Title

Adverse Childhood Experiences, Job Strain, Social Isolation, and Risk of Cardiovascular Disease in U.S. Workers: a Multi-Cohort Study with a Life-Course Perspective

Author

Matthews, Timothy Alan

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Adverse Childhood Experiences, Job Strain, Social Isolation, and Risk of Cardiovascular Disease in U.S. Workers:

a Multi-Cohort Study with a Life-Course Perspective

A dissertation submitted in partial satisfaction of

the requirements for the degree of

Doctor of Philosophy in Environmental Health Sciences

by

Timothy Alan Matthews

2023

ABSTRACT OF THE DISSERTATION

Adverse Childhood Experiences, Job Strain, Social Isolation, and Risk of Cardiovascular Disease in U.S. Workers:

a Multi-Cohort Study with a Life-Course Perspective

by

Timothy Alan Matthews

Doctor of Environmental Health Sciences

University of California, Los Angeles, 2023

Professor Jian Li, Chair

Abstract

Cardiovascular disease (CVD, including heart disease and stroke) is the leading cause of death in the United States and worldwide, making CVD a key priority in epidemiological and public health research. The utility of current exposure and risk assessment models utilizing traditional risk factors such as sociodemographic characteristics and health behaviors in CVD prevention

efforts has plateaued, with a large proportion of excess CVD morbidity and mortality risk remaining unexplained. In recent years, psychosocial stressors have gained prominence as important drivers of CVD etiology, with stressful exposures such as adverse childhood experiences (ACEs), social isolation, and job strain emerging as novel CVD risk factors.

The objective of this project was to conduct a systematic epidemiological investigation of ACEs, social isolation, job strain, cardiometabolic biomarkers implicated in allostatic load, and their associations with risk of CVD mortality using data from three large, population-based, nationally representative cohort studies characterizing the health and disease profiles of childhood, mid-life, and old age in the United States. This project implemented a secondary data analysis of the based National Longitudinal Study of Adolescent to Adult Health (Add Health), Mid-life in the United States (MIDUS), and the Health and Retirement Study (HRS) cohort studies, examining the contribution of psychosocial stressors at different life stages (childhood and adulthood), in different life domains (working life and non-working life) to the development and progression of CVD.

The primary aim of the study was to examine the associations of ACEs, social isolation, and job strain with CVD mortality risk in the Add Health, MIDUS, and HRS cohorts, implementing a comprehensive exposure assessment of work and nonwork related psychosocial factors across the life-course. The secondary aim of the study was to identify psycho-physiological pathways reflecting allostatic load, linking ACEs, social isolation, and job strain with CVD, offering insight into potential mechanisms underlying associations of psychosocial exposures with CVD etiology and pathogenesis.

The sample population was large and included workers from diverse occupational categories and broad sociodemographic strata, with detailed data on characteristics such as

household income, educational attainment, smoking, alcohol consumption, and physical exercise. ACE measures across the three cohorts included financial stress, household dysfunction, and abuse, with the Add Health dataset providing prospective data from childhood surveys. Job strain measures were based on Karasek's well-validated demand-control model of job strain, while the extensively used Berkman-Syme Social Network Index provided an assessment of social isolation. The national cohorts also implemented a rigorous biomarker data collection process and allowed for the analysis of seven cardiometabolic and inflammatory biomarkers related to CVD pathogenesis, enabling the construction of an allostatic load index as an indicator of general "wear and tear" and chronic stress on the body. Furthermore, the MIDUS dataset provided autonomic measures allowing for analyses of heart-rate variability, an index of overall cardiovascular functioning and reactivity. Multivariate Cox proportional hazard regression models were used to conduct survival analyses of associations of ACEs, social isolation, and job strain with CVD mortality risk, and multivariate Poisson regression models were implemented to estimate associations of ACES, social isolation, and job strain with allostatic load index. Statistical models included iterative adjustment for sociodemographic characteristics and lifestyle behaviors, and further stratified analyses by ACE exposure level were performed.

The results of the study indicated significantly increased risk of CVD mortality among participants with a high level of ACEs in the HRS study, and among participants with higher levels of social isolation and job strain in the Add Health and HRS studies. While findings for associations of psychosocial exposures with allostatic load and heart-rate variability were not statistically significant, a stable and consistent trend of increased effect size estimates with increasing exposures was observed in the MIDUS cohort.

This project conducted a comprehensive exposure assessment of work and nonwork related factors and their associations with CVD mortality and allostatic load biomarkers clinically implicated in CVD pathology. This novel and innovative approach to exposure modelling addressed the limitations of prior work in the field of occupational and cardiovascular epidemiology by highlighting the impact of cumulative exposures. The successful implementation of the analytic strategy and the detection of promising preliminary findings for associations of ACEs and APDs with CVD mortality and allostatic load offer an empirical foundation for future investigational and translational work targeting psychosocial exposures.

Collectively, these findings suggest that high exposure to ACEs and APDs are closely related to allostatic load and multimorbid disease conditions in adulthood, as well as increased risk of CVD mortality. While the findings of the present study were not always statistically significant across the three cohorts of the Add Health, MIDUS, and HRS studies, the general trend of results indicate increased risk of CVD mortality and potentially increased allostatic load due to high exposure to ACEs and APDs. In context of the rapidly expanding literature on ACEs, social isolation, job strain, and allostatic load and HRV, these results suggest cumulative psychosocial exposures may increase the risk of chronic cardiometabolic and inflammatory risk conditions implicated in CVD pathology and mortality.

The dissertation of Timothy Alan Matthews is approved.

Mary Rezk-Hanna

Wendie Robbins

Yifang Zhu

Jian Li, Committee Chair

University of California, Los Angeles

2023

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LIST OF ABBREVIATIONS

ACC	American College of Cardiology
ACEs	Adverse Childhood Experiences
ADC	Aid to Dependent Children
Add Health	National Longitudinal Study of Adolescent to Adult Health
AHA	American Heart Association
ALI	Allostatic Load Index
APDs	Adulthood Psychosocial Disadvantages
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CIs	Confidence Intervals
CRP	C-Reactive Protein
CRs	Count Ratios
CVD	Cardiovascular Disease
DALYs	Disability-adjusted Life Years
DaWCo	Danish Work Life Course Cohort Study
ECG	Electrocardiogram
HbA1C	Glycosylated hemoglobin
HF-HRV	High-frequency Heart-rate Variability

HDL	High-density Lipoprotein
HPA	Hypothalamic-pituitary-adrenal
HRS	Health and Retirement Study
HRs	Hazard Ratios
HRV	Heart-rate Variability
ICOH	International Commission on Occupational Health
ILO	International Labor Office
JCQ	Job Content Questionnaire
KORA	Cooperative Health Research in the Region of Ausburg
LF-HRV	Low-frequency Heart-Rate Variability
NDI	National Death Index
NHLBI	National Heart, Lung, and Blood Institute
MIDUS	Mid-life in the United States Study
MONIKA	Monitoring of Trends and Determinants in Cardiovascular Disease
NORA	National Occupational Research Agenda
RMSSD	Root Square of Mean Successive Differences
RSA	Respiratory Sinus Arrhythmia
SBP	Systolic Blood Pressure

SDRR	Standard Deviation of the RR Interval
SES	Socioeconomic Status
TC	Total Cholesterol
U.S.	United States
WHO	World Health Organization
WHR	Waist to Height Ratio

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VITA

Education

2018-2020	M.S. in Environmental Health Sciences, UCLA
2012-2016	B.A in Psychology, UCLA

Selected Publications

1. Li J, **Matthews TA**, Clausen T, Rugulies R. Workplace Discrimination and Risk of Hypertension: Findings from a Prospective Cohort Study in the US. Journal of the American Heart Association. 2023 May 2;12(9):e027374.

2. **Matthews TA**, Guardiano M, Omidakhsh N., Cushing L., Robbins W., Hong O., Li J. Associations of COVID-19 Related Work Stressors with Psychological Distress: Racial and Ethnic Disparities in Californian Workers. International Journal of Environmental Research and Public Health. 2023 Jan;20(1):144.

3. **Matthews TA**, Porter N, Siegrist J, Li J. Unrewarding work and major depressive episode: Cross-sectional and prospective evidence from the U.S. MIDUS study. Journal of Psychiatric Research. 2022 Dec 1;156:722–8.

4. **Matthews TA**, Zhu Y, Robbins W, Rezk-Hanna M, Macey M, Song Y, Li J. Adulthood Psychosocial Disadvantages and Risk of Hypertension in US Workers: The Health Modification Effect of Adverse Childhood Experiences. Life. 2022 Oct;12(10):1507.

Selected Presentations

1. **Matthews TA**, Li J. Negative Employment Changes during the COVID-19 Pandemic and Well-being in U.S. Workers: Substructures of Intersectional Vulnerability in Happiness and Sleep Quality. Oral presentation at the 6th International Conference on Wellbeing at Work 2022: Wellbeing in Hectic Times, June 13-15, 2022.

2. Li J, **Matthews TA**. Effort-reward Imbalance at Work and Risk of Major Depressive Episode: a Cohort Study in the U.S. Oral presentation at the 6th International Conference on Wellbeing at Work 2022: Wellbeing in Hectic Times, June 13-15, 2022.

Fellowships & Awards

1. Finalist, European Association of Psychosomatic Medicine Elsevier Young Investigator Award, 2022.

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1. Overview

Cardiovascular disease (CVD) is the leading cause of death in the United States (U.S), making CVD prevention a key priority in epidemiological and public health research. While considerable progress has been made in the identification and targeting of traditional CVD risk factors such as unhealthy lifestyle behaviors, an extensive proportion of the disability and mortality burden associated with CVD remains unexplained.

Recent evidence has posited stress as a central driver of CVD pathogenesis, and psychosocial stressors such as adverse childhood experiences (ACEs), social isolation, and job strain have demonstrated robust associations with risk of CVD, hence constituting novel risk factors for CVD. Importantly, the effects of these psychosocial stressors vary across the life-course, with differential impacts in childhood, adulthood, and old age. Furthermore, there is a lack of evidence regarding the psycho-physiological mechanistic pathways linking ACEs, social isolation, and job strain with allostatic load, a measure of cumulative stress and "wear and tear" on the body. Finally, there is a need for the systematic evaluation of the relative contributions of ACEs, social isolation, and job strain to CVD and allostatic load across all stages of the life-course.

The central hypotheses to be tested are that ACEs, social isolation, and job strain are associated with increased risk of CVD, and that exposure to these psychosocial stressors increases allostatic load, as operationalized via a profile of cardiometabolic biomarkers implicated in CVD. This project implements a novel conceptual framework synthesizing ACEs, social isolation, and job strain across the life-course, using data from three national cohorts – the National Adolescent Study of Health (Add Health), the Mid-life in the United States (MIDUS) study, and the Health and Retirement Study (HRS), to cross-validate hypotheses.

The utility of traditional models and methods of CVD risk assessment has plateaued, and novel research paradigms emphasizing the role of psychosocial stressors in CVD are needed to improve understanding of the causal and mechanistic pathways involved in CVD. This work lays the empirical foundations for a continuum of future translational and interventional work aimed towards the early identification and alleviation of psychosocial stressors implicated in CVD across the life-course.

1.1 Background and Motivation

CVD, including heart disease and stroke, is the leading cause of death worldwide and in the U.S., accounting for 2.8 million deaths in 2018 alone and with a prevalence nearing 50%[1]. Current risk assessment models using traditional CVD risk factors are severely limited in their ability to predict CVD, presenting a critical knowledge gap[2,3]. Recent evidence has demonstrated a central role of stress in the etiology of CVD, and psychosocial stressors such as ACEs, social isolation, and job strain have emerged as novel CVD risk factors, with potential differential impacts across the life-course, from childhood through adulthood and old age[4–8].

1.2 Statement of Purpose

The objective of this project is to conduct a systematic epidemiological investigation of ACEs, social isolation, job strain, cardiometabolic biomarkers implicated in allostatic load, and their association with risk of CVD mortality among three national cohorts characterizing the health and disease profiles of childhood, mid-life, and old age in the U.S. This project conducts a secondary data analysis utilizing the large, population-based National Longitudinal Study of Adolescent to Adult Health (Add Health), Mid-life in the United States (MIDUS), and the Health and Retirement Study (HRS) cohort studies, examining the contribution of psychosocial stressors

at different life stages (childhood and adulthood), in different life domains (working life and non-working life) to the development and progression of CVD.

The central hypothesis to be tested is that ACEs, social isolation, and job strain interact to produce a biological profile of high allostatic load represented by cardiometabolic biomarkers, ultimately leading to increased CVD risk. Importantly, this project presents the opportunity to cross-validate hypotheses with a multi-cohort research design across three national, cohort studies that collectively span the entirety of the life-course, increasing the robustness and generalizability of the results.

1.3 Innovation

The major innovative aspects of this project are the combination of three large, national, longitudinal cohorts that collectively cover childhood, mid-life, and old age, offering a life-course perspective, and an analytical strategy that centers around the investigation of work and nonwork related psychosocial exposures and their associations with CVD throughout the life-course, highlighting the relative contributions of each stressor at each life stage. Additionally, the inclusion of allostatic load based on indices of cardiometabolic and inflammatory biomarkers presents the opportunity to reveal mechanistic pathways underlying the associations. Another key innovation is that in most studies, ACEs were reported retrospectively by adult participants, possibly inducing recall bias, whereas the Add Health study is highly unique because ACEs were measured prospectively, when participants were children or adolescents[9,10].

This project advances the traditional methodology used to examine the health impacts of psychosocial exposures, both in the workplace and beyond, integrating the established exposure paradigms of ACEs, social isolation, and job strain in a broad-spectrum approach towards

modeling the psychosocial human exposome across the life-course. While prior studies have examined the singular contributions of ACEs, social isolation, or job strain to disease outcomes such as CVD, this project achieves a more holistic and integrated exposure model by accounting for this complement of life-course stressors.

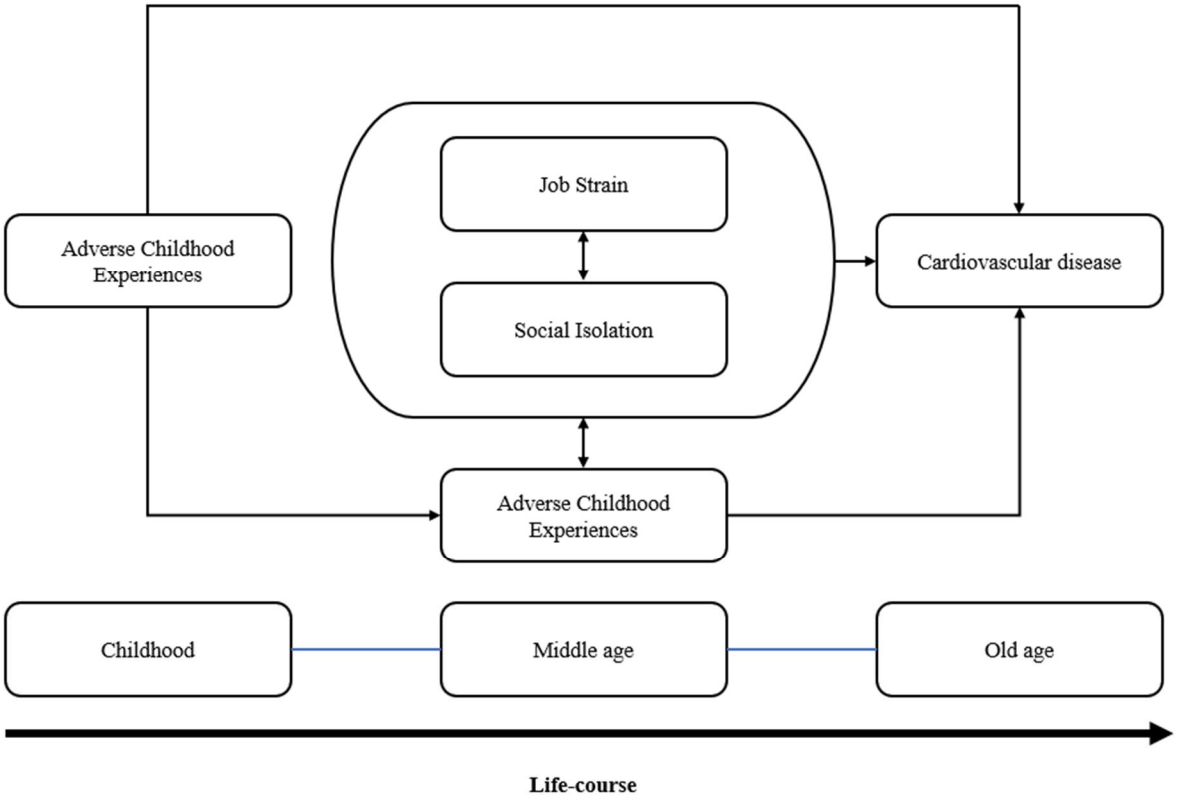
Previous analyses of the MIDUS dataset have demonstrated the utility of investigating health outcomes using comprehensive measurement of multiple psychosocial exposures. We previously observed significant associations of job strain, with increased risk of CVD mortality, major depressive episode, and incident hypertension. Increased job strain from Wave I to Wave II of the MIDUS study was associated with a greater than two-fold increased risk of CVD mortality after 20 years of follow-up[11]. Furthermore, we conducted analyses demonstrating obvious sex-specific associations of job strain and aggregate associations of social strain with risk of major depressive episode[12]. Finally, in analyses of combined ACEs, social strain, and job strain exposures at baseline, we reported significant associations with incident hypertension at 20-year follow-up[13].

Having passed peer-review, these initial publications thus serve as an empirical foundation for the exposure modeling approach implemented in this project. The publication of these manuscripts has ensured that the theoretical framework and exposure paradigm proposed are scientifically sound. These findings demonstrate the feasibility and efficacy of combining psychosocial exposures in analyses of health outcomes, showing a trend of accumulating risk with additional exposures, and highlight the public health significance of life course exposures.

1.3.1 Theoretical Framework

The theoretical framework underlying this project is displayed in Figure 1, summarizing the various components of the model, the proposed analysis of the relationships between them, and the adoption of a life-course epidemiology perspective.

Figure 1. Theoretical Framework – Life-course Epidemiology of Cardiovascular Disease



The objective of this life-course epidemiological approach is to reveal novel relationships in associations of ACEs, social isolation, and job strain with risk of CVD, strengthening and clarifying the body of literature linking such factors with CVD risk. We expect to observe significant associations of ACEs, social isolation, and job strain with risk of CVD, as well as evidence of allostatic load triggered by the influence of these stressors on psychophysiological pathways. This project lays the empirical and methodological foundations for the early recognition and alleviation of ACEs, social isolation, and job strain as CVD risk factors.

This research vertically advances the fields of occupational epidemiology and public health by identifying the mechanistic pathways linking ACEs and social isolation with disease states in adulthood, as well as the interactions of ACEs and social isolation with the psychosocial work environment, and their cumulative impacts on health. Importantly, this project also allows for the cross-validation of hypotheses across three national, longitudinal, population-based studies that together span the entirety of the life-course, from childhood through adulthood and old age, increasing the robustness and generalizability of the results.

The ultimate research contribution of this project is a comprehensive exposure assessment model spanning work and nonwork related psychosocial exposures across the life-course, and the systematic examination of their influence on CVD outcomes, as well as the potential psycho-psychological pathways involved.

2.1 Aim 1: Examine associations of ACEs, social isolation, and job strain with risk of CVD.

2.1.1 Hypothesis

The investigation of psychosocial work and nonwork related stressors across the life-course and their associations with CVD risk is the primary outcome of interest for this research project. We hypothesize that exposure to these stressors is associated with increased risk of CVD.

