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The impact of ultra-processed foods on cardiovascular diseases and cancer: Epidemiological and mechanistic insights

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ABSTRACT

Ultra-processed foods (UPFs) are increasingly recognized as contributors to the pathogenesis of cardiovascular diseases (CVDs) and cancer due to their adverse compositional and mechanistic effects. UPFs, distinguished by their high content of unhealthy fats, sodium, refined sugars, and synthetic additives, significantly increase dyslipidemia, hypertension, and obesity, which are key risk factors for CVDs. Chronic consumption leads to systemic inflammation, gut microbiota dysbiosis, endothelial dysfunction, and oxidative stress. Additives such as artificial sweeteners and sodium nitrites in UPFs are associated with carcinogenesis through mechanisms involving genotoxicity and promotion of inflammatory microenvironments. This review critically evaluates existing epidemiological, mechanistic, and clinical evidence linking UPFs consumption to CVDs and cancer, synthesizing insights into their underlying pathophysiological mechanisms and highlighting disparities in disease burden across diverse populations. Epidemiological evidence demonstrates that UPFs constitute over 50% of daily caloric intake in Western diets, with each 10% increase in UPF consumption associated with a 12% rise in CVDs risk and a comparable increase in cancer incidence. Addressing the global surge in UPF consumption through dietary guidelines, regulatory policies, and public health initiatives may mitigate these risks, improve metabolic and cardiovascular health, and reduce cancer prevalence.

1. Introduction

Ultra-processed foods (UPFs), as defined by the Nova classification system, represent industrially formulated products that undergo extensive chemical and physical processing, resulting in the significant modification or elimination of whole food components (Rico-Campà et al., 2019). These products are composed predominantly of refined ingredients, food additives such as emulsifiers, stabilizers, flavor enhancers, colorants, and preservatives, as well as industrially derived processing aids. UPFs are characterized by their poor nutritional quality, marked by low levels of essential micronutrients, unsaturated fatty acids, and dietary fiber, alongside elevated quantities of synthetic and industrially processed compounds. Regular consumption of UPFs has been strongly implicated in the etiology of chronic non-communicable diseases, including metabolic syndrome and its components (obesity, hypertension, and dyslipidemia), cardiovascular diseases, type 2

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diabetes mellitus, and various malignancies. Epidemiological and mechanistic evidence, including findings by Srour et al. (2019) strongly support these associations.

Consumption of UPFs has been significantly associated with an elevated risk of cardiovascular diseases (CVDs) and various types of cancer (Economou). Both conditions rank among the leading global causes of mortality, with dietary patterns, alongside other modifiable lifestyle factors, playing a critical role in their pathogenesis (Iacoviello et al., 2021). Recent systematic reviews and meta-analyses have consistently demonstrated that higher UPF consumption correlates with an increased incidence of obesity, hypertension, type 2 diabetes, and metabolic syndrome—a constellation of interrelated metabolic disturbances. Emerging research also show a robust association between UPF intake and cancer risk, highlighting its role in tumor initiation and progression (Kliemann et al., 2022). The high content of refined sugars, unhealthy fats, and sodium in UPFs is recognized as a major contributor to the development of CVDs (Ahmed et al., 2024). In addition, carcinogenic compounds generated during the industrial refinement and processing of these products, such as advanced glycation end-products and polycyclic aromatic hydrocarbons, have become critical areas of investigation (Young and Kindzierski, 2021).

The increased consumption of UPFs can result in a deficiency of essential nutrients, impairing the body's ability to maintain homeostasis and potentially leading to defective immune surveillance. This dysfunction has been well-documented across various cancer types and represents a plausible mechanistic link between UPF intake and carcinogenesis (Kliemann et al., 2022). Signaling pathways linked to insulin and leptin are being studied as possible causes of tumor development in breast cancer, where obesity and overweight are recognized risk factors (Ghasemi et al., 2019).

This review aims to provide a comprehensive analysis of the current scientific discourse on the health implications of UPF consumption, focusing on its association with CVDs and cancer. Evidence from systematic reviews, meta-analyses, cohort studies, and cross-sectional research, supplemented by expert opinions, is critically examined to elucidate the underlying connections between UPF intake and these diseases.

2. Epidemiological evidence

2.1. Geographical dietary trends and sociodemographic factors that impact the consumption of ultra-processed foods

Among unhealthy foods, the global consumption of UPFs is increasing. From 1990 to 2010, global consumption of unhealthy food items significantly worsened, with variations observed across different regions and countries (Romero Ferreiro et al., 2022). Ultra-processed foods make up a substantial portion of energy intake worldwide, contributing between 20% and over 60% depending on the country and age group (Elizabeth et al., 2020). In some high-income nations, such as the United States, the United Kingdom, Australia, and Canada, UPFs represent more than half of total daily energy consumption. Research has linked UPF consumption to unhealthy eating habits and has identified its association with overweight and obesity in studies conducted in the United States, Canada, France, Brazil, and many Latin American and European nations (Mambrini et al., 2023; Monda et al., 2024). Furthermore, some studies have shown a negative correlation between ultra-processed food consumption and overall mortality rates ((Rico-Campà et al., 2019; Taneri et al., 2022; Fang et al., 2024). In Spain, the share of ultra-processed foods in total food purchases nearly tripled from 1990 to 2010, increasing from 11.0% to 31.7% (Romero Ferreiro et al., 2022). Additionally, various factors, including cultural differences, education, personal preferences, geographic location, access to technology, and health attitudes, affect the availability and choices of food (Chen and Antonelli, 2020). Ultra-processed foods consumption varies significantly among countries, but within each nation, multiple sociodemographic factors are independently linked to UPF intake, such as age, race/ethnicity, marital status, education level, income, urban or rural living, and regional location. Younger individuals, particularly teenagers and young adults, tend to consume more ultra-processed foods, like snacks, sugary beverages, and fast food (Enes et al., 2019). This trend is likely due to marketing strategies targeting younger audiences and their inclination for convenient and appealing food options. Women, particularly those with jobs, might opt for UPFs due to time limitations and the ease of ready-made or pre-packaged meals (Organization, 2023). In contrast, men frequently select UPFs such as fast food and sugary drinks, which reflects lifestyle choices and a reduced emphasis on dietary quality (Ceretti et al., 2024). In urban settings, individuals with higher incomes typically enjoy better access to high-end UPFs, including imported snacks and packaged meals. Conversely, low-income families often lean towards more budget-friendly UPFs, like instant noodles and processed bread, as substitutes for fresh fruits and quality protein sources. Cultural norms and practices can influence food selections, while globalization and exposure to Western eating habits may lead to increased UPF consumption (Vignola et al., 2021), especially among urban youth. Those with demanding work schedules tend to rely more heavily on UPFs due to time constraints. Additionally, people with sedentary lifestyles, such as office workers or those with minimal physical activity, are more likely to consume higher quantities of UPFs (Haider et al., 2023), contributing to unhealthy eating behaviors and associated health problems. The degree of disparity in UPF consumption across sociodemographic groups is similar to the risks linked to obesity, cardiometabolic diseases, and overall mortality (Wang et al., 2023). Recognizing these factors can assist in developing public health policies and initiatives aimed at decreasing UPF intake and fostering healthier eating habits.

2.2. Cardiovascular diseases associated with ultra-processed foods

Cardiovascular diseases (CVDs) remain a leading cause of mortality worldwide, affecting the heart and blood vessels, with annual deaths projected to exceed 23 million by 2030 (Thomas et al., 2018). Low- and middle-income countries (LMICs) disproportionately bear this burden, accounting for over 80% of global CVD-related deaths (Pająk et al., 2022). In 2019, CVDs were responsible for 17.9 million deaths among individuals under 70, representing approximately 32% of global mortality (Giovanni et al., 2020). In 2020, 523 million people globally were living with CVDs, which caused nearly 19 million deaths that year (Deaton et al., 2011). Factors contributing to the increasing prevalence of CVDs include population growth, aging, inadequate preventive measures, and dietary patterns dominated by unhealthy foods (Deaton et al., 2011; Smith Jr, 2007).

Diet and nutrition play critical roles in CVDs risk, with extensive research highlighting associations between dietary intake and major cardiovascular conditions such as stroke and coronary heart disease (CHD). While high-income countries (HICs) have provided much of the evidence linking nutrition to CVDs, LMICs continue to face the highest mortality rates, exacerbated by risk factors such as hypertension, diabetes, and obesity (Deaton et al., 2011; Contractor et al., 2014). In Sub-Saharan Africa (SSA), ischemic heart disease (IHD), stroke, and hypertensive heart disease are predominant contributors to CVDs mortality, with SSA in the early stages of epidemiological transition (Yuyun et al., 2020). Unlike in HICs, where IHD predominates, hypertensive heart disease, cardiomyopathies, and rheumatic heart disease are the main causes of heart failure in SSA.

Dietary deficiencies, including inadequate intake of vegetables, fruits, and biomarkers such as folate and antioxidant vitamins, have been linked to an increased risk of CVDs in regions such as Central and Eastern Europe and the former Soviet Union (Peasey et al., 2006). Notably, CVDs has been the leading cause of mortality in these regions since the early 1980s (Ginter, 1998; Kesteloot et al., 2006). Consumption of UPFs has risen significantly, particularly in LMICs, contributing

to the global burden of CVDs. CVDs claims approximately 3.8 million lives annually in Europe, accounting for 44% of all deaths. This includes over 2 million deaths among women and nearly 1.76 million among men (Townsend et al., 2022). Since the 1990s, sales of UPFs have increased steadily, particularly in LMICs (Le, 2021). In the United States, UPFs account for approximately 60% of daily caloric intake, with similar trends observed in Canada and Brazil (Fardet and Rock, 2020; Polsky et al., 2020).

