Chronic Pain, Its Lifecourse Origins in Socioeconomic Status, and the Mediating Role of Chronic Stress-Related Biomarkers

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A Summary of the Work

Chronic pain (CP) imposes significant burdens on individuals and healthcare systems. Identifying its risk factors is essential for informing prevention and intervention strategies. While socioeconomic inequalities in health are well-established, the relationship between socioeconomic status (SES) and CP, particularly its mechanisms, remains underexplored. Given CP's strong link to chronic stress dysregulation, incorporating biomarkers into research provides critical insights. Biological processes such as allostatic load (AL) and hypothalamic-pituitary-adrenal (HPA) axis dysregulation illuminate how SES might contribute to CP, while the lifecourse model contextualizes how exposures across life stages influence CP risk. However, these frameworks remain underutilized in pain research.

This study addressed CP through four aims: (1) assessing AL's prospective association with CP outcomes, (2) examining HPA axis dysfunction, measured by diurnal salivary cortisol rhythms, and CP outcomes, (3) exploring the lifecourse SES-CP relationship, and (4) evaluating AL and salivary cortisol rhythms as mediators. Data from the MIDUS study provided longitudinal evidence spanning 20 years.

Findings revealed that metabolic dysregulation in AL predicted high interference CP and pain in three or more sites. Individuals without baseline CP but with blunted diurnal cortisol slopes were more likely to develop pain in three or more sites after seven years. Chain-of-risk models showed that adult SES mediated the effects of early-life disadvantage on cortisol dynamics and AL phenotypes. Lifecourse SES was directly associated with CP interference via recent SES, while its link to CP widespreadness appeared contingent on multimorbidity. Chronic stress biomarkers did not mediate these relationships. These results underscore the roles of chronic

stress dysregulation and SES disparities in shaping CP outcomes. Addressing these factors through targeted interventions can enhance prevention and management. Lifecourse SES perspectives and stress biomarkers offer valuable insights into CP, informing precise strategies for its mitigation.

Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

Chapter 2 of my thesis has been published in BMC Public Health (Liang and Booker, 2024), while Chapter 3 is currently undergoing a second revision and will be resubmitted to the Journal of Pain. Additionally, part of Chapter 4, which examined the mediating role of allostatic load, has been published in Frontiers in Public Health (Liang, 2024). As the first or sole author of these three articles, I made the primary contributions and was responsible for every stage of the research process, including formulating the research questions, conducting empirical analyses, and drafting and revising the manuscripts. Collaborators have been appropriately acknowledged as co-authors to recognize their valuable contributions to these studies.

Biographical Sketch

The author was born in Zhongshan, Guangdong, China. In 2016, he was admitted to China Youth University of Political Studies. In May 2017, the Graduate School of the Chinese Academy of Social Sciences established the University of the Chinese Academy of Social Sciences, integrating undergraduate and select graduate education resources from China Youth University of Political Studies. He graduated from the University of the Chinese Academy of Social Sciences in 2020. During his undergraduate studies, he worked briefly as a research assistant, conducting field research on migrant and at-risk children while evaluating organizations that provided social work services for these children. From 2020 to 2021, he pursued a Master of Science in Social Research Methods and Statistics at the University of Manchester. In January 2022, he began his doctoral research on chronic pain under the supervision of Dr. Cara Booker and Dr. Laura Fumagalli at the Institute for Social and Economic Research at the University of Essex.

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Abstract

Each year, chronic pain (CP) significantly impacts various aspects of life and imposes a substantial burden on healthcare systems. Identifying risk factors for CP is crucial to alleviate the burden on individuals, inform preventive and interventional medical strategies, and reduce public health demands. While research has established socioeconomic inequalities in disease prevalence, studies examining the relationship between socioeconomic status (SES) and CP within the general population remain limited. In particular, limited research has addressed whether and how SES is associated with chronic pain. Given the close link between CP and dysregulated chronic stress, epidemiological survey data incorporating biomarkers offers new opportunities to explore this association. Investigating biomarkers of chronic stress dysregulation in relation to CP not only provides insight into how SES may contribute to CP but also adds valuable risk factor information to the broader field of pain epidemiology, aiding the development of precise pain management. Additionally, the lifecourse model, which explains the origins of chronic diseases by outlining how disease risk exposures at various life stages relate to future disease outcomes, holds promise for informing optimal timing for interventions. However, this model has not been thoroughly examined in the context of chronic pain.

The first and second aims of this paper are to examine the associations between CP and biomarkers of chronic stress dysregulation. Typically, chronic stress dysregulation is reflected in dysregulation within the hypothalamic-pituitary-adrenal (HPA) axis and multisystem dysregulation, with the latter commonly measured through allostatic load (AL). These two investigations are essential, not only because they represent different mainstream measurements of chronic stress dysregulation but also because they provide detailed

information on how localized and multisystem stress dysregulation may contribute to chronic pain, enriching prevention strategies. The third and fourth aims of this study investigate the association between lifecourse SES and CP, and separately examine the potential mediating roles of AL and salivary cortisol.

To address these aims, we utilized different samples from the MIDUS study. Aim 1 examined the prospective relationship between AL, measured in the Biomarker Project of MIDUS 2 (2004-2006), and CP in MIDUS 3 (2013-2014). Aim 2 investigated the link between HPA axis dysregulation, as measured in the National Study of Daily Experiences (NSDE) of MIDUS 2, and CP in MIDUS 3. Aims 3 and 4 assessed the association between lifecourse SES and CP using three waves of MIDUS data spanning 20 years, with separate analyses examining the mediating roles of AL and salivary cortisol.

For Aim 1, findings indicated that metabolic dysregulation phenotypes in AL were prospectively associated with high interference CP and with pain at three or more sites. In Aim 2, we found that among individuals without baseline chronic pain, those with blunted early and mid post-wake diurnal cortisol slopes (DCSs) had higher odds of developing pain in three or more regions approximately seven years later. In Aims 3 and 4, findings supported chain-of-risk models linking SES with the mid post-wake DCS and the cortisol dynamic range (CDR), suggesting that proximal adult socioeconomic disadvantage mediates the adverse effects of early-life disadvantage and directly impacts these cortisol indicators. Additionally, we identified a risk chain for metabolic dysregulation phenotypes in AL, with both childhood and recent SES directly linked to these phenotypes. Our results further substantiated a chain-of-risk model connecting lifecourse SES with CP interference, highlighting the mediating role

of recent SES. For CP widespreadness, we found that the relationship between lifecourse SES and the number of pain sites may be contingent on the degree of multimorbidity. However, no mediating role of chronic stress biomarkers was observed.

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1 Introduction

1.1 What is chronic pain and what are its consequences?

According to the International Association for the Study of Pain (IASP), pain is defined as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (Raja et al., 2020). CP, on the other hand, is defined as pain that persists or recurs for longer than three months (Nicholas et al., 2019) according to IASP. Compared to the current definition, the previous definition of CP described it as "pain that persists past normal healing time" (Bonica and Hoffman, 1954). This earlier definition of pain and by extension, CP, implicitly acknowledges that CP originates from an initial injury or condition but is less explicit about the emotional aspects of pain or the possibility of CP occurring without an initial injury (Treede et al., 2019). These limitations in the early pain and CP definitions have been acknowledged and addressed in the current defintions.

The updated definition of pain reflects a further distinction between types of pain and signifies a shift in pain management from the traditional biomedical model to a biopsychosocial model. Chronic primary pain refers to pain persisting or recurring in one or more anatomical regions for more than three months, accompanied by significant emotional distress or functional disability, and cannot be better explained by another chronic pain condition (Nicholas et al., 2019). The diagnostic classifications within this group are divided into chronic widespread pain, complex regional pain syndromes, chronic primary headache and orofacial pain, chronic primary visceral pain, and chronic primary musculoskeletal pain (Treede et al., 2019). Chronic secondary pain syndromes, on the other hand, are associated with other diseases where pain arising as a symptom secondary to an underlying disease or

medical condition. Chronic secondary pain syndromes include chronic cancer-related pain, chronic postsurgical or posttraumatic pain, chronic neuropathic pain, chronic secondary headache or orofacial pain, chronic secondary visceral pain, and chronic secondary musculoskeletal pain (Treede et al., 2019).

Pain is subjective and personal, making self-reporting the most commonly used method for its assessment (Fillingim et al., 2016). Evaluations of pain encompass various domains, such as pain intensity and pain impact. Categorical scales, numerical rating scales, visual analog scales, the Faces Pain Scale (McGrath et al., 2008), the Brief Pain Inventory (Keller et al., 2004), and the Graded Chronic Pain Scale (Von Korff et al., 1990) are commonly used to measure pain intensity or pain impact. Other tools including the McGill Pain Questionnaire (Katz and Melzack, 2011), PainDetect (Freynhagen et al., 2006), the Neuropathic Pain Scale (Galer and Jensen, 1997), the Neuropathic Pain Symptom Inventory (Bouhassira et al., 2004), the Leeds Assessment of Neuropathic Symptoms and Signs (Bennett, 2001), and the Dolour Neuropathique-4 Questions (DN4). are used to measure perceived attributes of pain (Bouhassira et al., 2005). In addition, other pain assessments consider the temporal characteristics of pain, such as duration (e.g., time since chronic pain onset in months or years) and variability (e.g., the presence or absence of pain and fluctuations in its intensity over time). They also examine pain location and bodily distribution, often through pain drawings, as well as provocative pain measures and pain behaviors, such as straight leg raising, digital palpation, facial expressions, and actions like limping, guarding, or bracing (Fillingim et al., 2016).

CP and its poor prognosis are the primary cause of years lost to disability among Americans (US Burden of Disease Collaborators et al., 2018). In 2016, it was estimated that over fifty

million American adults experienced CP. By 2021, approximately 20.9% of American adults (51.6 million people) were reported to have experienced CP, with 6.9% (17.1 million people) suffering from high-impact CP, which significantly restricts daily activities and involves greater pain intensity (Rikard et al., 2023). CP imposes a substantial economic burden on both the public health system and individuals. For instance, a report by the Institute of Medicine in 2010 estimated that CP incurs annual costs ranging from $560 billion to $635 billion in medical expenses and productivity losses (Steglitz et al., 2012).

Furthermore, beyond the economic implications, CP exacerbates broader personal and societal challenges in the United States. Among CP patients, there is an increased prevalence of anxiety and depression, accompanied by observed reductions in brain gray matter, which are associated with alterations in emotional regulation and cognition (Bushnell et al., 2015). Additionally, research consistently reports a decline in the overall quality of life, deterioration in interpersonal relationships, and impaired workplace performance among CP patients (Fine, 2011; Meints and Edwards, 2018). Given the impacts of CP on individual well-being, public health, and the economy, continued research on etiology of CP is critical. Understanding the mechanisms of CP, as well as identifying effective interventions, is crucial for improving the prognosis and quality of life for those affected. The ongoing rise in CP prevalence, coupled with its connection to psychological distress and functional limitations, underscores the urgency to explore new strategies for prevention and treatment. Furthermore, with CP contributing to societal issues like reduced workplace productivity and increased mental health concerns, addressing this condition is essential to alleviating its broader social and economic burdens.

In recent years, the rising all-cause mortality rate among middle-aged Americans and the declining life expectancy in the U.S. have garnered significant public concern (Woolf and Schoomaker, 2019). Leading contributors to this trend are drug overdoses, alcohol-related deaths, and suicides, collectively referred to as "deaths of despair" (Case and Deaton, 2017). These deaths have been linked to several socioeconomic factors, including persistent trade deficits, ongoing deindustrialization, and long-term economic decline, particularly affecting industrial workers with lower educational attainment (Case and Deaton, 2022). The absence of robust social safety nets and the unique market for opioids and other drugs further exacerbate this sense of despair (King et al., 2022). The rising prevalence of CP parallels the trends in deaths of despair, with the rate of adult pain increasing steadily since the 1990s (Grol-Prokopczyk, 2017; Zajacova et al., 2021a; Zimmer and Zajacova, 2018). In this context, CP is increasingly recognized as a significant contributor to the epidemic of despair, both as a direct and indirect driver of these deaths (Macchia, 2023).

CP contributes to deaths of despair not only through its debilitating physical effects but also through its profound social and psychological consequences. For many, CP leads to unemployment, disability, and social isolation, which, in turn, increase the risk of suicide, substance abuse, and alcohol dependency (Racine, 2018). The link between CP and mental health is well-documented, with pain often triggering or exacerbating anxiety and depression (Fonseca-Rodrigues et al., 2022), both of which are closely tied to suicidality. Furthermore, CP is strongly associated with substance use disorders, including opioid and alcohol dependence (Egli et al., 2012; Martel et al., 2018). As CP patients turn to opioids or alcohol for relief, they become more vulnerable to drug overdose and alcohol-related deaths, further fueling the deaths of despair crisis. Addressing the rising burden of CP is therefore critical to mitigating

deaths of despair. Providing better pain management, access to mental health services, and economic support for those disabled by pain may potentially reduce the incidence of these preventable deaths. Given the substantial consequences of CP, identifying modifiable risk factors for CP may add information to pain prevention and management.

1.2 Confounders, colliders, mediators, and moderators

1.2.1 Confounders

Four key concepts are confounders, colliders, mediators, and moderators, each describing a distinct way a third variable can influence the relationship between an exposure and an outcome. Understanding these roles is essential for robust study design, accurate associations, and meaningful interpretation of findings in social epidemiologic research on CP.

In epidemiology, a confounder is classically defined as an extraneous variable that is associated with both the exposure and the outcome, but is not on the causal pathway between them. Because a confounder influences both variables of interest, it can create a spurious association or mask a true relationship if not properly controlled. In other words, the presence of a confounder can mix up the effects, making it unclear whether the exposure truly affects the outcome or if the observed association is partly or wholly due to the confounding factor. To qualify as a confounder, a variable generally must: (1) be correlated with the exposure, (2) have a causal (or at least independent) influence on the outcome, and (3) not be a result of the exposure (Morabia, 2011). When these conditions hold, failure to account for the confounder can bias the estimated exposure-outcome relationship.

By controlling for confounders, researchers remove the backdoor paths of spurious association and obtain a clearer estimate of the true causal effect of the exposure on the outcome. Neglecting a confounder can lead to biased conclusions, for instance, overstating the effect of exposures on pain when in reality part of that observed effect was due to unmeasured factors. Conversely, over-adjusting for variables that are not true confounders can attenuate or distort the effect estimates (Gao et al., 2025). In sum, accounting for confounders improves the internal validity of studies and strengthens confidence that an observed association reflects a likely causal relationship rather than a mere correlation due to some third factor.

1.2.2 Colliders

A collider is the conceptual opposite of a confounder. While a confounder is a variable that influences both the exposure and the outcome, a collider is influenced by both, it is a common effect of two variables, often the exposure and outcome. In causal diagrams, a collider appears where two arrows converge. Crucially, while failing to control for a confounder can bias results, controlling for or conditioning on a collider can also introduce bias, but for the opposite reason. Conditioning on a collider induces a spurious association between its causes, even if no true causal relationship exists between them. In epidemiology, this is known as collider bias, a type of selection bias that arises when analysis is restricted to individuals selected based on a variable that lies downstream of both the exposure and outcome (Hernán and Monge, 2023).

A classic illustration of collider bias can be seen in the context of U.S. college admissions. Among admitted students, there often appears to be an inverse relationship between

academic aptitude and athletic ability, that is, students with strong academic records tend to be less athletically inclined, and vice versa. However, this observed association is not necessarily causal; rather, it reflects the effect of conditioning on a collider. Since both academic ability and athletic talent can independently increase a student's likelihood of admission, restricting analysis to admitted students (i.e., conditioning on college admission) introduces a non-causal, negative association between these two traits (Griffith et al., 2020).

1.2.3 Mediators and moderators

A mediator is an intermediate variable that transmits the effect of the exposure to the outcome. In a causal sequence X→M→Y, the mediator M lies on the pathway from X to Y, meaning that X affects M, which in turn affects Y (Rijnhart et al., 2021). Understanding mediators is crucial for explaining how or why an exposure influences an outcome. Each validated mediator adds a layer of explanation to the biopsychosocial model, telling us how an upstream factor gets under the skin to influence CP. Identifying mediators allows researchers to unpack the black box between cause and effect and can suggest targets for intervention. It is important to note that mediators should not be adjusted for in analyses that aim to estimate the total effect of an exposure on outcome, because doing so blocks the very pathway through which the effect operates (Schisterman et al., 2009). Adjusting for a mediator would remove part of the causal effect. Instead, mediators are typically examined in mediation analyses to decompose total effects into direct and indirect components.

A moderator is a variable that alters the strength or direction of the relationship between an exposure and an outcome. In statistical terms, a moderator is involved in an interaction effect: the effect of X on Y depends on the level or value of the moderator Z. Unlike a mediator, a

moderator is not on the causal pathway between X and Y, but rather influences the magnitude of the X→Y association under different conditions. Epidemiologists often refer to this as effect modification, the effect of the exposure is modified by another factor. Identifying moderators is key to understanding for whom or under what conditions an exposure has a larger or smaller impact. This has practical importance as it can reveal vulnerable subgroups or suggest that interventions might need tailoring based on patient characteristics.

1.3 Biomarkers of chronic stress: potential risk factors and mediators for CP

Biological processes not only serve as proximal risk factors for disease but also act as mediators that link a wide range of psychosocial risk factors with disease outcomes. Biological investigations of CP have largely been conducted in laboratory settings, as well as within small-scale and clinical samples, which poses challenges to the generalizability of the results (Harris et al., 2008). In recent years, the collection of biomarkers in population-based epidemiological and social surveys has aided in addressing the objectives of the National Pain Strategy, which aims to identify risk factors for CP across populations (Interagency Pain Research Coordinating Committee, 2022). Although the underlying mechanisms of CP remain unclear, numerous studies suggest that stress dysregulation due to chronic stress may be an etiological risk factor for CP (Woda et al., 2016).

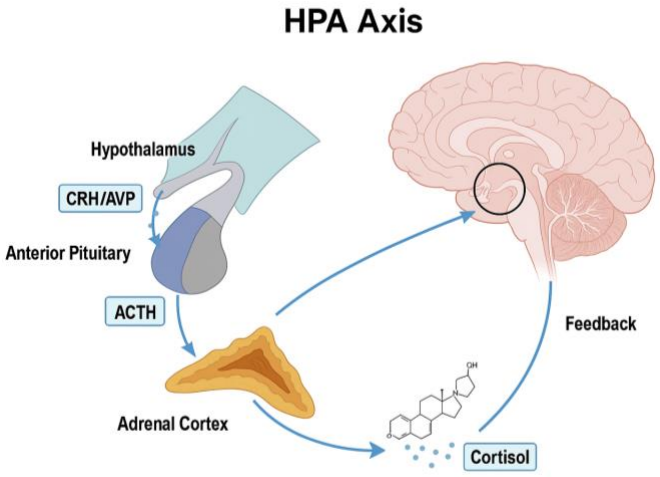
1.3.1 Biological response to chronic stress

An organism's response to stress involves a coordinated cascade of neuroendocrine and autonomic processes aimed at promoting adaptation and survival. Upon perceiving a stressor, the sympathetic nervous system (SNS) is rapidly activated via projections from the locus coeruleus and brainstem nuclei. This initiates the "fight or flight" response, characterized by increased heart rate, vasoconstriction, bronchodilation, and energy mobilization, largely

mediated by the adrenal medulla's secretion of catecholamines, adrenaline (epinephrine) and noradrenaline (norepinephrine) (McEwen, 2007).

Simultaneously, the hypothalamic-pituitary-adrenal (HPA) axis is engaged. The paraventricular nucleus (PVN) of the hypothalamus secretes corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) into the hypophyseal portal system, stimulating the anterior pituitary to release adrenocorticotropic hormone (ACTH) into systemic circulation. ACTH then acts on the adrenal cortex, promoting synthesis and secretion of cortisol, the primary glucocorticoid in humans (Herman and Cullinan, 1997). Cortisol helps maintain energy supply by increasing glucose levels. Cortisol also exerts negative feedback on both the hypothalamus and pituitary, reducing CRH and ACTH output through binding to glucocorticoid receptors (GRs) in these regions, thereby attenuating the stress response once the stressor is removed. Meanwhile, the parasympathetic nervous system (PNS), primarily through vagal activation, serves to restore autonomic balance by promoting digestive activity, reducing cardiovascular arousal, and supporting recovery processes (Thayer and Sternberg, 2006). This dynamic interplay between SNS activation, HPA-axis modulation, and PNS-mediated restoration ensures the body mounts an efficient acute stress response while returning to baseline once safety is re-established.

Figure 1-1 The hypothalamic-pituitary-adrenal axis pathway activated during stress (Kim, 2024)



The hypothalamic-pituitary-adrenal (HPA) axis and autonomic pathways activated during stress: External stressors (physical or psychological) trigger the hypothalamus to secrete corticotropin-releasing hormone (CRH) along with arginine vasopressin (AVP). CRH and AVP released from the hypothalamic paraventricular nucleus act on the anterior pituitary, stimulating the release of adrenocorticotropic hormone (ACTH). In turn, ACTH enters the circulation and prompts the adrenal cortex to synthesize and secrete glucocorticoid hormones (cortisol in humans). As cortisol levels rise, they exert negative feedback on the HPA axis: cortisol binds to glucocorticoid receptors in the hypothalamus and pituitary, suppressing further CRH and ACTH release.

However, the repeated and long-standing activation of the stress response system is harmful, a condition well described by dysregulations of the HPA axis and by the framework of allostatic load (AL). Prolonged activation of the HPA axis leads to sustained secretion of cortisol, which over time disrupts negative feedback regulation by impairing GR sensitivity and downregulating receptor expression in key brain regions such as the hippocampus and hypothalamus (Fries et al., 2005; McEwen and Gianaros, 2010). This impaired feedback loop results in inadequate suppression of CRH and ACTH, perpetuating hypercortisolemia and altering circadian rhythms of cortisol release. Initially, such dysregulation often presents as HPA-axis hyperactivity, but over time may transition to hypoactivity (Fries et al., 2005). In parallel, the autonomic nervous system undergoes maladaptive shifts. The SNS remains persistently activated, maintaining elevated norepinephrine and epinephrine levels, while the PNS becomes less effective in restoring homeostasis (McEwen and Seeman, 1999). This reduced vagal tone has been associated with poorer emotion regulation, increased inflammatory tone, and reduced cardiovascular flexibility. Research has found that dysregulation of the HPA axis is associated with various clinical outcomes (Miller et al., 2007).

Another concept reflecting chronic stress dysregulation is AL, which encompasses information about HPA axis dysregulation while additionally incorporating the long-term consequences of chronic stress, broadly involving dysregulation across downstream systems. AL refers to the cumulative wear and tear on the body and brain resulting from ongoing efforts to adapt to environmental demands (McEwen and Stellar, 1993). Changes in the core response systems, including the HPA axis, SNS and PNS, significantly affect the downstream systems.

Prolonged HPA axis activation leads to sustained cortisol secretion, which, while initially adaptive, can promote metabolic disturbances when chronically elevated, contributing to insulin resistance, visceral adiposity, and dyslipidemia (McEwen and Seeman, 1999). Importantly, chronic stress does not uniformly lead to hypersecretion; over time, some individuals exhibit hypoactivity of the HPA axis, including flattened diurnal cortisol rhythms or glucocorticoid resistance at the receptor level. Such dysregulation may paradoxically enhance pro-inflammatory signaling, since glucocorticoids normally exert anti-inflammatory effects (Hannibal and Bishop, 2014). Persistent SNS hyperactivation increases cardiac output and vascular tone, raising heart rate and blood pressure, thus burdening the cardiovascular system and promoting atherogenesis (Seeman et al., 2010). At the same time, blunted PNS activity impairs the body's capacity to return to baseline, leaving it in a persistent state of physiological arousal and compromised recovery (Thayer and Lane, 2007). This imbalance between activation and restoration constitutes a key mechanism underlying allostatic burden.

Collectively, these physiological changes constitute the secondary outcomes of allostatic load and have measurable impacts on various downstream systems, including metabolic (e.g., glucose and lipid regulation), immune (e.g., inflammation), cardiovascular (e.g., blood pressure), and even neural (e.g., hippocampal atrophy) domains. A recent systematic review reaffirmed that higher AL index scores are consistently associated with adverse outcomes across a range of conditions, including cardiovascular disease, diabetes, cognitive decline, and premature mortality (Guidi et al., 2021). Thus, AL offers a powerful integrative model for linking chronic psychosocial stress to long-term physiological dysregulation and adverse health outcomes. It also provides a valuable conceptual bridge between biological embedding of stress and the development of complex, stress-related chronic conditions such as CP.

1.3.2 Two proposed biological risk factors of chronic stress for CP: HPA axis dysfunction and AL

Regarding CP research, separate examinations of HPA axis dysfunction and systematic stress response dysregulation will add to current epidemiological studies of CP. The dysregulation of the HPA axis and AL are primary biomarkers for measuring chronic stress dysregulation. Therefore, studying the associations between HPA axis dysregulation, AL, and CP separately is essential. According to the AL framework, HPA axis dysregulation marks the onset of multisystem dysregulation, while AL may reflect a state of prolonged chronic stress dysregulation. Their associations with CP could provide additional insights into the chronicization of pain.

HPA axis is a primary stress response system and recent meta analysis has suggested trends toward specific deviations of HPA axis in CP patients (Beiner et al., 2023). The dysregulation of the HPA axis transitions from a state of hyperactivity to hypoactivity (Fries et al., 2005). This process is typically accompanied by the downregulation or resistance of glucocorticoid receptors and an increased affinity of cortisol for mineralocorticoid receptors, both of which are closely associated with chronic inflammation (Hannibal and Bishop, 2014). Furthermore, during the attenuation of HPA axis activity, antagonistic effects of the HPA axis on catecholamines is weakened, exacerbating inflammation in conjunction with the aforementioned conditions (Fries et al., 2005; Hannibal and Bishop, 2014). Inflammation is often directly related to pain perception (Ji et al., 2018). Moreover, genes related to the HPA axis play a crucial role in regulating stress responses and glucocorticoid signaling. Genetic variations in these genes are closely associated with the development of CP. For instance, the

methylation of HPA axis genes such as pro-opiomelanocortin and corticotropin-releasing hormone binding protein can predict the progression of CP (Branham et al., 2023). Additionally, impaired glucocorticoid receptor function leads to a failure to inhibit nuclear factor-κB (Pavlov et al., 2003), resulting in the transcription of algogens such as cytokines, growth factors, and chemokines like CCL2, which trigger inflammation and stimulate or sensitize nociceptors, inducing central sensitization and hyperalgesia (Kawasaki et al., 2008; Walsh and McWilliams, 2014). In addition, chronic inflammation linked to HPA axis dysregulation further enhances the excitability of sensory transmission pathways, leading to peripheral and/or central nervous system sensitization (Veldhuijzen et al., 2018). This increases synaptic efficiency and reduces inhibition, amplifying pain responses, and can allow low-threshold sensory inputs to activate pain circuits even in the absence of inflammation (Woolf, 2011).

In addition to HPA axis, AL encompasses a broader range of biological responses to stress, emphasizing the cumulative burden of chronic stress from a holistic perspective. Evidence suggests a substantial overlap between AL and CP in physiological and biological manifestations (Borsook et al., 2012; Woda et al., 2016). For example, dysfunctions in HPA axis, SNS, PNS, and immune system, which are manifestations of AL, are often observed in CP patients (Juster et al., 2010; Woda et al., 2016). Although the field has not yet reached a consensus on how the systematic stress response results in CP, peripheral and central sensitization is thought to be a possible mechanism (Veldhuijzen et al., 2018). For example, AL often comes with changes in the central nervous system's processing of pain (Apkarian et al., 2011). This includes alterations in the function and connectivity of brain regions involved in pain perception, such as the amygdala, prefrontal cortex, and anterior cingulate cortex

(Zambreanu et al., 2005). These changes can result in central sensitization, where the central nervous system becomes more responsive to pain signals, leading to an amplification of pain (Woolf, 2011). In addition, inflammation is extensively connected to various dysregulated stress response systems (Veldhuijzen et al., 2018), during which immune cells release pro-inflammatory cytokines (such as IL-1β, TNF-α, and IL-6), chemokines, and growth factors that sensitize nociceptors (Ji et al., 2014), contributing to pain. Chronic stress also disrupt cardiovascular and metabolic systems, potentially amplifying spinal nociception by weakening the descending inhibition of spinal pain processing, which is closely related to heightened pain perception (Rhudy et al., 2021).

HPA axis dysregulation and AL represent distinct but interrelated manifestations of the chronic stress response, each carrying important implications for understanding and managing CP. HPA axis dysregulation may serve as an early indicator of maladaptive stress responses (Juster et al., 2010), highlighting potential targets for timely interventions before long-term and widespread physiological damage occurs. By contrast, AL reflects the cumulative and systemic impact of ongoing stressors, encompassing widespread alterations across multiple biological systems. Investigating these two processes individually allows us to identify both the initial signs of dysregulation and the subsequent, more entrenched physiological consequences. From an epidemiological and public health perspective, understanding HPA axis dysregulation can inform early prevention strategies, improve clinical detection of populations at heightened risk, and guide the development of targeted behavioral and pharmacological therapies. Similarly, recognizing the evolution of AL offers insights into the mechanisms by which chronic stress contributes to downstream health complications, including CP, thus underscoring the need for comprehensive, long-term

interventions and policies aimed at reducing stress-related disease burden in the community. In summary, biomarkers related to chronic stress may serve as an intermediary mechanism linking distal risk factors to CP outcomes, offering a potential pathway to deepen the understanding of CP etiology.

1.4 Theoretical framework on the association between socioeconomic status and health

In recent years, the growing socioeconomic disparities in CP have garnered increasing attention. Understanding the potential mediating mechanisms linking SES and CP can inform the development of effective interventions to curb the prevalence of CP, with biological risk factors associated with chronic stress dysregulation being possible mediators. The prevalence of CP in the United States has followed a pattern where the most socioeconomically disadvantaged individuals suffer from more severe CP, with the situation worsening as the macroeconomic conditions deteriorate (Case and Deaton, 2022; King et al., 2022; Zajacova et al., 2021b). The origins of sociological studies on health can be traced back to the work of Émile Durkheim, whose research demonstrates that economic instability can lead to a state of anomie, increasing rates of suicide and other social pathologies (Durkheim, 2002). Following this perspective, socioeconomic instability may be related to an individual's health status.

The concept of socioeconomic status (SES) originated from the works of social theorists Karl Marx and Max Weber. Marx posited that an individual's social class is determined by their relationship to the means of production (Galobardes et al., 2007). Those who own the means of production occupy higher social class positions (Krieger et al., 1997). In contrast, Weber

expanded the definition to include not only economic status but also social status and political power. Weber proposed that disparities in economic opportunities, knowledge, and skills lead to differences in 'life chances,' resulting in unequal probabilities of individuals accessing specific economic goods (Lynch and Kaplan, 2000; Weber, 2009). SES has long been viewed as a fundamental cause of chronic disease inequalities (Phelan et al., 2010). In the field of social epidemiology, the fundamental cause theory (FCT) plays a dominant role in explaining the origins and disparities of chronic diseases. The FCT posits that individuals with higher SES possess more flexible resources, including knowledge, money, power, prestige, and beneficial social connections, enabling them to avoid health risks, thereby creating health disparities among groups (Clouston and Link, 2021; Phelan et al., 2010).

With the advancement of social epidemiology, new supplements to the theory of fundamental causes have emerged continuously. These new theoretical frameworks even extend to explaining the social stratification of infectious diseases, with the social history theory being a notable example. This theory encompasses explanations for the socioeconomic disparities observed in both infectious and chronic diseases. *The social history theory, with its inflection point approach*, proposes that temporal differences in the availability of new knowledge or technologies rooted in the SES hierarchy contribute to health inequalities (Clouston and Link, 2021). Specifically, diseases transition through four patterns in prevalence or mortality. At the onset of a disease outbreak, all social groups face similarly high levels of risk due to the limited availability of knowledge regarding its prevention and treatment. As new knowledge or technology diffuses disproportionately and at different paces between SES groups, the gaps in prevalence and prognosis will increase. Eventually, as innovations spread more widely and deeply, the inequalities will decrease and ideally be

eliminated (Clouston et al., 2016). For instance, greater access to colonoscopy screenings and the ability of individuals with higher SES to shelter in place and practice social distancing contribute to disparities in colorectal cancer mortality and COVID-19 prevalence, respectively, particularly during the early stages of disease-related knowledge dissemination. With the widespread adoption of colonoscopy, the deepening public awareness of social distancing, and the broad distribution of vaccines, mortality rate disparities have gradually diminished (Clouston et al., 2021, 2017). The social history theory seeks to elucidate the historical patterns of disease emergence and decline as stratified by SES, serving as a complement to the epidemiological transition theory. This perspective may shed light on the current phase of widening inequality in the prevalence of CP, potentially linked to the uneven progress in developing effective pain treatments and management strategies. However, the theory faces limitations in explaining CP-related SES disparities at the individual level due to the inherent risk of ecological fallacy.

The metamechanism theory is another extension to FCT, suggesting three metamechanisms—*spillovers, habitus, and institutional processing*—to account for the disparities without assuming agency lies exclusively with the individual, not with institutions (Freese and Lutfey, 2011). This theory complements to the theoretical narrative of purposive action with different means (Freese and Lutfey, 2011). Specifically, this theory addresses the dilemma that arises when health-promoting resources, such as health behaviors, are easily accessible and their benefits are widely known, yet disparities endure. Spillovers refer to the phenomenon in which individuals with higher SES experience better health outcomes than those with lower SES, largely as a result of contextual advantages rather than individual agency. Habitus emphasizes socialization and upbringing in different SES, leading to "habitual ways of acting

when performing routine tasks" (Cockerham, 2005). The health practice is not intentional but rather a result of unconscious inertia rooted in individuals' SES. Institutional processing describes how social institutions, such as the family and the health care system, reproduce health inequalities through differentiated treatment. For example, women who quit smoking may suffer from second-hand smoke from spouses and extended family members. Additionally, access to and practices by the healthcare system may vary based on patient socio-demographic characteristics (Clouston and Link, 2021; Freese and Lutfey, 2011).

In the CP settings, spillovers suggest that individuals in higher SES benefit from healthier environments (e.g., better healthcare, less stress) that reduce CP, even without active management, while lower SES individuals lack these contextual advantages. Habitus points to how socialization shapes habitual responses to pain, with lower SES individuals possibly normalizing pain or using less effective coping strategies, deepening disparities. Institutional processing highlights that healthcare systems often provide different levels of care based on SES, leading to under-treatment of CP in disadvantaged populations. Moreover, people with low SES are at higher risk for CP due to a compound effect of spillover, institutional handling, and habitual patterns.

A competitive theory to the metamechanism theory is *social stress theory* of SES. Stress is defined as "a state of arousal resulting either from the presence of socioenvironmental demands that tax the ordinary adaptive capacity of the individual or from the absence of the means to attain sought-after ends" (Aneshensel, 1992). Stressors are external challenges or obstacles, while stress refers to the internal response they trigger. Chronic stress, therefore, refers to stress that endures for a long time (Baum et al., 1999). Individuals facing unfavorable

socioeconomic conditions suffer doubly: they experience demands and have limited access to resources. Stressful situations like financial difficulties, family conflicts, bereavement, substandard living conditions, crime, violence, and discrimination are linked to adverse socioeconomic conditions. Secondly, these conditions restrict access to essential resources such as money, education, power, prestige, and valuable social networks, which are necessary to manage these demands. In addition to the severity of these stressors, characterized by the imbalance between demands and resources, repeated exposure to these stressors increases the likelihood of chronic stress (Crielaard et al., 2021). Both competing theories underscore the external and structural plight, as well as the restricted responses of individuals. This thesis adopts the social stress theory of SES as its theoretical foundation. The stress theory offers a biosocial framework that links social disadvantage to health outcomes, allowing us to explore mediating mechanisms beyond the classic health behavior approach. This provides more nuanced insights for interventions aimed at improving CP management and reducing the burden of pain across populations. Although recent systematic reviews have indicated an association between SES and dysregulation related to chronic stress (Dowd et al., 2009; Johnson et al., 2017), research on the biosocial mechanisms of CP remains limited. Moreover, CP may represent a biological consequence of prolonged exposure to chronic stress, making stress-related biological outcomes a critical mediator in the relationship between SES and CP. In the following chapters, I will delve into the connections between chronic stress-related biological responses and CP.

1.5 Association between SES indicators and CP

The study of SES and its relationship to health has a long history, but due to its complexity, there has not yet been a consensus on a unified definition. Currently, social epidemiology

suggest that the core of SES lies in the availability of flexible resources—such as knowledge, money, power, prestige, and beneficial social networks—which may reduce or increase health disparities (Clouston and Link, 2021). SES influences health outcomes because those with greater access to these flexible resources are better able to protect and promote their health (Phelan et al., 2010). For example, individuals with higher SES are often better equipped to adopt healthier behaviors, secure timely medical interventions, or avoid environmental risks, thus reducing their exposure to health hazards. In contrast, those with lower SES may lack access to these resources, making them more vulnerable to adverse health outcomes due to limited access to quality healthcare, nutritious food, safe living conditions, and social support networks.

Given the broad scope of SES, various regions have operationalized SES differently. For instance, in the U.S., social status is measured based on a series of questions regarding (a) ownership of capital assets, (b) control of organizational assets, and (c) possession of skill or credential assets. In Europe, particularly the U.K., social class measurement is based on long-standing occupational class divisions (Krieger et al., 1997). Occupational status can influence health inequalities through material resources, social networks, and lifestyle factors (Galobardes et al., 2006a). Despite the marginal effects of occupation on CP in a recent meta-analysis (Prego-Domínguez et al., 2021a), a substantially larger, more recent study using UK Biobank data, and genome-wide association analysis has suggested that lower occupational positions increase the risk of having CP (Farrell et al., 2023). Among a nationally representative sample of older adults in the United States, people who were not working due to disability had higher odds of having CP compared to those worked as a paid employee (LaRowe et al., 2024). Also, a longitudinal study from Sweden found non-skilled workers at

lower risk of moderate pain worsening compared with skilled and non-manual workers (Prego-Domínguez et al., 2021b).

Additionally, there have been numerous alternative proxies for SES. Income-related measures are often used to assess SES as income directly reflects an individual's ability to acquire material resources. This includes various components such as wages, dividends, interest, child support, alimony, transfers, and pensions. Poverty is a key income-related indicator as well. In the U.S., the poverty threshold is set at a basic level necessary for biological survival and is adjusted for factors such as year, household size, and the age of the household head (Krieger et al., 1997). Absolute deprivation, as measured by the poverty threshold, is just one lens for examining poverty; relative deprivation, which compares household income to the national poverty threshold, is also critical as it reflects the ability to meet survival needs (Diemer et al., 2013). Empirical findings have provided evidence supporting the associations between income measures and CP. For example, a recent internet-based cross-sectional study found that people with lower household income had higher probability of reporting pain lasting six months or more (Johannes et al., 2010). Similarly, more recent studies found people with lower income were more likely to report high impact CP (Strath et al., 2024) or CP (LaRowe et al., 2024).

Social epidemiology literature has long recognized the importance of relative deprivation for health, which is related to the fulfillment of human needs. In some Global South countries, the relationship between socioeconomic status and health is not driven by absolute deprivation but by relative deprivation (Marmot, 2005). Individuals' perception of their economic circumstances are important since they reflect the stress of living in poverty or

economic hardship and a subjective evaluation of one's actual economic resources. Studies have shown that perceived economic hardship is linked to various health outcomes (Diemer et al., 2013). A study using 30-day diaries suggested that daily financial worry and the respondents' ability to afford basic necessities were associated with daily pain experiences among women with a diagnosis of osteoarthritis, fibromyalgia, or both (Rios and Zautra, 2011).

Education is another commonly used SES indicator, typically measured by years of schooling or the highest level of educational attainment. Education serves as a key marker of both individual and family resources during the transition from childhood to adulthood and is a strong predictor of future employment and income. Additionally, education as a form of cultural capital reflects an individual's capacity to access health knowledge and resources, thereby influencing health outcomes (Galobardes et al., 2006b). Education has been suggested as a risk factor for CP. A recent longitudinal study based on samples from four medical clinics across Germany, using the Chronic Pain Grade questionnaire, found that compared to people with tertiary education, people with upper secondary education had higher levels of CP intensity and disability (Fliesser et al., 2018). A more recent study also found an association between lower levels of education and higher risks or having high impact CP (Strath et al., 2024).

In summary, SES is a multidimensional concept. While using a single SES indicator can provide benefits, such as model simplicity or clarifying the mechanisms linking specific aspects of SES to health outcomes, no single indicator can fully represent SES across all studies (Woo et al., 2023), nor can it capture the complexity of SES as a unified construct (Galobardes et al., 2006b). Research relying on single indicators often captures only one dimension of SES and

overlooks how its various dimensions interact to form the broader SES structure. So far, very few studies have used a multidimensional SES measure to examine the association of CP. A longitudinal study from Germany found higher multidimensional SES index were associated with lower CP disability and intensity (Fliesser et al., 2018).

1.6 Absence of life course studies on the association between SES and CP

Barker's hypothesis on fetal programming is widely recognized as a crucial foundation in the early evolution of life course epidemiology (Wagner et al., 2024). It integrates insights from both biomedical and social sciences, proposing that the origins of numerous chronic diseases can be traced back to the 'programming' of biological processes during embryonic development. These processes are significantly influenced by nutritional conditions during pregnancy, or even before conception, which are themselves shaped by the mother's developmental experiences in her own childhood or adolescence (Barker, 1997). After decades of development, the life course theory has evolved into a dominant paradigm in social epidemiology, with its specific components closely intertwined with the cumulative concept of social stress theory (Ben-Shlomo et al., 2014). The theory hypothesizes that risk factors at different life stages may influence health outcomes later in life in various combinations.

Focusing on how life course SES translates into the unequal distribution of health risks in the population is crucial for the prevention and intervention of chronic diseases at the population level (Jones et al., 2019). Life course research on CP can help identify effective periods for intervention, yet related studies remain inadequate (Khalatbari-Soltani and Blyth, 2022). In general, there are four life course models: (a) the accumulation of risk with uncorrelated

exposures, (b) the accumulation of risk with correlated exposures, (c) the chain of risk additive model, and (d) the chain of risk trigger model (Ben-Shlomo et al., 2014).