2.1.2 Overview

CVD, including heart disease and stroke, is the leading cause of death worldwide and in the U.S.[14]. The prevalence of CVD in U.S. adults is 49%, and the American Heart Association's (AHA) 2023 update on Heart Disease and Stroke Statistics reported 928,741 CVD deaths in the US in 2020[14]. Furthermore, the World Health Organization's (WHO) projections estimate that CVD will account for over 22.2 million annual deaths by 2030[15]. The economic burden of CVD in the U.S. is estimated at over $350 billion annually, with a projected increase to over $950 billion by 2035[14,16]. CVD broadly impacts demographic groups, affecting men and women of all ages and racial backgrounds[17]. While CVD was previously considered a disease of aging populations, the incidence of CVD in younger persons and working populations is rapidly increasing[18]. Additionally, although CVD mortality has declined over the course of the past two decades, the rate of decline has stagnated, and CVD continues to exert a heavy mortality burden, with recent data showing an increase again in the later 2010s to 2020[14,19–21].

Traditional risk factors such as unhealthy diets, smoking, and physical inactivity are unable to fully account for the burden of CVD risk, and recent evidence has identified an urgent need to evaluate the contribution of novel environmental, behavioral, and occupational risk factors to CVD[2,3,22–24]. Accordingly, the National Heart, Lung, and Blood Institute's (NHLBI) Strategic

Vision for Research has called for the targeted epidemiological investigation of novel risk factors for CVD[25]. Such risk factors can be broadly classified as stressors, and a rapidly emerging body of evidence has posited a central role of stress in the etiology and pathophysiology of CVD[5,26].

Research efforts have identified a continuum of novel stressors that contribute to CVD across all stages of the life-course, from childhood through adulthood and old age. Notably, psychosocial exposures are a major source of stress and increased CVD risk across the life-course, the effects of which can be dissected according to their associated life stage[4,27,28]. In childhood, ACEs, defined as a constellation of early life adversities such as childhood abuse, neglect, or household dysfunction, have emerged as a severe and causal risk factor for CVD[6,29,30], while in adulthood, social isolation[7,27] and job strain have demonstrated extensive and causal associations with CVD[4,8,31,32]. This collective set of stressors represents a holistic spectrum of work and nonwork related psychosocial stressors evidenced as CVD risk factors, across the life course.

While studies have demonstrated the independent associations of such psychosocial exposures with CVD outcomes, there is an extreme lack of evidence assessing their combined and interactive effects. Furthermore, there is a critical knowledge gap regarding the physiological mechanisms underlying the effects of such exposures – while cardiometabolic biomarkers have shown considerable utility in elucidating such mechanisms, the nature of their relationship with psychosocial exposures and CVD risk demands clarification[2,33,34].

Importantly, the systematic and integrated investigation of these novel stressors and their aggregate contributions to CVD at different life stages demands a novel conceptual framework. Most recently, the life-course model has emerged as a theoretical framework for effectively characterizing the differential effects of exposures across life stages[35–37]. The life-course model

has benefitted additionally from integration with the cumulative advantage/disadvantage model, which was developed to assess the issue of multiple overlapping exposures with potential additive or synergistic effects[38,39]. Finally, the life-course model has been expanded to include the chains of risk model, which accounts for sequences of linked exposures that can occur when one stressor gives rise to another, leading to a chain reaction that may "explain continuities between early experiences and adult psychosocial function"[40–42].

The objective of this project is to conduct a systematic epidemiological investigation of ACEs, social isolation, job strain, and their association with risk of CVD amongst three national cohorts characterizing the health and disease profiles of childhood, mid-life, and old age in the U.S. We propose a secondary data analysis research project utilizing the large, population-based Add Health, MIDUS, and HRS cohort studies, examining the contribution of psychosocial stressors at different life stages (childhood and adulthood) and in different life domains (working life and non-working life) to the development and progression of CVD. Our central hypothesis is that ACEs, social isolation, and job strain interact to produce a biological profile of high allostatic load represented by cardiometabolic biomarkers, ultimately leading to increased CVD risk.

There is a critical knowledge gap regarding the interaction of work and nonwork related psychosocial stressors in cardiometabolic disease processes. While many studies have evaluated the independent contributions of either work or nonwork related exposures, there is a paucity of empirical evidence assessing their interrelationships, and hence the National Occupational Research Agenda (NORA) has highlighted a need for research on the "relationship of occupational risk factors with known non-occupational risk factors for CVD"[43]. This project implements a comprehensive exposure assessment model incorporating the work and nonwork related psychosocial factors of ACEs, social isolation, and job strain, from childhood to adulthood and old

age, spanning the entirety of the life-course. We hypothesize that exposure to this complement of stressors is associated with increased risk of CVD mortality.

2.1.3 Literature Review

In childhood, ACEs, which encompass negative experiences such as physical, emotional, or sexual abuse and neglect, parental death, substance abuse, incarceration, or separation, and socioeconomic deprivation[44], are evidenced as an independent and causal risk factor for CVD, as well as a driver of premature mortality[6,45,46]. ACEs have been identified as critical factors in the development and progression of several chronic diseases and psychiatric disorders, increasing the risk of multiple health conditions in a clear, linear, and dose-dependent manner[47–49]. ACEs are also closely connected to dysfunctional health behaviors, with studies reporting graded associations of ACEs with activities such as illicit drug and alcohol use[50].

The prevalence of ACEs in the US is extremely high and increasing — in 2019, the Centers for Disease Control and Prevention (CDC) published findings that 60% of adults reported experiencing at least 1 type of ACE in their lifetime, a significant increase from the 2012 estimate of 46%[51,52]. Furthermore, a recent study estimated the annual costs of ACEs at $748 billion in North America, with substantially higher costs for CVD cases attributable to ACEs compared to other disease risk factors due to the higher number of disability-adjusted life years (DALYS) associated with CVD[53].

The AHA has issued scientific statements recognizing the association of ACEs with CVD, predicating ACEs as a social determinant of CVD risk and outcomes[29,54]. Based on current evidence, the AHA was able to conceptually outline pathways between ACEs and cardiometabolic health, but called for further epidemiological research on mechanisms and related factors that may

alter these pathways or offer targets for interventions, citing evidence gaps around a lack of longitudinal cohort studies and limited identification of the mechanisms linking ACEs with CVD[29]. In addition, researchers have highlighted a knowledge gap regarding differential associations of ACE exposure patterns with health outcomes later in life, raising questions about "how adversity affects the transition into adulthood"[55]. The research design and conceptualization of this project targets the trajectory of cumulative exposures to adversity over the life course, providing a novel and comprehensive overview of the psychosocial exposome.

While ACEs represent a major psychosocial stressor in childhood, social isolation, defined as a lack of social contacts and shortage of social relationships, is a critical psychosocial stressor in adulthood, providing an effective mid-life counterpart to ACEs[56]. Social isolation is an emerging issue that is especially relevant due to current demographic trends indicating widespread social isolation throughout the U.S. adult population. Approximately one-quarter of the U.S. adult population and 28% of older adults live alone, more than half of U.S. adults are unmarried, of which 20% have never been married, and less than a quarter of U.S. adults participate in a social club, sports group, or other organization[57,58].

From 1960 to 2022, the proportion of single-person households in the U.S. increased more than twofold, from 13% to 29% of all households[59]. Concurrently, there has been a rapid increase in the proportion of aging adults in the U.S. population[60]. The latest data from the U.S. Census Bureau indicate that by 2030, 73.1 million people – 21% of the population – will be aged 65 or older, with older adults outnumbering children by 2034[61]. Moreover, Medicare data indicate that social isolation among older adults accounts for an estimated $6.7 billion in annual hospital and nursing facility expenses[62].

These trends are concerning, as social isolation is associated with a 30-50% increased risk of heart disease and stroke, with a meta-analytic review also demonstrating increased risk of all-cause mortality[7,27,63]. In fact, in 2023, the U.S. Surgeon General published an advisory on the epidemic of loneliness and social isolation, delineating the problem as an urgent issue of major public health significance[64]. While social isolation constitutes an important psychosocial stressor in adulthood, given the fact that most adults spend a substantial portion of their lifetime in the workplace, we must also address occupational exposures, which are major inputs to the human exposome.

A longstanding body of evidence has demonstrated excess CVD risk amongst populations exposed to psychosocial work stressors[23,31,32]. Notably, the International Commission on Occupational Health (ICOH) reported that "about 10 to 20% of all causes of CVD deaths among the working age populations can be attributed to work, i.e., are work-related"[22]. Job strain, defined as the combination of high job demands with low job control[65] has shown consistent, robust, and dose-dependent associations with increased CVD risk[8,66–69]. Several longitudinal studies with extensive follow-up periods demonstrated associations of increasing job strain with CVD mortality, and with cardiometabolic risk factors for CVD such as hypertension[11,13,70,71].

The role of job strain in cardiovascular health outcomes has been emphasized in recent years, with larger and longer-term studies offering compelling data. For example, a study of 1.6 million Danish employees found that high job strain was associated with increased risk of CVD mortality, with job strain and income accounting for up to 54% and 33% of the excess CVD risk observed in men and women with cardiometabolic disease, respectively[72].

While some pioneering research efforts have identified interactions of job strain with psychosocial factors in the context of mental health outcomes[73–75], no study has examined the potential combined and interactive effects of ACEs, social isolation, and job strain on risk of CVD, presenting a research gap. A single study in 2007 assessed the contribution of early-life risk factors (in this case, parental socioeconomic status) to the association of job strain with atherosclerosis, stating that "even the best-designed prospective studies have failed to take into account the cumulative effects of early life factors", but found no evidence for such effects[76]. Therefore, this project therefore seeks to address these knowledge gaps via the systematic investigation of work and nonwork related psychosocial exposures across the life course.

2.2 Methodology

2.2.1 Study Sample and Design

This research project involved secondary data analyses of the Add Health, MIDUS, and HRS cohorts – three population-based, nationally representative samples of U.S. persons that cover the life course through adolescence, mid-life, and old age. In all cohorts, analyses were focused on individuals with employment experience, and participants with self-reported physician-diagnosed CVD (including heart disease and stroke) at baseline were excluded to produce accurate estimates of CVD mortality during follow-up and eliminate impact of pre-existing CVD on future CVD mortality. Data from the MIDUS and HRS studies were sourced from public-use datasets[77–82], whereas for the Add Health study, data were drawn from restricted datasets containing mortality data[83]. Follow-up time began upon enrollment in the surveys selected as the baseline time-points, and censoring occurred based on instances of CVD mortality.

In Wave IV of the Add Health Study, the baseline time-point for this epidemiologic investigation, there was a total of 38,676 participants, of which 25,022 were working at least 10 hours per week. Data collection for Wave IV of the Add Health study occurred in 2007-2008, with mortality data linked with the National Death Index (NDI) available up to 2019, representing a maximal follow-up period of 12 years. The final sample size for analyses of the Add Health study was 23,263, and the process of sample size selection for the Add Health Study Wave IV is shown in Figure 2.

The MIDUS study had an initial sample size of 7,108 participants in 1995 at MIDUS I, the baseline time-point for data analyses, with 4,535 participants working for pay at the time of data collection. The MIDUS cohort also contained additional linkage to mortality data via the NDI through 2020, culminating maximally in a follow-up period of 25 years. The final sample size for analyses was 4,337, and the process of sample size selection for the MIDUS study is shown in Figure 3.

The baseline sample for analyses of the HRS cohort originated in 2006-2008. Both 2006 and 2008 waves were combined to retrieve full data on target variables, as survey items corresponding to psychosocial stressors were administered to half of the study sample in 2006 and 2008, respectively. The HRS had a total sample size of 43,399 participants in 2006-2008, and 7,265 were working. Mortality data for the HRS cohort are available through 2018, representing a maximum follow-up period of 12 years. The size of the final analytic sample was 4,046, and the process of sample size selection for the HRS cohort is shown in Figure 4.

Figure 2. Sample Size Selection Flowchart for the Add Health Study Wave IV (2008)

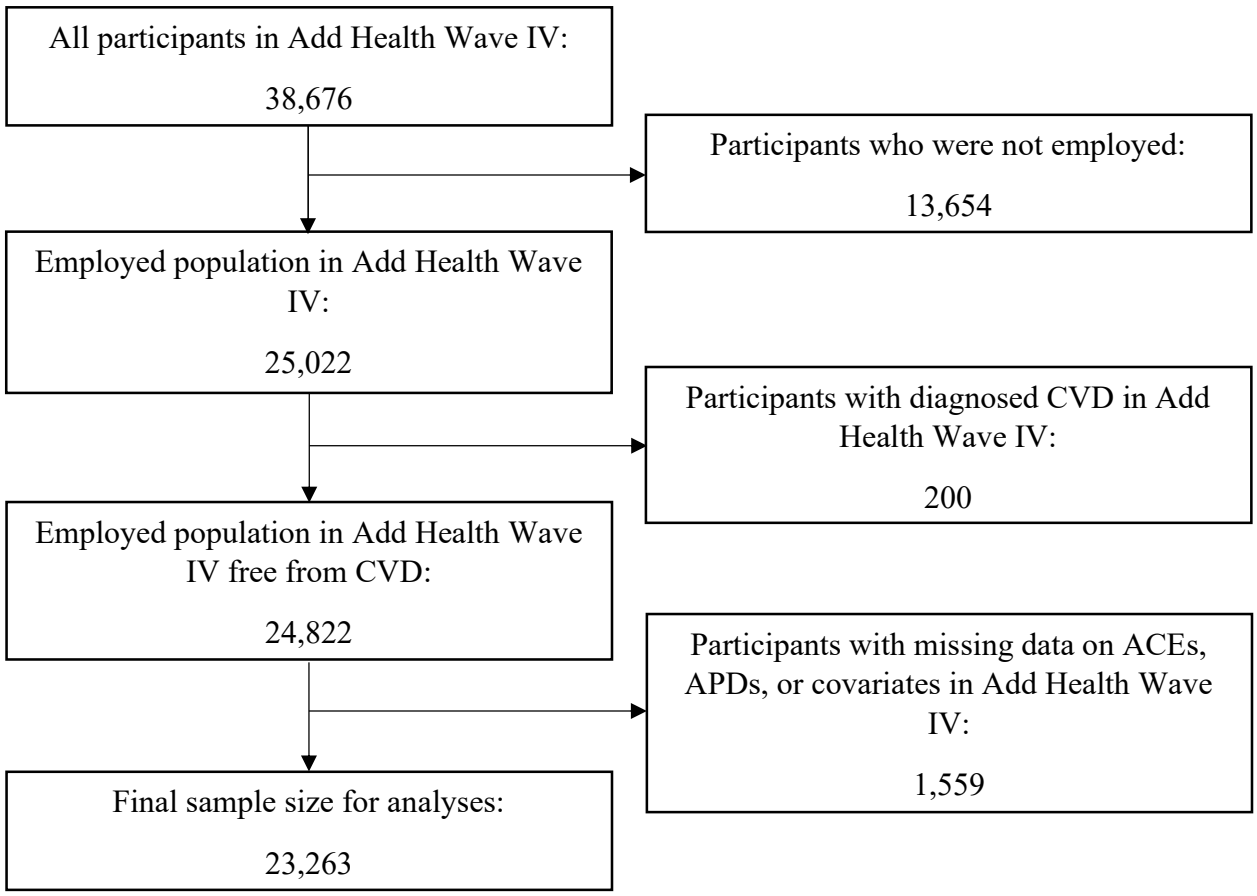


Figure 3. Sample Size Selection Flowchart for the MIDUS Study (1994)

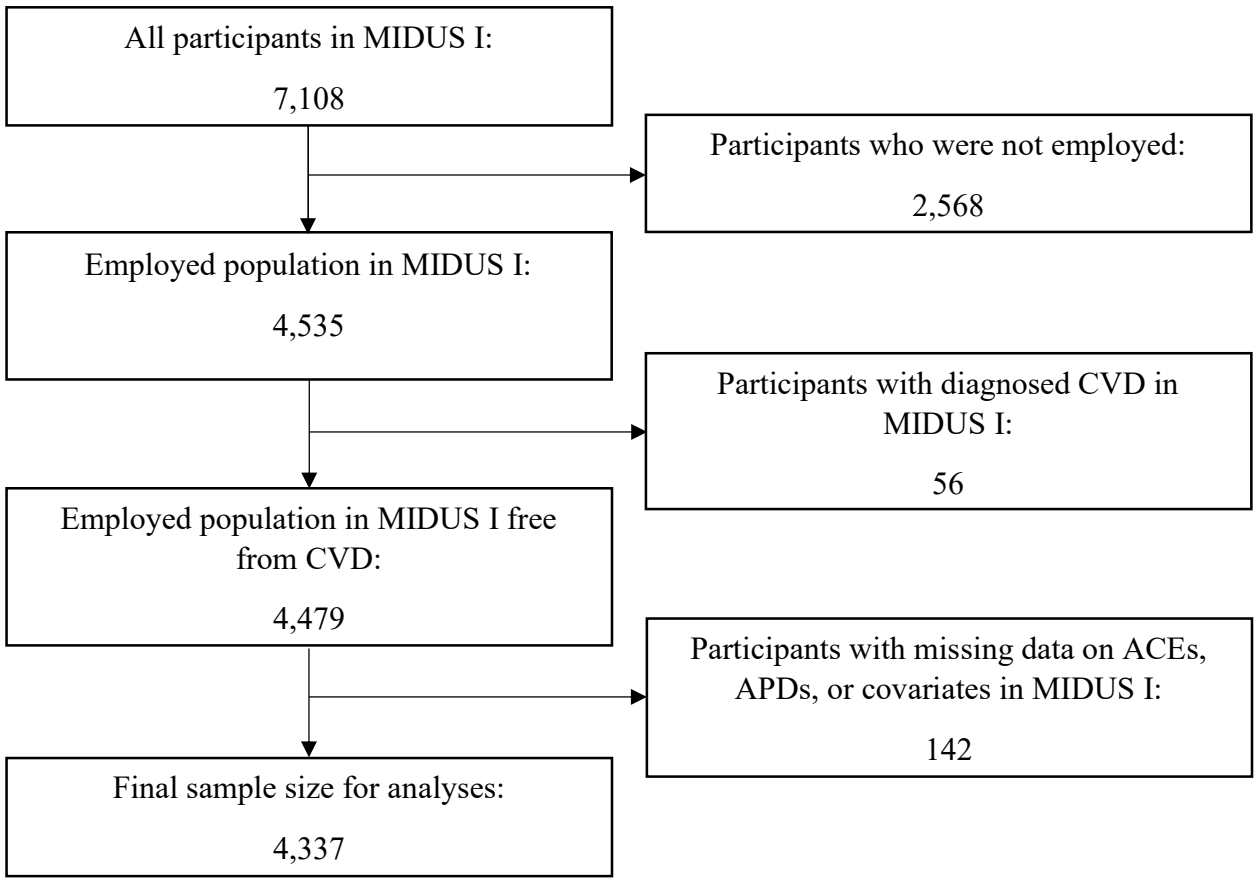
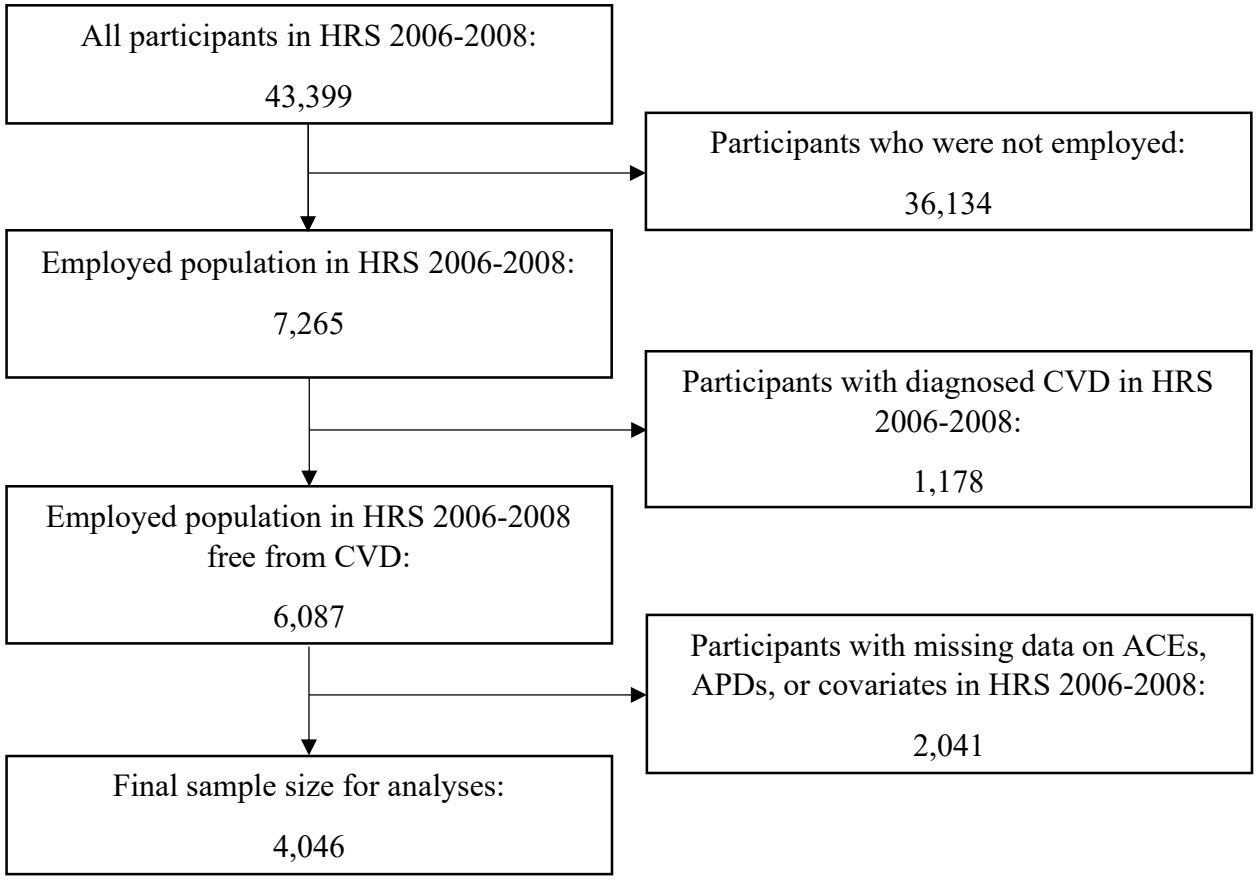


Figure 4. Sample Size Selection Flowchart for the HRS Study (2006-2008)



2.2.2 Measures

The key measures across the Add Health, MIDUS, and HRS studies are quite similar and comparable, allowing for the creation of harmonized operationalizations across the three studies. Consistency of measures and methodology between the three cohorts was emphasized throughout the processes of measure selection and variable generation to preserve rigor and robustness across analyses. The selected measures were designed to achieve a comprehensive investigation of work and nonwork related psychosocial stressors across the life course. In addition to sociodemographic characteristics and health behaviors such as age, sex, race, educational attainment, household income, smoking, alcohol consumption, and physical exercise, the key measures are detailed below.

