomes	Adjusted Variables	Quality Score
Blanco-Rojo et al. (2019, Spain)	Prospective cohort/ 7.7 years/the Study on Nutrition and Cardiovascular Risk in Spain (ENRICA)/ healthy subjects	N = 11,898/age 55 ± 12 years/BMI = NR (6008/5890)	24 h recalls/NOVA food classification/frequency of ultra-processed food intake	Adults in the highest quartile versus the lowest of UPF consumption had higher risk of mortality (HR: 1.44; 95% CI: 1.01, 2.07).	Sex and age, educational level, living alone, smoking status, former drinker, physical activity index, time watching television, time devoted to other sedentary activities, the number of medications per day, and specific chronic conditions diagnosed by a physician	+8/10
Rico-Campà et al. (2019, Spain)	Prospective cohort/ 15 years/the Seguimiento Universidad de Navarra (SUN) project/ healthy subjects	N = 19,899/age = 37.6 ± 12.3 years/ BMI = 23.5 ± 3.5/(12,113/7786)	FFQ/NOVA food classification/frequency of ultra-processed food intake	UPF consumption had a higher hazard for all-cause mortality compared with those in the lowest quarter (HR = 1.62: 95% CI: 1.13 to 2.33).	Age, sex, marital status, physical activity, smoking status, snacking, special diet at baseline, body mass index, total energy intake, alcohol consumption, family history of cardiovascular disease, diabetes at baseline, hypertension at baseline, self-reported hypercholesterolemia at baseline, CVD at baseline, cancer at baseline, depression at baseline, education level and lifelong smoking stratified by recruitment period, deciles of age, sedentary index, and television viewing	+9/10
Kim et al. (2019, USA)	Prospective cohort/ 19 years/the Third National Health and Nutrition Examination Survey (NHANES III, 1988–1994)/healthy subjects	N = 11,898/age = 42 ± 0.5 years/ BMI = 26.2 ± 0.2/(6067/5830)	FFQ/NOVA food classification/frequency of ultra-processed food intake	Higher frequency of ultra-processed food intake was associated with higher risk of all-cause mortality in a representative sample of US adults (HR = 1.31: 95% CI: 1.09 to 1.58).	Age, sex, race/ethnicity, total energy intake, poverty level, education level, smoking status, physical activity, alcohol intake, BMI, hypertension status, total cholesterol, and estimated glomerular filtration rate	+9/10
Bonaccio et al. (2021, Italy)	Prospective cohort/ 8.2 years/Moli-sani Study (2005–2010, Italy)/ healthy subjects	N = 22,475/age = 55 ± 12/ BMI = 28.2 ± 4.7/years/(10,702/11,733)	FFQ/NOVA food classification/proportion of UPF in the total weight of food and beverages consumed (g/day)	Adults in the highest quartile of UPF consumption had higher risk of CVD mortality (HR: 1.58; 95% CI: 1.23, 2.03).	Sex, age, energy intake, educational level, housing tenure, smoking, BMI, leisure time physical activity, history of cancer, CVDs, diabetes, hypertension, hyperlipidemia, and residence Mediterranean Diet Score	+9/10
Zhong et al. (2021, USA)	Prospective cohort/ 13.5 years/the Prostate, Lung, Colorectal, and Ovarian (PLCO)/ healthy subjects	N = 91,891/age = >35 years/ BMI = NR/(NR/NR)	FFQ/NOVA food classification/frequency of ultra-processed food intake	Participants in the highest vs. the lowest quintiles of ultra-processed food consumption had higher risks of death from cardiovascular disease (HR = 1.50; 95% CI: 1.36, 1.64) and heart disease (HR: 1.68; 95% CI: 1.50, 1.87) but not cerebrovascular disease (HR = 0.94; 95% CI: 0.76, 1.17).	Age, sex, race, educational, marital status, study center, aspirin use, history of hypertension, history of diabetes, smoking status, alcohol consumption, body mass index, physical activity, and energy intake from diet	+9/10
Schnabel et al. (2021, France)	Prospective cohort/ 2 years/the NutriNet-Santé Study/healthy subjects	N = 44 551/age = 56.7 ± 7.5 years/ BMI = NR/(32,459/12,092)	24-h recalls/NOVA food classification/proportion of total energy	An increase in the proportion of UPF consumed was associated with a higher risk of all-cause mortality (HR = 1.14; 95% CI: 1.04, 1.27).	Sex, age, income level, education level, marital status, residence, BMI, physical activity level, smoking status, energy intake, alcohol intake, season of food records, first-degree family history of cancer or cardiovascular diseases, and number of food records	+8/10
Romero Ferreiro et al. (2021, Spain)	Prospective cohort/ 27 years/the multicenter study Diet and Risk of Cardiovascular Diseases (CVDs) in Spain (DRECE)/healthy subjects	N = 4679/age = 35.5 ± 15.6 years/ BMI = 24.2 ± 5/(2391/2288)	FFQ/NOVA food classification/proportion of total energy	For every 10% of the energy intake from UPF consumption, an increase of 15% in the hazard of all-cause mortality was observed (HR, 1.15; 95% CI, 1.03–1.27).	Age, sex, BMI, physical activity, alcohol intake, smoking status and total energy intake, family history of CVDs, history of diabetes, hypertension, anger, myocardial infarction, and atherosclerosis	+9/10

UPF: ultra-processed foods, CVDs: cardiovascular diseases, HR: hazard ratio, FFQ: food frequency questionnaire, BMI: body mass index, NR: not reported.

Table 4.3.2. Characterisitics on included studies (Suksatan et al., 2022).

The results shown below in Figure 4.3.2.1. showed a significant association of UPF foods and their effects on mortality. Studies covered included the spanish, french, Italian population as well as also the USA. The study specific hazard ratio (HR) and applied 95% confidence interval (CI) are shown as black squares and horizaontal lines in Figure 4.3.2. The area of grey square surrounding the black square is proportional to the the specific study weight to the overall meta-analysis. The centre of the diamond and the vertical dashed line running down the image, represent the pooled HR, with the width representing the pooled 95% CI For all studies. Results showed that UPF consumption was associated with an increased risk of CD caused mortality (HR= 1.5; 95% CI: 1.37, 1.63: 1^2= 0.0% P<0.001) (Suksatan et al., 2022).

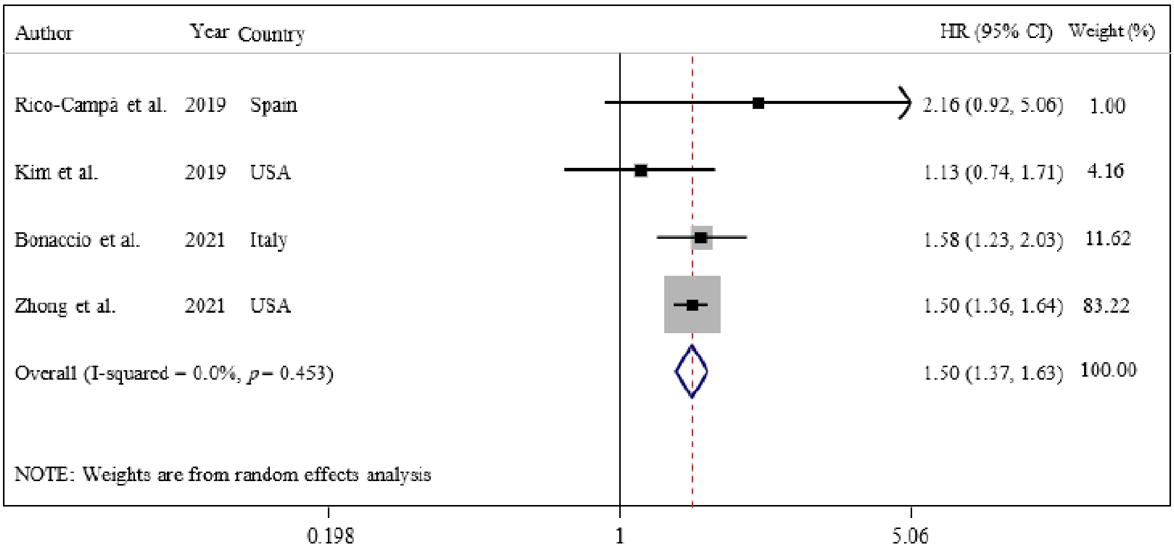

Figure 4.3.2.1. Forest plot, showing OR and 95 CI of pooled results from random effects modeld to demonstrate the relationship between UPF consumption and mortality risk, caused by cardiovascular disease (CD) (Suksatan et al., 2022).

Particpants in all studies were arranged into subgroups and analysed. For all regions including the European region there were significant associations between UPF consumption and CD caused mortality, with the sub-group analysis highlighting a key finding that UPF consumption was significantly associated with an enhanced risk of CD caused mortality among participants with a BMI >25 (HR= 1.4; 95% CI:1.02, 1.92; I^2= 44.8%; p= 0.039), but not less than 25 (Suksatan et al., 2022).

Subgrouped by	No. of Effect Size	HR [1]	95% CI	*p*-Value	Heterogeneity		
					p-Values for within Groups	I^2 (%)	*p*-Values for between Groups
CVDs-cause mortality							
Body mass index							
Less than 25	1	2.16	0.92 to 5.07	0.077	<0.001	0.0	0.175
More than 25	2	1.40	1.02 to 1.92	0.039	0.175	44.8	
Follow-up duration							
Less than 10 years	1	1.58	1.23 to 2.03	<0.001	<0.001	0.0	0.064
More than 10 years	3	1.22	1.08 to 1.37	0.001	0.397	0.0	
Region							
America	2	1.20	1.07 to 1.35	0.002	0.753	0.0	0.030
Europe	2	1.62	1.27 to 2.06	<0.001	0.496	0.0	

[1] Calculated by random-effects model.