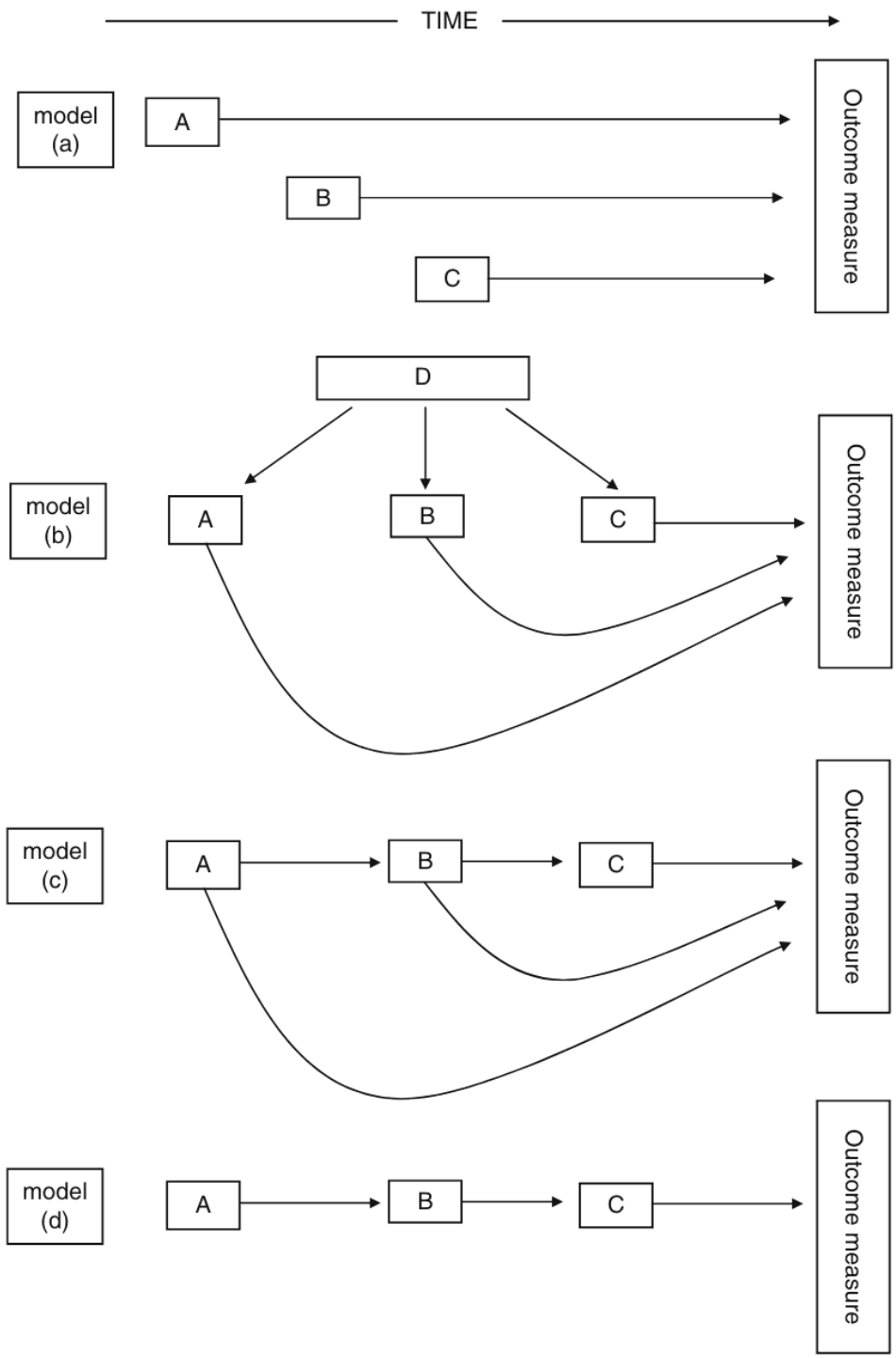
The accumulation of risk with uncorrelated exposures (Figure 1 model a) suggests that various risk factors contribute separately to the overall risk of developing a particular health outcome and these factors are independent of each other. For instance, a person might carry a genetic predisposition, experience the loss of a parent due to war, and face unemployment in adulthood. These exposures are not related to each other. If each exposure increases risk, even to varying extents, then those exposed to multiple factors will have a higher overall risk compared to those exposed to fewer factors. In contrast, *the accumulation of risk with correlated exposures model* (Figure 1 model b) assumes exposures are clustered to an upstream factor, and like *accumulation of risk with uncorrelated exposures*, the exposures collectively increase the overall risk of having a disease. For instance, residing in a disadvantaged neighborhood might be linked to limited access to healthy food options, fewer opportunities for physical activity, and stronger peer pressure to smoke. Each of these factors could cumulatively elevate the risk of developing coronary heart disease (Ben-Shlomo et al., 2014).

The chain of risk additive model (Figure 1 model c) indicates each exposure contributes to an increasing level of risk, with one factor influencing the next in a sequence. For instance, smoking might directly contribute to the development of subclinical atherosclerosis by causing inflammation in the arteries. Additionally, smoking can lead to respiratory issues that decrease physical activity, further lowering aerobic capacity and increasing the likelihood of obesity. Obesity, in turn, is associated with insulin resistance syndrome, which is a significant

risk factor for coronary heart disease. Addressing obesity could improve health outcomes, but individuals who have followed this pathway are still at a higher risk compared to those who were never obese, due to the cumulative effects of their life course exposures. Finally, *the chain of risk trigger model* (Figure 1 model d) suggests that only the final event in a sequence of risk exposures can ultimately lead to a significant health outcome (Ben-Shlomo et al., 2014).

In the case of SES, earlier SES strongly predicts future SES, and SES in different periods may be collectively and directly associated with CP, thus, *the chain of risk additive model* should be the most appropriate model (Ben-Shlomo et al., 2014). Models (a) and (b) disregard the temporal correlation among SES variables, while model (d) overlooks the possible direct association between SES and CP across different time periods. Furthermore, this theoretical model is particularly relevant in cases where the same exposure, such as SES, occurs at different time points, as its impact on later-life health outcomes may vary depending on the timing of exposure (Green and Popham, 2017). Furthermore, the critical period model and sensitive period model are embedded within the chain of risk additive model, offering a more comprehensive framework to explain how the timing of the same exposure can variably affect subsequent disease risk. *The Critical Period Model* suggests that exposure to certain factors during a specific time window can lead to a specific disorder. This model assumes no increased risk if exposure occurs outside this time window. In contrast, the *Sensitive Period Model* posits that exposure during different time windows may result in varying degrees of risk (Ben-Shlomo et al., 2014). Therefore, employing the chain of risk additive model in researching CP can reveal the relationship between SES and CP over the life course, and provide evidence for formulating scientific and targeted public health policies for CP.

Figure 1-2 Life course model (Ben-Shlomo et al., 2014, p. 1529)



1.7 Research aims

Aim 1: To investigate the prospective association between multisystem dysregulation, as indicated by AL, and CP. Evidence suggests a significant overlap between AL and CP symptoms. Although clinical evidence indicates a relationship between AL and CP, few studies have evaluated the cross-sectional association between AL and CP within general population samples. The first chapter aims to establish the prospective association between AL and CP using data from the Midlife in the United States (MIDUS) study, specifically the MIDUS 2 Biomarker Project and MIDUS 3, spanning from 2004 to 2014.

Aim 2: To examine the association between HPA axis function and CP. While clinical evidence suggests that impaired HPA axis function is related to CP, epidemiological findings are mixed. The second chapter focuses on exploring the prospective association between diurnal cortisol patterns and CP, utilizing data from the MIDUS study (2004 to 2014), specifically the MIDUS 2 National Study of Daily Experiences (NSDE) and MIDUS 3.

Aims 3 & 4: To investigate the association between life-course SES and CP, and to separately examine the potential mediating roles of AL and salivary cortisol. Currently, only a few studies have explored the relationship between life course SES and CP, and it remains unclear whether SES influences CP through stress-related biological mechanisms. Chapters three and four utilize data from MIDUS waves 1 through 3 to examine the association between life-course SES and CP, and to separately test the potential mediating roles of AL and salivary cortisol.

Overview of the MIDUS study

The Midlife in the United States (MIDUS) study is a comprehensive national longitudinal investigation into the psychosocial, behavioral, and sociodemographic factors contributing to healthy aging. The baseline survey (MIDUS 1) took place between 1995 and 1996, targeting non-institutionalized, English-speaking adults aged 25-74 years across the United States. Data collection involved detailed phone interviews and self-administered questionnaires (SAQs). This initial phase included a nationally representative probability sample of 3,487 individuals, supplemented by oversamples from specific metropolitan areas (757 individuals), a sample of 950 siblings of the main respondents, and a national sample of 1,914 twin pairs, bringing the total baseline sample to 7,108 U.S. adults. About 9 years later, the second phase (MIDUS 2) followed up with the original participants from 2004 to 2006, using similar methods of phone interviews and SAQs to replicate much of the baseline data collection. The third wave (MIDUS 3), conducted from 2013 to 2014, continued the longitudinal follow-up with the MIDUS 2 participants. This phase also employed phone interviews and SAQs, maintaining consistency with the baseline assessments.

This study utilizes MIDUS as the primary database because it is one of the few public datasets that directly inquires about chronic pain rather than other pain conditions, even though its definition of chronic pain may not be the most up-to-date due to the time of its inception. Other reputable secondary datasets, such as the Health and Retirement Study and the English Longitudinal Study of Ageing, collect data on pain of unspecified duration, while Understanding Society records pain interference over the past month. Additionally, MIDUS boasts a robust collection of biomarkers, including comprehensive AL data and more optimal HPA axis function measurements. Furthermore, compared to the National Child Development

Study, which gathers chronic pain and biomarker data in the same wave, MIDUS offers the added advantage of enabling prospective mediation analyses.

The Biomarker Project of MIDUS 2 contains data from the main survey sample (n = 1,054) and integrates biological, behavioral, and psychosocial factors. It aimed to identify biopsychosocial pathways affecting health outcomes and to explore how behavioral and psychosocial factors protect against or aid recovery from health challenges. The biomarker collection, relevant across multiple health endpoints, was conducted at University of California, Los Angeles (UCLA), the University of Wisconsin, and Georgetown University. Biomarkers assessed the hypothalamic-pituitary-adrenal axis, autonomic nervous system, immune system, cardiovascular system, musculoskeletal system, antioxidants, and metabolism. Specimens included fasting blood, 12-hour urine, and saliva. The protocol involved clinician assessments of vital signs, morphology, functional capacities, bone density, medication use, and physical exams.

Independent of the Biomarker Project of MIDUS 2, the Daily Diary Project (National Study of Daily Experiences, NSDE) of MIDUS 2 includes longitudinal survey samples from 1,842 participants, aiming to study how sociodemographic factors, health status, personality traits, and genetics influence daily stress exposure and reactivity. This project collects four saliva samples per day for cortisol assessment over four consecutive days, starting from day 2 of the diary study, which allows this research to measure the functioning of HPA axis. Before the first NSDE telephone interview, participants received an in-home saliva collection kit with instructions and 16 numbered, color-coded salivettes. Interviewers explained the collection process during the initial interview, and participants began saliva collection the next day.

Saliva samples were collected upon waking, 30 minutes after getting up, before lunch, and at bedtime. Exact times were recorded via nightly phone interviews and a paper log. Some participants used a "Smart Box" to store salivettes, which recorded opening and closing times. Correlations between self-reported and Smart Box times ranged from 0.75 to 0.95. Salivettes were frozen for storage and shipping, and cortisol levels were measured using a luminescence immunoassay (IBL, Hamburg, Germany). A detailed description of the study can be found on the MIDUS website (https://midus.wisc.edu/). Also, details of sample attrition are shown in the Data section in the following chapters.

2 Allostatic Load and Chronic Pain: A Prospective Finding from the National Survey of Midlife Development in the United States, 2004-2014

2.1 Background

Chronic pain (CP) is pain that lasts or recurs for more than 3 months (Treede et al., 2019). CP is becoming a major health issue worldwide. In the US, an estimated 20.5% of adults suffer from CP each year, causing significant burden to the healthcare system and costing over $296 billion in lost productivity (Yong et al., 2022). The pathological progression of CP has been linked to chronic stress-related physiological dysregulation across multiple systems (Borsook et al., 2012; Rabey and Moloney, 2022; Woda et al., 2016). Such dysregulation has been well described by the framework of allostatic load (AL). AL is defined as the physiological 'wear and tear' resulting from repeated adaptations to chronic stressors (McEwen and Stellar, 1993). Long-term response to chronic stress leads to prolonged activation of the hypothalamus-pituitary-adrenal (HPA) axis and sympathetic nervous system, resulting in elevated levels of glucocorticoids and catecholamines (Juster et al., 2010; McEwen, 1998). Over time, over-accumulation of these substances can have downstream consequences and contribute to subclinical conditions across cardiovascular, metabolic, and immune systems.

The history of the term "Allostatic load" dates back to the early 20th century, initially used to describe the new equilibrium that organisms achieve when adapting to environmental changes (Carbone et al., 2022). When these changes are extreme, organisms may develop maladaptive responses. It wasn't until 1988 that Sterling and Eyer published a groundbreaking work introducing the concept of allostasis (Sterling and Eyer, 1988). McEwen and Seeman were among the first scholars to operationalize AL, utilizing biomarkers such as DHEA-S,

urinary cortisol, norepinephrine, epinephrine, systolic and diastolic blood pressure, waist-to-hip ratio, serum HDL cholesterol, total cholesterol-to-HDL cholesterol ratio, and HbA1c (McEwen and Seeman, 1999). Although there is still no strong consensus on the specific biomarkers that must be included in the operationalization of AL, it is suggested that to reflect the dysregulation of chronic stress responses, primary mediators—biomarkers of the neuroendocrine system—and secondary outcomes, including immune, metabolic, and cardiovascular biomarkers, should be incorporated (Juster et al., 2010).

AL index is operationalized by summing the number of biomarkers that fall within high-risk quartiles, which represent physiological dysregulation across multiple systems. Although several methods exist for determining sample distribution cutoffs, the most commonly used is the high-risk quartile approach. In this method, participants in the top quartile of the risk distribution are categorized as dysregulated, while all others are classified as having normal values. Depending on the biomarker's clinical relevance, either the highest or lowest 25% of the sample is considered high risk. The AL index is then computed by summing the values of biomarkers deemed at risk. Sample-based cutoffs are often preferred over clinical cutoffs in AL research because clinical thresholds typically identify disease states, whereas AL theory in general focuses on subclinical markers that reflect the physiological wear and tear resulting from chronic stress (Carbone et al., 2022). Also, we selected the high-risk quartile index (based on sample 25th/75th percentiles) given its strong predictive utility for CP in population-based studies and clearer interpretability. Other formulations such as the z-score method or extreme decile-based index were not used due to their lower explanatory power and limited clinical interpretability, as highlighted in prior research (Sibille et al., 2017). However, this approach is not without limitations. As the quantile cutoffs were derived from the sample

distribution, the resulting index is sample-dependent and may limit comparability across studies. Additionally, dichotomizing continuous biomarkers can lead to information loss and may reduce the sensitivity to detect more subtle dose-response relationships.

In the past few decades, there has been substantial evidence indicating the association between AL and various chronic diseases and symptoms (Guidi et al., 2021), however, the examination of the association between AL and CP is still in its preliminary stage. Evidence supporting a role for AL in the etiology of CP mainly comes from studies based on clinical samples. Notably, dysregulations in the HPA axis, autonomic nervous system, steroids and immune system have been reported in patients with CP (Abdallah and Geha, 2017; Woda et al., 2016), which are also manifestations of people with AL. Furthermore, patients with CP often undergo a range of maladaptive stress responses related to AL, including an inability to habituate to repeated similar stressors, a failure to turn off stress responses, and altered or inefficient responses to stress (Borsook et al., 2012; Juster et al., 2010). These processes may represent adaptive responses of the brain and body systems to the chronicity of pain. The resulting multisystem biological wear and tear could play a significant role in the pathology of CP (Borsook et al., 2012).

Recent studies based on clinical samples found mixed results regarding the association between AL and CP. Research indicates that pediatric patients with pain exhibit a greater risk of experiencing AL, and AL is associated with pain-related functional impairments (Nelson et al., 2021). A prospective association between AL and CP has been suggested. A one-year longitudinal study reported a mild correlation between the AL index and pain severity among chronic low back pain patients (Wippert et al., 2022). Meanwhile, this study has found that a

combination of seven psychological factors and a set of five biomarkers, including norepinephrine, interleukin-6, triglycerides, waist-to-hip ratio, and resting pulse, has yielded good predictions of pain intensity and pain disability. However, another 6-year longitudinal study reported no longitudinal association between stress response systems, including HPA axis, immune system, and autonomic nervous system, and chronic widespread pain (CWP) (Generaal et al., 2016). While the use of validated CP assessments helped to control measurement errors, the inconsistent results may be due to inconsistencies in operationalizing chronic stress response dysregulation and in measuring CP outcomes. Additionally, the clinical samples limit the generalizability of these findings.

Several population-based studies have consistently demonstrated a positive association between AL and CP in cross-sectional analyses. For example, higher levels of AL are associated with an increased likelihood of reporting CP, especially widespread bodily pain, among adults in the U.S. (Slade et al., 2012). However, this study only computed AL based on metabolic, inflammatory, and cardiovascular biomarkers, disregarding primary mediators such as biomarkers in the HPA axis and in sympathetic nervous system (Juster et al., 2010). Among a sample of adults over the age of 50 in England, severe CP has been associated with a high level of AL, which encompassed HPA axis biomarkers, after adjusting for sociodemographic factors, health behaviors, and chronic conditions (Sibille et al., 2017). However, the measurement of CP duration was vague, using the term 'often' without specific time frames. Furthermore, the cross-sectional nature limits the ability to establish causal direction between AL and CP or to account for baseline confounders that might influence CP. Additionally, the AL index in previous research primarily relied on a summative score. This

computation lacks the ability to discern AL differences within each biological system or across systems (Carbone et al., 2022).

Employing a summative score for AL presents certain limitations. It combines several biomarkers into one index, which can oversimplify the complexity of physiological responses and obscure significant variations (Carbone et al., 2022). For example, this method assumes that each biomarker contributes equally to the total score, overlooking the possibility of unique patterns or combinations of biomarkers that could reflect distinct health profiles. In contrast, LCA identifies and characterizes latent subgroups by accounting for the covariances between biomarkers, adding information on the association between the specific risk profiles of AL and CP.

Our study aimed to investigate the prospective relationship between AL and CP using a community-dwelling sample. The research question is whether AL is prospectively associated with CP. We utilized latent class analysis (LCA) to capture the nuances of AL phenotypes (Carbone, 2021; Forrester et al., 2019). Additionally, we used CP measures that adheres to the definition of CP in terms of pain duration (Bonica and Hoffman, 1954), thereby enhancing the validity of our pain assessments. Our examination was also adjusted for a range of factors including sociodemographic characteristics, health-related behaviors, multiple chronic conditions, and detailed medication information. We hypothesized that AL phenotypes would be prospectively associated with increased risk of experiencing CP, increased number of pain locations, and greater pain interference after seven years.

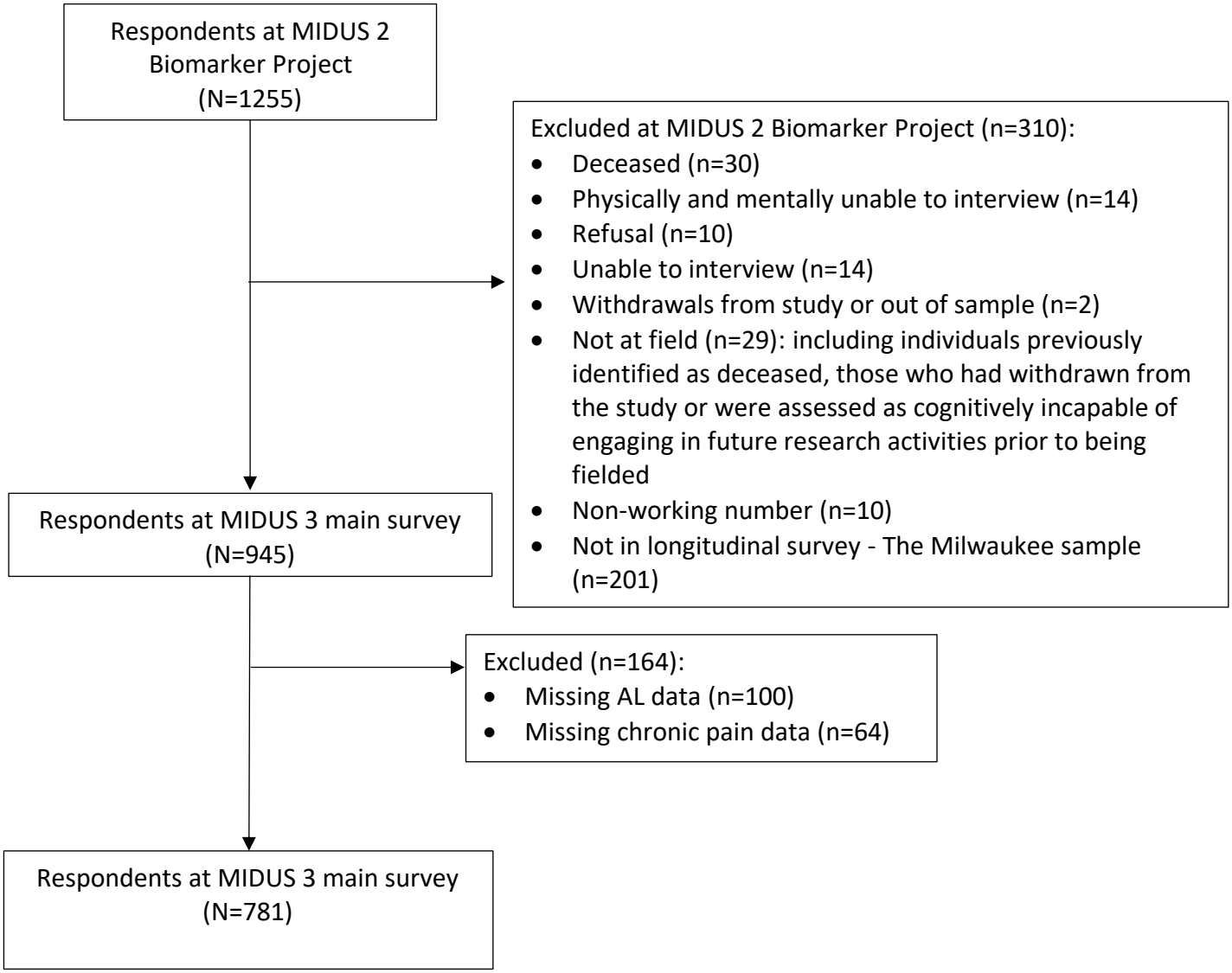
2.2 Methods

2.2.1 Data

This study used the Midlife in the United States (MIDUS) from 2004 to 2014, including two main survey waves (MIDUS 2 and MIDUS 3) and a Biomarker Project of MIDUS 2. MIDUS is a national, longitudinal study focusing on individual social status, psychological profiles, and biological processes of aging, initiated between 1995-1996 and followed 7,108 non-institutionalized Americans aged 25 to 74 in the contiguous United States. The main survey collected data by phone interviews and self-administered questionnaires. The MIDUS is publicly accessible secondary data. More details of the study are available on the MIDUS website (Available at: http://midus.wisc.edu/).

Of the participants, 1,255 were involved in the Biomarker Project of MIDUS 2, conducted from 2004 to 2009. Samples meeting the following criteria were incorporated into the analyses (See figure 2-1): 1) samples that participated in the biomarker program and the MIDUS 3 follow-up survey, 2) samples that provided complete information on the major variables (AL and CP).

Figure 2-1 Flow diagram for the study cohort



2.2.2 Measures

2.2.2.1 AL

AL biomarkers were collected from the Biomarker Project of MIDUS 2. The project collected 12-hour urine samples, fasting blood samples, as well as nervous system function data from respondents during a one-day stay at a General Clinical Research Center (GCRC) of either UCLA, University of Wisconsin, or Georgetown University, depending on the residence of respondents (Ryff et al., 2022).

For urine collection, two 2-liter containers were prepared: one acidified with 25 ml of 50% acetic acid for catecholamine (CATS) tests (red-labeled) and one without acid for cortisol (CORT) analysis (white-labeled). Participants began a 12-hour collection at 7:00 PM, voiding and discarding the initial sample. Subsequent voids were divided equally between the containers, refrigerated during the collection period, and concluded with a final void at 7:00 AM. Missed or incomplete samples were documented. Collected urine was processed by measuring and recording the volume of each container. From the CORT container, aliquots of 11 ml were transferred into two 13-ml tubes and 4 ml into two 5-ml vials. For the CATS container, the pH was adjusted below 5 with acetic acid, followed by the same aliquoting process.

For blood collection, three 10-ml serum-separating tubes (SST), two 4-ml lavender Ethylenediaminetetraacetic acid (EDTA) tubes (one foil-wrapped), and one 4-ml or 2.7-ml blue sodium citrate tube were labeled. Fasting blood was drawn between 6:30 and 7:00 AM,

starting with the SST tubes, followed by the lavender tubes and then the blue tube. Tubes were gently inverted after collection, and forms were completed. The non-foil lavender tube was refrigerated, and the foil-wrapped tube is placed in an ice bath.

Blood processing involved centrifuging the blue citrate tube at 4°C for 15 minutes, aliquoting 1 ml plasma into two vials, and freezing. SST tubes stand for 15-30 minutes before centrifugation at 4°C for 20 minutes. Sera were aliquoted into red, white, green, and orange-labeled vials. The foil-wrapped lavender tube was processed under dim lighting, centrifuged at 4°C for 15 minutes, and plasma was aliquoted into two yellow-labeled vials. All samples were stored in the -60°C to -80°C freezer for staff pickup (Ryff et al., 2022). The assay details are shown in the Assay descriptions in the MIDUS Biomarker Project (Ryff et al., 2022).

Following previous studies (Carbone et al., 2023, 2022; Juster et al., 2010), AL was constructed into seven physiological systems from 27 biomarkers (shown in Table 1-1). A high-risk quartile of biomarkers were used (McEwen and Seeman, 1999). Dehydroepiandrosterone sulfate (DHEA-S) and cortisol in the upper or lower 25th quartile were regarded as at high risk. When high-frequency heart rate variability (HFHRV), low-frequency heart rate variability (LFHRV), root mean square of successive differences (RMSSD), standard deviation of heart beat to heart beat intervals (SDRR), and high-density lipoprotein (HDL) cholesterol strength fell within their lower 25th quartile ranges, individuals were classified as high risk. Other biomarkers falling into their upper 25th quartile were assigned to the high-risk range. Then, biomarkers in their high-risk quartile were coded as 1; otherwise, 0. The high-risk thresholds are detailed in Table 2-1.

Then, LCA was used to capture the phenotypes of AL (package “poLCA” in R). The binary biomarkers were fitted into 1-7 clusters, and the selection of the optimum number of cluster was based on log-likelihood, Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), entropy, and interpretability of classification. Regarding entropy, an ideal value is close to 1, and above 0.8 is acceptable (Weller et al., 2020). As for AIC and BIC, lower values indicate a better fit (Sinha et al., 2021). However, BIC tends to favor simpler models in larger samples due to its complexity penalty, while AIC may lean towards more complex models. Given these considerations, seeking points of inflection or plateauing for BIC and AIC can balance model complexity against the risk of overfitting (Sinha et al., 2021). Also, the classification should be meaningful from a clinical or a biological perspective (Sinha et al., 2021). Additionally, each cluster should have at least 10% of the sample (Sinha et al., 2021; Weller et al., 2020). 5000 iterations were set to generate convergent estimation for each LCA model.

Table 2-1 Values for high-risk quartiles

Biomarkers	Simple High Risk Quartile
Hypothalamic Pituitary Adrenal Axis	
DHEA-s (ug/dL)	≤51 or ≥141
Urine cortisol (µg/g)	≤6.7 or ≥19
Sympathetic Nervous System	
Urine epinephrine (µg/g)	≥2.464
Urine norepinephrine (µg/g)	≥32.964
Urine Dopamine (µg/g)	≥182.964
Parasympathetic Nervous System	

HFHRV	≤55.9
LFHRV	≤103.4
RMSSD	≤12.02
SDRR (ms)	≤23.27
Cardiovascular	
Resting heart rate (bpm)	≥79.8
Resting systolic blood pressure (SBP) (mmHg)	≥144
Resting diastolic blood pressure (mmHg)	≥82
Metabolic-glucose	
Fasting glucose	≥105
Hemoglobin A1c (HbA1c) (%)	≥6.242
Homeostasis model of insulin resistance (HOMA-IR)	≥4.36
Metabolic-lipids	
Triglycerides (mg/dL)	≥156
Waist-to-hip ratio (WHR)	≥0.965
Body mass index (BMI) (kg/m^2)	≥33.028
Low-density lipoprotein (LDL) cholesterol (mg/dL)	≥127
High-density lipoprotein (HDL) cholesterol (mg/dL)	≤43
Inflammation	
C-reactive protein (CRP) (mg/L)	≥3.655
Interleukin-6 (IL6) (pg/mL)	≥1.23
Tumor necrosis factor-α (TNF-α) (pg/mL)	≥2.51
Fibrinogen (mg/dL)	≥399
Soluble endothelial leukocyte adhesion molecule-1 (sE-Selectin) (ng/mL)	≥51.88
Soluble intercellular adhesion molecule-1 (ICAM-1) (ng/mL)	≥335.185
Blood fasting insulin-like growth factor 1 (IGF1) (ng/mL)	≥157

2.2.2.2 Outcome: CP

The presence of CP, CP interference and the number of CP sites from MIDUS 3 were utilized. Respondents were first asked “Do you have CP, that is do you have pain that persists beyond the time of normal healing and has lasted from anywhere from a few months to many years?”, if so, they were then asked about CP interference. A pain interference index was generated by calculating a mean score of how much pain interfered with respondents’ activity, mood, relations, sleep, and enjoyment, ranging from 0 to 10 (Jensen, 2011; Li et al., 2021a). Then, the pain interference index was further categorized into no pain, low interference pain (≤4), and high interference pain (>4) as categorical variable (Jensen, 2011). In addition, if respondents reported having CP, they were asked about the location of the pain, including head, neck, back, arms, legs, shoulders, hips, knees, and other sites. We summed up the pain sites into an index and then categorized it into no pain, 1-2 sites, or 3 or more sites as a categorical variable (Li et al., 2021a, 2021b).

The categorization is based on the consistency with previous practices (Li et al., 2021a, 2021b), as well as the distributions of both CP interference and the number of pain locations, which are highly skewed toward the lower end. This skewness presents challenges for linear modeling techniques, which assume normality of residuals. While negative binomial regression is a potential approach to address the count nature of our pain location data, it may not adequately account for the observed high skewness in the distribution. In addition, the sample sizes in our study are unevenly distributed across the potential range of these variables, with a significant drop-off in frequency as the number of pain locations increases. This sparsity in the upper range can undermine the reliability of regression estimates, as the

models would be driven by a small subset of the sample with higher pain counts. Therefore, categorization helps to stabilize the variance across groups.

2.2.2.3 Covariates

Covariates were selected by current knowledge about the association between AL and CP (Mills et al., 2019; Sibille et al., 2017; Slade et al., 2012). Sociodemographic covariates were obtained from the MIDUS 2 main survey and were coded as categorical variables except for the age variable, which was treated as continuous. Sociodemographic covariates included gender (ref: male; comparison: female), age, ethnicity (ref: White; comparison: non-White), educational attainment (i.e., the highest educational certificate a respondent had obtained, ref: high school or less; comparison: bachelor's degree, or master's degree and above), marital status (ref: married; comparison: divorced/separated/never married/widowed), and the income-to-needs ratio (INR, ref: affluent; comparison: adequate-income, or low-income or below) (Diemer et al., 2013) which was computed by dividing total household income by Federal Poverty Threshold (United States Census Bureau, 2022). Additionally, behavior factors from the MIDUS 2 Biomarker Project were considered. They were alcohol intake status (ref: moderate or more drinker; comparison: light drinker, or non-drinker or rarely drinker), smoking status (ref: current smoker; comparison: ex-smoker, or non-smoker), and categories of the metabolic equivalent of task (MET, ref: between 500-1000 minutes per week; comparison: greater than 1000, or less than 500) minutes per week (Li et al., 2021a; Office of Disease Prevention and Health Promotion, 2008). Also, the time gap between the two data collections was controlled for. Finally, adverse childhood experiences (ACEs) also possibly confound the relationship between AL and CP (Graves and Nowakowski, 2017; Misiak et al.,

2022). In this case, we considered emotional abuse and physical abuse from parents. The ACE data were retrospectively collected in the MIDUS 1 and were treated as ordinal variables.

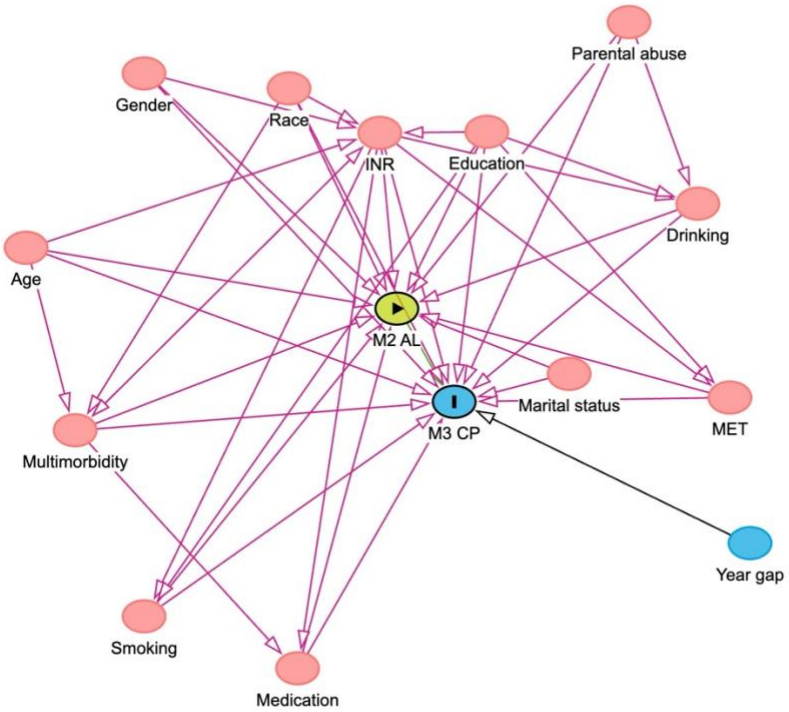
Multimorbidity was also adjusted for (Diederichs et al., 2011; Mills et al., 2019). The chronic condition index summed up a count of "Yes" responses to the chronic conditions-related questions (Ryff et al., 2022). Then, the index was coded as a binary variable (ref: <2; comparison: ≥2) and the index more than 2 was regarded as multimorbidity. Since mental health conditions were already incorporated in this variable, there were no extra adjustments for depression and anxiety.

MIDUS 2 Biomarker Project enhanced medication reports by linking medication names and IDs to Generic Names and Lexi-Data database and asking respondents for their reasons for taking medications (Ryff et al., 2022). A binary variable was created (ref: no; comparison: yes) to represent whether a participant had taken any medication from a selection of antihyperlipidemic agents, beta adrenergic blocking agents, antihypertensive combinations, anxiolytics sedatives and hypnotics, antidiabetic agents, sex hormones, thyroid hormones, antidepressants, and analgesics, including opioids and non-opioids.

To clarify the hypothesized relationships in our analysis, a Directed Acyclic Graph (DAG, Figure 2-2) was constructed to model the association between AL at MIDUS 2 (M2 AL) and CP at MIDUS 3 (M3 CP), while accounting for a comprehensive set of covariates. The DAG identifies potential confounding and mediating pathways based on existing literature and theoretical frameworks. Covariates include demographic factors (age, gender, race/ethnicity), psychosocial exposures (parental abuse), socioeconomic indicators (INR, education), health

behaviors (smoking, drinking, MET, medication use), health status (multimorbidity), and time between biomarker collection and pain assessment (year gap). These variables were included in the adjusted models to account for confounding effects.

Figure 2-2 DAG of the association between AL and CP with covariate adjustment



Abbreviations: AL, allostatic load; CP, chronic pain; INR, income-to-needs ratio; MET, the the metabolic equivalent of task

2.2.3 Statistical Methods

Regression models were chosen according to types of CP variables. For a binary CP variable, logistic regressions were used. The number of pain location and pain interference were categorical variables, therefore, multinomial regressions were utilized. All main analyses presented were fully adjusted for relevant confounders to reduce spurious associations and were generated from the complete cases.

Three sensitivity analyses were applied. Firstly, data missingness can lead to biased estimation (He, 2010; Sterne et al., 2009). Although Little's MCAR test indicated that the data were consistent with missing completely at random ($\chi^2 = 124.05$, df = 125, p = 0.507), there were more than 5% missing data (10.37%). Within this analytic dataset, variable-level missingness was generally low (mostly <5%, none >11%). To minimize potential bias and preserve statistical power, multiple imputation (MI) using the R package "MICE" (Buuren and Groothuis-Oudshoorn, 2011) was employed to address item nonresponse, based on the assumption of missing at random (MAR). Missing covariates were imputed in accordance with the specific distribution of each item, as recommended (Sterne et al., 2009). Twenty imputed datasets were generated, and the coefficients from all statistical models were combined using Rubin's rules. ANOVA tests and chi-squared tests were performed respectively for continuous variables and categorical variables to check the similarity of imputed datasets and the observed dataset. Secondly, bootstrapping method was used to estimate the variability and robustness of coefficients (Carpenter and Bithell, 2000). Bootstrap methods allow for the estimation of the standard errors and confidence intervals for various statistics without relying on strong parametric assumptions. This is particularly useful in small sample sizes or

when the sampling distribution of the statistic is complex or unknown. A total of 5000 bootstrap samples were generated with replacement, each with the same sample size as the original dataset. The bootstrapping process was conducted by R. Thirdly, CP status at MIDUS 2 was incorporated into the model and the binary measure of medication intake at MIDUS 2 was substituted with specific individual medications.

2.3 Results

2.3.1 Descriptive Statistics

Table 2-2 displays the descriptive statistics of the analytic sample (N=781). Of the participants, 62.7% reported no CP, 24.6% had low interference pain, and 12.7% had high interference pain. In terms of the number of pain locations, 23.8% of participants reported 1-2 pain sites and 13.4% of participants reported 3 or more pain sites. The back is the most common pain site among the participants. Additionally, participants with higher pain interference at follow-up were more likely to overlap with those experiencing more pain regions, regardless of baseline pain status (participants with baseline CP: $\chi 2=828$, $P<0.001$; participants without baseline CP: $\chi 2=400$, $P<0.001$). Among participants with 3 or more pain regions, about half of them reported low interference pain and the other half reported high interference pain; Among participants with one to two pain regions, about 75% reported low interference pain and 25% reported high interference pain. The majority of respondents were females, non-Hispanic Whites, affluent, and married, with over 48% of respondents being highly educated (above high school degree). Additionally, there were no significant differences between observed dataset and imputed datasets, supporting the validity of the imputation process.