Exposures: Adverse childhood experiences, social isolation, and job strain.

ACEs: In the Add Health, MIDUS, and HRS studies, ACEs were assessed via a series of detailed questions about the participant's childhood, relationships with parents, and socioeconomic status (SES) in early life. While the reliability of adult retrospective reports of ACEs has been questioned in the past due to potential recall bias, evidence suggests that retrospective reports are generally valid, with robust test-retest reliability and adequate kappa coefficients generally in the range of 0.52 to 0.72[84,85].

Specifically, the survey questions assess early-life exposures such as physical, emotional, and sexual abuse or neglect from parents, foster care, parental death, separation, incarceration, mental illness, and substance abuse, as well as the family's reception of welfare in childhood and related early-life financial issues. These questions span the core components of ACEs identified in the scientific literature, comprising a factorial structure with three key subdomains: (i) parental

abuse, (ii) financial stress, and (iii) household dysfunction; this compartmentalization identifies the fundamental aspects of ACEs and offers a basic methodological framework for their analysis[44,86].

The Add Health study included the most detailed information on exposure to ACEs. Measurement items for parental abuse included questions about physical and non-physical forced sexual activity before age 18, as well as emotional and verbal abuse, and physical abuse. Two items assessed financial stress, with example items such as "Did you usually feel safe in your neighborhood?" and "Before you were 18 years old, did anyone in your household ever receive public assistance, welfare payments, or food stamps?". Example items for household dysfunction included death of the biological or foster mother or father, living away from either the mother or father figure during childhood, incarceration of the mother or father figure before age 18, and arrest, conviction, or incarceration of the participant before age 18. Furthermore, the Add Health Study was unique in that it included prospective accounts of ACEs from when the participants were children or adolescents, thus offering increased sensitivity of exposure measurement. A binary variable for high and low exposure to ACEs was created, and participants with one or more ACEs were categorized as having high ACEs exposure.

In the MIDUS study, ACEs were assessed retrospectively at MIDUS I, with full coverage of the three subdomains of ACEs. Physical and emotional abuse from parents, siblings, and others during childhood were assessed, and household dysfunction items included the death of a parental figure, not living with a biological parent in childhood, having no male figure in the household, divorce during childhood, and foster care. Example items for abuse included "During your childhood, how often did your mother, or the woman who raised you, hit you?", and "During your childhood, how often did your father, or the man who raised you, insult you or swore at you?".

Items examining financial strain included self-reported worse than average financial level of the family when growing up, less than high school educational attainment of either parental figure, and the family receiving welfare or Aid to Dependent Children (ADC), a Social Security program involving cash transfers – "During your childhood and adolescence, was there ever a period of six months or more when your family was on welfare or ADC?"[87]. A dichotomous variable for high versus low ACEs exposure was generated, and participants with two or more ACEs were classified as having a high level of ACEs.

In the HRS cohort, ACEs were assessed in the Leave-Behind Questionnaire (LBQ), which was administered in two stages across the 2006 and 2008 cohorts, and has been used extensively for analyses of stress, childhood adversity, and health[88]. Physical abuse from parents was measured, and for household dysfunction, items included having to repeat a year of school and experiencing a parent causing problems in the family due to alcohol or drugs, all before age 18. Example items for abuse and household dysfunction were "Before you were 18 years old, were you ever physically abused by either of your parents?" and "Before you were 18 years old, did either of your parents drink or use drugs so often that it caused problems in the family?". Financial stress was assessed with a variety of items, including self-rated poor financial status, having to move to a different place or receiving help from relatives due to financial difficulties, and long-term unemployment of the father figure, all before age 16 – for example, "While you were growing up, did financial difficulties ever cause you or your family to move to a different place?". A binary variable was constructed based on high or low ACEs exposure, and participants with two or more ACEs were categorized as experiencing high exposure to ACEs.

While the level of detail regarding ACEs varies across the studies, the measures are common across the studies, with substantial overlap in survey item content and coverage. While

numerous studies have demonstrated associations of ACEs with health outcomes such as depression, systemic inflammation, and diabetes using the Add Health[89–92], MIDUS[90,93–99], and HRS datasets[100–105], thus validating the ACE measures offered by these studies, these data have not been used in conjunction with assessments of social isolation or job strain.

Social isolation: While the construct of social isolation is conceptually defined as the condition of being alone, the objective, direct indicators of social isolation are the frequency of social contacts and living status (i.e. living alone)[106–108]. It has been well established that the Berkman-Syme Social Network Index can be used to measure social isolation, asking if participants had regular contact with (i) both family members and friends (meeting in person, speaking on the phone, or writing/emailing), (ii) if they attended religious services, (iii) if they belonged to a social organization, club, or group, and (iv) if they lived alone[109]. Several earlier studies using data from the Add Health, MIDUS, and HRS studies have adapted this approach, showing promising findings regarding outcomes including all-cause mortality, hypertension, inflammation, and immune dysfunction[13,110–114].

In the Add Health study, items related to social isolation assessed household residence and marital status, and interactions with family, and religious services and activities. Example items included "How often do you and your mother or father figure see each other, talk on the telephone, exchange letters, or exchange email?", and "How often have you attended church, synagogue, temple, mosque, religious services, classes, retreats, small groups, or choir in the past 12 months?". Participants were scored on a scale of zero to four, depending on if they were married, if they lived alone, if they had at least weekly contact with family members, and if they had at least monthly religious service or activity attendance, and a social isolation score was constructed by reversing the resulting sum score. A binary variable with levels for high and low social isolation was

constructed, and participants with a social isolation score of three or more were categorized as having high exposure to social isolation.

In the MIDUS study, items measuring social isolation included marital status, frequency of contact with family and friends, frequency of religious service attendance, and meetings with unions, professional groups, sports and other social groups. Example items included “How often are you in contact with any of your friends – including visits phone calls, letters, electronic mail messages?”, and “In a typical month, about how many times do you attend meetings of religious groups?”. Participants were scored on a scale of zero to four, depending on if they were married, had at least weekly contact with both family and friends, at least monthly religious service attendance, and at least monthly contact with a group, and a social isolation score was calculated by reversing this resulting sum score. A binary variable for high or low social isolation was generated, and participants with a social isolation score of three or more were classified as socially isolated.

In the HRS study, social isolation measures included assessments of marital status, contact with family and friends, religious service attendance, and meetings with programs, groups, and social clubs. Example items included “How often do you have contact – either in person or by phone or mail – with your parents?” and “About how often have you attended religious services during the past year?”. Participants were assigned a score on a scale of zero to four depending on if they were married, if they had at least weekly contact with both family and friends, if they attended religious services at least monthly, and if they had at least monthly contact with a program, group, or social club. Similarly, a social isolation score was obtained by reversing the resulting sum score, and a dichotomous variable for high and low social isolation was created; participants with a social isolation score of three or more were considered socially isolated.

Job strain: Job strain is defined as per Karasek's Job Demand-Control model, namely the combination of high job demands with low job control[65]. In general, the Job Content Questionnaire (JCQ) is used to measure job strain[115]. Although the original survey items within the JCQ were not applied in the Add Health, MIDUS, and HRS studies, psychosocial work characteristics were measured in detail. Job demand and job control constructs have been validated across the three cohorts in several studies of physical and mental health, including suicide, stress, and cardiometabolic disease[11,13,116–121].

In the Add Health study, physical job demands were assessed with the item "In your current primary job, do you spend most of your time (1) standing, doing hard physical work, for example, doing construction work, (2) standing, doing moderate physical work, for example, nursing or being a mechanic, (3) standing, doing light physical work, for example, standing at a counter, teaching, or working at a conveyor belt, or (4) seated, for example, using a computer or driving. Job control was examined with two items – "Overall, how often do you have the freedom to make important decisions about what you do at work and how you do it?" and "How much of the time do you do the same things repeatedly, that is over and over?", with response categories "none or almost none of the time", "some of the time", "most of the time", and "almost all of the time". Job demand and job control were dichotomized into high and low groups by their median scores (1 and 3, respectively), and a binary job strain variable was generated, defined as the combination of high job demands with low job control. Job control and occupational strain related constructs in the Add Health study were validated in studies of worker stress and negative perceptions of work implicated in suicide[116,117], but no studies have assessed associations of job strain with CVD using the Add Health data.

In the MIDUS study, job demands were examined using five items (example item: “How often do you have to work intensively?”), and job control was assessed with nine items (example items: “How often do you learn new things at work?” “How often do you have a choice in deciding how you do your tasks at work?”). Responses for job demands and job control were recorded according to a 5-point Likert scale (1 = never, 5 = all of the time). The questionnaire items for job demands and job control in the MIDUS study are closely similar to those seen in the standard JCQ developed by Karasek[115], and have been implemented in previous publications using the MIDUS dataset[11–13]. Job demands and control were dichotomized into high and low groups by their median scores (16 and 34, respectively), and therefore binary job strain was defined as combined high job demands and low job control.

In the HRS study, job demands were measured with four items, with example items including “I am under constant time pressure due to a heavy workload” and “My job is physically demanding”, and job control was measured with three items, with example items such as “I have very little freedom to decide how I do my work” and “At work, I feel I have control over what happens in most situations”. Responses for job demands and job control were also recorded using a 4-point Likert scale (1 = strongly disagree, 4 = strongly agree). Again, job demands and control were dichotomized into high and low groups by their median scores (9 for both job demand and job control), and a binary job strain variable was constructed based on high job demands and low job control. Job strain data from the HRS study has been successfully implemented and validated in studies of hypertension, depression, drinking behavior, memory function, and long-term mortality[118–121].

Adulthood Psychosocial Disadvantages (APDS): While a handful of studies based on European datasets have attempted preliminary investigations of interactions between ACEs, job strain, and chronic disease in adulthood, findings were mixed and consistent, with no data from U.S populations[76,122–126]. Furthermore, while most prior studies of psychosocial exposures examined work and nonwork related factors separately, one study of Canadian workers found that a combined exposure matrix incorporating both work stress and social stress produced improved risk estimates for hypertension incidence over a 5-year follow-up period[127]. These data demonstrate that cumulative adulthood stress warrants further investigation, and thus the work and nonwork related exposures of social isolation and job strain were combined to form the construct of adulthood psychosocial disadvantages (APDs) as an index of cumulative adulthood stress.

This analytic approach to exposure assessment was designed to elicit the relative contributions of psychosocial exposures to cardiometabolic disease burden across the life course, examining ACEs in childhood and the construct of APDs in adulthood[13]. APDs were constructed identically across the Add Health, MIDUS, and HRS cohorts. APDs were defined as the combination of high job strain and/or high social isolation, resulting in a categorical variable with three levels—low (no disadvantages), moderate (one disadvantage, either high job strain or high social isolation), and high (two disadvantages, both high job strain and high social isolation).

Outcomes: Cardiovascular disease mortality.

The target outcome of interest was CVD mortality, including deaths from heart disease and stroke, and CVD data were available across all three cohorts. Furthermore, data on self-reported physician-diagnosed CVD were used to exclude participants with pre-existing CVD, thus increasing the robustness of CVD mortality analyses.

In the Add Health study, data on fatal CVD through 2019 were available via restricted-use dataset NDI record, with ICD codes I20-I25 and I30-I52 representing CVD mortality cases. Participants with pre-existing CVD at Add Health Wave IV were identified and excluded from analyses based on an affirmative response to the item "Has a doctor, nurse or other health care provider ever told you that you have or had: heart disease?".

In the MIDUS study, CVD mortality data through 2020 were available, also via linkage to the NDI records, with CVD mortality cases indicated by ICD 9 codes ranging from 4029 to 4439 and ICD 10 codes ranging from I10 to I776. Pre-existing CVD cases at MIDUS I were identified and removed from the study population via affirmative responses to either of two items: "Have you ever had a heart attack?" and "In the past 12 months, have you experienced or been treated for stroke?".

In the HRS study, CVD mortality data through 2018 were available biennially through exit interviews with surviving household members, with CVD mortality cases defined by ICD codes I121-129[128]. Nonfatal CVD was also assessed biennially in the HRS, and participants who responded affirmatively to any of the questions "In the last two years, have you had a heart attack or myocardial infarction?", "Has a doctor ever told you that you had a stroke, heart attack, coronary heart disease, angina, congestive heart failure, or other heart problems?" in either 2006 or 2008 were excluded from the sample based on pre-existing CVD.

NDI records across the three cohorts generally included variables specifying decedent status, source of decedent information, and the month, year, and cause of death.

2.2.3 Statistical Analysis

The investigation of psychosocial work and nonwork-related stressors and their association with risk of CVD mortality is the central outcome for this research project. Models included adjusted for the sociodemographic and lifestyle behavior covariates of age (continuous), sex, race, educational attainment, household income, current smoking, alcohol consumption, and physical exercise. To attain accurate measures of CVD mortality at follow-up, workers with CVD at baseline were excluded.

First, descriptive statistics were generated, and relative frequencies were examined for characteristics of the sample populations at baseline. Second, the prospective associations of ACE and APDs at baseline were assessed in independent, mutually-adjusted Cox proportional hazards regression models, and the results were expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). Multivariable models were calculated in three steps after unadjusted Model 0: Model I adjusted for age and sex; Model II included further adjustment for race, educational attainment, and annual household income; Model III additionally adjusted for current smoking, alcohol consumption, and physical exercise. Hypothesis tests were two-sided at the 5% α level. We tested for an interaction between ACEs and APDs with CVD mortality as the outcome, and further stratified analyses were conducted to assess effect modification by ACEs on associations between APDs and CVD mortality.

2.3 Results

2.3.1 Characteristics of the Sample Populations

The characteristics of the sample populations across the Add Health, MIDUS, and HRS cohorts are displayed in Tables 1-3.

In the Add Health study at Wave IV, the baseline time-point for this epidemiologic investigation, the sample of 23,263 working participants was made up of young to middle-aged adults, with a mean age of 29 and approximately equal numbers of men and women. They were primarily White (69.35%), with some inclusion of Black participants (24.70%) and limited representation of Asian (4.69%) and Other races (1.25%), had at least some college education, and most participants had an annual household income above $30,000. There was a high proportion of smokers in the sample (41.46%), but most participants reported low to moderate alcohol consumption (97.64%) and many engaged in high levels of physical activity (47.25%). The prevalence of high ACEs was 14.20%, while the prevalence of moderate to high APDs was approximately 57%. There were 37 cases of CVD mortality in the Add Health sample.

At the MIDUS I baseline study, the sample of 4,337 workers consisted of middle-aged adults with a mean age of 44 and similar numbers of men and women who were mostly White (90.39%), with limited numbers of Black (4.61%) and Other races (5.00%). Most participants had at least some college education and had an annual income over $45,000. There was a lower proportion of smokers (21.97%), and most participants engaged in low to moderate alcohol drinking (94.30%) and high levels of physical activity (68.23%). A high level of ACEs was reported by 40.81% of participants, and around 33% had moderate to high exposures to APDs. There were 150 cases of CVD mortality in the MIDUS sample.

In the 2006 and 2008 waves of the HRS study, the baseline time-point used for statistical analyses, the sample of 4,046 working participants had roughly equal numbers of men and women, with a slightly greater proportion of women (53.34%), and were older, with a mean age of 61. They were mostly White (80.55%), with some Black participants (12.14%) and small numbers of Other races (7.32%). They had more limited levels of educational attainment, with 61.05% having

completed high school or less, and generally had an annual household income of over $45,000. There was a low proportion of smokers (14.29%) and most participants had low or moderate alcohol consumption (96.59%) and high levels of physical activity (56.95%). The prevalence of high ACEs was 4.55%, and the prevalence of moderate to high APDs was 31.17%. There were 59 cases of CVD mortality in the HRS sample.

