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GeneEnvironment Interactions Between Metabolic Risk Factors and Socioeconomic Adversity in U.S. Cardiovascular Epidemiology: A Narrative Review

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Abstract: Cardiovascular disease (CVD) is a prominent contributor to morbidity and mortality within the United States, a result of complex interactions between genetic predisposition and patterned exposure within a social environment. Despite the improved ability to detect genetic risk for cardiometabolic phenotypes and CVD using advances within the field of genomics, these risks are not equally expressed or distributed within socioeconomic environments. This review integrates evidence from genetic epidemiology, social epidemiology, and the field of cardiovascular disease to critically evaluate how socioeconomic adversity modifies genetic risk via metabolic intermediate phenotypes, such as obesity, insulin resistance, dyslipidemia, and hypertension. Through a model of socioeconomic adversity that spans levels of analysis, from the individual to the structural, exposure to chronic stress, the obesogenic environment, access to health care, as well as cumulative physiological exposure, can be shaped, thereby potentiating cardiometabolic risk for genetically predisposed individuals. Studies using polygenic risk scores further illustrate that genetic risk can be improved by accounting for contextual factors, suggesting that genetically deterministic models of CVD may be overly simplistic. This review proposes that socioeconomic adversity, as a contextual element, be incorporated within models of interaction between genes and the environment, providing a means for improved etiologic understanding, risk stratification, and reduced health disparities for cardiovascular disease within a life course- and equity-focused approach for cardiovascular genomics that may provide a more realistic, as well as a responsive, means for translating genetic discoveries within the field for their ultimate use within a public health context.

Keywords: Gene-environment interaction; Socioeconomic; Cardiometabolic; Cardiovascular disease; Polygenic.

INTRODUCTION

Cardiovascular disease (CVD) remains the main source of morbidity and mortality in the United States and continues to exact high tolls on public health and economic resources despite many years of progress in prevention, risk stratification, and clinical care (American Heart Association, 2021). While there had been apparent reductions in age-adjusted rates of cardiovascular deaths that suggested real progress, emerging evidence now points to stagnation or even reversal of these gains, especially in younger individuals and those of lower socioeconomic status. Large socioeconomic disparities continue to be seen in common cardiometabolic risk factors of obesity, hypertension, lipids, and type 2 diabetes, highlighting continued importance of social and structural factors in influencing it risk (Kershaw *et al*., 2015; Kundrick *et al.*, 2024). The traditional view of cardiovascular epidemiology has too often sought explanations that lie exclusively on either the biological or social side of this dichotomy. Thus, on one side of this debate, there is now clear evidence from genetic epidemiology that obesity, blood pressure, lipids, and glycemic control are highly polygenic, meaning that risk of these conditions is distributed widely across many variants of small effect (Locke *et al*., 2015; Loos & Yeo, 2022). At the same time, social epidemiology has found robust associations between socioeconomic exposures, defined at the individual, neighborhood, and structural levels, and cardiovascular outcomes, even when adjusting for conventional risk factors (Diez Roux, 2001; Anand *et al*., 2019). However, explanations that seek only one side of this equation, be it on the side of biology or sociology, have not served well in explaining the extent, persistence, and variability of cardiovascular disparities that have been found in the US population.

However, the awareness of this shortcoming has led to a growing interest in the use of frameworks for gene-environment interaction (G×E), whereby cardiovascular risk can be conceptualized as a function of the interaction between genetic predisposition and patterned exposure to the environment (Hartiala *et al*., 2021). Instead, genetic predisposition acts as a source of differential susceptibility, whereby the expression of risk depends on factors like diet, physical activity, psychosocial stress, access to health care, as well as the neighborhood environment (Robinette *et al*., 2019; Diego *et al*., 2024). The use of G×E frameworks, therefore, has been part of a paradigm shift toward contextual biology,

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whereby there has been a growing need for a holistic approach that incorporates both biological as well as social principles throughout the life course for population health studies (Martikainen *et al*., 2021; Zarkasi *et al*., 2022). Theoretical frameworks that originated from psychiatry as well as behavioral genetics have been very useful in the development of G×E frameworks that can be used for contemporary G×E studies (Robinette *et al*., 2019; Diego *et al*., 2024). The diathesis-stress model, for instance, proposes that there is a predisposition to latent biological vulnerability that becomes expressed when exposed to stress from the environment, a model that has been very well validated using empirical evidence within the context of mental health studies (Colodro-Conde *et al*., 2018). An extension of this model, namely the theory of differential susceptibility, proposes that there is a heightened sensitivity to the effects of the environment, both negative as well as supportive, for certain individuals as a function of their genotype, a theory that has been validated using empirical evidence by (Belsky & Pluess, 2009; Dalle Molle *et al*., 2017). These models, however, have been increasingly used for cardiometabolic phenotypes (Hyun & Jun, 2023; Song *et al*., 2022), whereby factors like exposure to obesogenic food environments, chronic stress, as well as restricted access to health care can either exacerbate or mitigate genetic predisposition to disease (Diego *et al*., 2024; Ding *et al*., 2020; Zarkasi *et al*., 2022).

Cardiovascular disease remains an exemplary area for the analysis of gene-environment interaction, thanks to its prolonged latent period, complex etiology, and established connections to modifiable metabolic factors. Metabolic risk factors, such as obesity, insulin resistance, dyslipidemia, and hypertension, are known to be moderately to highly inheritable, but highly vulnerable to environmental and socioeconomic factors, thus being highly amenable to the analysis of gene-environment interactions (Berry *et al*., 2009; Hartiala *et al*., 2021). Longitudinal and cohort research has provided evidence that subclinical atherogenic lesions and cardiometabolic derangements are prone to occur in early life, well before the manifestation of cardiovascular events, thus highlighting the salience of metabolic factors in the etiology of the disease (Berry., 2009). Socioeconomic adversity has been identified to play an integral role in the modulation of these factors. Neighborhood deprivation, residential segregation, and life-course socioeconomic adversity are known to affect the vulnerability to obesogenic environments, chronic psychosocial stress, and healthcare inequities, hence contributing to metabolic derangements and cardiovascular risk (Kershaw *et al*., 2015). Inequality in the prevalence of metabolic risk factors according to family income varies considerably across different United States metropolitan statistical areas, reflecting the local social, economic, and healthcare context, which could condition the manifestation of genetic predisposition (Kundrick *et al*., 2024).

