The influence of ultra-processed food consumption on developing multimorbidity

Author: Machteld Stegenga
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Department of Epidemiology
Supervisor: E. Corpelijn

Foreword

Ultra-processed foods are nowadays a huge part of our diet. Besides that health care is improving which increases the possibility of the accumulation of diseases in persons. Therefore multimorbidity, having two or more diseases is becoming an emerging topic of interest. That multimorbidity and diet are related to each is scientifically known, but how does the consumption of ultra-processed foods influence this? That is what has been researched in this review. During my bachelor's, I always had a great interest in how nutrition can influence disease. For that reason, I followed a minor in nutrition and health at the University of Wageningen. This broadens my knowledge and interest in the relationship between disease and nutrition. Writing this thesis, was an experience where I learned a lot about performing a literature search on my own. I found it sometimes difficult to put things on paper but when I found an interesting topic, I could not stop writing about it.

Summary

The increasing incidence of multimorbidity in the last decade is drawing attention to governments and healthcare providers. Ultra-processed foods (UPFs) have become a major part of our diet over the past years. However, this has led to increased concern related to the general health. The consumption of UPFs has been associated with multiple diet-related non-communicable diseases. Therefore it is important to investigate the association between preventable risk factors such as consumption of UPFs and the risk of developing multimorbidity.

A systemic search was performed in PubMed, Embase, and Google Scholar in March 2023. Three papers about multimorbidity and UPFs consumption were identified. Other papers linking UPFs consumption to the first disease were also included. Non-communicable diseases that were included are cardiometabolic disease, cancer, cardiovascular diseases, non-alcoholic fatty liver disease, metabolic syndrome, and respiratory diseases. The review revealed that high consumption of UPFs is not only related to single diseases but also linked to an increased risk of developing multimorbidity. The UPFs subgroup artificially and sugar-sweetened beverages had the strongest associations with the increasing risk of developing a single disease or multimorbidity. Replacing UPFs with minimally processed foods leads to a reduction of the risk of developing disease or multimorbidity. Further research needs to be conducted to establish this association and to investigate other lifestyle factors that can influence this association.

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Introduction

The consumption of ultra-processed foods (UPFs) nowadays is rapidly increasing (Córdova et al., 2023). Everywhere around us, fast food chains are popping up. But beside the increase in consumption of UPFs the prevalence of people with multimorbidity has increased drastically (Córdova et al., 2023).
UPFs became unnoticed a part of our daily diet. Fresh and minimally processed foods are replaced through UPFs. The part of UPFs from our diet is increasing. UPFs represent even nowadays 50-60% of our daily intake of energy in high income countries and middle income countries (Córdova et al., 2023). UPFs therefore do not only affect the developed countries but also, developing countries are struggling with this increase**.** Food processing has over the years changed to the preference of consumers. This led to the addition of natural and artificial ingredients to processed foods. Those additions may negatively impact the nutritional quality of the products because this usually leads to high sugar, fat, and salt content (Marino et al., 2021). According to the NOVA food classification system, there are four categories where food can be placed. Those groups are named: unprocessed or minimally processed foods; oils, fats, salt, and sugar; processed foods; and ultra-processed foods (Monteiro et al., 2017). UPFs are defined as industrially manufactured food products comprising deconstructed and modified food components recombined with a variety of additives (Córdova et al., 2023). Common subgroups of UPFs include; ultra-processed breads and cereals; sauces, spreads, and condiments; sweets and desserts; savory snacks; plant-based alternatives; animal-based products; ready-to-eat/heat mixed dishes; and artificially and sugar-sweetened beverages (Córdova et al., 2023). UPFs are characterized by their poor nutritional quality, high energy density, and low content of fiber and micronutrients. The combination of those factors contributes to an unhealthy diet pattern. Also, UPFs contain trans fats which are classified as harmful to cardiovascular health. Besides that consumption of UPFs is harmful to general health, since it replaces minimally processed foods, such as vegetables and fruits, in the diet. Vegetables and fruits are known to have a protective role in the prevention of disease (Juul et al., 2021).

The proportion of patients who have more than one medical condition simultaneously is rising steadily, despite the improving health care. Multimorbidity is having more than one disease at a time. Multimorbidity has a global prevalence of 37.2% and the highest prevalence rates are found in South America. Multimorbidity is also more prevalent in females (Chowdhury et al., 2023). Because life expectancy is increasing through medical improvements, the prevalence of many noncommunicable diseases and the co-existence of multiple diseases is also increasing (Starfield & Kinder, 2011). The reason for this is that multiple diseases can accumulate in persons who survive one disease. The increase in multimorbidity has several negative consequences such as reduced quality of life, longer hospital stays, and increased healthcare expenses (Skou et al., 2022). This is becoming a big problem for the current healthcare systems since people with multimorbidity require complex care. This is because when the diseases in a patient are treated separately, will lead to less good outcomes. For a single disease, there is good vertical integration from bench to bedside; however, there is little to no horizontal integration between diseases that frequently coexist (Starfield & Kinder, 2011). Also, persons with more than 1 chronic disease may have more rapid declines in health status and have a greater likelihood of disability (Wolff et al., 2002). The costs of a person with multimorbidity range from 800 to 150.000 dollars per year. Those costs depend mostly on disease combination, country, and cost ingredients (Tran et al., 2022).

The influence of UPFs on health has become an increasing topic of interest in research in the past few years. Several studies that were performed showed a positive correlation between the increased intake of UPFs and the risk of getting a non-communicable disease. Diseases such as cardiovascular disease, inflammatory bowel disease, and diabetes are shown to have a positive association with UPFs consumption. However, there is a lot unknown when looking at the link between UPFs and multimorbidity. Especially when looking at mechanisms there needs to a lot more research

conducted. Multiple studies investigated the association between UPFs and single disease, but studies investigating the association between UPFs consumption and multimorbidity are lacking. It is important to investigate preventable risk factors such as UPFs consumption in order to reduce the burden of multimorbidity.

Therefore the primary aim of this review is to investigate the influence of consumption of ultra-processed foods on the risk of developing multimorbidity. The secondary aim was to investigate the associations of UPFs consumption with a first diseases such as, cardiovascular diseases, non-alcoholic fatty liver disease (NAFLD), metabolic syndrome (MetS), respiratory diseases, cardiometabolic diseases, and cancer .

