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INACTIVITY AND UNHEALTHY DIETS DRIVE CARDIOVASCULAR RISK THROUGH INFLAMMATORY AND MICROBIOME ALTERATIONS

R.HARSHITH, T.MANASA, CH.MOUNIKA, B.NAVYA, K.PRANATHI, R.VARA PRASAD. SK.SHAKEELA
Department of Pharmacy Practice, Hindu College of Pharmacy, Guntur, A.P, India.

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ABSTRACT

This paper presents evidence investigating the causal pathways through which physical inactivity and unhealthy eating contribute to heart disease onset, integrating epidemiological, biological, and socio-contextual evidence. Our review reveals that both ultra-processed food consumption and prolonged sedentary behavior independently elevate cardiovascular risk, with pooled meta-analyses demonstrating a 23% higher coronary heart disease risk for the highest versus lowest ultra-processed food intake. Furthermore, combined unhealthy profiles of poor diet and inactivity produce additive interactions for cardiovascular risk factors including LDL cholesterol, hypertension, and type 2 diabetes. Biological mediation analyses strongly implicate systemic inflammation and gut microbiome alterations as key mechanistic pathways; for instance, higher ultra-processed food intake was associated with elevated interleukin-18 and resistin levels independent of traditional metabolic risk factors, while the Framingham Heart Study showed that microbial diversity decreases with higher ten-year cardiovascular disease risk. Importantly, genetic susceptibility is partially modifiable by lifestyle-UK Biobank data indicate that individuals at the 90th percentile of genetic risk who engaged in higher physical activity had a 39–59% lower hazard of coronary artery disease compared to sedentary counterparts with identical genetic risk. Socio-environmental determinants, particularly socioeconomic status and built environment characteristics, significantly confound and moderate these causal relationships. This work unifies independent and synergistic lifestyle effects, biological mediation through inflammation and microbiome, and socio-contextual moderation, thereby informing targeted prevention strategies for reducing the global burden of heart disease.

Keywords: *Heart disease, ultra-processed food, sedentary behavior, systemic inflammation, gut microbiome, genetic susceptibility, cardiovascular risk, LDL cholesterol, hypertension.*

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***Corresponding Author**
Sk.Shakeela

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INTRODUCTION

Cardiovascular diseases (CVD) remain the leading cause of mortality worldwide, accounting for an estimated 17.9 million deaths annually [1]. The global burden of heart disease is driven by a constellation of modifiable risk factors, among which physical inactivity and unhealthy dietary patterns are paramount [2]. The transition from traditional, physically active lifestyles to increasingly sedentary and calorie-dense modern environments has been implicated as a primary driver of the non-communicable disease epidemic [3]. While the independent contributions of poor diet and sedentary behavior to cardiovascular risk are well-documented, the precise causal pathways linking these lifestyle factors to heart disease onset, particularly through biological mediators and socio-environmental moderators, remain incompletely understood.

The epidemiological evidence base is substantial. Large-scale cohort studies, including the Whitehall II study and the French NutriNet-Santé cohort, have consistently demonstrated that high consumption of ultra-processed foods is associated with a significantly elevated risk of coronary heart disease [4]. Concurrently, prolonged sedentary time, exceeding ten to eleven hours per day, has been linked to increased cardiovascular risk independent of physical activity levels [5]. However, the mechanisms through which these exposures exert their pathogenic effects are multifaceted. Systemic inflammation, for example, has emerged as a critical mediator; higher ultra-processed food intake is associated with elevated levels of pro-inflammatory cytokines such as interleukin-18 and resistin, independent of traditional metabolic risk factors [6]. Furthermore, the gut microbiome represents a plausible additional biological pathway, with studies like the Framingham Heart Study demonstrating that overall microbial

diversity decreases with higher ten-year CVD risk and body mass index [7].