Although there has been explosive growth in research focused on the genetic prediction of risk and the social determinants of health, the current evidence base regarding the interaction of genes and the environment is still piecemeal. Genetic research is increasingly using polygenic risk scores to predict the risk of cardiovascular diseases, and there is continuing documentation of strong associations between socioeconomic adversity and cardiometabolic risk using the paradigm of social epidemiology (Kershaw *et al*., 2015; Kundrick *et al*., 2024). These literatures are frequently developed separately and are characterized by considerable heterogeneity regarding the measurement of both genetic and environmental exposures (Anand *et al*., 2019; Zylbersztejn, 2019). Methodological issues regarding statistical power, population stratification, and model specification further obscure the interpretation of findings regarding G×E interaction (VanderWeele *et al*., 2010; Jayasinghe *et al*., 2024). Under these circumstances, the present narrative review is particularly appropriate to the task of consolidating the current evidence base, incorporating theoretical constructs, and contextualizing empirical findings according to a conceptual paradigm. This review aims to explore the interaction between genetic susceptibility to the key cardiometabolic risk factors of obesity, dysglycemia, dyslipidemia, and hypertension and the experience of socioeconomic adversity.

CONCEPTUAL FOUNDATIONS OF GENE-ENVIRONMENT INTERACTION

Gene-environment interaction (G×E) is the phenomenon in which the impact of genetic variation on the outcome is modified by the presence or absence of the environmental factor (Diego *et al*., 2024). Using the definition from epidemiology, the presence of interaction exists if

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the combination of genetic susceptibility and environmental factors has a different effect from the sum of the two factors. This is particularly true in the case of cardiovascular disease, a multifactorial disease in which the presence or absence of either factor does not account for the association in the outcome (Hartiala *et al*., 2021). It is critical to differentiate gene-environment interactions from other related, yet distinctly different, concepts like mediation, confounding, and gene-environment correlation (Diego *et al*., 2024; Martikainen *et al*., 2021). Mediation occurs when environmental exposures are situated along the causal path between genetic variation and the outcome of the disease, while confounding occurs when the relationship between genes and the environment is due to their correlation with common causes like population stratification and social class (Ding *et al*., 2020; Carter *et al*., 2021). Additionally, gene-environment correlation further adds to the complexity of interpreting results when the tendency to behave in certain ways due to genetic predisposition also shapes environmental exposures, whether behavioral and environmental (VanderWeele *et al*., 2010; Boardman *et al*., 2012). A failure to properly differentiate between these concepts has also contributed to the confusing interpretation of the results of G×E interactions in cardiovascular and metabolic diseases (Carter *et al*., 2021; Diego *et al*., 2024). In terms of analysis, the measure of interaction could be additive and multiplicative, both of which ask and provide the answer to two distinctly different scientific inquiries (Ding *et al*., 2020). Additive interactions measure the joint effect of both the environment and the gene when placed together to see whether they provide more risks above and beyond the additive risks posed by the environment and the gene individually, and is more applicable to public health and preventive measures (Ding *et al*., 2020; Martikainen *et al*., 2021).Multiplicative interactions measure the proportional risks posed by the environment and the gene when placed together and provide results when using regression analysis to determine the relationship between the two (VanderWeele *et al*., 2010).

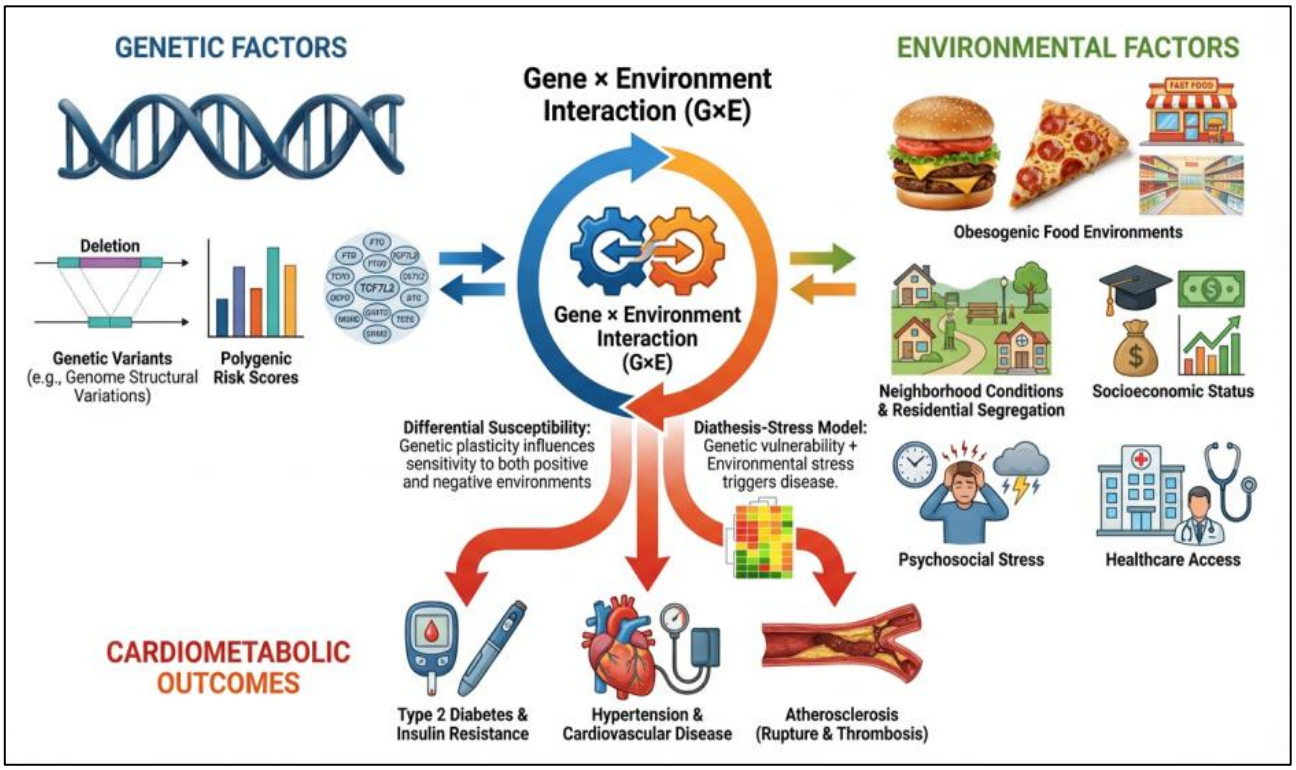

Figure 1: A summarised framework of gene–environment interaction (G×E) in cardiometabolic disease

There exist several theoretical models which currently form the basis of understanding the interaction between the genome and the environment (Robinette *et al*., 2019; Zarkasi *et al*., 2022). The diathesis-stress model of disease posits the existence of a hidden biological vulnerability which is activated through exposure to environmental stress (Robinette *et al*., 2019; Diego *et al*., 2024). This model was initially formulated within the field of psychiatric epidemiology. However, this model has been empirically supported through large-scale population studies