Results

Literature Search and Selection

A systemic research was conducted in March 2024 with the use of the following electronic databases: PubMed/MEDLINE, Embase, and Google Scholar. Search terms “cancer” or “Cardiovascular diseases” or “type 2 diabetes” or “Respiratory Disease” and ultra-processed foods were combined to be used in those databases. As a result, three main papers about multimorbidity and the association were identified. References of the identified multimorbidity papers were used to identify papers about single disease. Animal studies, maternal studies, COVID-19 studies and authors reply, were excluded. Diseases other than the diseases used in the three main papers were also excluded. Papers were also excluded when their main focus was mortality instead of morbidity.

Definition multimorbidity:

Multimorbidity is usually defined as the co-occurrence of at least two diseases or chronic conditions in one individual. The difference between multimorbidity and co-morbidity is that co-morbidity is usually defined as having more than one disease or condition at the same time, while multimorbidity is defined in the literature as having two diseases or more. In this review, multimorbidity is defined as having two diseases at the same time. Diseases that were the most prevalent in multimorbidity are diabetes, cardiovascular diseases, cancer, and respiratory diseases (Willadsen et al., 2016). Therefore the diseases included in this paper are cardiovascular diseases, non-alcoholic fatty liver disease (NAFLD), metabolic syndrome (MetS), respiratory diseases, cardiometabolic diseases, and cancer since they share common preventable risk factors including poor diet (Córdova et al., 2023). In this paper obesity is not seen as a disease but as a risk factor for developing certain diseases. Individuals with multimorbidity often experience poor quality of life, longer hospital stays, functional impairment, and more postoperative complications (Prados-Torres et al., 2014). Besides that, the coexistence of multiple diseases may lead to polypharmacy, which is the use of several medications. This is a problem in the treatment and survival of multimorbidity since polypharmacy increases the risk of drug-drug interactions. Those interactions may negatively impact physical and cognitive functioning. People with multimorbidity often experience an impairment cycle. This is because the complications of the first disease may lead to risk factors of developing the second disease and so on. For prevention, it is therefore important what the risk factors are for a single disease to prevent multimorbidity. Lifestyle risk factors such as unhealthy diet, smoking, and physical inactivity or smoking is known to have detrimental effects on health and well-being (Vajdi et al., 2020). For this paper, we investigate ultra-processed foods as risk factors for developing disease.

UPFs and disease

Cancer and cardiometabolic diseases

Multimorbidity

Córdova et al. (2023) are the first ones who perform a longitudinal prospective cohort study on the relationship between ultra-processed foods and the incidence of morbidity of cancer and cardiometabolic diseases. The study included 266.666 participants aged between 35 and 74 years, from seven European countries. They were all free of cancer, cardiovascular disease, and type 2 diabetes. They used data from the European Prospective Investigation into Cancer and Nutrition study (EPIC). Ultra-processed food intake was obtained through food frequency questionnaires. The mean consumption of UPFs accounted for men was 413 g/day (34% kcal of daily diet) and for women 326 g/day (32% kcal of daily diet). After 11.2 years, 4461 participants developed multimorbidity of cancer and cardiometabolic disease (Córdova et al., 2023). Cardiovascular disease was the first disease that occurred and cancer was the most common second multimorbidity disease that occurred, with a crude incidence rate of 17.1 events per 1000 person-years. UPFs consumption (an increase of 1 SD [260g/day]) was associated with a 9% increase in multimorbidity of cancer and

cardiometabolic disease (HR 1.09; 95% confidence interval (CI): 1.05-1.12). Subgroups analysis of UPFs showed that consumption of artificially and sugar-sweetened beverages and animal based products showed a positive association with the risk of getting multimorbidity (HR_{1SD} 1.09; 95% CI: 1.05-1.12). However ultra-processed breads and cereals showed an inverse association with getting the risk of multimorbidity (HR_{1SD} 0.97; 95% CI: 0.94-1.00). Remaining UPFs groups showed no association with the risk of multimorbidity.

Cancer and UPFs

According to the French NutriNet-Sante cohort (101.257 participants) there was a positive association between consumption of sugary drinks and risk of overall cancer (HR 1.18 for 100ml/d increase (SD), 95% CI: 1.10-1.27) and breast cancer (HR_{sd}: 1.22, 95% CI: 1.07-1.39). In addition in Canadian case-control study, consumption of high-sugar beverages (more than 7 drinks per week compared to less than 1 drink per week) was associated with early onset of colorectal cancer (OR 2.99, 95% CI: 1.57-5.68). The French NutriNet-Sante study found that a 10% increase of UPFs in total diet was associated with 12% (95% CI: 1.06-1.18) increased risk of getting cancer, 11% (95% CI: 1.02-1.22) increased risk of developing breast cancer. However, there was no association observed between colorectal cancer and prostate cancer. In addition, more recent studies found less consistent associations between UPFs and breast or prostate cancer, while there is a positive association found between UPFs and colorectal cancer risk. A 10% increase of UPFs as part of a normal diet, has been associated with 11% (OR 1.11, 95% CI: 1.04-1.18) higher risk of colorectal cancer. A study conducted in Spain found that there was no association between UPFs and chronic lymphocytic leukemia. However, when cases were limited to diagnosis within one year, a 10% increment was associated with a 22% (OR: 1.22; 95% CI 1.02-1.47) higher risk. The PROtEuS study observed that higher prostate cancer risk was associated with higher UPFs consumption (OR: 1.29, 95% CI 1.05-1.59 highest vs. lowest quartile) but not with the consumption of UPFs drinks and food. Fiolet et al. (2018) found that UPFs fats and sauces (P = 0.002), sugary products (P = 0.03), and drinks (P = 0.006) were all associated with increased risk of overall cancer. UPFs sugary drinks were specifically associated with an increased risk of breast cancer (P=0.006).