Variations in UPF consumption across nations are influenced by socio-economic, cultural, and political factors. Within Europe, UPF consumption ranges from 15% of total caloric intake in Romania to 57% in the United Kingdom (Skuland, 2020). Although precise data on UPF consumption in Africa are limited, trends indicate increasing consumption in both urban and rural areas since the 2000s (Chaturvedi et al., 2024). UPFs consumption also varies by age, socio-economic status, and geographic location, reflecting diverse dietary patterns. Individuals consuming the highest quantities of UPFs exhibit increased risks for cardiovascular and cerebrovascular events, type 2 diabetes, hypertension, obesity, and overall mortality compared to those with lower UPF intake. Cohort studies have linked UPFs to other non-communicable diseases, including depression, inflammatory bowel disease, gestational diabetes, malignancies, and chronic kidney disease (Srour et al., 2019).

Recent epidemiological studies demonstrate that UPF consumption is significantly associated with an increased risk of CVDs. The Framingham Offspring Study reported that each additional daily serving of UPFs increases the risk of incident CVDs by 7% over 18 years of follow-up (Juul et al., 2021). Similarly, findings from the French NutriNet-Santé cohort study linked higher UPF consumption to a 12% increase in CVDs risk (Srour et al., 2019). Meta-analyses corroborate these findings, showing strong associations between UPF components such as *trans*-fats, processed meats, and added sugars with elevated CVDs risk (Micha et al., 2017). Moreover, metabolic syndrome, hypertension, and obesity are linked to these risk factors (Elizabeth et al., 2020; Juul et al., 2021).

The American College of Cardiology/American Heart Association (ACC/AHA) guidelines advocate for minimizing consumption of specific UPFs—such as processed red meats, refined carbohydrates, and sugar-sweetened beverages—given their robust evidence base linking them to CVDs risk (Arnett et al., 2019). However, public health experts and clinicians remain insufficiently aware of the broader health risks posed by the diversity of UPFs beyond these well-studied categories.

2.3. Cancer associated with ultra-processed foods

Global cancer incidence and mortality are projected to escalate significantly, with 15.3 million cancer-related deaths and 29.9 million new cases anticipated by 2040 (Iwaloye et al., 2023). The World Cancer Research Fund and the American Institute for Cancer Research have emphasized the urgent need for further investigation into modifiable cancer risk factors. Notably, one-third of the most common cancers in high-income countries could potentially be prevented through modifications in dietary and lifestyle choices (Weiderpass, 2010).

Dietary factors contribute to 30–40% of cancer cases globally, highlighting the critical role of nutrition in cancer prevention. A varied and balanced diet, in conjunction with smoking cessation and reduced alcohol consumption, represents one of the most actionable strategies for primary cancer prevention (Gapstur et al., 2018). However, in recent decades, dietary patterns in many nations have shifted toward increased consumption of UPFs, driven by their sensory appeal, affordability, and convenience (Fuhrman, 2018).

Ultra-processed foods are industrially engineered products that undergo multiple physical, chemical, and biological modifications, rendering them palatable, microbiologically stable, and economically viable. These modifications, while enhancing consumer appeal, simultaneously reduce nutritional quality and introduce compounds with potential carcinogenic properties (Rupp, 2003). This dietary transition has become particularly pronounced in LMICs, paralleling economic development and urbanization, further underscoring the need for focused research and intervention in these settings.

According to several studies conducted across Europe, the United States, Canada, New Zealand, and Brazil, UPFs account for 25%–50% of daily energy intake (Fardet and Rock, 2020). These products possess characteristics that contribute significantly to disease pathogenesis, particularly cancer. Ultra-processed foods frequently contain pollutants such as bisphenol, acrylamide, heterocyclic amines, and polycyclic aromatic hydrocarbons, many of which exhibit carcinogenic properties (Fiolet et al., 2018). Additionally, food additives such as titanium dioxide (TiO_2), commonly used as a whitening agent, and sodium nitrite, prevalent in processed meats, have been implicated in cancer development in experimental models (Fiolet et al., 2018).

The Nova classification system, which categorizes foods based on processing levels, has facilitated research into the health impacts of UPFs, yet a paucity of robust epidemiological data remains. Existing evidence, largely derived from cross-sectional and ecological studies, highlights significant associations between UPF consumption and increased disease risk (Monteiro et al., 2018; Koios et al., 2022). A study by Wang et al. revealed that men consuming the highest amounts of UPFs faced a 29% greater risk of colorectal cancer compared to those consuming the least (Wang et al., 2022). Cancer, the second leading cause of death in Europe, accounts for 24% of male and 20% of female deaths, with cardiovascular diseases still leading mortality causes in women (47%) and men (38%) (Ferlay et al., 2018). Furthermore, a prospective study on middle-aged UK adults linked higher UPF consumption with elevated incidence and mortality rates across multiple cancer types (Chang et al., 2023).

Despite recent advancements in food processing frameworks, most evidence connecting UPFs to cancer risk stems from studies exploring specific food groups and their carcinogenic potential. The World Cancer Research Fund's (WCRF) Continuous Update Project (CUP), the largest resource for research on diet, nutrition, and cancer prevention, provided comprehensive insights in its 2018 review. This analysis confirmed strong evidence linking processed meat consumption to increased colorectal cancer risk. Additional associations were identified, including salt-preserved foods with stomach cancer and Cantonese-style salted fish with nasopharyngeal cancer (Monteiro et al., 2018; International, 2018; Clinton et al., 2020). Alcohol consumption similarly increases the risk of cancers affecting the mouth, throat, larynx, oesophagus, breast, colorectal region, stomach, liver, and kidneys, irrespective of the beverage type (Monteiro et al., 2019a).

Epidemiological data also demonstrate a relationship between UPF intake and obesity, a recognized risk factor for several malignancies. The WCRF report emphasizes limiting sugary drinks and high-fat, high-starch processed foods, as their consumption contributes to weight gain and metabolic dysregulation, thereby increasing cancer risk (International, 2018). A systematic review published in 2012 further corroborated the association between added sugars and cancer risk, emphasizing the importance of dietary modifications in cancer prevention (Romaguera et al., 2012). These findings underscore the necessity for public health interventions to mitigate the widespread consumption of UPFs and their associated cancer risks.

2.4. Impact of ultra-processed foods on cardiovascular diseases and cancer across different income levels

The consumption of UPFs has emerged as a significant global public health concern, with substantial implications for CVDs and cancer. In low-income countries, the association between UPF consumption and adverse health outcomes, including mortality, is particularly pronounced. A comprehensive analysis by Dehghan et al. (2023) involving 138,076 participants from countries such as Bangladesh, India, Pakistan, Tanzania, and Zimbabwe revealed significant correlations between high UPF intake (≥2 servings/day) and increased total mortality (Hazard

Ratio [HR]: 1.28; 95% Confidence Interval [CI]: 1.15–1.42) as well as non-CVDs mortality (HR: 1.32; 95% CI: 1.17–1.50). Notably, the interaction analysis indicated stronger associations in low- and middle-income regions compared to high-income counterparts (P-interaction = 0.02). This heightened vulnerability is likely due to several factors, including limited healthcare infrastructure, higher prevalence of infectious diseases, and potential nutritional deficiencies that exacerbate the adverse effects of UPFs. As these countries experience rapid urbanization and economic shifts, increased access to affordable UPFs may contribute to a rising burden of non-communicable diseases (NCDs), such as cardiovascular diseases and cancers.

In middle-income countries, the correlation between UPF consumption and health outcomes such as mortality remains significant but varies in strength across different regions. Dehghan et al. (2023) included diverse middle-income countries such as Argentina, Brazil, Chile, China, Colombia, Iran, Malaysia, Palestine, Poland, Philippines, South Africa, and Turkey in their study. They found that elevated UPF intake was associated with increased total and non-CVDs mortality in these countries. For example, studies conducted in China and Poland identified significant associations between UPFs consumption and increased mortality risks across populations with diverse dietary habits. These findings exemplify the ongoing dietary transitions in these countries, driven by economic development, urbanization, and increased availability of affordable, highly processed foods, which are contributing to the rising prevalence of chronic diseases.

In high-income countries, the relationship between UPF consumption and health outcomes, although still significant, manifests differently. The Canadian study by Nardocci et al. (2021) provides key insights into this demographic. Using data from the 2015 Canadian Community Health Survey–Nutrition, the study assessed 13,608 adults and found that individuals in the highest tertile of UPF consumption (73% of total daily energy intake) had markedly higher odds of obesity (Odds Ratio [OR] = 1.31; 95% CI: 1.06–1.60), diabetes (OR = 1.37; 95% CI: 1.01–1.85), and hypertension (OR = 1.60; 95% CI: 1.26–2.03) compared to those in the lowest tertile (24% energy intake from UPFs). These associations remained significant after adjusting for socio-demographic and lifestyle factors, indicating that UPFs contribute independently to the prevalence of these conditions. High-income countries, characterized by sedentary lifestyles, urbanization, and higher disposable incomes, provide an environment where UPFs are widely consumed, exacerbating the incidence of NCDs like obesity, diabetes, and hypertension.

Further studies from high-income countries provide additional evidence of the global impact of UPFs on health outcomes, particularly mortality and cancer risk. Blanco-Rojo et al. (2019) conducted a cohort study in Spain and found a significant association between high UPF consumption and all-cause mortality (HR: 1.44; 95% CI: 1.01–2.07) over a 7.7-year follow-up period. Their analysis also suggested that substituting UPFs with unprocessed or minimally processed foods could potentially reduce mortality risk, underscoring the modifiable nature of dietary patterns. Similarly, Fiolet et al. (2018) reported that a 10% increase in UPF proportion in the diet was associated with a 12% increase in overall cancer risk (Hazard Ratio = 1.12; 95% CI: 1.06–1.18) in the French NutriNet-Santé cohort. These findings further highlight the detrimental effects of UPFs on long-term health outcomes, particularly cancer, within high-income populations.

The NutriNet-Santé cohort study by Srour et al. (2019), also investigated the association between UPF intake and cardiovascular disease risk. This prospective study involved 105,159 French adults tracked over a median follow-up of 5.2 years. Dietary data were collected using repeated 24-h dietary records, and the degree of food processing was classified using the Nova system. The results indicated a significant 12% increase in overall cardiovascular disease risk with every 10% increment in UPF intake. This risk extended to specific conditions, with coronary heart disease and cerebrovascular disease risks rising by 13% and 11%, respectively. These associations remained significant after adjustments for confounders, including key dietary markers such as saturated fat, sodium, and fiber, suggesting that the detrimental effects of UPFs might stem from additives, packaging materials, and neo-formed contaminants rather than traditional dietary components alone.