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which have revealed the existence of a genetic vulnerability which is apparent only within the presence of a negative environmental influence (Colodro-Conde *et al*., 2018). Variations of this model, including the theory of differential susceptibility, have suggested the existence of a genetic background which is highly sensitive to the presence of a wide range of environmental conditions, including both negative and positive environments (Belsky & Pluess, 2009). There has been a growing number of applications of this model outside of the field of mental illness and within the field of cardiometabolic diseases. Obesity, insulin resistance, high blood pressure, and hyperlipidemia have been shown to have a moderate to high level of heritability as well as a high level of environmental sensitivity. This has made them ideal for the study of differential susceptibility (Dalle Molle *et al*., 2017; Locke *et al*., 2015; Loos & Yeo, 2022). According to this model of differential susceptibility, the genetic factor does not play a predictive role within the development of a disease. Instead, the genetic factor is a modifier of the level of sensitivity of the individual towards a number of socially patterned exposures which may include the quality of the diet of the individual, the level of physical activity available to the individual, the level of exposure of the individual towards a number theories of population health continue to develop the G×E paradigm by considering biological vulnerability in the context of larger social and structural processes. Ecosocial theory draws particular attention to the role of social factors, such as socioeconomic inequity and geographic segregation, in the biological embedding of social experience through lifelong exposure to stressful environments and conditions (Krieger, 2024). Related theories of biological embedding and weathering also illustrate the role of lifelong exposure to stressful environments in accelerating the biological wear and tear of physiological systems, and, as a result, the onset and severity of cardiometabolic disease in disadvantaged groups (Suglia *et al*., 2022). These theories also illustrate the important point that gene-environment interactions and effects do not exist or operate in isolation as purely biological processes, but instead as dynamic and temporally unfolding processes within historically and socially structured environments (Martikainen *et al*., 2021; Diego *et al*., 2024). The study of cardiovascular disease offers a uniquely interesting area of application for the theoretical frameworks discussed (Zarkasi *et al*., 2022). The disease has a sufficiently long latent period for the accumulation of environmental exposures throughout the life course, as well as established strong ties to modifiable biological pathways, offering clear biological mechanism by which the effects of social factors may be transmitted and shape the effects of genes and biological vulnerability (Martikainen *et al*., 2021; Robinette *et al*., 2019). The use of subclinical disease indicators has also shown that the onset of biological dysregulation and vascular dysfunction typically precedes the onset of clinical cardiovascular disease and suggests that there may be multiple points throughout the life course where the operation of gene-environment interaction and effects may be possible (Berry *et al*., 2009). Finally, recent progress in genetic epidemiology has also led to a transformation in the conceptualization of susceptibility itself. The shift towards polygenic risk scores over single-variant analyses represents an acknowledgement of the fact that genetic predisposition is now understood to be encoded in multiple loci that have individually small but jointly significant effects (Locke *et al*., 2015; Hartiala *et al*., 2021). Although polygenic analyses represent an important step forward in the ability of genetic association studies to detect aggregate genetic risk, these approaches also emphasize the need for attention to the role of context in the expression of genetic risk, in that the manifestation of aggregate genetic risk is potentially more strongly influenced by conditions of socioeconomic adversity than is the manifestation of individual variants. A set of methodological advances that have been developed to enhance robustness and interpretation of polygenic G×E interaction analyses further support the need for gene-environment interaction approaches that move towards more integrative, system-level models of cardiovascular risk (Jayasinghe *et al*., 2024). In sum, these conceptual premises place gene-environmental interaction at the forefront of efforts to more fully understand the joint impact of genetic susceptibility and socioeconomic adversity on cardiometabolic and cardiovascular risk. By integrating multiple perspectives in biology, society, and method, gene-environment interaction approaches represent an alternative in cardiovascular epidemiology that is more comprehensive and more equitable in its focus compared to approaches that emphasize the role of genetic or environmental factors.

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METABOLIC RISK FACTORS AS INTERMEDIATE PHENOTYPES

Conceptualizing Metabolic Traits as Intermediate Phenotypes

Intermediate phenotypes, also termed endophenotypes, are biological attributes that are intermediate in the pathway from genetic variation to disease outcomes. The endophenotype paradigm, formalized in psychiatric genetics, seeks to highlight attributes that are heritable, closer to genetic processes, and more affected by environmental factors than disease outcomes (Iacona, 2018). In cardiovascular epidemiology, metabolic risk factors, including obesity, insulin resistance, lipids, and high blood pressure, serve as exemplary intermediate phenotypes, translating genetic predisposition to overt cardiovascular disease. A focus on metabolic traits provides several key advantages to the study of gene-environmental interaction. First, metabolic abnormalities tend to precede disease outcomes in the life course, and their study allows one to investigate etiological processes prior to disease occurrence. Evidence from subclinical atherosclerosis studies indicates that those at high lifetime risk for cardiovascular disease demonstrate preclinical vascular abnormalities even in their youth, highlighting the primordial role of metabolic processes in disease etiology (Berry *et al*., 2009). Second, metabolic traits are continuously distributed and highly common, providing greater power to detect interaction effects, as opposed to disease endpoints like myocardial infarction or stroke. More importantly, metabolic risk factors occupy a privileged place at the crossroads of genetic and social forces (Diego *et al*., 2024; Song *et al*., 2022), being moderately to highly heritable, while being powerfully patterned according to socioeconomic status, environmental, and stress contexts (Ding *et al*., 2020; Zarkasi *et al*., 2022).

Obesity and Adiposity

Obesity has been one of the most investigated metabolic intermediate phenotypes using genetic epidemiology approaches. Large-scale genome-wide association studies have uncovered numerous loci associated with body mass index (BMI), indicating the polygenic nature of adiposity (Locke *et al*., 2015). Recent studies have expanded from locus discovery to understanding biological pathways implicated in appetite regulation, energy expenditure, and reward circuits, most of which have been found to be mediated by central nervous system pathways (Loos & Yeo, 2022). Despite high heritability, obesity remains extremely sensitive to environmental factors. Socioeconomic environments have been found to have strong influence on exposure to obesogenic environments, such as quality and availability of food, physical activity levels, and characteristics of the built environment (Swimburn *et al*.,2011). Factors such as walkability, property values, and availability of healthy food have been found to longitudinally influence body mass index (BMI), thereby ascertaining the importance of place-based exposures on obesity (Buszkiewicz *et al*., 2022). These exposures have been found not to be randomly distributed but instead reflect broader patterns of socioeconomic inequality. Gene-environment interaction studies have ascertained that penetrance of genetic risk factors associated with obesity varies across historical and social settings. For example, genetic association between Fat mass and obesity associated (FTO) gene and BMI has been found to vary across birth year, thereby ascertaining that increasingly obesogenic environments have amplified genetic predisposition towards increased BMI (Rosenquist *et al*., 2015). These observations have been found to be consistent with the concept of differential susceptibility theories, wherein genetic predisposition remains contingent on exposure to environmental factors (Dalle Molle *et al*., 2017).