Cardiometabolic and UPFs

Cardiometabolic disease is a combination of conditions from cardiovascular diseases (CVD) and metabolic diseases. Conditions related to CVD include; coronary heart disease (CHD), stroke, and hypertension. Metabolic disease conditions include; type 2 diabetes and obesity. In this paper, obesity is more seen as a contributing factor than as a disease since obesity contributes to most diseases that are found in multimorbidity. According to Juul et al. (2022), high consumption of UPFs was associated with a higher risk of getting metabolic syndrome in USA adults, ranging from 28% to 90% increased risk (Adjusted prevalence ratio USA [APR]: 1.28, 95% CI 1.09-1.50 for quintile 5 vs. 1) (adjusted odds ratio Canada [AOR]:1.90, 95% CI 1.14-3.17 for quintile 5 vs. 1). A study performed on Brazilian adults found that the group with highest UPFs consumption had a 2.5 chance higher risk (APR: 2.45, p = 0.012) of developing metabolic syndrome compared to the group who had the lowest UPFs consumption (Tavares et al., 2011). Even in Lebanese adults adherence to the minimally processed dietary pattern was associated with a lower risk of metabolic syndrome (OAR: 0.18, 95% CI: 0.04-0.77) (Nasredinne et al., 2017). The Spanish SUN study and ELSA-Brasil concluded that people who were in the highest tertile of UPFs consumption had a 21 to 23% higher risk of developing hypertension compared to those in the lowest tertile. Looking at the metabolic part, Juul et al. (2022) found that each 10% increase in UPFs consumption in the diet was associated with a 12 to 15% higher risk of developing type 2 diabetes (T2D). According to the SUN study participants who had the highest UPFs consuming patterns had a 53% chance of developing T2D compared to those who were in the lowest UPFs consuming patterns (HR 1.53; 95% CI 1.06-2.22). Juul et al. (2022) concluded that UPFs consumption was associated with hypertriglyceridemia and low HDL, while no significant association with high LDL cholesterol was found. Juul et al. (2022) overall supported the association of UPFs consumption and increased risk of cardiometabolic diseases.

Comparison of multimorbidity and single disease

Overall when looking at disease individually and when they are combined in multimorbidity, an increase in UPFs consumption is associated with higher risk developing disease, as shown is in figure 1. There are differences on the height of the risk. Since only one study performed analysis, on this combination of diseases in multimorbidity it is yet not significant. The consumption of ultra-processed sugary drinks showed a positive association with multimorbidity and cancer.

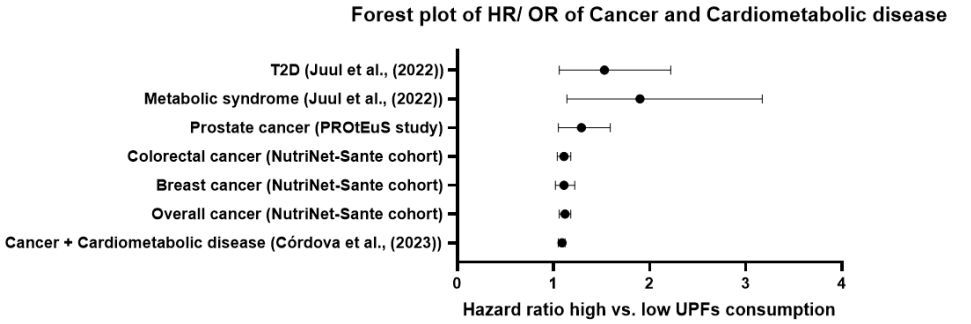

Fig. 1: Associations between ultra-processed food consumption and risk of developing single disease or multimorbidity. High versus low UPFs consumption was compared. For multimorbidity of cancer with cardiometabolic disease the HR for increase of 260g/day of UPFs was used. For overall cancer, breast cancer, and colorectal cancer the HR for a 10% increase of total diet was used. For prostate cancer and Metabolic syndrome OR was used instead of HR.

Cardiovascular and Respiratory disease

Multimorbidity

Li, Li et al. (2023b) is the only cohort study to examine the association of UPFs with multimorbidity of CVD and respiratory disease. They obtained data from a prospective cohort study that was based in the UK. They examined the association of UPFs consumption with mortality and incidence of CVD and respiratory disease. The study included 126.848 participants aged 40-69 years. For the analysis of the multimorbidity, 94.691 participants were included. 1682 participants developed CVD and respiratory disease. The main food groups that were contributing to UPFs intake were: beverages (34%) and sugary products (21%) followed by ultra-processed dairy products (17%) and salty snacks (11%). It was found that per 10% increase in UPFs in the diet there was an association with a 6% increased risk of CVD and respiratory disease multimorbidity (HR: 1.06; 95% CI 1.01-1.12) (Li, Li et al., 2023b).

Cardiovascular disease and UPFs

Pant et al. (2023) used data from the Australian Longitudinal Study on Women's Health. In that cohort, women aged between 50 and 55 years were followed for 15 years. In the study, CVD was identified as a physician-diagnosed self-reported heart disease or stroke. Secondary endpoints were incident hypertension, type 2 diabetes mellites, obesity, and all-cause mortality. The cohort included 10.006 participants. During the 15-year follow up there were 1038 reported CVD cases (10.8%), 4204 (43.8% cases of hypertension, 1219 cases of type 2 diabetes (12.7%), and 3596 cases of obesity (36%). Pant et al. (2023) concluded that there was no significant association between UPFs consumption and CVD ($p = 0.18$). There was no significant difference between the highest UPFs consumption (>34.2% of total dietary intake) compared to lowest UPFs consumption (<18.1% of total dietary intake) with the incidence of CVD cases (OR 1.22; 95% CI 0.92-1.61, $p = 0.16$). However, Pant et al. (2023) did find a significant association between hypertension and UPFs consumption. The highest UPFs consumption group had a 39% (OR 1.39; 95% CI 1.10-1.74) higher chance of getting hypertension compared to the lowest UPFs consumption group. UPFs products that were mostly consumed were: ready-made meals (24.7%), packaged bread (24.6%), milk-based drinks (18.2%), breakfast cereals (5.7%), and processed meat (4.9%).