Table 4.3.2.1. Table summarising subgroup analysis to evaluate the association between UPF consumption and risk of mortality caused by CD (Suksatan et al., 2022).

Dose response associations, revealed a positive linear relationship between the consumption of UPF and CD cause mortality (P nonlinearity= 0.868, P dose-response= p <0.001) (Suksatan et al., 2022).

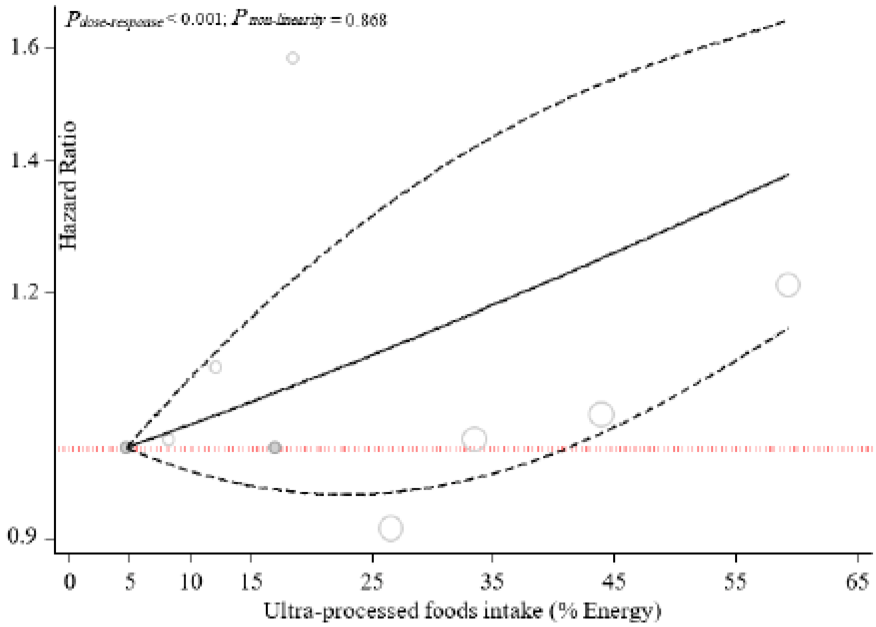

Figure 4.3.2.2. Dose response relationship between UPF consumption and risk of maortality caused by CD (Suksatan et al., 2022).

Study specific HR and 95% CI are shown as black squares and horizontal lines in figure Figure 4.3.2.3. the grey surrounding square is propotional to the specific-study weight to the overall meta-analysis. The centre of the diamond and vertically dashed line represent the pooled HR, with the width representing the pooled 95% CI. Findings showed that with a 10% increase in UPF consumotion as a function of daily calorie intake, was associated with a 15% higher risk of all cause mortality (OR= 1.15: 95% CI: 1.09, 1.21; I^2= 0.0%; p<0.001) (Suksatan et al., 2022).

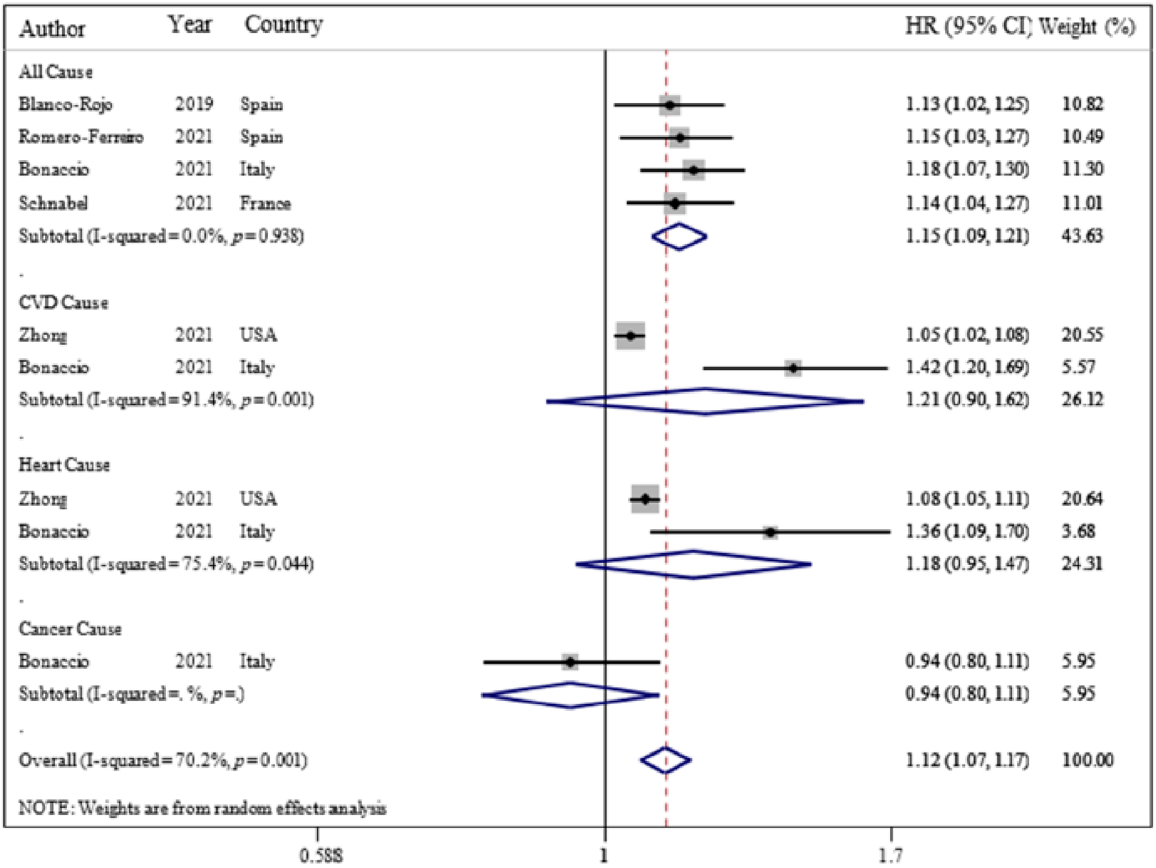

Figure 4.3.2.3. Forest plots showing linear dose response meta-analysis of mortality risk for 10% change in daily intake of UPF consumption (Suksatan et al., 2022).

4.3.3. Cardiovascular Disease Results Summary

In conclusion, both studies showed a significant association in CD risk based on UPF consumption. The observational cohort study by Srour *et al.*, showed a correlation between higher consumption of UPF and increase risk of cardiovascular, coronary heart and cerebrovascular diseases. An absolute increment of 10 in the percentage of UPF was linked to a 12, 13 and 11% increase in the rates of overall cardiovascular disease, coronary heart disease and cerebrovascular disease respectively (Srour *et al.*, 2019). The meta-analytical study by Suksatan *et al.*, demonstrated that UPF consumption was associated with an increased risk of all cause mortality in adults to include mortality caused by cardiovascular diseases. Furthermore A BMI >25kg/m^2 was associated with increased CD cause mortality and Interestingly, the study also demonstrated a 15% higher risk in all cause mortality, associated with a 10% increase in consumption of UPF, as a % of daily calorie intake (Suksatan et al., 2022).

Chapter 5

Discussion

The purpose and objective of this thesis was to analyse reputable and highly cited research on the effects of consumption of UPFs in the EU and the risk of obesity, T2D and CD. Based on a more impactful solution will be proposed on how the food industry can best address the effects of UPFs, with the aim to see a decline in the risk and rate of these diseases by 2030, in line with current EU strategy. The aim of this section is to discuss and summarise findings from the observed selected studies, by which these findings will be utilised to inform and frame potential solutions for the EU food industry and government agencies. All six selected studies gave an overview on the relationship between the consumption of UPFs and outcome of obesity, T2D and CD in an adult population. The selected studies accounted for important cofactors and sensitivities, to further verify findings.