Insulin Resistance and Type 2 Diabetes

Although Insulin resistance and type 2 diabetes mellitus are thus major metabolic intermediates in the progression of genetic predisposition to cardiovascular disease (Zarkasi *et al*., 2022). Genetic predispositions for dysglycemia have been clearly shown, with multiple gene variants now known to impact the mechanisms of insulin secretion, insulin resistance, and glucose regulation (Song *et al*., 2022; Hyun & Jun, 2023). However, like obesity, the progression of genetic predispositions for diabetes is also strongly subject to the influences of the socioeconomic environment (Diego *et al*., 2024; Ding *et al*., 2020). Adversities in the socioeconomic environment impact inequalities in exposure to dietary patterns of high energy density, poor nutritional quality, and food insecurity, which in turn impact the development of insulin resistance (Song *et al.*, 2022; Hyun & Jun, 2023). Inequities in access to health care, preventive screening, and management of the disease also impact the progression of diabetes, thereby accelerating the risk of cardiovascular diseases (Kundrick *et al*., 2024). Type 2 diabetes is thus a major risk factor

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for accelerating the progression of cardiovascular diseases, thereby significantly increasing the risk for atherosclerotic diseases, heart failure, and early death. Genetic studies have now clearly shown common etiological pathways for cardiometabolic risk factors that predispose for both cardiovascular and cerebrovascular diseases, thus emphasizing the central role of dysglycemia in cardiometabolic risk (Ding *et al*., 2024). As an intermediate phenotype, thus offering an important insight for the evaluation of gene-environmental interactions in the cumulative impact of cardiovascular risk over time.

Dyslipidemia

Dyslipidemia represents another key metabolic intermediate phenotype connecting genetic susceptibility and cardiovascular disease. Genetic influences on lipid metabolism are well characterized, with variants affecting pathways involved in lipoprotein synthesis, transport, and clearance. These genetic effects contribute to substantial interindividual variation in lipid profiles, including levels of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides (Nock, 2024). At the same time, lipid levels remain highly responsive to environmental and behavioral factors, particularly diet. Dietary fat composition, caloric intake, and food availability, each strongly shaped by socioeconomic context, play a significant role in modulating lipid profiles. Neighborhood deprivation and food environments influence dietary behaviors, contributing to socioeconomic gradients in dyslipidemia that parallel those observed for obesity and diabetes (Kundrick *et al*., 2024). From a gene-environment interaction perspective, dyslipidemia exemplifies how genetic predisposition may be magnified in adverse socioeconomic contexts characterized by limited access to healthy foods and preventive healthcare. Because lipid abnormalities are both modifiable and strongly predictive of cardiovascular events, dyslipidemia serves as a critical intermediate phenotype for understanding how social environments shape the clinical expression of genetic cardiovascular risk.

Hypertension

Hypertension is an important focal point in cardiovascular epidemiology because it is very common, highly heritable, and a direct cause of cardiovascular morbidity and mortality (Martikainen *et al*., 2021). The genetic architecture underlying blood pressure control is the product of polygenic susceptibility, rare genetic variants, and environmental factors. While genetic studies have discovered many loci that are associated with blood pressure traits, these genetic variants only account for a proportion of the variation in blood pressure in the population, and this highlights the role of the environment in modulating blood pressure control (Hartiala *et al*., 2021). There are several pathways by which socioeconomic disadvantage affects an individual's risk for hypertension. These include chronic psychosocial stress, sodium exposure in food, and lack of access to healthcare. The chronic activation of stress systems, particularly the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system, contributes to sustained elevations in blood pressure and vascular remodeling. These processes interact with genetic susceptibility to hypertension (McEwen, 2017). The stress pathways are more common and chronic in socioeconomically disadvantaged environments, and this raises the probability that genetic susceptibility to hypertension is converted to clinical disease. Hypertension is one of the most important risk factors for cardiovascular Its susceptibility to genetic and socioeconomic factors makes it an important endpoint in studies that investigate how social inequality and biological risk interact to influence cardiovascular health (Diego *et al*., 2024; Martikainen *et al*., 2021; Ding *et al*., 2020).

SOCIOECONOMIC ADVERSITY IN THE U.S. CONTEXT

Conceptualizing Socioeconomic Adversity

Socioeconomic adversity is a multidimensional construct which includes material deprivation, social marginalization, and structural constraints which define the accessibility of resources necessary for health (Diego *et al*., 2024; Robinette *et al*., 2019). In the field of cardiovascular and social epidemiology, socioeconomic status has been conventionally measured through individual-level variables such as income, educational attainment, and occupation (Martikainen *et al*., 2021). Although individual-level variables capture material and social advantages adequately, they do not capture the whole social environment within which the risk of cardiovascular diseases is created (Robinette *et al*., 2019). Modern research is focused increasingly on the notion of socioeconomic adversity as a multilevel phenomenon (Diego *et al*., 2024). Area deprivation, segregation of living places, and the inequitable allocation of resources for the maintenance of good health have been recognized as independent risk factors of cardiometabolic risk

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in addition to individual socioeconomic status (Robinette *et al*., 2019; Diego *et al*., 2024; Zarkasi *et al*., 2022). This is because they mirror the deep-rooted social and economic inequalities of the past (Kershaw *et al*., 2015). Importantly, socioeconomic adversity is a cumulative phenomenon rather than being episodic. Evidence provided through the study of the whole life course has revealed the onset of disadvantages at a very early age and the continuity of disadvantages through all stages of the life course. This is because the exposure at different stages of the life course adds independently and interactively to the cardiometabolic risk (Anand *et al*., 2019; Suglia *et al*., 2022; Zylbersztejn, 2019).

Neighborhood and Structural Dimensions of Adversity

The neighborhood environment represents an important structural factor by which socioeconomic adversity affects cardiovascular risk (Robinette *et al*., 2019; Diego *et al*., 2024). Residential segregation by race, ethnicity, and socioeconomic status has contributed to neighborhood conditions in the United States for decades, with systematic differences in exposure to environmental hazards, psychosocial stressors, and health resources (Robinette *et al*., 2019; Song *et al*., 2022). There is evidence from large multi-ethnic cohort studies that neighborhood-level racial and ethnic segregation is linked to the incidence of cardiovascular disease, independent of individual socioeconomic status (Kershaw *et al*., 2015). Neighborhood deprivation occurs through several interrelated mechanisms. Disadvantaged neighborhoods are more likely to be exposed to poor access to affordable healthy foods, opportunities for physical activity, and neighborhood environments. These factors cumulatively add to obesogenic and diabetogenic exposures, which interact with genetic predisposition to determine metabolic risk (Buszkiewicz *et al*., 2022). These exposures are structurally driven, rather than individual, underlining the relevance of gene-environment interaction within broader social structures. Healthcare access and quality represent an important structural factor of socioeconomic adversity. Socioeconomically disadvantaged groups face barriers to preventive care, diagnostic timeliness of cardiometabolic diseases, and disease management. Recent evidence shows large heterogeneity in metropolitan area differences in the association between income inequality and cardiovascular risk factors, underlining the relevance of metropolitan healthcare systems in shaping cardiometabolic risk (Kundrick *et al*., 2024). These structural factors not only shape disease prevalence but also determine the probability of genetic predisposition being expressed as disease.