Li, Li et al. (2023b) did a prospective cohort study about the associations between diet and health outcomes. They recruited people from Malmö (Sweden) and 26.369 individuals aged between 45 and 73 years were included. CVD includes coronary heart disease (CHD) and stroke. Median UPFs

consumption in the lowest quartile was 199.7 g/day and in the highest quartile 620.5 g/day. Li et al. (2023) found that highest UPFs consumption was associated with 18% (adjusted hazard ratio [AHR]: 1.18, 95% CI 1.08-1.29) greater risk of developing CVD, 20% (AHR 1.20, 95% CI 1.07-1.35) higher risk of developing CHD, and 17% (AHR 1.17, 95% CI 1.03-1.32) greater risk for developing ischemic stroke compared to lowest UPFs consumption quartile. For each 211 g/day increase intake of UPFs, there was an increased risk of 7% (HR 1.07; 95% CI 1.04-1.11) for CVD and CHD and 8% (HR 1.08; 95% CI 1.04-1.13) for ischemic stroke. Li et al. (2023) also replaced UPFs with the equivalent of minimally processed food which led to a 6% (HR 0.94; CI 95% 0.91-0.97) (HR 0.93; 95% CI 0.89-0.97) lower risk of CVD and ischemic stroke and 7% (HR 0.93; 95% CI 0.91-0.98) lower risk of CHD.
The prospective Framingham Offspring Study, which included 3003 participants, showed that there was 7% (HR 1.07; 95% CI 1.03-1.12) increase in risk of developing CVD with each 10% increase of UPFs consumption. The NutriNet-Santé cohort study, which included 105.159 participants showed that there was an 11 to 13% increased risk of developing CVD, CHD, and cerebrovascular disease with each 10% increase of UPFs consumption (Juul et al., 2022).
Li, Li et al. (2023b) found when comparing lowest UPFs consumption (8.3% of total dietary intake) to highest UPFs consumption (31.6% of total dietary intake), there was increased risk of 19% (HR 1.19, 95% CI 1.11-1.25) for CVD, 10% (HR 1.10; 95% CI 0.97-1.24) for cerebrovascular disease and 24% (HR 1.24; 95% CI 1.14-1.34) for CHD for the highest UPFs quartile.

Respiratory disease and UPFs
Li, Li et al. (2023b) discovered when comparing lowest UPFs consumption (8.3% of total dietary intake) to highest UPFs consumption (31.4% of total dietary intake), that there was increased risk of 12% (HR 1.12; 95% CI 1.05-1.18) for respiratory disease, 3% (HR 1.03; 95% CI 0.87-1.23) for chronic obstructive pulmonary disease (COPD), 3% (HR 1.03; 95% CI 0.89- 1.18) for asthma. They found that the association between UPFs consumption and respiratory disease was strongest for inactive participants (11% increased risk, HR 1.11; 95% CI 1.05-1.17) compared to active participants (2% increased risk, HR 1.02; 95% CI 1.00-1.05).
Azeredo et al. (2019) analyzed data from the 2004 Peletos Birth Cohort study. They included 2190 participants aged 11 years, who did not have asthma at age 6. The highest and lowest UPFs consumption quintiles at age 6 were compared there was no association found with wheeze (OR 0.85, 95% CI 0.54-1.34), asthma (OR 0.84; 95% CI 0.58-1.21) or severe asthma (OR 1.12, 95% CI 0.62-2.03) in early adolescence. When they analyzed the highest UPFs consumption and lowest UPFs consumption at age 11 no association was found with wheeze (OR 1.12; 95% CI 0.72-1.75), asthma (OR 1.00; 95% CI 0.7-1.44) or severe asthma (OR 1.05; 95% CI 0.59-1.86) (Azeredo et al., 2019).
Melo et al. (2018) did a cross-sectional study on the association of UPFs consumption and drink products with asthma and wheezing in Brazilian adolescents. 109.104 participants were included aged between 10 to 22 years. For asthma, there was an increased risk of 8% (AOR 1.08; 95% CI 1.03-1.13) when consuming sweets/candies and a 30% (AOR 1.30; 95% CI 1.21-1.40) increased risk when consuming ultra-processed meats compared to low consumption UPFs. Similar results were found for wheezing. Comparing the highest quintile UPFs consumption to the lowest quintile UPFs consumption was associated with 27% (AOR 1.27; 95% CI 1.14-1.41) increased risk for asthma and 42% (AOR 1.42; 95% CI 1.35-1.50) increased risk for wheezing. The association for asthma was stronger for male adolescents who did not consume fruits and vegetables regularly. The associations for wheezing were stronger for non-smokers, who did not consume vegetables and fruits regularly, had non-smoker parents, and lived in non-capital cities (Melo et al., 2018).

Comparison of multimorbidity and single disease
High consumption of UPFs leads to an increased risk of single disease and multimorbidity as shown is in figure 2. The risk varied between 3% and 42% dependent on factors such as type of disease, type of most consumed UPFs, and lifestyle factors such as smoking and physical activity levels.

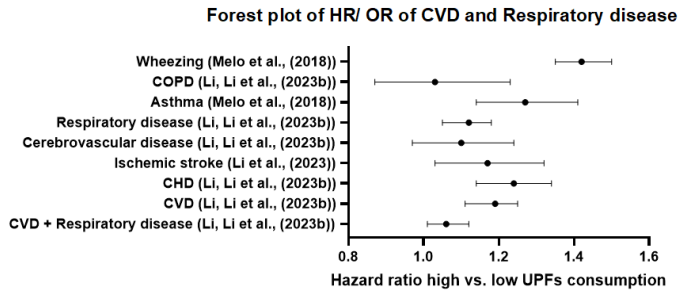

Fig. 2: Associations between ultra-processed food consumption and risk of developing single disease or multimorbidity. High versus low UPFs consumption was compared. For multimorbidity of CVD and respiratory disease the HR for a 10% increase of total diet was used. For Asthma and Wheezing the OR was used instead of HR.

Non-alcoholic fatty liver disease (NAFLD) and metabolic syndrome

Multimorbidity

Konieczna et al. (2022) did a prospective analysis of 5867 metabolic syndrome (MetS) patients from the PREDIMED-plus trial. They investigated the association between UPFs consumption and liver health biomarkers. The fatty liver index (FLI) and hepatic steatosis index (HSI) were used as surrogate measures for NAFLD. The mean UPFs consumption was 8.19% of total daily intake. The consumption of UPFs was divided into quintiles. The highest UPFs consumption quintile (Q5) accounted for a mean UPFs consumption of 19.0%, while the lowest quintile had a mean consumption of 2.12% (Q1). Participants in those quintiles were younger and had less healthy lifestyle habits compared to quintile 1. Sweets (28%), non-alcoholic beverages (26%), and processed meats (22%) were the main UPFs subgroups consumed. They showed that Q5 had a 3.73 times higher FLI score compared to Q1 (β estimates for Q5 3.73; 95% CI 3.10-4.35). Also, the HSI score of Q5 was 0.93 times higher compared to Q1 (β estimates for Q5 0.93; 95% CI 0.67-1.18). Therefore a higher UPFs consumption is associated with a higher risk of getting NAFLD in metabolic syndrome patients.