Regarding obesity, two studies were analysed, a cohort study, by Cordova *et al.*, and a prospective analysis by Beslay *et al.*, covering a total of 459,008 adult participants across 9 EU countries. The study objective for both studies was to evaluate the association between the consumption of UPFs with BMI change, weight gain and risk of overweight and obesity. Beslay *et al.*, conducted a large observational study on 110,260 participants from the NutriNet-Sante´ cohort. It was observed that participants that consumed a higher proportion of UPFs had a higher BMI increase during follow up and presented an increased risk of overweight and obesity. These associations were statistically significant, irrespective of adjusting for multiple cofounders such as socioeconomic status, lifestyle factors and nutritional quality (Beslay *et al.*, 2020). This outcome was also consistent with the EPIC cohort study conducted by Cordova *et al.*, where participants across 9 European countries demonstrated that a higher consumption of UPF resulted in a statistically significant higher weight gain in a 5-year period. A further 15% higher risk of overweight and obesity was attributed to participants that had a normal BMI at baseline, but who consumed the most UPF at the highest quintile (Q4) when compared to the lowest quintile (Q1). The findings were consistent across the 9 EU countries and resilient to sensitivity analysis and adjustment for various cofounders (Cordova *et al.*, 2021). These recent findings further support several past studies into the relationship between UPFs and obesity. A SUN cohort study conducted by Mendonca *et al.*, on 8451 Spanish adult participants, who were not overweight or obese at baseline, and followed up for a median of 8.9 years, saw a higher risk of overweight and obesity in association with UPF consumption in the follow up years (Mendonça *et al.*, 2016). Furthermore, several cross-sectional studies in non-European countries (USA, Canada) further corroborate the same findings, demonstrating a positive correlation in consumption of UPFs and obesity risk. In America, UPFs provide 58% of energy intake and 89% of added sugars in the American diet. A cross sectional analysis conducted on 15,977 adults (20-64 years old) American adults by Juul *et al.*, concluded that higher consumption of UPFs was associated with excess weight and abdominal obesity (Juul *et al.*, 2018). Among Canadian adults UPFs make up approximately 45% of daily energy intake. The cross-sectional study, conducted by Nardocci *et al*., on 19,363 Canadian adults (>18 years old) found a positive association with the consumption of UPFs and obesity, with participants in the highest quintile 32% more likely to become obese compared to the lowest quintile (Nardocci *et al.*, 2019). Additionally, a study that analysed global trends on UPF sales and their association with adult BMI trajectories, analysed 80 countries between 2002-2016. Results showed not only an increase in sales of UPF but also a significant association in adult BMI trajectories, with increasing sales, resulting proportionally in increasing BMI globally (Vandevijvere *et al.*, 2019). Lastly, a randomized control trial, conducted in 2019, by Hall *et al*., further investigated the effect UPF had on energy intake, compared to unprocessed food. 20 weight stable adults received either an ultra-processed or unprocessed diet for two weeks, and then received the alternate diet for another 2 weeks. Participants receiving the ultra-processed diet consumed a higher energy intake resulting in weight gain, whereas participants on the un-processed diet experienced a weight loss (Hall *et al.*, 2019). These findings suggest a strong relationship on increased obesity risk, in relation to UPF consumption, not only in the EU but globally. These findings can be attributed to the lower nutritional quality of UPFs, as they tend to be higher in energy, saturated fats, sugar and poorer in dietary fibre. All these factors favour and perpetuate the risk and onset of overweight and obesity. However, interestingly, the study by Beslay *et al*., adjusted for daily energy intake, as well as multiple other nutritional parameters, foods groups and dietary patterns, with results remaining statistically significant. This highlights that other factors aside for poorer nutritional quality are responsible for the observed association between UPFs and weight gain. These other factors could be the intrinsic non nutritive bioactive compounds contained within UPFs, usually in the form of additives, process contaminants or a change in food structure from the manufacturing process, all which can impact health in different ways. The bioavailability and delivery of nutrients, the gut microbiota profile and integrity is unfavourably affected, potentially leading to weight gain. Some food additives can further contribute to obesity aetiology. An example being saccharin, which is an artificial sweetener, can lead to insulin resistance and potentially weight gain, through the stimulation of insulin release from the pancreas. Carrageenan, a thickening additive has also been associated with insulin resistance, which can also induce weight gain. Other emulsifying additives such as carboxymethyl cellulose and polysorbate-80 tend to induce metabolic disruptions, and alter the gut microbiota, causing low grade inflammation in mice (Beslay *et al.*, 2020).

The associations between consumption of UPFs and Diabetes have not been extensively analysed in literature. The two studies assessed covered significant and well acclaimed cohort groups in the EU, the SUN project and the NutriNet-Santé study. Both studies covered a total of 124,767 Fench and Spanish adults, with a mean follow up of 6 years in the NutriNet-Santé study and 12 years in the SUN study. For both studies we see that a significant increased risk of development of T2D is associated with UPF consumption, unaffected by adjustments for confounders. Llavero-Valero *et al.*, assessed 20,060 participants from the SUN project. These participants were highly educated Mediterranean adults with a low absolute risk of developing T2D. They were followed up every 2 years for a median of 12 years. During the follow up period, 175 new cases of T2D were established, with participants in the highest tertile (highest consumption) of UPF, having a higher risk of T2D compared to the lowest tertile. Adjustments for a myriad of potential cofounding factors were applied and had no significant influence on the increased hazard/risk of development of T2D (Llavero-Valero *et al.*, 2021). Srour *et al.*, selected 104,707 adult participants (>18 years old) from the French NutriNet-Santé cohort study between 2009-19. These participants were followed up for a median of 6 years, with 821 new onsets of T2D recorded. Rates of development of T2D were lowest in the first quartile (lowest consumption of UPF) and increased with the highest T2D cases presented in the fourth quartile (highest consumption of UPF). Associations were unaffected by adjustments of various cofounders and remained significant (Srour *et al.*, 2020). The findings of both cohort studies were consistent with one another supporting the conclusion that a higher risk of developing T2D is associated with a higher consumption of UPFs. The findings of the SUN cohort study by Llavero-Valero *et al.*, was further solidified due to a longer follow up period in the NutriNet-Santé cohort study by Srour *et al*, and the use of repeated measurements of UPF consumption. To accurately compare findings from both studies, the proportion of UPF consumed in the SUN study by Llavero-Valero *et al.*, was calculated in grams/ as per the SUN cohort. A mean of 9.5% (SD: 6.6) was calculated compared to a mean of 17.29% (SD 9.81) in the NutriNet-Santé cohort study by Srour *et al.*, Despite a lower mean consumption of UPF in the SUN study, still a strong direct association was observed between increased risk of development of T2D based on increased consumption of UPFs (Llavero-Valero *et al.*, 2021). Furthermore, results from both cohort studies, are in line with other studies, one such by Levy *et al.*, who investigated the association of UPF food consumption and risk of T2D in a UK based cohort study. Adult participants (40-69 years old) were recruited from the UK biobank (2007-2019) presenting without Diabetes at recruitment. During a mean follow up of 5.4 years, 304 new cases of T2D were identified. Elevated risk of development of T2D was associated with increased UPF consumption, with increasing quartiles of UPF intake. These findings further support Llavero-Valero and Srour's studies, demonstrating significantly increased risk of T2D associated with increased UPF intake (Levy *et al.*, 2021).

Various scientific reasonings can be postulated to explain these significant findings between association between UPF and T2D risk. UPFs tend to have a higher energy density and a low nutritional density, often containing higher amounts of added sugars, and refined carbohydrates, which can create an energy imbalance and overweight/obesity, both of which are key factors in the development of T2D. (Llavero-Valero *et al.*, 2021). Similarly UPFs tend to be low in fibre and present a higher glycaemic index, both of which directly contribute to an increased risk of insulin resistance, and hence development of Diabetes (Srour *et al.*, 2020). There is a strong correlation between obesity and development of T2D, as often obesity perpetuates insulin resistance, a precursor that leads to T2D. Insulin resistance is a diminished response over time to insulin by cells in the body. Insulin is the hormone, made and released by the pancreas, that lowers blood sugar levels, so a diminished response to insulin results in hyperglycaemia (high serum glucose levels) over time, and can result in metabolic syndrome. Metabolic syndrome refers to a cluster of metabolic problems, associated with obesity (mainly abdominal), high blood pressure, high cholesterol, and insulin resistance, which over time, if left untreated leads to type 2 diabetes and cardiovascular diseases. The main cause of metabolic syndrome is a diet high in refined carbohydrates and saturated fats, and a sedentary lifestyle. The nutritional profile of UPFs is conducive for the perpetuation of metabolic disorder. The consistent consumption of UPF foods that are often highly glycaemic, high in energy, simple sugars, refined carbohydrates and low in fibre, will not only result in excess weight gain, that can lead to overweight and obesity, but will consistently spike blood sugar levels putting a strain on the pancreas, which over time will not be able to keep up with the increasing demand of insulin to combat the constantly raised blood sugar levels. Metabolic disorder can often be reversed simply by changing dietary habits and increasing activity. A diet high in whole foods, grains, lean protein, fibres, healthy fats, results in weight loss, hence reducing the risk of obesity and helps to prevent and treat metabolic disorder and reduce the risk of onset of T2D (Nilsson, Tuomilehto and Rydén, 2019), (Costa de Miranda, Rauber and Levy, 2021). Conclusively obesity, particularly with excess abdominal fat, is the strongest risk factor for the development of T2D. Furthermore those affected by T2D have a 15% increased risk of all-cause mortality, with cardiovascular diseases being the most significant cause of morbidity and mortality associated with Diabetes (Galicia-Garcia *et al.,* 2020). Furthermore, UPF tend to under-go more rigorous processing treatments such as high temperature heating and extrusion. These treatments can induce the creation of contaminants such as acrylamide and acrolein, both of which have been linked to insulin resistance, as well as polycyclic aromatic hydrocarbons, which have been positively linked to diabetes (Srour *et al.*, 2020).