Psychosocial Stress, Weathering, and Physiological Burden

The experience of psychosocial stressors represents a key biological embedding mechanism through which the effects of socioeconomic disadvantage are translated into biological systems. Repeated exposure to financial hardship, neighborhood disarray, discrimination, and insecurity can be expected to activate the body's stress response systems, resulting in the biological wear and tear or allostatic load that has been proposed to underlie metabolic dysregulation and cardiovascular risk (McEwen, 2017). In turn, the process of 'weathering' serves to highlight the role of chronic socioeconomic disadvantage in accelerating biological aging and increasing vulnerability to cardiometabolic disease. Historical and population-level studies support the role of chronic inflammatory exposures and chronic stress in the early onset of disease and shortened life span in disadvantaged groups (Finch & Crimmins, 2004). Such processes represent a plausible biological model of gene-environment interactions in which the biological vulnerability to metabolic dysregulation mediated by genetic factors would be expressed in the context of chronic stress exposures. Additionally, psychosocial stress interacts with behavioral pathways that are related to socioeconomic factors. Coping with stress, lack of sleep, as well as restricted opportunities to engage in physical activity and eat healthily can serve as additional factors that amplify metabolic risk (Robertson *et al*., 2015). These social patterns of exposures work together to create a synergistic interaction between genetic factors to amplify clustering of cardiometabolic risk factors.

Life-Course and Epigenetic Embedding of Social Adversity

Life-course approaches emphasize the roles of timing, duration, and accumulation of socioeconomic exposure to the development of cardiovascular risk. Early-life socioeconomic adversity has been shown to be associated with long-term changes to the regulation of stress and metabolism and health trajectories persisting throughout life (Suglia *et al*., 2022; Wickrama *et al*., 2022). These findings emphasize the point that the interaction between genes and the environment

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can differ by life stage, such that exposure to the environment in youth can have long-term effects upon biological susceptibility. Recent evidence suggests that the process of epigenetics can partially mediate the relationship between socioeconomic adversity and cardiometabolic risk. DNA methylation patterns have shown that both individual and contextual socioeconomic disadvantage are associated with epigenetic changes related to the presence of cardiovascular risk factors, which may help to identify the molecular mechanisms by which the relationship between socioeconomic adversity and cardiometabolic risk is mediated (Wang *et al*., 2022). These mechanisms help to identify the ways by which the expression of genes can be influenced by the presence of the environment, independent of the DNA sequence itself. Thus, life-course and epigenetics help to emphasize the point that socioeconomic adversity is more than just an outside factor that can shape the expression of genetic risk to cardiovascular diseases.

EMPIRICAL EVIDENCE OF GENE–ENVIRONMENT INTERACTIONS

Obesity Genetics and Socioeconomic Context

The strongest evidence for G x E interaction has been shown for obesity, for which both genetic predisposition and exposure have been well characterized. Genome-wide association scans have confirmed the polygenic architecture of adiposity, although the magnitude of detected genetic effects on body mass index (BMI) has been shown to vary considerably depending on the socioeconomic and environmental context (Locke *et al.*, 2015; Loos & Yeo, 2022). Cohort study data illustrate that the neighborhood and socioeconomic context modify the manifestation of genetic risk for obesity, for which larger genetic effects have been detected within environments characterized by high levels of exposure to obesogenic factors such as unfavorable food environments and a lack of opportunities for physical activity (Buszkiewicz *et al*., 2022). Longitudinal, historical, and cohort comparison evidence additionally support the idea that genetic risk for obesity is contextually enhanced. The association between the FTO gene variant and BMI has been shown to vary by birth year, indicating that increasingly unfavorable, obesogenic environments enhance the phenotypic manifestation of genetic predisposition for obesity (Rosenquist *et al*., 2015). Evidence obtained from older adults has additionally confirmed that genetic predisposition for obesity interacts with unfavorable socioeconomic environments to modulate BMI over time, by race, and by socioeconomic status, thereby underlining the pivotal role of socioeconomic context in modulating genetic effects on obesity risk (Thompson *et al*., 2020). These data support a model of G x E interaction, whereby genetic predisposition for obesity manifests as a vulnerability that develops, or manifests, within unfavorable socioeconomic environments (Dalle Molle *et al*., 2017).

Dysglycemia, Diabetes, and Socioeconomic Adversity

Evidence for the interaction of genes and the environment in insulin resistance and type 2 diabetes illustrate the significance of socioeconomic adversity in determining the trajectories of cardiometabolic risk factors. Genetic vulnerability to dysglycemia has been firmly established, but the implications of this vulnerability for the onset of clinical diabetes differ depending on the quality of the social context, which determines the availability of healthy food, medical facilities, and preventive services (Geng & Huang,2020). Large population studies illustrate the considerable variation in the degree of income-related disparities in the prevalence of diabetes and other related factors of cardiometabolic risk across US metropolitan areas, indicating the presence of contextual factors that may act as modifiers of genetic vulnerability (Kundrick *et al*., 2024). Longitudinal studies of the life course also illustrate the interaction of socioeconomic adversity and genetic vulnerability in determining the course of diabetes. It has been found that the cumulative effect of socioeconomic disadvantage in the early life course modifies the genetically based pathways between adversity and the risk of cardiometabolic disease, including diabetes, in the adult life course (Wickrama *et al*., 2018; Wickrama *et al*., 2022). The findings indicate that the onset and progression of diabetes may be accelerated by the cumulative effect of socioeconomic adversity, which may act as an amplifier of the vulnerability of the genes to the onset of dysglycemia. Diabetes also serves as an important amplifier of the risk of cardiovascular disease. Genetic studies indicate the presence of common etiological pathways between the risk factors of cardiometabolic disease and the risk factors of cardiovascular and cerebrovascular disease, which illustrate the cumulative nature of the burden of cardiometabolic disease (Ding *et al*., 2024). Gene-environment interaction theory also illustrates the possible role of socioeconomic

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adversity in increasing the co-aggregation of dysglycemia with other risk factors of the disease, which may serve as an amplifier of the risk of cardiovascular disease for the genetically vulnerable.

Blood Pressure Genetics, Stress, and Environmental Exposure

Hypertension is a paradigmatic model of the interplay between genes and the environment, particularly the impact of psychosocial and environmental factors. The regulation of blood pressure is a model that shows the interplay between polygenes and the environmental factors of chronic stress, dietary sodium, and accessibility to care (Hartiala *et al*., 2021). There is empirical evidence that the prolonged effects of the stressors in the socioeconomically poor psychosocial environment trigger neuroendocrine pathways that also regulate blood pressure, thereby increasing the probability that genetic risk leads to the development of hypertension (McEwen, 2017). The joint effects of genetic and social risk factors show that people who have a higher genetic risk experience a significantly greater probability of cardiovascular disease in a poor social environmental setting. For example, the national representative sample research has shown that the joint effect of genetic and social environmental factors leads to the development of myocardial infarction (Tang *et al*., 2023; Wu & Sheng, 2022).