NAFLD and UPFs

Grinshpan et al. (2023) performed a systemic review on the association between UPFs consumption and NAFLD, MetS, and insulin resistance. The prospective cohort study of Zhang et al. (2022), 16.168 participants, showed that the highest UPFs consumption compared to the lowest UPFs consumption had an 18% increased risk (HR 1.18, 95% CI 1.07-1.30) of developing NAFLD. 62,7 g/1000 kcal day increase in UPFs consumption was associated with a 6% (HR 1.06, 95% CI 1.03-1.09) risk increase of developing NAFLD (Zhang et al., 2021). A Spanish prospective cohort study showed that a 10% increase in UPFs consumption was associated with an increase in NAFLD-related biomarkers (FLI and HSI) (Konieczna et al., 2022).

Cross sectional studies showed that higher UPFs consumption (4^{th} quartile >68.3% compared to 1^{st} quartile <41.6%) was associated with 83% (OR 1.83; 95% CI 1.33-2.53) higher odds of developing NAFLD (Liu et al., 2022). The cross-sectional study by Friden et al. (2022) showed that there was no association when UPFs consumption increased by 10% (OR 1.32; 95% CI 0.84-2.09) on the prevalence of NAFLD (Fridén et al., 2022). However, the association of UPFs and NAFLD risk is not well established and therefore more prospective studies are needed to establish this association.

Metabolic syndrome and UPFs

Grinshpan et al. (2023) performed a systemic review on the association between UPFs consumption and NAFLD, MetS, and insulin resistance. They showed that prospective studies showed an increased risk of developing MetS ranging from 17% (HR 1.17; 95% CI 1.01-1.35) to 19% (RR 1.19; 95% CI 1.07-32) with high UPFs consumption compared to low consumption. The cross-sectional studies showed that higher UPFs consumption compared to low consumption was associated with higher odds (OR 1.88; 95% CI 1.31-2.71) (OR 1.90, 95% CI 1.14-3.17) and higher prevalence (PR 1.28; 95% CI 1.09-1.50) of MetS. Higher prevalence association was the strongest in young adults (PR 1.94; 95% 1.39-2.72) and it decreased with age.

Comparison of multimorbidity and single disease
High consumption of UPFs leads to an increased risk of single disease and multimorbidity. But in multimorbidity, there were looked liver health markers which were related to NAFLD. Therefore there is no significant comparison possible between multimorbidity and single-disease.

Discussion

Comparison data

This study reviewed the association between consumption of ultra-processed foods and multimorbidity and the difference compared to single disease and UPFs. All the studies showed that high consumption of UPFs was associated with increased risk of developing multimorbidity compared to low consumption of UPFs. The height of the risk of developing multimorbidity or disease when having high consumption of UPFs differ among the diseases. Consumption of UPFs beverages was contributing the most to UPFs consumption in most of the papers. UPFs beverages is associated with developing multimorbidity of cancer and cardiometabolic disease, cancer and multimorbidity of CVD and respiratory disease. This is line with the known literature (Córdova et al., 2023). High consumption of sugar sweets is also been associated with an increased risk of developing asthma. However, consuming ultra-processed breads showed a decreased risk of developing multimorbidity of cancer and cardiometabolic diseases. This is because ultra-processed contains fiber which has a proven beneficial health effect (Dreher, 2018). Several studies showed an analysis of replacing UPFs with minimally processed foods. All the studies indicated that the replacement of UPFs with minimally processed foods is been associated with a reduced risk of developing metabolic syndrome, CVD, Ischemic stroke, and CHD. This is a good indication of how diet can impact the risk of developing multimorbidity or a single disease.
The dietary assessment differed greatly among the papers. Food frequency questionnaires (FFQs) were used the most followed by 24-hour dietary recall. The FFQs were mostly several items FFQs, for example, a 148-item FFQs whereby the participants could indicate how many times they consumed it over the past year. All the dietary assessments that were used are verified and tested according to professionals such as dieticians. However, FFQs lack often the specificity to distinguish between the level of processing. 24-hour recalls may be insufficient to give a good indication of processing.
All the papers identified the degree of processing of the food items according to the NOVA classification. However, it is not possible to exclude the possibility of misclassification in the NOVA ultra-processed food category (Fiolet et al., 2018). The NOVA classification was developed in 2009, some dietary interventions are dated before that but are adjusted to nowadays processing. There is some criticism about NOVA classification saying that it is imprecise, vague, and qualitative. However, this caused the NOVA classification is still improving (Kliemann et al., 2022).
In addition, there is a great variation in the definition of high and low consumption among the papers. This is because the dates of when the dietary assessments were performed differ greatly. Dietary assessments from the '90s differ from dietary assessments that were done in 2010. However, it remained that high consumption was more harmful than low consumption of UPFs.

Mechanism

There are several explanations possible for why the consumption of UPFs is harmful for the chance of developing disease or multimorbidity.
Components of UPFs that have harmful characteristics
First, several epidemiological studies have shown that diets higher in UPFs contain overall less favorable nutrients such as fiber, essential vitamins/ minerals, and proteins (Li, Li, et al., 2023b). They usually contain high amounts of trans fat, added/free sugars, sodium, and saturated fat and are high in total energy and fat content. Added sugars and saturated fatty acids are known risk factors for developing NAFLD (Grinshpan et al., 2023)**.** Through particular activation states in macrophages, high salt consumption was associated with a possible risk of lung inflammation (Li, Li, et al., 2023b). It was