As previously stated, cardiovascular diseases (CD) make up a third of deaths globally, making them the leading cause of death worldwide. Dietary factors are the main contributing factors of death by this disease, with an average of 52% of (CD) deaths caused by dietary factors (Srour *et al.*, 2019). The two studies selected for the purpose of this research involved a prospective cohort study by Srour *et al*., taken from the French NutriNet-Santé cohort, and a Dose- response meta-analysis by Suksatan *et al*. A total of 312,450 adult (>18 years old) participants were analysed amongst both studies (Srour *et al.*, 2019), (Suksatan *et al.*, 2022). The objective of the NutriNet-Santé study, by Srour *et al*., was to assess the associations between the consumption of UPFs and the risk of CD (Srour *et al.*, 2019). The Objective of the meta-analysis by Suksatan *et al*., was to analyse the association between UPF consumption and adult mortality risk, with CD as one of the analysed disease outcomes (Suksatan *et al.*, 2022). The study by Srour *et al*., analysed a total of 105,159 adult participants between 2009-18 for a median of 5.2 follow up years. During this period, there were 1409 first incidents of CDs that occurred to include, myocardial infarctions, transient ischaemic events, strokes, angioplasties, and acute coronary syndromes. The outcome of the study showed a significant association in between UPF intake and overall risk of cardiovascular, coronary heart and cerebrovascular diseases. Interestingly, a significant finding in this study showed that a 10% increase in UPF consumption was associated with a 12, 13, and 11% increase in the rates of overall cardiovascular disease, coronary heart disease and cerebrovascular disease respectively (Srour *et al.*, 2019). The study by Suksatan *et al*., performed a systematic review of observational studies with data extracted from 7 cohort studies, totaling 207,291 adults from 4 countries (Spain, France, Italy, USA). The conclusion from the study showed an increased risk in all cause and CD cause mortality in association with the consumption of UPFs. Profoundly, the study also showed 15% higher risk of all-cause mortality (to include CD) with each 10% increase in UPF consumption. A significant association was also found among overweight adults with a BMI >25kg/m2. An increased risk of CD cause mortality in association with UPF consumption was observed in this category of participants who were overweight/obese (Suksatan *et al.*, 2022).

These findings can be explained yet again by the general composition of UPFs. UPFs have a poorer nutritional quality than unprocessed or minimally processed foods, and are also higher in energy, saturated fat, sodium, sugar, poorer in fibre, and yield a higher glycaemic response (Srour *et al.*, 2019). As discussed, dietary factors, are the main contributing factor for CD mortality, and several compounds in UPFs are directly attributable to the perpetuation of cardiometabolic diseases. Significant evidence shows a diet high in sodium, saturated fat, added sugars, low dietary fibre a high glycaemic load, contribute significantly to risk of development of CD. Additionally, as UPFs tend to have a higher energy density in the form of excessive fat, refined sugar, and carbohydrates, this can lead to weight gain and an increased risk of overweight and obesity, which is a significant risk factor for CD. Additionally, part of the association with increased consumption of UPFs, equates to a lower consumption of non-processed foods, such as fruits and vegetables, by which a high level of evidence suggests consumption of these foods are beneficial to cardiovascular health. Contrastingly, the study by Srour *et al*., saw an unaffected significant relationship between the consumption of UPF and increased CD risk, even after adjustment for BMI, healthy and western dietary patterns, energy, fat, sugar, salt, and fibre composition in the diet, including consumption of sugary, and salty products, fats, sauces, beverages, fruit and vegetables, red and processed meats. This suggests that the nutritional composition is not the only factor contributing to the risk of CD from UPF and that other intrinsic bioactive compounds contained within UPFs could be contributing to the association (Srour *et al.*, 2019). UPFs also tend to be manufactured with a wide range of additives. Although the use and safety of additives are governed by European wide legislation, the cumulative impact, and super additive effect upon ingestion of multiple additives contained across multiple UPFs and potential interactions during processing and consumption are widely unknown. In recent years many experimental studies on animal or cellular models in vivo, have suggested several adverse effects on cardiovascular health in association with some of the approximately 350 authorised additives in the EU. An example would be sulphites, that are commonly used in ultra-processed vinegar containing sauces, which have been found to cause damage to the heart of rats in experimental studies at high doses. Experimental studies have also shown that mono sodium glutamate (MSG), which are often present in ultra-processed sauces and ready to eat soups and noodles, have been found to induce oxidative stress through lipid peroxidation at a >4mg/g body weight in mice, which could result in coronary heart diseases. Additionally, certain emulsifiers, such as carboxymethyl cellulose and polysorbate-80, which are ubiquitous in UPFs, have been found to induce low grade inflammation, obesity, and metabolic syndrome in mice (Srour *et al.*, 2019). Furthermore, it is important to consider the processing of UPFs, which often undergo intense heat treatments, that can lead to the formation of chemical contaminants such as acrylamide, which is most likely to occur in UPFs such as biscuits, bread, coffee, or acrolein which is often found in grilled sausages and caramel candies. Both contaminants have been associated with higher risk of CD, amongst other adverse health effects (Srour *et al.*, 2019). The industrialised partial hydrogenation process for unsaturated fats result in the creation of trans unsaturated fatty acids (trans fats), with strong evidence linking trans fats to increased risk of CD and T2D, due to fatty deposits in blood vessels, and potential inflammation induced by these fats that influence the risk of T2D (Srour *et al.*, 2020).

All studies had their strengths and limitations. What was similar amongst all studies was that they all defined and categorised their foods according to the NOVA classification system, all studies also accounted and adjusted for significant cofounding factors that could potentially skew results. The strengths of the studies lay primarily in their prospective design, in the form of longitudinal cohort studies with one study being a meta-analysis of cohort studies. They all also had long follow up times, with a large sample size. All studies also used validated methods to evaluate, estimate and extrapolate their findings, and all studies adjusted for cofactors that could potentially skew results. Limitations in the studies, lay in the fact that causation of associations could not be established in the experimental design. Furthermore, due to the observational design of the study, residual cofounding factors could not be completely omitted, regardless of all potential cofounders that were accounted for. Additionally recall bias, and potential misclassification of participants in terms of UPF consumption may have been possible, as well as misclassification of NOVA categories, despite highly trained consensus between scientists, cannot be completely ruled out either. Lastly the majority of participants were women in all studies.

The studies discussed in this research on the relationship with UPFs and the rise in obesity, T2D and CD, highlight important targets points to frame the solution. These are summarised as following:

- Increasing % of UPF intake, is associated with increased risk of obesity, T2D and CD (Suksatan *et al.*, 2022).

- A 10% increase in UPF consumption is related to a 15% higher risk in all-cause mortality, to include CD (Suksatan *et al.*, 2022).
- A 10% increase in UPF consumption is related to a 12% increased risk of CD (Suksatan *et al.*, 2022).
- An overweight BMI (>25) was associated with increased risk of death from CD (Suksatan et al., 2022).
- A 10% increase in UPF consumption is associated with a significant increase in the development of T2D (Srour *et al.*, 2020).
- Nutritional composition was not the only factor potentially contributing to obesity, CD and T2D, but the intrinsic non-nutritive bio active compounds could have an effect (Beslay *et al.*, 2020).

It can be purported that the solutions should aim to reduce consumption of UPFs in the EU, by at least 10% to have a significant impact on risk factors and development onset of obesity, T2D and cardiovascular diseases, whilst simultaneously increasing the quality and health components of UPF foods through effective and smart reformulations, to create 'true to health' food products. The food industry should drive an innovation strategy across the four areas below to address and achieve this objective:

- **Nutritional composition:** To smartly address high energy levels, sugar, refined carbohydrates, sodium, saturated and trans-fat and to increase fibre content and lower glycaemic index of UPFs
- **Processing conditions**: To address known process contaminants as well as providing less processed UPF alternatives.
- **Incorporation of more functional ingredients into more foods**: with the aim of addressing overall immune health, cardiovascular health, hyperglycaemia, inflammation, and obesity.
- **More research**: Based on research summarized in these studies, it is evident that non-nutritive bioactive compounds could play a role into the propagation on disease risk. More research is needed to investigate the effects of consumption of multiple food additives and chemicals obtained from multiple sources of UPFs, known as the super additive effect. This will help understand the impact of replacing additives or ingredients with additives when reformulating food products.

Chapter 6

Solution

6.1. Financial Burden of Non-Communicable Diseases

The four major Non communicable diseases (NCDs) are cardiovascular disease (CD), diabetes mellitus, cancers, and chronic respiratory disease. They are all associated with common risk factors to include obesity, unhealthy diets, physical inactivity. it is estimated that 80% of all heart disease, stroke and diabetes could be prevented by addressing these major risk factors (WHO, 2017). NCDs such as cardiovascular disease (CD), diabetes mellitus, cancer and chronic respiratory disease, represent 71% of all deaths globally, and up to 90% of all deaths in the EU, with 40% of deaths in the EU caused by CD and 2% by Diabetes. NCDs pose a significant strain on European health care systems and a significant financial burden on the country's economy. These diseases also pose an economic burden and hinder economic development due to the loss of productivity in daily work and life of patients suffering from the ailments. Unhealthy, unbalanced diets, characteristic of UPFs, with a high proportion of processed foods, low in fibre minerals and vitamins, contribute to the risk factors of the development of obesity, T2D and CD. Often we see multiple and co-morbidities with people suffering from more than one chronic ailment (Vandenberghe and Albrecht, 2020). As previously discussed, Obesity is the strongest risk factor for development of T2D and a significant risk factor for CD, with CD being the main cause of morbidity and mortality for those suffering with T2D (Galicia-Garcia *et al.*, 2020). A systemic review on the financial burden of non-communicable diseases in the EU, found that the four main NCDs, to include CD and T2D, took a significant share of total healthcare budget between 2008-18, equating to at least 25% of spending, as well as imposed a significant economic loss of approximately 2% of GDP (Vandenberghe and Albrecht, 2020).