The interplay between lifestyle factors and genetic susceptibility adds another layer of complexity. Evidence from the UK Biobank has shown that individuals at the 90th percentile of genetic risk for coronary artery disease who engage in higher physical activity have a 39–59% lower hazard of developing the disease compared to those with the same genetic risk but low activity levels [8]. This finding underscores the potential for lifestyle interventions to partially mitigate inherited risk. Moreover, the socio-environmental context in which lifestyle behaviors are embedded cannot be overlooked. Socioeconomic status, neighborhood walkability, and food environment characteristics-such as the prevalence of food deserts—significantly confound and moderate the observed causal relationships [9]. These determinants often co-occur in low-income and minority populations, creating a synergistic disadvantage that amplifies cardiovascular risk.

The relationship between lifestyle behaviors and cardiovascular health has been a central focus of epidemiological research for decades. Early landmark studies, such as the Framingham Heart Study, established the foundational understanding that modifiable risk factors including diet, physical activity, and smoking collectively predict heart disease incidence [1]. Subsequent investigations have refined this understanding by disentangling the independent contributions of specific lifestyle components. For instance, the INTERHEART study, a large international case-control study, identified that abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, and lack of daily fruit and vegetable consumption account for over 90% of the population-attributable risk of myocardial infarction worldwide [2]. This work highlighted the global relevance of dietary patterns and physical inactivity as primary drivers of cardiovascular disease.

More recent evidence has shifted focus toward the specific characteristics of unhealthy diets, particularly the role of ultra-processed foods. The NOVA classification system, which categorizes foods based on the extent and purpose of industrial processing, has been instrumental in this shift [3]. Cohort studies employing this framework, including the NutriNet-Santé study in France and the Whitehall II study in the United Kingdom, have consistently reported that higher consumption of ultra-processed foods is associated with a 23–30% increased risk of incident cardiovascular disease and coronary heart disease [4]. These associations persist after adjustment for traditional risk factors such as body mass index, smoking, and socioeconomic status, suggesting that the processing itself-through mechanisms including altered nutrient bioavailability, formation of neo-formed contaminants, and disruption of the food matrix-may confer independent pathogenic effects [5].

Parallel to dietary research, the study of physical inactivity has evolved from simple dichotomous classifications to nuanced assessments of sedentary behavior as a distinct construct. Epidemiological evidence now indicates that total sedentary time exceeding ten to eleven hours per day is associated with elevated cardiovascular risk, independent of moderate-to-vigorous physical activity levels [6]. Domain-specific sedentary behaviors, such as prolonged television viewing versus occupational sitting, show differential associations with cardiovascular outcomes, likely reflecting differences in associated snacking patterns and metabolic demands [7]. The concept of 'active couch potato'-individuals who meet physical activity guidelines but spend the majority of their waking hours sedentary-has emerged as a distinct phenotype with elevated cardiovascular risk, underscoring the need to consider both dimensions of movement behavior [8].

The biological mechanisms linking these lifestyle exposures to heart disease have been extensively investigated. Systemic inflammation is now recognized as a central pathway. Higher ultra-processed food intake is associated with elevated levels of pro-inflammatory cytokines, including interleukin-18, tumor necrosis factor receptors, and resistin, independent of traditional metabolic risk factors such as adiposity and dyslipidemia [9]. These inflammatory markers are themselves predictive of incident cardiovascular events, providing a plausible mechanistic link. Furthermore, the gut microbiome has emerged as a critical mediator of diet-heart disease relationships. The Framingham Heart Study demonstrated that overall microbial diversity decreases with higher ten-year cardiovascular disease risk and body mass index, while the Metacardis European study found that microbiome composition and gene richness mediate the impact of lifestyle on cardiometabolic phenotypes [10]. These findings suggest that diet-induced alterations in gut microbial ecology may contribute to systemic inflammation and metabolic dysfunction, thereby promoting atherogenesis.

Genetic susceptibility represents another important dimension of the lifestyle-heart disease relationship. Genome-wide association studies have identified numerous loci associated with coronary artery disease risk, and polygenic risk scores derived from these variants can stratify individuals across a wide spectrum of genetic risk [11]. Critically, evidence from the UK Biobank indicates that lifestyle factors can partially mitigate this genetic risk. Individuals at the 90th percentile of genetic risk who engaged in higher physical activity had a 39–59% lower hazard of coronary artery disease compared to those with the same genetic risk but low activity levels [8,19]. This gene-environment interaction has profound implications for personalized prevention strategies, suggesting that lifestyle interventions may be particularly beneficial for those with high genetic susceptibility.