also associated with an increased risk of hypertension, which is a major risk factor for developing stroke and CVD (Juul et al., 2021).
Advanced glycation end products are abundant in UPFs and have been linked to the production of pro-inflammatory cytokines like tu-alpha. They can also increase or induce oxidative stress. Which are mediators in the development of several diseases (Li, Li, et al., 2023b).
In addition, high levels of fat, salt, sugar, and artificial flavorings make ultra-processed products highly palatable, for which endogenous satiety mechanisms may be superseded (Juul et al., 2021).
Satiety mechanisms of humans are more sensitive to volume than caloric content, therefore UPFs , which are energy-dense may promote excessive intake of energy products. Experimental studies suggest that increasing eating rates may result in increased energy intakes, possibly due to delayed satiety signaling.
The nutrients present in highly processed foods are predominantly acellular. Experimental studies suggest that the substantial proportion of acellular nutrients present in highly processed foods results in a high level of nutrient availability in the small intestine, thereby promoting an inflammatory gut microbiota associated with cardiometabolic conditions (Juul et al., 2021).
The consumption of low-calorie sweeteners has the potential to disrupt the diversity and equilibrium of the gut microbiota, leading to metabolic disorders and insulin resistance. In animal studies, it has been shown that emulsifiers increase the pro-inflammatory potential of the microbiome by increasing the microbiotic virulence factor (Juul et al., 2021). The abundance of certain specific taxa has been related to the pathophysiology of NAFLD.

Processing of food

UPFs usually entails the addition of additives like flavors, thickeners, emulsifiers, sweeteners, and preservatives. These substances have the potential to exacerbate chronic inflammation by interacting with the microbiome, host, and diet resulting in detrimental health effects (Li, Li, et al., 2023b).
During food processing contaminants, such as heterocyclic amines, polycyclic aromatic hydrocarbons, oxyhalides, and haloacetic acids, are formed. Those contaminants have been linked to increased cancer risk. Additives that are commonly part of UPFs have been authorized and evaluated for general safety. However not much is known about the accumulation of those additives on the long term. Experimental studies have suggested that several additives have carcinogenic properties (Juul et al., 2022).
The additives present within UPFs have the potential to contribute to NAFLD, possibly through their pro-oxidative and pro-inflammatory properties, such as the presence of endocrine-disrupting chemicals (EDCs) and advanced glycation end products (AGEs) (Grinshpan et al., 2023). AGE plays a role in NAFLD pathogenesis, the mechanism behind this is that activation in the liver of RAGE by AGE leads to downstream cascade signaling which includes hepatocyte ballooning and oxidative stress (Grinshpan et al., 2023).

Consumption pattern of UPFs

Excessive obesity has been linked to higher UPFs consumption in both experimental and epidemiological studies. Several studies demonstrated that the consumption of UPFs leads to excess energy intake, which is a key factor in developing obesity (Juul et al., 2021). Obesity is a well-established risk factor for several cancers including breast, prostate, and colorectal cancer (Juul et al., 2022).
UPFs consumption is one of the main causes of excessive sugar intake, which has been associated with multiple CVD risk factors. Those include overall and abdominal adiposity, hypertension, insulin resistance, type 2 diabetes, and dyslipidemia (Juul et al., 2021).
In addition, the gut microbiome is greatly influenced by the diet. UPFs consumption usually causes that there is less fiber consumed, therefore the gut microbial metabolism shifts toward utilization of proteins and host mucins. It results in a degradation of the intestinal mucus layer and an increased susceptibility to chronic inflammatory disease, which is mostly seen in multimorbidity (Juul et al., 2021).

Besides the high that a UPFs diet is less nutritious, the high consumption of UPFs replace also the more nutritious foods such as fruits and vegetables. Therefore the protective effect of high fruit and vegetable consumption is reduced (Juul et al., 2021).
UPFs are on average more hyperglycemic than minimally processed foods. The glycemic response is influenced by the quantity and quality of carbohydrates, fat, protein, and fiber content, food matrix structure, and degree of processing. Hyperglycemia increases the risk of CVD by promoting weight gain, inflammation, oxidative stress, and endothelial dysfunction (Juul et al., 2021).
Packaging of food
The use of UPFs may raise exposure to phthalates and bisphenol A (BPA), which are used in the production and packaging of food. Di(ethylhexyl)phthalate (DHEP) is commonly used as a plasticizer. Exposure to DHEP is been associated with cancer induction through multiple molecular signals which include DNA damage (Kliemann et al., 2022).
Previous research suggests a potential link between BPA exposure and lipid peroxidation, DNA damage, and inflammation, all of which are recognized risk factors for endothelial cell damage and respiratory diseases (Li, Li, et al., 2023b). In addition, epidemiological evidence suggests that greater exposure to BPA is associated with increased prevalence of important risk factors, which include diabetes, overall and abdominal obesity, and hypertension, for cardiovascular diseases. Studies on animals also corroborate the link between BPA, oxidative stress, and inflammation. Due to increased oxidative stress and inflammatory levels, many cardiovascular disorders have certain markers, which may play a significant part in the pathogenesis of CVD brought by BPA exposure (Li, Li, et al., 2023b). It has been demonstrated that BPA can enhance insulin resistance, oxidative stress, inflammation, adipogenesis, and pancreatic B-cell dysfunction by binding to estrogen-related receptors. However, the exact mechanisms are not yet fully understood. Foods stored or reheated in BPA-lined containers are believed to be the primary source of human exposure (Juul et al., 2021).

Future research possibilities

Despite that both multimorbidity and UPFs are becoming popular research topics, nowadays still is unknown or unclear about the combination of them. There are only 3 papers that identify the association between UPFs and multimorbidity. Therefore there should be more research conducted on the combination of multimorbidity and diet in general. There is a lot unknown about the underlying mechanisms of how UPFs interact with multimorbidity. Also to understand the influence of UPFs on multimorbidity, it is important to understand how diseases in multimorbidity interact with each other. Only a few papers describe the interaction of disease-disease and therefore there needs to be more research conducted on how diseases interact with each other to understand how diet can influence this interaction.
It has been shown that different subgroups of UPFs can have different influences on the risk of developing multimorbidity. However, different subgroups of UPFs are only linked to multimorbidity of cancer with cardiometabolic diseases, cancer, and asthma. Therefore more research should be conducted on how the different subgroups of UPFs can influence the association between UPFs consumption and developing multimorbidity or disease.
Several studies showed how other lifestyle factors such as physical activity can influence the association of UPFs consumption and developing disease. However, more research needs to be conducted to investigate the interaction of lifestyle factors on developing diseases.
Since there was a lot of variation in the definition of high consumption it should be researched, what is considered as the threshold for high consumption. This is important for implementing possible dietary advice to the general public.
A few studies noticed a difference between sex and the chance of developing a disease. The chance of developing diseases is known to differ between sexes, but not known why it differs. Therefore more research should be performed to know the risk factors for each sex.