Polygenic Risk Scores and Contextual Modification of Risk

Recent breakthroughs in genetic epidemiology made it feasible to apply the concept of polygenic risk scores (PRS) to quantify the population-level genetic vulnerability to cardiometabolic and cardiovascular diseases. The application of PRS has shown enhanced predictive accuracy for coronary artery disease, especially for people who fall in the intermediate risk category (Patel *et al*., 2023; Ratman *et al*., 2025). There are, however, new findings that suggest the predictive role of PRS could be modified by socioeconomic-environmental factors. Research on the interaction between PRS and sociocultural factors has shown that genetic risk interacts differentially according to the social environment. Results obtained from different populations suggest that genetic ancestry, together with the sociocultural environment, affects the interaction between genes and the environment, stressing the need to account for the impact of population structure and social environment on the application of the PRS approach (Sharma *et al*., 2024). There are also new methodological contributions that suggest the need for caution in terms of the impact of type I errors on the application of interaction analysis for polygenic risk (Jayasinghe *et al*., 2024).

Multimorbidity and Cross-Trait Interactions

Gene-environment interaction effects seldom involve single metabolic traits alone. Rather, common architectures of gene effects contribute simultaneously to multiple cardiometabolic risk factors, such as obesity, lipids, diabetes, and hypertension. Recent gene-level interaction analysis has found common etiological factors that simultaneously relate these risk factors to cardiovascular and cerebrovascular diseases, thus reiterating that cardiometabolic risk factors share an integrated relationship (Ding *et al*., 2024). Socioeconomic adversities tend to enhance the convergence of metabolic risk factors, thereby increasing multimorbidity patterns that particularly target vulnerable social classes (Finch & Crimmins, 2004). The epigenetics of gene-environment interaction effects have provided additional evidence on cross-trait mechanisms that relate social adversities and cardiometabolic risk factors. Analysis of gene-level interaction effects on DNA methylation patterns showed that both individual-level and neighborhood-level socioeconomic adversities tend to relate epigenetically to gene modifications of cardiovascular risk factors, thereby providing molecular mechanisms at which social exposures may simultaneously interact with multiple metabolic traits (Wang *et al*., 2022).

BIOLOGICAL AND SOCIAL MECHANISMS UNDERLYING GENE–ENVIRONMENT INTERACTION

Stress Physiology and Neuroendocrine Pathways

Stress physiology is one of the key biological mechanisms that mediates the relationship between socioeconomic adversity and the manifestation of genetic susceptibility to cardiometabolic and cardiovascular disease (Abi Karam *et al*., 2025). The chronic experience of socioeconomic stressors, such as financial difficulties, neighborhood disorder, discrimination, and social marginalization, triggers the repeated activation of neuroendocrine systems that are involved in maintaining physiological homeostasis (Johnson, 2020). Specifically, the chronic activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system causes dysregulation in the pathways that are involved in metabolisms,

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cardiovascular functions, and the inflammatory processes that are associated with stress (McEwen, 2017). The interaction between genetic susceptibility and stress physiology determines the manifestation of cardiometabolic phenotypes. Genetic variation in the pathways that are involved in regulating stress responsiveness, vascular tone, glucose processing, and lipid homeostasis could increase susceptibility to the negative effects that are associated with chronic exposure to socioeconomic stressors (Dato *et al*.,2013). In the context of socioeconomic adversity, increased levels of cortisol secretion and sympathetic activity are associated with insulin resistance, increased central obesity, dyslipidemia, and increased blood pressure, which are key intermediate phenotypes that determine the development of cardiovascular disease (McEwen, 2017). Using the framework that is provided by the interaction between genetic factors and the environment, stress physiology is one of the biological mechanisms that provides a plausible pathway by which socioeconomic environments are linked to the manifestation of genetic susceptibility.

Behavioral Mediation and Social Constraint

Behavioral pathways offer yet another mechanism by which socioeconomic environments interact with genetic risk factors to shape cardiometabolic risk. Health behaviors like diet, physical activity, sleeping patterns, and substance use patterns are not exclusively personal choices, as they are deeply embedded in social and environmental factors that constrain or enable those choices (Diez Roux, 2001). In socioeconomic environments that lack access to healthy food, safe spaces for physical activity, and stable routines that enable healthy sleeping patterns, people experience greater exposure to risk-related health behaviors (Diez Roux, 2001). The role of genetic factors may play in shaping behavioral predispositions concerning appetite, reward-seeking, stress responses, and physical activity preferences (Boardman *et al*., 2012). These predispositions may be strengthened or weakened by socioeconomic environments, giving rise to gene-behavior correlations that make it difficult to interpret gene-environment interaction effects (Boardman *et al*., 2012). Empirical studies show that obesogenic environments enhance gene expression of adiposity risk, especially in those environments that experience prolonged exposure to socioeconomic disadvantage (Thompson *et al*., 2020). These studies illustrate that behavioral pathways serve as social mechanisms that translate genetic risk into cardiometabolic risk.

Epigenetic Embedding and Molecular Pathways

Epigenetic mechanisms have emerged as a potential molecular mechanism through which socioeconomic adversity can lead to the long-term modification of gene expression (Roth, 2013). Certain environmental exposures, associated with socioeconomic disadvantage and with sensitive developmental ages, can lead to epigenetic modifications, such as DNA methylation, that can alter gene expression without changing the DNA sequence itself (Finch & Crimmins, 2004). These modifications can persist into adulthood and impact the long-term trajectories of metabolic and cardiovascular risks. Empirical evidence has accumulated to support the role of epigenetic embedding in the development of cardiometabolic risks. In studies that have investigated the relationship between DNA methylation patterns, both individual and neighborhood levels of socioeconomic disadvantage have been found to be associated with epigenetic modifications that have been linked to cardiovascular risk factors, such as blood pressure, lipid levels, and glycemic control (Wang *et al*., 2022). These findings have provided molecular support for models of social-biological embedding, implying that socioeconomic disadvantage can lead to the persistent biological embedding of socioeconomic experiences, which can interact with genetic predispositions. Epigenetic mechanisms can also mediate the co-occurrence of multiple metabolic traits. They can regulate pathways that share multiple cardiometabolic traits, thus helping to explain the role of socioeconomic disadvantage in the development of multimorbidity and cumulative cardiovascular load in genetically predisposed individuals.

Developmental Timing and Life-Course Processes

Life-course theories underscore that the interplay between genes and the environment happens over a period of time, whereby the timing, duration, and accumulation of exposure matter for the development of cardiovascular risk factors. Moreover, socioeconomic adversity experienced in early life has been shown to have long-term effects on stress physiology, metabolism, and health development, extending into adulthood (Suglia *et al*., 2022). Genetically informative longitudinal designs have further shown that the cumulative effects of socioeconomic adversity in childhood

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and adolescence shape the pathways between genetic predisposition and cardiometabolic risk factors for adults (Wickrama *et al*., 2018; Wickrama *et al*., 2022) The importance of developmental timing cannot be overstated, as biological systems that regulate stress, metabolism, and cardiovascular function show increased plasticity during early life. Adverse experiences accumulated within these sensitive phases can predispose biological systems to heightened vulnerability to subsequent stress, potentiating the expression of genetic predisposition over the life course. These concepts fit within theories of biological embedding and weathering, whereby early-life socioeconomic adversity accelerates the process of physiological wear and tear, culminating in earlier onset of cardiometabolic diseases (Finch & Crimmins, 2004).