6.2. Current EU Strategy on Non-Communicable Diseases

The EU has adopted and committed to supporting its member states in achieving the 9 voluntary targets set out by the United Nations and the World Health Organisation (WHO) as part of their global monitoring framework aimed at addressing the global burden of NCDs. WHO has set the sustainable development health target to reduce premature deaths from NCDs by a third by 2030. One of these voluntary targets for the EU was to reduce overall mortality from CD, diabetes, cancer, or chronic respiratory disease by 25% between 2010-2025 (WHO, 2017). The European commission established a steering group on health promotion, disease prevention and management of NCDs, that serves to advise and support member states in the implementation of validated best practices to reach the health targets of the WHO sustainable development goals. An area where policy has been implemented and worked on is to address nutrition and physical inactivity (European Commission, 2022). In May 2007 a white paper was issued by the commission of the European communities, on a strategy for Europe on Nutrition, overweight and obesity related issues. The purpose of the white paper was to set out an EU wide integrated approach on tackling the unfavourable health associated with poor nutrition, overweight and obesity. The scope was to cover a local, regional, national, and European wide level to reduce these risks associated with poor nutrition and limited physical exercise. The white paper encouraged collaboration and partnerships between the private sector, governments, experts in the field of nutrition and physical activity and the European Commission and WHO. A set of challenges was set out for the food industry to encourage:

- Better informed consumers- with nutritional labelling targeted as the main area of improvement.
- Making healthy options available- primarily addressed through the promotion of fruit and vegetables in schools, as wells as the call to food manufacturers to reformulate food products to make them healthier, i.e., reduction in levels of fat, saturated and trans-fat, salt, and sugar
- Encouraging physical activity- through the development of sustainable urban transport and walking and cycling schemes
  (Commission of the European Communities, 2007)

In 2022 the EU Commission introduced the 'Healthier together' initiative, aimed at improving the health and well-being of citizens by reducing the burden of NCDs. The initiative proposes to tackle the 5 leading causes of NCDs across the 5 main areas to include CD and diabetes, as well as their contributing risk factors. The aim of this refreshed initiative is to provide a 5-year action plan between 2022- 2027 to support member states in achieving the WHO sustainable development goal targets by 2030 to reduce premature deaths from NCDs by a third, and to reduce overall mortality from CD, diabetes, cancer, or chronic respiratory disease by 25% by 2025 (European Commission, 2022). Currently the EU is on track to meet only 2 of the 9 voluntary targets and are unlikely to meet the goals of the other 7 voluntary targets, as shown in table 6.0. below. The EU is off track to halt the rise in diabetes and obesity, and off track to reduce the mean population intake of salt/sodium by 30% (WHO, 2017).

Target	Progress/projections for the WHO European Region "business as usual" scenario
1. A 25% relative reduction in the overall mortality from cardiovascular diseases, cancer, diabetes or chronic respiratory disease	If current trends continue, the Region is on course to exceed the target
2. At least 10% relative reduction in the harmful use of alcohol, as appropriate, within the national context	If trends continue, alcohol per capita consumption is expected to reduce by 9% by 2025
3. A 10% relative reduction in prevalence of insufficient physical activity	It is not possible to make projections to 2025, but based on trends from surveys of adolescents and adults the Region is unlikely to achieve the target
4. A 30% relative reduction in mean population intake of salt/sodium	It is not currently possible to make projections to 2025, but the Region is unlikely to achieve the target, given the current pace of change
5. A 30% relative reduction in prevalence of current tobacco use	Projections are that the Region as a whole will not meet the target, nor will 36 of the 53 countries in the Region unless something more is done
6. A 25% relative reduction in the prevalence of raised blood pressure or contain the prevalence of raised blood pressure, according to national circumstances	If current trends continue, the Region is on course to achieve the target, but widening of inequalities across Europe is likely
7. Halt the rise in diabetes and obesity	The Region is off track for reaching the 2025 target; prevalence of overweight/obesity is projected to rise and diabetes prevalence can be expected to do likewise
8. At least 50% of eligible people receive drug therapy and counselling (including glycaemic control) to prevent heart attacks and strokes	This is challenging to measure and projections to 2025 are not currently possible
9. An 80% availability of the affordable basic technologies and essential medicines, including generics, required to treat major NCDs in both public and private facilities	This is challenging to measure and projections to 2025 are not currently possible

Source: The WHO Global Monitoring Framework on noncommunicable diseases *(5)*.
Note: Colour coding is red (Region is off course and unlikely to achieve the target), amber (Region may or may not reach the target, progress/projections are difficult to measure) and green (Region is on course to achieve the target).

Table 6.0: Summary scorecard for EU against nine voluntary targets of the global monitoring framework (WHO, 2017).

More work needs to be done to significantly reduce the rise and onset of obesity, T2D and CD in the EU. As we see from this research, it is proposed that the most impactful solution lies within the food industry, as the surge in UPF consumption seems to be a key driver in the risk factors that drive the development of overweight and obesity, T2D and CD.

6.3. Solution

The responsibility of food business operators is to place safe food products onto the market. The EU has one the most highly regulated food regulations, providing a high level of protection on human health and consumer interest in relation to food. As previously discussed, the food landscape and consumer patterns have drastically changed since the industrial revolution and rise in urbanisation, with the increase in obesity, T2D and CD happening concurrently also

(Huebbe and Rimbach, 2020). Therefore, at the core of food consumption, exists a need to address the food industry and place an onus on them to contribute to the promotion of truly healthier food products, which will be termed 'true to health' products for the purpose of this research. However, Food businesses are still a business that need to make a profit to operate, and the selling point of UPFs is that they are often cheaper to manufacture, with cheaper ingredients than the more natural and minimally processed foods, creating better profit margins. Contrastingly, we see that the overall healthcare and GDP burden is most likely greater than the increased cost burden to the food and drink industry in the EU (Vandenberghe and Albrecht, 2020). Therefore, a truly multifaceted approach should encompass the cost impact, distribution and incentives across all sectors involved in the solution for significantly decreasing the rate of obesity, T2D and CD by 2030. Although the promotion of a healthy diet, corresponds to eating whole unprocessed and minimally processed foods with a balanced nutritional profile, we see that with the modern world as we know it, UPF consumption is ubiquitous in society and unlikely to change, so what needs to change is the health profile itself of UPFs, to contribute to the reduction of NCD risk factors. As part of the EU commissions 'Healthier together' initiative, the food industry should be at the forefront of change, to achieve the goals of promoting healthier food and reducing risk factors and onset of obesity, T2D and CD by 2030. As previously highlighted, the studies analysed in this thesis, show a correlation with increased consumption of UPFs and increased risk of obesity, T2D and CD. Key findings from the research indicate significant impact with incremental increases of 10% of UPF consumption in association with increased risk of all-cause mortality, obesity, T2D and CD. We also see that other factors outside of nutritional composition, such as bioactive compounds, food additives, process contaminants could potentially contribute to the perpetuation of disease risk of obesity, T2D and CD (Suksatan *et al.*, 2022), (Srour *et al.*, 2020), (Beslay *et al.*, 2020). Therefore, solutions should aim to reduce the consumption of UPF foods by at least 10% in the EU, whilst simultaneously increasing the nutritional, health, and ingredient quality of UPF foods through effective smart reformulations that result in 'true to health' formulations. The food industry should drive an innovation strategy across four key areas to achieve the goal of 'true to health' formulations. As discussed, these areas are nutritional composition, processing conditions, the incorporation of functional ingredients into more foods and more insightful research.