Table 2-2 Sample description

	Observed dataset				Imputed dataset			
Variable	**Mean / N**	**SD / Proportion**	**Median**	**Available value %**	**Mean / N**	**SD / Proportion**	**Median**	**Test**
Presence of CP	781			1.000				X^2=0
No pain	490	62.70%				62.70%		
CP	291	37.20%				37.20%		
Pain interference at MIDUS 3	781			1.000				X^2=0
No pain	490	62.70%				62.70%		
Low interference pain	192	24.60%				24.60%		
High interference pain	99	12.70%				12.70%		
Number of pain sites at MIDUS 3	781			1.000				X^2=0
No pain	490	62.70%				62.70%		
1-2	186	23.80%				23.80%		
3+	105	13.40%				13.40%		

AL phenotypes	781			1.000				X^2=0
Baseline	403	51.60%				51.60%		
Parasympathetic dysregulation	189	24.20%				24.20%		
Metabolic dysregulation	189	24.20%				24.20%		
Sociodemographic								
Education	780			0.999				X^2=0
high school or less	397	50.90%				50.90%		
bachelor's degree	233	29.90%				29.90%		
Master's degree and above	150	19.20%				19.20%		
Gender	781			1.000				X^2=0
Male	351	44.90%				44.90%		
Female	430	55.10%				55.10%		
Age	54	10.907	54	1.000	54	10.9	54	F=0
Race/ethnicity	780			0.999				X^2=0
White	723	92.70%				92.70%		

Non-White	57	7.30%				7.30%		
Marital Status	780			0.999				X^2=0
Married	570	73.10%				73.10%		
Divorced & Separated	113	14.50%				14.50%		
Never married & Widowed	97	12.40%				12.40%		
Income-to-needs ratio	767			0.982				X^2=0.008
Affluent	437	57%				57%		
Adequate-income	211	27.50%				27.50%		
Low-income or below	119	15.50%				15.50%		
Year gap between data collections								
MIDUS 2 Biomarker Project to MIDUS 3	6.7	1.249	6.833	1.000	6.7	1.249	6.833	F=0
Childhood adversity								

Childhood parent emotional abuse	724		0.927		X^2=0.1
1 (Never)	225	31.10%		30.70%	
1.5	111	15.30%		15.40%	
2	200	27.60%		27.40%	
2.5	101	14%		14.20%	
3 (Most frequent)	87	12%		12.20%	
Childhood parent physical abuse	732		0.937		X^2=0.147
1 (Never)	309	42.20%		41.90%	
1.5	116	15.80%		16.20%	
2	184	25.10%		24.90%	
2.5	71	9.70%		10%	
3 (Most frequent)	52	7.10%		7.10%	
Health behavior					

Total number of Metabolic Equivalent of Task (MET) minutes per week	776		0.994		X^2=0.001
500-1000	151	19.50%		19.50%	
Greater than 1000	319	41.10%		41.10%	
Less than 500	306	39.40%		39.40%	
Smoking behavior	780		0.999		X^2=0
Current Smoker	87	11.20%		11.10%	
Ex-Smoker	247	31.70%		31.70%	
non-Smoker	446	57.20%		57.20%	
Drinking behavior	781		1.000		X^2=0
Moderate + drinker	308	39.40%		39.40%	
Light drinker	228	29.20%		29.20%	
Non-drinker or rarely drink	245	31.40%		31.40%	
Health conditions					

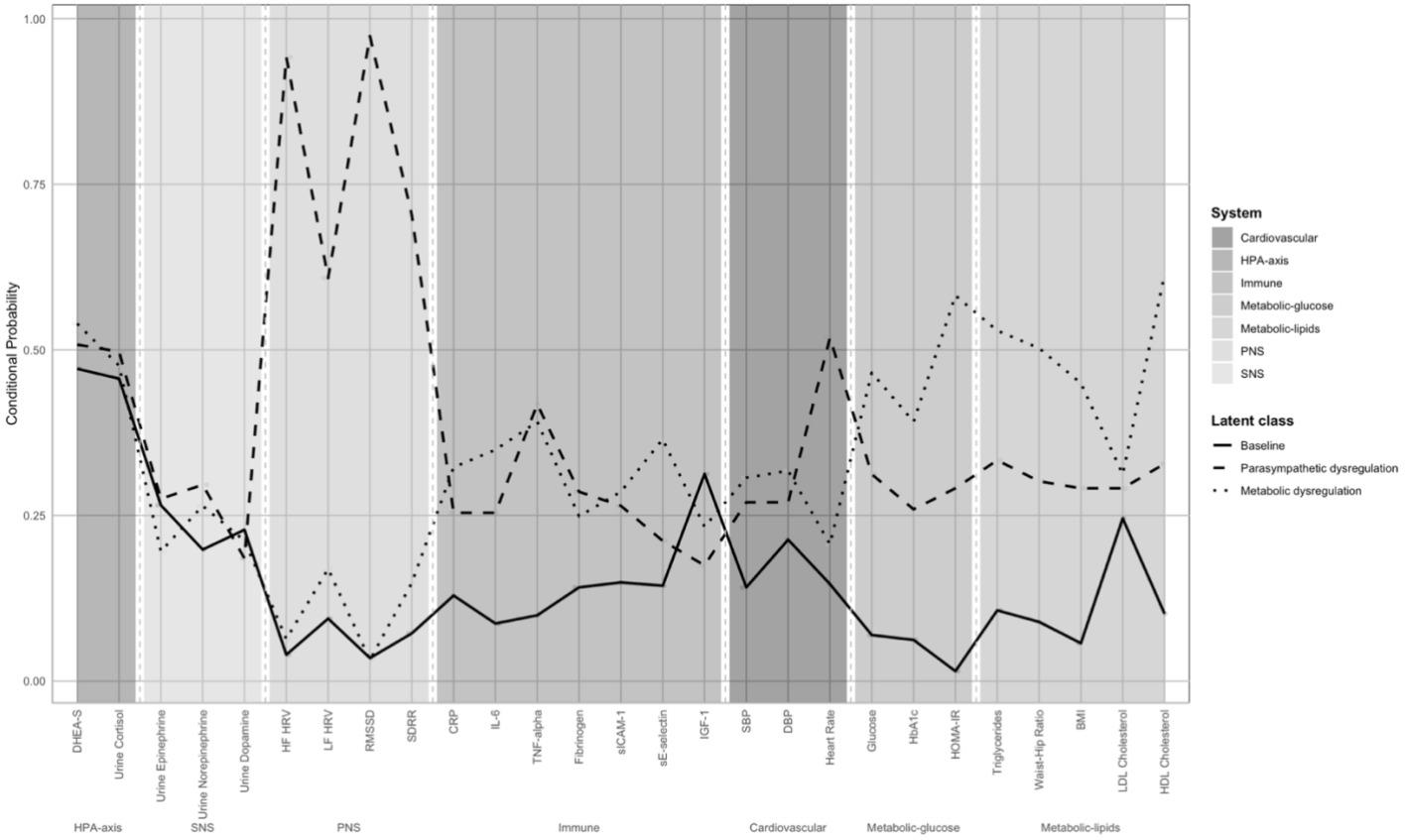
Multimorbidity	781		1.000		X^2=0
<2	168	21.50%		21.50%	
2+	613	78.50%		78.50%	
Medication					
Medication intake	781		1.000		X^2=0
Yes	204	26.10%		26.10%	
No	577	73.90%		73.90%	

For continuous variables, values are reported as Mean, Standard Deviation (SD), and Median. For categorical variables, values are reported as Number (N) and Proportion. “Available value %” refers to the percentage of non-missing data for each variable. The “Test” column indicates the statistical test used to compare groups (e.g., ANOAV test and chi-square test), depending on variable type and distribution.

Supplementary Table 1-1 presents the fit statistics for latent class model with 1-7 clusters, the 3-cluster model was considered the optimal clustering. Despite the continuous reduction in AIC and BIC, along with the progressive improvement in log-likelihood, the enhancement in the fitness of the model with 4 and 5 clusters was rather moderate. On the other hand, the 3-cluster model exhibited the best entropy, suggesting a good classification. Additionally, the 3-cluster model had an ample number of observations within each cluster and presented meaningful separation. Therefore, the 3-cluster model was adopted.

According to Supplementary Table 1-2, class 1 is designated as 'Baseline' due to its association with a low risk across most biomarkers. Class 2, termed 'Parasympathetic Dysregulation,' is distinguished by significantly lower values in HFHRV, LFHRV, RMSSD, and SDRR, suggesting potential impairments in parasympathetic system functioning. Class 3 is characterized by marked increases in fasting glucose, HbA1c, HOMA-IR, triglycerides, WHR, and BMI, coupled with a notable decrease in HDL concentrations. These characteristics are consistent with the physiological patterns commonly observed in metabolic dysregulation. Figure 2-3 shows the phenotypes of AL. 51.6% of the participants were classified as low AL risk group, 24.2% of participants were in the phenotype of parasympathetic dysregulation, and an additional 24.2% demonstrated signs of metabolic dysregulation.

Figure 2-3 Identified phenotypes of AL.



Biomarkers are grouped by physiological systems: HPA-axis, sympathetic nervous system, parasympathetic nervous system, immune, cardiovascular, metabolic-glucose, and metabolic-lipids. Shaded backgrounds indicate system groupings.

2.3.2 Model Results

Table 2-3 presents regression results. In the fully adjusted binary logistic regression models, there was no statistically significant association between any AL dysregulation phenotype and CP status compared to the low AL risk phenotype. In addition, compared to those with higher incomes, individuals with low or very low incomes had 130% higher odds of having CP at MIDUS 3. Those who engaged in more than 1,000 minutes per week of MET had 64% higher odds of having CP at MIDUS 3, compared to individuals with 500-1,000 minutes per week of MET. Additionally, people taking medication had 110% higher odds of having CP at MIDUS 3 (Please refer to Supplementary Table 1-2).

Table 2-3 Results from the logistic regression for the association between AL at MIDUS 2 Biomarker Project and CP status at MIDUS 3

	No CP vs reporting CP in MIDUS 3
AL phenotypes	**Odds ratios (95% CI)**
Baseline	Ref
Parasympathetic dysregulation	
Main analysis	0.97 (0.64, 1.48)
Sensitivity analysis	
Multiple Imputation	1.04 (0.70, 1.55)
Bootstrapping Method (5000 iterations)	0.85 (0.51, 1.43)
Adjustment for CP at MIDUS 2 and individual medications‡	1.01 (0.64, 1.60)
Metabolic dysregulation	
Main analysis	1.18 (0.76, 1.81)
Sensitivity analysis	

Multiple Imputation	1.14 (0.77, 1.7)
Bootstrapping Method (5000 iterations)	1.40 (0.80, 2.45)
Adjustment for CP at MIDUS 2 and individual medications‡	1.18 (0.74, 1.89)

† Adjusted for gender, age at MIDUS 2, race/ethnicity, marital status at MIDUS 2, INR at MIDUS 2, emotional/physical abuse from parents, multimorbidity at MIDUS 2 Biomarker Project, MET, drinking behavior, smoking behavior, medication intake (yes/no) and year gap between MIDUS 2 Biomarker Project and MIDUS 3 main surveys

‡ Medications included antihyperlipidemic agents, beta adrenergic blocking agents, antihypertensive combinations, analgesics, anxiolytics sedatives and hypnotics, sex hormones, thyroid hormones, antihistamines, antidepressants, analgesic (both opioids and non-opioids).

Statistical significance markers: * $p<0.05$; ** $p<0.01$; *** $p<0.001$

The bold values denote statistically significant results; CI denotes confidence interval.

In the multinomial regression models (Table 2-4), the prospective association between the metabolic dysregulation phenotype and high interference CP was significant (RRR=2.00, 95% CI: 1.06, 3.79, P<0.05), compared to the baseline phenotype. In the prospective association between the number of pain sites and biological dysregulation phenotypes, metabolic dysregulation was significantly associated with 3 or more CP sites (RRR=2.03, 95% CI: 1.08, 3.83, P<0.05). There were no other significant associations between the parasympathetic phenotype of AL and CP outcomes found. People who were never married or widowed and experienced moderate emotional abuse had lower odds of having high interference pain. Non-smokers were less likely to report high interference pain and more pain regions, while women were more likely to report these pain outcomes. Ethnically minoritized people and people with low incomes were more likely to have more pain sites (Please refer to Supplementary Tables 1-3 to 1-4).

In the sequent sensitivity analyses, the results remained similar. The similar results generated from the imputed datasets indicated that data missingness did not significantly biased the estimates. Also, the results generated from the bootstrapping samples were similar to the main analyses, indicating that the association was expected to persist even when accounting for potential uncertainties. Additionally, after extra adjusting for medication intakes as separate factors and CP status at MIDUS 2, the results remained stable.

Table 2-4 Results from the multinomial logistic regression for the association between AL at MIDUS 2 Biomarker Project and CP interference and the number of CP sites at MIDUS 3

	No pain vs low interference pain	**No pain vs high interference pain**
AL phenotypes	**Relative risk ratios (95% CI)**	**Relative risk ratios (95% CI)**
Baseline	Ref	Ref
Parasympathetic dysregulation		
Main analysis	0.87 (0.54, 1.39)	1.24 (0.65, 2.39)
Sensitivity analysis		
Multiple Imputation	0.96 (0.61, 1.49)	1.22 (0.66, 2.26)
Bootstrapping Method (5000 iterations)	0.82 (0.49, 1.38)	0.99 (0.41, 2.38)
Adjustment for CP at MIDUS 2 and individual medications‡	0.93 (0.56, 1.53)	1.23 (0.60, 2.55)
Metabolic dysregulation		
Main analysis	0.92 (0.56, 1.52)	**2.00 (1.06, 3.79)***
Sensitivity analysis		

Multiple Imputation	0.92 (0.58, 1.46)	**1.82 (1.01, 3.28)***
Bootstrapping Method (5000 iterations)	1.08 (0.58, 2.02)	**2.46 (1.10, 5.47)***
Adjustment for CP at MIDUS 2 and individual medications‡	0.94 (0.55, 1.59)	**2.03 (1.01, 4.11)***

	No pain vs 1-2 pain locations	**No pain vs 3+ pain locations**
AL phenotypes	**Relative risk ratios (95% CI)**	**Relative risk ratios (95% CI)**
Baseline	Ref	Ref
Parasympathetic dysregulation		
Main analysis	0.84 (0.51, 1.36)	1.30 (0.69, 2.44)
Sensitivity analysis		
Multiple Imputation	0.91 (0.58, 1.45)	1.33 (0.73, 2.39)
Bootstrapping Method (5000 iterations)	0.85 (0.50, 1.46)	0.83 (0.27, 2.62)
Adjustment for CP at MIDUS 2 and individual medications‡	0.90 (0.54, 1.51)	1.22 (0.61, 2.42)
Metabolic dysregulation		
Main analysis	0.89 (0.54, 1.47)	**2.03 (1.08, 3.83)***

Sensitivity analysis		
Multiple Imputation	0.91 (0.57, 1.44)	**1.85 (1.03, 3.34)***
Bootstrapping Method (5000 iterations)	1.00 (0.55, 1.81)	**2.57 (1.15, 5.76)***
Adjustment for CP at MIDUS 2 and individual medications‡	0.89 (0.52, 1.52)	**2.09 (1.06, 4.11)***

† Adjusted for gender, age at MIDUS 2, race/ethnicity, marital status at MIDUS 2, INR at MIDUS 2, emotional/physical abuse from parents, multimorbidity at MIDUS 2 Biomarker Project, MET, drinking behavior, smoking behavior, medication intake (yes/no) and year gap between MIDUS 2 Biomarker Project and MIDUS 3 main surveys

‡ Medications included antihyperlipidemic agents, beta adrenergic blocking agents, antihypertensive combinations, analgesics, anxiolytics sedatives and hypnotics, sex hormones, thyroid hormones, antihistamines, antidepressants, analgesic (both opioids and non-opioids).

The proportional odds assumption for ordinal logistic regression was violated. Therefore, multinomial logistic regression was opted for.

Statistical significance markers: * $p<0.05$; ** $p<0.01$; *** $p<0.001$; the bold values denote statistically significant results; CI denotes confidence interval.

2.3.3 Predicted Probabilities for CP outcomes by AL phenotypes

Table 2-5 presents the adjusted prevalence for CP outcomes grouped by AL phenotypes. Using the average adjusted predicted probabilities from the models, we calculated the probability of CP outcomes by AL phenotypes. The metabolic dysregulation phenotype was significantly associated with high interference pain and 3 or more CP sites as shown in Table 2-4. Respondents with the metabolic dysregulation phenotype were more likely to experience a higher degree of CP conditions than those with a low AL risk profile. Specifically, those with metabolic dysregulation driven AL had a 4.88% adjusted probability of reporting high pain interference and had a 4.58% adjusted probability of reporting more than 3 pain locations. In contrast, these probabilities were lower, at 2.48% and 2.29% respectively, among respondents with a baseline AL profile.

To interpret the clinical relevance of our findings, we prespecified thresholds of an absolute risk difference (ARD) ≥ 2 percentage points and a relative risk (RR) ≥ 1.5 (VanderWeele and Ding, 2017). A 2% absolute increase corresponds approximately to a number-needed-to-treat (NNT) of 50, which is commonly regarded as a moderate and meaningful effect size in long-term health outcomes (Cook and Sackett, 1995). We found that the metabolic dysregulation phenotype significantly increased the probability of high interference pain (4.88% vs. 2.48%) and pain with 3 or more pain locations (4.58% vs. 2.29%,), surpassing the predefined threshold.

Table 2-5 Adjusted prevalence for CP outcomes grouped by AL phenotypes

CP status	**No pain**	**Reporting CP**	
AL phenotypes	**Average adjusted predicted probabilities**		
Baseline	89.02%	10.98%	
Parasympathetic dysregulation	89.31%	10.69%	
Metabolic dysregulation	87.34%	12.66%	
CP interference	**No pain**	**Low interference pain**	**High interference pain**
AL phenotypes	**Average adjusted predicted probabilities**		
Baseline	89.74%	7.77%	2.48%
Parasympathetic dysregulation	90.14%	6.76%	3.10%
Metabolic dysregulation	88.11%	7.02%	**4.88%**
The number of CP locations	**No pain**	**1-2**	**3+**
AL phenotypes	**Average adjusted predicted probabilities**		
Baseline	90.17%	7.54%	2.29%
Parasympathetic dysregulation	90.66%	6.35%	3.00%
Metabolic dysregulation	88.80%	6.62%	**4.58%**

Note: Findings in bold are statistically significant at $p < 0.05$ based on binary/multinomial logistic regression results.

2.4 Discussion

The present study identified three phenotypes of AL through LCA, encompassing low levels of biological dysregulation, AL driven by parasympathetic dysregulation, and AL driven by metabolic dysregulation. Also, consistent with previous research (Loevinger et al., 2007; Sibille et al., 2017, 2016; Slade et al., 2012), we found that AL driven by metabolic dysregulation is associated with more severe CP interference and a greater number of CP sites. For instance, a cross-sectional study based on a sample of population aged over 50 in the UK revealed that, after controlling for sociodemographic factors and comorbid conditions, high-risk biomarker, defined by the upper quartile and including HDL, HBA1c, and WHR, are related to increased severity of CP (Sibille et al., 2017). Similarly, in American adults, higher BMI and triglyceride levels are associated with a higher prevalence of widespread bodily pain (Slade et al., 2012).

Compared to previous studies, our research offers several advantages. Firstly, we employed a more comprehensive set of biomarkers, including those from the HPA axis, and the sympathetic and parasympathetic nervous systems, to construct a more valid AL measurement (Juster et al., 2010). Moreover, our use of LCA to identify AL phenotypes captures the common variability of biomarkers, while previous studies that used single biomarkers for regression with CP overlooked the interrelationships among biomarkers within the AL framework (Sibille et al., 2017; Slade et al., 2012). On the other hand, prior operationalizations of AL, based on summative computation that assigns equal weight to each biomarker, may obscure the specific impacts of different AL components on CP. In summary, LCA offers a nuanced method for exploring the specific components of AL that drive CP.

Furthermore, this study's strengths include its prospective design, community-dwelling sample, adjustments for early confounders, and the substantial avoidance of trivial and recent pain in measurement by adhering to the definition of CP in terms of pain duration. Thus far, this research may be the first community-dwelling study to examine the prospective association between AL and CP.

However, this study also has limitations. Firstly, the measurement of pain is self-reported. Even when controlling for potential reporting biases from relevant sociodemographic factors, unobserved factors can still introduce biases in pain assessment. Furthermore, the variability in CP measures across various surveys partly limits the comparability of findings. For instance, the MIDUS survey assesses pain interference, which differs from the pain severity measurements used in other studies. While pain interference is associated with pain severity, their association is affected by patients' beliefs about pain, their tendency towards catastrophizing, and their pain coping strategies (Jensen et al., 2017). Stress biomarkers may be particularly relevant predictors of the broader impact or severity of pain, such as pain interference with daily activities or functional impairment, rather than simply the presence or absence of CP itself. Thus, it is plausible that stress biomarkers predominantly reflect how individuals experience and manage pain, rather than directly determining whether they experience pain at all. Therefore, there is a need for further prospective research to explore the link between AL and CP severity in more depth.

Additionally, the available data on AL was only collected in MIDUS 2, however, the new biomarker data present opportunities for future research on the association between AL trajectories and the development of CP. Also, the sample composition is predominantly White,

and future studies including larger samples of ethnic minorities are encouraged. Moreover, our findings from U.S. data may not generalize to other countries. For instance, variations in access to healthcare, such as universal versus privatized systems, can influence the extent to which socioeconomic status affects CP through differential access to effective pain treatments. This could modify the impact of AL on pain progression or chronicity. Furthermore, sociocultural differences in pain expression, perceptions of pain severity, and medicalization practices could impact self-reporting patterns, thus affecting observed associations between socioeconomic status, physiological stress markers, and CP prevalence (Grol-Prokopczyk, 2017). Thus, cross-national variation in these factors might lead to differing associations between AL and CP.

Lastly, this study only examined the prospective association in one direction and future research on the reverse association may be beneficial elucidate the causal direction. Distinguishing causal relationships from mere associations remains challenging in observational designs. Although our prospective approach strengthened temporal inferences, causality cannot be definitively established without quasi-experimental or intervention studies. Future studies employing causal inference techniques may help disentangle causality.

While the underlying mechanism remains undetermined, several potential explanations could account for the prospective positive association between the metabolic dysregulation phenotype of AL and both high interference pain as well as an increased number of pain sites. The AL model proposes, when undergoing repeated stress adaptation, the prolonged secretion of stress hormones and inflammatory cytokines can disrupt the normal regulation of downstream physiological systems, such as the metabolic system (Juster et al., 2010).

Dyslipidemia and high BMI may be associated with upregulation of cytokines, leading to low-grade inflammation, a condition frequently observed in patients with fibromyalgia (Ghafouri et al., 2022). Additionally, a high waist-to-hip ratio may be related to structural changes in intervertebral discs and being consistently subjected to high biomechanical loads (Hussain et al., 2017). This highlights the significant role that metabolic dysregulation related to adiposity may play in low back pain. Meanwhile, elevated blood glucose is associated with peripheral neuropathy or synergistically interacts with high BMI and the sequential inflammation, thereby potentially increasing the likelihood of experiencing daily pain (Mäntyselkä et al., 2008). Also, metabolic dysregulation could potentially reduce the pain activation threshold via its interplay with inflammatory mechanisms. This interaction may intensify pain response by increasing synaptic strength and reducing inhibition, allowing even low-threshold stimuli to activate pain pathways (Veldhuijzen et al., 2018; Woolf, 2011).

Therefore, broadly collecting a range of biomarkers related to chronic stress responses, including primary biomarkers and secondary outcomes, and identifying metabolic dysregulation phenotypes, could help establish a baseline for high-risk biomarkers. Detecting distinct metabolic dysregulation phenotypes could serve as an early indicator of vulnerability to CP. In clinical practice, such biomarker screening could be integrated into routine assessments by primary care providers or occupational health professionals, especially among middle-aged adults. This approach could support early identification of individuals at elevated risk for having high interference or multisite CP, enabling more targeted prevention and intervention strategies.

Nevertheless, we did not find any prospective associations between AL driven by the parasympathetic nervous system and CP. Low parasympathetic nervous system activity may represent low capacity to respond to chronic stress. A meta-analysis, which thoughtfully sieved through 26 moderate-high-quality studies from a pool of 17,350 publications, uncovered that biomarkers relating to the parasympathetic nervous system (LFHRV, HFHRV, RMSSD, R-R interval, and SDRR) exhibited an association with CP (Tracy et al., 2016). However, the association appears to be predominantly influenced fibromyalgia and its significance may vary across CP conditions (Woda et al., 2016). CP may also maladapt parasympathetic nervous system directly. Therefore, future research is encouraged to focus on exploring the potential links between the parasympathetic nervous system and different subtypes of CP to clarify these relationships. Datasets with larger sample sizes will facilitate the examinations for the associations between parasympathetic dysregulation of AL and pain at different sites.

2.5 Conclusion

In conclusion, our findings indicate that metabolic dysregulation as a phenotype of AL is prospectively associated with high interference CP and 3 or more CP sites. Differentiating nuances of biological dysregulation of AL could facilitate the development of clinical interventions aimed at specific biological mechanisms, which may alleviate the impacts of AL on the conditions of CP.

3 Association of Diurnal Cortisol Rhythm with Chronic Pain: Evidence from a Prospective Cohort Study in Community-Dwelling Adults

3.1 Introduction

Chronic pain (CP), defined as pain persisting or recurring for over three months (Treede et al., 2019), is highly prevalent and associated with significant societal and economic impacts, poor prognosis, and limited options for monitoring and prevention (Interagency Pain Research Coordinating Committee, 2022). The interference caused by CP, along with its widespread occurrence throughout the body, contributes to adverse outcome including poor health (Ezzati et al., 2019; Glei and Weinstein, 2023; Kamaleri et al., 2008), reduced quality of life (Hider et al., 2015; Jensen et al., 2007), negative effects on employment status (Gerdle et al., 2008; Pooleri et al., 2023), and increased medical costs (Mose et al., 2021; Stockbridge et al., 2015). These challenges highlight the need to investigate its mechanisms. One appealing biological factor is the hypothalamic-pituitary-adrenal (HPA) axis (Woda et al., 2016).

The HPA axis plays a crucial role in the body's stress response, operating through a regulatory circuit involving the hypothalamus, pituitary gland, and adrenal cortex. During stress, the hypothalamus releases corticotropin-releasing hormone (CRH), which stimulates the anterior pituitary to secrete adrenocorticotropic hormone (ACTH). This, in turn, prompts the adrenal cortex to produce cortisol, a stress hormone with widespread effects. Typically, HPA axis function is assessed by measuring cortisol levels in blood, saliva, or urine samples. While established methods, these short-term measures reflect either acute circulating cortisol levels (in plasma or saliva) or cumulative secretion over a collection period typically not exceeding 24 hours (in urine) (Stalder and Kirschbaum, 2012). They may not accurately reflect

the long-term changes in the function of the HPA axis. Also, the 24-hour urine cortisol measurement method has certain limitations, as it does not account for fluctuations in cortisol levels throughout the day or the peaks and troughs that occur after medication administration (Jung et al., 2014). Different patterns of cortisol secretion throughout the day may indicate varying functions of the HPA axis, therefore, using single-point measurements make it challenging to discern potential differences in the underlying pathogenic mechanisms.

The dexamethasone suppression test is another method used to assess HPA axis function. This test involves administering the synthetic steroid dexamethasone to suppress cortisol production, thereby evaluating the feedback regulation of the HPA axis (Findling et al., 2004). However, the dexamethasone suppression test is limited in that it primarily assesses short-term feedback regulation and hypercortisolism, rather than providing a comprehensive view of the natural fluctuations of cortisol throughout the day. Hair cortisol measurement, a novel technique, provides an indicator of long-term cortisol exposure (Stalder and Kirschbaum, 2012). Although hair cortisol is considered a better tool for measuring the cumulative consequences of chronic stress responses, its levels may be highly correlated with overall cortisol secretion, reflecting only one aspect of HPA axis function (Short et al., 2016). This high correlation limits the opportunity for a comprehensive examination of the relationship between the HPA axis and CP.

Collecting salivary cortisol samples multiple times over several days provides an opportunity to assess HPA axis function rather than short-term stress responses. Salivary cortisol is one of the end products of the HPA axis, and its natural daily cycle—peaking in the morning and declining throughout the day—characterizes the diurnal cortisol rhythm, reflective of the HPA

axis functioning (Adam and Kumari, 2009; Wesarg-Menzel et al., 2024). The cortisol awakening response (CAR), the rapid increase in cortisol levels within 30-45 minutes after waking, is activated by a central control network originating in the hypothalamus (Stalder et al., 2024). A reduced CAR disrupts circadian alignment, energy metabolism, immune regulation, and neurocognitive and emotional processes (Stalder et al., 2024) - mechanisms that are involved in CP pathology (Apkarian et al., 2011; Bumgarner et al., 2021; Bunk et al., 2021; Held et al., 2019; Koechlin et al., 2018; van Tilburg et al., 2020). The surge then triggers negative feedback primarily involving the suprachiasmatic nucleus (SCN), mediated by glucocorticoid and mineralocorticoid receptors (GRs and MRs) (Lightman et al., 2020; Papadopoulos and Cleare, 2012). GRs restrain cortisol secretion when levels exceed basal values, while MRs maintain inhibitory control during the diurnal nadir due to their high cortisol affinity (Oster et al., 2017; Young et al., 1998). This regulation is captured by the diurnal cortisol slope (DCS), which measures the rate of cortisol decline from its peak throughout the day. A blunted DCS, commonly indicative of GR down-regulation and increased MR affinity (Jarcho et al., 2013), is associated with various diseases (Adam et al., 2017), including CP (Hannibal and Bishop, 2014). The area under the curve (AUC) reflects total daily cortisol secretion, while cortisol dynamic range (CDR) measures the peak-to-nadir difference. Both parameters share the mechanisms regulating CAR and DCS while providing additional information: a lower AUC may indicate long-term epigenetic changes (Abelson et al., 2023), while a narrower CDR may capture biological aging (Karlamangla et al., 2022; Oster et al., 2017), linking AUC and CDR to mechanisms associated with CP (Aroke et al., 2024; Descalzi et al., 2015).

A recent meta-analysis (Beiner et al., 2023) and a cross-sectional study (Generaal et al., 2014) have suggested lower HPA axis activity, reflected in lower cortisol levels, in patients with fibromyalgia and chronic multisite pain. The recent meta-analysis found no difference in blood and urine cortisol levels between fibromyalgia patients and control groups. However, cortisol levels measured using saliva samples showed a decreasing trend in people with fibromyalgia (Beiner et al., 2023). The cross-sectional study found that various cortisol measurements—such as waking cortisol levels, the AUC relative to ground (AUCg), the AUC relative to increase (AUCi), evening cortisol levels, the diurnal slope, and cortisol suppression rate—were not associated with the intensity of CP. However, in individuals without depression or anxiety, lower waking cortisol levels, lower AUCg, and flatter diurnal slopes were significantly associated with a higher likelihood of experiencing chronic widespread musculoskeletal pain (Generaal et al., 2014). Another study found that the presence of chronic widespread pain was associated with lower salivary cortisol levels and higher post-stressor serum cortisol levels. Additionally, failure to suppress cortisol in the dexamethasone suppression test were linked to chronic widespread pain (McBeth et al., 2005).

However, prospective epidemiological findings have been mixed (Generaal et al., 2017, 2016; McBeth et al., 2007; Paananen et al., 2015). Two studies using the same database have shown that dysfunction of the HPA axis is not associated with either the onset or persistence of pain (Generaal et al., 2017, 2016). However, another research has found that high post-dexamethasone cortisol levels, low morning salivary cortisol levels, and high evening salivary cortisol levels are associated with chronic widespread pain (McBeth et al., 2007). Compared to women with normal HPA axis function, women with low HPA axis reactivity who have a cold pain threshold above the median are more likely to experience musculoskeletal pain, and

this pain is more severe. Additionally, women with low HPA axis reactivity who have a cold pain threshold below the median are more likely to suffer from more severe musculoskeletal pain (Paananen et al., 2015).

Inadequate sample sizes (Beiner et al., 2023), blood measurements sensitive to acute stressors (Paananen et al., 2015), a high proportion of participants with depression and/or anxiety (Generaal et al., 2017, 2016), and short-duration salivary assessments (Generaal et al., 2016, 2014; McBeth et al., 2007, 2005), which may not capture long-term cortisol rhythms due to situational stress (Hellhammer et al., 2007; Hruschka et al., 2005), may contribute to the discrepancy. Furthermore, the role of different cortisol parameters in pain pathology is unclear.

Given the uncertainty, a population-based sample with a more ideal cortisol measurement protocol is needed to clarify the prospective association between HPA axis dysfunction and CP, which could inform the prevention of CP among at-risk individuals. Additionally, the extent of pain interference in daily life and its presence in one or multiple body locations are important due to their broad implications, including but not limited to various health outcomes (Ezzati et al., 2019; Glei and Weinstein, 2023; Kamaleri et al., 2008), poorer quality of life (Hider et al., 2015; Jensen et al., 2007), negative effects on employment status (Gerdle et al., 2008; Pooleri et al., 2023), and increased medical costs (Mose et al., 2021; Stockbridge et al., 2015). Thus, examining the relationship between HPA axis dysfunction and CP conditions could enhance pain management and mitigate broader disadvantages.

Using the Midlife in the United States (MIDUS) study and its sub-project, the National Study of Daily Experiences (NSDE), we examined the prospective association between different parameters of diurnal cortisol rhythm and CP outcomes over an average follow-up period of seven years. Moreover, we explored the associations between cortisol diurnal rhythm and CP separately in those with and without CP at baseline, given that the relationship may depend on pain chronicity (Reyes del Paso et al., 2024).

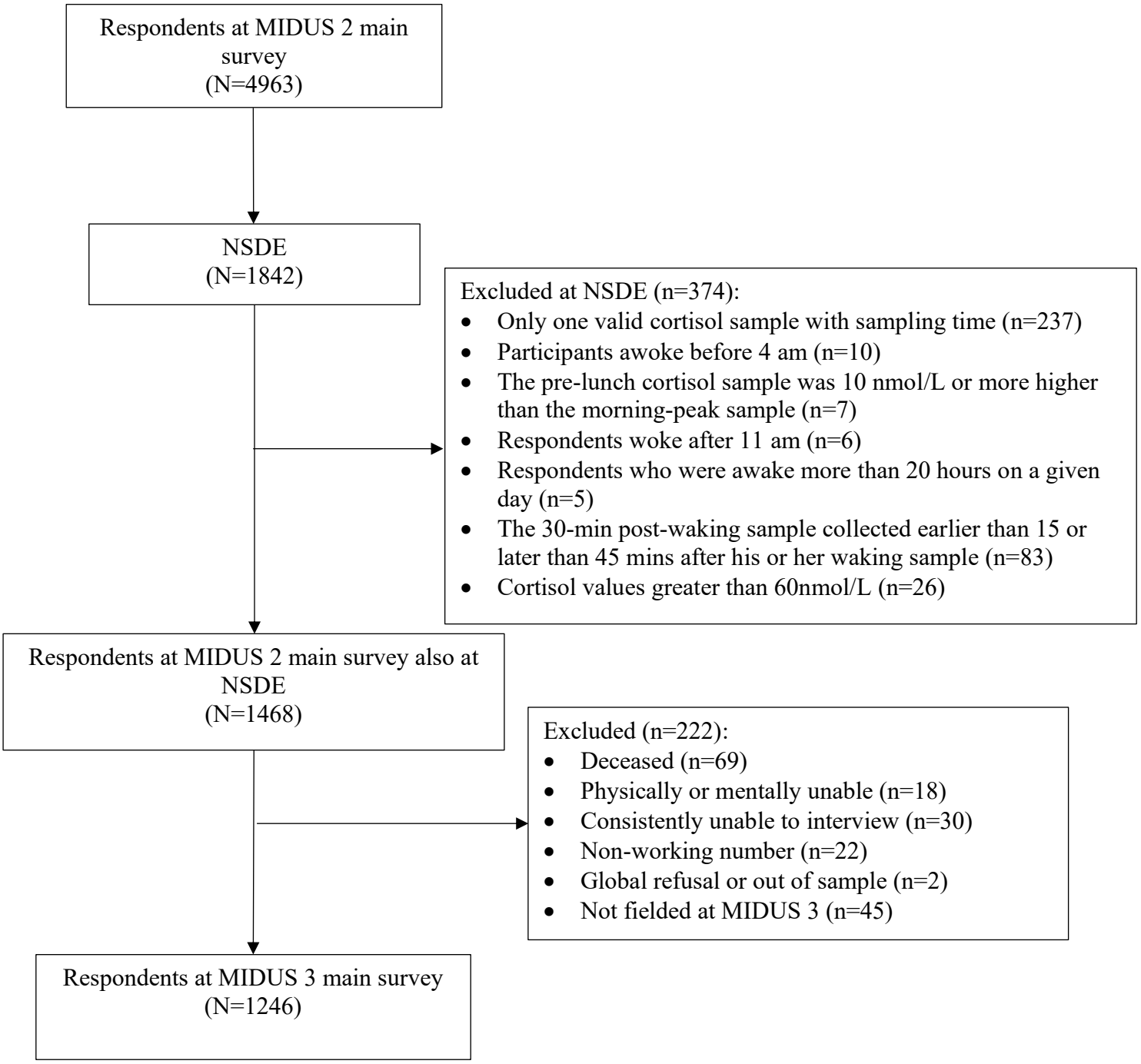
3.2 Method

3.2.1 Data

MIDUS is a longitudinal study, focusing on the impact of social, psychological, and physiological factors on health as people age from early adulthood to later life. The baseline survey (MIDUS 1) recruited non-institutionalized, English-speaking adults aged 25 to 74 from various locations across the United States in 1995-1996. The study included a national probability sample, with over-sampling from selected metropolitan areas, a sample of siblings of the main respondents, and a national sample of twin pairs. MIDUS 2 was conducted in 2004-2006 as a follow-up to MIDUS 1 and MIDUS 3 is a follow-up to MIDUS 2 conducted in 2013-2014. The study gathered comprehensive data via telephone interviews and self-administered questionnaires (Brim et al., 2020). To examine the day-to-day lives, information on daily experiences over a span of consecutive eight days was collected through NSDE between 2004 and 2009 as a part of MIDUS 2. In the NSDE, participants completed brief daily phone interviews for eight days and answered questions about their past week on the last interview day. Participants were also asked to provide four saliva samples each day from days two to five.

Our study examined diurnal cortisol rhythm measured during NSDE at MIDUS 2, in association with CP outcomes measured at MIDUS 3. We excluded participants who did not provide at least one valid cortisol sample within the sampling time, had anomalous sleep patterns, experienced cortisol measurement errors, or dropped out at MIDUS 3 (Dmitrieva et al., 2013; Karlamangla et al., 2013). Anomalous sleep patterns and cortisol measurement errors may significantly affect cortisol levels, and extreme values can also impact model estimation. A flow diagram for the study cohort is illustrated in Figure 3-1.

Figure 3-1 Flow diagram for the study cohort



3.2.2 Measures

3.2.2.1 Salivary cortisol sample collection information and calculation of diurnal cortisol rhythm parameters

Saliva samples were collected immediately upon awakening, 30 minutes after awakening, prior to lunch, and at bedtime (Ryff and Almeida, 2009). Participants were advised to gather samples prior to consuming food or beverages or brushing their teeth. Furthermore, they were requested to avoid any caffeinated items such as coffee, tea, soda, or chocolate before sample collection (Ryff and Almeida, 2009).

Data on the precise timing of each saliva sample collection provided by respondents were collected through nightly phone interviews and a paper log included with the collection kit, which included an instruction sheet and sixteen numbered, color-coded salivettes. Additionally, a subset of respondents were given a "Smart Box" to store their salivettes. These boxes were equipped with a computer chip that tracks when the box was opened and closed (Karlamangla et al., 2013; Ryff and Almeida, 2009). The correlations between self-reported times (from both paper-pencil logs and nightly phone interviews) exceeded 0.9 at each of the four sampling points. The correlations between self-reported times and those recorded by the "smart box" ranged between 0.75 and 0.95 (Karlamangla et al., 2013). Participants sent all 16 salivettes using a pre-addressed, prepaid courier package. The salivettes were shipped to the MIDUS Biological Core at the University of Wisconsin and stored at -60°C. Cortisol concentrations were measured using a luminescence immunoassay (IBL, Hamburg, Germany), with intra- and inter-assay variation below 5% (Ryff and Almeida, 2009).

3.2.2.2 Calculation of diurnal cortisol rhythm parameters

The parameters of diurnal cortisol rhythm were operationalized as CAR, DCSs, the AUC with respect to ground, and CDR. Specifically, linear spline multilevel modeling was utilized with fixed knots to model the diurnal cortisol trajectory with natural log-transformation, setting the fixed knots at 0.5 hours, 4.5 hours, and 15 hours after awakening, consistent with prior practices (Adam et al., 2006; Charles et al., 2020; Karlamangla et al., 2013).

Data from the NSDE were used to compute the diurnal cortisol rhythm (see Supplementary Table 2-1). To capture the nonlinearity of the diurnal cortisol rhythm, linear spline multilevel modeling was utilized. Linear spline model has shown a better fit for the rhythm compared to linear-cubic and quadratic spline models (Karlamangla et al., 2013). This model divides the data into distinct segments at specified knots and fits a separate regression for each segment. Knots are typically placed based on domain knowledge or data-driven methods; however, the latter can be unsatisfying due to a lack of robust and efficient statistical approaches. Therefore, we set the knots at 0.5 hours, 4.5 hours, and 15 hours after awakening, aligned with previous practice that has demonstrated good model fit (Yang et al., 2023). Additionally, based on a visual examination of Supplementary Figure 2-1, the knots are reasonable for capturing changes in the linear slopes.

Although linear spline models offer intuitive interpretability and flexibility in modeling piecewise linear relationships, there are several limitations associated with their use. In this study, the knots were determined based on previous literature and visual inspection of the data. While this pragmatic approach is common in applied work, it is inherently subjective and may introduce bias or omit important change-points not readily apparent. Furthermore,

the estimation of knots is challenging due to nondifferentiability of the spline basis functions at the knots. Although recent advances, such as the semismooth estimating equation approach, address some of these computational challenges, their methods are still complex and may require careful implementation (Yang et al., 2023).

In the linear spline model, the growth curve was adjusted for the following covariates: average wake time length (at the individual level), wake time (at the daily level), and the status of weekends versus weekdays (at the daily level) (Charles et al., 2020). Additionally, all growth curves accounted for random effects in cortisol measurements by incorporating random intercepts at the family level, random slopes for all growth curve parameters at the individual level, and random intercepts as well as random slopes for the early post-wake decline (from 0.5 hours to 4.5 hours after waking) at the daily level (Karlamangla et al., 2013).

The regression results of the linear spline model were shown in Supplementary Table 2-2. For each one-unit increase in time within the interval between 0 to 30 minutes after awakening, the log-transformed cortisol level increases by 0.50. In the intervals between 30 minutes to 4.5 hours, and after 15 hours post-awakening, the log-transformed cortisol level decreases by 0.13. In the interval between 4.5 to 15 hours after awakening, the log-transformed cortisol level decreases by 0.16. Model-based cortisol diurnal pattern was shown in the Supplementary Figure 2-2.

Fixed-effects estimates were combined with corresponding random effects at both familial and individual levels to obtain individual-specific estimates of growth curve parameters (Charles et al., 2020). The slope in the linear splines was used to compute the cortisol slopes.

The first linear spline (from awakening to 0.5 hours) represents the CAR, the second linear spline delineates the early post-wake DCS occurring from 0.5 to 4.5 hours post-awakening, and the third linear spline characterizes the mid post-wake DCS spanning 4.5 to 15 hours post-awakening. The fourth linear spline represents the late post-wake DCS, extending beyond 15 hours post-awakening, with a maximum duration of 20 hours; 95% of observed days conclude by 18 hours post-awakening. Then, cortisol estimates at specific individual timings (relative to awakening) were computed, and the logarithmic AUC was calculated using the trapezoidal formula (Pruessner et al., 2003), by first adding the areas of each trapezoid from awakening time to 30 minutes post-awakening, from 30 minutes post-awakening to lunchtime, and from lunchtime to bedtime. For individuals whose bedtime occurred less than 15 hours after awakening, the area from 4.5 hours post-awakening to bedtime was directly added. For individuals whose bedtime occurred more than 15 hours after awakening, the areas from 4.5 to 15 hours post-awakening and from 15 hours post-awakening to bedtime were calculated separately and then summed. The CDR was calculated as the logarithmic peak cortisol minus the logarithmic nadir cortisol (Charles et al., 2020; Karlamangla et al., 2013). We then conducted Principal Component Analysis (PCA) to identify underlying structures. The PCA revealed that two significant factors sufficiently explained the variance in the data (see Supplementary Table 3). DCSs predominantly loaded onto Factor 1, while CAR, CDR, and AUC loaded onto Factor 2. Cortisol parameters were standardized at the between-individual level to facilitate comparison of the predictive utility of the different parameterizations in the regressions (Charles et al., 2020; Kumari et al., 2011).