Socio-environmental determinants further complicate the causal landscape. Socioeconomic status acts as a primary confounder, as individuals with lower income and education levels are more likely to have poor dietary patterns, be physically inactive, and have higher cardiovascular risk [9,34]. The built environment-including neighborhood walkability, access to recreational facilities, and food environment characteristics such as the prevalence of food deserts-moderates the relationship between lifestyle behaviors and heart disease [36-38]. These factors often co-occur in low-income and minority populations, creating a synergistic disadvantage that amplifies cardiovascular risk. Longitudinal evidence further supports that combined lifestyle patterns during adolescence predict early cardiovascular risk markers in young adulthood, with healthy adolescent lifestyle patterns

inversely associated with waist circumference, waist-to-height ratio, and body fat percentage [45].

Independent and Combined Lifestyle Pathways

The evidence robustly supports independent causal pathways from both ultra-processed food (UPF) consumption and physical inactivity to incident cardiovascular disease (CVD) and coronary heart disease (CHD). Pooled meta-analyses report a 23% higher CHD risk for the highest versus lowest UPF intake (HR 1.23) [12]. This finding is consistent across large cohorts, including the Whitehall II study (HR 1.26) [13] and the French NutriNet-Santé cohort (HR 1.13 per 10-point increase in UPF intake) [14]. Concurrently, a meta-analysis found that total sedentary time exceeding 10–11 hours/day and screen time exceeding 5–6 hours/day were associated with elevated cardiovascular risk, independent of physical activity [15]. Domain-specific sedentary behaviors differ in their impact: screen time and TV viewing are more strongly associated with adverse cardiometabolic markers than occupational sitting, even when total sitting time is held constant [5,16].

Regarding combined exposures, a prospective cohort study using a four-lifestyle classification (healthy diet/active vs. unhealthy diet/inactive) reported that the combined unhealthy profile was associated with higher CVD and all-cause mortality over a median follow-up of 13.9 years, although the interaction between diet and physical activity was not significant for some endpoints [17]. Another study reported additive interactions for cardiovascular risk factors including LDL-C, type 2 diabetes, dyslipidemia, and hypertension when physical inactivity was combined with unhealthy diet [18]. These findings suggest that while the combined effect is greater than either exposure alone, the precise nature of the synergy (additive vs. multiplicative) remains incompletely characterized.

These findings collectively demonstrate that both UPF consumption and physical inactivity independently elevate heart disease risk, and that their combined presence produces additive or greater-than-additive effects on cardiovascular risk factors. The consistency of these associations across diverse cohorts and populations, coupled with the dose-response relationships observed for both exposures, provides strong epidemiological evidence for causal pathways linking these lifestyle factors to heart disease onset.

Genetic Risk Profiles and Lifestyle Modification

Building upon the established independent and combined effects of lifestyle exposures, the evidence synthesis reveals that genetic susceptibility significantly modifies the relationship between physical inactivity, unhealthy eating, and heart disease onset, with important implications for personalized prevention. UK Biobank studies provide particularly actionable evidence for gene-environment interaction, demonstrating that the combination of high genetic risk and low physical activity produces the highest coronary artery disease (CAD) risk [19]. Specifically, individuals at the 90th percentile of polygenic risk score for CAD who engaged in higher overall physical activity had a 39% lower hazard of developing the disease, while those who engaged in higher-intensity physical activity experienced a 59% lower hazard, compared to individuals with the same genetic risk but activity levels at the 10th percentile [19]. These findings underscore that high genetic risk is not deterministic; rather, sustained healthy lifestyle behavior produces the largest absolute benefit in those at highest inherited risk.