6.3.1 Nutritional Composition

Over the years, the food industry has implemented plans on reducing the levels of nutrients linked with negative health effects such as sugar, fat, and salt. The aim is to promote a healthier diet with minimum effort required by the consumer, particularly in individuals who are averse to behavioural changes to their dietary habits. Reformulating food products without compromising significantly on the consumer experience and cost, has straddled a fine line. Often clean label products, such as sugar free, fat free, low sodium products all replace one problem for another with more artificial food additives than before. Sugar in sugar free products are often replaced with a combination of non-nutritive sweeteners such as sucralose, acesulfame potassium (Ace-K) and aspartame, while fat free products replace the fat with a blend of texturants and stabilisers, such as carrageenan's, xanthan gums, etc. to match the mouthfeel and texture usually experienced with fat (Harastani *et al.*, 2020). In 2015 the World Health Organisation (WHO) published a guideline on the sugar intake for adult and children, with a recommendation to reduce the consumption of free sugars to below 10% of total daily calories, to reduce risk of non-communicable diseases, and to prevent and control unhealthy weight gain (WHO, 2015). The release of this guideline sparked the creation of sugar tax legislation, that has gained traction now in over 50 countries, where a tax is applied to sugar sweetened products, often beverages above a stated threshold, with the aim to support the reduction in consumption of added free sugar. In response food manufacturers reviewed their product portfolios and reformulated sugar sweetened beverages to fall below the threshold for sugar tax (Kerry, 2021). Often these reformulations involved the replacement of sugars with non-nutritive artificial sweeteners, which current evidence suggest adverse health effects associated with these additives, such as insulin insensitivity (Beslay *et al.*, 2020). In addition to the implementation of sugar tax, more research needs to be conducted into the true effects of the most used artificial sweeteners, i.e., aspartame, Ace-K, saccharin, and sucralose, as well as the innovation into more natural forms should be focussed on. Some natural forms include, monk fruit, as well as sugar alcohols, xylitol and erythritol which don't have the same potential harmful effects as the most used artificial sweeteners. Research and innovation into coupled with the gradual reduction of sweetness in foods should be applied as a solution to reduce the amount of free sugar in consumed in products. Issues also exist surrounding trans fatty acids (TFAs) in the EU. TFAs are unsaturated fatty acids, containing at least one double bond in the trans configuration. Natural TFAs are naturally occurring in low amounts in foods from milk and meat from ruminant animals, such as cattle and sheep. Although industrial forms are created through industrial processes involving the partial hydrogenation of poly unsaturated vegetable oils. They are also as formed in high temperature heating of oils. High intake of TFAs is a significant risk factor for the development of cardiovascular diseases and pose a public health risk, as they can be common in a large variety of processed foods. A 2% increase in the intake of TFAs is associated with a 23% increase in risk of CD (Islam *et al.*, 2019). In 2019 the EU commission updated Regulation (EC) 1925/2006 on the addition of vitamins and minerals and of certain other substances to foods. It set a restriction on industrial trans fats in foods to no more than 2g per 100g. This regulation sets a standard to Food business operators to ensure their final product does not exceed the 2% limit for trans-fat. However, with UPF products making up to 50% of the EU diet (Mertens, Colizzi and Peñalvo, 2022), it is possible that consumers could be ingesting more than the 2% limit of trans fat across multiple food products. Often the solution to the reduction of industrially produced unhealthy fats has been by substituting with an alternative healthy fat form, which initially was thought to be cost ineffective and expensive by the margarine industry. It turned out the replacement to healthy fats didn't incur a huge price increase as initially thought and the food industry has been embracing this change. The most natural solution to eliminate trans fat in UPF food is to replace with healthier mono/poly unsaturated fat sources. However due to the physio-chemical properties that fat contributes to a lot of food products, such as viscosity, melting point, mouthfeel, this may not always be possible for all foods. Starch based fat replacers in combination with healthier fat options could be an optimal solution in the right ratios. The starch based fat replacers simulate the functionality of saturated/ partially hydrogenated fat globules in products, whilst not including the saturated/ partially hydrogenated fat itself, therefore maintaining the texture and mouthfeel amongst other physiochemical properties (Chen *et al.*, 2020). To keep the formulation true to health, as discussed, the whole formula must be taken into consideration so one problem is not being replaced with another, as starch itself can be highly glycaemic. Using an oat based starch, high in beta glucans could present additional functional attributes to the formulation (Chen *et al.*, 2020). Many UPF foods contain refined carbohydrates and have a high glycaemic index (GI), which should be addressed for better true to health formulations. The incorporation of fibre into more food products, in line with the reduction of highly glycaemic carbohydrates would be highly beneficial to overall health and diabetes incidence. A lot of starch and refined flours are used in UPFs. The EU population is used to what the food industry sells us, and the palates have become accustomed to these refined high GI grains. Being able to slowly wean the population to less refined grains over time by reducing the ratio of high GI refined starch and flour, to less processed whole grains alongside the immediate incorporation of added fibre will serve to provide health benefits to UPF products that are typically low on fibre. Similarly, to a sugar tax, a similar incentive on GI and refined carbohydrates should also be introduced to encourage the reformulations of these products. As part of the 9 EU voluntary targets, one of them is to reduce the mean population intake of salt/sodium by 30%. The EU is currently off track to accomplish this by 2025 (WHO, 2017). Research suggests consumers are willing to accept reformulated salt free and reduced salt products. A gradual reduction in sodium over time as well as suitable salt replacements should be more closely researched and implemented in the EU. Often, the first line solution for whole or partial sodium replacement is through the use of potassium chloride, however more novel ingredients are up and coming in the food industry that can prove effective in salt replacement, such as the addition of a water-soluble seaweed extract *Palmaria palmata* as a flavouring for cooked meats. Furthermore, we see the use of hydrogels providing an overall enhanced perception of saltiness, through the inclusion of air within hydrogels. It is important to note that salt also serves as a preservative in many food products, so this function must be considered in replacement/reformulation strategies implemented. Novel processing technologies, such as high hydrostatic pressure and ultrasound, can be implemented to ensure microbiological safety. It’s important for the food industry to look at salt replacement in a multi-faceted approach, implementing multiple tools to ensure the maintenance of sensory and safety attributes of food through the application of novel ingredients and technologies, as well as simultaneously gradually reducing the amount of salt in certain foods incrementally over time. Mapping out the strategy best suited for the various high salt food groups will ensure a higher rate of success. (Belc *et al.*, 2019).

6.3.2 Food Processing

Food Processing conditions and their effect on the food matrix and nutritional composition is another key aspect to consider. Emerging evidence suggests that the food matrix, which is defined as the nutrient and non-nutrient components of food and their molecular interactions, are changed during extensive and rigorous food processing conditions, resulting in the alteration in structure and size of food particles, nutrient bioavailability, digestion kinetics, satiety, antioxidant, or alkalinizing potential, as well as the gut microbiota, all of which can influence the risk of non-communicable diseases. (Lane *et al.*, 2021). Furthermore, rigorous processing conditions such as high temperatures, contribute to the formation of process contaminants such as acrylamide, acrolein and trans-fat. These are some of the main process contaminants in the spotlight in the food industry currently as all of which have been linked to insulin resistance, a precursor to diabetes and CD (Srour *et al.*, 2020), (Srour *et al.*, 2019). Alternative non thermal processes (NTPs) should be explored more by the food industry to work to reduce the level and creation of process contaminants, that are often caused by high heat processes. In recent times, NTPs have started gaining more attention by the food industries upon mounting increased pressure to discover alternative sustainable processing solutions to conventional high energy, high heat processes. NTPs are beneficial in that they preserve the nutritional value of food, while improving bio-accessibility of nutrients, without compromising on the sensory attributes of the food (Arshad *et al.*, 2021). They fall under three main technology groups, including, mechanical technologies, pressure-based technologies and electrotechnology's. Some of these NTP technologies include, high power ultrasound, pulsed electric fields, high pressure processing (HPP), UV-LED, and high pressure homogenization (HPH) all of which have their own advantages and limitations. Thermal processes are the most used method of food preservation in the food industry. Technologies such as HPP should be explored more amongst food manufacturers to understand the suitability of this method in their food processes. HPP has been proven to be an equally effective method for the reduction of microorganisms in water based food products. Other benefits of NTP technologies is that it reduces food wastage, reduces energy consumption and cost, as well as reduces C02 emissions (Režek Jambrak *et al.*, 2021). With multifaceted benefits in the realm of sustainability, preservation of food quality, reduction/elimination of high temperature process contaminants and cost reduction, NTP methods could prove revolutionary for the food industry in achieving true to health food formulations with all the other additional benefits.

6.3.3. Functional Foods

The concept of functional foods was birthed in Japan in the mid-1980s where the government linked a reduction of disease risk to a greater consumption of certain food types, which could help control rising health costs. Functional foods are recognised as foods that are fortified with additional concentrated ingredients that provide added health benefits. The beneficial effects of functional foods are often attributed to improving physical condition and reducing the risk of the onset of chronic diseases such as obesity, T2D and CD. Often natural bioactive compounds such as resveratrol, catechins, curcumin, quercetin, ellagic acid, anthocyanins, b-glucans, and other biomolecules have been studied with evidence of direct and indirect effects on specific metabolic pathways, associated with the pathophysiology of both obesity, CD and

T2D. Epidemiological data also supports the consumption that a high intake of natural functional foods such as specific fruits and vegetables containing these bioactive compounds are associated with a decreased risk of chronic diseases. The commonality seen in these bioactive compounds in their mode of action in the body is having high antioxidant and free radical scavenging properties as well as anti-inflammatory properties which are significantly beneficial properties to the immune system and general metabolic functioning (Konstantinidi and Koutelidakis, 2019). Most chronic diseases are often marked by increased inflammation and deregulation of the immune system (Sassi, Tamone and D'Amelio, 2018). However it's important to note that functional foods exert a beneficial effect in human health as part of a well-balanced diet (Konstantinidi and Koutelidakis, 2019). Functional foods are part of a lot of the current innovation strategy by the food industry, driven by increased consumer awareness and health and wellbeing trends. However, are all functional foods, truly functional, with health promoting benefits? Or is their effect cancelled out by the other ingredients and nutritional components of the formulation? A lot of current pre-packaged functional foods fall under the category of UPFs, i.e., functional beverages, soups, breakfast cereals, confectionary e.t.c. all sporting various functional claims such as high fibre, high protein, supports gut health, immunity boosting e.t.c. However, with trends of increased chronic diseases associated with increased UPF consumption, the food industry needs to provide more smartly formulated, true to health, functional foods to ensure that the functionality is not cancelled out by an unbalanced nutritional profile and food matrix i.e., a high fibre vegetable soup that's high in sodium, or a prebiotic plant-based milk drink made with over 80% synthetic additives. Food manufacturers will have more impact in contributing to the reduction of obesity, T2D and CD by considering the processing conditions, food matrix alongside the nutritional profile of the functional food in which they formulate, to bring out the highest impact functionality of the incorporated functional ingredient. Additionally, by applying functional ingredient mapping, functional ingredients can be grouped with suitable food groups based on sensory aspects, marketed claims and process conditions to ensure the highest quality functional foods, with high potency, with a balanced nutritional profile and reduction of process contaminants that can impact functionality of the food.