Table 1. Characteristics of the Sample Population at Add Health Wave IV (*N*=23,263)

Variables (*N*, %)	
Age (mean, SD)	28.71 (1.74)
Sex	
Male	11494 (49.41)
Female	11769 (50.59)
Race	
White	16134 (69.35)
Black	5747 (24.70)
Asian	1091 (4.69)
Others	291 (1.25)
Educational attainment	
University or more	6128 (26.34)
Some college	11415 (49.07)
High school or less	5720 (24.59)
Household income (annual U.S. dollars)	
< 30,000	4947 (21.27)
30,000-99,999	14879 (34.52)
≥ 100,000	3437 (14.77)
Smoking status	
No	13617 (58.54)
Yes	9646 (41.46)
Alcohol consumption	
Low to moderate drinking	22714 (97.64)
Heavy drinking	549 (2.38)
Physical activity	
High	10992 (47.25)

Moderate	6796 (29.21)
Low	1312 (5.64)
Adverse childhood experiences	
Low	19959 (85.80)
High	3304 (14.20)
Adulthood psychosocial disadvantages	
Low	9930 (42.69)
Moderate	12091 (51.67)
High	1312 (5.64)
Cardiovascular disease mortality	
No	23226 (99.84)
Yes	37 (0.16)

Table 2. Characteristics of the Sample Population at MIDUS I (*N*=4,337)

Variables (*N*, %)	
Age (mean, SD)	44.00 (11.07)
Sex	
Male	2250 (51.88)
Female	2087 (48.12)
Race	
White	3920 (90.39)
Black	200 (4.61)
Other	217 (5.00)
Educational attainment	
University or more	1570 (36.20)
Some college	1367 (31.52)
High school or less	1400 (32.28)
Household income (annual U.S. dollars)	
< 45,000	1483 (34.19)
45,000-89,999	1497 (34.52)
≥ 90,000	1357 (31.29)
Smoking status	
No	3384 (78.03)
Yes	953 (21.97)
Alcohol consumption	
Low to moderate drinking	4090 (94.30)
Heavy drinking	247 (5.70)
Physical activity	
High	2959 (68.23)
Moderate	894 (20.61)

Low	484 (11.16)
Adverse childhood experiences	
Low	2567 (59.19)
High	1770 (40.81)
Adulthood psychosocial disadvantages	
Low	2867 (66.11)
Moderate	1292 (29.79)
High	178 (4.10)
Cardiovascular disease mortality	
No	4187 (96.54)
Yes	150 (3.46)

Table 3. Characteristics of the Sample Population in the HRS, 2006-2008 (*N*=4,046)

Variables (*N*, %)	
Age (mean, SD)	61.16 (6.99)
Sex	
Male	1888 (46.66)
Female	2158 (53.34)
Race	
White	3259 (80.55)
Black	491 (12.14)
Other	296 (7.32)
Educational attainment	
University or more	1229 (30.38)
Some college	347 (8.68)
High school or less	2470 (61.05)
Household income (annual U.S. dollars)	
< 45,000	1594 (39.40)
45,000-89,999	1358 (33.56)
≥ 90,000	1094 (27.40)
Smoking status	
No	3468 (85.71)
Yes	578 (14.29)
Alcohol consumption	
Low or moderate drinking	3908 (96.59)
Heavy drinking	138 (3.41)
Physical activity	
High	2304 (56.95)
Moderate	481 (11.89)

Low	1261 (31.71)
Adverse childhood experiences	
Low	3862 (95.45)
High	184 (4.55)
Adulthood psychosocial disadvantages	
Low	2785 (68.83)
Moderate	1149 (28.40)
High	112 (2.77)
Cardiovascular disease mortality	
No	3987 (98.54)
Yes	59 (1.46)

2.3.2 Associations of ACEs and APDs with Cardiovascular Disease Mortality

Tables 4-6 demonstrate the results of the Cox proportional hazards regression models assessing the independent prospective associations of ACEs and APDs with CVD mortality in the Add Health, MIDUS, and HRS studies.

In the Add Health study, during 244,476 person-years of follow-up time across a 11-year follow-up period, 37 cases of CVD mortality were reported, representing an overall CVD mortality rate of 0.15 per 1000 person-years. CVD mortality rates were 0.14 and 0.23 per 1000 person-years among participants with low and high levels of ACEs, respectively. For APDs, CVD mortality rates were 0.06, 0.21, and 0.36 per 1000 person-years for low, moderate, and high levels of baseline APDs, respectively. While no significant associations of CVD mortality with ACEs reported at baseline were observed, moderate and high levels of APDs were significantly associated with CVD mortality (fully-adjusted HR and 95% CIs = 3.81 (1.54, 9.39) and 6.15 (1.81, 20.95)), respectively, compared to low levels of APDs.

In the MIDUS study, during 101,496 person-years of follow-up across a 28-year follow-up period, 150 cases of CVD mortality occurred, culminating in a total CVD mortality rate of 1.48 per 1000 person-years. CVD mortality rates were 1.29 and 1.76 per 1000 person-years in participants with low and high exposure to ACEs, respectively. For APDs, CVD mortality rates were 1.56, 1.29, and 1.44 per 1000 person-years, respectively. No significant associations with CVD mortality were detected for either ACEs or APDs.

In the HRS study, during 42,149 person-years of follow-up time across approximately 12 years of follow-up, 59 cases of CVD mortality were reported, constituting an aggregate CVD mortality rate of 1.40 per 1000 person-years. CVD mortality rates were 1.31 and 3.26 per 1000 person-years for participants with low and high levels of ACE exposure, respectively. CVD mortality rates for APDs were 1.16, 1.63, and 5.34 for low, moderate, and high levels of ADPs, respectively. Compared to low ACE exposure, high ACE exposure was significantly associated with increased CVD mortality (fully-adjusted HR and 95% CI = 3.49 (1.46, 8.36)). High levels of APDs were also significantly associated with CVD mortality, compared to low levels of APDs (fully-adjusted HR and 95% CI = 6.01 (2.43, 14.89)).

Table 4. Independent Prospective Associations of Adverse Childhood Experiences (ACEs), Adulthood Psychosocial Disadvantages (APDs) at Add Health Wave IV with Cardiovascular Disease Mortality (HRs and 95% CIs) (*N* = 23,263)

	Number of exposed participants (number of cardiovascular disease mortality cases)	Cardiovascular disease mortality rate (per 1,000 person-years)	Model I	Model II	Model III
Adverse Childhood Experiences					
Low	19959 (29)	0.14	1.00	1.00	1.00
High	3304 (8)	0.23	1.95 (0.89, 4.28)	1.89 (0.85, 4.20)	1.71 (0.77, 3.82)
Adulthood Psychosocial Disadvantages					
Low	9930 (6)	0.06	1.00	1.00	1.00
Moderate	12021 (26)	0.21	3.72 (1.51, 9.14)**	3.31 (1.35, 8.13)**	3.81 (1.54, 9.39)**
High	1312 (5)	0.36	6.47 (1.92, 21.77)**	5.82 (1.73, 19.61)**	6.15 (1.81, 20.95)**

CI, confidence interval; HR, hazard ratio.
Cox proportional hazards regression, ** $p < 0.01$.
Model I: adjustment for age and sex at baseline.
Model II: Model I + additional adjustment for race, educational attainment, and household income at baseline.
Model III: Model II + additional adjustment for smoking, alcohol consumption, and physical exercise at baseline.

Table 5. Independent Prospective Associations of Adverse Childhood Experiences (ACEs), Adulthood Psychosocial Disadvantages (APDs) at MIDUS I with Cardiovascular Disease Mortality (HRs and 95% CIs) (*N* = 4,337)

	Number of exposed participants (number of cardiovascular disease mortality cases)	Cardiovascular disease mortality rate (per 1,000 person-years)	Model I	Model II	Model III
Adverse Childhood Experiences					
Low	2567 (78)	1.29	1.00	1.00	1.00
High	1770 (72)	1.76	1.27 (0.92, 1.75)	1.20 (0.87, 1.66)	1.05 (0.76, 1.46)
Adulthood Psychosocial Disadvantages					
Low	2867 (105)	1.56	1.00	1.00	1.00
Moderate	1292 (39)	1.29	1.04 (0.72, 1.50)	0.96 (0.66, 1.40)	0.85 (0.58, 1.25)
High	178 (6)	1.44	1.39 (0.61, 3.17)	1.09 (0.48, 2.52)	0.74 (0.32, 1.72)

CI, confidence interval; HR, hazard ratio.
Cox proportional hazards regression.
Model I: adjustment for age and sex at baseline.
Model II: Model I + additional adjustment for race, educational attainment, and household income at baseline.
Model III: Model II + additional adjustment for smoking, alcohol consumption, and physical exercise at baseline.

Table 6. Independent Prospective Associations of Adverse Childhood Experiences (ACEs) and Adulthood Psychosocial Disadvantages (APDs) with Cardiovascular Disease Mortality in the HRS 2006-2008 (HRs and 95% CIs) (*N* = 4,046)

	Number of exposed participants (number of cardiovascular mortality cases)	Cardiovascular disease mortality rate (per 1,000 person-years)	Model I	Model II	Model III
Adverse Childhood Experiences					
Low	3862 (53)	1.31	1.00	1.00	1.00
High	184 (6)	3.26	3.67 (1.56, 8.62)**	3.92 (1.66, 9.26)**	3.49 (1.46, 8.36)**
Adulthood Psychosocial Disadvantages					
Low	2751 (34)	1.16	1.00	1.00	1.00
Moderate	1130 (19)	1.63	1.54 (0.88, 2.71)	1.55 (0.88, 2.73)	1.50 (0.85, 2.65)
High	106 (6)	5.34	6.21 (2.58, 15.00)****	6.76 (2.76, 16.56)****	6.01 (2.43, 14.89)***

CI, confidence interval; HR, hazard ratio.
Cox proportional hazards regression, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$.
Model I: adjustment for age and sex at baseline.
Model II: Model I + additional adjustment for race, educational attainment, and household income at baseline.
Model III: Model II + additional adjustment for smoking, alcohol consumption, and physical exercise at baseline.

2.3.3 Associations of ACEs and APDs with Cardiovascular Disease Mortality, Stratified by ACEs Exposure Level

A significant interaction between ACEs and APDs with CVD mortality as the outcome was observed in the Add Health study ($p < 0.01$), but not in the MIDUS or HRS studies. Tables 7-9 exhibit the results of the stratified analyses by ACE exposure level, thus assessing effect modification of the association between APDs with CVD mortality by ACEs in the Add Health, MIDUS, and HRS studies.

In the Add Health cohort, among participants with low levels of ACEs, CVD mortality rates were 0.07, 0.16, and 0.43 per 1000 person-years for low, moderate, and high levels of APDs, respectively, and exposure to a high level of APDs was significantly associated with CVD mortality (fully-adjusted HR and 95% CI = 5.42 (1.58, 18.61)), compared to low APDs. Among participants with high levels of ACEs, there were no cases of CVD mortality in the low or high exposure groups, precluding the computation of hazard estimates.

In the MIDUS study, in participants with low levels of ACEs, CVD mortality rates were 1.44, 0.95, and 0.91 per 1000 person-years for low, moderate, and high levels of APDs, respectively. In participants with high levels of ACEs, CVD mortality rates were 1.77, 1.72, and 2.05 per 1000 person-years, respectively. The stratified associations of APDs with CVD mortality were not significant across both high and low levels of ACE exposures.

In the HRS Study, among participants with low exposure to ACEs, the CVD mortality rates were 1.03, 1.62, and 5.98 per 1000 person-years for low, moderate, and high levels of APDs, respectively. Among participants with high exposure to ACEs, CVD mortality rates were 4.30, 1.79, and 0.00 per 1000 person-years for low, moderate, and high levels of APDs,

respectively. Among participants with low ACEs exposure, significant associations of high APDs with increased CVD mortality risk were observed (fully-adjusted HR and 95% CI = 5.49 (2.28, 13.23). However, the limited number of participants in the high ACEs exposure group and the lack of cases of CVD mortality in the high APDs group prevented model convergence and retrieval of hazard estimates.

Table 7. Independent Prospective Associations of Adulthood Psychosocial Disadvantages at Add Health Wave IV with Cardiovascular Disease Mortality, Stratified by ACEs Exposure (HRs and 95% CIs) (*N*=23,263)

	Number of exposed participants (number of cardiovascular disease mortality cases)	Cardiovascular disease mortality rate (per 1,000 person-years)	Model I	Model II	Model III
			Adverse Childhood Experiences (low) (*N* = 19,959)		
Adulthood Psychosocial Disadvantages					
Low	8380 (6)	0.07	1.00	1.00	1.00
Moderate	10478 (18)	0.16	2.23 (0.88, 5.66)	2.11 (0.83, 5.37)	2.47 (0.96, 6.33)
High	1101 (5)	0.43	6.20 (1.83, 20.94)**	5.42 (1.58, 18.61)**	5.59 (1.61, 19.41)**
			Adverse Childhood Experiences (high) (*N* = 3304)		
Adulthood Psychosocial Disadvantages					
Low	1550 (0)	0.00	1.00	1.00	1.00
Moderate	1535 (8)	0.50	-	-	-
High	211 (0)	0.00	-	-	-

CI, confidence interval; HR, hazard ratio.
Cox proportional hazards regression, ** $p < 0.01$.
Model I: adjustment for age and sex at baseline.
Model II: Model I + additional adjustment for race, educational attainment, and household income at baseline.
Model III: Model II + additional adjustment for smoking, alcohol consumption, and physical exercise at baseline.

Table 8. Independent Prospective Associations of Adulthood Psychosocial Disadvantages at MIDUS I with Cardiovascular Disease Mortality, Stratified by ACEs Exposure (HRs and 95% CIs) (N=4,337)

	Number of exposed participants (number of cardiovascular disease mortality cases)	Cardiovascular disease mortality rate (per 1,000 person-years)	Model I	Model II	Model III
			Adverse Childhood Experiences (low) (*N* = 2,567)		
Adulthood Psychosocial Disadvantages					
Low	1758 (60)	1.44	1.00	1.00	1.00
Moderate	716 (16)	0.95	0.80 (0.46, 1.40)	0.77 (0.44, 1.35)	0.65 (0.37, 1.15)
High	93 (2)	0.91	1.00 (0.24, 4.10)	0.77 (0.19, 3.20)	0.34 (0.07, 1.54)
			Adverse Childhood Experiences (high) (*N* = 1770)		
Adulthood Psychosocial Disadvantages					
Low	1109 (45)	1.77	1.00	1.00	1.00
Moderate	576 (23)	1.72	1.30 (0.78, 2.16)	1.18 (0.71, 1.97)	1.16 (0.69, 1.95)
High	85 (4)	2.05	1.74 (0.62, 4.87)	1.32 (0.46, 3.77)	0.99 (0.34, 2.87)

CI, confidence interval; HR, hazard ratio.
Cox proportional hazards regression.
Model I: adjustment for age and sex at baseline.
Model II: Model I + additional adjustment for race, educational attainment, and household income at baseline.
Model III: Model II + additional adjustment for smoking, alcohol consumption, and physical exercise at baseline.

Table 9. Independent Prospective Associations of Adulthood Psychosocial Disadvantages at HRS 2006-2008 with Cardiovascular Disease Mortality, Stratified by ACEs Exposure (HRs and 95% CIs) (N=4,046)

	Number of exposed participants (number of cardiovascular disease mortality cases)	Cardiovascular disease mortality rate (per 1,000 person-years)	Model I	Model II	Model III
			Adverse Childhood Experiences (low) (*N* = 3,862)		
Adulthood Psychosocial Disadvantages					
Low	2669 (29)	1.03	1.00	1.00	1.00
Moderate	1092 (18)	1.62	1.73 (0.96, 3.13)	1.75 (0.97, 3.17)	1.53 (0.85, 2.75)
High	101 (6)	5.98	7.67 (3.24, 18.71)****	8.43 (3.39, 20.97)****	5.49 (2.28, 13.23)***
			Adverse Childhood Experiences (high) (*N* = 184)		
Adulthood Psychosocial Disadvantages					
Low	116 (5)	4.30	1.00	1.00	1.00
Moderate	57 (1)	1.79	0.36 (0.04, 3.19)	0.28 (0.03, 2.54)	0.22 (0.02, 2.17)
High	11 (0)	0.00	-	-	-

CI, confidence interval; HR, hazard ratio.
Cox proportional hazards regression, *** $p < 0.001$, **** $p < 0.0001$.
Model I: adjustment for age and sex at baseline.
Model II: Model I + additional adjustment for race, educational attainment, and household income at baseline.
Model III: Model II + additional adjustment for smoking, alcohol consumption, and physical exercise at baseline.

2.4 Discussion

This secondary data analysis of the large, population-based, nationally representative Add Health, MIDUS, and HRS studies examined the prospective associations of ACEs and APDs with CVD mortality. ACEs were significantly associated with CVD mortality in the HRS study, and APDs were significantly associated with CVD mortality in the Add Health and HRS studies. Furthermore, while hazard estimates did not always reach statistical significance, a stable trend of increased CVD mortality rates with increased ACEs exposure was observed across all three cohorts. In the stratified analyses, sample sizes for the high ACEs groups were small, with very few cases of CVD mortality – thus, we were unable to calculate HRs for high ACEs groups. Together, these results suggest a pathological influence of psychosocial stressors in the etiology of CVD. Our hypotheses were therefore partially supported by the findings.

The significant associations of ACEs with CVD mortality detected in the HRS sample are consistent with the literature on the adverse cardiometabolic health impacts of ACEs exposure. The primary reason for the detection of significant associations of ACEs with CVD mortality in the HRS studies compared to the Add Health and MIDUS studies may be the older mean age of the sample (61 versus 29 and 44, respectively), as the risk of cardiometabolic conditions increases with age[129,130]. In a study of over 130,000 Chinese adults, socioeconomic and psychosocial risk factors were found to be prominent determinants of CVD outcomes among participants aged 55 years or above, accounting for 27% of the population attributable risk for mortality[131]. Therefore, the restriction of the analytic sample to the working population may have limited the ability to detect significant associations.

Review studies assaying evidence on ACEs and CVD later in life have reported that adults with high exposure to ACEs have a "more than 2-fold higher risk of developing CVD and an almost 2-fold higher risk of premature mortality"[30]. ACEs are widely implicated in cardiometabolic health conditions, including clinically proven risk factors for CVD such as hypertension[13,29,132]. The AHA has also published scientific statements acknowledging ACEs as a social determinant of CVD risk and cardiometabolic health outcomes and calling for targeted longitudinal investigations – this project suitably addressed this call for further research by providing survival analysis data from prospective cohort studies[29,54].

Such findings provide preliminary evidence in support of the "chains of risk" model, where an early stress exposure might lead to further stressful experiences later in life[40–42]; ACEs may lead to more adverse working conditions and augment perceptions of stressful work environments in adulthood[133]. ACEs may also lead to impaired social functioning in adolescence and adulthood, based on neurobiological evidence showing disruptions of neural networks involved in social functioning[134]. This has been documented to lead to deficits in processing social cues and body language such as facial expressions, with neuroimaging studies of physically abused children showing effects of bias towards angry faces and negative emotions[135–138]. Alternative explanations explored by life-course exposure models[40,139] and the "biological embedding" model of stress and disease posit that early childhood is a critical period that greatly influences responses to environmental and psychosocial stressors later in life[140,141]. Long-term biological consequences of ACEs include disruption of regulatory and homeostatic mechanisms, including the immune, metabolic, neuroendocrine, and autonomic nervous systems[142]. ACEs have been shown to produce chronic inflammation, as evidenced by elevated proinflammatory signaling molecules such as interleukin-6, CRP, and fibrinogen[95,143,144].

The increased CVD mortality observed with high APDs representing exposure to social isolation and job strain are largely in accordance with prior investigations of such psychosocial exposures and CVD. Social isolation has a plethora of effects that undermine an individual's health and overall well-being, with recent data aggregated in a comprehensive report disseminated by the U.S. Surgeon General[64]. Indeed, evidence illustrates a strong connection between social isolation and heart disease and stroke outcomes, with many studies demonstrating significant increases in morbidity and mortality[145–148]. Estimates for the effect of social isolation range from 30-50% for increased risk of heart disease and stroke[7,27], as well as drastically increased risk of hospitalization (68%) and emergency department visits (57%) related to chronic cardiovascular conditions[149]. The increased risk of death and healthcare use associated with social isolation clearly demonstrate clinical relevance in CVD.

There is also a pragmatic element of social isolation that is relevant to CVD outcomes – instances of fatality from myocardial infarction are less likely when household members or social contacts are able to provide immediate help and calls for medical attention. In context of population-level demographic trends apparent in the U.S., where the percentage of single-person households reached 29% in 2022, these data call attention to social isolation as an urgent and pressing issue of public health significance. The rapidly increasing prevalence of social isolation in the U.S. and the burgeoning body of literature on associated cardiovascular health consequences prompted the AHA to issue a 2022 statement underscoring social isolation as a "common, yet underrecognized determinant of cardiovascular health and brain health"[148].

Job strain has also been strongly substantiated as a major risk factor for CVD and worsened CVD mortality outcomes. A review of evidence from over 600,000 adults from 27 studies across the U.S., Europe, and Japan found that occupational stressors such as job strain

were associated with an up to 40% increased risk of incident coronary heart disease and stroke[8]. Meta-analyses of over 190,000 participants from 13 European cohort studies found robust associations of job strain with coronary heart disease and stroke, with the population attributable risk for coronary heart disease due to job strain estimated at 3.4%[67,68]. Similarly, a multicohort study drawing on data from Finland, France, Sweden, and the United Kingdom with over 100,000 individuals found evidence for excess CVD mortality risk among participants with prevalent cardiometabolic diseases at baseline[66]. These data highlight the importance of including novel and psychosocial exposures such as APDs in investigations of CVD mortality in working populations.