Moreover, Rico-Campà et al. (2019) examined the impact of UPFs on mortality using data from 19,899 participants in the SUN cohort study. This Spanish study spanned nearly two decades, using a validated food frequency questionnaire to categorize UPF consumption. The findings revealed that individuals in the highest quartile of UPF intake had a 62% higher risk of all-cause mortality compared to those in the lowest quartile. Moreover, each additional serving of UPFs increased mortality risk by 18%, demonstrating a clear dose-response relationship. The researchers highlighted the role of UPFs in systemic inflammation and metabolic dysfunction as likely contributors to this elevated risk, emphasizing the urgent need for public health interventions to curb UPF consumption.

The link between UPFs and obesity was explored in depth by Juul et al. (2021) in a cross-sectional analysis of 15,977 adults from the NHANES dataset. This study revealed that UPFs constituted 58% of total energy intake among U.S. adults and accounted for 89% of added sugars in their diets. Higher UPF consumption was strongly associated with adverse anthropometric outcomes, including increased BMI, waist circumference, and obesity prevalence. Women appeared to be particularly vulnerable, as indicated by significant interactions between UPF intake and female sex. These findings underscore the pervasive role of UPFs in the American diet and their contribution to the obesity epidemic, particularly among women.

The detrimental effects of UPFs are not limited to adults; evidence from the Avon Longitudinal Study of Parents and Children (ALSPAC) highlights the risks in younger populations. Chang et al. (2021) tracked the dietary habits and body composition of 9025 children from age 7–24 years. Those in the highest quintile of UPF consumption exhibited significantly steeper annual increases in BMI, weight, and waist circumference compared to peers with lower UPF intake. Additionally, higher fat mass index and body fat percentage were observed, suggesting that high UPF consumption during childhood has long-term implications for adiposity and obesity risk in adulthood.

Further evidence comes from de Deus Mendonça et al. (de Deus Mendonca et al., 2016), who assessed 8451 middle-aged adults in the SUN cohort study over a median follow-up of 8.9 years. The study found that participants with the highest UPF consumption had a 26% greater risk of developing overweight or obesity compared to those with lower intake levels. These results align with findings from other cohorts, reinforcing the role of UPFs in promoting excessive weight gain over time.

Furthermore, Hall et al. (2019) conducted a controlled inpatient trial to explore the effects of UPF consumption on energy intake and weight regulation. Twenty weight-stable adults alternated between diets composed of ultra-processed or unprocessed foods for two weeks each. The diets were matched for caloric content, macronutrient composition, sugar, sodium, fiber, and energy density, ensuring that food processing was the sole variable. Despite these controls, participants on the UPF diet consumed significantly more calories (508 ± 106 kcal/day), driven by increased carbohydrate (280 ± 54 kcal/day) and fat intake (230 ± 53 kcal/day), while protein intake remained unaffected. This excess caloric intake correlated strongly with weight changes ($\mathbf{r = 0.8}$), with participants gaining 0.9 ± 0.3 kg on the UPF diet and losing the same amount during the unprocessed diet. These findings underscore the obesogenic nature of UPFs, suggesting that their reduction could be a cornerstone strategy for managing obesity.

In another pioneering study, Adjibade et al. (2019) investigated the association between UPFs and depressive symptoms in the NutriNet-Santé cohort. Following 26,730 adults for a mean of 5.4 years, the study assessed dietary intake using repeated 24-h dietary records and depressive symptoms via the CES-D scale. The results revealed a significant positive association between UPF consumption and

depression risk. A 10% increase in UPFs in the diet corresponded to a 21% higher risk of incident depressive symptoms (**HR = 1.21; 95% CI: 1.15–1.27**) after controlling for sociodemographic and lifestyle factors. Notably, the association was particularly pronounced for UPFs categorized as beverages and sauces or added fats. These findings suggest that reducing UPF consumption may play a role in promoting mental health and preventing depression.

Julia et al. (2018) conducted a comprehensive cross-sectional analysis of 74,470 adults to quantify the contribution of UPFs to the French diet. UPFs accounted for 18.4% of the food consumed by weight but contributed 35.9% of total energy intake. The study highlighted significant sociodemographic disparities, with higher UPF consumption associated with male gender, younger age, lower education levels, smoking, and higher BMI (**all p < 0.0001**). Nutritionally, participants with higher UPF consumption had lower intakes of fiber, β-carotene, and calcium and higher intakes of added sugars and soft drinks. This pattern of nutritional imbalances underscores the role of UPFs in perpetuating poor dietary quality, particularly in vulnerable populations.

Silva et al. (2018) explored the relationship between UPF consumption and obesity metrics in the Brazilian ELSA-Brasil cohort. Using data from 8977 participants, the study found that UPFs accounted for 22.7% of total energy intake. Participants in the highest quartile of UPF

Table 1
Ultra-processed foods and disease risks across income levels.

Study Type	Location	Sample Size	Duration	Gender	Age Group	Findings	References
Cohort Study	Bangladesh, India, Pakistan, Tanzania, Zimbabwe, Argentina, Brazil, Chile, China, Colombia, Iran, Malaysia, Palestine, Poland, Philippines, South Africa, Turkey, Canada, Saudi Arabia, Sweden, United Arab Emirates	138,076	10.2 years	N/A	Adults (35–70 years)	Higher consumption of ultra-processed foods associated with increased risk of mortality and cardiovascular disease	Dehghan et al. (2023)
Prospective cohort	France	104,980	8 years	N/A	18 years and above (Median age of 42.8 years)	Increased risk of overall cancer and breast cancer with higher ultra-processed food consumption.	Fiolet et al. (2018)
Prospective cohort	Spain	19,899	19 years	12,113 women and 7786 men	20–91 years	Higher consumption of ultra-processed foods linked to higher hazard for all-cause mortality	Rico-Campà et al. (2019)
Cross-sectional	France	74,470	Not specified	Not specified	Not specified	Higher consumption of ultra-processed foods associated with increased risk of prostate cancer.	Julia et al. (2018)
Prospective cohort	United States	26,720	5.4 years	20,380 women and 6350 men	18–86 years	Ultra-processed food consumption associated with increased risk depressive symptoms	Adjibade et al. (2019)
Prospective cohort	Canada	20	2 weeks	N/A	29–31years	Higher intake of ultra-processed foods associated with increased risk of obesity	Hall et al. (2019)
Population based cohort	France	105,159	9 years	N/A	18 years and above	Positive correlation between ultra-processed food intake and coronary heart, cardiovascular and cerebrovascular diseases	Srour et al. (2019)
Cross-sectional	Italy	1171	10.6 years	N/A	57–77 years	Association between ultra-processed food consumption and increased risk of cardiovascular disease	Bonaccio et al. (2022)
Cohort Study	Spain	11,898	7.7 years	50.5% are women	Median age of 46.9	Higher consumption of ultra-processed foods was associated with increased risks of mortality.	Blanco-Rojo et al., 2019
Cross-sectional	United States	15,977	9 years	N/A	20–64 years	Significant association between ultra-processed food consumption and higher BMI, waist circumference, and cardiovascular risk factors.	Juul et al. (2021)
Cross-sectional	Brazil	8977	2 years	N/A	35–64 years	Positive correlation between ultra-processed food intake and cardiovascular risk factors, including higher BMI and waist circumference	Silva et al. (2018)
Prospective cohort	United kingdom	19,7426	12 years	54.6% are women	Adults	Higher intake of ultra-processed foods was associated with mortality for overall and certain site-specific cancers especially ovarian cancer in women	Chang et al. (2023)
Longitudinal Study	England	9025	19 years	49.7 are female and 50.3% are male	Children	Higher intake of ultra-processed foods was associated with greater increases in adiposity from childhood to early adulthood	Chang et al. (2021)
Prospective cohort	Spain	8451	8.9 years	N/A	N/A	Higher ultra-processed food consumption was associated with increased risks of overweight and obesity.	de Deus Mendonca et al. (2016)
Cross-sectional	Canada	13,608	Not Specified	N/A	19 years and above	Positive association between ultra-processed food consumption and obesity, diabetes and hypertension	Nardocci et al. (2021)

consumption exhibited significantly higher BMI (β = 0.80; 95% CI: 0.53–1.07) and waist circumference (β = 1.71; 95% CI: 1.02–2.40), as well as increased odds of being overweight (OR = 1.31; 95% CI: 1.13–1.51), obese (OR = 1.41; 95% CI: 1.18–1.69), or having central obesity (OR = 1.41; 95% CI: 1.20–1.66). These findings suggest a dose-response relationship between UPFs and obesity markers, independent of total energy intake, emphasizing the need for dietary interventions to address this public health issue.

Bonaccio et al. (2022) also provided compelling evidence linking UPF consumption with increased mortality in individuals with CVD. In a longitudinal analysis of 1171 participants followed for 10.6 years, the study found that higher UPF intake (>11.3% of total food) was associated with elevated risks of all-cause mortality (**HR = 1.38; 95% CI: 1.00–1.91**) and CVD-specific mortality (**HR = 1.65; 95% CI: 1.07–2.55**). Notably, the study identified altered renal function, as indicated by elevated cystatin C levels, as a mediator of the relationship between UPFs and mortality, explaining 18.3% of the association with all-cause mortality. These findings highlight the potential biological pathways through which UPFs exert their deleterious effects and signify the urgency of dietary modifications in secondary prevention strategies. The collective evidence presented in these studies demonstrates the multifaceted risks associated with UPF consumption (Table 1).

3. Pathophysiological mechanisms linking ultra-processed food consumption to cardiovascular diseases and cancer

Ultra-processed foods are industrial formulations comprising numerous ingredients, including modified starches, protein isolates, and various additives such as emulsifiers, artificial sweeteners, and artificial flavors. These formulations undergo extensive processing, often utilizing techniques like extrusion, and are characterized by minimal whole-food content (Bonaccio et al., 2022). Ultra-processed foods are typically rich in *trans*-fats, sodium, and added sugars, while being deficient in dietary fiber, protein, and essential micronutrients, making them a significant contributor to the development of CVDs and cancer (International, 2018). Recent studies have highlighted the adverse health effects of prolonged UPF consumption, although the underlying pathophysiological mechanisms remain complex and incompletely understood. These mechanisms can be attributed to both the nutrient composition and non-nutritional factors inherent in UPFs (Bonaccio et al., 2022).