3.2.2.3 Measurement of CP at follow-up

The presence of CP, CP interference and the number of CP sites were measured in both MIDUS 2 and MIDUS 3. Respondents were asked “Do you have CP, that is do you have pain that

persists beyond the time of normal healing and has lasted from anywhere from a few months to many years?", if they answered positively, they would be then asked about CP interference. A pain interference index was generated by calculating a mean score of how much pain interfered with respondents' activity, mood, relations, sleep, and enjoyment, ranging from 0 to 10 (Jensen, 2011; Li et al., 2021a). The pain interference index was further categorized into no pain, low interference pain (≤4), and high interference pain (>4) as categorical variable, based on the recommended threshold for the Pain Interference Subscale (Jensen, 2011). In addition, if respondents reported having CP, they were asked about the location of the pain, including head, neck, back, arms, legs, shoulders, hips, knees, and other sites. The pain sites were summed up into an index and then categorized it into no pain, pain at 1-2 regions, or pain at 3 or more regions as a categorical variable (Hoftun et al., 2012; Li et al., 2021b).

3.2.2.4 Covariates

The MIDUS 2 individual level covariates were chosen based on their known influences on both cortisol patterns and CP outcomes. These variables included income-to-needs ratio, education, age, sex assigned at birth (ref: male; comparison: female), race (ref: White; comparison: Black, Indigenous and People of Color (BIPOC)), marital status (ref: divorced/separated/widowed/never married; comparison: married), physical activity, smoking (ref: current smoker; comparison: ex-smoker or non-smoker) and drinking status (ref: moderate; comparison: more drinker, light drinker, or non-drinker or rarely drink), parental abuse (1: never-3: most frequent), body mass index (BMI), multimorbidity (ref: no; comparison: yes), and CP at MIDUS 2 (ref: no; comparison:yes) (Adam et al., 2017; Bernard et al., 2017; Karlamangla et al., 2013; Mills et al., 2019). Furthermore, the present study controlled for the use of steroid inhalers, oral steroids (Jevtovic-Todorovic et al., 2009; Woods et al., 2015), antidepressants or anti-anxiety medications (Manthey et al., 2011; Verdu et al.,

2008), birth control pills (Jensen et al., 2018; Kirschbaum et al., 1999), and other hormonal medications (ref: no or yes).

The income-to-needs ratio and education levels were coded on a scale ranging from 0 to 2 (Gruenewald et al., 2012). Using the Poverty Thresholds by Size of Family and Number of Children from the United States Census Bureau (https://www.census.gov/data/tables/time-series/demo/income-poverty/historical-poverty-thresholds.html), we calculated the ratio between household income and poverty thresholds. A ratio below 1 indicates poverty, 1 to 2 indicates low income, and above 2 indicates adequate or affluent income, following established classification practices. These categories were then scaled from 2 to 0, where 2 represents high socioeconomic disadvantage and 0 represents low socioeconomic disadvantage. Similarly, educational attainment was scaled into three levels: possessing a bachelor's degree or higher, completion of high school/GED or some college, and less than a high school education. Age and BMI were coded as continuous variables. Race and ethnicity were self-reported and categorized into White and BIPOC because of the limited number of participants from minoritized groups. The summary score for physical activity was calculated using three questions that inquired about the frequency of engagement in light, moderate, and vigorous activities, rated on a 6-point scale (1-never to 6-several times a week). To emphasize the importance of more vigorous activities, weights of 1, 3, and 5 were assigned to light, moderate, and vigorous activities respectively. The summary score was determined by taking the weighted average of the responses, ranging from 9 to 54 (Gruenewald et al., 2012). Smoking status was categorized into three groups, current smoker, ex-smoker, and non-smoker. Acohol consumption patterns were defined in terms of moderate or severe drinker, light drinker, and non-drinker or rarely drink. Parental abuse was categorized into

two ordinal variables: emotional and physical abuse (Li et al., 2021b). These were derived from averaging the reported abuse from both parents. The scale ranges from 1 to 3, with 1 indicating no abuse and 3 indicating severe abuse. The scale increases in increments of 0.5. Chronic condition index (Ryff et al., 2007) was coded as binary variable (<2; comparison: ≥2) to indicate multimorbidity (Dominick et al., 2012). Medication uses were coded as yes vs no.

3.2.3 Statistical methods

We compared characteristics between participants without CP at baseline and those with CP at baseline. For continuous variables that followed a normal distribution, analysis of variance (ANOVA) was applied. The Kruskal-Wallis tests were used for continuous variables that did not meet normality assumptions. Categorical variables were compared using the Chi-Square tests. The comparisons were further examined with effect size measures (Cohen's d/Phi/Cramér's V) and their confidence intervals. Cohen's d measures the standardized difference between two means in continuous data, Phi assesses the association between binary variables, and Cramér's V evaluates the strength of association in categorical variables with more than two categories.

Subsequently, mixed-effects logistic regressions were used to examine the prospective associations between each specific cortisol parameter and CP outcomes at follow-up, with each cortisol parameter analyzed in separate models. Family-level random intercepts were included to account for correlations between individuals from the same family (Karlamangla et al., 2022). Pooled analyses were performed to estimate the overall effect while adjusting for baseline CP and other covariates. To examine the role of diurnal cortisol rhythm in the development or persistence of CP, we conducted analyses stratified by baseline CP status,

adjusting for all covariates except baseline CP. The subgroup analyses would highlight important nuances related to pain chronicity.

The present study also conducted a set of robustness checks, including multiple imputation, inverse probability of attrition weighting, exclusion of respondents with depression or anxiety, exclusion of respondents who used steroid inhalers, oral steroids, other hormonal treatments, antidepressants, anti-anxiety medications, and birth control, additional adjustment for daily stressor severity, using Bonferroni correction, and moderation analysis to reduce the risk of false negatives in subgroup analysis.

Firstly, we adjusted the associations using the inverse probability of attrition weighting (IPAW) (Metten et al., 2022) to reduce the attrition bias. A multinomial logistic regression was used to examine participation outcomes in the MIDUS 3 among the eligible sample with income-to-needs ratio, education, age, sex assigned at birth, marital status, physical activity, smoking and drinking status, parental abuse, BMI, multimorbidity, and baseline CP as predictors. These participation outcomes included participation, death, being physically or mentally unable, refusal, being unreachable for interviews, non-functional phone numbers, being outside the U.S., and not being fielded for various reasons. Then, we calculated the probability of a respondent being present at the follow-up and determined attrition weights by taking the inverse of this probability (See Supplementary Table 2-3). Secondly, to address the potential bias arising from item missingness in our main analysis, we made an assumption that the data was missing at random and then used multivariate imputation by chained equations (MICE), employing 10 imputations. Random forest imputation was used to accommodate nonlinearities and interactions and it does not require a particular regression model to be

specified (Shah et al., 2014). Thirdly, to further account for the confounding effects of depression and anxiety, we excluded respondents with these conditions in our analysis. We then examined the impact of medication use by excluding those with steroid inhalers, oral steroids, other hormonal treatments, antidepressants, anti-anxiety medications, and birth control uses from the sample. Also, we controlled for daily stressor severity to further reduce the influence of acute stress. In addition, the Bonferroni correction was used to reduce the likelihood of Type I errors when conducting multiple statistical tests, thereby enhancing the overall power of the study (Sedgwick, 2012). Finally, we performed a moderation analysis on the full sample to reduce the risk of false negatives inherent in subgroup analysis.

3.3 Results

3.3.1 Sample description

Table 3-1 compares the characteristics of participants without CP (n=762) to those reporting CP (n=429), over a median follow-up of 7.6 years (IQR 6.3-8.3). Compared to those without CP at baseline, participants with CP at baseline reported higher degrees of pain interference and pain widespreadness at follow-up. Additionally, participants with higher pain interference at follow-up were more likely to overlap with those experiencing more pain regions, regardless of baseline pain status (participants with baseline CP: χ^2=761, P<0.001; participants without baseline CP: χ^2=400, P<0.001).

As shown in Table 3-1, participants with CP at baseline exhibited a flatter CAR and late post-wake DCS, and a narrower CDR, compared to those without CP. However, the effect sizes of these differences were small. Compared to participants without CP, those reporting CP at baseline were more likely to be taking birth control pills, to have more socioeconomic

disadvantages in terms of their income-to-needs ratio and education, to be older, more likely to be assigned female at birth, to report multimorbidity, and to have a higher BMI. The effect size measures indicated that differences in pain outcomes at follow-up, as well as in education, multimorbidity, and BMI, were significant.

Table 3-1 Baseline characteristics of study participants with non-standardized cortisol parameters stratified by the presence of baseline CP

Pain status at baseline (MIDUS 2)		No CP (N=762)	Reporting CP (N=429)		
Variables	**N**	**Mean (SD) / N (%)**	**Mean (SD) / N (%)**	**P-value**	**Cohen's d/phi/ Cramér's V (95% CI)[1]**
Pain outcomes at follow-up (MIDUS 3)[2]					
Presence of CP	1124			<0.001	0.36 (0.31, 1.00)**
No		525 (72.8%)	147 (36.5%)		
Yes		196 (27.2%)	256 (63.5%)		
Pain interference	1092			<0.001	0.36 (0.31, 1.00)**
No pain		525 (73.7%)	147 (38.7%)		
Low interference CP		137 (19.2%)	133 (35.0%)		
High interference CP		50 (7.02%)	100 (26.3%)		
Pain widespreadness	1116			<0.001	0.39 (0.34, 1.00)**

No pain		525 (73.0%)	147 (37.0%)		
CP with 1-2 sites		144 (20.0%)	123 (31.0%)		
CP with 3 or more sites		50 (6.95%)	127 (32.0%)		
Cortisol parameters at baseline (MIDUS 2)[3]					
CAR (0-30 mins)	1185	0.53 (0.29)	0.47 (0.38)	0.011	0.16 (0.04, 0.28)
Early post-wake DCS (30 mins-4.5 hours)	1185	-0.14 (0.05)	-0.13 (0.05)	0.211	-0.08 (-0.20, 0.04)
Mid post-wake DCS (4.5 hours-15 hours)	1185	-0.16 (0.04)	-0.15 (0.04)	0.066	-0.11 (-0.23, 0.01)
Late post-wake DCS (after 15 hours)	1185	-0.14 (0.04)	-0.13 (0.04)	0.019	-0.14 (-0.26, -0.02)
CDR	1183	2.49 (0.48)	2.38 (0.57)	0.001	0.21 (0.08, 0.33)*
AUC	1183	4.84 (0.32)	4.81 (0.40)	0.110	0.10 (-0.02, 0.22)
Covariates at baseline (MIDUS 2)					
Pain outcomes					
Pain interference	422	/			
Low interference CP			311 (73.7%)		
High interference CP			111 (26.3%)		

Pain widespreadness	429	/			
CP with 1-2 sites			259 (60.4%)		
CP with 3 or more sites			170 (39.6%)		
Medication uses					
Steroid inhaler	1191			0.622	0.02 (0.00, 1.00)
No		739 (97.0%)	413 (96.3%)		
Yes		23 (3.02%)	16 (3.73%)		
Oral steroid meds	1191			1.000	0.00 (0.00, 1.00)
No		741 (97.2%)	417 (97.2%)		
Yes		21 (2.76%)	12 (2.80%)		
Other hormonal meds	1191			0.122	0.05 (0.00, 1.00)
No		739 (97.0%)	423 (98.6%)		
Yes		23 (3.02%)	6 (1.40%)		
Anti-depressant or anti-anxiety meds	1191			0.146	0.04 (0.00, 1.00)
No		685 (89.9%)	373 (86.9%)		

Yes		77 (10.1%)	56 (13.1%)		
Birth control pills	1191			0.001	0.09 (0.05, 1.00)
No		674 (88.5%)	350 (81.6%)		
Yes		88 (11.5%)	79 (18.4%)		
Sociodemographics					
Income-to-needs scale	1169	0.21 (0.54)	0.32 (0.65)	0.004	-0.18 (-0.30, -0.05)
Education	1189	0.55 (0.54)	0.66 (0.58)	0.001	-0.20 (-0.32, -0.08)*
Age	1191	54.7 (11.3)	56.9 (11.3)	0.001	-0.19 (-0.31, -0.07)
Ethnicity	1170			0.702	0.02 (0.00, 1.00)
White		721 (95.9%)	398 (95.2%)		
Black, Indigenous and People of Color (BIPOC)		31 (4.12%)	20 (4.78%)		
Sex assigned at birth	1191			0.024	0.07 (0.02, 1.00)
Male		355 (46.6%)	170 (39.6%)		
Female		407 (53.4%)	259 (60.4%)		
Marital status	1190			0.107	0.05 (0.00, 1.00)

Divorced/separated/widowed/never married		180 (23.6%)	120 (28.0%)		
Married		582 (76.4%)	308 (72.0%)		
Health behavior					
Physical activity	1109	29.6 (10.4)	29.5 (10.9)	0.873	0.01 (-0.11, 0.13)
Smoking status	1191			0.054	0.07 (0.00, 1.00)
Current smoker		76 (9.97%)	52 (12.1%)		
Ex-smoker		455 (59.7%)	274 (63.9%)		
Non-Smoker		231 (30.3%)	103 (24.0%)		
Drinking status	1191			0.260	0.05 (0.00, 1.00)
Moderate + Drinker		240 (31.5%)	136 (31.7%)		
Light Drinker		234 (30.7%)	114 (26.6%)		
Non-Drinker or Rarely Drink		288 (37.8%)	179 (41.7%)		
Health conditions					
Multimorbidity	1191			<0.001	0.25 (0.20, 1.00)*
No		401 (52.6%)	115 (26.8%)		

Yes		361 (47.4%)	314 (73.2%)		
BMI	1146	27.2 (5.01)	28.6 (6.11)	<0.001	-0.25 (-0.38, -0.13)*
Parental abuse at MIDUS 1					
Childhood emotional abuse	1100			0.975	0.02 (0.00, 1.00)
1 (Never)		246 (34.6%)	128 (32.9%)		
1.5		103 (14.5%)	57 (14.7%)		
2		189 (26.6%)	103 (26.5%)		
2.5		89 (12.5%)	52 (13.4%)		
3 (Most frequent)		84 (11.8%)	49 (12.6%)		
Childhood physical abuse	1108			0.587	0.05 (0.00, 1.00)
1 (Never)		318 (44.6%)	161 (40.8%)		
1.5		112 (15.7%)	59 (14.9%)		
2		174 (24.4%)	102 (25.8%)		
2.5		59 (8.27%)	41 (10.4%)		
3 (Most frequent)		50 (7.01%)	32 (8.10%)		

[1]Tests for effect size: Cohen's d: *small effect (≥0.20 & <0.50); **medium effect (≥0.50 & <0.80); *** large effect (≥0.80); Phi: *small effect (≥0.10 & <0.30); **medium effect (≥0.30 & <0.50); *** large effect (≥0.50); Cramer's V: *small effect (≥0.10 & <0.30); **medium effect (≥0.30 & <0.50); *** large effect (≥0.50).

[2]At follow-up, low interference pain includes 196 with CP with 1-2 sites and 80 with CP with 3 or more sites, while high interference pain includes 66 and 86, respectively. Similarly, CP with 1-2 sites includes 196 with low interference pain and 66 with high interference pain, while CP with 3 or more sites includes 80 and 86, respectively. Among participants with no baseline pain, 80.0% with CP with 1-2 sites reported low interference pain, while 20.0% reported high interference pain. For those with multisite pain, 53.2% had low interference pain, and 46.8% had high interference pain (χ^2=761, P<0.001). Among participants with baseline pain, 68.7% of those with CP with 1-2 sites had low interference pain, while 31.3% reported high interference pain. For multisite pain, 45.8% had low interference pain, and 54.2% had high interference pain (χ^2=400, P<0.001).

[3]Note that cortisol parameters were non-standardized. An increase of CAR indicates a steeper CAR, whereas an increase of in DCSs indicates flatter DCSs. A higher value in CDR indicates a wider CDR, while a higher value in AUC indicates a larger AUC.

3.3.2 Regression results

Table 3-2 shows results from the mixed-effects logistic regressions for the prospective associations between diurnal cortisol rhythm and CP conditions at follow-up, for both the stratified subgroup analysis and pooled analysis. In those without CP at baseline, blunter late post-wake DCS was associated with higher odds of developing CP (OR=1.26, 95% CI=1.03-1.55, P<0.05); no significant associations were observed for those with CP at baseline or for the pooled analysis.

Regarding pain interference, in those without CP at baseline, blunter early post-wake DCS and mid post-wake DCS were associated with higher odds of developing high interference pain. Specifically, for each one standard deviation increase in the early post-wake DCS and mid post-wake DCS, the odds of developing high interference pain were 85% (OR=1.85, 95% CI=1.09-3.16, P<0.05) and 82% (OR=1.82, 95% CI=1.09-3.02, P<0.05) higher respectively. Also, the blunter early post-wake DCS was significantly associated with higher odds of experiencing high interference pain compared to low interference pain both among individuals without CP at baseline (OR=2.60, 95% CI=1.44-4.70, P<0.01) and within the pooled sample (OR=1.37, 95% CI=1.04-1.81, P < 0.05). No significant associations were observed between cortisol diurnal parameters at baseline and low interference pain at follow-up, in either subgroup or pooled analysis.

Similarly, in those without CP at baseline, blunter early post-wake DCS (OR=2.16, 95% CI=1.41-3.32, P<0.001), mid post-wake DCS (OR=1.93, 95% CI=1.28-2.90, P<0.01), and late post-wake DCS (OR=1.58, 95% CI=1.03-2.43, P<0.05) were associated with higher odds of developing CP

with 3 or more sites. Additionally, the early post-wake DCS was significantly associated with higher odds of CP with 3 or more sites compared to CP with 1-2 sites both among individuals without CP at baseline (OR=2.73, 95% CI=1.49-4.99, P< 0.01) and within the pooled sample (OR=1.33, 95% CI=1.01-1.75, P<0.05). The wider AUC was significantly associated with lower odds of CP with 3 or more sites compared to CP with 1-2 sites both within the pooled sample (OR=0.76, 95% CI=0.58-0.98, P<0.05). Furthermore, the mid post-wake DCS was significantly associated with higher odds of CP with 3 or more sites compared to CP with 1-2 sites among individuals without CP at baseline (OR=2.21, 95% CI=1.24-3.91, P < 0.01). In those with pre-existing CP at baseline, no significant associations were observed between cortisol diurnal parameters at baseline and pain widespreadness at follow-up.

To aid in interpreting the associations, Figure 3-2 illustrates the diurnal cortisol trajectories of participants by CP conditions at follow-up, stratified by baseline CP status.

Table 3-2 Results from the mixed-effects logistic regression for the prospective association between diurnal cortisol rhythm and CP interference and pain at 1-2 regions/at 3 or more regions †

	Subgroups				Pooled sample	
	No baseline CP		Reporting CP at baseline		Adjusting for CP at baseline	
No pain vs presence of CP at MIDUS 3	**N**	**OR (95% CI)**	**N**	**OR (95% CI)**	**N**	**OR (95% CI)**
CAR (0-30 mins)	610	0.93 (0.77, 1.13)	310	1.08 (0.81, 1.42)	920	0.96 (0.83, 1.12)
Early post-wake DCS (30 mins-4.5 hours)	610	1.02 (0.84, 1.24)	310	1.07 (0.80, 1.43)	920	1.03 (0.89, 1.20)
Mid post-wake DCS (4.5 hours-15 hours)	610	1.08 (0.89, 1.32)	310	1.05 (0.79, 1.40)	920	1.07 (0.92, 1.25)
Late post-wake DCS (after 15 hours)	610	**1.26 (1.03, 1.55)***	310	0.94 (0.71, 1.26)	920	1.15 (0.99, 1.35)
CDR	610	0.90 (0.74, 1.09)	310	0.89 (0.66, 1.20)	920	0.89 (0.77, 1.04)
AUC	610	1.09 (0.89, 1.33)	310	0.97 (0.73, 1.30)	920	1.03 (0.88, 1.20)
No pain vs low interference pain at MIDUS 3	**N**	**OR (95% CI)**	**N**	**OR (95% CI)**	**N**	**OR (95% CI)**
CAR (0-30 mins)	568	1.11 (0.90, 1.37)	224	0.95 (0.69, 1.29)	792	1.05 (0.89, 1.24)
Early post-wake DCS (30 mins-4.5 hours)	568	1.16 (0.93, 1.45)	224	0.96 (0.69, 1.33)	792	1.08 (0.91, 1.29)

Mid post-wake DCS (4.5 hours-15 hours)	568	1.08 (0.86, 1.35)	224	0.97 (0.70, 1.34)	792	1.03 (0.86, 1.22)
Late post-wake DCS (after 15 hours)	568	0.83 (0.66, 1.04)	224	1.03 (0.76, 1.40)	792	0.89 (0.75, 1.05)
CDR	568	1.06 (0.86, 1.30)	224	1.15 (0.83, 1.58)	792	1.08 (0.92, 1.28)
AUC	568	0.90 (0.72, 1.13)	224	1.04 (0.75, 1.43)	792	0.95 (0.80, 1.13)
No pain vs high interference pain at MIDUS 3	**N**	**OR (95% CI)**	**N**	**OR (95% CI)**	**N**	**OR (95% CI)**
CAR (0-30 mins)	490	1.01 (0.67, 1.53)	190	1.09 (0.71, 1.67)	680	0.97 (0.75, 1.25)
Early post-wake DCS (30 mins-4.5 hours)	490	**1.85 (1.09, 3.16)***	190	0.89 (0.59, 1.33)	680	1.28 (0.98, 1.66).
Mid post-wake DCS (4.5 hours-15 hours)	490	**1.82 (1.09, 3.02)***	190	0.83 (0.55, 1.24)	680	1.26 (0.68, 2.33)
Late post-wake DCS (after 15 hours)	490	1.52 (0.95, 2.45).	190	0.70 (0.46, 1.06)	680	1.09 (0.83, 1.43)
CDR	490	0.79 (0.53, 1.19)	190	0.87 (0.56, 1.37)	680	0.81 (0.63, 1.04)
AUC	490	1.08 (0.71, 1.64)	190	0.92 (0.59, 1.42)	680	0.94 (0.73, 1.23)
Low interference pain vs high interference pain at MIDUS 3	**N**	**OR (95% CI)**	**N**	**OR (95% CI)**	**N**	**OR (95% CI)**
CAR (0-30 mins)	154	1.10 (0.68, 1.77)	174	0.91 (0.64, 1.28)	328	0.94 (0.73, 1.20)
Early post-wake DCS (30 mins-4.5 hours)	154	**2.60 (1.44, 4.70)****	174	1.10 (0.74, 1.62)	328	**1.37 (1.04, 1.81)***
Mid post-wake DCS (4.5 hours-15 hours)	154	2.48 (0.94, 6.55)	174	1.01 (0.70, 1.47)	328	1.26 (0.96, 1.64)

Late post-wake DCS (after 15 hours)	154	1.25 (0.75, 2.08)	174	0.86 (0.59, 1.26)	328	0.97 (0.75, 1.26)
CDR	154	0.77 (0.37, 1.59)	174	0.92 (0.65, 1.29)	328	0.88 (0.69, 1.14)
AUC	154	0.89 (0.49, 1.62)	174	0.86 (0.60, 1.22)	328	0.86 (0.66, 1.11)
No pain vs CP with 1-2 sites at MIDUS 3	**N**	**OR (95% CI)**	**N**	**OR (95% CI)**	**N**	**OR (95% CI)**
CAR (0-30 mins)	570	1.08 (0.88, 1.34)	214	0.82 (0.56, 1.19)	784	1.01 (0.84, 1.21)
Early post-wake DCS (30 mins-4.5 hours)	570	1.15 (0.93, 1.43)	214	0.96 (0.68, 1.34)	784	1.09 (0.91, 1.29)
Mid post-wake DCS (4.5 hours-15 hours)	570	1.06 (0.85, 1.31)	214	0.99 (0.7, 1.39)	784	1.02 (0.86, 1.21)
Late post-wake DCS (after 15 hours)	570	0.83 (0.66, 1.04)	214	1.06 (0.78, 1.45)	784	0.87 (0.74, 1.04)
CDR	570	1.09 (0.88, 1.34)	214	1.02 (0.70, 1.48)	784	1.06 (0.89, 1.26)
AUC	570	0.87 (0.69, 1.09)	214	0.91 (0.63, 1.32)	784	0.88 (0.73, 1.06)
No pain vs CP with 3 or more sites at MIDUS 3	**N**	**OR (95% CI)**	**N**	**OR (95% CI)**	**N**	**OR (95% CI)**
CAR (0-30 mins)	491	0.83 (0.56, 1.21)	227	0.88 (0.62, 1.26)	703	0.89 (0.71, 1.10)
Early post-wake DCS (30 mins-4.5 hours)	491	**2.16 (1.41, 3.32)*** **	227	0.93 (0.64, 1.34)	703	1.26 (0.99, 1.60).
Mid post-wake DCS (4.5 hours-15 hours)	491	**1.93 (1.28, 2.90)** **	227	0.92 (0.64, 1.34)	703	1.22 (0.96, 1.55)
Late post-wake DCS (after 15 hours)	491	**1.58 (1.03, 2.43)***	227	0.87 (0.59, 1.29)	703	1.11 (0.87, 1.44)

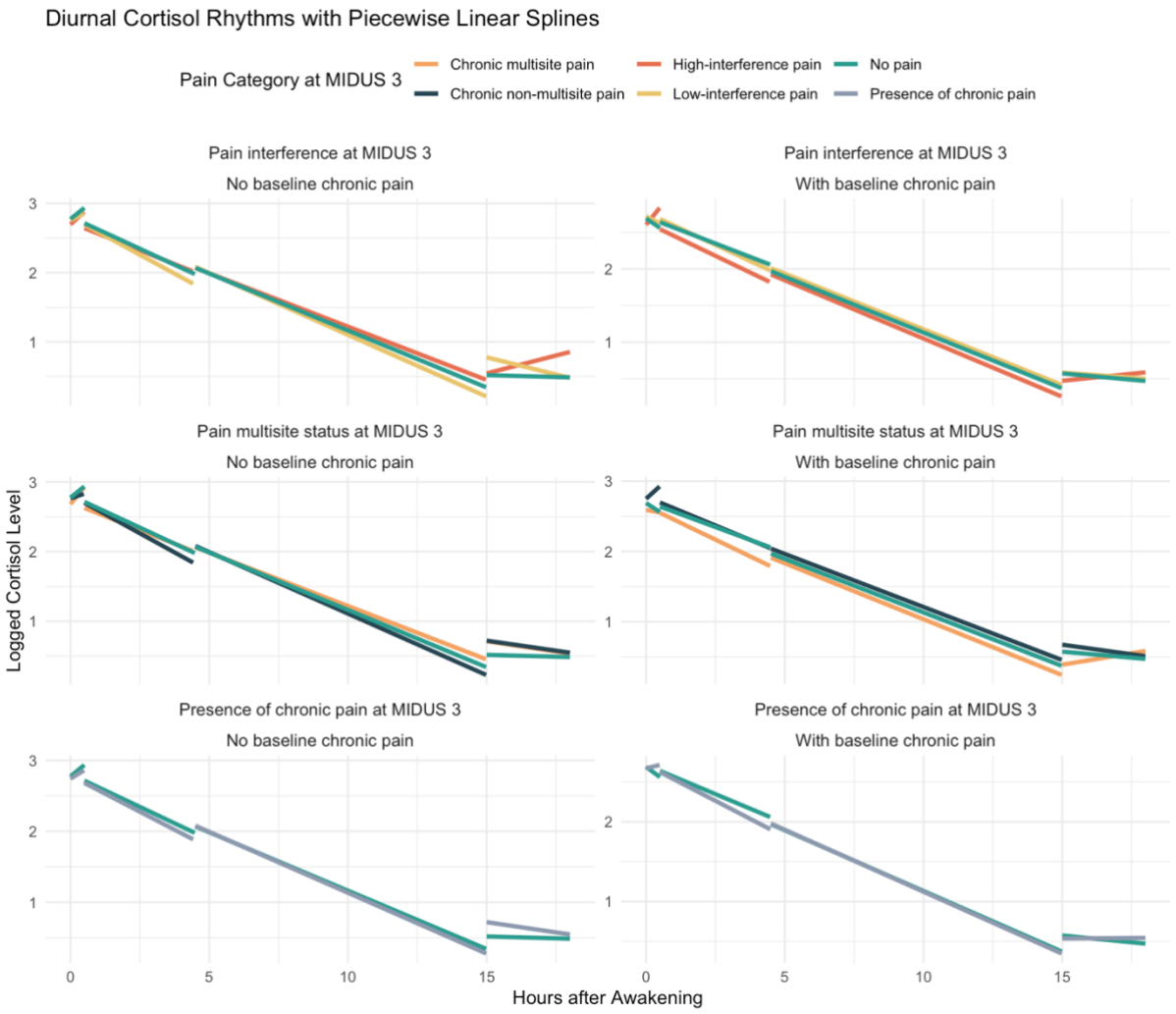
CDR	491	0.74 (0.51, 1.06)	212	0.77 (0.53, 1.12)	703	0.81 (0.65, 1.01)
AUC	491	0.81 (0.54, 1.21)	212	0.76 (0.51, 1.12)	703	0.83 (0.66, 1.04)
CP with 1-2 sites vs CP with 3 or more sites at MIDUS 3	**N**	**OR (95% CI)**	**N**	**OR (95% CI)**	**N**	**OR (95% CI)**
CAR (0-30 mins)	157	1.14 (0.71, 1.84)	186	0.80 (0.56, 1.14)	343	0.87 (0.68, 1.12)
Early post-wake DCS (30 mins-4.5 hours)	157	**2.73 (1.49, 4.99)****	186	0.95 (0.65, 1.39)	343	**1.33 (1.01, 1.75)***
Mid post-wake DCS (4.5 hours-15 hours)	157	**2.21 (1.24, 3.91)****	186	0.98 (0.68, 1.41)	343	1.21 (0.93, 1.57)
Late post-wake DCS (after 15 hours)	157	1.17 (0.71, 1.93)	186	0.96 (0.67, 1.37)	343	0.98 (0.76, 1.27)
CDR	157	1.00 (0.62, 1.62)	186	0.80 (0.57, 1.12)	343	0.85 (0.67, 1.09)
AUC	157	0.86 (0.54, 1.38)	186	0.69 (0.48, 1.00)	343	**0.76 (0.58, 0.98)***

Statistical significance markers: * p<0.05; ** p<0.01; *** p <0.001

† Adjusted for age, race, sex assigned at birth, income-to-needs ratio, education, marital status, physical activity index, smoking and drinking status, multimorbidity, BMI, childhood experiences of parental emotional and physical abuse, and medication intakes (e.g., steroid inhalers, oral steroids, antidepressants, anti-anxiety medications, birth control pills, and other hormonal medications). A random intercept at the family level was included, to allow for correlations between individuals from the same family.

Note that cortisol parameters were standardized. An increase of one standard deviation in CAR indicates a steeper CAR, whereas an increase of one standard deviation in DCSs indicates flatter DCSs. One standard deviation increase in CDR indicates a wider CDR, while one standard deviation increase in AUC indicates a larger AUC.

Figure 3-2 Diurnal cortisol trajectories of participants by chronic pain conditions at follow-up, stratified by baseline chronic pain status



3.3.3 Robustness Check

Results of the robustness checks are presented in Supplementary Tables 2-5 to 2-9. Among participants without baseline CP, late post-wake DCS was not significantly associated with CP development after multiple imputations, Bonferroni correction, exclusion of medication users, and controlling for daily stressors (see Supplementary Table 2-5).

Early and mid post-wake DCSs were initially associated with high interference CP. However, these associations became non-significant following Bonferroni correction and additional adjustments (see Supplementary Table 2-6). Moderation analyses revealed no significant interactions between baseline CP status and these cortisol parameters for high interference CP compared to individuals with no pain at follow-up (see Supplementary Table 2-9).

Associations between early and mid post-wake DCSs and CP with 3 or more sites remained consistent with the main analyses (see Supplementary Table 2-7). Significant moderation effects were observed for baseline CP and early and mid post-wake DCSs on the development of CP with 3 or more sites (see Supplementary Table 2-9).

Only early post-wake DCS remained robust in its association with CP with 3 or more sites at MIDUS 3, compared to CP with 1-2 sites in samples without baseline pain. Most associations between other post-wake DCSs or AUC and pain types at MIDUS 3 were non-significant in this subgroup or in the pooled samples (Supplementary Table 2-8). Additionally, moderation analyses showed that the absence of baseline pain significantly interacted with early and mid

post-wake DCSs, linking them to CP with 3 or more sites compared to CP with 1-2 sites, and to high interference pain compared to low interference pain (Supplementary Table 2-9).

3.4 Discussion

In this U.S. cohort of community-dwelling adults with multi-day cortisol collection, we found among individuals who did not report CP at baseline, those with blunter early and mid post-wake DCSs had higher odds of developing CP with 3 or more sites about seven years later. Also, early post-wake DCS was associated with CP with 3 or more sites compared to CP with 1-2 sites, among individuals without baseline CP. Sensitivity analyses did not substantially change these associations. No other robust associations were found in the same subgroup. Among those with pre-existing CP, no clear associations were found between diurnal cortisol rhythm and CP outcomes. Moreover, in the pooled sample, no robust associations were found between diurnal cortisol rhythm and CP outcomes.

A previous study found that a blunted diurnal cortisol rhythm predicted an increased risk of new-onset chronic widespread pain 15 months later (McBeth et al., 2007). However, it had a smaller cohort size (n=269). Additionally, the previous study used actual clock time, and cortisol samples might have been taken at different points in each individual's diurnal cycle, potentially leading to measurement bias (Adam and Kumari, 2009). Using waking time as a reference in our study ensured that the measurements consistently reflected the natural rhythms of the participants. Our research findings echo the previous results. The DCS is primarily regulated by a negative feedback mechanism mediated jointly by GRs in peripheral and brain regions and MRs expressed in limbic structures (Kloet et al., 1998; Stalder et al., 2024). However, GRs typically exhibit stronger inhibitory effects following the diurnal rhythm

peak, and as cortisol levels decline, MRs become more significant, particularly in maintaining the basal activity of the HPA axis (Kloet et al., 1998; Oster et al., 2017). Our linear spline modeling of DCS may capture the extent to which different receptors mediate negative feedback mechanisms at different time intervals. Our PCA analysis (Supplementary Table 2-3) shows that Factor 1 may reflect the synergistic functions of GRs and MRs, with GRs being dominant. Early post-wake DCS may primarily reflect GR activity, with minimal influence from MRs, resulting in lower factor loadings. Mid post-wake DCS may involve both GRs and slightly increased MR activity, leading to the highest factor loading. In late post-wake DCS, MR activity predominates while GR participation decreases, reducing synergy and yielding the lowest factor loadings.

Therefore, on the one hand, our results emphasize the important role of GR downregulation in the development of pain with multiple sites as characterized by the flattening of early post-wake DCS and mid post-wake DCS. GR downregulation reduces cortisol inhibition of catecholamine release (Fries et al., 2005; Hannibal and Bishop, 2014), which exacerbate inflammation and induce nociception. Additionally, the inflammation heightens the excitability of sensory transmission pathways, leading to both peripheral and central sensitization (Veldhuijzen et al., 2018). Moreover, impaired GR function fails to inhibit nuclear factor-κB (Pavlov et al., 2003), promoting algogen transcription and further sensitization and hyperalgesia (Kawasaki et al., 2008; Walsh and McWilliams, 2014). On the other hand, late post-wake DCS did not show robust association with CP with 3 or more sites, and in the comparison between CP with 1-2 sites and CP with 3 or more sites, only early post-wake DCS was significant. This may indicate that the MR mechanism has a limited role in the development of CP with 3 or more sites.

Furthermore, our results highlight the significant role of identifying DCS flattening in indicating the developmental stages of CP with 3 or more sites (McBeth et al., 2007). Recent studies collectively demonstrate that individuals experiencing acute pain or non-chronic regional pain, representing the early to mid-stages of CP development, often exhibit higher cortisol levels, such as elevated CAR and AUC (Begum et al., 2022; Reyes del Paso et al., 2024; Riva et al., 2012). However, as pain becomes chronic, cortisol levels gradually decline (Reyes del Paso et al., 2024). Although some studies have still observed increased cortisol levels following the onset of CP (Begum et al., 2022), recent research has clarified these associations. It suggests that cortisol levels may temporarily rise due to pain episodes within CP, but in the long term, the HPA axis function becomes downregulated, leading to decreased cortisol levels (Reyes del Paso et al., 2024). The latest meta-analyses and cross-sectional epidemiological studies consistently indicate that individuals with fibromyalgia and chronic multisite musculoskeletal pain have lower cortisol levels (Beiner et al., 2023; Generaal et al., 2014; McBeth et al., 2005). Similarly, our supplementary analyses showed that, after controlling for the same set of covariates, a flatter CAR and lower AUC were cross-sectionally associated with higher odds of CP with 3 or more sites (see Supplementary Table 2-10). Therefore, DCS flattening serves as a mid-to-late stage marker of HPA axis dysregulation, linking elevated cortisol levels at the early stage with reduced cortisol levels as a longer-term consequence of the dysregulation.

Contrary to our findings, a study from the Netherlands Study of Depression and Anxiety (NESDA) reported that diurnal rhythm of cortisol was not associated with the development of chronic widespread pain (Generaal et al., 2016). However, incorporating cohorts with a high

proportion of patients with a history of depression and anxiety (71.4% of those who did not develop chronic widespread pain and 81.9% of those who did) (Generaal et al., 2016) could obscure the relationship between cortisol levels and the development of CP (Generaal et al., 2014), as the cortisol changes in these conditions may introduce variability unrelated to pain, masking the true association (Knorr et al., 2010). This was confirmed in our supplementary analysis when we further excluded participants reporting anxiety, depression, or other emotional disorders in the past 12 months. Both early post-wake (OR=2.36, 95% CI=1.40-3.97, P<0.01) and mid post-wake (OR=2.20, 95% CI=1.33-3.64, P<0.01) DCSs showed even higher effect sizes among those without anxiety, depression, or other emotional disorders in the past 12 months, compared to the main analysis (see Supplementary Table 2-7).

Among respondents with baseline CP, we found no associations between diurnal cortisol rhythm and CP outcomes at follow-up, echoing the null association found in a previous study (Generaal et al., 2017). This may attenuate the association in the pooled analysis, resulting in nonsignificant findings. CP may become self-sustaining through central sensitization, in which neurons become hypersensitive, responding chaotically to normal stimuli or producing amplified responses to noxious stimuli (Woolf, 2011). Sustained pain may be less dependent on the HPA axis. Although participants who reported low interference pain and CP with 1-2 sites after seven years exhibited more active HPA axis among those with CP with 3 or more sites at baseline (see Supplementary Table 2-11), the small subgroup sizes based on specific baseline CP conditions limit the ability to conduct systematic examinations, warranting cautious interpretation. Future studies with larger samples are needed to further clarify these relationships.

We did not find a robust association between diurnal cortisol rhythms and pain interference. One possibility is that reports of pain interference may reflect modulation by the anterior cingulate cortex (Rainville, 2002), shaping the pain experience through mechanisms such as attentional focus, emotional distress, and cognitive appraisal (Villemure and Bushnell, 2002; Wiech et al., 2008). In our sample, 47% of individuals with pain at 3 or more regions overlapped with those reporting high interference pain. The observed differences in the association between the HPA axis and pain outcomes suggest that the reports of pain interference by those with pain at 3 or more regions may be further affected by the complex interplay of biopsychosocial factors rather than by the pain condition alone (Miettinen et al., 2019). Given the significant clinical implications of pain interference, further studies on its underlying mechanisms are needed.

Our study has several key advantages, including repeated measurements of salivary cortisol over multiple days in naturalistic settings and a community-based cohort study design. Repeated measurements of salivary cortisol over multiple days in naturalistic settings can reduce the masking of the average diurnal rhythm of cortisol due to intra-individual differences in stress events during the week (Hellhammer et al., 2007). Additionally, by employing multiple knots in a multilevel model to parametrically define diurnal cortisol rhythm, our study enhances the ability to capture non-linearities in these trajectories, offering a more nuanced approach than a uniform declining slope post-peak (Ranjit et al., 2005b). Furthermore, compared to a previous population-based prospective study, we additionally controlled for medication uses, thereby further clarifying the confounding effects on the associations (McBeth et al., 2007).

The study has the following limitations. We could not obtain clinically validated pain measures from the MIDUS, such as chronic widespread pain or fibromyalgia, possibly including patients with milder symptoms (Generaal et al., 2014). Additionally, the measurement of CP lacks a minimum duration of three months and implicitly assumes preexisting tissue damage, making it less reflective of the broader biopsychosocial dimensions of pain. Given the global burden of CP, we call for the inclusion of rigorous measures of CP in population-based epidemiological studies. Second, the study could not detect changes in CP status between MIDUS 2 NSDE and MIDUS 3, potentially misclassifying those who recovered by MIDUS 3 as not experiencing CP during the seven-year follow-up.

Another limitation of the study is the stringent criteria for selecting participants with viable cortisol data, which may introduce selection bias and limit the generalizability to the wider U.S. population. Meanwhile, BIPOC participants are underrepresented, indicating the need to increase the inclusion of ethnic minorities in future studies. Despite our cautious adjustment for confounders, the possibility of residual confounding due to imprecise measurements or unknown factors cannot be excluded in our study.

In addition, as with all associations yielding insignificant results, the true differences may be obscured by Type II errors. Although further moderation analysis by pooling the samples did not substantially alter our findings (See Supplementary Table 2-9), future larger-scale studies are necessary to further elucidate these associations.

Despite the advantages of cortisol collection via NSDE, factors like differences in collection times between groups, discrepancies between actual and intended collection times, and knot

selection may affect the accuracy of diurnal cortisol rhythm modeling. Future studies will benefit from strategies to improve collection compliance and precise knot estimation techniques.

Finally, by restricting analyses to participants without chronic pain at baseline, we may have conditioned on a variable influenced by both diurnal cortisol patterns and unmeasured risk factors for CP, potentially inducing a spurious association. Future studies using causal inference methods may help address this issue.

Our research has important implications for public health. First, we clarified the prospective associations between diurnal cortisol rhythms and the development of CP with 3 or more sites, providing information for identifying at-risk populations and informing strategies to monitor CP progression. While we did not estimate the proportion of future CP cases attributable to blunted DCS, future studies could use receiver operating characteristic (ROC) curve analysis to establish optimal cut-off values and assess sensitivity and specificity for risk stratification. Second, recent research shows that inhibiting FKBP51 upregulation can reduce pronociceptive GR signaling in inflammation and promote antinociceptive functions (Maiarù et al., 2016). Our findings may provide preliminary support for the potential of GR-related pharmacology in CP treatment. Longitudinal studies with repeated assessments of diurnal cortisol patterns and CP in large samples are needed to clarify their dynamic relationship and assess whether managing GR downregulation, indicated by blunted DCS, could reduce the burden of CP with 3 or more sites at the population level.