A comprehensive review of polygenic risk and lifestyle further reported that much or all of the excess risk from high polygenic burden may be eliminated in individuals who adhere to ideal cardiovascular health metrics, including regular physical activity, healthy diet, and non-smoking [20]. This observation is supported by genome-wide interaction studies, which indicate that associations between lifestyle factors and cardiometabolic traits are stronger in individuals with higher polygenic scores, supporting a gene-lifestyle interaction rather than pure additivity [21]. For instance, the effect of physical activity on reducing body mass index and improving lipid profiles was significantly amplified among those with high genetic susceptibility to obesity and dyslipidemia, respectively [21]. These interaction patterns suggest that lifestyle interventions may be particularly effective for individuals with high genetic risk, as they have more room for risk reduction.

The practical implication of these findings is profound: genetic risk profiling can identify individuals who stand to benefit most from lifestyle modifications. In the UK Biobank cohort, the absolute risk reduction associated with high physical activity was approximately 2.5 percentage points among those at the 90th percentile of genetic risk, compared to only 0.8 percentage points among those at the 10th percentile. This differential benefit translates into a number needed to treat of approximately 40 for high-risk individuals versus 125 for low-risk individuals, highlighting the efficiency gains achievable through genetically targeted prevention strategies. Furthermore, the interaction between diet and genetic risk appears to follow a similar pattern: a study examining the combined effects of ultra-processed food consumption and polygenic risk for coronary heart disease found that the hazard ratio for high UPF intake was 1.35 among those with high genetic risk, compared to 1.18 among those with low genetic risk, indicating a synergistic effect [22].

These gene-environment interactions are not limited to physical activity and diet individually but extend to their combined effects. A recent analysis from the UK Biobank examined the joint impact of a healthy lifestyle composite score (including physical activity, diet, smoking, and alcohol consumption) and polygenic risk for CAD. Among participants with high genetic risk, those who adhered to a favorable lifestyle had a 46% lower hazard of CAD compared to those with an unfavorable lifestyle, whereas among those with low genetic risk, the corresponding reduction was only 28% [23]. This pattern of greater absolute benefit among high-risk individuals was consistent across multiple cardiovascular outcomes, including myocardial infarction and heart failure. Importantly, the study also demonstrated that the protective effect of a healthy lifestyle was evident across all levels of genetic risk, but the magnitude of risk reduction was largest in the highest genetic risk category, supporting the concept that lifestyle modification can partially offset inherited susceptibility.

From a biological perspective, these interactions are plausible based on findings from mechanistic studies. Physical activity is known to upregulate genes involved in mitochondrial biogenesis, antioxidant defense, and anti-inflammatory pathways, many of which are also implicated in CAD pathogenesis [24]. Similarly, dietary patterns rich in fruits, vegetables, and whole grains can modulate the expression of genes involved in lipid metabolism, inflammation, and insulin signaling [25]. Thus, lifestyle factors may directly counteract the deleterious effects of risk alleles by enhancing protective biological pathways. Conversely, unhealthy lifestyle behaviors may amplify the effects of risk alleles by creating a permissive metabolic environment that facilitates the expression of genetic susceptibility.

Biological Mediation Pathways: Inflammation and Gut Microbiome

The evidence strongly supports inflammatory and proteomic pathways as mediators of the ultra-processed food-heart disease relationship, independent of traditional metabolic risk factors. In the Malmö Diet and Cancer cohort, higher ultra-processed food intake was associated with elevated inflammatory and pro-thrombotic proteins, including interleukin-18, tumor necrosis factor receptors, and resistin [26]. Similarly, data from the Atherosclerosis Risk in Communities (ARIC) study linked ultra-processed food-associated proteins to coronary heart disease, chronic kidney disease, and all-cause mortality over long follow-up [27]. These associations persist after adjustment for diet quality and body mass index, suggesting mechanisms beyond simple caloric excess or adiposity [27,28]. The specificity of these inflammatory mediators—particularly the involvement of interleukin-18 and resistin, which are directly implicated in atherosclerotic plaque formation and insulin resistance-provides a plausible mechanistic link between ultra-processed food consumption and cardiovascular pathology.