3.1. Nutritional content and its impact

Ultra-processed foods are characterized by high energy density and poor nutritional quality compared to minimally processed foods. They contain elevated levels of sodium, *trans*-fats, saturated fats, and added sugars while being deficient in dietary fiber and micronutrients. This imbalance promotes systemic inflammation, dyslipidemia, and endothelial dysfunction, contributing to the pathogenesis of both CVDs and cancer. Additionally, excessive heat treatment and degradation of the food matrix during processing can alter gut microbiota composition, further exacerbating inflammatory pathways (Tristan Asensi et al., 2023).

3.2. Non-nutritional factors and inflammatory pathways

Non-nutritional factors in UPFs also play a significant role in promoting low-grade inflammation, a key driver of chronic diseases. These include additives such as sweeteners (e.g., acesulfame potassium, sucralose, aspartame) and emulsifiers, which enhance sensory qualities and shelf life but can disrupt gut homeostasis and immune responses (Tristan Asensi et al., 2023). Artificial sweeteners, widely used in soft drinks, may induce dysbiosis and elevate markers of systemic inflammation. Furthermore, bisphenols and phthalates—chemical substances that can leach from food packaging into UPFs—are associated with endocrine disruption and inflammatory responses. These compounds contribute to oxidative stress, DNA damage, and altered cell signaling, which are critical mechanisms in the development of both CVDs and cancer (Tristan Asensi et al., 2023).

The combined impact of poor nutritional quality and harmful non-nutritional factors creates a pro-inflammatory environment, disrupts metabolic pathways, and induces oxidative stress. These effects collectively contribute to the pathophysiological progression of CVDs through mechanisms such as endothelial dysfunction and atherogenesis and to cancer through processes like tumor initiation, promotion, and progression (Tristan Asensi et al., 2023).

3.3. Mechanisms linking ultra-processed foods to cardiovascular diseases

3.3.1. Impact of high sodium intake on blood pressure and vascular health

Sodium, a critical component of dietary salt, is indispensable for maintaining homeostasis and normal physiological function. However, UPFs are a major contributor to excessive dietary sodium intake due to their widespread consumption and high salt content. Sodium in UPFs is often added during processing for preservation, flavor enhancement, and texture modification, resulting in sodium levels that far exceed those found in unprocessed or minimally processed foods. Studies have demonstrated that UPFs contribute disproportionately to daily sodium intake in various populations. Monteiro et al. (2018) and Juul et al. (2018) report that UPFs account for more than 50% of dietary sodium in Western diets. Furthermore, Moubarac et al. (2013) highlight that UPFs, including packaged snacks, ready-to-eat meals, and processed meats, contain sodium levels that are significantly higher than recommended dietary allowances, thereby driving excessive sodium consumption. Excessive sodium intake beyond physiological requirements is strongly associated with adverse cardiovascular outcomes, primarily through sustained elevations in blood pressure and vascular damage (O'Donnell et al., 2020). Elevated sodium intake induces fluid retention, increases extracellular fluid volume, and elevates cardiac output, contributing to hypertension, a major risk factor for CVDs. Excessive sodium consumption also promotes endothelial stiffness, impairs vasodilation through reduced nitric oxide bioavailability, and exacerbates vascular remodeling, collectively leading to cardiovascular damage. These mechanisms underline the importance of sodium reduction as a key public health strategy for preventing and managing hypertension (O'Donnell et al., 2020; Felder et al., 2022).

Salt reduction have proven effective in lowering blood pressure in both hypertensive and normotensive individuals, demonstrating significant improvements in vascular health. However, the implementation of these strategies requires caution, as excessive sodium restriction can have deleterious effects. A meta-analysis investigating the effects of low- versus high-sodium diets revealed that rapid and substantial reductions in sodium intake can trigger compensatory physiological responses, including increased levels of renin, aldosterone, catecholamines, and cholesterol (Ruzicka et al., 2014). These responses may offset the benefits of sodium reduction and pose additional risks to cardiovascular health (O'Donnell et al., 2020; Felder et al., 2022). Balancing sodium intake within recommended physiological limits remains essential for optimizing cardiovascular health. Excessive dietary sodium intake is well-established as a major contributor to hypertension, a leading risk factor for CVDs and stroke (Pająk et al., 2022). The elevated sodium content of UPFs significantly contributes to increased sodium intake at the population level. Analysis of the NHANES dataset by Juul et al. (2018) demonstrated that UPFs accounted for 58% of total energy intake and 89% of added sodium in the United States. The pathophysiological mechanisms linking high sodium intake to elevated blood pressure and vascular health involve complex interactions between renal, vascular, and neuro-hormonal systems, often influenced by individual salt sensitivity (Giovanni et al., 2020; Deaton et al., 2011).

High sodium consumption disrupts renal sodium homeostasis, reducing the kidney's ability to excrete excess sodium effectively. This dysfunction leads to fluid retention, extracellular volume expansion, and

increased cardiac preload, which elevate blood pressure. Additional pathways involve direct effects on vascular walls, promoting endothelial stiffness and impaired vasodilation (Pilic et al., 2016; Jaques et al., 2021).

The kidney plays a pivotal role in blood pressure regulation via the pressure natriuresis mechanism, as described by Guyton (1990). In this model, elevated blood pressure enhances renal sodium and water excretion, reducing extracellular fluid volume and cardiac output, thereby normalizing blood pressure. However, in the context of excessive sodium intake, this compensatory mechanism becomes overwhelmed, leading to sustained hypertension (Bereda, 2022). Increased sodium intake also raises plasma osmolarity, triggering a fluid shift from intracellular to extracellular compartments (Fig. 1). The rise in osmolarity stimulates the release of vasopressin, promoting water retention and further expanding extracellular fluid volume. These changes exacerbate vascular resistance and contribute to the pathogenesis of hypertension (Bereda, 2022). Moreover, sodium exerts direct effects on the hypothalamus, vasculature, and immune system, mediating inflammation and vascular remodeling. These effects further impair endothelial function, promoting stiffness and reduced nitric oxide bioavailability, which collectively increase vascular resistance (Bereda, 2022). **The extensive consumption of sodium-rich UPFs exacerbates these effects, highlighting the importance of dietary interventions to reduce UPF intake as a critical public health strategy for addressing hypertension and CVD.**

3.3.2. Role of trans-fats and saturated fats in atherosclerosis and dyslipidemia

Ultra-processed foods (UPFs) are a significant dietary source of trans fats and saturated fats, both of which are established contributors to dyslipidemia and atherosclerosis. UPFs are characterized by industrial formulations containing refined sugars, salts, fats, and additives, frequently incorporating partially hydrogenated oils and high levels of saturated fats that disrupt lipid metabolism and promote cardiovascular disease (Monteiro et al., 2019a; Mozaffarian et al., 2010). These lipids impair lipoprotein profiles and trigger systemic inflammation, thereby accelerating the progression of atherosclerosis.

Dyslipidemia, a metabolic disorder characterized by reduced high-density lipoprotein cholesterol (HDL-C) and elevated low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), and triglycerides (TG), is a key contributor to atherosclerosis and CVDs (Estadella et al., 2013). Saturated and *trans*-fats, commonly found in ultra-processed foods, have significant detrimental effects on lipid metabolism and cardiovascular health (Mozaffarian et al., 2010).

Trans-fats adversely influence lipid profiles by upregulating LDL receptor expression in hepatocytes, increasing LDL-C ("bad cholesterol") while simultaneously reducing HDL-C ("good cholesterol"). This leads to smaller, denser LDL particles, which are more atherogenic. *Trans*-fats also impair enzymes such as lipoprotein lipase (LPL) and hepatic lipase (HL), critical for lipoprotein metabolism, resulting in lipoprotein accumulation in the bloodstream (Fernandez and West, 2005; Lichtenstein, 2014). These effects promote systemic inflammation, thrombogenesis, and endothelial dysfunction by disrupting prostaglandin balance (Mozaffarian et al., 2010). Elevated LDL levels stimulate the release of pro-inflammatory cytokines (e.g., TNF-α, IL-6) and upregulate adhesion molecules on endothelial cells, facilitating monocyte recruitment into the arterial wall. This initiates fatty streak formation and leads to plaque development—a hallmark of atherosclerosis (Lottenberg et al., 2012).

Saturated fats similarly exacerbate dyslipidemia by increasing LDL-C and promoting the formation of small, dense LDL particles prone to oxidation. These oxidized LDL particles trigger chronic inflammation, further contributing to endothelial dysfunction and atherogenesis. Saturated fats contribute to the pathogenesis of dyslipidemia and CVDs through their impact on lipid metabolism and lipoprotein particle size. They upregulate genes involved in cholesterol biosynthesis, increasing hepatic cholesterol production and elevating LDL-C levels. Simultaneously, saturated fats downregulate LDL receptor activity, impairing LDL clearance from the bloodstream and resulting in elevated plasma lipoprotein concentrations (Mozaffarian et al., 2010). A notable effect of saturated fats is their influence on lipoprotein particle size, increasing the proportion of small, dense LDL particles. These particles are highly susceptible to oxidation, making them more atherogenic and capable of triggering inflammatory responses within arterial walls (Mozaffarian et al., 2010).

Trans-fats and saturated fats collectively exacerbate dyslipidemia by elevating LDL-C levels, impairing endothelial function, and inducing chronic inflammation. Elevated LDL levels promote the production of pro-inflammatory cytokines (e.g., TNF-α, IL-6) and adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) on endothelial cells. This facilitates monocyte recruitment to the arterial wall, where they differentiate into macrophages and release cytokines and oxidizing agents that accelerate cholesterol oxidation (Lottenberg et al., 2012).