4 Life Course Socioeconomic Status, Chronic Pain, and the Mediating Role of Biological Dysregulation in Stress Response Systems: Findings from the Midlife in the United States

4.1 Introduction

Among the leading causes of disability, the top three are all non-communicable diseases. Notably, the first and third leading causes—low back pain and headaches—are both conditions that commonly present as chronic pain (CP) (Ferrari et al., 2024). The economic and societal impact of CP is substantial. A report from the Institute of Medicine in 2010 estimated that about one-third of the U.S. population experiences CP, with annual costs for healthcare and lost productivity ranging from $560 billion to $635 billion (Steglitz et al., 2012). CP, however, does not affect everyone equally. Data from the Centers for Disease Control and Prevention (CDC) indicate that women, individuals with lower socioeconomic status (SES), veterans, and rural residents tend to have higher rates of CP (Dahlhamer et al., 2018). Research consistently demonstrates that CP has a pronounced social patterning, with the prevalence of CP exhibiting clear socioeconomic disparities. Recent studies in the United States have found a SES gradient in CP trends over time, with increasing disparities in pain (Grol-Prokopczyk, 2017; Zajacova et al., 2021a; Zimmer and Zajacova, 2018). Given the significant consequences of CP and the widening inequalities in its prevalence, it is essential to take immediate steps to address socioeconomic disparities related to CP, ease its burden, and enhance the resilience of those most affected.

4.1.1 Association between life course SES and CP

Life course epidemiology provides multiple theoretical models to help understand how exposures throughout an individual's life influence health outcomes in later years and may facilitate understanding and prevention of CP. However, only few studies have focused on the association between SES during childhood and across the lifespan with CP. The critical period model suggests that exposure to unfavorable socioeconomic conditions during key developmental stages, such as early childhood, can result in long-term biological changes in the body's pain regulation systems, leading to a higher risk of CP in adulthood. This phenomenon is often referred to as biological programming. According to this model, exposure during these critical periods can have permanent effects on how individuals perceive and respond to pain. The sensitive period model shares some similarities with the critical period model, but differs in that it argues that certain phases of life are particularly important for health outcomes, yet the negative effects of exposures during these periods might still be partially reversed if conditions improve later in life. For instance, although low SES during certain life stages may elevate the likelihood of having CP, better access to resources after these sensitive periods could reduce this risk. The accumulation of risk model proposes that prolonged exposure to low SES over the course of life gradually imposes an increasing strain on the body's pain regulation systems, ultimately heightening the risk of CP. In this case, the frequency, intensity, and duration of harmful exposures accumulate over time, amplifying the damage to health. Meanwhile, the pathway model focuses on how early-life socioeconomic disadvantages influence opportunities throughout adulthood, setting individuals on a course where limited access to education, employment, and healthcare increases the risk of CP later in life. Finally, the chain of risk additive model integrates aspects of both the accumulation of risk and pathway models. This model highlights how exposure to

multiple risk factors at various life stages can form a chain, where each additional exposure compounds the overall risk. In relation to CP, repeated exposures to low SES at different times in life may collectively increase susceptibility to CP as the individual grows older. Moreover, the chain of risk additive model can help identify whether certain periods of exposure to risk factors act as sensitive periods or critical periods (Ben-Shlomo et al., 2014; Kuh et al., 2003).

Limited research studied the association between childhood SES and adulthood CP. Childhood SES, including the average educational attainment of both parents and family income, was found to be unrelated to the risk of chronic back pain in adulthood (Gonzalez et al., 2012). Two birth cohort studies revealed detailed associations between life course SES and chronic widespread pain (CWP). Based on the 1958 British Birth Cohort, the research found that after controlling for recent life events, self-rated health, mental health, body mass index, and physical activity, individuals in skilled manual, partly skilled, and unskilled social classes at age 42 were at a higher risk of having CWP three years later compared to those in the professional class at the same age. Moreover, lower social class at age 42 was associated with CP in the forearm, lower back, and knee while only father's social class was associated with chronic forearm pain (Macfarlane et al., 2009). Another study using the 1946 British Birth Cohort found that groups reporting moderate to severe financial hardship at age 43 had a 1.3- and 3.4-times higher risk of reporting CWP at age 68 compared to those who did not report financial hardship. Additionally, individuals renting at age 53 had a 62% increased risk of reporting CWP at age 68 compared to property owners. Compared to highly educated women, women with lower educational attainment had a 93% increased risk of reporting chronic regional pain (CRP) at age 68; however, for men, educational level was associated with CWP but not with CRP. Finally, compared to those who either reported no or only minimal

economic hardship, those reporting moderate to severe economic difficulties at ages 43 and between 60 to 64 had a 2.9 times higher risk of CWP. Childhood and SES from ages 60 to 64 were unrelated to CWP at age 68 (Jay et al., 2019). In addition, a retrospective study found that parental educational years, government assistance during childhood, and hunger were associated with CP, but this association was attenuated after adjusting for adult SES indicators, including income, education, and public assistance in adulthood, indicating a potential mediating role of SES in adulthood (Goosby, 2013).

However, previous studies on life course SES and CP have limitations. Firstly, SES and health conditions are largely determined by prior circumstances, such as how health status may affect occupational transitions (Hoffmann et al., 2018), and a history of chronic diseases and pain significantly predicts future pain reports (Mills et al., 2019). Thus, the lack of control for important confounding factors may exaggerate the association between SES and CP throughout the life course. Furthermore, previous life course studies were unable to provide information on additive effects and risk chains. Although a study has attempted to sum the same SES indicators collected at different times, this assumes that the effect of this indicator on CP is equal at different times, potentially overestimating or underestimating the effects of certain periods (Jay et al., 2019). Finally, previous research has either regressed SES indicators with CP alone or adjusted SES indicators against each other to explore the association between SES and CP. These measurements of SES either measures only one dimension of SES or overlooks the covariance present among various indicators, thus failing to represent the overall impact of SES as a multidimensional structure.

Scholars have long recognized the importance of relative deprivation indicators in health research because these involve a broader range of methods, capabilities, and psychological resources to cope with health risks, particularly for rich countries with low levels of material deprivation (Clouston and Link, 2021; Marmot, 2005). They are actually habitual and unconscious, internalized reflections of current socioeconomic plight. However, few life course CP studies have captured people's SES through relative deprivation indicators. Although some studies have included relative deprivation indicators, such as financial hardship (Jay et al., 2019), most have neglected the measurement of individuals' subjective perceptions of poverty and their experiences and adaptations to impoverished living (Diemer et al., 2013). Consequently, addressing the aforementioned disparities could prove advantageous in elucidating the relationship between life course SES and CP.

4.1.2 Biological dysregulations of chronic stress and its association with SES

Biological dysregulation associated with chronic stress is common among patients with CP (Woda et al., 2016) and low SES populations (Johnson et al., 2017), making it a potential mediator in the association between lifecourse SES and CP. However, only few studies have explored the potential of these biomarkers to link SES and CP (Slade et al., 2012; Strath et al., 2024). Allostatic load (AL) describes the biological consequences of an organism's continuous adaptation to prolonged and repeated stress (Juster et al., 2010; McEwen, 1998). The biological cost of chronic stress initially manifests in alterations of the hypothalamic-pituitary-adrenal (HPA) axis. A normal HPA axis, through its reactive hormonal secretion, prepares the organism for stress response (Herman et al., 2016). However, prolonged activation of the HPA axis, leading to over- or under-secretion of glucocorticoids and catecholamines, may eventually disrupt the production of substances necessary for maintaining the normal

functioning of downstream physiological systems. This disruption can result in anomalies in biomarkers from multiple physiological systems (Juster et al., 2010).

Individuals living in adverse socioeconomic conditions often endure dual hardships: there are needs for basic necessities, support, and opportunities, yet the resources available to meet them are limited. They are more likely to live with economic difficulties, family conflicts, bereavement, poor living conditions, crime, violence, and discrimination. These conditions in turn restrict opportunities to access essential resources such as money, education, power, prestige, and valuable social networks, which are critical for managing life's demands (Aneshensel, 1992). In addition to the severity of these stressors, characterized by the imbalance between demands and resources, repeated exposure to these stressors increases the likelihood of chronic stress (Crielaard et al., 2021), leading to AL and dysregulations of HPA axis. It is essential to separately examine AL as a consequence of overall chronic stress dysregulation and HPA axis dysfunction as an early indicator of chronic stress dysregulation. This distinction can reveal differential associations between SES and various stages of chronic stress dysregulation throughout the life course, while also providing insights into the potential pathogenic mechanisms linked to SES. Moreover, the dysregulation of these two types of biomarkers may encompass the significant and different roles that chronic stress dysregulation plays at CP, thereby offering critical information for the early prevention and intervention of CP.

People from low SES are more likely to have higher AL. A recent systematic review analyzed 287 articles up to 2017, selecting 26 that met the criteria for studies on SES and AL. Despite the heterogeneity in the operationalization of SES and AL, 23 studies consistently found

higher AL indices in low SES populations compared to their higher SES counterparts and three studies found moderated effects by gender or by ethnicity (Johnson et al., 2017). All of the studies in the review operationalized AL with at least one cardiovascular and one metabolic biomarker, and 85% of the studies included at least one inflammatory biomarker. However, only 58% of the studies included at least one biomarker from the HPA axis. Recent research on life course SES and AL has found that cumulative low SES is associated with higher levels of AL. These studies measured SES through composite indices (Lunyera et al., 2020), occupational class (Robertson et al., 2014), and neighborhood disadvantage (Gustafsson et al., 2014). These associations might be explained through home ownership, income, smoking, poor diet, or physical activity (Barboza Solís et al., 2016; Robertson et al., 2015). However, despite the extensive literature on SES and AL, there is still a lack of research integrating a life course model into the study of the relationship between SES and AL, particularly regarding the examination of additive effects, sensitive periods, and critical periods.

Dysregulations in the HPA axis are often observed among those in low SES. Previous research has indicated that lower SES is associated with a pronounced CAR (Kunz-Ebrecht et al., 2004a, 2004b; Wright and Steptoe, 2005). SES has been measured using occupational status (Kunz-Ebrecht et al., 2004a, 2004b) and perceived social status (Wright and Steptoe, 2005). However, the choice of SES measurements and variations in cortisol parameters may influence this association. For instance, a lower CAR has been observed among individuals experiencing financial strain (Steptoe et al., 2005). Lower income, educational attainment (Cohen et al., 2006a), and occupational status (Li et al., 2007) are associated with higher levels of AUC for cortisol. Moreover, material hardship (Ranjit et al., 2005a), lower occupational grades among civil servants (Chandola et al., 2018; Kumari et al., 2010), and low individual and neighborhood

SES (Miller et al., 2021) are related to a flatter DCS. Similarly, individuals with lower education levels exhibit a slower decline in diurnal cortisol levels (Groffen et al., 2015; Karlamangla et al., 2013). Studies modeling cortisol levels at different times of the day have shown inconsistent results. For example, lower income and educational levels are associated with higher evening cortisol levels (Cohen et al., 2006b), while other research indicates lower morning and afternoon cortisol levels related to lower income and education with no relationship to nighttime levels (Brandtstädter et al., 1991; Groffen et al., 2015). Furthermore, there is still a lack of studies applying a life course approach to the association between SES and cortisol.

4.1.3 Biological dysregulations of chronic stress and its association with CP

AL and CP are pathologically associated, as evidenced not only by overlapping dysregulations in biological systems (Abdallah and Geha, 2017; Woda et al., 2016) but also by similar alterations in stress response manifestations (Borsook et al., 2012; Juster et al., 2010). Despite mixed results found in the clinical studies (Generaal et al., 2016; Nelson et al., 2021; Wippert et al., 2022), possibly due to differences in measurements of pain and chronic stress response dysregulation, several population-based studies have consistently demonstrated a positive association between AL and CP in cross-sectional analyses. For example, people reporting pain lasting more than 24 hours and widespread bodily pain are more likely to experience higher levels of AL (Slade et al., 2012). Moreover, severe CP is correlated with AL regardless of the method used to calculate AL (Sibille et al., 2017). Recent research using a different approach for AL operationalization has shown that a dysregulated metabolic phenotype of AL is prospectively associated with high interference CP and 3 or more CP sites (Liang and Booker, 2024). To date, only one cross-sectional study has explored the mediating role of AL in the

association between SES and pain, and it did not find evidence of a mediating effect (Slade et al., 2012). However, it is likely that the pain measured in this study was acute pain rather than CP. Given that acute pain may involve entirely different pathological mechanisms compared to CP, this could explain the absence of a significant mediating effect. Additionally, the study did not include biomarkers related to the HPA axis when constructing AL, which raises challenges to the validity of the AL. Therefore, a gap exists in the literature regarding the intersection of SES, AL, and CP.

In addition, given the socioeconomic gradient of CP and HPA axis activity, the diurnal pattern of cortisol may serve as a potential mediator in the link between SES and CP. Patients with CP often display reduced salivary cortisol levels, although the majority of evidence stems from fibromyalgia patients and case-control studies (Beiner et al., 2023). Yet, the results from population studies are not consistent. In the UK, a prospective study utilizing a population register sample from three general practitioners indicated that a blunted diurnal cortisol rhythm and higher levels of post-dexamethasone serum cortisol were associated with the development of CWP (McBeth et al., 2007). A cross-sectional study from the Netherlands Study of Depression and Anxiety (NESDA) showed that individuals with chronic multisite musculoskeletal pain exhibited significantly reduced cortisol levels at awakening and in the evening, with a decreased diurnal slope, particularly among those without depression or anxiety (Generaal et al., 2014). However, another longitudinal study using the same dataset did not confirm the association between cortisol levels and the onset or improvement of CP (Generaal et al., 2017, 2016). A prospective study from the Western Australian Pregnancy Cohort (Raine) Study found that lower cortisol reactivity to stress in young women with higher pain sensitivity was associated with chronic musculoskeletal pain (Paananen et al., 2015). The

inconsistency may be attributed to limited cortisol collection procedures in previous epidemiological surveys (Adam and Kumari, 2009). Although evidence supports the potential mediating role of cortisol in the association between SES and CP, no studies have yet examined the mediating role.

To address the current research gap, this study utilizes the Midlife in the United States study (MIDUS) to explore the prospective association between life course SES, CP, and biological dysregulations of chronic stress response systems, and to examine the mediating effects of the dysregulations. SES during adulthood was collected in MIDUS 1 (1995-1996) and MIDUS 2 (2004-2006), with retrospective childhood SES collected during MIDUS 1. AL biomarkers were collected in the MIDUS 2 Biomarker Project (2004-2006). Additionally, salivary cortisol was collected during the National Study of Daily Experiences (NSDE) phase of MIDUS 2 (2004-2009). MIDUS 3 (2013-2014) collected the CP outcomes for this study, facilitating prospective research. Based on the identified research gaps, I propose the following research questions (RQs):

(1) How is SES at different life states associated with future CP and are these associations independent of each other?

H1: Childhood SES, MIDUS 1 SES, and MIDUS 2 SES are directly prospectively associated with MIDUS 3 CP, indicating an additive effect;

H2: This study hypothesizes that earlier SES significantly influences later SES, and later SES has a direct and significant association with CP;

H3: The impact of earlier SES on CP is mediated by later SES;

(2) How is SES at different life states associated with biological dysregulations in stress response systems and are these associations independent of each other?

H4: Childhood SES, MIDUS 1 SES, and MIDUS 2 SES are directly prospectively associated with biological dysregulations in stress response systems, indicating an additive effect;

H5: This study hypothesizes that earlier SES significantly influences later SES, and later SES has a direct and significant association with biological dysregulations in stress response systems;

H6: The impact of earlier SES on biological dysregulations in stress response systems is mediated by later SES.

(3) Are there mediating effects of biological dysregulations in stress response systems to the associations between life course SES and CP?

H7: The impact of SES on CP is mediated through biological dysregulations in stress response systems

4.2 Methods

4.2.1 Data

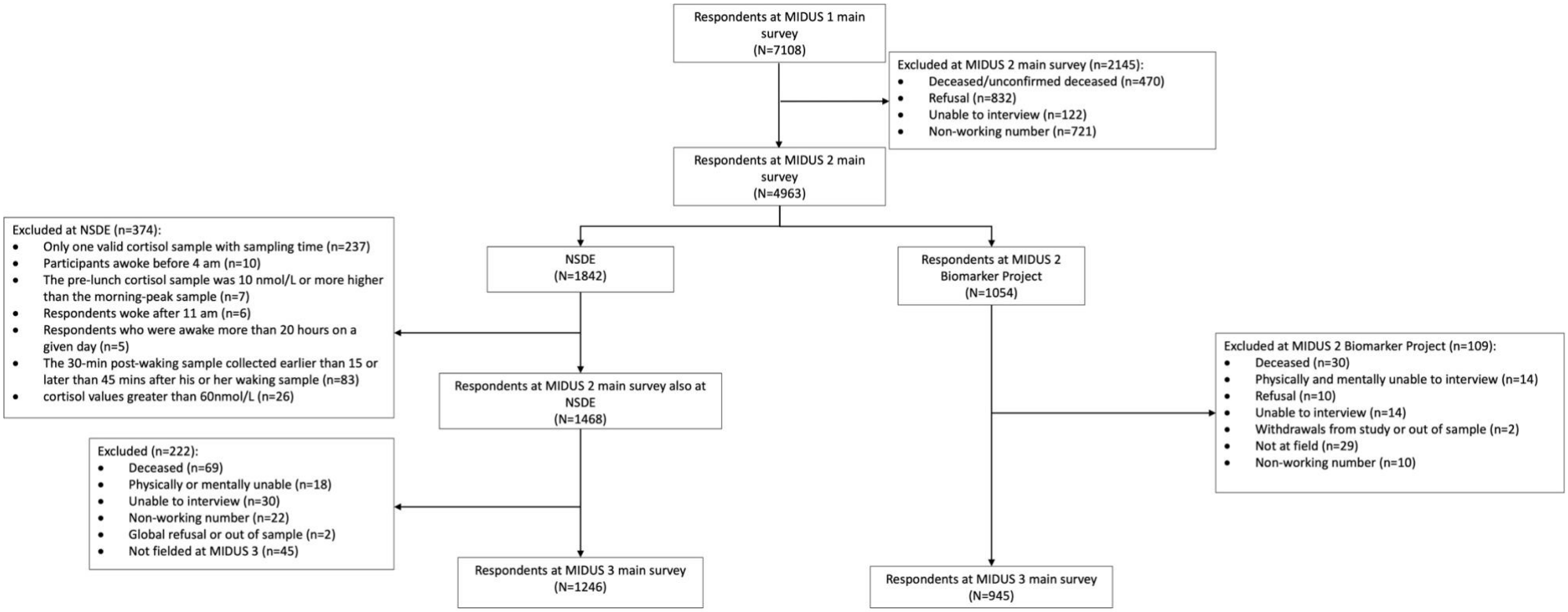
This research utilized data from the MIDUS. The MIDUS main survey is a national, longitudinal study on individual social status, psychological profiles, and biological processes of ageing, begun between 1995-1996 and followed 7108 non-institutionalized Americans aged 25 to 74 in the contiguous United States. The MIDUS 2 and MIDUS 3 main surveys followed the original respondents and collected data through phone interviews and self-administered questionnaires between 2004-2006, and 2013-2014 respectively. More details of the study are available on the MIDUS website (Available at: http://midus.wisc.edu/, accessed on April 18, 2024).

Based on participation in the MIDUS biomarker project or in the NSDE, the study sample was divided into two streams for analysis. A total of 1,054 respondents from the main longitudinal survey participated in the Biomarker Project of MIDUS 2 conducted from 2004 to 2009. Samples meeting the subsequent criteria were incorporated into the final analysis: samples that completed the baseline survey of the longitudinal survey, two MIDUS follow-up surveys and participated in the biomarker program (Details in Figure 4-1).

MIDUS 2 collected information on daily experiences over a span of consecutive 8 days through NSDE in the same wave. From a total of 2,022 respondents participated in NSDE, 1,842 respondents took part in the main longitudinal survey (MIDUS 1 to MIDUS 2), having been selected through random digit dialing. We excluded participants who did not provide at least one valid cortisol sample within the sampling time, had anomalous sleep patterns,

experienced cortisol measurement errors, or dropped out at MIDUS 3 (Dmitrieva et al., 2013; Karlamangla et al., 2013) (Details in Figure 4-1).

Figure 4-1 Flowchart for the analytic sample



4.2.2 Measures

4.2.2.1 Dependent variable: CP in MIDUS 3

Assessing the level of pain interference and the number of CP sites, as opposed to simply reporting the presence of CP, can provide valuable insights into the intensity of pain, its impact on daily activities, and the extent of pain distribution across the body, which are crucial for devising effective pain interventions (Guerriero and Reid, 2019; Von Korff et al., 1990). Respondents were first asked “Do you have CP, that is do you have pain that persists beyond the time of normal healing and has lasted from anywhere from a few months to many years?”; if so, they were then asked about CP interference. A pain interference index was generated by a mean score of how much pain interfered with respondents’ activity, mood, relations, sleep, and enjoyment, ranging from 0 to 10 (Cleeland and Ryan, 1994). Then, the CP interference index was further categorized into no pain, low interference pain (≤4), and high interference pain (>4) as a categorical variable based on the Brief Pain Inventory Subscale cutpoint (Jensen, 2011; Li et al., 2021b). In addition, if respondents reported having CP, they were asked about the location of the pain, including head, neck, back, arms, legs, shoulders, hips, knees, and other sites. The pain sites were summed up to an index and then categorized it into no pain, 1-2 sites, or 3 or more sites as a categorical variable.

The categorization is based on the consistency with previous practices (Li et al., 2021a, 2021b), as well as the distributions of both CP interference and the number of pain locations, which are highly skewed toward the lower end. This skewness presents challenges for linear modeling techniques, which assume normality of residuals. While negative binomial regression is a potential approach to address the count nature of our pain location data, it

may not adequately account for the observed high skewness in the distribution. In addition, the sample sizes in our study are unevenly distributed across the potential range of these variables, with a significant drop-off in frequency as the number of pain locations increases. This sparsity in the upper range can undermine the reliability of regression estimates, as the models would be driven by a small subset of the sample with higher pain counts. Therefore, categorization helps to stabilize the variance across groups.

4.2.2.2 AL - potential mediator

AL biomarkers were collected from the MIDUS 2 Biomarker Project. Followed by previous studies (Carbone et al., 2022; Gruenewald et al., 2012; Hastings et al., 2022; Juster et al., 2010; Karlamangla et al., 2014), AL was constructed by seven physiological systems and 27 biomarkers (shown in Supplementary Table 3-1). High-risk quartiles of biomarkers were used to compute AL (McEwen and Seeman, 1999). DHEA-S and urinal cortisol in the upper or lower 25^{th} quartiles were regarded as at high risk. When HFHRV, LFHRV, RMSSD, and SDRR strength fell within their lower 25^{th} quartile ranges, they were at high risk. Other biomarkers falling into their upper 25^{th} quartiles were assigned as at high risk. Meanwhile, biomarkers in their high-risk quartiles were coded as 1; otherwise, 0. Then, an AL index was computed by summing up biomarker risk scores, which theoretically would range from 0 to 27.

LCA was applied to identify AL phenotypes, utilizing the "poLCA" package in R. Binary biomarkers were grouped into clusters ranging from 1 to 7, with the optimal cluster count selected based on several statistical criteria, including log-likelihood, Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), entropy, and the clinical or biological relevance of the classification (Sinha et al., 2021). The log-likelihood measures model fit, with higher values generally indicating better fit for a given data and model structure. AIC and BIC

are used to balance fit quality with model simplicity, with lower values suggesting a preferable model. BIC, however, penalizes complex models more heavily in large samples, often favoring simpler solutions, while AIC may support more complex structures. Examining points of inflection or plateaus in AIC and BIC values can help determine an appropriate balance between model complexity and overfitting risk (Sinha et al., 2021). Entropy, reflecting classification quality, ranges from 0 to 1, with values above 0.8 generally considered acceptable for adequate cluster distinction (Weller et al., 2020). Also, the classification should be meaningful from a clinical or a biological perspective (Sinha et al., 2021). For reliable estimation, each model underwent 5000 iterations to ensure convergence (Please refer to Supplementary Table 3-2 for the LCA results).

4.2.2.3 Diurnal Cortisol Rhythm - potential mediator

Diurnal cortisol rhythm parameters were defined as CAR, DCSs, AUC relative to the ground, and CDR. Detailed description please refer to Sections 3.2.2.1 to 3.2.2.2. To model this rhythm, we used linear spline multilevel modeling with fixed knots at 0.5, 4.5, and 15 hours after waking, following prior work (Adam et al., 2006; Charles et al., 2020; Karlamangla et al., 2013). This model divides the cortisol curve into segments, fitting a separate regression for each, which helps capture nonlinear changes across the day more effectively than other models (Karlamangla et al., 2013).

Data from the NSDE were analyzed to construct the diurnal cortisol rhythm. Supplementary Table 4-1 shows the charateristics of the participants in the NSDE. For each cortisol measurement, random intercepts were included at the family level and slopes at the individual level to account for variability. Week average wake time, daily wake times, and weekday/weekend status, were adjusted within the model (Charles et al., 2020). Regression

results are shown in Supplementary Table 4-2. To calculate the cortisol slope in each interval, we combined fixed- and random-effects estimates, providing individual-specific cortisol patterns. CAR represents the initial 0-0.5 hour post-wake increase, followed by early DCS from 0.5 to 4.5 hours, mid DCS from 4.5 to 15 hours, and late DCS after 15 hours. Individual cortisol levels at specific time points were used to compute the AUC, utilizing the trapezoidal method from wake to bedtime (Pruessner et al., 2003). For individuals whose bedtime occurred more than 15 hours after awakening, the areas from 4.5 to 15 hours post-awakening and from 15 hours post-awakening to bedtime were calculated separately and then summed. CDR was calculated as the log-transformed difference between peak and nadir cortisol levels. For comparison, cortisol parameters were standardized (Charles et al., 2020; Kumari et al., 2011).

4.2.2.4 SES

In addition to utilizing objective SES indicators, metrics assessing respondents' relative deprivation were integrated into the composite SES variable construction. This integration aimed to reflect respondents' broader methodologies, capabilities, and mental resources for addressing health risks (Marmot, 2005). The integration of both objective SES indicators and relative deprivation indicators to construct SES have been employed in previous studies, which identified significant associations between the composite indices and various health outcomes (Glover et al., 2023; Gruenewald et al., 2012; Surachman et al., 2019). There were three SES periods: childhood, adulthood in MIDUS 1 and MIDUS 2. Each SES indicator was recoded into an index ranging from 0 to 2, where 0 represented high SES conditions, 1 represented middle SES conditions, and 2 signified the low SES conditions. Childhood SES was collected retrospectively during the MIDUS 1 period, including the highest level of parental education (0=bachelor's degree or more, 1=high school/GED/some college, 2=less than high school), financial situation growing up (2 = a lot/somewhat/a little worse off than average

family, 1 = same as average family, 0 = a lot/somewhat, a little better off than average family), and father's/male head of the household's occupation (0=managerial and professional specialty occupations/technical, sales, and administrative support occupations/service occupations, 1=operators, fabricators, and laborers/farming, forestry, and fishing occupations, 2=precision production, craft, and repair occupations/experienced unemployed not classified by occupations).

SES during adulthood (MIDUS 1 and MIDUS 2) included the income-to-needs ratio adjusted for family size and year (0=affluent/adequate-income, 1=low-income, 2=poor/extreme poverty) (United States Census Bureau, 2022), education (0=bachelor's degree or more, 1=high school/GED/some college, 2=less than high school), rating of current financial situation (0=best, 1=medium, 2=worst), money to meet needs (0=more than enough money, 1=just enough money, 2=not enough money), difficulty to pay monthly bills (0=not at all difficult, 1=not very difficult/somewhat difficult, 2=very difficult), and occupation (0=managerial and professional specialty occupations/technical, sales, and administrative support occupations/service occupations, 1=operators, fabricators, and laborers/farming, forestry, and fishing occupations, 2=precision production, craft, and repair occupations/experienced unemployed not classified by occupations).

Table 4-1 SES indicators used to compute the latent SES score

	SES categories and values assigned		
SES indicators	**0 (High SES)**	**1 (Medium SES)**	**2 (Low SES)**
Childhood SES			
Highest level of parental education (father's and mother's)	bachelor's degree or more	high school/GED/some college	less than high school
Financial level growing up	1.a lot better off, 2.somewhat better off, 3.a little better off	4. same as average family	5.a little worse off, 6.somewhat worse off, 7.a lot worse off
Father's/ male head of the household's occupation	1.managerial and professional specialty occupations, 2.technical, sales and administrative	1.operators, fabricators and laborers,	1.precision production, craft and repair occupations,

(Census 1980 classification) *	support occupations, 3.service occupations	2.farming, forestry and fishing occupations	2.experienced unemployed not classified by occupations
Adulhood SES (MIDUS 1 & MIDUS 2)			
Income-to-needs ratio adjusted for family size and year	affluent/adequate-income	low-income	poor/extreme poverty
Highest level of education	bachelor's degree or more	high school/GED/some college	less than high school
Rating of current financial situation	best	medium	worst
Money to meet needs	more than enough money	just enough money	not enough money
Difficulty to pay monthly bills	not at all difficult	not very difficult/somewhat difficult	very difficult

Occupation (Census 1980 classification for MIDUS 1, Census 1990 classification for MIDUS 2) †	1.managerial and professional specialty occupations, 2.technical, sales and administrative support occupations, 3.service occupations	1.operators, fabricators and laborers, 2.farming, forestry and fishing occupations	1.precision production, craft and repair occupations, 2.experienced unemployed not classified by occupations

*Noting that if a father/male head of the household never worked due to disability, addiction, or mental issues, they were classified as unemployed. Occupational measures are in some sense transferable (Galobardes et al., 2006b). If they didn't work for other reasons like raising children at home, the mother's/female head of the household's occupation represented the father's/male head of the household's when childhood occupation variable was constructed (Galobardes et al., 2006b).

†Noting that if the current employment status of a respondent was unemployed, permanently disabled, never worked, or due to other reasons, they were classified as unemployed. If they were temporarily laid off, on maternity or sick leave, or retired, their occupation was represented by their last held position (Stone et al., 2014). If they were a homemaker or a part-time student, their spouse or partner's occupation was represented (Galobardes et al., 2006b). The occupation of a full-time student was represented by their father's/male head of the household's occupation (Galobardes et al., 2006b).

Confirmatory factor analysis (CFA) is a statistical method used to validate the structure of latent variables by optimizing the measurement of their multidimensional aspects, thereby simplifying their representation. Unlike other data reduction methods, such as principal component analysis and exploratory factor analysis, which are more descriptive and focus on elucidating relationships between variables that may represent underlying constructs, CFA aims to assess the structural model of a construct (Bryant and Yarnold, 1995). We utilize CFA to evaluate how well our SES variable set measures SES as a latent construct.

Initially, these metrics were utilized in measurement invariance tests, as prior research employed identical item weights in computing the composite SES indices, assuming measurement invariance across items and over time (Glover et al., 2023; Gruenewald et al., 2012; Surachman et al., 2019). By explicitly examining the temporal invariance of the SES factor structure and the factor loadings of each item, we aim to minimize the mis-specification errors when estimating the SES structure across different adult periods. Subsequent steps involved assessing configural invariance (identical factor structure), metric invariance (identical factor loadings), scalar invariance (identical intercepts), and residual invariance (identical residuals) (Meredith, 1993). Configural invariance assesses whether the same factor structure (e.g. the same set of observed variables corresponds to the same underlying constructs) holds across time, ensuring that the construct is defined similarly. Metric invariance goes further by testing if factor loadings are equal across time. Scalar invariance examines whether item intercepts are the same, allowing for valid comparisons of group means. Finally, residual invariance tests if the measurement error, or residuals, are identical, ensuring that any unexplained variance is consistent across groups.

The significance of the χ^2 change for two nested models was not only employed to assess the performance of the test invariance, but the ΔRMSEA was also utilized to avoid the oversensitivity of χ^2 to minor variations in large samples. A change rate below 0.015 is deemed acceptable (Putnick and Bornstein, 2016). Childhood SES was excluded from the measurement invariance analysis due to the inconsistency of indicators constructing childhood SES with those of adulthood. Supplementary Tables 3-3 and 4-3 reveal that, compared to configural invariance, models fitting metric, scalar, and residual invariance are less ideal, thus not supporting the hypothesis of measurement invariance.

Subsequently, the SES of different periods was fitted separately using CFA. A comparative fit index (CFI) above 0.95 is considered an acceptable fit, and below 0.90 is perceived as a poor fit, while a Tucker-Lewis Index (TLI) above 0.90 indicates well-fitting models. CFI compares the fit of a proposed model to the fit of a baseline model and TLI also compares the fit of the model to a baseline model but it adjusts for model complexity, penalizing overly complex models. The root mean square error of approximation (RMSEA) is an absolute fit index that evaluates how well the model fits the sample-based covariance matrix, considering the complexity of the model. RMSEA below 0.08 is considered an acceptable fit (Hu and Bentler, 1999; Yuan et al., 2016). Table 4-2 shows that the fit statistics of SES across different periods is satisfactory.

Table 4-2 Confirmatory factor analysis for SES

	Biomerker project stream			NSDE stream		
SES items	**Childhood SES**	**MIDUS 1 SES**	**MIDUS 2 SES**	**Childhood SES**	**MIDUS 1 SES**	**MIDUS 2 SES**
Father education	0.810			0.847		
Mother education	0.592			0.626		
Financial status growing up	0.389			0.391		
Father occupation	0.436			0.427		
Rate current financial situation		0.434	0.339		0.411	0.342
Money to meet needs		0.445	0.386		0.487	0.487
How difficult to pay monthly bills		0.411	0.262		0.314	0.266
Education		0.321	0.456		0.299	0.443
Income-to-needs ratio		0.642	0.439		0.596	0.446
Occupation		0.307	0.357		0.272	0.314

Test statistic	1.283	20.82	4.641	15.524	11.002	4.744
Degrees of freedom	2	4	4	2	4	4
Comparative Fit Index (CFI)	1.000	0.981	0.999	0.979	0.994	0.999
Tucker-Lewis Index (TLI)	1.00	0.93	0.997	0.937	0.976	0.997
AIC	6746.921	8555.15	9165.501	8675.286	11428.837	11553.788
BIC	6784.478	8636.331	9246.565	8714.938	11514.836	11639.177
RMSEA	0.00	0.069	0.014	0.08	0.039	0.013
SRMR	0.01	0.022	0.011	0.031	0.015	0.011

4.2.2.5 Covariates

To account for time-invariant covariates, our analyses of SES measures and cortisol parameters and CP included controls for demographic and abuse-related variables. These included sex (ref: male; comparison: female), race (ref: White; comparison: non-White), parental emotional abuse, parental physical abuse, and living status with biological parents (ref: no; comparison: yes) (Mills et al., 2019; Misiak et al., 2022).

For time-variant covariates, we further adjusted for age, marital status (ref: not married; comparison: married) (Leonard et al., 2006; Rote, 2017), multimorbidity (ref: <2; comparison: ≥2) (Mills et al., 2019), health insurance (ref: yes; comparison: no) (Meghani et al., 2012), and CP (ref: no; comparison: yes) at different waves of the MIDUS study. Specifically, age, marital status, and chronic conditions from MIDUS 1 were controlled for in analyzing the association between SES in MIDUS 1, SES in MIDUS 2, and CP or biological dysregulations. Adjustments were made for the association between MIDUS 2 SES and CP or cortisol parameters, including age, marital status, chronic conditions, and health insurance. CP status (Mills et al., 2019) from MIDUS 2 was also adjusted for; however, the latter two variables were not collected in MIDUS 1.

Parental abuse was categorized into two continuous variables: emotional and physical abuse (Li et al., 2021b). These were derived from averaging the reported abuse from both parents. The scale ranges from 1 to 5, with 1 indicating no abuse and 5 indicating the most severe abuse. Chronic condition index (Ryff et al., 2007) was coded as a binary variable to indicate multimorbidity (Dominick et al., 2012). The chronic conditions included asthma, bronchitis, emphysema, tuberculosis, other lung problems, joint or bone diseases, sciatica, lumbago,

backache, skin trouble persistent, thyroid disease, hay fever, stomach trouble, urinary or bladder, constipated all or most, gall bladder trouble, foot trouble persistent, varicose veins, AIDs or HIV, lupus or autoimmune disorder, gum or mouth trouble, teeth trouble persistent, high blood pressure or hypertension, anxiety or depression, alcohol or drug problem, migraine headaches, chronic sleep problems, diabetes or high blood sugar, neurological disorder, stroke, ulcer, hernia, piles or hemorrhoids, swallowing problems (Ryff et al., 2018). The item of swallowing problems was not included in the chronic condition index at MIDUS 1.

In the association between AL and CP, we additionally controlled for physical activity levels, smoking status (ref: current smoker; comparison: ex-smoker or non-smoker), drinking status (ref: moderate or more drinker; comparison: light drinker, or non-drinker or rarely drink), as well as medication use such as antihyperlipidemic agents, beta adrenergic blocking agents, antihypertensive combinations, anxiolytics sedatives and hypnotics, antidiabetic agents, sex hormones, thyroid hormones, antidepressants, and analgesics (ref: no; comparison: yes). In the associations between cortisol parameters and CP, we additionally controlled for medication use such as steroid inhalers, oral steroids, other hormonal medications, antidepressants or anti-anxiety medications, and birth control pills (ref: no; comparison: yes). Body mass index was also adjusted for. The total score for physical activity was calculated by assigning different weights to responses from three questions that measured the frequency of participation in light, moderate, and vigorous activities, reported in the main study survey. Specifically, weights of 1, 3, and 5 were assigned to light, moderate, and vigorous activities, respectively, to emphasize the increased significance of more intense physical efforts in the overall score (Gruenewald et al., 2012).

4.2.3 Statistical methods

All analyses were conducted using R Studio 'Lavaan' package and structural equation modeling (SEM) was used (Rosseel, 2012). First, confirmatory factor analysis was employed to measure latent variables for SES and to assess the efficacy of the single SES indicators used in measuring SES as a whole. Then, path analysis was used to examine the chain of risk additive model (see figure 4-2 a to e). In the context of a "chain of risk" framework, SEM allows us to estimate how earlier exposures may mediate later outcomes while accounting for complex interrelationships among exposures and mediators. We used separate path models with a 'probit' link and treated the categorical dependent variables as binary variables because 'Lavaan' is unavailable for multinomial outcomes.

We used the following approach to derive each component of the mediation model, including the calculation of specific indirect effects and the subsequent estimation of total and proportion-mediated effects. For childhood SES, we estimated its direct effect on chronic pain outcomes, and then quantified three specific indirect effects: one operating via MIDUS 1 SES, one via the MIDUS 2 SES, and one via the sequential chain through both MIDUS 1 SES and MIDUS 2 SES. Each specific indirect effect was calculated as the product of the coefficients linking the variables along that path, and their sum gave the total indirect effect for childhood SES. Adding the direct effect to this total indirect effect yielded the total effect of childhood SES on pain. We then expressed each pathway's contribution as a proportion mediated, that is, each specific indirect effect divided by the total effect, and also calculated the overall mediated proportion. For MIDUS 1 SES, we applied the same logic: its direct effect on pain and its indirect effect via MIDUS 2 SES were estimated, summed to derive its total effect, and the single indirect pathway's share of that total effect was computed as its proportion

mediated. By the same token, mediation analyses for stress-related biomarkers were conducted using an identical procedure. The proportion mediated is expected to fall between 0% and 100%, reflecting the extent to which the mediator accounts for the total effect. However, when the direct and indirect effects operate in opposite directions, the mediated proportion can exceed 100%. It may imply that the mediator is associated with the outcome both as a mediator and through an additional, independent effect.

Although the counterfactual framework has become increasingly popular in epidemiology for causal mediation analysis (Imai et al., 2010), it requires several strong identification assumptions, most notably the absence of unmeasured confounding at each step of the mediated pathway and the stability of treatment assignment. These assumptions can be difficult to satisfy in observational settings, especially when multiple mediators are present or mediators are correlated with one another. By contrast, path analysis within a structural equation modeling framework provides a more direct way to model hypothesized chains of risk with multiple mediators, as long as the relationships among exposures, mediators, and outcomes are carefully specified.

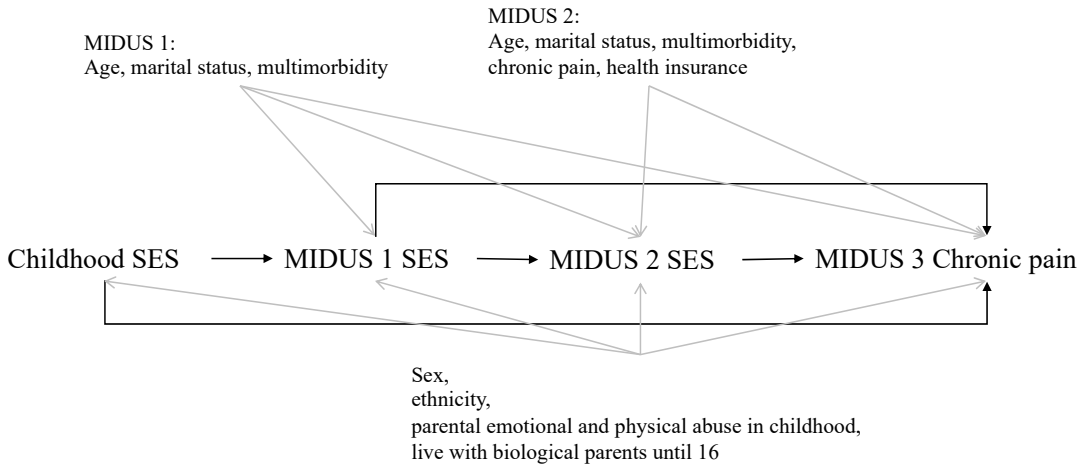
Full information maximum likelihood (FIML) method was applied to all models to handle missingness because it was found efficient under the assumptions of data being missing completely at random or missing at random (Enders and Bandalos, 2001). In addition, while FIML tends to have higher rejection rates compared to other missing data handling techniques like listwise deletion, pairwise deletion, mean imputation, and similar response pattern imputation, its parameter estimates are less biased and generally more efficient than those from ad hoc methods (Enders, 2001). Also, the rejection advantage of listwise deletion,

pairwise deletion, mean imputation, and similar response pattern imputation will disappear as missing data increase (Enders, 2001).