METHODOLOGICAL CHALLENGES IN GENE–ENVIRONMENT INTERACTION RESEARCH

Measurement of Socioeconomic and Environmental Exposure

One of the core issues in gene-environment interaction (G×E) studies regards the valid assessment of socioeconomic adversity and environmental exposure. Socioeconomic factors are complex, reflecting both individual-level factors, such as income, education, and employment, and contextual factors, such as area-level deprivation, residential segregation, and life-course accumulation of socioeconomic adversity. There is considerable variability in the operationalization of these exposures across studies, which, in turn, has contributed to the observed discrepancies in interaction effects (Anand *et al*., 2019; Zylbersztejn, 2019). Assessments of context are further confounded by issues of spatial resolution, temporal congruence, and duration of exposure. Neighborhood conditions are not fixed entities, fluctuating over time, while cross-sectional designs are unable to provide valid assessments of the accumulation or developmental aspects of socioeconomic adversity (Suglia *et al*., 2022). There are implications for the assessment of life-course socioeconomic adversity, which has been shown to be fundamental to the prediction of cardiometabolic risk, for the duration of environmental exposures in longitudinal designs, which are able to provide valid assessments of these factors (Suglia *et al*., 2022). Inaccurate assessment of environmental exposures may result in the masking of interaction effects or the generation of fallacious inferences about the existence or absence of gene-environment interactions.

Genetic Ancestry, Population Stratification, and Equity

Genetic ancestry offers a range of challenges, from methodological to equity-focused, to the study of G×E interactions. Most genetic association analyses have been carried out mainly in people of European ancestry, and these analyses are less generalizable and difficult to interpret in terms of interaction effects in different ancestral groups. In addition, there are disparities in genetic allele distribution, linkage disequilibrium, and environmental exposure across ancestral groups, and these disparities can result in biased estimation if not properly accounted for (Hartiala *et al*., 2021). Socioeconomic disadvantages do not randomly vary across ancestral groups in the US, and there are strong correlations between genetic ancestry and social environment. These correlations are prone to confounding and spurious interaction effects, which are more indicative of unmeasured structural or social processes, as opposed to biological modification of genetic effects. Though ancestry principal components adjustment reduces these biases, it does not address the problems associated with highly entwined social and historical processes (Kershaw *et al*., 2015). More recent findings indicate the need to consider sociocultural and genetic ancestry together in studying processes of G×E interaction. Cohort analyses from different ancestry backgrounds indicate that sociocultural elements and ancestry variability affect the measurement of gene-environment interaction, and there is an imperative need to employ ancestry-aware and equity-focused analytic methods (Sharma *et al*., 2024). In the absence of these methods, there is a high probability that G×E interaction analyses would end up exacerbating inequities, as opposed to providing insight into their amelioration.

IMPLICATIONS FOR CARDIOVASCULAR EPIDEMIOLOGY AND HEALTH EQUITY

Reframing Genetic Risk as Context-Dependent

Evidence integrated within this review indicates that the expression of genetic liability to cardiometabolic phenotypes is not deterministically fixed but rather is contingently expressed across socially patterned environments. For obesity, dysglycemia, dyslipidemia, and hypertension, the experience of socioeconomic adversity has been shown to modify the expression

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and clustering of genetic liability across all four conditions, highlighting the limitations of models of genetic liability that view the latter as homogeneous across populations (Hartiala *et al*., 2021). Viewing the expression of genetic liability through the lens of environmental context offers a more nuanced account of the persistent relationship between socioeconomic disadvantage and cardiovascular disease and helps to integrate recent advances within the field of genetic epidemiology with the existing literature regarding the role of social determinants of health. This conceptual move also serves to realign the interpretation of the relationship between cardiovascular epidemiology and the social environment from efforts to identify high-risk genotypes to the role of environmental and structural factors in shaping the biological expression of genetic liability to cardiovascular disease (Anand *et al*., 2019; Kershaw *et al*., 2015).

Implications for Precision Prevention and Risk Stratification

The implications of gene-environment interactions on precision preventive approaches in cardiovascular health cannot be overemphasized. Although polygenic risk scores have enhanced the predictive power of coronary artery disease and other outcomes, especially in intermediate clinical risk individuals, their use remains dependent on social environments (Patel *et al*., 2023; Ratman *et al*., 2025). Genetic risk predictions that fail to incorporate socioeconomic factors may thus lead to inaccurate predictions, potentially underestimating risk exposure in some social groups and overestimating it in others who have better access to resources and social environments. The use of genetic susceptibility predictions combined with social and environmental exposures can potentially improve risk predictions and help target communities most at risk from preventive interventions. From the analysis using genetic and social risk interactions, there appears conclusive proof that genetic susceptibility combined with unfavorable social environments poses proportionately greater risk to cardiovascular health (Tang *et al*., 2023; Wu & Sheng, 2022).

Structural Interventions as Biological Modifiers

One of the important implications of gene-environment interaction studies is the understanding that structural and policy-level interventions serve as biological modifiers of genetic risk. Enhancements of the neighborhood environment, food system, healthcare access, and social context may mitigate the expression of genetic risk along the pathways of cardiovascular disease. The findings of the relationship of neighborhood deprivation, residential segregation, and healthcare disparities to cardiovascular disease establish the role of structural and place-level interventions as modifiers of biological risk and outcomes (Kershaw *et al*., 2015; Kundrick *et al*., 2024). Under this view, the role of social policies addressing the reduction of socioeconomic adversity may be considered an upstream strategy for the prevention of cardiovascular disease. Structural interventions may provide a more effective population-level strategy for reducing cardiovascular risk than the current focus of preventive and therapeutic efforts on the biological and behavioral levels of analysis by modifying environmental exposures of the population, such as chronic stress, unhealthy food environments, and compromised healthcare access, which serve to enhance the expression of genetic risk.

Advancing Equity in Cardiovascular Genomics

Finally, frameworks involving gene-environment interactions also have significant implications for equity in cardiovascular genomics. By neglecting the social context, the research in genomics may end up perpetuating inequities by pointing to the biological basis for differential outcomes, instead of the differential social context. The evidence cited in this paper makes it amply clear that the impact of genetics is manifested in, and influenced by, a socially stratified setting, thereby highlighting the fact that the impact of genetics in cardiovascular inequities is a product of the interplay between biology and structure, and not genetics alone (Suglia *et al*., 2022). Equity in cardiovascular genomics, therefore, demands a representative study population, attention to the concept of genetic ancestry, and the use of research approaches that focus explicitly on the impact of differential social contexts in modifying the effects of genetics (Sharma *et al*., 2024).