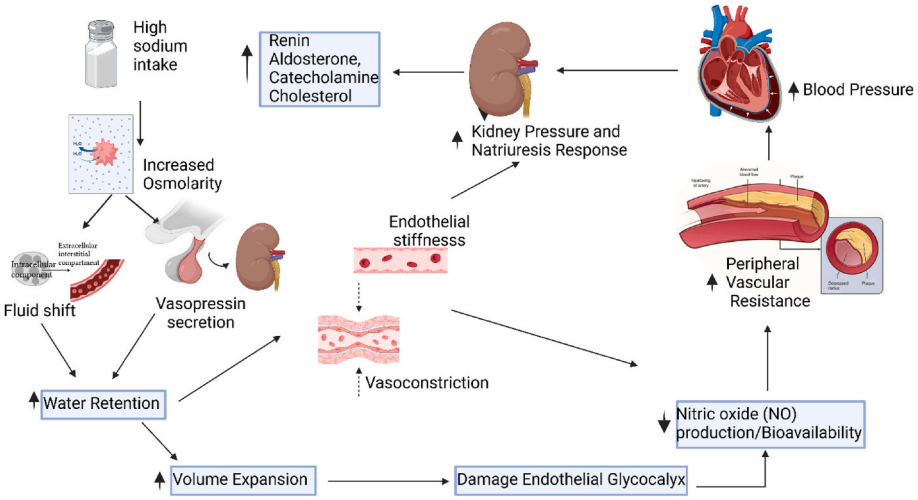

Fig. 1. Pathophysiological Impact of High Sodium Intake on Blood Pressure and Vascular Health. High sodium intake increases osmolarity, causing fluid shifts to extracellular compartments and stimulating vasopressin secretion. This leads to water retention, extracellular fluid expansion, vasoconstriction, endothelial stiffness, and reduced nitric oxide (NO) bioavailability, collectively raising peripheral resistance and blood pressure. Elevated blood pressure triggers the kidney's pressure natriuresis mechanism, but chronic sodium overload disrupts this balance, further increasing renin, aldosterone, catecholamines, and cholesterol, exacerbating hypertension and vascular dysfunction.

Oxidized LDL is absorbed by macrophages, forming foam cells that deposit within arterial walls, creating fatty streaks. This process ultimately culminates in the development and progression of atherosclerotic plaques (Lottenberg et al., 2012; Cicerchi et al., 2014).

Accumulated plasma LDL is transported across the endothelial cell layer into the extracellular matrix of the sub-endothelial space, where it becomes retained. This retention facilitates the oxidation and non-enzymatic glycation of LDL. Mildly oxidized LDL promotes the recruitment of monocytes to the arterial wall, where they differentiate into macrophages. These macrophages amplify the production of reactive oxygen species (ROS) and inflammatory mediators, further accelerating LDL oxidation and enhancing the expression of adhesion molecules on endothelial cells. This inflammatory environment drives the migration and proliferation of vascular smooth muscle cells and endothelial cells, leading to the formation of atherosclerotic plaques. The accumulation of foam cells, formed from macrophages engulfing oxidized LDL, contributes to fatty streaks within the arterial wall. Over time, this results in the progressive narrowing of the arterial lumen, a hallmark of atherosclerosis, and a major contributor to cardiovascular disease (Monteiro et al., 2019a).

3.3.3. Contribution of sugar to insulin resistance and metabolic syndrome

Ultra-processed foods are typically high in simple sugars, often in the form of sucrose (a disaccharide composed of glucose and fructose) or high-fructose corn syrup (a mixture of glucose and fructose monosaccharides). These sugars confer a high glycemic index and glycemic load, leading to rapid and significant increases in blood glucose and insulin levels following consumption (Skuland, 2020; Bhupathiraju and Hu, 2016). Chronic consumption of high-sugar UPFs contributes substantially to total dietary sugar intake, creating a metabolic environment conducive to the development of insulin resistance. Prolonged hyperinsulinemia, a compensatory response to repeated glucose spikes, desensitizes insulin receptors on peripheral tissues, impairing glucose uptake and exacerbating hyperglycemia. Additionally, high fructose intake promotes hepatic lipogenesis, resulting in increased triglyceride synthesis, ectopic fat deposition, and dyslipidemia (Samuel and Shulman, 2012).

The high sugar content in UPFs leads to postprandial hyperglycemia, triggering insulin secretion from pancreatic β-cells within the islets of Langerhans (Snel et al., 2012). Insulin facilitates glucose uptake by stimulating the translocation of GLUT4 transporters to the plasma membrane, enabling glucose entry into muscle and liver cells for energy production or glycogen storage, thereby reducing blood glucose levels (Snel et al., 2012).

Chronic consumption of high-sugar UPFs, however, contributes to prolonged and frequent insulin secretion, desensitizing insulin receptors on target cells and resulting in insulin resistance (Hotamisligil, 2006). This condition is further aggravated by hyperglycemia-induced fatty acid synthesis and storage in adipose tissue. When adipose tissue reaches its storage capacity, excess free fatty acids are taken up by non-adipose tissues, such as skeletal muscle, liver, and pancreatic β-cells. Excessive fatty acid deposition in these tissues leads to lipotoxicity, disrupting insulin signaling pathways. In skeletal muscle and liver, lipotoxicity impairs the action of insulin, further exacerbating glucose intolerance. In pancreatic β-cells, lipotoxicity can lead to β-cell dysfunction, reducing insulin production and worsening glycemic control (Lowell and Shulman, 2005).

Chronic consumption of high-sugar foods, particularly from UPFs, has been associated with systemic inflammation, mitochondrial dysfunction, and metabolic disturbances that contribute to insulin resistance and metabolic syndrome. Inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) interfere with insulin signaling pathways by inhibiting insulin receptor substrate phosphorylation, reducing cellular responsiveness to insulin and promoting insulin resistance (Roncal-Jimenez et al., 2011).

High-sugar diets have also been linked to mitochondrial dysfunction due to oxidative stress. Lowell and Shulman (2005) demonstrated that the continuous demand for insulin production in pancreatic β-cell mitochondria induces oxidative stress, resulting in the excessive generation of ROS. These ROS impair mitochondrial integrity and function, reducing energy production efficiency and exacerbating insulin resistance (Lowell and Shulman, 2005; Sundborn et al., 2019).

Fructose, a major component of sucrose and high-fructose corn syrup found in UPFs, plays a particularly detrimental role in metabolic syndrome. Chronic intake of fructose upregulates glucose transporter 5 (GLUT5) and fructokinase expression in the intestine and liver, accelerating fructose absorption and metabolism (Proquin et al., 2018). Fructokinase C rapidly phosphorylates fructose to fructose-1-phosphate in the liver, depleting intracellular ATP and promoting the breakdown of AMP to uric acid. Elevated uric acid levels inhibit AMP-activated protein kinase, a key regulator of energy homeostasis, leading to mitochondrial oxidative stress, increased lipogenesis, impaired fatty acid oxidation, and enhanced gluconeogenesis. These effects collectively contribute to insulin resistance, dyslipidemia, hypertension, and non-alcoholic fatty liver disease (Cáceres-Matos et al., 2024). The high fructose and glucose content in UPFs positions them as major contributors to the development of insulin resistance and metabolic syndrome (Fig. 2).

3.4. Mechanisms linking ultra-processed foods to cancer

3.4.1. Carcinogenic potential of certain additives and preservatives

UPFs often contain a wide range of additives, including artificial sweeteners, preservatives, and cosmetic agents such as dyes and emulsifiers, many of which have been implicated in carcinogenesis (Kliemann et al., 2022). Experimental evidence has demonstrated that specific additives, such as sodium nitrite and titanium dioxide, exhibit carcinogenic properties (Kliemann et al., 2022). Artificial sweeteners used as additives in ultra-processed foods leads to an increase in postprandial glucose responses when it is consumed excessively. This condition stimulates the production of free radicals that induce DNA damage, thus increasing the risk of tumors. It also generates advanced endogenous glycation products, which are highly reactive metabolites that trigger cytokine secretion and increased markers of oxidative stress production (Sindelar and Milkowski, 2011).

Experimental studies have indicated that sodium nitrate, commonly utilized as a preservative in processed meats and poultry, may contribute to cancer risk through the formation of nitroso-compounds, which can yield carcinogenic nitrosamines (Jones and Clemmons, 1995; Bettini et al., 2017). Epidemiological evidence supports this association, showing a significant correlation between processed meat consumption and an increased risk of colorectal cancer, with particularly strong links to colon cancer (Bettini et al., 2017). Titanium dioxide (TiO_2), frequently employed as a preservative and coloring agent in UPFs, has also been implicated in carcinogenesis. Recent findings suggest that TiO_2 is not safe for human consumption as a food additive, with animal studies demonstrating its ability to induce gene expression changes in the colon, which may contribute to tumor development (Bischoff et al., 2022).

Emulsifiers, another class of additives commonly used in ultra-processed foods to stabilize mixtures of immiscible substances, have been postulated to drive metabolic alterations associated with cancer etiology. These compounds disrupt gut microbiota composition, promoting microbial invasion and elevating levels of pro-inflammatory molecules such as flagellin and lipopolysaccharide. This creates a chronic pro-inflammatory state in the gut, leading to disruptions in cellular proliferation and apoptosis, thereby exacerbating carcinogenesis (Sindelar and Milkowski, 2011).