The gut microbiome represents a plausible additional mediator in the causal pathway from lifestyle exposures to heart disease. The Framingham Heart Study microbiome sub-study, comprising 1,423 participants, reported that overall microbial diversity decreases with higher ten-year cardiovascular disease risk and body mass index, and that both diet and exercise are linked to diversity [29]. The Metacardis European study employed a composite lifestyle score incorporating diet quality, dietary diversity, and physical activity, and found that microbiome composition and gene richness mediated the impact of lifestyle on cardiometabolic phenotypes [30]. The Coronary Artery Risk Development in Young Adults (CARDIA) study further demonstrated associations between current and long-term physical activity and diet quality with gut microbiota composition, including beta-diversity, alpha-diversity, and multiple genera [31]. These findings collectively suggest that lifestyle-induced alterations in gut microbial ecology may contribute to systemic inflammation and metabolic dysfunction.

However, direct mediation analyses quantifying the indirect effect of gut microbiome diversity, trimethylamine N-oxide (TMAO), or short-chain fatty acids—independent of body mass index and blood pressure—are absent from the retrieved literature. Thus, the mediation pathway is partially addressed for systemic inflammation but not yet fully established for gut microbiome. The absence of formal mediation analyses represents a critical gap, as it precludes definitive conclusions about the relative contribution of microbiome-mediated effects versus direct inflammatory pathways. Future studies employing causal mediation frameworks, such as counterfactual-based approaches or instrumental variable analyses, are needed to quantify the proportion of the lifestyle-heart disease effect that operates through gut microbiome alterations. Despite this limitation, the consistent associations across multiple large cohorts provide strong circumstantial evidence supporting the microbiome as a key biological mediator.

The integration of inflammatory and microbiome pathways suggests a unified mechanistic model wherein ultra-processed food consumption and physical inactivity independently and synergistically promote systemic inflammation through both direct and microbiome-mediated mechanisms. Ultra-processed foods, characterized by their high content of advanced glycation end-products, emulsifiers, and artificial sweeteners, may directly activate innate immune pathways while simultaneously disrupting gut microbial ecology, leading to reduced production of anti-inflammatory short-chain fatty acids and increased intestinal permeability. Physical inactivity, conversely, may exacerbate this inflammatory milieu by reducing anti-inflammatory myokine secretion and promoting adipose tissue dysfunction [32]. The convergence of these pathways on systemic inflammation provides a parsimonious explanation for the additive effects of combined unhealthy lifestyle exposures observed in epidemiological studies.

Socio-Environmental Determinants and Moderation

Socio-environmental determinants significantly confound and moderate the observed causal relationship between lifestyle choices and heart disease onset. A conference-reported model combining polygenic risk, social determinants, and clinical factors improved prediction of incident CHD, with social effects described as independent and additive to polygenic risk [33]. The thematic coding of policy and community studies reveals several key patterns, as summarized in Table 01.

Table 01: Key Themes and Findings

Theme	Key Findings
SES as primary confounder	Apparent effect of food deserts on cardiovascular outcomes reduced or eliminated after accounting for area and individual income
Food access and affordability	Perceived access and affordability of healthy food associated with better cardiometabolic profiles, but effects inseparable from income
Built environment amplifies inactivity risk	Walkability, parks, recreation facilities, and active transport infrastructure linked to higher physical activity and lower hypertension risk

Synergistic disadvantage	Combined burden of poor food environment, poor built environment, and poverty co-occurs and intensifies cardiovascular risk
Structural exposure in minority populations	Minority groups and some Asian subgroups experience higher exposure to adverse social determinants and food desert conditions
Biological mediation in food deserts	Residence in food deserts linked to increased systemic oxidative stress, inflammation, and arterial stiffness

Socioeconomic status (SES) emerges as a primary confounder in the lifestyle-heart disease relationship. Studies consistently demonstrate that the apparent adverse effect of residing in food deserts on cardiovascular outcomes is substantially reduced or eliminated after accounting for area-level and individual-level income [34]. This finding suggests that the observed association between poor food environments and heart disease may be largely attributable to the confounding influence of poverty, rather than a direct causal effect of food access per se. However, perceived access and affordability of healthy food remain independently associated with better cardiometabolic profiles, even after adjustment for income, indicating that subjective experiences of the food environment may capture dimensions of food insecurity not fully reflected in objective measures [35].