LIMITATIONS AND METHODOLOGICAL CHALLENGES

One of the main issues is how socioeconomic adversity should be measured. Socioeconomic status is a multidimensional measure that includes separate domains of education, income, employment and neighborhood context, which measure a different aspect of disadvantage and show different associations with health outcomes (Diego *et al*., 2024; Martens *et al*., 2023; Manusov *et al*., 2023). The use of one indicator or composite index has been a limitation of many earlier studies

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that may obscure domain-specific effects and mask heterogeneity in the relation between adversity and health. Moreover, area-level measures can potentially not capture the individual-level socioeconomic conditions and individual indicators can ignore the contextual and structural factors that act on the neighborhood or community level (Manning *et al*., 2023; McDaniel *et al*., 2021). Measuring discrepancies makes interpretation and cross-study comparability difficult.

There are also limitations associated with polygenic risk scores (PRSs). Even though PRSs have created new opportunities in understanding genetic susceptibility, the existing scores can explain a relatively small part of the phenotypic variations and thus they are not perfect predictors of disease risks (Manning *et al*., 2023; Franks, 2023; Cromer *et al*., 2023). The predictive ability of most PRSs is also widely differentiated between different groups of ancient origin since they have been developed and tested in many European descent populations (Sharma *et al.*, 2024; Hardy *et al*., 2024). Significant consequences of this imbalance on health equity and the overall generalizability of gene-environment (GxE) results to different populations are discussed. Moreover, PRSs are generally more effective at capturing common variants of small effects and are generally not as effective at capturing rare variants of large effect or structural genetic variation, which could also be meaningfully contributing to disease risk (Manning *et al*., 2023).

There are other challenges of statistical power and detection of interactions. Axial GxE interactions, especially multiplicative interactions, have been shown to be large and thus necessitate large sample sizes to detect (Manning *et al*., 2023; Franks, 2023). The small but potentially significant interaction effects may not be detected in many studies because they may be underpowered, and, by default, a false-negative result is more likely. Additionally, statistical detection and substantive interpretation depend on the decision between additive and multiplicative models of interaction. Although multiple studies have revealed additive interactions but no multiplicative ones, both types of interactions are both relevant in the contexts of public health and etiologic inference (Manning *et al*., 2023; Franks, 2023).

Causal inference continues to be a problem. Most of the current research is based on observational designs, which do not allow making causal conclusions about the processes of GxE (Cromer *et al*., 2023; Wickrama *et al*., 2018; McDaniel *et al*., 2021). The interaction effects may be biased due to residual confounding because of unmeasured genetic or environmental factors. Methods based on the principles of Mendelian randomization can more strongly support causal inference but are rarely used more specifically to test GxE interactions (Martens *et al*., 2023; Powell *et al*., 2021). The longitudinal and repeated-measures designs are more effective in terms of time-ordering and of strengthening inference, but they are still not adequate to prove causality (Thompson *et al*., 2020).

Lastly, mechanistic knowledge is not comprehensive. Even though individual epigenetic, behavioral, psychosocial, and physiological pathways to explain GxE interaction have been investigated in a limited number of studies, the compiled mechanisms have not been combined to formulate any unified explanation (Wickrama *et al*., 2018; Wang *et al*., 2022; Abi Karam *et al*., 2025). Current studies tend to focus on individual processes instead of interdependent processes that act within both biological and social. Additionally, it is possible that mechanistic processes differ between populations, development stages, or even particular genetic structures, which stress more life-course-aware, more stressful approaches.

FUTURE DIRECTIONS AND RECOMMENDATIONS

In future studies of gene-environment interactions (GxE) in cardiometabolic health, more focus should be placed on population diversity and a more sophisticated description of socioeconomic exposures. Generalizability also requires expansion of analyses to include racially, ethnically, and ancestrally diverse populations to enhance the promotion of health equity, especially since the existing polygenic risk scores have restricted transferability across populations (Sharma *et al*., 2024; Hardy *et al*., 2024). The multi-ancestry methods can help to identify the shared and population-specific loci in interactions between GxE. Simultaneously, including extensive socioeconomic indicators that reflect individual-level for example education, income, occupation, wealth, area-level, and cumulative life-course adversity (Diego *et al*., 2024; Wickrama *et al*., 2018; Diego, Manusov, *et al*., 2023) should be part of the studies. The integration of genomic,

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epigenomic, transcriptomic, and metabolomic data and the use of behavioral, psychosocial, and physiological and health care access measures are bound to be instrumental in clarifying the underlying mechanisms and gaining the pathways in which socioeconomic contexts influence genetic risk. The longitudinal, life-course, and intergenerational designs are especially appropriate in terms of serving and explaining the dynamic nature of GxE processes during early development and older adulthood (Thompson *et al*., 2020; Wickrama, *et al*., 2022; Baker *et al*., 2024).

In future research, the focus must be on bigger samples and more refined analytical procedures to enhance the quality of interaction effects identification and interpretation. This needs sufficient power to measure additive and multiplicative interactions, and machine-learning methods can assist in finding complex and nonlinear relationships between genetic and environmental variables (Manning *et al*., 2023; Franks, 2023). One of the priorities is cis-ancestry PRSs, functional annotation, and attention to rare and structural variants, which would help to improve predictive accuracy. Differentiating between true and gene-environment correlations, as well as causal mechanisms, will be necessary, and methods of causal inference, like Mendelian randomization and instrumental variable analysis, will need to be further used (Martens *et al*., 2023; Powell *et al*., 2021). Precision prevention by targeted prevention shows potential in translational work, such as intervention trials that change social determinants of health and clinical decision-support systems to incorporate genetic risks and socioeconomic risk, but needs to be supported by clear guidance, clinician education, and with special care to ethical issues, including privacy and informed consent and potential to increase health.

CONCLUSION

The interaction between genetic predisposition to core cardiometabolic risk factors, including obesity, dysglycemia, dyslipidemia, and hypertension, was explored in the context of socioeconomic adversity in the United States. Through the literature synthesis, the interaction between socioeconomic factors and the presence, clustering, and accumulation of genetic predisposition to these core cardiometabolic risk factors was clearly established, demonstrating the context-dependent, non-deterministic role of genetic predisposition to cardiovascular diseases. Metabolic risk factors serve as core intermediate phenotypes, where socially patterned environments, chronic stress, and structural inequities serve to magnify or mitigate these risks. Through the combination of genetic, metabolic, and social epidemiological approaches, this literature review addresses the limitations of reductionism in the study of cardiovascular risk, the need to incorporate socioeconomic context in the study of cardiovascular genomics, where an equity-informed gene-environment interaction framework plays an integral role in the etiology of cardiovascular diseases, providing insights for the development of prevention strategies to address socioeconomic inequities in cardiovascular health.

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