3.4.2. Impact of high sugar intake on insulin-like growth factors and cancer proliferation

Insulin-like Growth Factors (IGFs), particularly IGF-1 and IGF-2, are peptide hormones with structural similarity to insulin, playing critical

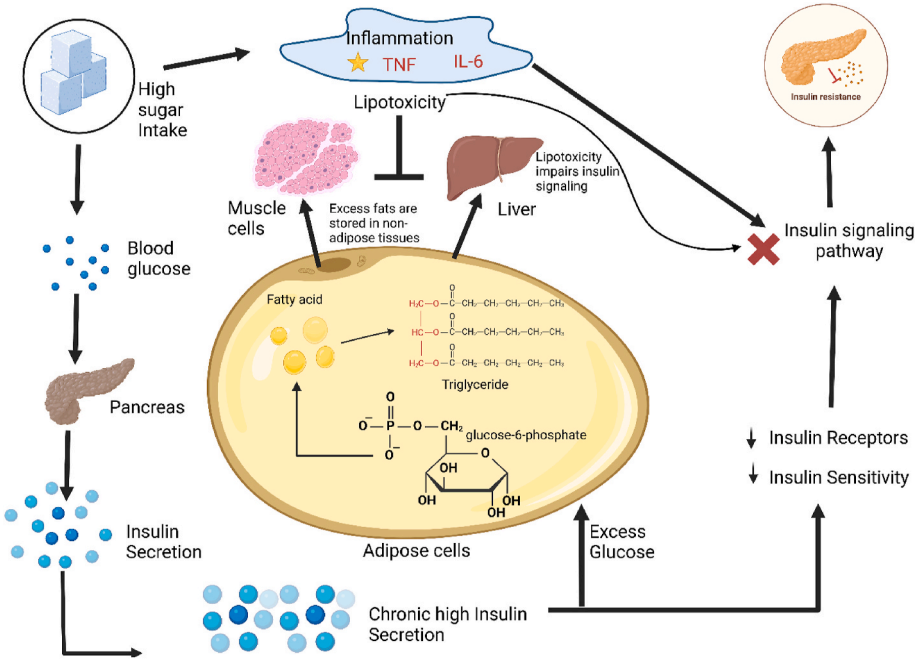

Fig. 2. Contribution of sugar to insulin resistance. High sugar intake leads to a postprandial increase in the blood glucose levels and increases insulin secretion. Prolonged insulin secretion due to persistence high sugar intake, causes cells to become desensitized to insulin, resulting in insulin resistance. Also, high blood glucose level increased fatty acid synthesis and storage in adipose tissue. Excess of adipose tissue storage capacity induces the skeletal muscle and liver to absorb free fatty acids from serum and to store them as excess fat which drives further fatty acid oxidation in these cells. Accumulation of fatty acids in these non-adipose tissues, like the liver and muscle causes lipotoxicity, which impairs insulin signaling pathway, and results in insulin resistance. High sugar intake also results in the generation of Inflammatory cytokines such as TNF-α and IL-6 which interfere with insulin signaling pathways, reducing the ability of cells to respond to insulin, resulting in insulin resistance.

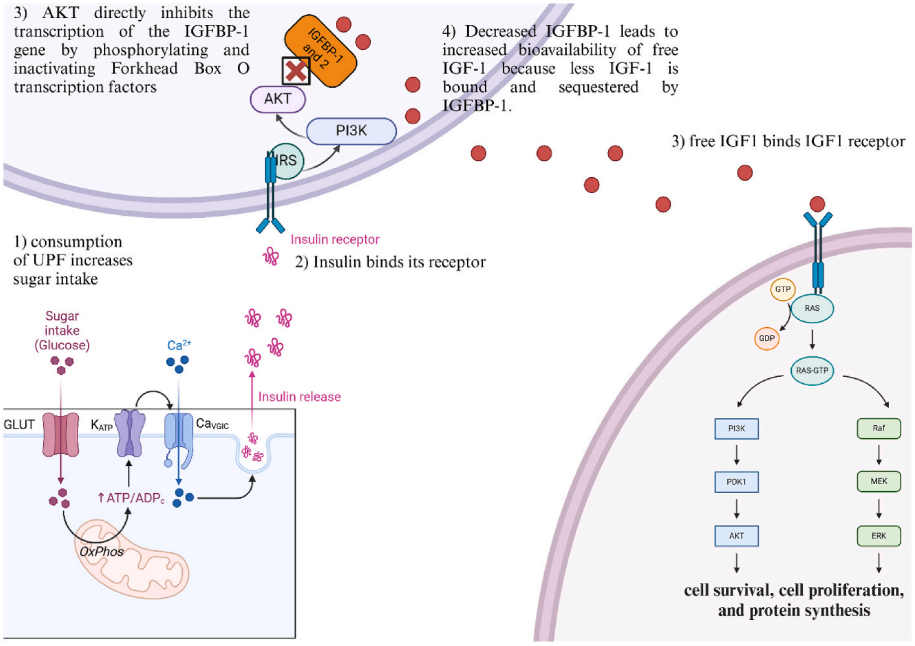

Fig. 3. Mechanism of High Sugar Intake in Modulating Insulin-Like Growth Factors and Promoting Cancer Proliferation. Chronic high sugar intake elevates insulin levels and suppresses the production of insulin-like growth factor-binding proteins 1 and 2 (IGFBP-1 and IGFBP-2). This reduction increases the availability of unbound IGF-1, leading to sustained activation of IGF-1 signaling pathways across various tissues. Prolonged IGF-1 signaling drives uncontrolled activation of the RAS/RAF/MEK/ERK pathway, promoting unchecked cell proliferation. Simultaneously, it inhibits apoptotic processes via activation of the PI3K/AKT pathway, enhancing cell survival. Additionally, IGF-1 signaling stimulates the production of vascular endothelial growth factor (VEGF), fostering angiogenesis, and activates matrix metalloproteinases (MMPs), which degrade extracellular matrix components. These processes collectively contribute to cancer proliferation, angiogenesis, and metastasis.

roles in cellular growth, differentiation, and survival. IGF-1, characterized by its mitogenic and anti-apoptotic properties, has been implicated in cancer biology (LeRoith and Roberts Jr, 2003). The production of IGF-1 is primarily stimulated by growth hormone (GH), which induces hepatic synthesis of IGF-1. Upon binding to its receptor, IGF-1R, IGF-1 activates intracellular signaling pathways through autophosphorylation, initiating a cascade of molecular events (LeRoith and Roberts Jr, 2003). When IGF-1 binding to its receptor (IGF-1R), it induces autophosphorylation of the receptor, activating the phosphatidylinositol 3-kinase (PI3K) pathway. PI3K phosphorylates and activates AKT, a serine/threonine kinase. Activated AKT facilitates cell survival and proliferation by inhibiting apoptotic pathways, enhancing protein synthesis, and promoting cell cycle progression (Pollak, 2008). IGF-1R activation also stimulates the RAS-RAF-MEK-ERK signaling cascade. This pathway involves sequential phosphorylation events, leading to the activation of extracellular signal-regulated kinases (ERKs). ERKs regulate the expression of genes essential for cell division and differentiation, contributing to cellular proliferation (Folkman, 2002).

Ultra-processed foods are a major dietary source of added sugars, contributing significantly to chronic high sugar intake. Foods and beverages such as sugar-sweetened drinks, candy, baked goods, and other UPFs are formulated with high levels of free sugars and high-fructose corn syrup to enhance palatability and shelf-life (Monteiro et al., 2019b). Chronic high sugar intake induces insulin resistance, leading to elevated insulin levels, a condition known as hyperinsulinemia. Hyperinsulinemia suppresses the production of insulin-like growth factor-binding proteins 1 and 2 (IGFBP-1 and IGFBP-2), which are critical regulators of IGF-1 activity (Fig. 3). Reduced IGFBP levels result in increased circulating IGF-1, leading to chronic activation of IGF-1 signaling pathways as unbound IGF-1 interacts with its receptors across various tissues (Wang et al., 2022). Prolonged activation of IGF-1 signaling pathways significantly contributes to cancer proliferation through various mechanisms. Persistent stimulation of the RAS/RAF/-MEK/ERK pathway drives uncontrolled cellular proliferation, which is a hallmark of cancer (Wang et al., 2022). Additionally, activation of the PI3K/AKT pathway promotes cell survival by inhibiting apoptotic processes, enabling cancer cells to evade programmed cell death despite genetic and cellular stress (Pollak, 2008). Chronic IGF-1 signaling also enhances the production of vascular endothelial growth factor (VEGF), facilitating angiogenesis and providing tumors with an adequate blood supply necessary for growth and metastasis (Quetglas-Llabrés et al., 2023). Furthermore, IGF-1 signaling activates matrix metalloproteinases (MMPs), which degrade extracellular matrix components. This degradation enables cancer cells to invade surrounding tissues, thereby promoting motility and metastasis (Quetglas-Llabrés et al., 2023).

3.4.3. Chronic inflammation induced by ultra-processed foods as a driver of tumor development

The association between chronic inflammation and cancer was first proposed by Rudolf Virchow in 1863. Today, it is well established that chronic inflammation plays a significant role in tumor development by promoting the release of pro-inflammatory cytokines and other immunomodulatory factors. These mediators create a tumor-promoting microenvironment that facilitates cancer progression and metastasis (Monteiro et al., 2019b).

The consumption of UPFs induces a pro-inflammatory state through various mechanisms. The high sugar content in UPFs causes a postprandial increase in blood glucose levels, leading to elevated insulin secretion and the subsequent promotion of systemic inflammation (Tristan Asensi et al., 2023). Additionally, the high levels of salt, saturated fats, and *trans*-fatty acids characteristic of UPF-rich diets directly contribute to the development of chronic inflammation. The low fiber content of UPFs, due to the removal of the protective fiber layer during processing, further exacerbates this effect by altering gut microbiota composition, diversity, and epigenetic regulation. This disruption creates a pro-inflammatory gut microbiota profile, a condition referred to as intestinal dysbiosis (Vissers et al., 2022). Dysbiosis compromises the integrity and permeability of the intestinal mucosa, leading to localized chronic inflammation and the systemic migration of lipopolysaccharides. These changes drive pro-oxidative and inflammatory processes throughout the body, and the persistence of these processes results in sustained chronic inflammation, which plays a critical role in promoting various pathophysiological conditions including cancer (Chiurchiu and Maccarrone, 2011).

Chronic inflammation plays a pivotal role in tumor development through various mechanisms. Inflammatory cells such as myeloid-derived suppressor cells (MDSCs), fibroblasts, tumor-associated macrophages (TAMs), and lymphocytes are recruited to inflammatory sites (Fig. 4) where they release cytokines, chemokines, and other signaling molecules, promoting immune responses, inflammation, and cellular proliferation (Greten and Grivennikov, 2019). During chronic inflammation, an excess of inflammatory cells, cytokines, growth factors, chemokines, and proteases accumulates at these sites, stimulating tissue regeneration and remodeling of the extracellular matrix (ECM). This creates a microenvironment conducive to carcinogenesis, characterized by immunosuppression, angiogenesis, sustained cell proliferation, and tumor initiation (Colotta et al., 2009).