Prior analyses of the MIDUS data also reported increased risk of CVD mortality with increased job strain[11], as well as increased risk of hypertension with both ACEs and the APDs of social isolation and job strain[13,71]. The stratified analyses of APDs by ACEs exposure did not produce significant associations, which is consistent with a Finnish study and an analysis of the Whitehall II study, which found that pre-employment factors such as early life adversity did not moderate associations of job strain with CVD[76,126].

Strengths

The major strengths of this study are founded upon the large, population-based, nationally representative sample populations that cover the entirety of the life course from childhood to old age, via the integrated use of the Add Health, MIDUS, and HRS datasets. The samples included strong representation of sociodemographic ranges and occupations and provided long follow-up lengths ranging from 12 to 25 years, thus addressing limitations of previous studies and the lack of longitudinal cohort data highlighted by the AHA's 2022 scientific statement on ACEs[29].

Furthermore, the measures used were detailed and reliable; job strain measures generally adhered to Karasek's well-established model job strain[65], especially the measures used in the MIDUS study, which are closely similar to the original JCQ devised by Karasek[115], and the well-validated Berkman-Syme Social Network Index was utilized to assess social isolation[150]. ACE measures across the studies were also rich and detailed, with the additional advantage of the Add Health dataset offering prospective rather than only retrospective accounts of ACEs. Mortality data were also detailed, reliable, and valid, based on linkage to NDI records. The datasets also provided data on sociodemographic characteristics that were used to account for potential confounders, including smoking, alcohol consumption, and physical exercise.

Limitations

There are several limitations of this study that may have impacted the findings. While the reliability of adult retrospective reports of ACEs has also come under question due to potential recall bias, studies assessing retrospective reports have observed robust test-retest reliability ranging from 0.45 to 0.90, and adequate kappa coefficients ranging from 0.52 to 0.72[84,85] – this limitation is also somewhat addressed by the inclusion of prospective ACE data from the Add Health study. Similarly, because all exposure data was collected at baseline, the results may be influenced by exposure misclassification bias due to the possibility of changes in the APDs of social isolation and job strain during follow-up.

Additionally, while the sample populations were large and included a broad range of demographic strata, most participants were White, with limited representation of Black and other racial groups, limiting the generalizability of the results. Future studies with better representation of racial and ethnic minorities would allow for further extrapolation and comparison of results with broader populations. Finally, while these findings showed significant associations of ACEs

and APDs with CVD mortality, they raise further questions regarding the biological mechanisms underlying such observations and the means by which such exposures impact cardiometabolic health. Hence, the contributions of ACEs and APDS to manifested diseases and relevant biomarkers deserve further investigation.

2.5 Conclusions and Future Directions

In this secondary data analysis of the large, population-based, nationally-representative Add Health, MIDUS, and HRS cohorts, ACEs and APDs were significantly associated with increased risk of CVD mortality in a subset of the samples. Detailed measures of early life adversity and social isolation and job strain in midlife were used to construct comprehensive exposure assessments of work and nonwork related factors implicated in CVD outcomes, and associations of ACEs and APDs with CVD mortality were assessed via Cox proportional hazards regression modeling. These findings add to the weight of evidence identifying psychosocial exposures as clinically relevant risk factors for CVD.

The findings resulting from this project can be further clarified and cross-validated through comparison with additional international datasets. For instance, the PsyCoLaus study in Switzerland[151], the Whitehall II study in the United Kingdom[152], and the Danish Work Life Course Cohort study (DaWCo) in Denmark[153] are ongoing cohort studies in Europe that include assessments of psychosocial exposures with life-course perspectives and CVD risk. These datasets offer a promising avenue for iterative future work expanding on this current project, increasing the generalizability of the results and overall scientific rigor as a multi-cohort, multi-national research project. Ultimately, this project establishes a rationale and justification for a continuum of future translational and interventional work targeting a broad spectrum of the adverse health effects posed by stressors across the life-course.

3. Aim 2: Identify psycho-physiological mechanistic pathways reflecting allostatic load, linking ACEs, social isolation, and job strain with CVD.

3.1.1 Hypothesis

The hypothesis to be tested is that exposure to psychosocial stressors increases allostatic load, operationalized via a profile of cardiometabolic biomarkers implicated in CVD.

3.1.2 Overview

While an expansive body of literature has repeatedly documented robust associations of ACEs, social isolation, and job strain with CVD risk, there is a comparative dearth of evidence illuminating the physiological mechanisms responsible for such observations. Hence, this project also aims to bridge this knowledge gap by identifying mechanistic factors and further substantiating the observed associations by examining cardiometabolic biomarkers and allostatic load.

In outlining the trajectory of current and anticipated needs in occupational health research, NORA has underscored the necessity to "better understand the mechanisms by which occupational factors may be associated with initiating CVD or contributing to its progression"[43]. While the relationship between psychosocial stressors and pathological outcomes such as CVD is well-evidenced, there has been limited appraisal of the mechanisms underlying these associations. A growing body of evidence has suggested that allostatic load, a measure of "wear and tear" on the body, has a primary mediating role in associations of psychosocial exposures with disease[154–156].

The construct of allostatic load captures the cumulative effects of stress on psychophysiological functioning, as indicated by cardiometabolic and inflammatory biomarkers that indicate stress-induced aberrations from homeostasis[154]. For example, ACEs have been shown

to potentiate the effects of stress in adulthood, resulting in "cumulative physiological dysregulation"[157–159]. Furthermore, social isolation is associated with endocrine and immune system dysfunction, with studies reporting outcomes such as a flattened diurnal cortisol slope and high levels of C-reactive protein (CRP), an inflammatory biomarker[106]. For job strain, studies have demonstrated robust associations with components of allostatic load such as increased blood pressure, altered blood lipids, and elevated cortisol release[160–164].

While these studies have identified respective associations of ACEs, social isolation, and job strain with allostatic load, and one study in 2012 found increased allostatic load among individuals who experienced both adolescent adversity at age 16 and job strain in mid-life[123], no study has examined the tripartite combined or interactive effects of these psychosocial stressors on allostatic load. Prior studies have used SES as a nonspecific general indicator of cumulative allostatic load[165], but the cumulative effects of psychosocial exposures on allostatic load have not been investigated, comprising an additional research gap.

This project expands the secondary analyses of the Add Health, MIDUS, and HRS datasets via the systematic investigation of cardiometabolic biomarkers and allostatic load in the context of ACEs, social isolation, and job strain. Critically, evaluating the role of allostatic load in the relationships of ACEs, social isolation, and job strain provides objective, physiological evidence of their adverse impacts, complementing the subjective, self-reported questionnaire data collected from the participants regarding their experiences of these psychosocial stressors. Correlating data gained from self-report measures with physiological parameters indexing allostatic load offers an empirical verification of the psychobiological impacts of ACEs, social isolation, and job strain. Achievement of this aim outlines a trajectory linking psychosocial exposures with CVD outcomes – fully evidenced by mechanistic pathways – across the life-course.

These analyses offer the opportunity to delineate the relative contributions of psychosocial stressors to biological pathways implicated in CVD at different points in life, addressing questions raised by previous studies about the extent to and mechanisms by which events or exposures in childhood and adulthood lead to pathological outcomes. For example, the early critical period hypothesis of development posits that early life stress has a greater influence on health outcomes than stressors at later points in life[166]. Importantly, the analytical models have the potential to demonstrate which stressors, and at which life stage, are most influential in the context of allostatic load and CVD. Revealing the interaction and relative contributions of each stressor at each life stage with CVD biomarkers allows for improved estimates of population attributable risk.

3.1.3 Literature Review

The perturbations of inflammatory processes involved in allostatic load are indicative of hypothalamic-pituitary-adrenal (HPA) axis dysregulation, thus presenting a common psychophysiological pathway between ACEs, social isolation, and job strain[158]. Other possible mechanistic pathways underlying associations of stressors with health consequences include the chronic overactivation of the sympathetic nervous system and the dysregulation of immune function[167,168]. The assessment of allostatic load allows for the detection of physiological conditions that constitute cardiometabolic risk factors, which are proven to have a causal role in the development of CVD. Identifying the mechanisms underlying the associations of ACEs, social isolation, and job strain with CVD observed in the literature demonstrates biological plausibility and elucidates the causal role of psychosocial exposures in CVD, as well as identifying suitable targets for intervention.

An extensive literature characterizes the role of ACEs in allostatic load, positing that early life stress leads to chronically elevated allostatic load and worsened health outcomes later in

life[169,170]. The concept of allostatic load offers an instrumental framework for the study of long-term health consequences stemming from traumatic experiences, both in childhood and later in life. Data from the landmark "ACE Study" of over 17,000 participants presented both population-level epidemiological and mechanistic neurobiological evidence of persistent health effects across the life course[140]. ACEs demonstrated a strong, dose-dependent relationship with both the prevalence and risk of 18 physical and mental health outcomes, including depression, anxiety, obesity, and illicit drug use.

Evidence also suggests a possible influence of ACEs on health behaviors, social support systems, and psychological coping mechanisms, which serve as mediating pathways between childhood adversity and impaired health in adulthood[169,171]. Furthermore, recent data from a study of over 25,000 Canadian participants indicated that both social engagement and allostatic load were significantly associated with multimorbidity of chronic disease conditions in adulthood[171]. These findings demonstrate the need to integrate analyses of ACEs and allostatic load with assessments of social isolation. However, this large study did not account for potential confounders such as SES or health behaviors, representing a severe methodological limitation that the current project ameliorates.

Social isolation has also been proven as a social determinant of health, with pervasive impacts on both allostatic load and CVD mortality. In a study of over 4,000 adults from the Monitoring of Trends and Determinants in Cardiovascular Disease/Cooperative Health Research in the Region of Ausburg (MONICA/KORA) cohort study, allostatic load was found to be a significant predictor of CVD mortality, and the psychosocial factor of social isolation was a significant risk factor for stroke mortality; in this analysis, no significant associations of job strain with CVD mortality were captured[172]. Indeed, social isolation has such pronounced influences on

CVD outcomes that clinical investigators have argued for the inclusion of social connectedness in primary-care screening protocols for CVD, with a systematic review of 20 studies providing overwhelming support for social isolation as a risk factor for increased allostatic load[173].

Studies of the relationship between ACEs exposure and social isolation also suggest that the deleterious impacts of ACEs are strongly mediated by social support and overall adulthood stress[41]. This evidence substantiates a pathway by which participants subjected to both high ACEs and social isolation may have increased allostatic load and risk for cardiometabolic disease conditions. Such mediation analyses assessing the role of social support and general chronic stressors in adulthood call attention to psychosocial exposures in other domains of life that may exert a strong influence on allostatic load, namely occupational exposures such as job strain.

The relationship between job strain and allostatic load is strongly substantiated, with a number of large cohort studies showing clinically relevant elevations in allostatic load biomarkers among participants experiencing high job strain[123,172,174–176]. Allostatic load has captured significant research attention as a mediator of the association between psychosocial risk factors and CVD, with more pronounced impacts among workers already experiencing stress due to sleep impairment, depression, or low physical activity[174]. In a study of over 90,000 working adults in France, adverse employment histories and job strain indices were significantly related to elevated allostatic load based on a composite profile of ten blood-based biomarkers[176]. Similarly, a pilot study of job strain and CVD biomarkers among paramedics reported associations of job strain and shift work with elevated allostatic load, as indicated by flattened cortisol diurnal slopes and overall increased daily cortisol secretion, reduced salivary amylase, and impaired circulatory system function[160].

While studies have provided evidence associations of psychosocial stressors with cardiometabolic health outcomes such as CVD mortality and allostatic load, most prior investigations assessed only single components of the integrated exposure model proposed in this project, examining the individual and separate ACEs, social isolation, or job strain. One study found that social adversity in adolescence increased physiological vulnerability to job strain in adulthood based on the allostatic load markers of body fat, blood pressure, inflammatory markers, glucose, blood lipids, and cortisol regulation[123]. Job strain was only associated with allostatic load among participants who had experienced early life adversity, showing direct evidence for increased biological vulnerability to psychosocial stressors due to developmental stressors. Studies assessing combined exposures of job strain with social stressors in adulthood have also presented evidence for interactive effects, with an analysis of 7,000 British civil servants from the Whitehall II cohort study reporting the strongest increases in allostatic load among participants subjected to both high job strain and high caregiving burden[175].

The exposure modeling framework implemented in this project expands upon previous analyses by identifying biologically plausible pathways that potentially underlie the previously observed associations of ACEs and APDs with CVD mortality. This project has the capacity to offer psychophysiological and mechanistic explanations for the excess CVD mortality risk linked to the psychosocial exposures of ACEs and APDS.

3.2 Methodology

3.2.1 Study Sample and Design

The study design for this secondary data analysis of the Add Health, MIDUS, and HRS cohorts investigating associations of ACEs and APDs with allostatic load utilizes additional

biomarker data collected from a subset of participants. The objective was to identify potential biological pathways underlying the previously observed associations of early and mid-life stressors with CVD mortality. The Add Health, MIDUS, and HRS cohorts included measures of cardiometabolic and inflammatory biomarkers linked to a host of chronic disease conditions.

The Add Health and HRS cohorts included biomarker data at baseline, providing data for both cross-sectional and longitudinal components of analyses. Associations of ACEs with allostatic load were longitudinal, whereas associations of APDs with allostatic load were cross-sectional. The MIDUS cohort included a subsample in MIDUS II (2004-2006) that underwent detailed laboratory and instrumental testing of anthropometric and cardiovascular metrics, allowing for longitudinal analysis of both ACEs and APDs. In the Add Health study, biomarker data were collected during Wave IV in 2008, and biomarker data were available for the majority of the sample population. The MIDUS Biomarker Project was conducted from 2004-2009, where individuals who had participated in MIDUS I were invited for further laboratory assessments[177]. The MIDUS II biomarker sample also included indices of heart-rate variability (HRV), allowing for further investigations of associations of stress with cardiovascular reactivity (for details, please see below). In the HRS study 2006-2008, biomarker data were also collected for a large proportion of the sample population.

In order to improve the accuracy of analyses, in a similar procedure as detailed previously, participants with pre-existing CVD at baseline were excluded from the sample population.

At Wave IV of the Add Health study, out of the 23,236 participants who were working and had full data on ACEs, APDs, and covariates, a total of 19,897 participants had complete

data on the biomarkers indexed. The process of sample size selection for the Add Health Biomarker Sample is shown in Figure 5.

The MIDUS II biomarker subsample comprised of 771 participants who were working in MIDUS I and had complete data on ACEs, APDs, and covariates. The sample size selection procedure for the MIDUS biomarker sample is detailed in Figure 6.

In the HRS study 2006-2008, of the 4,046 participants who were working and had full data on ACEs, APDs, and covariates, the final analytic sample with complete biomarker data yielded 3,837 participants. The process of sample size selection for the HRS biomarker sample is shown in Figure 7.

Figure 5. Sample Size Selection Flowchart for the Add Health Study Biomarker Sample