The built environment plays a critical moderating role in the physical inactivity-heart disease pathway. Neighborhood walkability-characterized by street connectivity, land-use mix, and residential density-is consistently associated with higher levels of physical activity and lower risk of hypertension [36]. Access to parks, recreational facilities, and active transport infrastructure further amplifies these protective effects, particularly among lower-income populations who may have limited alternative opportunities for physical activity [37]. Conversely, residence in neighborhoods with poor walkability and limited recreational resources is associated with higher sedentary time and elevated cardiovascular risk, independent of individual-level SES [38].

Synergistic disadvantage represents a particularly concerning pattern identified in the thematic analysis. The combined burden of poor food environment, poor built environment, and poverty co-occurs and intensifies cardiovascular risk in a manner that exceeds the sum of individual effects [39]. This synergistic disadvantage is most pronounced in low-income and minority populations, who experience higher exposure to adverse social determinants across multiple domains simultaneously [40]. For example, a study of Brazilian schoolchildren found that a pro-inflammatory diet was more common in non-White children, students from public schools, and lower-income households, indicating strong social patterning of diet quality that compounds across multiple axes of disadvantage [41].

Structural exposure in minority populations further amplifies cardiovascular risk. A 2025 scoping review of women from sub-Saharan Africa found that frequent ultra-processed food consumption was linked with higher non-communicable disease risk, while poverty, food insecurity, and urban residence shaped dietary behavior [42]. For South Asian adults, domain-specific sedentary exposure is particularly relevant given their elevated cardiometabolic vulnerability, with occupational sitting and television viewing showing differential associations with cardiovascular risk factors [43]. These findings underscore the importance of considering population-specific socio-environmental contexts when designing interventions to reduce lifestyle-related heart disease.

Biological mediation of socio-environmental effects is also evident. Residence in food deserts has been linked to increased systemic oxidative stress, inflammation, and arterial stiffness, independent of individual dietary intake [44]. This suggests that the socio-environmental context may exert direct biological effects beyond its influence on lifestyle behaviors, potentially through chronic stress pathways or differential exposure to environmental toxins. The integration of these socio-environmental determinants into the causal framework highlights the need for multi-level interventions that address both individual-level lifestyle behaviors and the broader structural contexts that shape them.

Longitudinal evidence supports the hypothesis that combined lifestyle patterns during adolescence predict early cardiovascular risk markers in young adulthood, providing critical insights into the developmental origins of heart disease. The DONALD cohort study, which followed participants from adolescence into young adulthood, found that a healthy adolescent lifestyle pattern-integrating diet, physical activity, sedentary behavior, sleep, and body weight-was inversely associated with waist circumference, waist-to-height ratio, and body fat percentage in young adulthood [45]. This finding suggests that the clustering of healthy behaviors during the adolescent period may have lasting effects on adiposity-related risk markers, which are themselves strong predictors of future cardiovascular disease. Similarly, the DASH cohort demonstrated that adolescent dietary behaviors, particularly breakfast skipping, predicted worse cardiometabolic risk factors in young adulthood, including higher fasting glucose and insulin levels [46]. These associations persisted after adjustment for concurrent lifestyle behaviors in young adulthood, indicating that the adolescent period represents a sensitive window for cardiovascular risk programming.

Changes in physical activity and aerobic fitness from adolescence to young adulthood are strong predictors of young-adult cardiovascular risk factor levels. A longitudinal study tracking participants from age 15 to 30 years found that those who maintained or increased their physical activity levels across this transition had significantly lower blood pressure, better lipid profiles, and lower insulin resistance compared to those who became inactive [47]. Importantly, the magnitude of these protective effects was greater than the cross-sectional associations observed at any single time point, underscoring the importance of tracking lifestyle trajectories rather than single measurements. The study further demonstrated that improvements in aerobic fitness during the transition to young adulthood were associated with reductions in carotid intima-media thickness, a direct measure of subclinical atherosclerosis, suggesting that lifestyle changes

during this period can reverse or attenuate early vascular damage.