Persistent inflammation contributes to genomic instability by activating oncogenes and/or inactivating tumor suppressor genes. This disruption promotes cellular transformation and tumorigenesis (Elinav et al., 2013). Moreover, chronic inflammation leads to the excessive production of ROS and inflammatory cytokines, which accumulate at inflammatory sites. ROS induce DNA damage and aberrant expression of activation-induced cytidine deaminase (AID) (Fig. 4), a B-cell enzyme involved in somatic hypermutation and antibody diversification. Overexpression of AID can result in mutations in key tumor-related genes such as TP53 and MYC, driving tumor development (Jiao et al., 2023). Activation-induced cytidine deaminase (AID) exerts its mutagenic effect primarily through its cytidine deamination activity, which converts cytosine to uracil in single-stranded DNA, generating U:G mismatches. This lesion triggers DNA repair pathways, including base excision repair (BER) and mismatch repair (MMR), both of which can introduce mutations due to error-prone DNA polymerases. Additionally, AID-induced double-strand breaks (DSBs) during class switch recombination (CSR) can lead to chromosomal translocations, such as those involving the MYC oncogene, resulting in its overexpression and promoting oncogenesis. Overexpression or dysregulation of AID can extend its activity to non-immunoglobulin loci, including tumor suppressor genes, leading to loss-of-function mutations that disrupt genomic stability and promote tumorigenesis (Barreto and Magor, 2011). ROS-induced DNA damage activates DNA repair mechanisms by initiating cell cycle checkpoints through the activation of checkpoint kinases such as ATM (ataxia telangiectasia mutated) and ATR (ataxia telangiectasia and Rad3-related protein). These checkpoints temporarily halt the cell cycle, allowing time for DNA repair to maintain genomic stability. However, excessive ROS and inflammatory cytokines can overwhelm these repair mechanisms, leading to persistent DNA damage. This can result in apoptosis or senescence if repair is incomplete or inadequate (Kidane et al., 2014).

Chronic inflammation can disrupt key cell cycle checkpoint pathways through the downregulation or inactivation of checkpoint kinases such as ATM and ATR. These impairments hinder their ability to effectively initiate cell cycle arrest in response to DNA damage. Additionally, inflammatory signals interfere with the tumor suppressor protein p53, compromising its role in inducing cell cycle arrest or apoptosis, which are crucial for maintaining genomic stability. Inflammatory mediators also suppress the expression or activity of cyclins and cyclin-dependent kinases (CDKs), essential regulators of cell cycle progression. This suppression results in unchecked cell proliferation despite the presence of DNA damage. The cumulative effect of these disruptions leads to an accumulation of random genetic mutations and genomic instability, fostering tumorigenesis (Kidane et al., 2014; Mantovani et al., 2008).

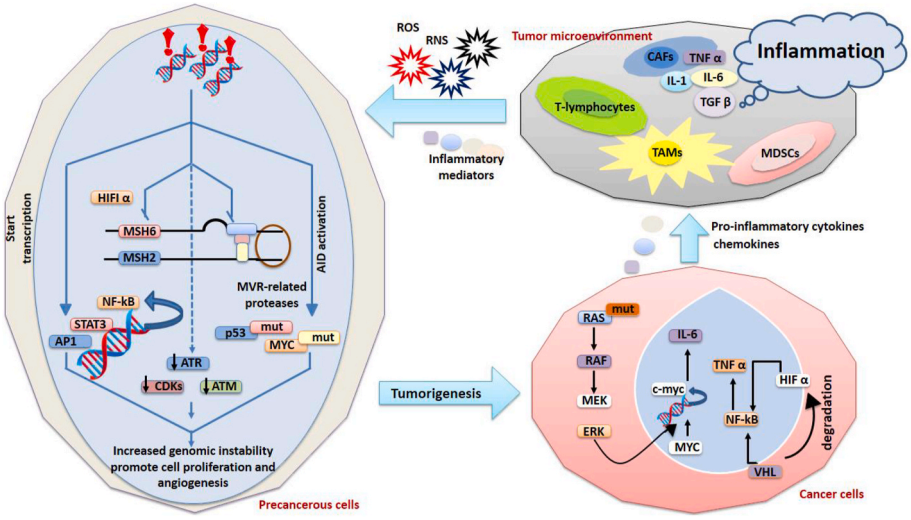

Fig. 4. Role of chronic inflammation in tumor development. Chronic inflammation promotes tumorigenesis by recruiting inflammatory cells, cytokines, chemokines, and proteases, which induce DNA damage and genomic instability. Inflammatory mediators activate oncogenes, inactivate tumor suppressors such as p53, and disrupt cell cycle regulation. Reactive oxygen species (ROS) and cytokines generated during inflammation exacerbate DNA damage and induce aberrant expression of activation-induced cytidine deaminase (AID), leading to mutations in TP53 and MYC. ROS impair checkpoint proteins ATM and ATR, disrupting cell cycle arrest. Inflammatory mediators downregulate mismatch repair (MMR) proteins and cyclins, facilitating genomic instability and uncontrolled proliferation. These processes drive tumor progression and maintain a pro-inflammatory microenvironment.

The p53 protein plays a central role in maintaining genomic integrity by regulating DNA repair, cell cycle arrest, and apoptosis in response to stressors such as DNA damage or oncogene activation. Chronic inflammation induces p53 inactivation, disrupting genomic surveillance mechanisms that prevent mutagenesis. This leads to an accelerated accumulation of mutations in cancer cells, further promoting tumor progression. The compromised activity of p53 reduces the cell's ability to efficiently repair DNA damage, increasing the likelihood of tumorigenic transformations (Williams and Schumacher, 2016).

Chronic inflammation also inhibits the mismatch repair (MMR) pathway, increasing DNA replication error rates. Inflammatory cytokines such as TNF-α and IL-6, suppress MMR protein expression and activity via transcriptional repression and activation of pro-inflammatory signaling pathways, including NF-κB. Oxidative stress and epigenetic modifications associated with inflammation further compromise MMR efficiency, leading to genomic instability and the accumulation of mutations that drive cancer development (Mantovani et al., 2008).

Inflammatory cells, cytokines, and chemokines recruited to chronic inflammation sites are also influenced by cancer-associated genes such as RAS, MYC, and HIF1α. Oncogenic RAS stimulates the secretion of chemokines (e.g., CXCL1, CXCL2, CXCL5, CXCL8), cytokines (e.g., IL-1, IL-6, IL-8, IL-23), and activates signaling pathways such as STAT3, NF-κB, and MAPK, all of which facilitate tumor progression. IL-6 secreted by oncogenic RAS establishes a direct link between chronic inflammation and cancer, promoting malignant tumor growth through NF-κB and JAK/STAT signaling pathways (Shchors et al., 2006; Johnson et al., 2018). The MYC oncogene contributes to tumorigenesis by regulating tissue remodeling, angiogenesis, and chronic inflammation. MYC activation in β-cells induces the release of interleukin-1β (IL-1β), stimulating endothelial cell proliferation and complex vessel formation. MYC also facilitates mast cell recruitment, which is critical for tumor angiogenesis and expansion (Browning et al., 2018).

Tumor suppressor proteins, such as Von Hippel-Lindau (VHL), play a role in inhibiting inflammatory mediators and suppressing cancer development. Mutations in VHL disrupt its regulatory functions, leading to constitutive activation of hypoxia-inducible factors (HIF-1α and HIF-2α). These factors alter cellular metabolism, promote angiogenesis, and enhance metastasis, contributing to the development of cancers such as clear cell renal cell carcinoma (CCRCC). Activated HIF-1α interacts with NF-κB, inducing the production of TNF-α and CXCR4, which are implicated in the progression of malignant tumors (Korbecki et al., 2021).

4. Challenges in implementing ultra-processed foods intake reduction in low- and middle-income countries

It is crucial to recognize that no individual policy is free from difficulties; implementing strategies to decrease the consumption of UPFs, such as levies on sugary beverages and obligatory nutritional labeling, encounters significant hurdles in LMICs (Menon and OLNEY, 2024). A primary barrier is the strong opposition from influential food and beverage sectors, which frequently lobby against such measures, claiming potential economic damage and job losses. Numerous LMICs depend significantly on these sectors for economic development and employment, leading to government reluctance to enforce strict regulations (Irshad and Ghafoor, 2023). Furthermore, the inadequate infrastructure and governance prevalent in many LMICs diminishes the capacity to enforce policies like tax and labeling mandates. Issues like corruption, limited regulatory capabilities, and ineffective monitoring systems intensify these challenges, undermining the success of such initiatives.

Another challenge originates from the socio-economic and cultural contexts of LMICs. Ultra-processed foods tend to be more budget-friendly and readily available than fresh and minimally processed foods, making them a dietary mainstay for low-income families (Amaraggi et al., 2024). This cost advantage presents a major obstacle to altering eating habits, particularly in areas facing food insecurity. Low levels of education, insufficient funding, and competing public health concerns such as infectious disease management also impede public awareness efforts regarding the health dangers associated with UPFs (Wood et al., 2024). In addition, the challenge of promoting healthier options is further complicated by fragile agricultural systems and supply chains that struggle to deliver fresh and cost-effective produce (Weerabahu et al., 2022). These interrelated factors make it difficult to implement effective public health strategies aimed at reducing UPF consumption in LMICs.

The persistent shortage of financial resources to sustain comprehensive public health programs constitutes a significant and ongoing

challenge in LMICs (Rabbani et al., 2016). Governments often grapple with competing demands, with limited budgets mostly directed toward addressing infectious diseases, leaving issues related to non-communicable diseases (NCDs) and diets underfunded. Furthermore, many LMICs are unable to subsidize healthier food choices or assist local farmers in enhancing the availability of fresh and minimally processed foods (Popkin et al., 2021). Insufficient investment in nutrition education, agricultural initiatives, and community health schemes further obstruct efforts to mitigate UPF consumption. Without considerable financial and technical backing from international entities and collaborations, LMICs find it increasingly challenging to establish sustainable policies aimed at decreasing UPF intake and enhancing public health outcomes.