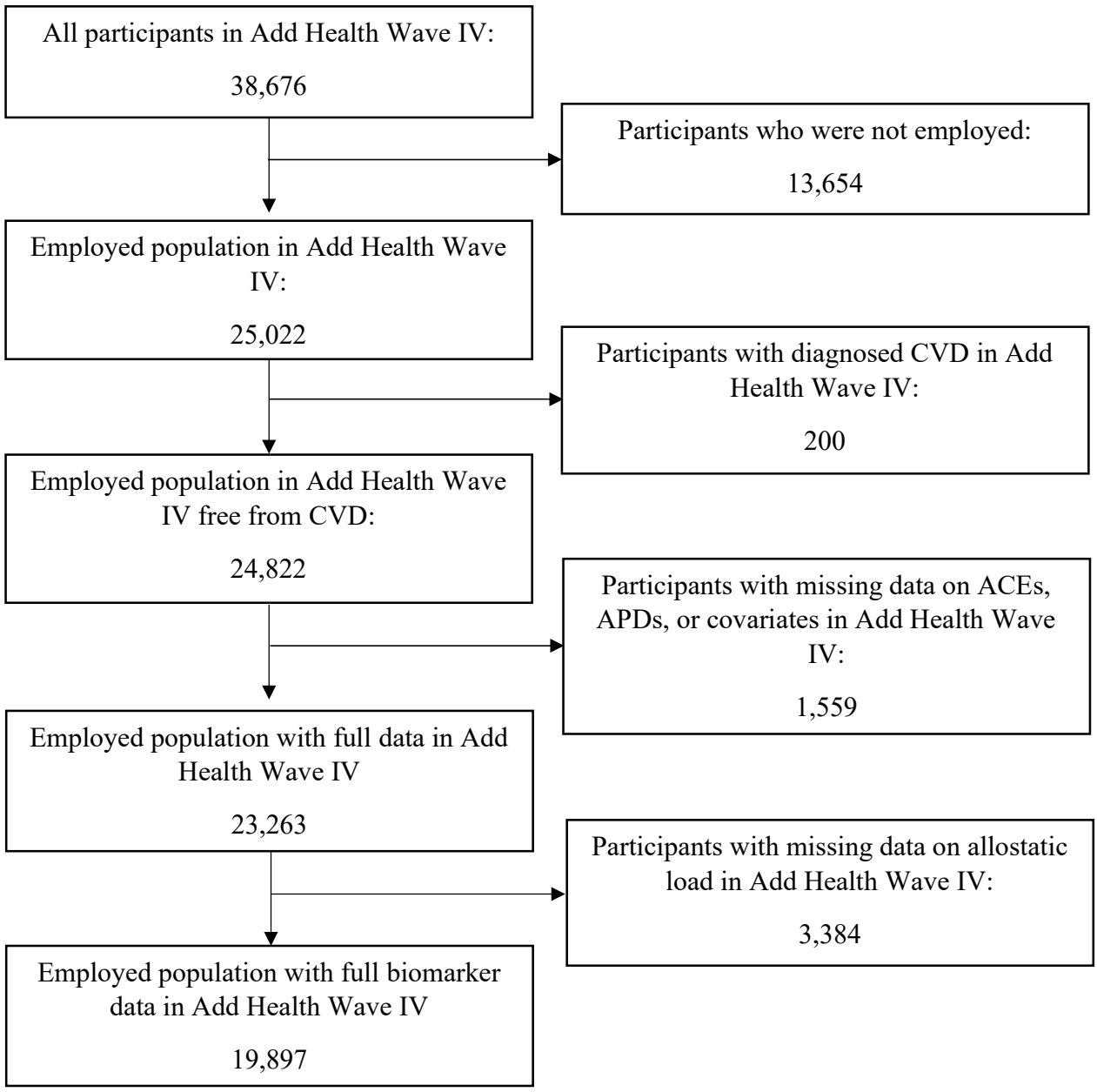


Figure 6. Sample Size Selection Flowchart for the MIDUS Study Biomarker Sample

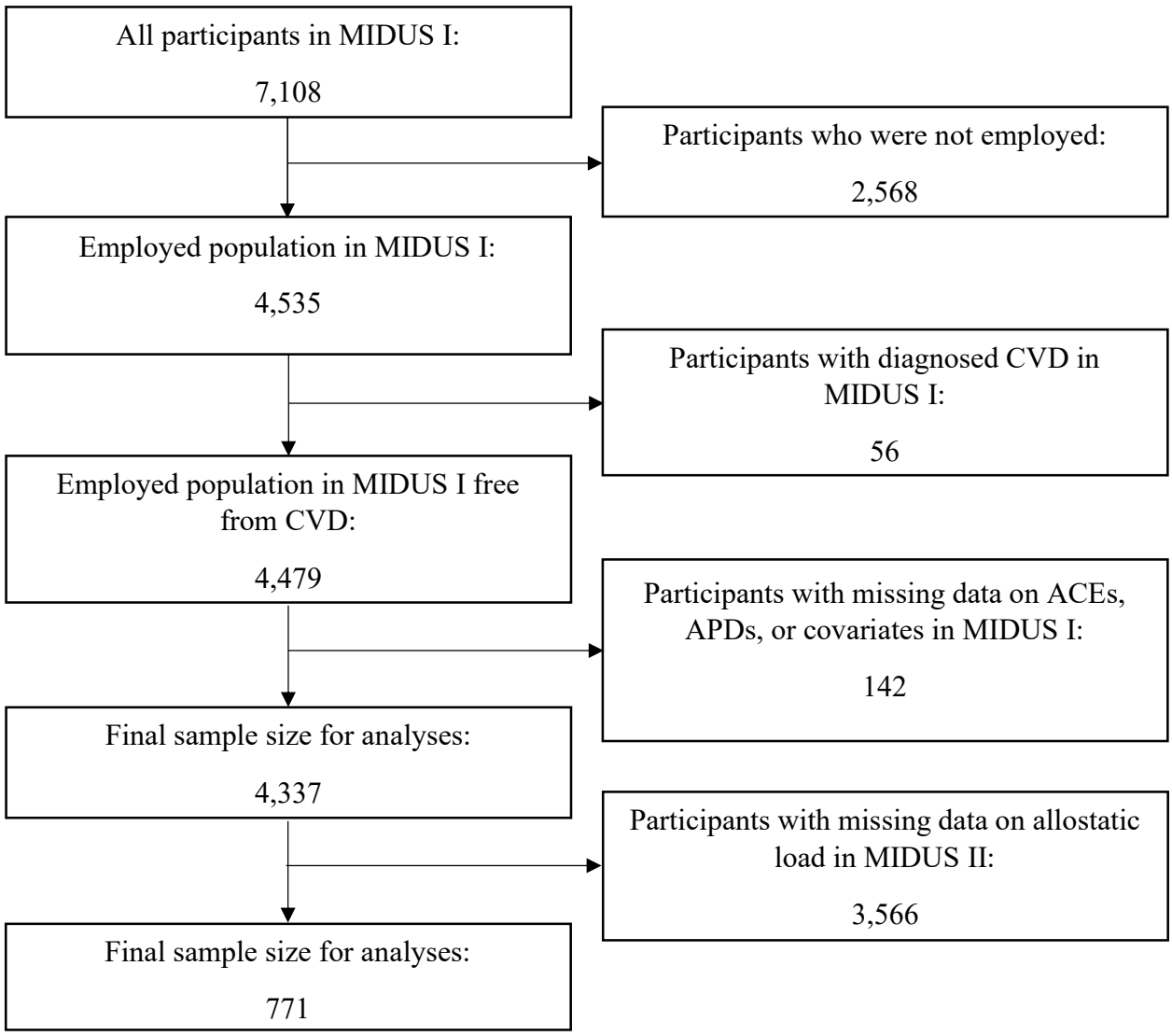
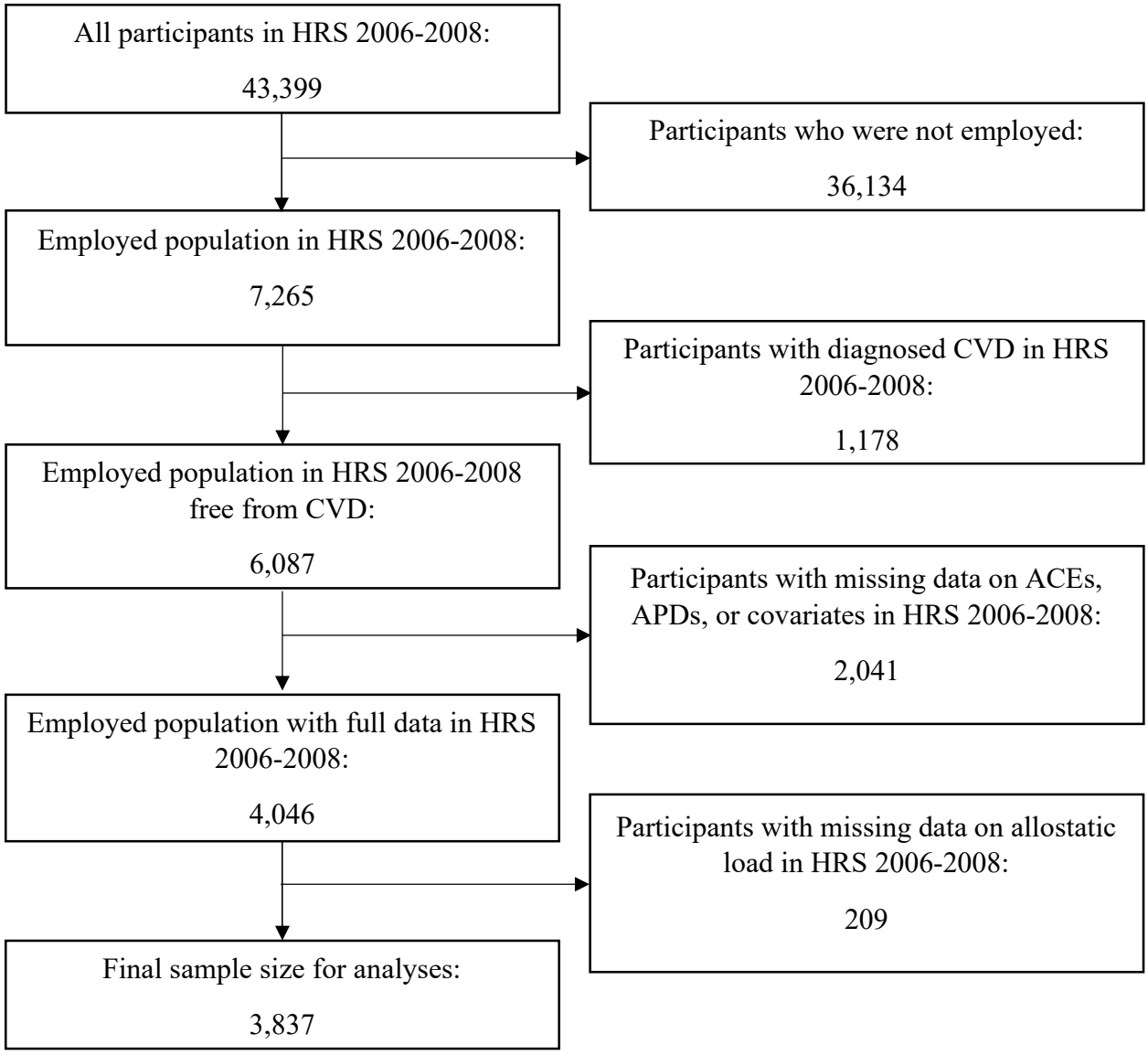


Figure 7. Sample Size Selection Flowchart for the HRS Study Biomarker Sample



3.2.2 Measures

Exposures: Adverse childhood experiences, social isolation, and job strain.

Exposure modeling for ACEs and APDs for the biomarker analyses of allostatic load utilized the same measures as detailed previously, across the Add Health, MIDUS, and HRS cohorts, with no changes to items or coding of generated variables. Exposure assessment models applied were fully consistent with those used for analyses of CVD mortality.

Participants were categorized into high and low exposure groups for ACEs, job strain, and social isolation, and APDs were defined as the combination of high job strain and/or high social isolation. The resulting categorical variable for APDs thus had three levels—low (no disadvantages), moderate (one disadvantage, either high job strain or high social isolation), and high (two disadvantages, both high job strain and high social isolation).

Outcome: Allostatic load.

The Add Health, MIDUS, and HRS studies included data collection on a complement of cardiometabolic and inflammatory biomarkers, allowing for in-depth mechanistic assessments of various physiological parameters relevant to the development and progression of CVD. Several of these biomarkers were combined to create an index representing allostatic load. While not all biomarkers are available across all three studies, there is a substantial degree of overlap between them, offering comparable indices of allostatic load that are amenable to statistical analyses. In recent years, the novel concept of "streamlined allostatic load index" has been proposed, which is a short form allostatic load index originally developed for pragmatic use by industry-affiliated physicians[178]. Notably, a five-item short form "streamlined" allostatic load index offered improved estimates of the association between work stress and allostatic load index compared to a 15-item

allostatic load index. Furthermore, in a study examining associations of perceived stress with allostatic load index in the MIDUS study, models implementing a five-item allostatic load index detected a significant association, whereas the results based on a ten-item allostatic load index did not reach significance[179]. These researchers also called for further studies exploring the use of a streamlined allostatic load index.

The present biomarker analysis project reaches a methodological compromise between a maximally streamlined allostatic load index and consistency of measures between the three cohorts via selection of seven biomarkers available across all three studies, allowing for comparison and cross-validation. The seven specific biomarkers used to index allostatic load that were common across the Add Health, MIDUS, and HRS studies were: (1) waist to height ratio (WHR), (2) systolic blood pressure (SBP), (3) diastolic blood pressure (DBP), (4) glycosylated hemoglobin (HbA1C), (5) high-density lipoprotein (HDL), (6) total cholesterol (TC), and (7) C-reactive protein (CRP). This set of biomarkers assaying allostatic load together serve as an index of the cardiovascular, autonomic, and inflammatory processes involved in biological responses to stress, in line with a recent large investigation including 21 European cohorts[180].

Routinely, clinical cut-offs for each of the seven biomarkers were implemented uniformly across the three cohorts to identify individuals at risk for cardiometabolic conditions based on their biomarker status, and a resulting sum score was computed based on binary risk profiles for each biomarker[181–208]. Hence, all participants received a sum score for allostatic load, with scores ranging from zero to seven.

Recent literature has substantiated a WHR of 0.5 or above as an indicator of cardiometabolic risk and obesity, with compelling data suggesting that WHR is a far better discriminatory measure of metabolic and “early health” risk than body-mass index (BMI)[181–184].

Clinical cut-offs for SBP and DBP were assigned in line with the American College of Cardiology (ACC)/AHA 2017 guidelines for hypertension diagnosis; participants with DBP over 79 mmHg or SBP over 129 mmHg were classified as at risk for those biomarkers, respectively[185].

A glycosylated hemoglobin HbA1c level of above 5.7% has been empirically demonstrated as a risk factor for numerous disease conditions beyond diabetes mellitus alone, also encompassing metabolic syndrome and hypertension[186–189], and hence, participants with a HbA1c above 5.7% were classified as at risk.

For HDL, the published literature has shown HDL to have an inverse relationship to CVD and identified low levels of HDL below 40 mg/dL and 50 mg/dL as risk factors for CVD in men and women, respectively[190–194,196]. Male participants with HDL under 40 mg/dL and female participants with HDL under 50 mg/dL were categorized as at risk due to HDL status.

With regard to TC, clinical evidence has outlined TC levels of above 200 mg/dL as a risk condition for dyslipidemia and CVD, with numerous studies demonstrating impaired cardiometabolic function and increased atherosclerotic progression with high levels of TC[195,197–201]. Participants with a TC over 200 mg/dL were considered at risk due to clinically elevated levels of cholesterol.

Finally, for CRP, an indicator of systemic inflammation in the body, CRP levels above 3.0 mg/L have been linked to severe inflammatory consequences implicated in a host of disease conditions, as well as CVD risk[202–208]. The clinically substantiated cut-off level of CRP above 3.0 mg/L was utilized, and participants above the cut-off were categorized as at risk due to CRP.

The biomarker data collected in the three studies reflect the functioning of the cardiovascular and autonomic nervous systems, the HPA axis, and general metabolic processes.

They have been used extensively in both the scientific study and clinical treatment of CVD[33,34,209–211] and have exhibited strong associations with ACEs, social isolation, and job strain[29,159,212–214]. However, these studies have not assessed the potential of cumulative stress exposures across the life-course and their relationships with allostatic load.

Outcome: Heart rate variability.

HRV refers to the changes in time intervals between consecutive heartbeats, which oscillate according to psychophysiological demands and potential challenges to nervous system homeostatic equilibrium[215]. HRV is defined by the beat-to-beat variation in heart rate that occurs in tandem with breathing – heart rate accelerates during inspiration and decelerates during expiration in a process known as respiratory sinus arrhythmia (RSA)[216]. Notably, impaired HRV is distinguished in its ability to not only diagnose CVD but also predict adverse CVD outcomes, largely due to the propensity for HRV to reflect deviations from homeostatic cardiac nervous system function[217].

HRV also offers an evaluation of the relative sympathetic and parasympathetic nervous system function, with imbalances in either regulatory branch indicating both current and impending cardiometabolic conditions[218]. The use of HRV as a cardiovascular biomarker in scientific investigations has increased in recent decades due to the ease and non-invasiveness of assessment and its capacity to assess the health and overall functioning of the autonomic nervous system[219]. Reduced HRV is clinically relevant as a well-established risk factor for CVD mortality, with strong associations of increased HRV with improved survival outcomes in some intervention studies[220].

The MIDUS study also offered additional in-depth measurements of HRV, allowing for the opportunity of further investigations of cardiovascular function. Participants underwent a resting-state, 5-minute electrocardiogram (ECG) recording. HRV data from the MIDUS II biomarker sample were analyzed separately in order to assess associations of ACEs and APDs with cardiovascular and stress reactivity. HRV parameters available in the MIDUS study included the time-domain measures of root square of mean successive differences (RMSSD) and the standard deviation of the RR interval (SDRR), and the frequency-domain measures of high-frequency heart-rate variability (HF-HRV) and low-frequency heart-rate variability (LF-HRV)[215,221–225].

RMSSD is considered a short-term measure of HRV and an indicator of parasympathetic nervous system function, whereas SDRR indexes overall and longer-term HRV; SDRR has been shown to "reliably predict the prognosis" of CVD[217]. HF-HRV is also a marker for parasympathetic nervous system activity, whereas LF-HRV reflects both sympathetic and parasympathetic nervous system impacts on heart rate.

All HRV parameter variables were log-transformed to normalize the distribution of the data structure and optimize treatment of extreme values, and log-transformed HRV variables were implemented for all HRV analyses.

3.2.3 Statistical Analysis

The approach for measuring biomarkers tapping allostatic load across the three studies is primarily based on a recent publication comparing the adverse health effects of ACEs between the Add Health and MIDUS studies, which constitutes a model paper that was used to inform the

analytical strategy[90]. We hypothesize a linear accumulation of risk for allostatic load with cumulative psychosocial exposures.

Models included adjusted for the sociodemographic and lifestyle behavior covariates of age (continuous), sex, race, educational attainment, household income, current smoking, alcohol consumption, and physical exercise. To maintain consistency with prior analyses of CVD mortality, workers with pre-existing CVD were excluded.

First, descriptive statistics were generated, and relative frequencies were examined for characteristics of the sample populations at baseline. Second, associations of ACE and APDs with allostatic load index were assessed in independent, mutually-adjusted Poisson regression models, and the results were expressed as count ratios (CRs) and 95% CIs[226]. Analyses were primarily cross-sectional for the Add Health and HRS studies, whereas longitudinal analyses were implemented for the MIDUS study, with participants followed-up from MIDUS I in 1994 to their laboratory visit in the MIDUS II biomarker sample in 2004, providing 10 years of follow-up time. Third, independent, mutually-adjusted multivariable linear regression models were constructed to investigate associations of ACEs and APDS with HRV in the MIDUS study, and results were expressed as βs and 95% CIs.

Multivariable models were calculated in three steps after unadjusted Model 0: Model I adjusted for age and sex; Model II included further adjustment for race, educational attainment, and annual household income; Model III additionally adjusted for current smoking, alcohol consumption, and physical exercise. Hypothesis tests were two-sided at the 5% α level. We tested for an interaction between ACEs and APDs with allostatic load index as the outcome, and further stratified analyses were conducted to assess effect modification by ACEs on associations between APDs and allostatic load.

3.3 Results

3.3.1 Characteristics of the Sample Populations

The characteristics of the sample populations for the Add Health, MIDUS, and HRS biomarker study samples are shown in Tables 10-12.

In the Add Health biomarker study sample at Wave IV, the sample of 19,897 working participants was made up of young to middle-aged adults with a mean age of 29 and approximately equal numbers of men and women. They were primarily White (70.42%), with some inclusion of Black participants (23.50%) and lower representation of Asian (4.80%) and Other races (1.28%), had at least some college education, and most participants had an annual household income above $30,000. There was a high proportion of smokers in the sample (41.46%), but most participants reported low to moderate alcohol consumption (97.64%) and nearly half engaged in high levels of physical activity (47.26%). The prevalence of high ACEs was 14.01%, while the prevalence of moderate to high APDs was 57.71%. Allostatic load index ranged from 0-7, with most participants falling in the risk categories of two to three biomarkers (>20% in these categories).

At the MIDUS I baseline study, the sample of 771 workers who were included in the MIDUS II biomarker sample consisted of middle-aged adults with a mean age of 45 and similar numbers of men and women. They were mostly White (93.64%), with smaller numbers of Black (2.72%) and Other races (3.63%). Most participants had at least some college education and had an annual income over $45,000. There was a low proportion of smokers (14.27%), and most participants engaged in low to moderate alcohol drinking (96.11%) and high levels of physical activity (70.56%). A high level of ACEs was reported by 40.21% of participants, and around 30% had moderate to high exposures to APDs. Allostatic load index values ranged from 0-7, and

most participants were considered in the risk categories of three to four biomarkers (>20% in these categories).

In the 2006 and 2008 waves of the HRS biomarker study sample, the sample of 3,837 working participants had roughly equal numbers of men and women, with a slightly greater proportion of women (51.79%), and were older, with a mean age of 61. They were mostly White (82.56%), with some Black participants (10.35%) and limited numbers of Other races (7.09%). They had more limited levels of educational attainment, with 60.67% having completed high school or less, and mostly had an annual household income of over $45,000. There was a smaller proportion of smokers (13.55%) and most participants had low or moderate alcohol consumption (96.40%) and high levels of physical activity (57.05%). The prevalence of high ACEs was 4.56%, and the prevalence of moderate to high APDs was 30.8%. The allostatic load index ranged from 0-7, and most participants were classified in the risk categories of three to four biomarkers (>20% in these categories).

Table 10. Characteristics of the Study Population in the Add Health Wave IV Biomarker Sample (*N*=19,897)

Variables (*N*, %)	
Age (mean, SD)	28.70 (1.74)
Sex	
Male	9617 (48.33)
Female	10280 (51.67)
Race	
White	14011 (70.42)
Black	4676 (23.50)
Asian	955 (4.80)
Others	255 (1.28)
Educational attainment	
University or more	5025 (25.26)
Some college	10003 (50.27)
High school or less	4869 (24.47)
Household income (annual U.S. dollars)	
< 30,000	4312 (21.67)
30,000-99,999	12695 (63.80)
≥ 100,000	2890 (14.52)
Smoking status	
No	11612 (58.36)
Yes	8285 (41.64)
Alcohol consumption	
Low to moderate drinking	1927 (97.64)
Heavy drinking	470 (2.36)
Physical activity	

High	9404 (47.26)
Moderate	58011 (29.16)
Low	4692 (23.58)
Adverse childhood experiences	
Low	17109 (85.99)
High	2788 (14.01)
Adulthood psychosocial disadvantages	
Low	8414 (42.29)
Moderate	10324 (51.89)
High	1159 (5.82)
Allostatic load index	
0	1277 (6.42)
1	3305 (16.61)
2	4743 (23.84)
3	4710 (23.67)
4	3590 (18.04)
5	1766 (8.88)
6	464 (2.33)
7	42 (0.21)

Table 11. Characteristics of the Study Population at MIDUS I in the MIDUS Biomarker Sample (*N*=771)

Variables (*N*, %)	
Age (mean, SD)	44.61 (10.61)
Sex	
Male	363 (47.08)
Female	408 (52.92)
Race	
White	722 (93.64)
Black	21 (2.72)
Other	28 (3.63)
Educational attainment	
University or more	370 (47.99)
Some college	211 (27.37)
High school or less	190 (24.64)
Household income (annual U.S. dollars)	
< 45,000	214 (27.76)
45,000-89,999	276 (35.80)
≥ 90,000	281 (36.45)
Smoking status	
No	661 (85.73)
Yes	110 (14.27)
Alcohol consumption	
Low to moderate drinking	741 (96.11)
Heavy drinking	30 (3.90)
Physical activity	

High	544 (70.56)
Moderate	162 (21.01)
Low	65 (8.43)
Adverse childhood experiences	
Low	461 (59.79)
High	310 (40.21)
Adulthood psychosocial disadvantages	
Low	536 (69.52)
Moderate	208 (26.98)
High	27 (3.50)
Allostatic load index	
0	39 (5.06)
1	87 (11.28)
2	146 (18.94)
3	189 (24.51)
4	175 (22.70)
5	89 (11.54)
6	35 (4.54)
7	11 (1.43)

Table 12. Characteristics of the Study Population in the HRS 2006-2008 Biomarker Sample, (*N*=3,837)

Variables (*N*, %)	
Age (mean, SD)	61.43 (6.91)
Sex	
Male	1850 (48.21)
Female	1987 (51.79)
Race	
White	3168 (82.56)
Black	397 (10.35)
Other	272 (7.09)
Educational attainment	
University or more	1191 (31.04)
Some college	318 (8.29)
High school or less	2328 (60.67)
Household income (annual U.S. dollars)	
< 45,000	1440 (37.53)
45,000-99,999	1348 (35.13)
≥ 100,000	1049 (27.34)
Smoking status	
No	3317 (86.45)
Yes	520 (13.55)
Alcohol consumption	
Low or moderate drinking	3699 (96.40)
Heavy drinking	138 (3.60)
Physical activity	
High	2189 (57.05)

Moderate	471 (12.28)
Low	1177 (30.78)
Adverse childhood experiences	
Low	3662 (95.44)
High	175 (4.56)
Adulthood psychosocial disadvantages	
Low	2655 (69.19)
Moderate	1076 (28.04)
High	106 (2.76)
Allostatic load index	
0	42 (1.09)
1	292 (7.61)
2	677 (17.64)
3	968 (25.23)
4	925 (24.11)
5	671 (17.49)
6	222 (5.79)
7	40 (1.04)

3.2.2 Associations of ACEs and APDs with Allostatic Load Index

Tables 13-15 exhibit the results of the Poisson regression models examining associations of ACEs and APDs with allostatic load in the Add Health, MIDUS, and HRS studies. Table 16 displays the results of the analyses examining associations of APDs with HRV by ACE exposure level in the MIDUS biomarker sample.