Implications for public health

Co-occurrence of diseases leads to many negative outcomes such as; impaired health-related quality of life, high costs of care, etc. Therefore it is important to inform patients with primary non-communicable diseases of the negative impacts of consuming UPFs. This group is especially targeted since they are at higher risk of developing multimorbidity compared to those who don't have a disease already. Other target groups are those with less healthy lifestyle habits, to who have lower education, and people with obesity (Skou et al., 2022).
Overall policy makers should target to reduce the consumption of UPFs since several studies found that high consumption of UPFs is strongly associated with the increasing risk of developing single non-communicable disease and multimorbidity.

Conclusion

To answer the question of this paper, high consumption of ultra-processed foods increases the risk of developing multimorbidity compared to low consumption of ultra-processed foods. The strongest associations were found for consuming ultra-processed sugary beverages. However future research needs to be conducted to establish the association between ultra-processed foods and multimorbidity.

Afterword

During writing of the thesis, I learned a lot about finding the right articles when a subject is relatively new topic of research. I learnt how to deal with limiting research available. Besides that, I learned how to critically read papers and form my own opinion about their results and research methods. During the writing of my thesis, I found out how many lifestyles can influence each other and disease. This helped me to decide which academic career I would like to pursue after finishing my bachelor's. I would like to thank Mrs. E. Corpelijn for first being the supervisor for my bachelor thesis, helping with find a topic to do my bachelor thesis about, and thinking together about possible ideas for the thesis. I also would like to thank Miss. Q. Zou for helping answer all the questions I could ask at any time about the thesis and for helping with ways to improve my thesis.

References

Azeredo, C. M., Cortese, M., Costa, C., Bjørnevik, K., Barros, A. J. D., Barros, F. C., Santos, I. S., & Matijasevich, A. (2019). Ultra-processed food consumption during childhood and asthma in adolescence: Data from the 2004 Pelotas birth cohort study. *Pediatric Allergy and Immunology*, *31*(1), 27–37. https://doi.org/10.1111/pai.13126
Chowdhury, S. R., Das, D. C., Sunna, T. C., Beyene, J., & Hossain, A. (2023). Global and regional prevalence of multimorbidity in the adult population in community settings: a systematic review and meta-analysis. *EClinicalMedicine*, *57*, 101860. https://doi.org/10.1016/j.eclinm.2023.101860
Córdova, R., Viallon, V., Fontvieille, E., Peruchet-Noray, L., Jansana, A., Wagner, K., Kyrø, C., Tjønneland, A., Katzke, V., Bajracharya, R., Schulze, M. B., Masala, G., Sieri, S., Panico, S., Ricceri, F., Tumino, R., Boer, J. M. A., Verschuren, W. M. M., Van Der Schouw, Y. T., . . . Freisling, H. (2023). Consumption of ultra-processed foods and risk of multimorbidity of cancer and cardiometabolic diseases: a multinational cohort study. *the Lancet Regional Health. Europe*, *35*, 100771. https://doi.org/10.1016/j.lanepe.2023.100771
Dreher, M. L. (2018). Whole fruits and fruit fiber emerging health effects. *Nutrients, 10*(12), 1833. https://doi.org/10.3390/nu10121833

Fiolet, T., Srour, B., Sellem, L., Kesse-Guyot, E., Allès, B., Méjean, C., Deschasaux, M., Fassier, P., Latino-Martel, P., Beslay, M., Herçberg, S., Lavalette, C., Monteiro, C. A., Julia, C., & Touvier, M. (2018). Consumption of ultra-processed foods and cancer risk: results from NutriNet-Santé prospective cohort. *BMJ. British Medical Journal*, k322. https://doi.org/10.1136/bmj.k322
Fridén, M., Kullberg, J., Åhlström, H., Lind, L., & Rosqvist, F. (2022). Intake of Ultra-Processed food and ectopic-, visceral- and other fat depots: A Cross-Sectional Study. *Frontiers in Nutrition*, *9*. https://doi.org/10.3389/fnut.2022.774718
Grinshpan, L. S., Eilat-Adar, S., Ivancovsky-Wajcman, D., Kariv, R., Gillon-Keren, M., & Zelber–Sagi, S. (2023). Ultra-processed food consumption and non-alcoholic fatty liver disease, metabolic syndrome and insulin resistance: a systematic review. *JHEP Reports*, 100964. https://doi.org/10.1016/j.jhepr.2023.100964
Juul, F., Deierlein, A., Vaidean, G., Quatromoni, P. A., & Parekh, N. (2022). Ultra-processed Foods and Cardiometabolic Health Outcomes: from Evidence to Practice. *Current Atherosclerosis Reports*, *24*(11), 849–860. https://doi.org/10.1007/s11883-022-01061-3
Juul, F., Vaidean, G., & Parekh, N. (2021). Ultra-processed foods and cardiovascular diseases: Potential mechanisms of action. *Advances in Nutrition (Bethesda, Md. Print)*, *12*(5), 1673–1680. https://doi.org/10.1093/advances/nmab049
Kliemann, N., Nahas, A. A., Vámos, E., Touvier, M., Kesse-Guyot, E., Gunter, M. J., Millett, C., & Huybrechts, I. (2022). Ultra-processed foods and cancer risk: from global food systems to individual exposures and mechanisms. *British Journal of Cancer*, *127*(1), 14–20. https://doi.org/10.1038/s41416-022-01749-y
Konieczna, J., Fiol, M., Colom, A., Martínez-González, M. Á., Salas-Salvadó, J., Corella, D., Soria-Florido, M. T., Hernández, J. a. M., Alonso-Gómez, Á. M., Wärnberg, J., Vioque, J., López-Miranda, J., Estruch, R., Bernal-López, R., Lapetra, J., Serra-Majem, L., Bueno-Cavanillas, A., Tur, J. A., Martín, V., . . . Romaguera, D. (2022). Does Consumption of Ultra-Processed Foods Matter for Liver Health? Prospective Analysis among Older Adults with Metabolic Syndrome. *Nutrients*, *14*(19), 4142. https://doi.org/10.3390/nu14194142
Li, H., Li, S., Yang, H., Zhang, Y., Ma, Y., Hou, Y., Zhang, X., Sun, L., Borné, Y., & Wang, Y. (2023a). Association of Ultra-Processed Food Intake with Cardiovascular and Respiratory Disease Multimorbidity: A Prospective Cohort Study. *Molecular Nutrition & Food Research (Print)*, *67*(11). https://doi.org/10.1002/mnfr.202200628
Li, H., Li, S., Yang, H., Zhang, Y., Ma, Y., Hou, Y., Zhang, X., Sun, L., Borné, Y., & Wang, Y. (2023b). Association of Ultra-Processed Food Intake with Cardiovascular and Respiratory Disease Multimorbidity: A Prospective Cohort Study. *Molecular Nutrition & Food Research (Print)*, *67*(11). https://doi.org/10.1002/mnfr.202200628
Li, H., Wang, Y., Sonestedt, E., & Borné, Y. (2023). Associations of ultra-processed food consumption, circulating protein biomarkers, and risk of cardiovascular disease. *BMC Medicine*, *21*(1). https://doi.org/10.1186/s12916-023-03111-2
Liu, Z., Huang, H., Zeng, Y., Chen, Y., & Xu, C. (2022). Association between ultra-processed foods consumption and risk of non-alcoholic fatty liver disease: a population-based analysis of NHANES 2011–2018. *British Journal of Nutrition*, *130*(6), 996–1004. https://doi.org/10.1017/s0007114522003956
Marino, M., Puppo, F., Del Bò, C., Vinelli, V., Riso, P., Porrini, M., & Martini, D. (2021). A Systematic Review of Worldwide Consumption of Ultra-Processed Foods: Findings and Criticisms. *Nutrients*, *13*(8), 2778. https://doi.org/10.3390/nu13082778
Melo, B. D. C., Rezende, L. F. M., Machado, P., Gouveia, N., & Levy, R. B. (2018). Associations of ultra-processed food and drink products with asthma and wheezing among Brazilian adolescents. *Pediatric Allergy and Immunology*, *29*(5), 504–511. https://doi.org/10.1111/pai.12911
Monteiro, C. A., Cannon, G., Moubarac, J., Levy, R. B., Da Costa Louzada, M. L., & Jaime, P. C. (2017). The UN Decade of Nutrition, the NOVA food classification and the trouble with ultra-processing. *Public Health Nutrition*, *21*(1), 5–17. https://doi.org/10.1017/s1368980017000234
Nasreddine, L., Tamin, H., Itani, L., Nasrallah, M., Isma'eel, H., Nakhoul, N., Abou-Rizk, J., & Naja, F.