6.3.4. Deterrent Marketing

A meta-analysis conducted on the effects food labelling has on consumer diet behaviours and industry practices, showed a reduction in intake of certain nutrients by consumers, and influence on industry practices to reduce contents of sodium and industrial trans-fat. A total of 60 studies, across 11 countries, including 2 million observations demonstrated that food labelling reduced consumer consumption of energy by 6.6.%, total fat by 10.6%, other unhealthy dietary options by 13%, while increasing vegetable consumption by 13.5%. Food labelling also yielded an 8.9% decrease in sodium and 64.3% decrease in industrial trans fact by the food industry between 1st January 1990 to 28th February 2014 (Shangguan *et al.*, 2019). Since this time frame, food labelling, regulations and marketing strategies have continued to evolve as consumer behaviours have evolved. Consumers are now more informed about what they eat and care about the impact on their health and wellbeing. These reasons are at the forefront underpinning consumer food choices. There is a drive for more natural and minimally processed foods, as well as a drive for functional foods with added health benefits particularly targeting immunity. In 2022, the global health and wellness food market was valued at $841 Bn, with projections to reach $1Tn by 2026 (Statista, 2022). Regardless of this trend, we still see a rise in consumption of UPF's associated with a rise in obesity, T2D and CD (Vandevijvere *et al.*, 2019). As previously discussed, part of the EU strategy to address issues of overweight, obesity was adopted into a white paper introduced in May 2007 by the commission of the European communities to tackle issues of overweight, obesity and other related health issues. highlighted within the white paper was an area of policy to promote better informed consumers. A consumers knowledge base, behaviours and preferences are influenced by their surrounding environment. So, lifestyle, eating habits, food preferences are all impacted by the information accessible to the consumer (Commission of the European Communities, 2007). We see in the EU, one such tool that has been utilised to better inform and influence consumer is through marketing strategies. For the food industry, the food label is seen as one of the most effective ways to clearly inform, promote and attract consumers to a product within governed parameters. The way food information is communicated to a consumer is set out by EU wide regulation. Regulation (EU) 1169/2011 on the provision of food information to consumers sets out general principles, guidelines, mandatory requirements, surrounding food information to consumers, particularly food labelling, to ensure a high level of consumer protection in relation to information surrounding the pre-packaged food they purchase. Additionally, Regulation (EC) 1924/2006 on nutrition and health claims made on foods, sets out the various nutrition claims that can be made on food and their conditions by which those claims can be made. It also sets out the specific requirements pertaining to the use of health claims. A public EU register has also been established where all authorised nutrition claims are listed, alongside authorised and unauthorised health claims. The objective of this regulation is to ensure that any claim made on the labelling of a food is authorised, meaning it is accurate, based on scientific evidence and does not mislead the consumer. Additionally, the food industry itself implemented additional plans on pre-packaged foods to provide consumers with a clearer indication on the proportion of salt, sugar, and fats contained within products relevant to their daily intake. This was referred to as the traffic light system and was a voluntary scheme first introduced in the UK in 2013, allowing consumers to promptly decide on a pre-packaged food. This is based on the visual aid of green, amber, and red colour backgrounds surrounding the amounts and proportions of sugar, salt, and fats in a serving of a product. Green represents a low amount, orange being medium and red meaning high amounts of those nutrients in that food serving (Euractiv, 2017). Although the European Parliaments environment, public health and food safety committee voted against making the traffic light labelling system mandatory, as part of an update to the Regulation (EU) 1169/2011 on the provision of food information to consumers, the voluntary system has proven very popular in the food industry and has garnered traction (Euractiv, 2017). Furthermore, we see the food industry capitalising on health and wellness trends surrounding clean labelling and functional foods, and creating health promoting processed foods, sporting various nutrition and health claims to promote their products. Although a concerted effort to influence consumers to making healthier decisions, it is evident, with the continued increased consumption in UPFs and increased incidence of obesity, T2D and CD that the food industry have found a way to capitalise on beneficial marketing in the form of the nutrition and health claims, as well as the traffic light system. The food industry has utilised the promotion of clean label nutrition and functional health claims as a marketing strategy in line with growing health and wellness trends. Often, the main beneficial focal point of the food is on a functional ingredient, reduction or lack of an ingredient, without a wholistic focus on the whole food matrix itself. It begs the question, as to whether a lot of these health promoting UPF foods are truly healthy and supporting the reduction in risk of obesity, T2D and CD or are they contributing to it? As discussed previously, promoting sugar free, fat free, low sodium products as well as promoting the health claims on functional foods, may not be truly beneficial on health if the focus is only on one nutrient, as opposed to the complete nutritional profile and food matrix. A solution to this, is using ‘deterrent marketing’. In the same way regulations governing nutritional and health claim benefits exist to promote the benefits of certain foods based on scientific evidence, there should also be disclaimers and claims on food labelling packaging that highlights some of the adverse health effects associated with certain high nutritional components and food groups, like what we see on the marketing on cigarette packaging. This is where a stronger deterrent marketing could be of use. Making this into a mandatory requirement by EU regulation, could help to push the food industry, who would want to avoid using deterrent marketing disclaimers on their packaging to think wholly about new formulation development and to truly evaluate the full nutritional profile, processing conditions, and overall food matrix of a product. This would involve deeper research and development by evaluating the whole food formulation and how interactions between ingredients, especially in the different processing conditions, as well as whether the nutritional profile, functional ingredient (if any), truly come together to support a healthy diet with no added, or even reduced risk of obesity, T2D and CD. Often, food manufacturers focus on a beneficial ingredient and try to incorporate it into as many food types as feasible to be able to use the nutrition/ health claims as a marketing selling point, i.e. a high fibre breakfast bar that is high in sugar and saturated fat. Rules around when to use deterrent marketing disclaimers would be based on assessment of the whole product, considering the nutritional profile evaluation, food matrix, purported claims, processing conditions and intended use. If this was made as a mandatory labelling requirement for pre-packaged foods, consumers will be better informed on the potentially adverse effect of the product to balance out any positive claims, to make even more informed decisions and deterred from making certain food choices with the additional information. On the other hand, the food business would be compelled to make and reformulate more ‘true to health’ formulations, considering all elements and factors of the food product rather than just focusing on achieving a beneficial claim. As we see with the meta-analytical study conducted by Shangguan *et al.*, food labelling is an impactful tool, and can be made even more impactful to consumers and the food industry through the use of deterrent marketing.

Examples of deterrent claims:

- Regular consumption of more than 2g/100g trans-fat contributes to a 23% increased risk of cardiovascular diseases (Islam *et al.,* 2019).
- This food product is a source of acrylamide/acrolein and is associated with an increased risk of cardiovascular disease (Srour *et al.,* 2019).

- Reducing intake of ultra-processed foods (such as this) by 10% has been linked to a reduced risk of obesity, diabetes, and cardiovascular diseases (Suksatan *et al.*, 2022).
- A high consumption of sugar/sodium/salt/saturated fat has been linked to a higher risk of obesity/ diabetes/ high blood pressure/ cardiovascular diseases.

6.3.5. Solution Summary

Conclusively, to create truer to health formulations, nutritional composition and ingredients need to be looked at wholistically. It is important for more research and development to be conducted into the most suitable and beneficial replacement additives for various food groups and intended uses, that doesn't present potential additional health risks. Furthermore, incentivising the food industry on lowering the GI of food products whilst incorporating more added fibre to more food products would work as a beneficial solution propelling the use of less refined grains in UPF foods. More effort needs to be put into the utilisation of more natural food additives, as well as incorporating more novel ingredient and technological solutions to eliminate and reduce the amount of saturated/ trans fats, sodium, sugar, refined carbohydrates, and processing contaminants in food products. The biggest impact in achieving all the different above-mentioned elements leading to the creation of true to health formulations, is the novel solution of Deterrent marketing.