No significant findings regarding exposure to ACEs and APDs and allostatic load were observed in the Add Health, MIDUS, or HRS studies. In the Add Health Wave IV biomarker sample, the fully-adjusted CR and 95% CI was 0.99 (0.95, 1.03) for high ACEs exposure, compared to low ACEs, and the fully-adjusted CR and 95% CI for high APDs exposure was 1.04 (0.98, 1.10), compared to low APDs. In the MIDUS II biomarker sample, fully-adjusted CRs and 95% CIs were 1.08 (1.00, 1.16) for high ACEs, compared to low ACEs, and 0.95 (0.74, 1.21) for exposure to high APDs, compared to low APDs. In the HRS 2006-2008 biomarker sample, the fully-adjusted CR and 95% CI for high ACEs exposure was 0.97 (0.90, 1.05), compared to low ACEs, and the fully-adjusted CR and 95% CI for high exposure to APDs was 0.96 (0.87, 1.06), compared to low APDs.

Table 13. Independent Cross-sectional Associations of Adverse Childhood Experiences (ACEs), Adulthood Psychosocial Disadvantages (APDs) with Allostatic Load Index in the Add Health Wave IV Biomarker Sample (CRs and 95% CIs) (*N*=19,897)

	Model I	Model II	Model III
Adverse Childhood Experiences			
Low (*N*=17109)	1.00	1.00	1.00
High (*N*=2788)	1.02 (0.98, 1.06)	0.98 (0.94, 1.04)	0.99 (0.95, 1.03)
Adulthood Psychosocial Disadvantages			
Low (*N*=8414)	1.00	1.00	1.00
Moderate (*N*=10324)	1.03 (1.00, 1.06)*	1.03 (1.00, 1.05)	1.02 (0.99, 1.05)
High (*N*=1159)	1.09 (1.03, 1.15)**	1.05 (0.99, 1.11)	1.04 (0.98, 1.10)

CI, confidence interval; CR, count ratio.
Poisson regression, * $p < 0.05$, ** $p < 0.01$.
Model I: adjustment for age and sex at baseline.
Model II: Model I + additional adjustment for race, educational attainment, and household income at baseline.
Model III: Model II + additional adjustment for smoking, alcohol consumption, and physical exercise at baseline.

Table 14. Independent Prospective Associations of Adverse Childhood Experiences (ACEs), Adulthood Psychosocial Disadvantages (APDs) at MIDUS I with Allostatic Load Index in the MIDUS II Biomarker Sample (CRs and 95% CIs) (*N*=771)

	Model I	Model II	Model III
Adverse Childhood Experiences			
Low (*N*=461)	1.00	1.00	1.00
High (*N*=310)	1.12 (1.04, 1.20)**	1.08 (1.01, 1.17)*	1.08 (1.00, 1.16)
Adulthood Psychosocial Disadvantages			
Low (*N*=536)	1.00	1.00	1.00
Moderate (*N*=208)	0.93 (0.86, 1.01)	0.93 (0.86, 1.01)	0.92 (0.85, 1.00)
High (*N*=27)	0.99 (0.77, 1.27)	0.97 (0.76, 1.24)	0.95 (0.74, 1.21)

CI, confidence interval; CR, count ratio.
Poisson regression, * $p < 0.05$, ** $p < 0.01$.
Model I: adjustment for age and sex at baseline.
Model II: Model I + additional adjustment for race, educational attainment, and household income at baseline.
Model III: Model II + additional adjustment for smoking, alcohol consumption, and physical exercise at baseline.

Table 15. Independent Cross-sectional Associations of Adverse Childhood Experiences (ACEs) and Adulthood Psychosocial Disadvantages (APDs) with Allostatic Load Index in the HRS 2006-2008 Biomarker Sample (CRs and 95% CIs) (*N* = 3,837)

	Model I	Model II	Model III
Adverse Childhood Experiences			
Low (*N*=3662)	1.00	1.00	1.00
High (*N*=175)	0.98 (0.90, 1.06)	0.97 (0.90, 1.05)	0.97 (0.90, 1.05)
Adulthood Psychosocial Disadvantages			
Low (*N*=2655)	1.00	1.00	1.00
Moderate (*N*=1076)	1.04 (1.01, 1.08)*	1.03 (1.00, 1.07)	1.03 (1.00, 1.07)
High (*N*=106)	0.99 (0.89, 1.09)	0.97 (0.88, 1.07)	0.96 (0.87, 1.06)

CI, confidence interval; CR, count ratio.
Poisson regression, ** $p < 0.01$.
Model I: adjustment for age and sex at baseline.
Model II: Model I + additional adjustment for race, educational attainment, and household income at baseline.
Model III: Model II + additional adjustment for smoking, alcohol consumption, and physical exercise at baseline.

Table 16. Independent Prospective Associations of Adverse Childhood Experiences (ACEs), Adulthood Psychosocial Disadvantages (APDs) at MIDUS I with Heart-Rate Variability (HRV) at MIDUS II (βs and 95% CIs) (*N*=771)

		Model I	Model II	Model III
Log SDRR	Adverse Childhood Experiences			
	Low (*N*=461)	0.00	0.00	0.00
	High (*N*=310)	0.90 (-2.43, 4.23)	0.68 (-2.74, 4.10)	0.68 (-2.74, 4.10)
	Adulthood Psychosocial Disadvantages			
	Low (*N*=536)	0.00	0.00	0.00
	Moderate (*N*=208)	-1.95 (-5.65, 1.75)	-1.93 (-5.64, 1.79)	-1.89 (-5.63, 1.85)
	High (*N*=27)	-6.36 (-15.27, 2.55)	-6.19, -15.19, 2.80)	-6.51 (-15.50, 2.49)
Log RMSSD	Adverse Childhood Experiences			
	Low (*N*=461)	0.00	0.00	0.00

	High (*N*=310)	0.93 (-2.42, 4.28)	0.72 (-2.72, 4.16)	0.58 (-2.86, 4.03)
	Adulthood Psychosocial Disadvantages			
	Low (*N*=536)	0.00	0.00	0.00
	Moderate (*N*=208)	-2.00 (-5.73, 1.72)	-1.99 (-5.73, 1.75)	-1.95 (-5.72, 1.81)
	High (*N*=27)	-6.42 (-15.39, 2.54)	-6.28 (-15.33, 2.77)	-6.60 (-15.65, 2.45)
Log LF-HRV	Adverse Childhood Experiences			
	Low (*N*=461)	0.00	0.00	0.00
	High (*N*=310)	0.95 (-2.32, 4.21)	0.77 (-2.59, 4.13)	0.65 (-2.71, 4.01)
	Adulthood Psychosocial Disadvantages			
	Low (*N*=536)	0.00	0.00	0.00
	Moderate (*N*=208)	-1.83 (-5.46, 1.80)	-1.80 (-5.45, 1.85)	-1.76 (-5.44, 1.91)
	High (*N*=27)	-6.29 (-15.03, 2.46)	-6.13 (-14.96, 2.70)	-6.42 (-15.25, 2.42)

Log HF-HRV	Adverse Childhood Experiences			
	Low (*N*=461)	0.00	0.00	0.00
	High (*N*=310)	0.92 (-2.37, 4.21)	0.71 (-2.67, 4.09)	0.58 (-2.80, 3.96)
	Adulthood Psychosocial Disadvantages			
	Low (*N*=536)	0.00	0.00	0.00
	Moderate (*N*=208)	-1.99 (-5.65, 1.66)	-1.98 (-5.65, 1.70)	-1.94 (-5.64, 1.76)
	High (*N*=27)	-6.34 (-15.15, 2.47)	-6.20 (-15.09, 2.69)	-6.52 (-15.41, 2.37)

CI, confidence interval.
Linear regression.
Model I: adjustment for age and sex at baseline.
Model II: Model I + additional adjustment for race, educational attainment, and household income at baseline.
Model III: Model II + additional adjustment for smoking, alcohol consumption, and physical exercise at baseline.

3.3.3 Associations of APDs with Allostatic Load Index, Stratified by ACE Exposure Level

No significant interactions of ACEs by APDs with allostatic load index as the outcome were observed across the Add Health, MIDUS, or HRS biomarker samples. Tables 17-19 show the results of the stratified analyses assessing associations of APDs with allostatic load index by ACEs exposure level in the Add Health, MIDUS, and HRS biomarker samples. Table 20 exhibits the results of the stratified analyses examining associations of APDs with HRV by ACE exposure level in the MIDUS biomarker sample.

Similar to the results of the analyses for the aggregate samples, no significant findings were observed for associations of exposure to APDs with allostatic load. However, while findings were not statistically significant and CIs generally spanned one, there was a stable and consistent trend of increased CR estimates with increasing exposures across the three cohorts.

In the Add Health Wave IV biomarker sample, the fully-adjusted CRs and 95% CIs for moderate and high exposure to APDs in the low ACE exposure group were 1.02 (0.99, 1.05) and 1.03 (0.97, 1.09), respectively, compared to low APDs. For the high ACEs exposure group, fully-adjusted CRs and 95% CIs for moderate and high exposure to APDs were 1.05 (0.98, 1.13) and 1.11 (0.96, 1.29), respectively, compared to low APDs.

In the MIDUS II biomarker sample, fully-adjusted CRs and 95% CIs for moderate and high APDs in the low ACEs group were 0.21 (0.83, 1.03) and 0.91 (0.62, 1.33), respectively, compared to low APDs. For the high ACEs group, CRs and 95% CIs for moderate and high APDs were 0.93 (0.83, 1.05) and 1.01 (0.76, 1.33), respectively, compared to low APDs.

In the HRS 2006-2008 biomarker sample, the fully-adjusted CRs and 95% CIs for moderate and high exposure to APDs in the low ACEs group were 1.03 (0.99, 1.07) and 0.95 (0.86, 1.07), respectively, compared to low APDs. For the high ACEs group, fully-adjusted CRs

and 95% CIs for moderate and high APDs were 0.92 (0.78, 1.09) and 0.92 (0.76, 1.12), respectively, compared to low APDs.

3.3.4 Associations of ACEs and APDs with Heart Rate Variability

The HRV analyses of the MIDUS II biomarker sample also did not detect significant findings, but all HRV metrics exhibited a consistent trend and pattern of overall decreased HRV and lower cardiovascular reactivity with increasing exposure to APDs. For log SDRR, fully-adjusted βs and 95% CIs were -1.89 (-5.63, 1.85) and -6.51 (-15.50, 2.49) for moderate and high exposure to APDs, respectively, compared to low APDs. For log RMSSD, fully-adjusted βs and 95% CIs were -1.95 (-5.72, 1.81) and -6.60 (-15.65, 2.45) for moderate and high APDs exposures, respectively, compared to low APDs. Regarding log LF-HRV, fully-adjusted βs and 95% CIs for moderate and high exposures to APDs were -1.76 (-5.44, 1.91) and -6.42 (-15.25, 2.42), respectively, compared to low APDs. Finally, for log HF-HRV, fully-adjusted βs and 95% Cis for moderate and high exposures to APDs were -1.94 (-5.64, 1.76) and -6.52 (-15.41, 2.37), respectively, compared to low APDs.

3.3.5 Associations of ACEs and APDs with Heart Rate Variability, Stratified by ACEs Exposure Level

The results of the interaction analyses of APDs by ACE exposure level with HRV indices as the outcome did not show evidence of statistical interaction. The stratified HRV analyses of the MIDUS II biomarker sample assessing potential effect modification by ACEs exposure did not show significant findings. However, in a similar pattern to the aggregate analyses, all four HRV metrics displayed a stable trend and pattern of reduced HRV and cardiovascular reactivity

with increasing APDs exposure. Furthermore, while not statistically significant, effect sizes for high APDs exposure increased according to ACEs exposure level, with consistently higher estimates for participants with high APDs exposures who also had high ACES exposures, compared to those with low ACEs.

For log SDRR, in the low ACE exposure group, fully-adjusted βs and 95% CIs were -2.92 (-7.67, 1.84) and -6.34 (-17.84, 5.17) for moderate and high exposure to APDs, respectively, compared to low APDs. For the high ACEs exposure group, fully-adjusted βs and 95% CIs were -1.08 (-7.18, 5.02) and -8.13 (-22.78, 6.41) for moderate and high exposure to APDs respectively, compared to low APDs.

For log RMSSD, fully-adjusted βs and 95% CIs in the low ACE exposure group were -3.00 (-7.79, 1.79) and -6.45 (-18.03, 5.12) for moderate and high APDs exposures, respectively, compared to low APDs. For the high ACEs group, fully-adjusted βs and 95% CIs were -1.12 (-7.25, 5.02) and -8.19 (-22.82, 6.43), respectively, compared to low APDs.

Regarding log LF-HRV, fully-adjusted βs and 95% CIs for moderate and high exposures to APDs in the low ACEs group were -2.76 (-7.44, 1.92) and -6.28 (-17.59, 5.03), respectively, compared to low APDs. For the high ACEs group, fully-adjusted βs and 95% CIs were -0.98 (-6.95, 5.00) and -7.98 (-22.23, 6.27) for moderate and high APDs exposures, respectively, compared to low APDs.

Finally, for log HF-HRV, in the low ACEs exposure group. fully-adjusted βs and 95% Cis for moderate and high exposures to APDs were -3.03 (-7.73, 1.68) and -6.38 (-17.76, 5.00), respectively, compared to low APDs. For the high ACEs exposure group, fully-adjusted βs and 95% CIs were -1.04 (-7.06, 4.97) and -8.09 (-22.43, 6.26) for moderate and high exposure to APDs, respectively, compared to low APDs.

Table 17. Independent Cross-sectional Associations of Adulthood Psychosocial Disadvantages (APDs) with Allostatic Load Index in the Add Health Wave IV Biomarker Sample, Stratified by Adverse Childhood Experiences (ACEs) Exposure (CRs and 95% CIs) (*N*=19,897)

	Model I	Model II	Model III
	Adverse Childhood Experiences (low) (*N*=17,109)		
Adulthood Psychosocial Disadvantages			
Low (*N*=7136)	1.00	1.00	1.00
Moderate (*N*=8991)	1.03 (1.00, 1.06)	1.02 (0.99, 1.05)	1.02 (0.99, 1.05)
High (*N*=982)	1.08 (1.01, 1.15)	1.04 (0.98, 1.10)	1.03 (0.97, 1.09)
	Adverse Childhood Experiences (high) (N=2788)		
Adulthood Psychosocial Disadvantages			
Low (*N*=1278)	1.00	1.00	1.00
Moderate (*N*=1333)	1.06 (0.99, 1.15)	1.06 (0.98, 1.14)	1.05 (0.98, 1.13)
High (*N*=177)	1.15 (1.00, 1.33)	1.13 (0.97, 1.31)	1.11 (0.96, 1.29)

CI, confidence interval; CR, count ratio.
Poisson regression.
Model I: adjustment for age and sex at baseline.
Model II: Model I + additional adjustment for race, educational attainment, and household income at baseline.
Model III: Model II + additional adjustment for smoking, alcohol consumption, and physical exercise at baseline.

Table 18. Independent Prospective Associations of Adulthood Psychosocial Disadvantages (APDs) at MIDUS I with Allostatic Load Index in the MIDUS II Biomarker Sample, Stratified by Adverse Childhood Experiences (ACEs) Exposure (CRs and 95% CIs) (*N*=771)

	Model I	Model II	Model III
	Adverse Childhood Experiences (low) (*N*=461)		
Adulthood Psychosocial Disadvantages			
Low (*N*=332)	1.00	1.00	1.00
Moderate (*N*=114)	0.92 (0.83, 1.03)	0.92 (0.83, 1.03)	0.92 (0.83, 1.03)
High (*N*=15)	0.92 (0.61, 1.40)	0.92 (0.62, 1.37)	0.91 (0.62, 1.33)
	Adverse Childhood Experiences (high) (*N*=310)		
Adulthood Psychosocial Disadvantages			
Low (*N*=204)	1.00	1.00	1.00
Moderate (*N*=94)	0.94 (0.83, 1.06)	0.93 (0.83, 1.05)	0.93 (0.83, 1.05)
High (*N*=12)	1.05 (0.80, 1.38)	1.03 (0.78, 1.36)	1.01 (0.76, 1.33)

CI, confidence interval; CR, count ratio.
Poisson regression.
Model I: adjustment for age and sex at baseline.
Model II: Model I + additional adjustment for race, educational attainment, and household income at baseline.
Model III: Model II + additional adjustment for smoking, alcohol consumption, and physical exercise at baseline.

Table 19. Independent Cross-Sectional Associations of Adulthood Psychosocial Disadvantages (APDs) with Allostatic Load Index in the HRS 2006-2008 Biomarker Sample, Stratified by Adverse Childhood Experiences (ACEs) Exposure (CRs and 95% CIs) (*N*=3,837)

	Model I	Model II	Model III
	Adverse Childhood Experiences (low) (*N* = 3,662)		
Adulthood Psychosocial Disadvantages			
Low (*N*=2540)	1.00	1.00	1.00
Moderate (*N*=1028)	1.05 (1.01, 1.08)	1.04 (1.00, 1.07)*	1.03 (1.00, 1.07)
High (*N*=94)	0.97 (0.87, 1.09)	0.96 (0.86, 1.07)	0.95 (0.86, 1.07)
	Adverse Childhood Experiences (high) (*N* = 175)		
Adulthood Psychosocial Disadvantages			
Low (*N*=115)	1.00	1.00	1.00
Moderate (*N*=48)	0.98 (0.81, 1.19)	0.93 (0.78, 1.11)	0.92 (0.78, 1.09)
High (*N*=12)	1.10 (0.89, 1.38)	0.96 (0.80, 1.15)	0.92 (0.76, 1.12)

CI, confidence interval; CR, count ratio.
Poisson regression, * $p < 0.05$.
Model I: adjustment for age and sex at baseline.
Model II: Model I + additional adjustment for race, educational attainment, and household income at baseline.
Model III: Model II + additional adjustment for smoking, alcohol consumption, and physical exercise at baseline.