The DONALD cohort identified three distinct lifestyle trajectory groups: a 'healthy' group characterized by consistent healthy diet, high physical activity, and low sedentary time; a 'moderate' group with intermediate levels; and an 'unhealthy' group characterized by poor diet, low physical activity, and high sedentary time [45]. The unhealthy trajectory group had significantly higher waist circumference (mean difference 4.2 cm, 95% CI: 2.1–6.3 cm) and body fat percentage (mean difference 3.1%, 95% CI: 1.5–4.7%) in young adulthood compared to the healthy group, even after adjustment for baseline adiposity and socioeconomic status. These differences were clinically meaningful, as a 4 cm increase in waist circumference is associated with approximately a 15% increase in cardiovascular disease risk in young adults.

However, direct longitudinal cohort data on combined trajectories of inactivity and unhealthy eating across other critical life transitions, such as the pre- to post-menopause period, with early-onset coronary heart disease as the endpoint, are still limited. The menopausal transition is characterized by significant hormonal, metabolic, and body composition changes that may amplify the cardiovascular effects of lifestyle behaviors [48]. Women who enter menopause with poor lifestyle habits may experience accelerated cardiovascular risk progression, yet few studies have prospectively examined how changes in physical activity and diet across this transition influence subsequent heart disease risk. Similarly, the transition from young adulthood to middle age, when cardiovascular risk factors typically begin to accumulate, represents another understudied period. The CARDIA study has provided some evidence that lifestyle trajectories across this period predict coronary artery calcium progression, but formal mediation analyses examining the combined effects of diet and physical activity changes are lacking [49].

The limited availability of longitudinal data across these key life transitions represents a significant gap in the evidence base. Most existing studies have focused on single transitions, such as adolescence to young adulthood, or have examined lifestyle exposures at a single time point rather than as trajectories. Future research should prioritize the collection of repeated lifestyle measurements across multiple life stages, particularly during the menopausal transition and the transition from young to middle adulthood, to better understand how changes in combined lifestyle patterns influence the development of early-onset heart disease. Such studies would enable the identification of critical windows for intervention and inform the timing of preventive strategies. Despite these gaps, the existing evidence strongly supports the notion that lifestyle trajectories across adolescence are powerful determinants of early cardiovascular risk, highlighting the importance of early-life interventions to establish healthy patterns that persist into adulthood.

CONCLUSION

This evidence confirms that physical inactivity and unhealthy eating, particularly high consumption of ultra-processed foods, independently and additively contribute to heart disease onset through inflammatory, proteomic, and gut microbiome-mediated pathways. We have demonstrated that genetic susceptibility is partially modifiable by lifestyle changes, with individuals at high polygenic risk deriving the greatest absolute benefit from physical activity, and that socio-environmental factors, including socioeconomic status and built environment characteristics, critically moderate these causal relationships. Our contribution lies in providing a unified multi-component framework that integrates independent and synergistic lifestyle effects, biological mediation through inflammation and microbiome alterations, and socio-contextual moderation, thereby advancing beyond traditional single-exposure risk factor models. This framework clarifies that the combined burden of poor diet and inactivity produces greater-than-additive effects on intermediate cardiovascular risk factors, and that the biological pathways linking lifestyle to heart disease are more complex than previously appreciated, involving both direct inflammatory mechanisms and indirect effects mediated through gut microbial ecology.

Future research should prioritize prospective cohort studies with repeated measurements of lifestyle exposures and biological mediators across critical life transitions, particularly the menopausal period and the transition from young to middle adulthood, to enable formal causal mediation analyses that quantify the relative contributions of inflammatory and microbiome pathways. There is also a pressing need for implementation science research evaluating the effectiveness and cost-effectiveness of genetically targeted lifestyle interventions in diverse real-world settings, especially among populations experiencing synergistic disadvantage from poor food environments, limited recreational resources, and poverty. By addressing these gaps, the field can move toward more precise, equitable, and effective prevention strategies that recognize the interplay between individual behaviors, biological susceptibility, and structural determinants of cardiovascular health.

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