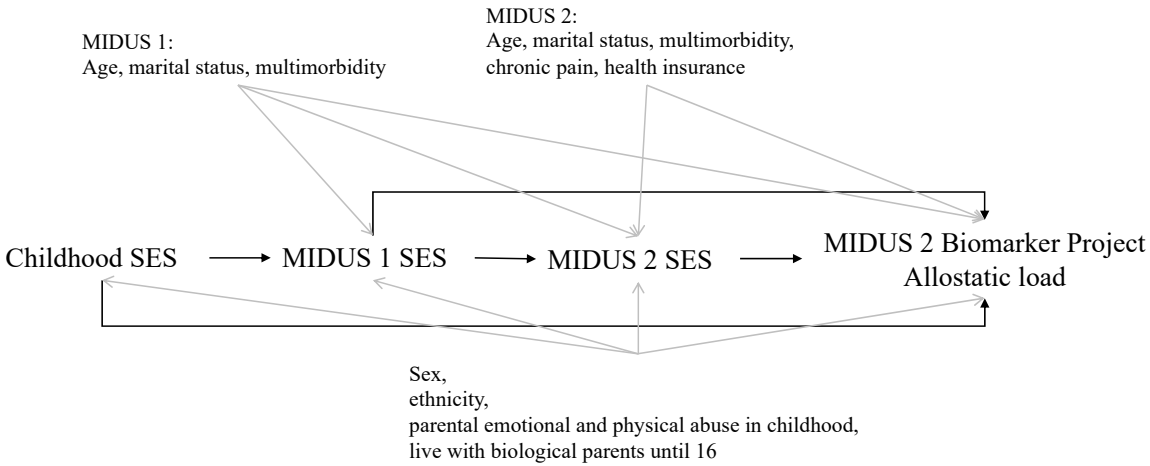
To test the robustness of the estimations, we further fitted the path models with different specifications. First, we used complete case analyses to detect biases from the FIML as a missing data handling technique. Second, we employed maximum likelihood with robust standard errors (MLR) as the estimator for the SEM with FIML to handle the missing values. MLR is an approach for binary outcomes and is compatible with FIML as a missing data handling technique in Lavaan settings. It has been shown to produce relatively unbiased parameter estimates and standard errors compared to diagonally weighted least squares, another technique for categorized and non-normally distributed data (Bandalos, 2014; Savalei and Rosseel, 2022).

A comprehensive assessment of each model fit can be achieved by simultaneously evaluating a set of specified indices. Generally, the CFI greater than 0.95 is considered acceptable fit and less than 0.90 is perceived as poor fit and TLI greater than 0.90 indicates good fitting models. The RMSEA less than 0.08 is considered acceptable fit (Hu and Bentler, 1999; Yuan et al., 2016). As the number of variables within the model increases, the RMSEA improves, while the CFI and TLI decrease (Kenny and McCoach, 2003).

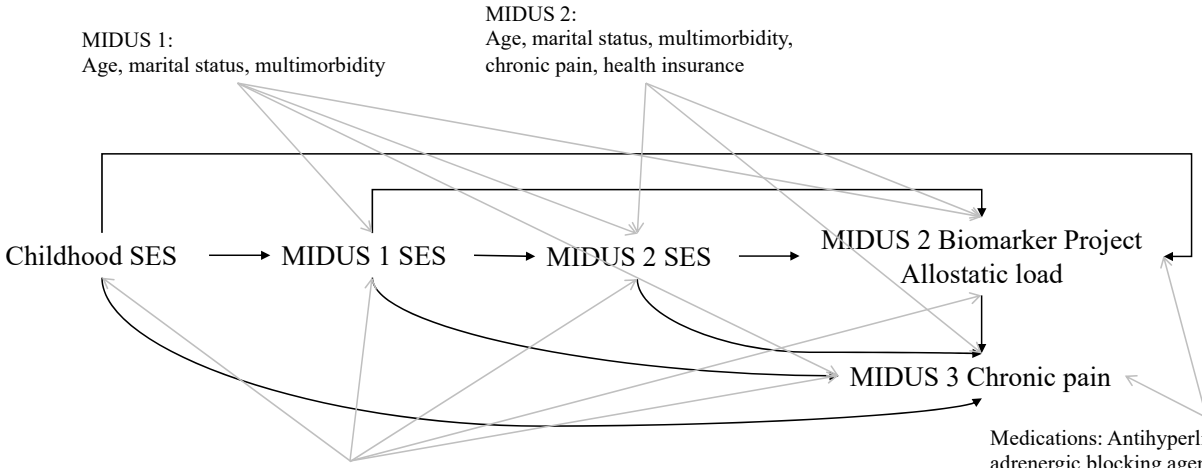
Figure 4-2 Chain of risk additive model of SES



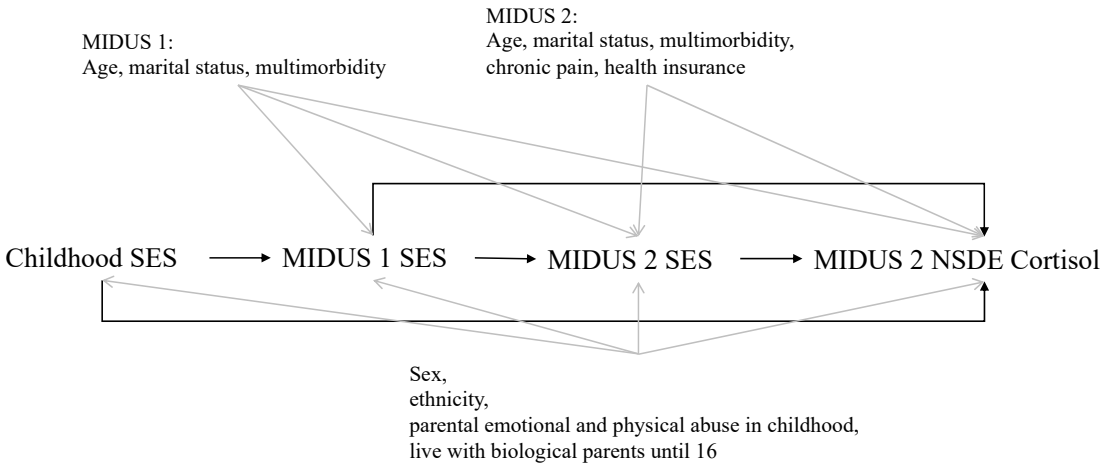
(a)


MIDUS 1:
Age, marital status, multimorbidity
MIDUS 2:
Age, marital status, multimorbidity,
chronic pain, health insurance
Childhood SES
MIDUS 1 SES
MIDUS 2 SES
MIDUS 2 Biomarker Project
Allostatic load
Sex,
ethnicity,
parental emotional and physical abuse in childhood,
live with biological parents until 16

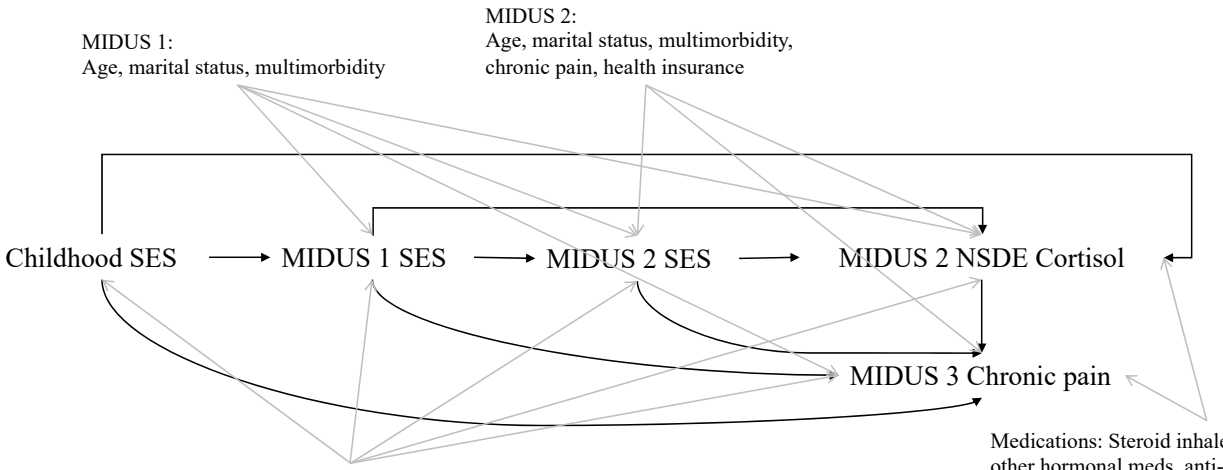
(b)


MIDUS 1:
Age, marital status, multimorbidity
MIDUS 2:
Age, marital status, multimorbidity,
chronic pain, health insurance
Childhood SES
MIDUS 1 SES
MIDUS 2 SES
MIDUS 2 Biomarker Project
Allostatic load
MIDUS 3 Chronic pain
Sex,
ethnicity,
parental emotional and physical abuse in childhood,
live with biological parents until 16
Medications: Antihyperlipidemic agents, beta adrenergic blocking agents, antihypertensive combinations, analgesics, anxiolytics sedatives and hypnotics, antidiabetic agents, sex hormones, thyroid hormones, antidepressants;
Health behaviors: Physical activities, drinking status, and smoking status.

(c)


MIDUS 1:
Age, marital status, multimorbidity
MIDUS 2:
Age, marital status, multimorbidity,
chronic pain, health insurance
Childhood SES
MIDUS 1 SES
MIDUS 2 SES
MIDUS 2 NSDE Cortisol
Sex,
ethnicity,
parental emotional and physical abuse in childhood,
live with biological parents until 16

(d)



(e)

Note: black arrows represent hypothesized pathways among key study variables, including childhood SES, adulthood SES, biological mediators, and CP. Grey arrows indicate covariates adjusted for in the model.

4.3 Results

4.3.1 Descriptive statistics

Table 4-3 shows that there are significant differences in adulthood SES among samples from the Biomarker Project stream based on pain interference and pain distribution in a body. Childhood SES also differs significantly by the widespreadness of CP. Among participants with no pain at follow-up, about 52% had a healthy AL profile, while 24% showed parasympathetic and metabolic dysregulation. For participants with high interference CP and pain at three or more sites, approximately 43-44% had a healthy AL profile, 25-26% exhibited parasympathetic dysregulation, and 30-31% showed metabolic dysregulation.

Table 4-4 indicates significant differences in adulthood SES among samples from the NSDE stream based on pain interference and the widespreadness of CP. Childhood SES also differs significantly by the widespreadness of CP. Significant differences in CAR, AUC, and CDR are observed across pain interference levels and pain regions. For example, individuals with more severe pain conditions tend to have flatter CAR, narrower CDR, and smaller AUC. Additionally, differences were found in late post-wake DCS. Individuals with no pain have a steeper late post-wake DCS compared to those in the other two groups. Supplementary Tables 3-4 and 4-4 summarize the descriptive statistics of confounding variables across levels of pain widespreadness and pain interference.

Supplementary Tables 3-5 and 4-5 compare the characteristics of participants who were retained with those who were lost to attrition. In the Biomarker Project stream, individuals who were male, ethnically minoritized, older, unmarried, had experienced more parental

physical abuse in childhood, had more chronic conditions, and were more socioeconomically disadvantaged both in childhood and at baseline were more likely to attrit. Participants in the NSDE stream show a similar pattern, but those who lived with their biological parents during childhood were more likely to attend the follow-up surveys.

Table 4-3 Analytic sample characteristics of SES and AL phenotype, stratified by CP conditions, among samples from Biomarker Project stream

Pain interference	**No pain**			**Low interference pain**			**High interference pain**			
Variable	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**Test**
Childhood SES	479	-0.015	0.98	178	-0.031	1	97	0.15	1.1	F=1.159
MIDUS 1 SES	517	-0.1	0.9	193	-0.018	1	99	0.39	1.2	F=10.676***
MIDUS 2 SES	511	-0.13	0.89	194	-0.013	0.98	98	0.46	1.2	F=15.855***
AL	490			192			99			X^2=3.538
Baseline	255	52%		99	52%		43	43%		
Parasympathetic Dysregulation	119	24%		49	26%		25	25%		
Metabolic Dysregulation	116	24%		44	23%		31	31%		
Pain locations	**No pain**			**1-2**			**3+**			
Variable	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**Test**
Childhood SES	479	-0.015	0.98	175	-0.1	1	110	0.27	0.95	F=5.043***

MIDUS 1 SES	517	-0.1	0.9	190	-0.062	0.86	116	0.47	1.4	$F=16.535^{***}$
MIDUS 2 SES	511	-0.13	0.89	189	0.011	0.96	114	0.43	1.2	$F=16.144^{***}$
AL	490			195			108			$X^2=2.423$
Baseline	255	52%		99	51%		48	44%		
Parasympathetic Dysregulation	119	24%		49	25%		28	26%		
Metabolic Dysregulation	116	24%		47	24%		32	30%		

Statistical significance markers: * p<0.05; ** p<0.01; *** p<0.001; N denotes the number of observations and SD denotes standard deviation; The “Test” column indicates the statistical test used to compare groups (e.g., ANOAV test and chi-square test), depending on variable type and distribution.

Table 4-4 Analytic sample characteristics of SES and diurnal cortisol parameters, stratified by CP conditions, among samples from NSDE stream

CP interference	No pain			Low interference pain			High interference pain			
Variable (standardized)	N	Mean	Sd	N	Mean	Sd	N	Mean	Sd	Test
SES										
Childhood SES	599	-0.038	0.990	227	-0.007	1.00	125	0.150	1.000	F=1.843
MIDUS 1 SES	663	-0.110	0.870	254	0.007	1.10	137	0.380	1.100	F=14.541***
MIDUS 2 SES	640	-0.120	0.920	255	-0.026	1.00	135	0.500	1.100	F=22.902***
Diurnal cortisol parameters										
CAR	697	0.047	0.960	276	-0.002	1.000	150	-0.220	1.200	F=4.253**
Early post-wake DCS	697	-0.024	0.990	276	-0.058	0.980	150	0.120	1.100	F=1.676
Mid post-wake DCS	697	-0.038	0.990	276	-0.038	0.990	150	0.140	1.000	F=2.086
Evening DCS	697	-0.056	1.000	276	0.049	0.950	150	0.110	0.910	F=2.385
CDR	697	0.084	0.940	150	-0.300	1.100	276	-0.033	1.100	F=9.519***

AUC	696	0.029	0.960	150	-0.180	1.200	275	0.038	1.000	F=2.885*
CP locations	**No pain**			**1-2**			**3 or more**			
Variable (standardized)	**N**	**Mean**	**Sd**	**N**	**Mean**	**Sd**	**N**	**Mean**	**Sd**	**Test**
SES										
Childhood SES	599	-0.038	0.990	226	-0.082	1.000	148	0.340	0.950	F=9.728**
MIDUS 1 SES	663	-0.110	0.870	248	-0.053	0.920	167	0.480	1.400	F=24.472***
MIDUS 2 SES	640	-0.120	0.920	248	-0.043	0.940	161	0.500	1.200	F=26.481***
Diurnal cortisol parameters										
CAR	697	0.047	0.960	274	0.024	0.940	177	-0.190	1.200	F=4.148**
Early post-wake DCS	697	-0.024	0.990	274	-0.056	0.950	177	0.110	1.100	F=1.73
Mid post-wake DCS	697	-0.038	0.990	274	-0.022	0.950	177	0.130	1.000	F=2.036
Evening DCS	697	-0.056	1.000	274	0.091	0.940	177	0.091	0.920	F=3.034*
CDR	697	0.084	0.94	274	-0.01	0.98	177	-0.27	1.2	F=9.021***
AUC	696	0.029	0.96	273	0.095	0.95	177	-0.2	1.2	F=4.922***

Statistical significance markers: * p<0.05; ** p<0.01; *** p<0.001; N denotes the number of observations and SD denotes standard deviation; The “Test” column indicates the statistical test used to compare groups (e.g., ANOAV test and chi-square test), depending on variable type and distribution.

Note that cortisol parameters were standardized. An increase of one standard deviation in CAR indicates a steeper CAR, whereas an increase of one standard deviation in DCSs indicates flatter DCSs. One standard deviation increase in CDR indicates a wider CDR, while one standard deviation increase in AUC indicates a larger AUC.

4.3.2 Path analysis results for the Biomarker Project (AL) stream

Path analysis found that people who lived in lower SES during their early life stage had an increased likelihood of continuing to live in lower SES in adulthood. Lower SES in MIDUS 2 was associated with high interference pain (direct path: f, β=0.058, SE=0.017), and socioeconomic disadvantage in MIDUS 2 completely mediates the impact of low childhood SES (indirect path: cf, β=0.012, SE=0.004) and MIDUS 1 SES (indirect path: bf, β=0.023, SE=0.007) on high interference pain (see Figure 4-3 (a)). Additionally, low SES in childhood was associated with high interference CP completely through socioeconomic disadvantages in MIDUS 1 and MIDUS 2 (indirect path: abf, β=0.005, SE=0.002). In the sensitivity analyses, the associations remained significant, indicating the missing values or nonnormality may not bias the results (please refer to Supplementary Table 3-6).

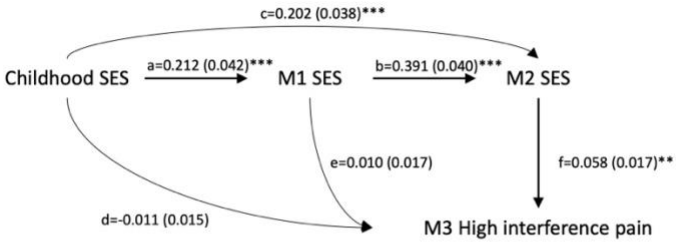
Also, Figure 4-3 (c) shows that low MIDUS 2 SES is associated with 3 or more pain sites (direct path: f, β=0.037, SE=0.018). The impact of socioeconomic disadvantage in MIDUS 1 on multiple pain sites is completely transmitted through MIDUS 2 SES (indirect path: bf, β=0.015, SE=0.007). However, the associations were not statistically significant in the complete-case sample or with the MLR estimator (please refer to Supplementary Table 3-6).

The results also indicate that a lower degree of MIDUS 2 SES is associated with 1-2 pain sites (direct path: f, β=0.048, SE=0.022), and childhood (indirect path: cf, β=0.009, SE=0.004) and MIDUS 1 (indirect path: bf, β=0.019, SE=0.009) socioeconomic disadvantages completely transmit through MIDUS 2 SES (Details see Figure 4-3 (d)). In the sensitivity analyses, the associations remained significant (please refer to Supplementary Table 3-6).

Supplementary Tables 3-9 present the covariate associations within the main associations between lifecourse SES and CP, which remained robust following sequential sensitivity analyses. Among participants in the Biomarker Project stream, being female, having multimorbidity in MIDUS 1 and MIDUS 2, being unmarried in MIDUS 2, and having CP in MIDUS 2 increased the likelihood of experiencing high interference CP in MIDUS 3. Additionally, participants with CP and multimorbidity in MIDUS 2 were more likely to have 1-2 pain locations.

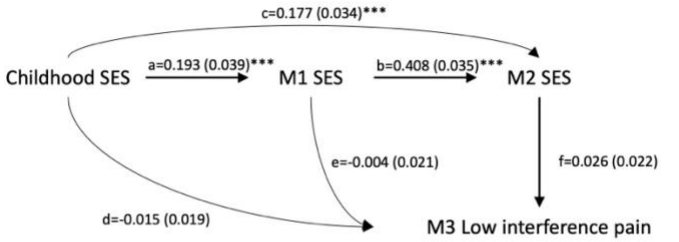
Figure 4-3 Path analysis of SES and CP among sample of Biomarker Project stream

(a) SES pathways to high interference chronic pain



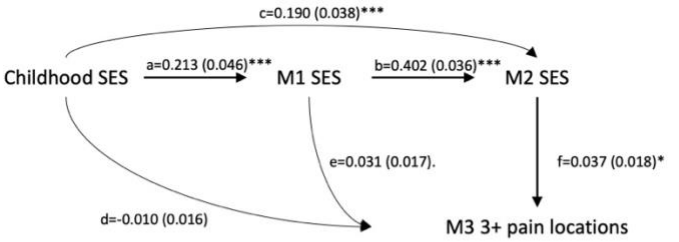
Indirect effect: ab=0.083 (0.018)***, ae=0.002 (0.004), abf=0.005 (0.002)**, cf=0.012 (0.004)**, bf=0.023 (0.007)**; **Total effect (starting at childhood)**=0.008 (0.015), (i) proportion mediated (ae)=0.277 (0.697), (ii) proportion mediated (cf)=1.488 (2.838), (iii) proportion mediated (abf)=0.610 (1.172), (i)+(ii)+(iii)=2.376 (4.506); **Total effect (starting at MIDUS 1)**=0.033 (0.016)*, (i) proportion mediated (bf)=0.688 (0.393).. **Chi-square (DF)=243.025 (59), CFI=0.964, TLI=0.934, RMSEA=0.070.**

(b) SES pathways to low interference chronic pain



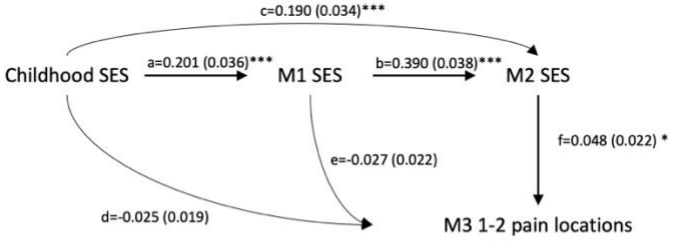
Indirect effect: ab=0.079 (0.017)***, ae=-0.001 (0.004), abf=0.002 (0.002), cf=0.005 (0.004), bf=0.010 (0.009); **Total effect (starting at childhood)**=-0.009 (0.018), (i) proportion mediated (ae)=0.074 (0.473), (ii) proportion mediated (cf)=-0.494 (1.062), (iii) proportion mediated (abf)=-0.220 (0.472), (i)+(ii)+(iii)=-0.640 (1.385); **Total effect (starting at MIDUS 1)**=0.007 (0.019), (i) proportion mediated (bf)=1.506 (4.399). **Chi-square (DF)=252.004 (59), CFI=0.966, TLI=0.938, RMSEA=0.067.**

(c) SES pathways to chronic pain with 3+ locations



Indirect effect: ab=0.085 (0.020)***, ae=0.007 (0.004)., abf=0.003 (0.002)., cf=0.007 (0.004)., bf=0.015 (0.007)*; **Total effect (starting at childhood)**=0.027 (0.016)., (i) proportion mediated (ae)=0.246 (0.197), (ii) proportion mediated (cf)=0.259 (0.202), (iii) proportion mediated (abf)=0.116 (0.091), (i)+(ii)+(iii)=0.621 (0.400); **Total effect (starting at MIDUS 1)**=0.046 (0.015)**, (i) proportion mediated (bf)=0.321 (0.192).. **Chi-square (DF)=241.949 (59), CFI=0.965, TLI=0.937, RMSEA=0.069.**

(d) SES pathways to chronic pain with 1-2 locations



Indirect effect: ab=0.078 (0.016)***, ae=-0.005 (0.005), abf=0.004 (0.002)**, cf=0.009 (0.004)*, bf=0.019 (0.009)*; **Total effect (starting at childhood)**=-0.018 (0.018), (i) proportion mediated (ae)=0.301 (0.387), (ii) proportion mediated (cf)=-0.503 (0.555), (iii) proportion mediated (abf)=-0.207 (0.226), (i)+(ii)+(iii)=-0.409 (0.523); **Total effect (starting at MIDUS 1)**=-0.008 (0.020), (i) proportion mediated (bf)=-2.206 (5.417). **Chi-square (DF)=255.734 (59), CFI=0.965, TLI=0.937, RMSEA=0.069.**

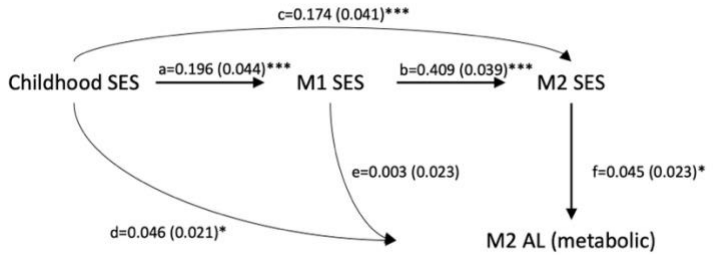
Figure 4-3. a = a path, effect of childhood SES on M1 SES; b = b path, effect of M1 SES on M2 SES; c = effect of childhood SES on M2 SES; d = d path, effect of childhood SES on M3 pain outcomes; e = e path, effect of M1 SES on M3 pain outcomes; f = f path, effect of M2 SES on M3 pain outcomes; ab = indirect effect of childhood SES on M2 SES via M1 SES; ae = indirect effect of childhood SES on M3 pain outcomes via M1 SES; abf = indirect effect of childhood SES on M3 pain outcomes via M1 SES and M2 SES; cf = indirect effect of childhood SES on M3 pain outcomes via M2 SES; bf = indirect effect of M1 SES on M3 pain outcomes via M2 SES; Abbreviations and Notes: SES = socioeconomic status; M = MIDUS. Values are unstandardized path estimates; standard errors are in parentheses; . = p<0.10, * = p<0.05, ** = p<0.01, *** = p<0.001.

Covariates Sex, race, parental emotional abuse, parental physical abuse, and whether the participant lived with both biological parents during childhood, age, marital status, multimorbidity, health insurance at MIDUS 2, and CP status at MIDUS 2

In the analysis of the association between SES and AL across the life course, we found that low childhood SES was associated with metabolic dysregulation of AL (direct path: d, β=0.046, SE=0.021). Low SES in MIDUS 2 was associated with metabolic dysregulation of AL (direct path: f, β=0.045, SE=0.023) (See Figure 4-4 (a)). In the sensitivity analyses, the associations remained significant (please refer to Supplementary Table 3-7). No mediating effects of SES in other life stages on metabolic dysregulation of AL were observed. Supplementary Tables 3-9 present the covariate associations within the main associations between lifecourse SES and AL, which remained robust following sequential sensitivity analyses. Females were less likely to have metabolic dysregulation related to AL, whereas participants with multimorbidity were more likely to experience metabolic dysregulation of AL.

Figure 4-4 Path analysis of SES and AL phenotype

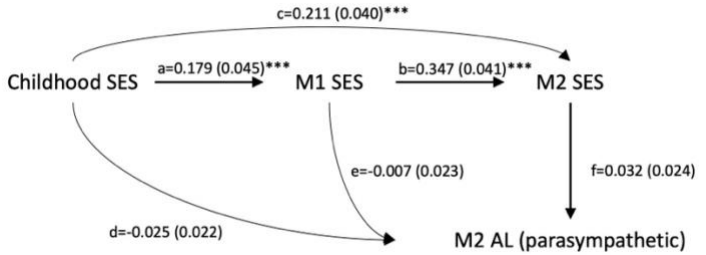
(a) SES pathways to metabolic dysregulation subtype of allostatic load



Indirect effect: ab=0.080 (0.019)***, ae=0.001 (0.004), abf=0.004 (0.002)., cf=0.008 (0.004)., bf=0.018 (0.010).; **Total effect (starting at childhood)**=0.058 (0.020)**, (i) proportion mediated (ae)=0.009 (0.077), (ii) proportion mediated (cf)=0.135 (0.088), (iii) proportion mediated (abf)=0.062 (0.042)., (i)+(ii)+(iii)=0.207 (0.125).; **Total effect (starting at MIDUS 1)**=0.021 (0.020), (i) proportion mediated (bf)=0.872 (0.958). **Chi-square (DF)=233.083 (59), CFI=0.963, TLI=0.932, RMSEA=0.070.**

Figure 4-4. a = a path, effect of childhood SES on M1 SES; b = b path, effect of M1 SES on M2 SES; c = effect of childhood SES on M2 SES; d = d path, effect of childhood SES on M2 AL outcomes; e = e path, effect of M1 SES on M2 AL outcomes; f = f path, effect of M2 SES on M2 AL outcomes; ab = indirect effect of childhood SES on M2 SES via M1 SES; ae = indirect effect of childhood SES on M2 AL outcomes via M1 SES; abf = indirect effect of childhood SES on M2 AL outcomes via M1 SES and M2 SES; cf = indirect effect of childhood SES on M2 AL outcomes via M2 SES; bf = indirect effect of M1 SES on M2 AL outcomes via M2 SES; Abbreviations and Notes: SES = socioeconomic status; AL = allostatic load; M = MIDUS. Values are unstandardized path estimates; standard errors are in parentheses; . = p<0.10, * = p<0.05, ** = p<0.01, *** = p<0.001.

(b) SES pathways to parasympathetic dysregulation subtype of allostatic load



Indirect effect: ab=0.062 (0.017)***, ae=-0.001 (0.004), abf=0.002 (0.002), cf=0.007 (0.005), bf=0.011 (0.008); **Total effect (starting at childhood)**=-0.032 (0.021), (i) proportion mediated (ae)=-0.040 (0.134), (ii) proportion mediated (cf)=-0.210 (0.213), (iii) proportion mediated (abf)=-0.062 (0.064), (i)+(ii)+(iii)=-0.232 (0.253); **Total effect (starting at MIDUS 1)**=0.004 (0.022), (i) proportion mediated (bf)=2.802 (15.675). **Chi-square (DF)=262.630 (59), CFI=0.958, TLI=0.923, RMSEA=0.075.**

Covariates Sex, race, parental emotional abuse, parental physical abuse, and whether the participant lived with both biological parents during childhood, age, marital status, multimorbidity, health insurance at MIDUS 2, and CP status at MIDUS 2

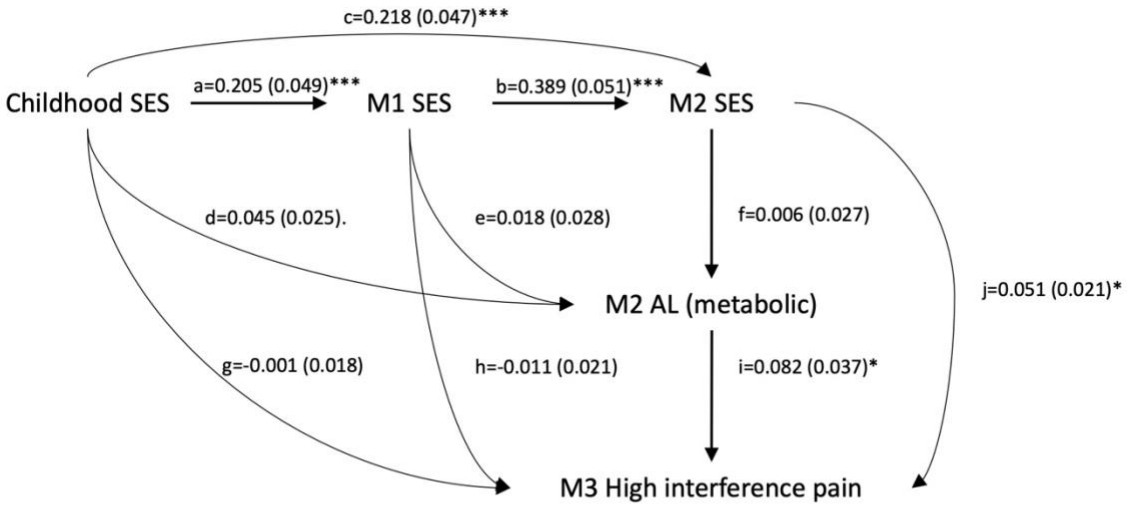
Regarding the association between AL and CP, the metabolic dysregulation phenotype is associated with higher odds of high interference pain (β=0.091, SE=0.040) (See Table 4-5). In the sensitivity analyses, the associations remained significant (please refer to Supplementary Table 3-8).

Table 4-5 Path analysis of AL and CP outcomes

Pain: high pain interference	**Estimate**	**Standard error**	**P-value**
AL - metabolic dysregulation	0.091	0.040	**0.038**
Chi-square (df)=298.784 (175); CFI=0.956; TLI=0.939; RMSEA=0.045			
AL - parasympathetic dysregulation	0.019	0.038	0.615
Chi-square (df)=328.786 (175); CFI=0.947; TLI=0.926; RMSEA=0.050			
Pain: low pain interference	**Estimate**	**Standard error**	**P-value**
AL - metabolic dysregulation	-0.057	0.052	0.269
Chi-square (df)=311.466 (175); CFI=0.958; TLI=0.942; RMSEA=0.044			
AL - parasympathetic dysregulation	-0.010	0.049	0.844
Chi-square (df)=313.862 (175); CFI=0.958; TLI=0.942; RMSEA=0.043			
Pain: 3+ pain locations	**Estimate**	**Standard error**	**P-value**
AL - metabolic dysregulation	0.014	0.043	0.667
Chi-square (df)=307.591 (175); CFI=0.956; TLI=0.939; RMSEA=0.046			
AL - parasympathetic dysregulation	-0.043	0.041	0.291
Chi-square (df)=300.987 (175); CFI=0.957; TLI=0.940; RMSEA=0.044			
Pain: 1-2 pain locations	**Estimate**	**Standard error**	**P-value**
AL - metabolic dysregulation	-0.018	0.051	0.720
Chi-square (df)=293.542 (175); CFI=0.962; TLI=0.947; RMSEA=0.041			
AL - parasympathetic dysregulation	0.013	0.049	0.796
Chi-square (df)=331.004 (175); CFI=0.953; TLI=0.935; RMSEA=0.046			

There are significant associations between SES and high interference CP, between SES and metabolic dysregulations of AL, and between metabolic dysregulations of AL and high interference CP, suggesting that metabolic dysregulations of AL may be a potential mediator between SES and high interference CP. However, we did not find the mediating role of metabolic dysregulations of AL in the association between life course SES and high interference CP (See Figure 4-5).

Figure 4-5 Path analysis of the mediation effects of AL



Mediation effects of AL

Total effect (starting at childhood SES)=0.016 (0.018); **Indirect effects:** aei=0.000 (0.001), cfi=0.000 (0.000), abfi=0.000 (0.000), di=0.004 (0.003); (i) proportion mediated (di)=0.232 (0.298), (ii) proportion mediated (aei)=0.019 (0.038), (iii) proportion mediated (cfi)=0.007 (0.031), (iv) proportion mediated (abfi)=0.003 (0.012); **Total effect (starting at M1 SES)**=0.011 (0.020); **Indirect effects:** ei=0.001 (0.002), bfi=0.000 (0.001); (i) proportion mediated (ei)=-0.139 (0.324), (ii) proportion mediated (bfi)=0.019 (0.089); **Total effect (starting at M2 SES)**=0.051 (0.021)*; **Indirect effects:** fi=0.001 (0.002); (i) proportion mediated (fi)=0.010 (0.043); **Chi-square (DF)=367.882 (202), CFI=0.952, TFL=0.929, RMSEA=0.044.**

Figure 4-5. a = effect of childhood SES on M1 SES, b = effect of M1 SES on M2 SES, c = effect of childhood SES on M2 SES, d = effect of childhood SES on AL, e = effect of M1 SES on AL, f = effect of M2 SES on AL, g = effect of childhood SES on pain, h = effect of M1 SES on pain, j = effect of M2 SES on pain, i = effect of AL on pain, aei= = indirect effect of childhood SES on the pain outcome via M1 SES and AL, cfi = indirect effect of childhood SES on the pain outcome via M2 SES and AL, abfi = indirect effect of childhood SES on the pain outcome via M1 and M2 SES and AL, di = indirect effect of childhood SES on the pain outcome via AL, ei = indirect effect of M1 SES on the pain outcome via M2 SES, bfi indirect effect of M1 SES on the pain outcome via M2 SES and AL, fi = indirect effect of M2 SES on the pain outcome via AL; Abbreviations and Notes: SES = socioeconomic status; AL = allostatic load; M = MIDUS. Values are unstandardized path estimates; standard errors are in parentheses; . = p<0.10, * = p<0.05, ** = p<0.01, *** = p<0.001.

4.3.3 Path analysis results for the NSDE stream

Path analysis results indicate that early socioeconomic disadvantage increases the likelihood of socioeconomic disadvantage in adulthood. Individuals with lower SES during MIDUS 2 are more likely to experience high interference CP (direct path: f, β=0.055, SE=0.016) and multiple pain sites (direct path: f, β=0.035, SE=0.016) (See Figure 4-6 (a), (c)). In the sensitivity analyses, the associations remained significant (please refer to Supplementary Table 4-6). Furthermore, a significant association was found between low SES in MIDUS 1 and 3 or more pain sites (direct path: e, β=0.033, SE=0.015). However, in the sensitivity analyses, the association became insignificant (please refer to Supplementary Table 4-6).

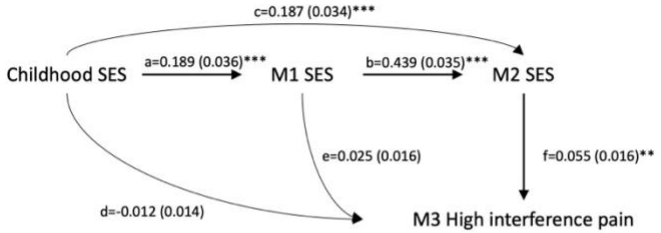
SES in MIDUS 2 completely mediated the associations between childhood SES and high interference CP (Figure 4-6 (a), indirect path: cf, β=0.010, SE=0.004), as well as CP with 3 or more pain sites (Figure 4-6 (c), indirect path: cf, β=0.007, SE=0.003), and between MIDUS 1 SES and high interference CP (Figure 4-6 (a), indirect path: bf, β=0.024, SE=0.007) and CP with 3 or more pain sites (Figure 4-6 (c), indirect path: bf, β=0.015, SE=0.007). Additionally, SES in both MIDUS 1 and MIDUS 2 jointly and completely mediated the effects of childhood SES on high interference CP (Figure 4-6 (a), indirect path: abf, β=0.005, SE=0.002). In the sensitivity analyses, the results remained significant. No other mediation pathways were found to be significant in both the main analyses and sensitivity analyses (please refer to Supplementary Table 4-6).

Supplementary Tables 4-9 present the covariate associations within the main associations between lifecourse SES and CP, which remained robust following sequential sensitivity

analyses. Among participants in the NSDE stream, having multimorbidity in MIDUS 1 and having no health insurance in MIDUS 2 increased the likelihood of experiencing high interference CP and 3 or more pain sites in MIDUS 3. Additionally, participants with CP in MIDUS 2 were more likely to have 3 or more pain sites.

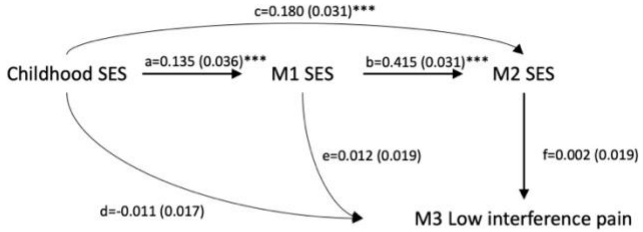
Figure 4-6 Path analysis of SES and CP among sample of NSDE stream

(a) SES pathways to high interference chronic pain



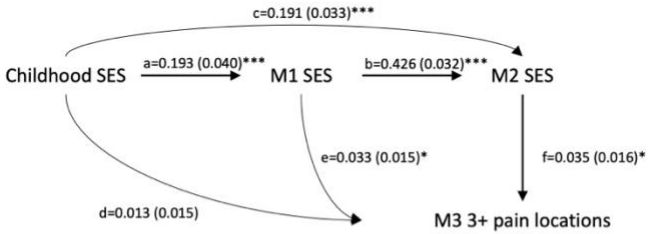
Indirect effect: ab=0.083 (0.017)***, ae=0.005 (0.003), abf=0.005 (0.002)**, cf=0.010 (0.004)**, bf=0.024 (0.007)**; **Total effect (starting at childhood)**=0.007 (0.014), (i) proportion mediated (ae)=0.640 (1.286), (ii) proportion mediated (cf)=1.414 (2.728), (iii) proportion mediated (abf)=0.629 (1.215), (i)+(ii)+(iii)=2.684 (5.129); **Total effect (starting at MIDUS 1)**=0.049 (0.015)**, (i) proportion mediated (bf)=0.496 (0.210)*. **Chi-square (DF)=329.956 (59), CFI=0.958, TFL=0.923, RMSEA=0.076.**

(b) SES pathways to low interference chronic pain



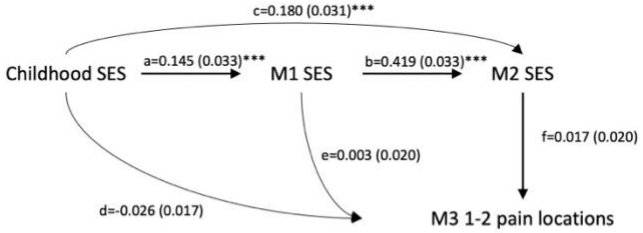
Indirect effect: ab=0.056 (0.015)***, ae=0.002 (0.003), abf=0.000 (0.001), cf=0.000 (0.003), bf=0.001 (0.008); **Total effect (starting at childhood)**=-0.009 (0.016), (i) proportion mediated (ae)=-0.174 (0.422), (ii) proportion mediated (cf)=-0.043 (0.386), (iii) proportion mediated (abf)=-0.013 (0.120), (i)+(ii)+(iii)=-0.230 (0.603); **Total effect (starting at MIDUS 1)**= 0.013 (0.017), (i) proportion mediated (bf)= 0.071 (0.643). **Chi-square (DF)=317.730 (59), CFI=0.964, TFL=0.934, RMSEA=0.069.**

(c) SES pathways to chronic pain with 3+ locations



Indirect effect: ab=0.082 (0.018)***, ae=0.006 (0.003)*, abf=0.003 (0.001)*, cf=0.007 (0.003)*, bf=0.015 (0.007)*; **Total effect (starting at childhood)**=0.029 (0.014)*, (i) proportion mediated (ae)=0.221 (0.148), (ii) proportion mediated (cf)=0.231 (0.158), (iii) proportion mediated (abf)=0.099 (0.068), (i)+(ii)+(iii)=0.551 (0.301).; **Total effect (starting at MIDUS 1)**=0.048 (0.013)***, (i) proportion mediated (bf)=0.310 (0.167).. **Chi-square (DF)=333.338 (59), CFI=0.960, TFL=0.926, RMSEA=0.075.**

(d) SES pathways to chronic pain with 1-2 locations



Indirect effect: ab=0.061 (0.014)***, ae=0.000 (0.003), abf=0.001 (0.001), cf=0.003 (0.004), bf=0.007 (0.008); **Total effect (starting at childhood)**=-0.021 (0.017), (i) proportion mediated (ae)=-0.021 (0.139), (ii) proportion mediated (cf)=-0.146 (0.203), (iii) proportion mediated (abf)=-0.049 (0.069), (i)+(ii)+(iii)=-0.027 (0.267); **Total effect (starting at MIDUS 1)**=0.010 (0.018), (i) proportion mediated (bf)=0.696 (1.479). **Chi-square (DF)=324.946 (59), CFI=0.962, TFL=0.931, RMSEA=0.070**

Figure 4-6. a = a path, effect of childhood SES on M1 SES; b = b path, effect of M1 SES on M2 SES; c = effect of childhood SES on M2 SES; d = d path, effect of childhood SES on M3 pain outcomes; e = e path, effect of M1 SES on M3 pain outcomes; f = f path, effect of M2 SES on M3 pain outcomes; ab = indirect effect of childhood SES on M2 SES via M1 SES; ae = indirect effect of childhood SES on M3 pain outcomes via M1 SES; abf = indirect effect of childhood SES on M3 pain outcomes via M1 SES and M2 SES; cf = indirect effect of childhood SES on M3 pain outcomes via M2 SES; bf = indirect effect of M1 SES on M3 pain outcomes via M2 SES; Abbreviations and Notes: SES = socioeconomic status; M = MIDUS. Values are unstandardized path estimates; standard errors are in parentheses; . = p<0.10, * = p<0.05, ** = p<0.01, *** = p<0.001.