5. Regulatory and policy approaches to mitigating the health risks of ultra-processed foods

The increasing global consumption of UPFs has necessitated the implementation of policy interventions to mitigate associated health risks. Ultra-processed foods, defined by their high content of refined sugars, unhealthy fats, sodium, and synthetic additives, significantly contribute to the rising prevalence of non-communicable diseases, including cardiovascular diseases and cancer. Addressing these health challenges requires a comprehensive approach that integrates public health initiatives, regulatory frameworks, and education to influence dietary patterns toward healthier alternatives. Regulatory and policy measures are essential for reducing UPF consumption by targeting factors such as affordability, accessibility, and consumer behavior. These strategies aim to promote the consumption of minimally processed, nutrient-dense foods, limit the intake of harmful components, and foster healthier dietary environments.

5.1. Fiscal and labeling policies to curb the consumption of ultra-processed foods

Regulatory measures, such as taxes on sugary beverages and unhealthy foods, are widely implemented to reduce the consumption of UPFs by increasing their cost and limiting accessibility. In Mexico, the introduction of a tax on sugary drinks in 2014 resulted in a significant reduction in the purchase of taxed beverages (Colchero et al., 2017; James et al., 2020). Similarly, Berkeley, California, became the first U.S. city to implement an excise tax on sugar-sweetened beverages in 2014. Studies reported a 6% decrease in sugary drink purchases during the first year, which increased to 10% in the second year (Falbe et al., 2016).

Mandatory nutritional labeling has also proven effective in informing consumers about the nutritional value of UPFs. FOP labeling systems, such as traffic light labeling and warning labels, encourage healthier food choices by providing clear and accessible nutritional information. Chile has been a leader in this domain, implementing black stop-sign labels on foods high in calories, sugar, salt, and saturated fat in 2016 (Correa et al., 2019). This measure significantly reduced the purchase of labeled products and prompted food manufacturers to reformulate their products to avoid the warnings (Khandpur et al., 2018; Taillie et al., 2020). Similar effects have been observed in Peru, where FOP labels decreased the consumption of high-sugar beverages (Jáuregui et al., 2022).

Several countries have implemented policies targeting UPFs consumption with notable public health outcomes. In Mexico, the revenue generated from sugary drink taxes has been reinvested into public health initiatives, amplifying the positive health impact (Gómez, 2023). Chile's comprehensive food labeling and marketing restrictions have set a global precedent, resulting in substantial declines in unhealthy food and beverage purchases and promoting product reformulation (Boza et al., 2017). In the United Kingdom, the 2018 Soft Drinks Industry Levy led to a 28.8% reduction in the sugar content of soft drinks sold, illustrating the effectiveness of fiscal measures in fostering healthier food environments (Scarborough et al., 2020). Similarly, Berkeley's sugary drink tax not only reduced sugary beverage consumption but also increased water intake while generating funds for community health programs (Falbe et al., 2016).

Public health authorities in countries such as Brazil, Uruguay, Ecuador, Peru, France, and Canada have incorporated restrictions on UPFs consumption into their national dietary guidelines (Baker et al., 2020). International organizations, including the Food and Agriculture Organization and the World Cancer Research Fund, recommend replacing UPFs with minimally processed foods such as fruits, vegetables, whole grains, and beans, alongside increased consumption of water and unsweetened beverages, to reduce the risk of cancer and chronic diseases (Poore and Nemecek, 2018). Although reducing UPFs consumption is a primary objective, food reformulation may play a supplementary role by mitigating associated risks. Reformulation efforts should focus on reducing harmful substances, such as acrylamide and nitrosamines, to facilitate the transition toward healthier food systems based on fresh and minimally processed foods Emerging technologies offer potential to produce processed foods with enhanced nutritional profiles, reduced levels of toxic contaminants, and minimized environmental impact (Carwile et al., 2011; Ozyurt and Ötles, 2016; McClements et al., 2021; Seferidi et al., 2021). However, evidence indicates that voluntary agreements with the food industry for reformulation are generally ineffective without strict governmental oversight (Scrinis, 2016; Popkin, 2019; Laverty et al., 2019; Seferidi et al., 2020). Additional governmental actions could include banning extensive commercial promotion of UPFs and supporting small-scale, family, and cooperative farmers to ensure affordable and accessible fresh and nutritious foods (Wood et al., 2021). Policies targeting UPF reduction should be rigorously evaluated to determine their effectiveness in mitigating risks to human health and environmental sustainability.

5.2. The need for regulatory action to reduce sugar content in baby foods

Over the last twenty years, childhood obesity along with its related health issues has become a significant burden on the nation's health (Ghosh et al., 2019). Research indicates that roughly one-third of the total caloric content in various commercial baby foods analyzed across ten European nations comes from sugar (Maslin and Venter, 2017). This level is concerning as it conflicts with the existing WHO guideline to restrict free sugars in foods for infants and considerably exceeds the WHO recommendation of less than 10% of total energy intake for older children (Organization, 2015). In most food categories, the average sugar contribution was over 10%, even present in savory pureed meals in countries like the United Kingdom, Denmark, Malta, and Estonia, potentially misleading caregivers (Hutchinson et al., 2021). Added sugars are commonly found in many product categories, and a notable portion of savory meals contains pureed fruit, especially in the United Kingdom (Amoutzopoulos et al., 2018). Due to the characteristics of these products, primarily being highly processed fruit puree-based, most of the sugars present can indeed be classified as free sugars (Hutchinson et al., 2021). The total amounts of added and free sugars in baby foods raise significant concerns since sugar consumption is associated with adverse health outcomes later in life, such as the onset of dental cavities, excessive weight gain, and a heightened risk of non-communicable diseases including type 2 diabetes, cardiovascular issues, certain cancers, and non-alcoholic fatty liver disease (Alexei et al., 2022). Therefore, prioritizing the improvement of sugar levels in baby foods should be considered critical in both governmental and organizational policies, in addition to manufacturing practices, to protect young children from frequently consuming excessively sweet products (Velázquez et al., 2021). In the lack of strict regulatory measures, the sugar levels in processed foods, particularly in so-called health drinks for expectant and nursing mothers, remain significantly high. Instant foods designed for infants aged 6 months and older are heavily loaded with sugar (Organization, 2023). Similarly, sugary health beverages for children

are marketed cleverly with claims to enhance growth and strength. Surprisingly, these items originate from prominent companies that possess specialized nutrition research and development departments. It is baffling how such a serious issue as childhood obesity continues to be neglected in favor of making instant baby foods and health drinks more appealing and profitable (Lutter et al., 2021). Furthermore, the discussion around perinatal programming of obesity and diabetes linked to the consumption of high-sugar health drinks during pregnancy and lactation remains largely unaddressed. Although a UN report warns that achieving the 2030 sustainable development goals may be extremely challenging, it is not yet too late to take a more responsible approach towards ensuring healthy nutrition in early life for a healthier future population. The government must enact strict regulations to limit sugar content in instant baby foods and health drinks, adhering to WHO recommendations.

6. Summary and future directions

Ultra-processed foods pose significant risks to cardiovascular health and cancer development due to their deleterious nutrient composition and metabolic impacts. Ultra-processed foods are characterized by high levels of refined sugars, *trans*-fats, saturated fats, and sodium, which contribute to hypertension, dyslipidemia, and obesity, which are primary risk factors for cardiovascular diseases. Chronic consumption of UPFs induces low-grade systemic inflammation, endothelial dysfunction, and arterial blockages, further exacerbating cardiovascular pathologies. UPFs disrupt gut microbiota composition and integrity, increasing intestinal permeability and promoting systemic inflammation, which compounds their detrimental effects on cardiovascular health. In relation to cancer, several components of UPFs, such as artificial sweeteners, preservatives, and certain processing byproducts, are associated with carcinogenicity. The consumption of UPFs contributes to obesity, a well-established risk factor for cancers including breast, colorectal, and pancreatic cancers. Furthermore, UPFs elevate oxidative stress and systemic inflammation, creating a tumor-promoting microenvironment. Epidemiological evidence indicates that UPFs constitute over half of daily caloric intake in many Western diets, with a 10% increase in UPF consumption correlating with a 12% higher risk of cardiovascular diseases and a 10–12% increased risk of cancer. Reducing UPF consumption has the potential to significantly lower the burden of cardiovascular and cancer-related morbidity and mortality, improve overall metabolic and mental health, and reduce healthcare costs. These benefits would also alleviate pressures on healthcare systems and contribute to enhanced societal productivity.

Future research should focus on elucidating the molecular and physiological mechanisms underlying the adverse health effects of UPFs, with particular attention to the role of specific additives and industrial processing techniques. It is also critical to investigate the differential effects of UPFs across diverse populations to inform culturally specific public health interventions. Furthermore, robust evaluations of public health policies, including taxation, labeling, and marketing restrictions, are essential to assess their efficacy in reducing UPF consumption and improving health outcomes. This comprehensive approach is essential to combat the public health challenges posed by UPFs and promote healthier dietary patterns globally.

CRediT authorship contribution statement

Olorunfemi Oyewole Babalola: Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Data curation. **Ebenezer Akinnusi:** Visualization, Conceptualization. **Paul Olamide Ottu:** Writing – review & editing, Conceptualization. **Kpomah Bridget:** Conceptualization. **Godspower Oyubu:** Writing – review & editing. **Samuel Ayomikun Ajiboye:** Conceptualization. **Sakariyau Adio Waheed:** Conceptualization. **Amafili Chibuzo Collette:** Writing – original draft. **Hameedah Oluwatoyin Adebimpe:** Writing – original draft. **Chibuzo Valentine Nwokafor:** Writing – original draft. **Ebenezer Ayomide Oni:** Visualization. **Precious Olayinka Aturamu:** Writing – original draft. **Opeyemi Iwaloye:** Writing – review & editing, Validation, Supervision, Formal analysis.

Declaration of competing interest

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