(2017). A minimally processed dietary pattern is associated with lower odds of metabolic syndrome among Lebanese adults. *Public Health Nutrition (Wallingford), 21*(1), 160-171. https://doi.org/10.107/s1368980017002130
Pant, A., Gribbin, S., Machado, P., Hodge, A., Wasfy, J. H., Moran, L. J., Marschner, S., Chow, C. K., & Zaman, S. (2023). Ultra-processed foods and incident cardiovascular disease and hypertension in middle-aged women. *European Journal of Nutrition*. https://doi.org/10.1007/s00394-023-03297-4
Prados-Torres, A., Calderón-Larrañaga, A., Hancco-Saavedra, J. A., Poblador-Plou, B., & Van Den Akker, M. (2014). Multimorbidity patterns: a systematic review. *Journal of Clinical Epidemiology*, *67*(3), 254–266. https://doi.org/10.1016/j.jclinepi.2013.09.021
Skou, S. T., Mair, F. S., Fortin, M., Guthrie, B., Nunes, B. P., Miranda, J. J., Boyd, C. M., Pati, S., Mtenga, S., & Smith, S. M. (2022). Multimorbidity. *Nature Reviews. Disease Primers*, *8*(1). https://doi.org/10.1038/s41572-022-00376-4
Starfield, B., & Kinder, K. (2011). Multimorbidity and its measurement. *Health Policy*, *103*(1), 3–8. https://doi.org/10.1016/j.healthpol.2011.09.004
Tavares, L. F., Fonseca, S. C., Rosa, M. L. G., & Yokoo, E.M. (2011). Relationship between ultra-processed foods and metabolic syndrome in adolescents from a Brazilian Family Doctor Program. *Public Health Nutrition, 15*(1), 82-87. https://doi.org/10.1017/s1368980011001571
Tran, P. B., Kazibwe, J., Nikolaidis, G., Linnosmaa, I., Rijken, M., & Van Olmen, J. (2022). Costs of multimorbidity: a systematic review and meta-analyses. *BMC Medicine*, *20*(1). https://doi.org/10.1186/s12916-022-02427-9
Vajdi, M., Nikniaz, L., Asl, A. M. P., & Farhangi, M. A. (2020). Lifestyle patterns and their nutritional, socio-demographic and psychological determinants in a community-based study: A mixed approach of latent class and factor analyses. *PloS One*, *15*(7), e0236242. https://doi.org/10.1371/journal.pone.0236242
Willadsen, T. G., Bebe, A., Køster-Rasmussen, R., Jarbøl, D. E., Guassora, A. D., Waldorff, F. B., Reventlow, S., & De Fine Olivarius, N. (2016). The role of diseases, risk factors and symptoms in the definition of multimorbidity – a systematic review. *Scandinavian Journal of Primary Health Care*, *34*(2), 112–121. https://doi.org/10.3109/02813432.2016.1153242
Wolff, J. L., Starfield, B., & Anderson, G. F. (2002). Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. *Archives of Internal Medicine*, *162*(20), 2269. https://doi.org/10.1001/archinte.162.20.2269
Zhang, S., Gan, S., Zhang, Q., Liu, L., Meng, G., Yao, Z., Wang, H., Gu, Y., Wang, Y., Zhang, T., Wang, X., Sun, S., Wang, X., Zhou, M., Jia, Q., Song, K., Qi, L., & Niu, K. (2021). Ultra-processed food consumption and the risk of non-alcoholic fatty liver disease in the Tianjin Chronic Low-grade Systemic Inflammation and Health Cohort Study. *International Journal of Epidemiology*, *51*(1), 237–249. https://doi.org/10.1093/ije/dyab174