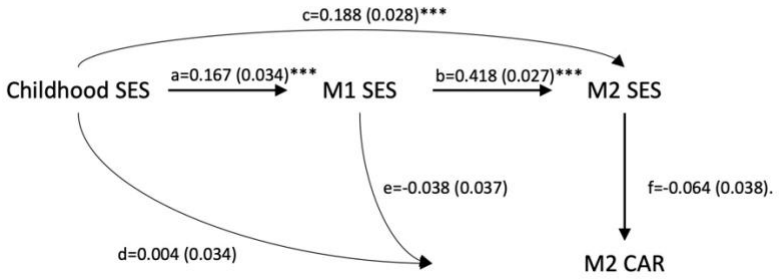
Covariates Sex, race, parental emotional abuse, parental physical abuse, and whether the participant lived with both biological parents during childhood, age, marital status, multimorbidity, health insurance at MIDUS 2, and CP status at MIDUS 2

Figure 4-7 shows the path analyses of lifecourse SES and cortisol parameters. We found that SES in MIDUS 2 was directly associated with mid post-wake DCS (Figure 4-7 (c), direct path: f, β=0.099, SE=0.038) and CDR (Figure 4-7 (e), direct path: f, β=0.114, SE=0.038), and these associations were also significant in different model specifications for sensitivity analyses (please refer to Supplementary Table 4-7). SES in MIDUS 2 mediated the effects of childhood SES and MIDUS 1 SES on mid post-wake DCS and CDR (See Figures 4-7 (3) and (5), indirect paths cf and bf), respectively, with results from sensitivity analyses remaining significant. However, SES in both MIDUS 1 and MIDUS 2 jointly and completely mediated the effects of childhood SES on CDR (Figure 4-7 (e), indirect path: abf, β=0.008, SE=0.003), while the joint mediation effects of SES in both MIDUS 1 and MIDUS 2 on the association between childhood SES and mid post-wake DCS were less robust (Figure 4-7 (c), indirect path: abf, β=0.007, SE=0.003). The associations between lifecourse SES, CAR, early post-wake DCS, and AUC were not robust.

Supplementary Tables 4-9 present the covariate associations within the main associations between lifecourse SES and cortisol parameters, which remained robust following sequential sensitivity analyses. Among participants in the NSDE stream, those who were female, older at MIDUS 1, and unmarried at MIDUS 2 had steeper mid post-wake DCS slopes. In contrast, individuals who were from minoritized ethnic groups and older at MIDUS 2 had flatter mid post-wake DCS slopes. Additionally, females and older participants at MIDUS 2 had narrower CDR, while younger individuals at MIDUS 1 had wider CDR.

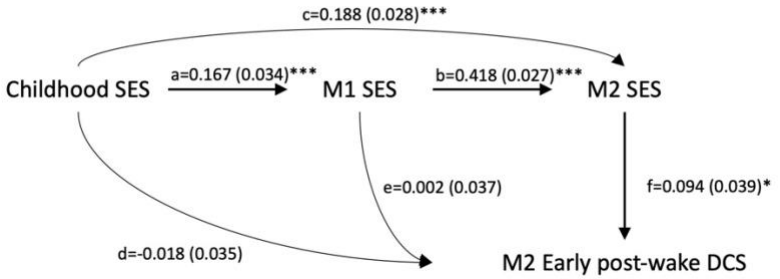
Figure 4-7 Path analysis of SES and cortisol parameters

(a) SES pathways to cortisol awakening response



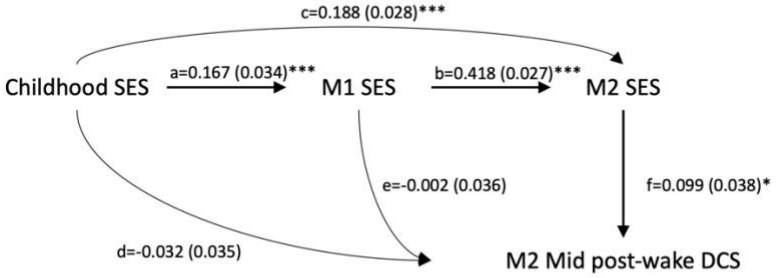
Indirect effect: ab=0.070 (0.015)***, ae=-0.006 (0.006), abf=-0.004 (0.003), cf=-0.012 (0.007), bf=-0.027 (0.016).; **Total effect (starting at childhood)**=-0.019 (0.033), (i) proportion mediated (ae)=0.331 (0.649), (ii) proportion mediated (cf)=0.628 (1.151), (iii) proportion mediated (abf)=0.234 (0.429), (i)+(ii)+(iii)=1.192 (2.103); **Total effect (starting at MIDUS 1)**=-0.065 (0.033)*, (i) proportion mediated (bf)=0.414 (0.330). **Chi-square (DF)=450.986 (59), CFI=0.957, TFL=0.921, RMSEA=0.076.**

(b) SES pathways to early post-wake diurnal cortisol slope



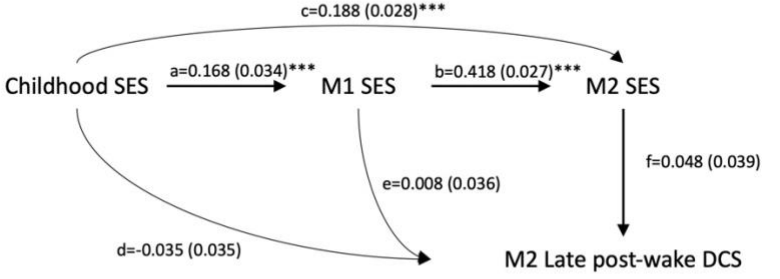
Indirect effect: ab=0.070 (0.015)***, ae=0.000 (0.006), abf=0.007 (0.003)*, cf=0.018 (0.008)*, bf=0.039 (0.016)*; **Total effect (starting at childhood)**=0.006 (0.034), (i) proportion mediated (ae)=0.067 (1.083), (ii) proportion mediated (cf)=2.938 (16.459), (iii) proportion mediated (abf)=1.089 (6.101), (i)+(ii)+(iii)=3.960 (22.161); **Total effect (starting at MIDUS 1)**= 0.037 (0.033), (i) proportion mediated (bf)=1.065 (1.043). **Chi-square (DF)=450.708 (59), CFI=0.957, TFL=0.921, RMSEA=0.076**

(c) SES pathways to mid post-wake diurnal cortisol slope



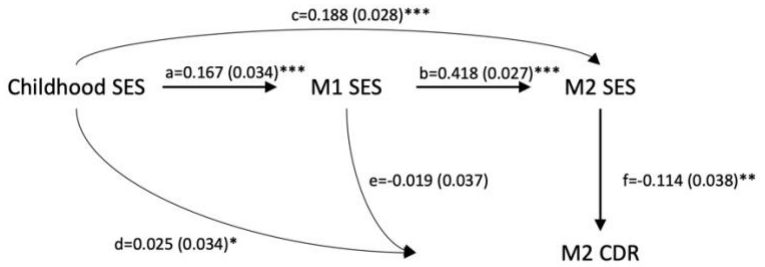
Indirect effect: ab=0.070 (0.015)***, ae=0.000 (0.006), abf=0.007 (0.003)*, cf=0.019 (0.008)*, bf=0.041 (0.016)*; **Total effect (starting at childhood)**=-0.007 (0.033), (i) proportion mediated (ae)=0.059 (0.925), (ii) proportion mediated (cf)=-2.709 (13.252), (iii) proportion mediated (abf)=-1.005 (4.918), (i)+(ii)+(iii)=-3.655 (17.878); **Total effect (starting at MIDUS 1)**= 0.039 (0.032) (i) proportion mediated (bf)= 1.062 (0.979). **Chi-square (DF)=450.664 (59), CFI=0.957, TFL=0.921, RMSEA=0.076.**

(d) SES pathways to late post-wake diurnal cortisol slope



Indirect effect: ab=0.070 (0.015)***, ae=0.001 (0.006), abf=0.003 (0.003), cf= 0.009 (0.007), bf=0.020 (0.016); **Total effect (starting at childhood)**=-0.021 (0.034), (i) proportion mediated (ae)=-0.066 (0.311), (ii) proportion mediated (cf)=-0.432 (0.765), (iii) proportion mediated (abf)=-0.161 (0.286), (i)+(ii)+(iii)=-0.659 (1.130); **Total effect (starting at MIDUS 1)**=0.029 (0.033), (i) proportion mediated (bf)=0.709 (0.992). **Chi-square (DF)=450.969 (59), CFI=0.957, TFL=0.921, RMSEA=0.076**

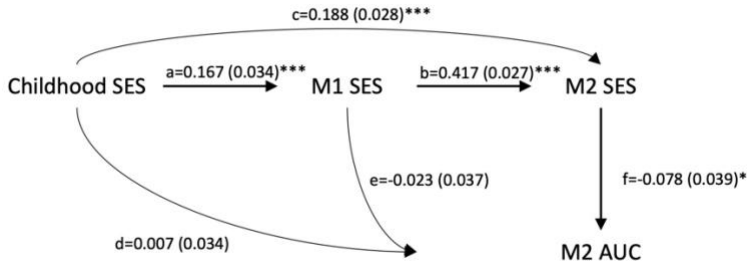
(e) SES pathways to cortisol dynamic range



Indirect effect: ab=0.070 (0.015)***, ae=-0.003 (0.006), abf=-0.008 (0.003)*, cf=-0.021 (0.008)**, bf=-0.048 (0.016)**; **Total effect (starting at childhood)**=0.008 (0.033), (i) proportion mediated (ae)=0.405 (1.896), (ii) proportion mediated (cf)= 2.763 (11.878), (iii) proportion mediated (abf)= 1.028 (4.419)., (i)+(ii)+(iii)=4.196 (17.999); **Total effect (starting at MIDUS 1)**=-0.066 (0.033)*, (i) proportion mediated (bf)=0.717 (0.431).. **Chi-square (DF)=450.902 (59), CFI=0.957, TFL=0.921, RMSEA=0.076.**

Figure 4-7. a = a path, effect of childhood SES on M1 SES; b = b path, effect of M1 SES on M2 SES; c = effect of childhood SES on M2 SES; d = d path, effect of childhood SES on M2 cortisol outcomes; e = e path, effect of M1 SES on M2 cortisol outcomes; f = f path, effect of M2 SES on M2 cortisol outcomes; ab = indirect effect of childhood SES on M2 SES via M1 SES; ae = indirect effect of childhood SES on M2 cortisol outcomes via M1 SES; abf = indirect effect of childhood SES on M2 cortisol outcomes via M1 SES and M2 SES; cf = indirect effect of childhood SES on M2 cortisol outcomes via M2 SES; bf = indirect effect of M1 SES on M2 cortisol outcomes via M2 SES; Abbreviations and Notes: SES = socioeconomic status; CAR = cortisol awakening response; DCS = diurnal cortisol slope; CDR = cortisol dynamic range; AUC = area under curve; M = MIDUS. Values are unstandardized path estimates; standard errors are in parentheses; . = p<0.10, * = p<0.05, ** = p<0.01, *** = p<0.001.

(e) SES pathways to area under diurnal cortisol curve



Indirect effect: ab=0.070 (0.015)***, ae=-0.004 (0.006), abf=-0.005 (0.003)., cf=-0.015 (0.008)., bf=0.033 (0.016)*; **Total effect (starting at childhood)**=-0.017 (0.033), (i) proportion mediated (ae)=0.233 (0.582), (ii) proportion mediated (cf)=0.870 (1.766), (iii) proportion mediated (abf)=0.324 (0.657), (i)+(ii)+(iii)=1.427 (2.844); **Total effect (starting at MIDUS 1)**=0.056 (0.033), (i) proportion mediated (bf)=0.581 (0.455). **Chi-square (DF)=450.890 (59), CFI=0.957, TFL=0.921, RMSEA=0.076**

Covariates Sex, race, parental emotional abuse, parental physical abuse, and whether the participant lived with both biological parents during childhood, age, marital status, multimorbidity, health insurance at MIDUS 2, and CP status at MIDUS 2

The results showed significant associations between CDR (β = -0.033, SE=0.013), AUC (β = -0.033, SE=0.014), and the number of CP locations (see Table 4-6). Larger CDR and AUC values predicted lower odds of having 3 or more pain locations.

Table 4-6 Path analysis of cortisol parameters and CP outcomes

Pain: high pain interference	Estimate	Standard error	P-value
CAR	-0.006	0.013	0.632
Chi-square (df)=445.040 (154); CFI=0.943; TLI=0.921; RMSEA=0.055			
Early post-wake DCS	0.023	0.013	0.070
Chi-square (df)=444.164 (154); CFI=0.943; TLI=0.921; RMSEA=0.055			
Mid post-wake DCS	0.020	0.013	0.131
Chi-square (df)=444.214 (154); CFI=0.943; TLI=0.921; RMSEA=0.055			
Late post-wake DCS	0.003	0.013	0.845
Chi-square (df)=444.841 (154); CFI=0.943; TLI=0.921; RMSEA=0.055			
CDR	-0.022	0.014	0.110
Chi-square (df)=444.699 (154); CFI=0.943; TLI=0.921; RMSEA=0.055			
AUC	-0.015	0.014	0.279

Chi-square (df)=445.996 (154); CFI=0.943; TLI=0.921; RMSEA=0.055

Pain: low pain interference	**Estimate**	**Standard error**	**P-value**
CAR	-0.010	0.017	0.544
Chi-square (df)=398.863 (154); CFI=0.957; TLI=0.939; RMSEA=0.047			
Early post-wake DCS	-0.009	0.016	0.567
Chi-square (df)=398.170 (154); CFI=0.957; TLI=0.939; RMSEA=0.047			
Mid post-wake DCS	-0.005	0.016	0.738
Chi-square (df)=398.433 (154); CFI=0.957; TLI=0.939; RMSEA=0.047			
Late post-wake DCS	0.017	0.016	0.287
Chi-square (df)=398.909 (154); CFI=0.957; TLI=0.939; RMSEA=0.047			
CDR	-0.013	0.017	0.420
Chi-square (df)=398.619 (154); CFI=0.957; TLI=0.939; RMSEA=0.047			
AUC	0.002	0.017	0.910
Chi-square (df)=398.701 (154); CFI=0.957; TLI=0.939; RMSEA=0.047			

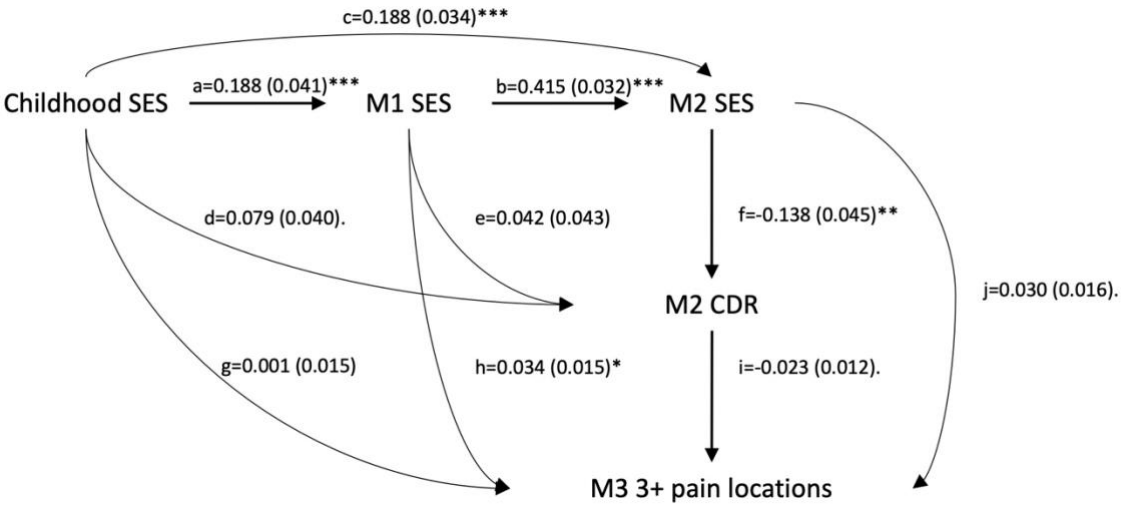
Pain: 3+ pain locations	Estimate	Standard error	P-value
CAR	-0.024	0.013	0.065
Chi-square (df)=432.056 (154); CFI=0.949; TLI=0.928; RMSEA=0.052			
Early post-wake DCS	0.025	0.013	0.063
Chi-square (df)=430.823 (154); CFI=0.949; TLI=0.928; RMSEA=0.052			
Mid post-wake DCS	0.024	0.013	0.078
Chi-square (df)=431.102 (154); CFI=0.949; TLI=0.928; RMSEA=0.052			
Late post-wake DCS	0.011	0.013	0.426
Chi-square (df)=431.832 (154); CFI=0.949; TLI=0.928; RMSEA=0.052			
CDR	**-0.033**	**0.013**	**0.014**
Chi-square (df)=431.544 (154); CFI=0.949; TLI=0.928; RMSEA=0.052			
AUC	**-0.033**	**0.013**	**0.015**
Chi-square (df)=431.958 (154); CFI=0.949; TLI=0.928; RMSEA=0.052			

Pain: 1-2 pain locations	Estimate	Standard error	P-value
CAR	0.010	0.017	0.561
Chi-square (df)=397.803 (154); CFI=0.956; TLI=0.938; RMSEA=0.047			
Early post-wake DCS	-0.013	0.016	0.427
Chi-square (df)=397.488 (154); CFI=0.956; TLI=0.938; RMSEA=0.047			
Mid post-wake DCS	-0.009	0.017	0.592
Chi-square (df)=397.459 (154); CFI=0.956; TLI=0.938; RMSEA=0.047			
Late post-wake DCS	0.015	0.016	0.342
Chi-square (df)=397.891 (154); CFI=0.956; TLI=0.938; RMSEA=0.047			
CDR	0.001	0.017	0.964
Chi-square (df)=397.620 (154); CFI=0.956; TLI=0.938; RMSEA=0.047			
AUC	0.027	0.017	0.120
Chi-square (df)=397.772 (154); CFI=0.956; TLI=0.938; RMSEA=0.047			

Based on the main results presented in Figures 4-5, 4-6, and Table 4-6, as well as in Supplementary Tables 4-6 through 4-8, CDR is considered a potential mediator in the association between lifecourse SES and having three or more CP locations. However, there is no evidence supporting the mediating role of the diurnal pattern of cortisol in the association between life course SES and CP (See Figure 4-8).

Chapter 3 of the thesis found significant associations between early and mid post-wake DCSs and pain in 3 or more locations among the participants without baseline pain. We tested the mediation effects of the diurnal pattern of cortisol in the association between life course SES and pain in 3 or more locations among the participants without baseline pain and found no significant mediation effect of the diurnal pattern of cortisol (Supplementary Table 4-10).

Figure 4-8 Path analysis of the mediation effects of CDR



Mediation effects of CDR

Total effect (starting at childhood SES)=0.015 (0.014); **Indirect effects:** aei=0.000 (0.000), cfi=0.001 (0.000), abfi=0.000 (0.000), di=-0.002 (0.001); (i) proportion mediated (di)=-0.124 (0.153), (ii) proportion mediated (aei)=0.012 (0.018), (iii) proportion mediated (cfi)=0.041 (0.047), (iv) proportion mediated (abfi)=0.017 (0.019); **Total effect (starting at M1 SES)**=0.047 (0.013)*; **Indirect effects:** ei=-0.001 (0.001), bfi=0.001 (0.001); (i) proportion mediated (ei)=-0.020 (0.025), (ii) proportion mediated (bfi)=0.028 (0.019); **Total effect (starting at M2 SES)**=0.033 (0.016)*; **Indirect effects:** fi=0.003 (0.002); (i) proportion mediated (fi)=0.096 (0.076); **Chi-square (DF)=609.374 (175), CFI=0.937, TFL=0.905, RMSEA=0.056.**

Figure 4-8. a = effect of childhood SES on M1 SES, b = effect of M1 SES on M2 SES, c = effect of childhood SES on M2 SES, d = effect of childhood SES on AL, e = effect of M1 SES on AL, f = effect of M2 SES on AL, g = effect of childhood SES on pain, h = effect of M1 SES on pain, j = effect of M2 SES on pain, i = effect of AL on pain, aei= = indirect effect of childhood SES on the pain outcome via M1 SES and AL, cfi = indirect effect of childhood SES on the pain outcome via M2 SES and AL, abfi = indirect effect of childhood SES on the pain outcome via M1 and M2 SES and AL, di = indirect effect of childhood SES on the pain outcome via AL, ei = indirect effect of M1 SES on the pain outcome via M2 SES, bfi indirect effect of M1 SES on the pain outcome via M2 SES and AL, fi = indirect effect of M2 SES on the pain outcome via AL; Abbreviations and Notes: SES = socioeconomic status; CDR = cortisol dynamic range; M = MIDUS. Values are unstandardized path estimates; standard errors are in parentheses; . = p<0.10, * = p<0.05, ** = p<0.01, *** = p<0.001.

4.4 Discussion

4.4.1 Discussion of lifecourse SES and CP

Utilizing MIDUS data, this study explored the prospective association between SES across the life course and CP outcomes, and examined the potential mediating role of biological dysregulations of stress response systems. The research not only identified a direct link between recent socioeconomic disadvantages (MIDUS 2) and CP conditions but also confirmed the mediating role of recent SES on SES in earlier adulthood. In both the Biomarker Project stream and the NSDE stream, we observed a direct effect of recent SES (MIDUS 2) on high interference CP. Additionally, MIDUS 2 SES served as a mediator for childhood SES and MIDUS 1 SES. The effect of childhood SES on CP was also mediated by the combined influence of MIDUS 1 and MIDUS 2 SES. However, in the Biomarker Project stream, recent SES was associated with 1-2 CP locations, while in the NSDE stream, recent SES was linked to 3 or more pain sites.

Our findings revealed that people with lower recent SES may have higher odds of having high interference CP and more pain locations and previous lifecourse studies have also documented similar associations. For example, using 1958 British Birth Cohort, a study found being in a lower social class at age 42 was associated with a higher risk of CWP at age 45 (Macfarlane et al., 2009). In additional, our results confirmed the mediating effects of recent SES on CP conditions among the participants in the Biomarker Project stream. Specifically, the effects on high pain interference and pain widespreadness of childhood and MIDUS 1 SES were totally mediated by recent SES. In spite of the potential mediating role of adulthood SES suggested by previous studies, they did not formally examine the mediation effects of SES in

later life stages (Goosby, 2013; Macfarlane et al., 2009). Using path analysis, our results may support the chain of risk model of the life course (Ben-Shlomo et al., 2014, p. 1531). Early socioeconomic disadvantages can influence the risk of having high interference pain in the future through ongoing socioeconomic challenges.

The significant association of proximal SES, rather than distal SES, aligns with the broader literature on the relationship between SES and health outcomes across the life course (Elo et al., 2014; Pudrovska and Anikputa, 2014). Using a 10% household sample from the 1950 Finnish Census, research found that the association between childhood SES and mortality after age 35 was significantly weakened once adult SES was taken into account (Elo et al., 2014). Another study using data from the Wisconsin Longitudinal Study revealed that, compared to SES from high school in 1957 and SES measured in 1975, the more recently collected SES data from 1993 was directly associated with all-cause mortality. Furthermore, the association between 1957 SES and mortality was fully mediated by SES in 1975 and 1993 combined (Pudrovska and Anikputa, 2014). These findings underscore the importance of mitigating recent socioeconomic disadvantage across the life course as a preventative approach for CP and suggest that interventions targeting SES during earlier periods may have limited effects on CP prevention.

In our study on the widespreadness of CP, we found that lifecourse SES was associated with 1-2 pain sites in participants from the Biomarker Project stream, while in NSDE stream, lifecourse SES was linked with pain in 3 or more sites. A possible explanation is that the number of pain sites, rather than pain interference, may be more sensitive to biological mechanisms associated with aging (Jay et al., 2019), potentially manifesting as an

intensification of multimorbidity. In the associations between covariates and CP conditions, it is possible that the synergy between multiple chronic conditions and low SES could be related to widespreadness of pain. When comparing the significance of covariates related to pain, we observed that the significance of the association between lifecourse SES and CP may largely depend on the development of multiple chronic conditions from MIDUS 1 to MIDUS 2.

In NSDE stream participants, multiple chronic conditions at MIDUS 1 were significantly associated with the number of pain sites at MIDUS 3 (P=0.019 for 1-2 pain sites; P=0.000 for 3 or more sites), suggesting that respondents had already experienced multimorbidity by MIDUS 1. Therefore, when pain data were collected at MIDUS 3, pain was likely widespread across multiple body areas. Conversely, in the Biomarker Project flow, multiple chronic conditions at MIDUS 2 (rather than MIDUS 1) were associated with both 1-2 pain sites (P=0.008) and 3 or more pain sites (P=0.047), indicating that multimorbidity may have developed later, around MIDUS 2. Thus, by the time pain data were collected at MIDUS 3, pain was more localized rather than widespread. This may explain the differences in the association between lifecourse SES and the distribution of pain. Several cohort studies have substantiated the relationship between SES and various chronic conditions (Kivimäki et al., 2020). Our findings suggest that CP is both a symptom and a condition in its own right (Treede et al., 2019). Low SES may limit individuals' access to resources, increasing their health risk exposure and reducing their capacity to manage disease risks. Our results highlight the importance of addressing the long-term healthcare needs of low-SES groups with multimorbidity and secondary widespread pain.

Following mechanisms may explain the association between SES and CP at certain anatomical regions. A key pathway linking SES to CP at certain anatomical regions involves physically demanding occupations common among lower SES groups. For instance, lower occupational class is associated with higher prevalence of chronic low back pain, largely due to physical job demands accelerating spinal wear-and-tear or causing lumbar injuries (Mehlum et al., 2008). Additionally, repetitive arm movements, overhead work, or heavy tool use typical in lower-status occupations significantly contribute to chronic shoulder and arm pain (Mehlum et al., 2008). Similarly, physically strenuous work, particularly involving frequent squatting, kneeling, or lifting, explains a substantial proportion of SES-related disparities in knee pain, and these effects are amplified among individuals who are obese (Cutler et al., 2020).

Moreover, lower SES, particularly lower educational attainment, is linked to disparities in pain management that may contribute to persistent pain in specific regions like the back, knees, and hips. A 2022 scoping review found that lower SES, particularly lower education, limits patients' access to appropriate CP management, including evidence-based treatments for conditions like osteoarthritis and back pain (Atkins and Mukhida, 2022). Patients with less education are more likely to be prescribed opioids due to limited awareness of their lower effectiveness in managing pain and their potential side effects (Shmagel et al., 2018) and less likely to receive referrals for surgery or rehabilitation. These disparities are especially harmful for pain in the back, knees, and hips, where early, multidisciplinary intervention is essential to prevent chronicity.

Previous studies suggest that compared to individuals who continually report no or only minimal economic hardship, those reporting moderate or severe economic hardship at ages

43 and 60-64 had a 2.9 times higher risk of CWP (Jay et al., 2019). However, previous studies simply summed economic hardships from different periods, potentially overstating the effect of economic hardships at 60-64 and understating the effect at age 43. For instance, compared to those without economic hardship, individuals reporting the most severe economic hardship at age 43 had a 340% higher risk of reporting CWP, a more significant effect than the summed index of economic hardship across both periods. To our knowledge, this is the first study to test the additive effects in the life course model between SES and CP. The additive effect is directly reflected in the association between SES at different periods and pain outcomes. Our study suggests that the additive effect of SES may emerge only in adulthood and is likely contingent upon the extent of development of multiple chronic conditions.

4.4.2 Discussion of lifecourse SES and AL

Our results found that childhood SES and recent SES were directly associated with the metabolic dysregulation phenotype of AL, and no indirect effects of life course SES on AL were found. However, there is no evidence supporting the mediating role of AL in the association between SES and CP. We might be the first in applying the life course model to the study of the association between SES and AL. Although prior research has explored the relationship between life course SES and AL, employing summative additive methods to operationalize concurrent or lifetime socioeconomic disadvantages (Gruenewald et al., 2012; Gustafsson et al., 2014; Lunyera et al., 2020) or inter-adjusting for SES across different periods (Robertson et al., 2014), these studies either assumed equal weights of the components within concurrent or lifetime socioeconomic disadvantages or failed to consider the sequential relationships of SES over different periods, thus not examining formal life course models.

Our findings that SES in childhood and MIDUS 2 is directly related to metabolic dysregulation of AL support the cumulative effects of these periods on AL. A community-based study of middle-aged and elderly African American adults found that lower SES was often associated with higher AL scores in females, driven more by metabolic and immune dimensions than by neuroendocrine dysregulation (Hickson et al., 2012), echoing our findings. The focus on metabolic dysregulation under a chronic stress framework is increasingly becoming a focal point for health interventions as it is associated not only with poorer mental health outcomes, higher risks of cancer and cardiovascular diseases (Gluckman et al., 2009; Kappelmann et al., 2021; Naaman et al., 2022), but also increased mortality risks (Carbone et al., 2023). Our study used path analysis and controlled for potential confounders, further clarifying the association between life course SES and AL. Efforts focused solely on recent SES risk exposure may not effectively mitigate the adverse consequences of early-life SES disadvantages on AL. However, addressing socioeconomic disadvantages both in childhood and recent years can help reduce the risks of metabolic dysregulation, thereby enhancing overall health outcomes.

4.4.3 Discussion of lifecourse SES and cortisol parameters

To our knowledge, this study may be the first to examine the association between life course SES and diurnal cortisol patterns using a community-based adult sample. The findings support the risk chain model for mid post-wake DCS and CDR, but not the critical period or cumulative effects hypotheses. The SES in MIDUS 2 is directly associated with mid post-wake DCS and CDR. Moreover, SES in MIDUS 2 mediates the effects of childhood SES and SES in MIDUS 1 on these variables. Additionally, the influence of childhood SES on CDR was solely through the combined effects of SES in MIDUS 1 and MIDUS 2. Currently, there is ongoing debate regarding how to measure DCS. By using segmented linear spline functions to model DCS, our

model accounted for 76.1% of the variability. Additionally, this model allows for a more detailed decomposition of DCS compared to the uniform DCS throughout the day decline, providing deeper insights into the social patterns of DCS over different time periods and their implications for health (Charles et al., 2020; Karlamangla et al., 2013; Ranjit et al., 2005b).

Our findings on the associations between lower SES and blunted mid post-wake DCS, rather than CAR, early or late post-wake DCS, partly echoed those of previous studies (Chandola et al., 2018; Groffen et al., 2015; Kumari et al., 2010; Miller et al., 2021; Ranjit et al., 2005a). Previous research has linked material hardship (Ranjit et al., 2005a) and lower occupational grades among civil servants (Chandola et al., 2018; Kumari et al., 2010) to a flatter cortisol diurnal slope. Furthermore, individuals with lower educational levels exhibit a slower decline in daytime cortisol levels (Groffen et al., 2015; Karlamangla et al., 2013). However, these studies, which simplified the full-day DCS into a uniform slope, failed to capture the nonlinear characteristics of DCS. Simultaneously, previous research has identified contradictory associations between SES and CAR. In addition to the sole SES indicator, insufficient days of cortisol collection may also account for the inconsistencies in the results (Kunz-Ebrecht et al., 2004a, 2004b; Steptoe et al., 2005; Wright and Steptoe, 2005).

The CDR reflects the diurnal reactivity level of the HPA axis, with a flatter CDR associated with higher all-cause mortality over 7-12 years, poorer executive function, cognitive decline, and greater heterogeneity in AL (Charles et al., 2020; Karlamangla et al., 2022). While we observed an association between lifecourse SES and CDR, this finding warrants cautious interpretation, as robust significant association was detected between CAR, early and late post-wake DCSs and lifecourse SES. Given the correlations between CDR, CAR, and DCSs shown in

Supplementary Figure 4-1, this observed link may primarily be driven by the marginal effects of life-course SES on diurnal cortisol rhythms.

Another interpretation is that, in addition to capturing the impairments in glucocorticoid receptor and mineralocorticoid receptor functions as reflected by mid post-wake DCS, the CDR may also convey additional information related to aging while reflecting the long-term consequences of chronic stress disorders similar to AL (Karlamangla et al., 2022; Oster et al., 2017). This could provide additional insights into the pathogenic mechanisms linking SES with aging, thereby offering new avenues for interventions aimed at the prevention of age-related decline. However, further studies with larger sample sizes are needed to clarify the association.

Additionally, we found no robust association with AUC. However, previous research has identified inconsistent associations between SES and AUC. Although one study measured cortisol under naturalistic conditions and found a prospective association between SES and lower cortisol levels, this study only collected cortisol at three time points in a single day, substantially influenced by situational factors and wake-up times (Brandtstädter et al., 1991). Another study was also constrained by a limited number of cortisol collection days and the few collection occurrences each day (Li et al., 2007). Remaining studies were limited by their small sample size (N=193 and N=488), making it difficult to generalize the results (Cohen et al., 2006a; Miller et al., 2021). In summary, compared to previous studies, the NSDE provides a more ideal protocol for cortisol collection, involving saliva cortisol collected four times daily over four days in a naturalistic setting, minimizing the bias from situational effects and

improving the fit of the diurnal cortisol pattern (Hellhammer et al., 2007; Ranjit et al., 2005b), thus generating more stable associations.

4.4.4 Discussion of AL, cortisol parameters, and CP

A recent study demonstrated a prospective association between the metabolic dysregulation phenotype of AL and high interference CP, as well as the presence of CP in three or more body sites (Liang and Booker, 2024). In contrast, our study, which controlled for a broader range of potential confounders—including, but not limited to, SES across three life stages—found that the association between the metabolic dysregulation phenotype of AL and high interference CP remained significant. However, the association with CP in three or more body sites disappeared. This finding may suggest that AL operates through distinct mechanisms to influence different pain outcomes. For instance, the experience of pain interference may involve stress-related processes, potentially mediated by the anterior cingulate cortex (Rainville, 2002), which shapes pain perception through mechanisms such as attentional focus, emotional distress, and cognitive appraisal (Villemure and Bushnell, 2002; Wiech et al., 2008). These processes are closely tied to AL, itself a consequence of chronic stress.

Furthermore, we found that daily cortisol secretion levels and diurnal variations are associated with a greater number of pain sites in the pooled sample, which is inconsistent with our earlier findings. In the previous section, we controlled for the income-to-needs ratio and education level from the MIDUS 2 SES constructs, rather than SES as a latent variable, which may suggest that specific SES mechanisms impose more substantial confounding effects on the association between cortisol and multisite pain. A larger sample size will help clarify these relationships.

4.4.5 Discussion of the mediation effects of AL, cortisol parameters on CP

Prior studies have highlighted the potential mediating role of AL, this research did not demonstrate a mediating effect of AL in the prospective association between SES and CP. Similarly, a cross-sectional study in the United States found no mediating effect of AL between SES and CP (Slade et al., 2012). However, their definition of pain accorded with acute rather than chronic conditions, potentially diminishing mediation effects of AL. Acute pain often results from specific diseases or injuries (Grichnik and Ferrante, 1991) and may not involve the same chronic stress-related pathways as CP. Furthermore, the CP measures utilized in this study assessed a general CP profile of the participants, wherein specific CP subtypes may not be associated with the dysregulation of the chronic stress response (Cohen et al., 2021). Therefore, a general measure of CP could obscure the potential correlation between AL and CP specific to chronic stress (Nicholas et al., 2019).

This is also the first article to explore the mediating role of cortisol in the association between life course SES and CP, finding that the diurnal rhythm of cortisol did not mediate the association between SES and CP, both in the full sample analysis and in the subset not reporting CP in MIDUS 2. Although our results did not confirm the mediating role of the diurnal pattern of cortisol, the findings still hold significant implications. The results suggest that interventions targeting dysregulations in the diurnal pattern of cortisol may not effectively prevent CP related to low SES.

As the social security system crumbles and economic pressures increase, the societal prevalence of CP is also rising (Zajacova et al., 2021b). However, the specific mechanisms by which adverse social structures impact individuals and trigger CP remain unclear, adding

complexity to the social aspects of pain management. On the one hand, our study underscores the urgent need for more in-depth research into other sociobiological mechanisms of CP, to more effectively inform public health policies and interventions. For example, recent study found epigenetic aging mediated the associations among income, education and chronic knee pain impact, highlighting the importance of epigenetic aging as a modifiable factor for CP (Strath et al., 2024).

On the other hand, the lack of significant biological mediation in our study may underscore SES disparities in the day-to-day management of CP, highlighting the critical role of metamechanisms. Metamechanisms refer to overarching pathways linking low SES to worse health, for example, fewer flexible resources, spillover effects of living in more stressful or less health-oriented environments, an ingrained “health habitus,” or even bias in institutional interactions (Freese and Lutfey, 2011). For instance, individuals residing in more affluent neighborhoods or engaged in higher-status occupations may benefit from preventive pain management services without any proactive effort. Those with higher SES may also be more inclined to adopt behaviors conducive to pain control, such as routinely seeking proactive treatment and maintaining a more positive outlook. Additionally, disparities in the quality of pain management services available may exist based on SES. However, the influence of these metamechanisms on CP remains exploratory, underscoring the need for systematic empirical research in these areas.

Also, in MIDUS, CP was measured using the question, “Do you have chronic pain, that is do you have pain that persists beyond the time of normal healing and has lasted from anywhere from a few months to many years?” Because this broad definition does not distinguish

between “primary” pain (often stress-related) and “secondary” pain (driven by underlying medical conditions), a substantial portion of the CP in our sample may stem from structural or disease-related causes. These “secondary” pain conditions are less reliant on chronic stress-related biological processes. Consequently, if much of the reported pain arises through mechanisms like injury, stress biomarkers may not fully capture their etiology. This heterogeneity makes it more difficult to detect mediation by stress-based biological pathways and could help explain why we did not observe significant mediation effects by AL or cortisol parameters.

Finally, the extended interval between initial SES assessment, biomarker sampling, and CP measurement may have diluted the causal pathway we aimed to capture (Rijnhart et al., 2022). One plausible explanation is that the physiological impacts of socioeconomic adversity develop and fluctuate dynamically over time rather than following a linear trajectory. Thus, even though SES is associated with current biomarkers, the relatively long interval between biomarker assessment and CP measurement may have allowed other factors, such as intervening health conditions, lifestyle changes, or medical treatments, to intervene, weakening the pathway from biomarkers to CP. In other words, while biomarkers measured at one point may still reflect SES-related physiological disturbances, their capacity to predict future CP could weaken considerably over longer intervals. Future research employing shorter intervals or repeated biomarker measurements could better clarify how timing affects the mediation process and potentially uncover stronger evidence for biological mediation between SES and CP.

4.4.6 Advantages and limitations

This study has following additional advantages. Firstly, by integrating both primary and secondary biological indicators of chronic stress response to construct AL, it may enhance the measurement's validity. Beyond the classic summative method for operationalizing AL, this study utilized LCA to capture the interrelations among AL biomarkers. Additionally, it utilizes data from a more ideal cortisol collection protocol, making HPA axis measurements more reliable. In addition, compared to previous birth cohort studies, the sequential collection of biomarkers of stress response systems and CP data allows us to examine the prospective mediating role.

Also, we consolidated SES into a composite index to capture its multidimensionality and our findings highlight the distinct contributions of its individual components. Affordability-related indicators (e.g., current financial situation, bill payment difficulty, income-to-needs ratio) are more salient in early adulthood, when financial strain is common, but their relevance diminishes with age. In contrast, traditional indicators like education and occupation gain importance over time. These shifting patterns suggest that SES-sensitive health policies should be tailored to life stage—prioritizing financial support in early adulthood and enhancing structural resources in later life to address social inequalities and improve health outcomes.

Moreover, the prospective nature of this study allows for the inclusion of early confounders, thereby minimizing potential confounding effects and establishing a temporal sequence in the relationship between SES and CP. Finally, we applied life course models to these

associations, allowing for a formal and detailed examination of how SES is linked to biological dysregulations in stress response systems and CP.