Table 20. Independent Prospective Associations of Adverse Childhood Experiences (ACEs), Adulthood Psychosocial Disadvantages (APDs) at MIDUS I with Heart-Rate Variability (HRV) at MIDUS II, Stratified by ACEs Exposure (βs and 95% CIs) (*N*=771)

		Model I	Model II	Model III
		Adverse Childhood Experiences (low) (*N* =461)		
Log SDRR	Adulthood Psychosocial Disadvantages			
	Low (*N*=536)	0.00	0.00	0.00
	Moderate (*N*=208)	-2.69 (-7.39, 2.00)	-2.70 (-7.42, 2.03)	-2.92 (-7.67, 1.84)
	High (*N*=27)	-5.85 (-17.24, 5.55)	-5.79, (-17.29, 5.71)	-6.34 (-17.84, 5.17)
		Adverse Childhood Experiences (high) (*N*=310)		
	Adulthood Psychosocial Disadvantages			
	Low (*N*=204)	0.00	0.00	0.00
	Moderate (*N*=94)	-1.05 (-7.08, 4.97)	-1.14 (-7.21, 4.93)	-1.08 (-7.18, 5.02)

	High (*N*=12)	-7.15 (-21.54, 7.24)	-7.06 (-21.63, 7.50)	-8.13 (-22.67, 6.41)
		Adverse Childhood Experiences (low) (*N*=461)		
Log RMSSD	Adulthood Psychosocial Disadvantages			
	Low (*N*=536)	0.00	0.00	0.00
	Moderate (*N*=208)	-2.76 (-7.49, 1.96)	-2.78 (-7.53, 1.97)	-3.00 (-7.79, 1.79)
	High (*N*=27)	-5.93 (-17.39, 5.54)	-5.90 (-17.46, 5.67)	-6.45 (-18.03, 5.12)
		Adverse Childhood Experiences (high) (*N*=310)		
	Adulthood Psychosocial Disadvantages			
	Low (*N*=204)	0.00	0.00	0.00
	Moderate (*N*=94)	-1.08 (-7.14, 4.98)	-1.17 (-7.28, 4.93)	-1.12 (-7.25, 5.02)
	High (*N*=12)	-7.18 (-21.65, 7.30)	-7.11 (-21.76, 7.55)	-8.19 (-22.82, 6.43)
		Adverse Childhood Experiences (low) (*N*=461)		

Log LF-HRV	Adulthood Psychosocial Disadvantages			
	Low (*N*=536)	0.00	0.00	0.00
	Moderate (*N*=208)	-2.54 (-7.16, 2.07)	-2.55 (-7.19, 2.10)	-2.76 (-7.44, 1.92)
	High (*N*=27)	-5.82 (-17.02, 5.38)	-5.76 (-17.06, 5.55)	-6.28 (-17.59, 5.03)
		Adverse Childhood Experiences (high) (*N*=310)		
	Adulthood Psychosocial Disadvantages			
	Low (*N*=204)	0.00	0.00	0.00
	Moderate (*N*=94)	-0.96 (-6.87, 4.95)	-1.05 (-7.00, 4.90)	-0.98 (-6.95, 5.00)
	High (*N*=12)	-7.01 (-21.11, 7.09)	-6.93 (-21.21, 7.34)	-7.98 (-22.23, 6.27)
		Adverse Childhood Experiences (low) (*N*=461)		
Log HF-HRV	Adulthood Psychosocial Disadvantages			
	Low (*N*=536)	0.00	0.00	0.00

	Moderate (*N*=208)	-2.79 (-7.43, 1.85)	-2.81 (-7.48, 1.86)	-3.03 (-7.73, 1.68)
	High (*N*=27)	-6.34 (-15.15, 2.47)	-5.83 (-17.21, 5.55)	-6.38 (-17.76, 5.00)
		Adverse Childhood Experiences (high) (*N*=310)		
	Adulthood Psychosocial Disadvantages			
	Low (*N*=204)	0.00	0.00	0.00
	Moderate (*N*=94)	-1.01 (-6.96, 4.94)	-1.11 (-7.10, 2.89)	-1.04 (-7.06, 4.97)
	High (*N*=12)	-7.05 (-21.25, 7.16)	-7.00 (-21.38, 7.38)	-8.09 (-22.43, 6.26)

CI, confidence interval.
Linear regression.
Model I: adjustment for age and sex at baseline.
Model II: Model I + additional adjustment for race, educational attainment, and household income at baseline.
Model III: Model II + additional adjustment for smoking, alcohol consumption, and physical exercise at baseline.

3.4 Discussion

In this secondary data analysis project, ACEs, social isolation, and job strain were not significantly associated with allostatic load in any of the Add Health, MIDUS, or HRS cohorts. An overall pattern of slightly elevated CRs for high ACEs exposure was observed across all three cohorts, compared to low ACES, whereas for high APDs, CRs generally fell just under one, compared to low APDs. This trend of increased CRs with increasing exposure levels was also observed in the stratified analyses, wherein greater exposure to APDs produced higher estimates, and estimates further increased according to ACE exposure level. While these results did not reach statistical significance, they imply potential effect modification by ACEs in associations of APDs with allostatic load. Thus, these findings offered partial support of our hypotheses.

The present null findings regarding ACEs are in contrast with the prevailing literature documenting the adverse impacts of ACEs on a variety of health conditions. These inconsistencies may be in part explained by the restriction of the sample to the working population, given that most studies on ACEs and adulthood cardiometabolic diseases are in the general population, especially ageing people[29,227]. Studies have also found evidence that the working population may be of overall better health status than the general population, as they have the health and energy levels to maintain employment – this phenomenon is known as the Health Worker Survivor Effect (HWSE)[228–230]. Moreover, in the Add Health and HRS cohorts, associations of APDs with allostatic load were assessed cross-sectionally, and thus it is possible that the mid-life impacts of APDs were not detectable due to the length of exposure time – the time frame for exposure assessment may have been inadequate. The latent impact of early-life adversity on allostatic load may have been represented by the inflated CRs observed, yet the effect was not statistically significant.

Systematic reviews and meta-analyses of ACEs and allostatic load have reported consistent and significant associations contributing to chronic systemic and psychiatric disease conditions in adulthood[169]. The seminal "ACE Study" conducted by Kaiser Permanente and the CDC of 17,000 U.S. adults noted a "continuous, dose-dependent relationship between number of childhood adversities and heightened risk for cardiometabolic disease"[29,140]. A sample of over 25,000 participants from the Canadian Longitudinal Study of Aging also found significant associations of ACEs with multiple worsened health outcomes in mid-life, with a strong mediating role of social engagement[171]. However, the Canadian study did not control for important sociodemographic characteristics, including income, smoking and alcohol consumption, or physical exercise, all of which have been related to both ACEs and disease in adulthood and were included in the analyses of the present project[171].

These data provide some initial support for the "chains of risk" model of exposure assessment, which accounts for sequences of linked exposures that can occur when one stressor gives rise to another, leading to a chain reaction that may "explain continuities between early experiences and adult psychosocial function" – in this case, it is possible that exposure to ACEs in childhood increases the risk of social isolation later in life[40–42]. Another model proposed by researchers posits a "biological embedding" model of stress and disease, wherein physiological perturbations during the critical period of neurobiological development mediate associations of ACEs with impaired adult health outcomes[140,141,231]. This argument serves to explain the wide profile of chronic disease conditions related to ACEs exposure; the multitude of biological impacts produced by childhood stress persist throughout life, leading to systemically worsened health.

Studies investigating possible mechanisms underlying the effect of early life trauma on long-term adverse health outcomes report disruption of the endocrine, immune, and nervous systems[158]. Neuroimaging studies have also demonstrated smaller brain volumes of the hippocampal and prefrontal cortex areas, in tandem with increased amygdala volume – such perturbations lead to problems with executive function, planning, and goal-directed behavior, as well as greater emotional and psychological distress[158,232]. Dopaminergic circuits are pervasively impacted, leading to impaired motivation and reward processing[232]. These pervasive effects are also mediated by disturbed HPA axis function[138].

Critically, these neurological impacts are linked to social learning and processing of social situations – thus, impaired systemic and nervous system function due to early-life experiences of abuse and neglect may also lead to worsened social function and ultimately, social isolation[134]. For example, children who experienced physical abuse exhibited heightened sensitivity and perception of negative emotions such as anger, such that they were biased to respond more quickly to angry faces during cognitive tasks[135–137]. Misperceptions of social cues and facial expressions may restrict social function in adulthood, increasing the likelihood of social isolation[136]. Conversely, studies show that even in the face of early-life financial stress, one of the primary categories of ACEs, parental support offers protective effects, demonstrated via neuroimaging[233]. Similarly, in a study of 1,200 U.S adults, associations between ACEs and adult health were almost fully accounted for by adult SES and adult stress exposure, highlighting the potential impacts of adulthood exposures such as social isolation and job strain[41]. These data suggest potential synergistic impacts of ACEs with social isolation, wherein one exposure may lead to or exacerbate the effects of another, further highlighting the deleterious impact of cumulative psychosocial exposures.

Studies specifically examining social isolation and allostatic load have demonstrated significant associations leading to adverse health outcomes[145–149,173]. The AHA recently issued a scientific statement on the effects of social isolation on cardiovascular and brain health, presenting compelling evidence substantiating consistent and direct associations between social isolation and heart disease and stroke mortality[148]. Notably, in these data, the effect estimates were small, which is in agreement with the effect sizes observed across the present analyses. Studies have repeatedly documented associations of social isolation with inflammatory processes[37], highlighting chronic inflammation as a common mechanism accounting for the effects of social isolation on mental, physical, and behavioral health outcomes[234–237]. These pathways are further elucidated in studies of the protective effects of social interaction on health, with robust evidence demonstrating improvements in physiological measures of cardiovascular function, spanning hypertension[238], autonomic and stress reactivity[239], molecular markers of stress[240], and neuroendocrine regulation[241,242].

Data also suggest that the effect size of social isolation may increase with age; several studies assessing social support networks in old age observed reduced accretion of allostatic load and disease morbidity[171,236,243]. The mechanisms underlying such effects are thought to involve improved markers of gene expression and aging, improved engagement with healthy lifestyle behaviors, and general protective effects of social support[244–247]. Moreover, it is important to acknowledge that social isolation has a multitude of impacts on general function and capacity across several domains of life – the chronic stress response induced by social isolation has been associated with impaired work performance[248] and academic achievement[249,250], as well as stress-related work absenteeism amounting to $154 billion annually[251].

Importantly, prevailing models of gerontological science and healthy aging emphasize the role of social support throughout life, and especially in elderly life[247,252]. The contributions of social isolation to allostatic load are multifaceted and linked to biological, social, and behavioral factors that impair function and produce systemic stress. Critically, allostatic load has been proven as a reliable and significant predictor of mortality from CVD, with social isolation also showing to be a significant predictor of stroke mortality[172].

Job strain is well substantiated as a risk factor for allostatic load, with a preponderance of evidence demonstrating associations of multiple cardiometabolic and inflammatory biomarkers with indicators of occupational stress[172,174–176,253,254]. Many studies have reported significant associations of job strain with hypertension, a major component of allostatic load and cardiovascular functioning[13,71,121,255], with meta-analyses of large cohort studies exhibiting increased incidence of hypertension in workers experiencing high job strain[256,257]. A study of 1,156 French workers captured significant associations of job strain with increased SBP within a five year follow-up period, with only associations for job strain persisting after adjustment for sociodemographic characteristics and lifestyle behaviors, whereas other occupational stressors had associations attenuated[258]. Similarly, a cohort study of workers utilizing health check-up record data observed significant associations of job strain based on the job demand-control model with multiple CVD risk factors, including hypertension, hyperlipidemia, and cigarette smoking[253]. In a study of female workers that included physiological laboratory measurements of CRP, HbA1C, HDL, and cortisol, job strain was significantly associated with high allostatic load scores, and high allostatic load values were in turn associated with having one or more chronic disease conditions[254]. These findings are in concert with studies demonstrating the poignant influence of allostatic load as a mediator between psychosocial exposures and CVD outcomes[174].

While effect modification of APDs by ACEs exposure on allostatic load was not observed in the present analyses, evidence from Europe has shown potential moderating effects of job strain by ACEs in the context of allostatic load. A Swedish cohort study showed effect modification by early life adversity, wherein associations of job strain with allostatic load were detected only among participants who had experienced adversity in adolescence[123]. In a similar vein, an analysis of three population-based cohorts found that workers with "impaired capacity of response" experienced high allostatic load when also subjected to job strain[174]. These data indicate potential interactions between psychosocial stressors and job strain in the context of clinically elevated allostatic load biomarkers.

More detailed, specific, and data-rich measures of autonomic function such as HRV may offer further insights as to the relationships of psychosocial stressors with cardiometabolic disease[221], and the HRV findings from the MIDUS biomarker subsample show initial promise and warrant further exploration. The stable and consistent trend of worsened HRV metrics with increasing psychosocial exposure levels suggests that ACEs and APDS may exert some influence on cardiovascular reactivity; some estimates approached statistical significance, and such patterns were observed across all four indices of HRV – RMSSD, SDNN, HF-HRV, and LF-HRV.

Reductions in HRV have been consistently linked to increased risk of CVD mortality and systemically impaired cardiometabolic function[217,222]. Studies have also reported robust negative correlations between multiple HRV measures and allostatic load, demonstrating the efficacy and utility of HRV as an indicator of allostatic load and associated health risks[259]. A systematic review and meta-analysis of childhood adversity found distinct alterations in vagal regulation and HRV, with participants who were diagnosed with a psychiatric disorder showing associations

of childhood adversity with lower baseline vagal activity, reflecting disruptions in autonomic nervous system processes[260]. Notably, a pilot study utilizing a biomarker profile integrating typical HPA axis biomarkers such as blood pressure and cortisol with HRV found that a combined biomarker index representing both the HPA axis and the autonomic nervous system, via HRV, offered improved discrimination of stress responses between participants with and without exposure to ACEs[261]. Social isolation has also been linked to altered parasympathetic nervous system in experimental studies – for example, chronic and state loneliness were associated with both lower resting HRV and HRV reactivity in a study of 316 adult women[262]. Furthermore, an integrative review of eight studies assessing social support and HRV found that perceived social support improved parasympathetic control, with protective associations for rest, stress induction, and acute stress recovery[263]. These studies are also supported by experimental data demonstrating increased HRV among individuals susceptible to social isolation during conversational tasks[264], as well as animal models of social isolation showing significant increases in resting heart rate, reductions in HRV, and elevated cardiac responses to stress[265]. Systematic reviews of occupational stress and autonomic nervous system indicators such as HRV identified robust and consistent associations of impaired HRV with work stress[163]. Similarly, another systematic review assessing sympathetic and parasympathetic function showed significant negative associations of job stress with multiple HRV measures, as well as associations of job stress with increased heart rate, suggesting perturbed autonomic nervous system activity and cardiovascular strain[266].

The marginally impaired HRV measures observed in the MIDUS biomarker subsample may reflect challenges to psychophysiological demands brought about by exposure to ACEs and APDs, including the mobilization of energy resources via the sympathetic nervous system[218].

Strengths

The prevailing strengths of this study are rooted in the large, population-based, and nationally representative samples that provide coverage of the whole life course, from early life to adulthood and old age, due to the tripartite treatment of the Add Health, MIDUS, and HRS cohort studies. The samples included workers across a broad range of occupational categories, and included detailed sociodemographic data that were used to adjust for confounders and cardiometabolic risk factors, including annual household income, educational attainment, smoking, alcohol consumption, and physical exercise. ACE measures covering the three-factor structure of financial stress, household dysfunction, and abuse were available across the three cohorts, with the Add Health study providing richer prospective data from childhood surveys. The measures for job strain were based on Karasek's classic model of job strain[65], with the MIDUS study including measures similar to the original JCQ[115], and the strongly validated Berkman-Syme Social Network Index was used to provide accurate assessments of social isolation[150]. Finally, the collection of rich and detailed biomarker data and rigorous laboratory analyses conducted allowed for the construction of an allostatic load index drawing upon seven cardiometabolic and inflammatory biomarkers implicated in CVD pathogenesis, with fully consistent and reliable measures between all three studies.

Limitations

The results of this study may be influenced by several methodological limitations. First and foremost, the primarily cross-sectional nature of the research designs in the Add Health and HRS studies limited the ability to make causal inferences due to a lack of temporal trend data. Longitudinal biomarker analyses implementing repeated biomarker measures over time would offer improved data quality and mitigate possible effects of exposure misclassification bias.

While sample populations were large, population-based, and designed to be nationally representative, the majority of participants across the three cohorts were White, with some Black individuals and small numbers of other racial ethnic and minority groups. Further investigations with sample populations augmented with participants from less represented racial and ethnic minority groups would increase the generalizability of the findings and potentially identify especially vulnerable populations. Furthermore, the subsamples of the populations who underwent biomarker data collection were smaller and potentially qualitatively different from those who completed the biomarker sampling, raising the possibility of selection bias. Comparative analyses of the participants who completed biomarker sampling with those who did not complete biomarker sampling via Chi square and t-tests showed limited differences. In the Add Health study, the 3,384 participants without biomarker data were more likely to be female, White, and with higher educational attainment compared to the 19,897 participants with biomarker data. In the MIDUS study, the 771 participants who were part of the MIDUS II biomarker subsample were more likely to be female, have more education, higher income, non-smokers, low to moderate alcohol consumption than the rest of the cohort of 3,566 participants. In the HRS study, the 209 individuals who did not complete biomarker sampling were more likely to be White or Black than a racial or ethnic minority, compared to the 3,837 participants with biomarker data.

3.5 Conclusions and Future Directions

In this secondary analysis of the large, population-based, and nationally representative Add Health, MIDUS, and HRS datasets, ACEs and APDs were not significantly associated with allostatic load and HRV. An allostatic load profile based on seven biomarkers common across the three datasets was constructed, and associations of ACEs and APDs with allostatic load were

tested via multivariate Poisson regression modelling. The cross-sectional nature of the Add Health and HRS datasets may have limited the ability of the statistical analyses to detect associations. While the MIDUS dataset allowed for longitudinal analysis, the limited size of the biomarker subsample likely restricted statistical power.

While the results of the present study were not statistically significant, evidence from an extensive body of empirical literature indicates robust and consistent associations of ACEs, social isolation, and job strain with allostatic load and HRV. These data demonstrate a need for early intervention in situations of childhood trauma, highlighting the amelioration of childhood adversity as a powerful lever for preventive medicine and improved public health. Hence, the contributions of ACEs and APDs to manifested diseases and clinically relevant biomarkers deserve further investigation. Accordingly, occupational health researchers have identified a need for "longitudinal studies using multi-systemic variables" to evaluate allostatic load and HRV. These findings also identify individuals who experienced ACEs, social isolation, and job strain as at increased risk for allostatic load and related chronic disease conditions in adulthood; such populations who suffered high stress exposures may be considered especially vulnerable and thus promising targets for health intervention programs and government and employer policy directives.

4. Conclusion

This project conducted a comprehensive exposure assessment of work and nonwork related factors and their associations with CVD mortality and allostatic load biomarkers clinically implicated in CVD pathology. This novel and innovative approach to exposure modelling addresses the limitations of prior work in the field of occupational and cardiovascular epidemiology by highlighting the impact of cumulative exposures. The successful

implementation of the analytic strategy and the detection of promising preliminary findings for associations of ACEs and APDs with CVD mortality and allostatic load offer an empirical foundation for future investigational and translational work targeting psychosocial exposures.

Collectively, these findings suggest that high exposure to ACEs and APDs are closely related to allostatic load and multimorbid disease conditions in adulthood, as well as increased risk of CVD mortality. While the findings of the present projects were not always statistically significant across the three cohorts of the Add Health, MIDUS, and HRS studies, the general trend of results indicate increased risk of CVD mortality and potentially increased allostatic load due to high exposure to ACEs and APDs. In context of the rapidly expanding literature on ACEs, social isolation, job strain, and allostatic load and HRV, these results suggest cumulative psychosocial exposures may increase the risk of chronic cardiometabolic and inflammatory risk conditions implicated in CVD pathogenesis and mortality.

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