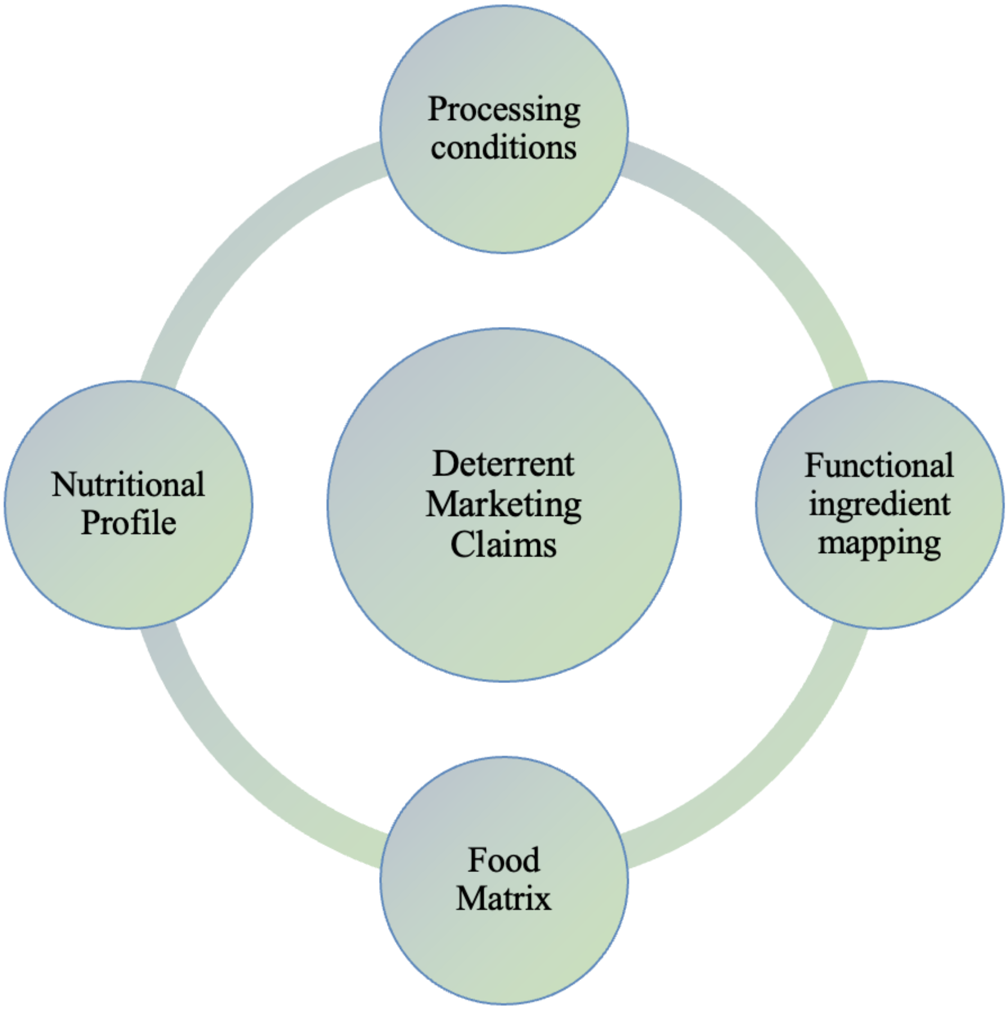

Figure 6.3.5. An illustration summarising the factors assessed in a food formulation that determines the deterrent marketing claims to be applied to pre-packaged food products

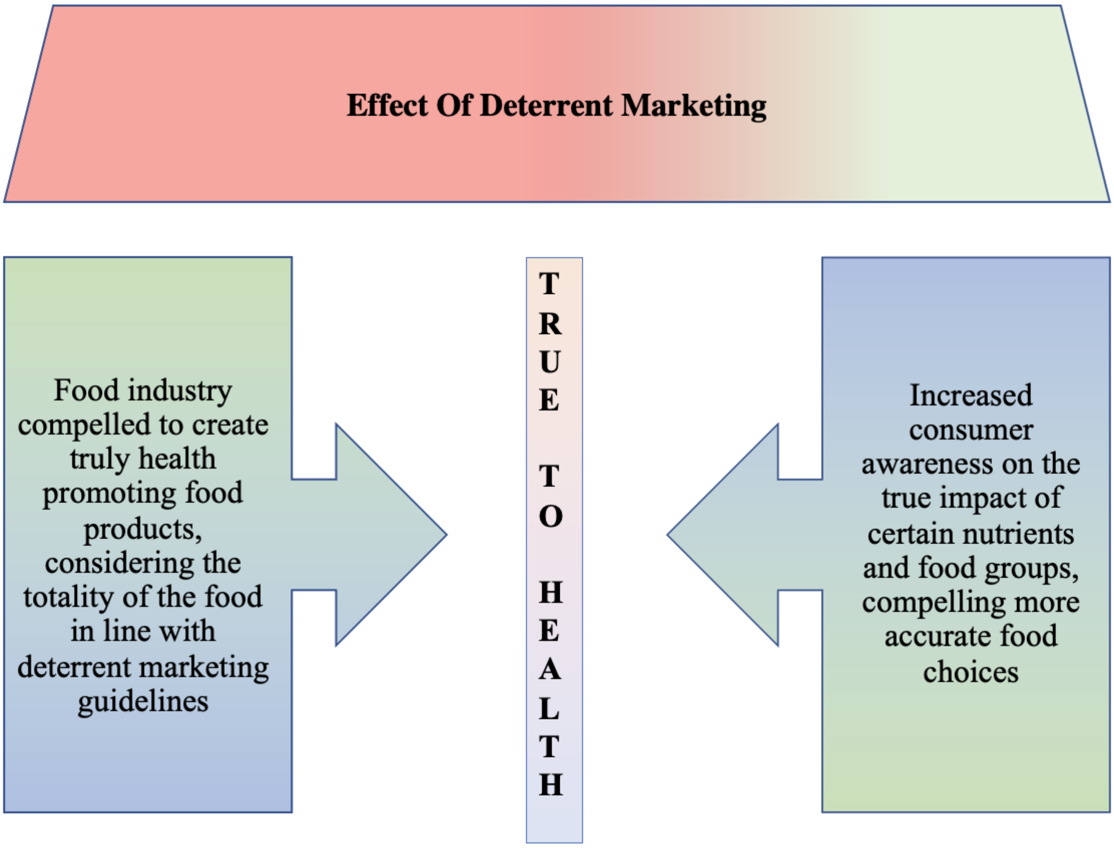

Figure 6.3.5.1 Shows the effect of deterrent marketing when applied.

Chapter 7

Conclusion & Future Work

7.0. Conclusion

In conclusion, the association between the rise in consumption of UPFs, as defined by the NOVA classification system, and the effect on obesity, T2D and CD in the EU was reviewed. the most relevant and current scientific research on this topic was evaluated, with the objective of analysing the relationship between UPFs and these diseases. Six studies were analysed across 9 EU countries, across 896,225 participants. All studies showed significant correlation between increased consumption of UPFs and increased risk of development of obesity, T2D and CD. Results also showed that a 10% incremental increase in consumption of UPFs was associated with a 15% higher risk in all-cause mortality, 12% increased risk of CD, and a significant increased risk in T2D (Suksatan *et al.*, 2022), (Srour *et al.*, 2020). Although all studies showed a relationship in increased risk in the onset of these diseases, the main limitation of the research is that causality of these associations were not captured, due to the study design. It can be postulated that the nature of UPFs contributes to increased disease risk of obesity, type 2 diabetes, and cardiovascular disease. As discussed, UPFs, are made from a series of industrial processes, incorporating a myriad of additives to enhance organoleptic properties, they typically have a low nutritional quality and are often energy dense, high in refined carbohydrates, sugars, salt, saturated fats with a low fibre content. They are void of whole unprocessed foods (Lane *et al.*, 2021). Foods high in saturated fat and salt, are known risk factors for the onset of cardiovascular diseases, and high energy foods with a high amount of refined carbohydrates and added sugars, are known risk factors for overweight and obesity, as well as the development of type 2 diabetes. Interestingly, all studies when adjusted for daily energy intake and other nutritional parameters, still showed a significant correlation between the consumption of UPFs and the risk of obesity, T2D and CD. This suggests that other nonnutritive factors perpetuate the risk of the development of these diseases. These non-nutritive factors could be bioactive compounds contained within the UPFs such as additives and possible process contaminants (Beslay *et al.*, 2020). The findings from this research were used to provide a more effective solution to reducing the rate of onset of obesity, T2D and CD, by 2030 in line with current EU strategy. The financial burden imposed by these non-communicable diseases (NCDs) equated to approximately 25% share of the EU healthcare budget as well as a 2% economic loss of GDP (Vandenberghe and Albrecht, 2020). The EU has implemented measures to support its member states in achieving the 9 voluntary targets set out by the United Nations and the World Health Organisation (WHO) as part of their global monitoring framework aimed at addressing the global burden of NCDs. As part of this, the targets set by WHO for the EU, aims to reduce premature deaths from NCDs by one third by 2030, as well as the reduction of overall mortality from CD, diabetes and other NCDs by 25% by 2025, from 2010. Currently the EU is off track to achieving 7 out of the 9 voluntary targets. A greater onus needs to be put on the food industry to supporting these goals, as poor diet is a main contributing risk factor to the onset of NCDs. UPFs are ubiquitous in society, and capitalise on current consumer health and wellness trends, sporting functional claims to sell their products. However, to achieve true to health formulations, the food industry needs to focus on all aspects of food formulation and not just the marketable ingredient or claim. A wholistic approach to evaluate the nutritional profile, food matrix, process conditions and functional ingredient mapping to understand which functional ingredients are better suited to which formulas, will ensure a truer to health formulation. More research into the effects of food additives, food ingredient substitutes, elimination of process contaminants and non-thermal processing need to be actively prioritised in the food industry, to truly understand the health impact of ingredients and processes. Lastly introducing legislation around deterrent marketing that considers the whole food formula, and applies deterrent marketing claims to pre-packaged food products, will help propel the food industry to create truly health promoting foods to avoid using deterrent marketing claims on their product. The increased consumer awareness through the implementation of these claims will facilitate more accurate and better food choices. This results in having pre-packaged foods that are true to health, without just being marketed as such.

7.1. Future work

From the findings of this study, further areas to be explored, is to analyse true causality of the association between UPF foods and the onset of obesity, T2D and CD. Exploring if certain foods, ingredients, or additives contribute a higher risk than others is essential, as well as further investigating the health effects associated with certain food additives that are common in UPF foods. To conduct this work, a review of the existing studies could be disseminated further and grouped to understand the common foods consumed by participants and the most common additives. Further primary research can be conducted initially to further investigate the effects of these ingredients and additives in the body. The implementation of legislation of deterrent marketing in the food industry, will prove impactful to balance out information to consumers, and help shift consumer choices, while propelling the food industry to created truer to health formulations. Lastly, process contaminants are usually formed in high heat processes, so exploring further alternative non- thermal processes and their compatibility with various foods is essential, to not only reduce process contaminants, but to provide more cost-effective sustainable options for the food industry. Investment into research and development is needed to achieve this goal.

Chapter 8

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