There are limitations in the present study. Like all observational studies, SEM is susceptible to unmeasured confounding, which occurs when there are unknown or unmeasured variables that influence both the predictor and the outcome. If such variables exist, the estimated relationships in the path model may be distorted, potentially leading to incorrect conclusions about direct or indirect effects. Although the demographic and health characteristics of the biomarker sample closely align with those of the national survey sample (Dienberg Love et al., 2010), the analytic sample demonstrates an underrepresentation of ethnic minorities. Racial disparities in health outcomes are a profound concern in the United States (Clouston and Link, 2021). The increasing disparity in the prevalence and treatment of CP among ethnic minorities, driven by structural factors such as discrimination and the chronic stress of socioeconomic disadvantage, calls for attention (Maly and Vallerand, 2018). Thus, future studies can prioritize the inclusion of ethnic minority groups to address this gap.

Also, the association between SES and CP may be influenced by attrition bias, as participants with more SES disadvantages at baseline were more likely to drop out. This could lead to an underestimation of the true impact of SES on CP outcomes (See Supplementary Tables 3-8 & 4-12). Furthermore, childhood indicators were measured retrospectively, which are subject to recall bias. However, the impact of this bias might be minimal. Studies validating the concordance of childhood SES indicators in MIDUS, using sibling and twin samples, have shown that recall measures were generally reliable (Ward, 2011). Nonetheless, employing prospective indicators for childhood conditions is recommended for future research.

In addition, we addressed missing values in the SES composite index, which includes the occupation of fathers or male heads and the educational level of mothers or female heads, using the full information maximum likelihood method. However, this approach is not without its limitations. For male heads of household who stayed home to raise children or were absent from the labor market for other reasons, we imputed their occupation based on the female head of household's occupation during childhood. On the one hand, this aligns with the household dominance framework for measuring the occupational status of the head of household in childhood (Krieger et al., 1997). On the other hand, given the social context of childhood in the MIDUS sample, using the occupation of the female head of household, typically representing the mother, to stand in for the male head's occupation may underestimate the occupational effect on pain. This is because women at that time were more likely to hold jobs with higher social status but relatively lower wages. Additionally, we were unable to distinguish respondents who lacked either a male or female head of household in childhood because MIDUS did not provide detailed information for the missingness. Given the association between single-parent households and poverty (Bradley and Corwyn, 2002), imputing data for these respondents may potentially weaken the association between SES and pain.

4.5 Conclusion

In conclusion, our findings underscore that recent low SES mediates the adverse impact of previous socioeconomic disadvantages on CP outcomes, particularly highlighting the importance of intervening in recent SES to effectively prevent CP. However, reducing the prevalence of multisite pain may require alleviation of multimorbidity burdens. We

emphasize that the metabolic dysregulation phenotype of AL is influenced by the cumulative effects of childhood SES disadvantages and recent SES disadvantages, which points to the potential importance of these life stages in shaping long-term physiological outcomes. Similarly, interventions focused on recent individual SES may have some relevance for mitigating HPA axis dysregulation. However, we did not find evidence for dysregulations in stress response systems as mediators. How socioeconomic disadvantages profoundly get to the skin to cause or sustain CP remains an uncharted territory. Future research is needed to explore different mediating mechanisms and provide a basis for personalized interventions for CP.

5 Summary and Future Directions

5.1 Summary of thesis work

CP affects at least one-fifth of American adults (Yong et al., 2022), and this number is likely to continue rising. Calls to address the population-level crisis of CP emerged as early as the first decade of this century (Interagency Pain Research Coordinating Committee, 2022). Sociologists and economists have continuously emphasized that understanding the social causes of CP might be key to alleviating this major public health crisis. Additionally, experts in pain management have underscored the importance of a multidimensional approach to pain management (Case et al., 2020; Cohen et al., 2021; Zajacova et al., 2021b). Despite these calls, there remain significant gaps in the research on the social determinants of CP (Khalatbari-Soltani and Blyth, 2022).

In recent decades, the role of SES in health disparities has become widely recognized, whether in chronic diseases (Phelan et al., 2010) or infectious diseases (Clouston and Link, 2021). By limiting individuals' access to resources, lower SES groups are more likely to be exposed to higher-risk environments and have fewer means to prevent and manage diseases. The recent COVID-19 pandemic has starkly highlighted these inequalities, from national to individual levels (McGowan and Bambra, 2022). Furthermore, health disparities are likely rooted in individuals' life histories (Jones et al., 2019; Kuh et al., 2003). Therefore, expanding the research perspective on SES and chronic diseases through life course theory can identify critical intervention periods, enhancing the ability of public health systems and individuals to intervene effectively. This approach can also reduce unnecessary public spending by avoiding redundant interventions during less critical periods.

In addition, identifying early risk factors for CP and examining how SES influences CP risk provides additional insights into pain management for underserved populations. CP is considered a condition closely linked to chronic stress (Borsook et al., 2012). Prolonged exposure to chronic stressors can lead to systemic physiological dysregulation, starting with the HPA axis and extending to various downstream physiological systems (Juster et al., 2010; Woda et al., 2016). Social stress theory suggests that individuals with low SES often face persistent environmental challenges and constraints on coping and adaptation, which serve as long-term stressors (Aneshensel, 1992; Baum et al., 1999). Consequently, there may be a higher likelihood of observing systematic chronic stress response dysregulation in low SES populations. Clinical literature and some population-based studies indicate that CP appears to be a product of physiological dysregulation of the stress response system. However, research gaps still exist (Liang and Booker, 2024).

The first and second aims of our study are to explore whether chronic stress-related biological dysregulations, such as HPA axis dysregulation and systemic physiological dysregulation, are prospectively associated with CP. Our study separately examines HPA axis dysfunction, measured by the diurnal pattern of salivary cortisol, and systemic chronic stress dysregulation through AL. Studying both HPA axis dysregulation and AL is essential for a comprehensive understanding of the physiological impacts of chronic stress. The HPA axis provides specific insights into hormonal responses and regulatory mechanisms directly related to stress. In contrast, AL encompasses the broader, cumulative effects of chronic stress across various bodily systems, capturing the long-term wear and tear that can lead to significant health consequences. By examining both, researchers can gain a detailed and nuanced picture of

how chronic stress-related biological responses are associated with CP, thereby enabling more effective interventions and preventive measures for stress-related disorders.

We find that the diurnal cortisol rhythms from early to mid post-wake periods are related to the development of CP in 3 or more body sites. AL, particularly metabolic dysregulation, is associated with higher odds of chronic high interference and multisite pain in the future. Our findings carry significant public health implications. Diurnal cortisol rhythms may indicate early-stage outcomes of chronic stress dysregulation, while AL may reflect a long-term outcomes of chronic stress dysregulation. Identifying individuals exhibiting both a flattened diurnal cortisol slope and metabolic dysregulation phenotypes within AL can help selectively target high-risk populations at different stages of CP. For instance, a flattened diurnal cortisol slope may signal mid-to-late stages in the progression of CP with 3 or more sites, whereas the metabolic phenotype of AL is associated with altered odds of future CP interference and CP with 3 or more sites. Moreover, our results inform precision intervention targets at various stages (e.g., interventions aiming at glucocorticoid receptor downregulation, metabolic health optimization). Secondly, these findings provide prospective power estimates and insights into intervention effects, thereby guiding the design of future public health research.

Our third and fourth aims are to explore the mediating role of HPA axis dysregulation and systemic chronic stress dysregulation in the association between life course SES and CP, aiming to address the unresolved question of how current SES influences CP. Specifically, we found chain of risk models regarding SES and mid post-wake DCS and CDR, suggesting that proximal adult socioeconomic disadvantage mediates the adverse effects of early life and directly impacts these cortisol indicators. Our findings highlight the importance of addressing

proximal socioeconomic inequalities to prevent HPA axis dysregulation, thereby averting a wider range of adverse health outcomes linked to it. Additionally, by applying a comprehensive measure of chronic stress dysregulation, we identified a risk model chain for AL metabolic dysregulation phenotypes, where both childhood SES and recent SES are directly associated with these phenotypes. These findings underscore the critical role of alleviating socioeconomic disadvantages not only in adulthood but also during childhood to prevent systemic dysregulation related to chronic stress in later life.

Moreover, our findings confirm the chain of risk model linking life course SES with CP interference, emphasizing the mediating role of recent SES. Regarding the widespreadness of CP, we found that the relationship between lifecourse SES and the number of pain sites may depend on the degree of multimorbidity development. Early onset of chronic conditions associated with pain may lead to a broader extent of pain in the future. Our findings suggest that CP is both a symptom of underlying disease and a condition in its own right. Low SES may limit individuals' access to and utilization of various resources, thereby increasing exposure to health risks and reducing their capacity to manage disease risks. Our results highlight the importance of meeting the long-term healthcare needs of low-SES populations suffering from multiple chronic conditions in multisite pain management.

These findings highlight that interventions aimed at alleviating socioeconomic disadvantage at specific life stages may help improve chronic stress dysregulation and CP, underscoring the importance of relevant social policies. However, we did not find evidence that stress-related biological dysregulation mediated the association between SES and CP. This highlights not only the importance of biological mechanisms beyond chronic stress but also suggests that in

addressing SES inequalities in CP, efforts to reduce CP disparities solely through alleviating biological wear and tear from individual stress may have limited benefits. Structural inequalities embedded in individuals' everyday pain management practices may require broader public health interventions, such as inclusive pain treatment access, widespread dissemination of pain management knowledge, and more equitable healthcare services.

5.2 Future Directions

Firstly, improving the participation rate in biomarker collections within population surveys is crucial. An increasing number of population-based surveys have either started or plan to collect biological samples. However, there is still a significant lack of research on how to enhance participation rates in sample collection and follow-up retention rates in in biomarker collections. This issue is particularly important for surveys that aim to represent the general population through complex probability sampling. The MIDUS study collects comprehensive biological data through a rigorous protocol. Although participants are similar to the baseline population in terms of sociodemographic characteristics, the participation rates for biological sample collection and diary data remain a challenge for research. This is especially problematic in longitudinal studies, where it poses difficulties for the generalizability of the data. Future research on strategies to incentivize participation in biomarker collection and improve follow-up retention under strict protocols will provide valuable insights for the implementation of large-scale population surveys with biomarker collections.

Secondly, due to the current stage of the MIDUS survey, we can only explore the association between stress-related biomarkers and CP through a single follow-up with a long interval. However, the state of biomarkers is likely to change with the progression of pain. Although

future cohort studies with higher frequency and shorter collection intervals of biological information would help explore the relationship between biological changes and the development of CP, such studies are extremely costly. We propose a compromise approach: collecting biological information only at baseline and CP information at baseline and multiple follow-ups. By examining the relative timing of baseline biomarkers and the development of CP, we can determine the stages of pain progression. Additionally, collecting multiple instances of pain information helps reduce misclassification, thereby providing more accurate estimates. Despite the high costs, it is essential to conduct multiple collections not only of pain status but also of stress-related biomarkers, particularly cortisol, from community-dwelling adults. Ideally, these collections could utilize probability sampling cohort to reveal the complex association between pain development, pain chronicity, and the dysregulation of stress response systems for better generalizability. The related research will facilitate a better understanding of CP pathology, improve biopsychosocial pain management, and support population-level prevention efforts, ultimately alleviating the population's pain burden and reducing medical costs for both individuals and the healthcare system.

Thirdly, although self-reports remain the "gold standard" for measuring CP, incorporating validated pain scales or physician diagnoses, through linked data, into large-scale epidemiological studies will undoubtedly enhance the reliability and validity of pain measurement. Currently, only limited data include CP indicators that meet the defined criteria. Measuring the duration of pain in population-based surveys may also provide more detailed insights. In addition, CP measures in MIDUS capture a general CP condition, limiting the ability to conduct a more detailed investigation into different pain syndromes. In MIDUS, the question 'Do you have CP, that is, do you have pain that persists beyond the time of normal

healing and has lasted anywhere from a few months to many years?' is used to measure CP. This question implies the presence of previous injuries and, therefore, includes secondary pain syndromes, where various mechanisms, besides chronic stress, may exist. Future epidemiological research on specific pain syndromes may offer extra information.

Fourth, we encourage further exploration of structural-level research. While individualized prevention strategies that target biological and behavioral mediations are often emphasized in policy discussions, these approaches alone are insufficient to address the adverse effects brought by broader determinants of health. Our findings suggest that merely improving the biological conditions associated with chronic stress may not reduce socioeconomic inequalities in CP. A focus on the structural conditions tied to SES is essential. In addition, individual CP disparities may be rooted in structural plight such as daily medical practice for CP, geographic location and industrial structure. We look forward to significant future research outcomes in these areas. Additional measures are needed to address the social determinants of health.

Supplementary Materials to Chapter: Allostatic Load and Chronic Pain

Supplementary Table 1-1 Fit statistics for latent classes of AL

Model Class k	- llik (maximum value of the log-likelihood)	AIC	BIC	Entropy	Class 1 %	Class 2 %	Class 3 %	Class 4 %	Class 5 %	Class 6 %	Class 7 %
1	-11670.67	23395.33	23521.17	NaN	1.00						
2	-11067.14	22244.28	22500.61	0.85	0.62	0.38					
3	-10813.98	21793.96	22180.79	0.86	0.24	0.51	0.25				
4	-10706.04	21634.09	22151.41	0.85	0.23	0.18	0.49	0.10			
5	-10606.58	21491.16	22138.98	0.84	0.17	0.14	0.43	0.11	0.15		
6	-10539.69	21413.38	22191.70	NaN	0.18	0.31	0.10	0.18	0.05	0.19	
7	-10463.27	21316.53	22225.35	NaN	0.11	0.12	0.17	0.11	0.25	0.13	0.12

Supplementary Table 1-2 Biomarkers levels stratified by AL phenotype

AL driven pattern	Class 1		Class 2		Class 3		
Biomarkers	**Mean**	**Median**	**Mean**	**Median**	**Mean**	**Median**	**Test**
Hypothalamic Pituitary Adrenal Axis							
DHEA-s (ug/dL)	110	94	106	86	115	90	F=0.688
Urine cortisol (μg/g)	17	15	15	11	13	10	F=5.782***
Sympathetic Nervous System							
Urine epinephrine (μg/g)	2.1	1.8	2	1.8	1.7	1.4	F=6.251***
Urine norepinephrine (μg/g)	26	24	28	27	28	24	F=2.785*
Urine Dopamine (μg/g)	151	142	144	136	146	133	F=1.37
Parasympathetic Nervous System							
High-frequency HRV	348	176	31	30	371	141	F=15.035***
Low-frequency HRV	562	339	112	90	457	258	F=36.218***
RMSSD	26	21	8.5	8.6	25	19	F=88.199***
SDRR (m s)	41	36	21	20	37	34	F=115.491***
Cardiovascular							
Resting SBP (mmHg)	126	126	133	131	136	137	F=30.225***
Resting DBP (mmHg)	74	73	76	76	77	77	F=9.386***
Resting heart rate (bpm)	70	70	80	80	71	71	F=74.174***
Inflammation							
CRP (mg/L)	1.8	0.89	3.1	1.6	3.2	2.2	F=13.511***
IL6 (pg/mL)	0.76	0.63	1.1	0.92	1.2	1	F=26.438***
TNF-α (pg/mL)	1.9	1.9	2.5	2.3	2.4	2.3	F=47.766***
Fibrinogen (mg/dL)	322	319	356	356	349	345	F=14.897***
ICAM-1 (ng/mL)	264	244	297	276	297	289	F=12.488***
E-Selectin (ng/mL)	37	34	41	38	49	45	F=23.056***

Blood Fasting IGF1 (Insulin-like Growth Factor 1) ng/mL)	133	126	123	115	119	113	F=6.492***
Metabolic-glucose							
Fasting glucose	93	93	102	98	113	103	F=51.566***
Hemoglobin A1c%	5.7	5.7	6.1	5.9	6.3	6	F=37.938***
HOMA-IR	1.9	1.7	3.8	2.7	5.8	4.7	F=107.247***
Metabolic-lipids							
Triglycerides (mg/dL)	100	92	148	121	181	162	F=80.591***
WHR	0.85	0.85	0.92	0.91	0.95	0.96	F=89.071***
BMI	26	26	30	30	33	32	F=119.981***
LDL cholesterol (mg/dL)	105	103	110	104	109	102	F=1.358
HDL cholesterol (mg/dL)	62	59	53	51	43	41	F=85.106***

Supplementary Table 1-3 Full results from the main logistic regression for the association between AL at MIDUS 2 Biomarker Project and CP status at MIDUS 3

	OR (95% CI)	P-value
AL pattern		
Baseline	Ref	
Parasympathetic dysregulation	0.97 (0.64, 1.48)	0.889
Metabolic dysregulation	1.18 (0.76, 1.81)	0.464
Year gap between data collections		
MIDUS 2 Biomarker Project to MIDUS 3	1.13 (0.99, 1.3)	0.069
Education		
high school or less	Ref	
bachelor's degree	0.87 (0.59, 1.29)	0.497
Master's degree and above	0.97 (0.61, 1.53)	0.899
Age	0.99 (0.97, 1.01)	0.190
Marital Status		
Married	Ref	
Divorced & Separated	0.83 (0.51, 1.35)	0.450
Never married & Widowed	0.61 (0.36, 1.04)	0.071
Income-to-needs ratio		
Affluent	Ref	
Adequate-income	1.25 (0.85, 1.85)	0.262
Low-income or below	2.30 (1.42, 3.74)	**0.001**
Race/ethnicity		
White	Ref	
Non-white	1.53 (0.79, 2.97)	0.203
Gender		
Male	Ref	
Female	1.37 (0.96, 1.95)	0.085
Total number of Metabolic Equivalent of Task (MET) minutes per week		
500-1000	Ref	
Greater than 1000	1.64 (1.03, 2.6)	**0.036**
Less than 500	1.06 (0.67, 1.69)	0.797
Smoking behavior		
Current Smoker	Ref	
Ex-Smoker	0.87 (0.49, 1.54)	0.640
non-Smoker	0.67 (0.39, 1.15)	0.145
Drinking behavior		
Moderate + drinker	Ref	
Light drinker	1.19 (0.79, 1.79)	0.408
Non-drinker or rarely drink	1.14 (0.75, 1.72)	0.543

Childhood parent emotional abuse		
1 (Never)	Ref	
1.5	1.58 (0.93, 2.71)	0.093
2	1.05 (0.69, 1.60)	0.826
2.5	0.85 (0.55, 1.31)	0.461
3 (Most frequent)	1.15 (0.79, 1.68)	0.469
Childhood parent physical abuse		
1 (Never)	Ref	
1.5	0.95 (0.51, 1.76)	0.863
2	0.75 (0.46, 1.20)	0.230
2.5	1.01 (0.63, 1.62)	0.955
3 (Most frequent)	0.69 (0.47, 1.03)	0.068
Medication intake		
No	Ref	
Yes	2.10 (1.37, 3.24)	**0.001**
Multimorbidity		
<2	Ref	
2+	1.57 (0.98, 2.53)	0.062

Supplementary Table 1-4 Full results from the main multinomial logistic regression for the association between AL at MIDUS 2 Biomarker Project and CP interference and the number of CP sites at MIDUS 3

No pain vs	CP interference				The number of pain locations			
	Low interference pain		High interference pain		1-2 pain locations		3+ pain locations	
	RRR (95% CI)	P-value	RRR (95% CI)	P-value	RRR (95% CI)	P-value	RRR (95% CI)	P-value
AL pattern								
Baseline	Ref		Ref		Ref		Ref	
Parasympathetic dysregulation	0.87 (0.54, 1.39)	0.552	1.24 (0.65, 2.39)	0.512	0.84 (0.51, 1.36)	0.474	1.30 (0.69, 2.44)	0.411
Metabolic dysregulation	0.92 (0.56, 1.52)	0.742	2.00 (1.06, 3.79)	**0.033**	0.89 (0.54, 1.47)	0.654	2.03 (1.08, 3.83)	**0.029**
Year gap between data collections								
MIDUS 2 Biomarker Project to MIDUS 3	1.13 (0.97, 1.32)	0.107	1.13 (0.92, 1.39)	0.239	1.14 (0.98, 1.33)	0.094	1.13 (0.93, 1.39)	0.224
Education								
high school or less	Ref		Ref		Ref		Ref	
bachelor's degree	0.86 (0.56, 1.34)	0.518	0.87 (0.47, 1.61)	0.653	1.04 (0.67, 1.62)	0.858	0.6 (0.32, 1.12)	0.108
Master's degree and above	0.82 (0.48, 1.39)	0.464	1.31 (0.66, 2.59)	0.436	1.03 (0.61, 1.73)	0.911	0.9 (0.45, 1.81)	0.770
Age	0.99 (0.97, 1.01)	0.466	0.98 (0.96, 1.01)	0.158	0.98 (0.97, 1)	0.114	1 (0.97, 1.02)	0.842
Marital Status								
Married	Ref		Ref		Ref		Ref	
Divorced & Separated	0.92 (0.53, 1.6)	0.768	0.65 (0.3, 1.39)	0.267	0.83 (0.47, 1.47)	0.519	0.75 (0.37, 1.54)	0.440
Never married & Widowed	0.74 (0.41, 1.33)	0.319	0.37 (0.15, 0.94)	**0.037**	0.59 (0.32, 1.1)	0.099	0.58 (0.26, 1.3)	0.189
Income-to-needs ratio								
Affluent	Ref		Ref		Ref		Ref	

Adequate-income	1.28 (0.82, 1.99)	0.281	1.17 (0.65, 2.11)	0.602	1.26 (0.8, 1.96)	0.319	1.24 (0.69, 2.22)	0.466
Low-income or below	2.55 (1.5, 4.34)	0.001	1.82 (0.87, 3.83)	0.114	2.1 (1.21, 3.66)	0.009	2.63 (1.32, 5.25)	**0.006**
Race/ethnicity								
White	Ref		Ref		Ref		Ref	
Non-white	1.6 (0.78, 3.31)	0.203	1.41 (0.52, 3.8)	0.495	1.24 (0.57, 2.71)	0.583	2.47 (1.02, 5.99)	**0.046**
Gender								
Male	Ref		Ref		Ref		Ref	
Female	1.06 (0.71, 1.58)	0.780	2.46 (1.39, 4.36)	**0.002**	0.93 (0.62, 1.39)	0.720	3.34 (1.86, 5.98)	**0.000**
Total number of Metabolic Equivalent of Task (MET) minutes per week								
500-1000	Ref		Ref		Ref		Ref	
Greater than 1000	1.58 (0.94, 2.65)	0.084	1.83 (0.88, 3.77)	0.104	1.54 (0.9, 2.61)	0.114	1.82 (0.91, 3.6)	0.088
Less than 500	1.05 (0.61, 1.78)	0.869	1.14 (0.56, 2.34)	0.722	1.17 (0.68, 2.01)	0.561	0.86 (0.43, 1.72)	0.662
Smoking behavior								
Current Smoker	Ref		Ref		Ref		Ref	
Ex-Smoker	1.11 (0.57, 2.17)	0.759	0.57 (0.26, 1.24)	0.154	1.1 (0.55, 2.18)	0.788	0.61 (0.29, 1.3)	0.202
non-Smoker	1 (0.53, 1.87)	0.994	0.31 (0.15, 0.65)	**0.002**	0.98 (0.51, 1.87)	0.945	0.34 (0.16, 0.71)	**0.004**
Drinking behavior								
Moderate + drinker	Ref		Ref		Ref		Ref	
Light drinker	1.17 (0.75, 1.85)	0.490	1.27 (0.66, 2.44)	0.473	1.21 (0.76, 1.95)	0.418	1.13 (0.62, 2.08)	0.683
Non-drinker or rarely drink	0.9 (0.56, 1.44)	0.649	1.81 (0.97, 3.37)	0.061	1.23 (0.77, 1.97)	0.382	0.97 (0.52, 1.8)	0.913
Childhood parent emotional abuse								
1 (Never)	Ref		Ref		Ref		Ref	
1.5	1.45 (0.79, 2.66)	0.236	1.9 (0.85, 4.24)	0.116	1.65 (0.9, 3.03)	0.106	1.29 (0.57, 2.91)	0.539
2	0.95 (0.59, 1.55)	0.851	1.35 (0.72, 2.55)	0.348	0.96 (0.59, 1.57)	0.877	1.23 (0.67, 2.26)	0.504
2.5	1.1 (0.67, 1.79)	0.716	0.44 (0.21, 0.92)	**0.029**	0.82 (0.51, 1.32)	0.406	0.92 (0.45, 1.86)	0.811

3 (Most frequent)	1.2 (0.78, 1.83)	0.407	1.26 (0.66, 2.4)	0.489	0.97 (0.64, 1.48)	0.898	1.73 (0.93, 3.2)	0.082
Childhood parent physical abuse								
1 (Never)	Ref		Ref		Ref		Ref	
1.5	0.83 (0.41, 1.7)	0.616	1.25 (0.51, 3.09)	0.629	0.66 (0.31, 1.39)	0.272	1.73 (0.72, 4.21)	0.223
2	0.83 (0.48, 1.44)	0.509	0.67 (0.33, 1.34)	0.252	0.64 (0.35, 1.15)	0.134	0.9 (0.47, 1.73)	0.757
2.5	1.25 (0.73, 2.16)	0.414	0.66 (0.33, 1.31)	0.235	1.01 (0.59, 1.75)	0.962	0.86 (0.44, 1.69)	0.656
3 (Most frequent)	0.73 (0.46, 1.16)	0.184	0.71 (0.4, 1.26)	0.238	0.65 (0.42, 1.02)	0.064	0.8 (0.45, 1.43)	0.451
Medication intake								
Yes	Ref		Ref		Ref		Ref	
No	2.01 (1.24, 3.26)	0.005	2.42 (1.18, 4.99)	**0.016**	2.01 (1.23, 3.29)	0.005	2.53 (1.25, 5.11)	**0.010**
Multimorbidity								
<2	Ref		Ref		Ref		Ref	
2+	1.51 (0.89, 2.56)	0.131	1.8 (0.79, 4.1)	0.162	1.48 (0.87, 2.51)	0.151	1.97 (0.87, 4.47)	0.105

Supplementary materials to Chapter: Association of Diurnal Cortisol Rhythm with Chronic Pain

Supplementary Table 2-1 Sample characteristics of NSDE

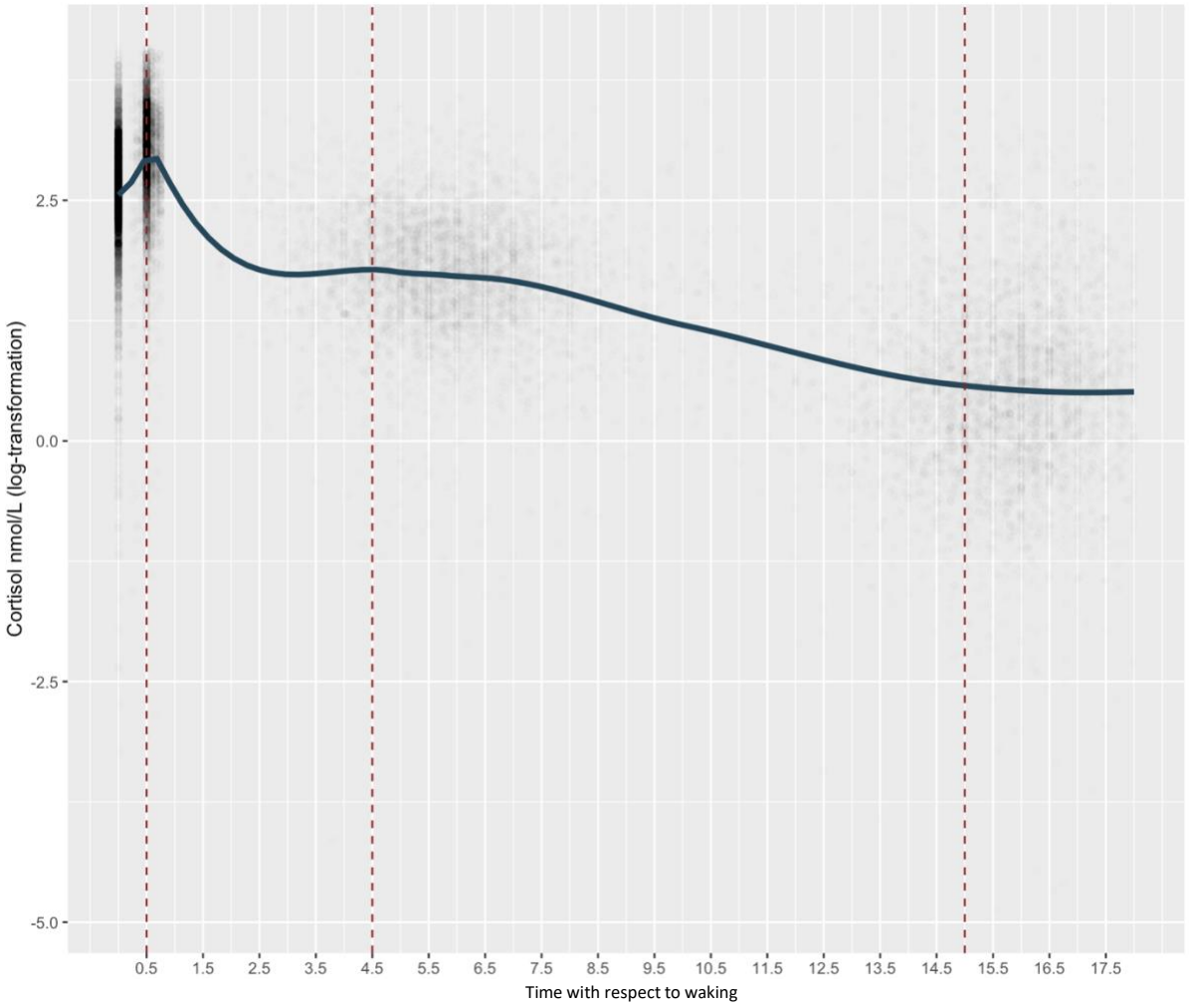
Variable	N (day-observations)	Mean	Median
Cortisol: awakening (nmol/L)	3841	15.31	8.31
Cortisol: 30 mins after awakening (nmol/L)	3841	21.75	10.78
Cortisol: lunchtime (nmol/L)	3841	6.74	4.36
Cortisol: bedtime (nmol/L)	3841	2.78	3.83
Cortisol collection time (hours): awakening	3841	6.72	1.25
Cortisol collection time (hours): 30 mins after awakening	3841	7.25	1.25
Cortisol collection time (hours): lunchtime	3836	12.65	1.38
Cortisol collection time (hours): bedtime	3841	22.50	1.27
Collection day	3841		
Day 1	1246	32.44%	
Day 2	1120	29.16%	
Day 3	904	23.54%	
Day 4	571	14.87%	
Average wake-day length (individual-level)	3841	6.72	1.25
Waking hours	3841	16.75	0.86
Weekend vs. workday status	3841		
Weekday	2879	74.95%	
Weekend	962	25.05%	
Length of sleep the previous night	3701		
6-8	2776	75.01%	
<6	320	8.65%	
>8	605	16.35%	

Supplementary Table 2-2 Parameters of the mean log-cortisol trajectory

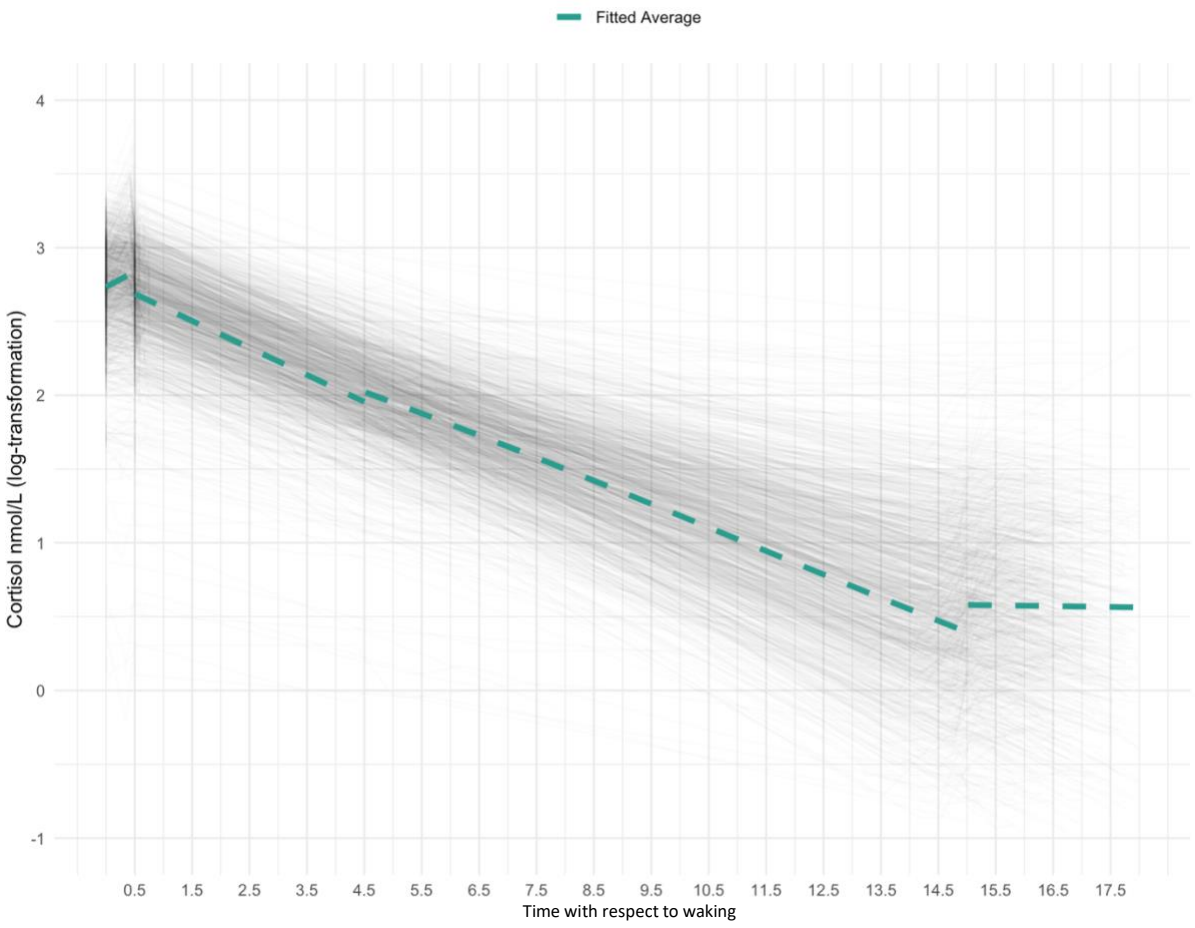
Fixed effects:	**Estimate**	**P-value**
(Intercept)	3.48 (0.25)	<0.001
CAR (0-30 mins)	0.50 (0.11)	<0.001
Early post-wake DCS (30 mins-4.5 hours)	-0.13 (0.01)	<0.001
Mid post-wake DCS (4.5 hours-15 hours)	-0.16 (0.00)	<0.001
Late post-wake DCS (after 15 hours)	-0.13 (0.00)	<0.001
Waking time	-0.04 (0.01)	<0.001
Average wake-day length (individual-level)	-0.03 (0.01)	0.078
Length of sleep the previous night		
6-8 hours	Ref	
<6 hours	-0.06 (0.01)	0.112
>8 hours	-0.04 (0.02)	0.042
Weekend vs. workday status		
Weekday	Ref	
Weekend	-0.04 (0.02)	<0.001
Random effects:	**Variance**	**SD**
Between persons SD		
(Intercept)	0.146	0.383
CAR (0-30 mins)	0.211	0.459
Early post-wake DCS (30 mins-4.5 hours)	0.009	0.095
Mid post-wake DCS (4.5 hours-15 hours)	0.003	0.050
Late post-wake DCS (after 15 hours)	0.002	0.046
Between days SD		
(Intercept)	0.000	0.000
Early post-wake DCS (30 mins-4.5 hours)	0.000	0.000
Between family SD		
(Intercept)	0.032	0.180
Residual SD	0.336	0.580
R^2	0.761	

†Adjusted for waking time on day of measurement, weekend vs. workday status, length of sleep the previous night, average wake-day length (individual-level).

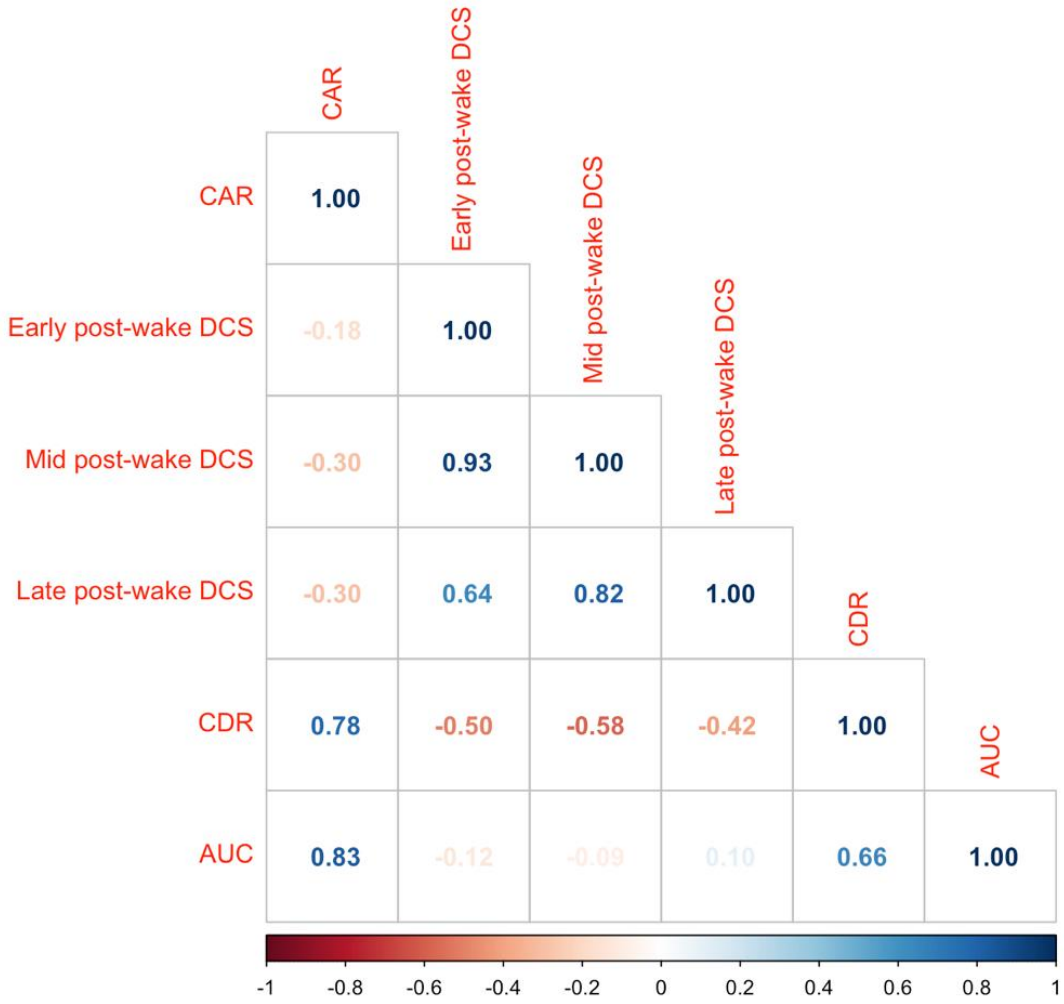
Supplementary Figure 2-1 Sample-based cortisol diurnal pattern



Supplementary Figure 2-2 Model-based cortisol diurnal pattern



Supplementary Figure 2-3 Correlation matrix of cortisol parameters



Supplementary Table 2-3 Principal Component Analysis of Cortisol Parameters

	Loadings		Variance explained by the factors
	Factor 1	**Factor 2**	
Early post-wake DCS	0.97		0.88
Mid post-wake DCS	1.00		1.00
Late post-wake DCS	0.80		0.67
CAR		1.00	1.00
CDR	-0.36	0.68	0.75
AUC		0.90	0.73

According to Kaiser's Rule, components with eigenvalues greater than 1 were retained. The eigenvalue for Dimension 1 is 3.41, for Dimension 2 is 1.87, for Dimension 3 is 0.46, for Dimension 4 is 0.19, for Dimension 5 is 0.04, and for Dimension 6 is 0.02. Therefore, two factors were retained.

Supplementary Table 2-4 Baseline characteristics of the analytic sample

Variable	Attrition (n=222) Mean (SD) / %	Analytic sample (n=1,246) Mean (SD) / %	P-value
Steroid inhaler			0.614
No	96.50%	97.00%	
Yes	3.50%	3.00%	
Oral steroid meds			0.903
No	97.60%	97.40%	
Yes	2.40%	2.60%	
Other hormonal meds			<0.001
No	96.50%	89%	
Yes	3.50%	11%	
Anti-depressant or anti-anxiety meds			0.277
No	88.10%	86.40%	
Yes	11.90%	13.60%	
Birth control pills			0.005
No	99.40%	97.50%	
Yes	0.60%	2.50%	
Income-to-needs scale	0.43 (0.70)	0.26 (0.59)	<0.001
Education	0.80 (0.55)	0.59 (0.56)	<0.001
Age	62.40 (14.60)	55.50 (11.30)	<0.001
Ethnicity			0.013
White	93.50%	95.80%	
Non-white	6.50%	4.20%	
Sex assigned at birth			0.694
Male	45.00%	44.10%	
Female	55.00%	55.90%	
Marital status			<0.001
Divorced/separated/widowed/never married	33.40%	24.50%	
Married	66.60%	75.50%	
Physical activity	27.40 (12.40)	29.40 (10.70)	<0.001
Smoking status			<0.001
Current smoker	15.40%	10.20%	
Ex-smoker	61.80%	60.60%	
Non-Smoker	22.80%	29.30%	
Drinking status			0.007
Moderate + Drinker	30.70%	31.50%	
Light Drinker	24.10%	29.30%	
Non-Drinker or Rarely Drink	45.20%	39.30%	
Multimorbidity			<0.001
No	32.90%	44.50%	

Yes	67.10%	55.50%	
Baseline chronic pain			<0.001
No	49.70%	64.30%	
Yes	50.30%	35.70%	
BMI	29.10 (6.11)	27.70 (5.46)	<0.001
Childhood emotional abuse			0.062
1 (Never)	35.30%	34.20%	
1.5	18.00%	14.20%	
2	23.90%	27.50%	
2.5	10.20%	12.10%	
3 (Most frequent)	12.70%	12.10%	
Childhood physical abuse			<0.001
1 (Never)	42.20%	43.00%	
1.5	13.70%	15.60%	
2	26.40%	25.40%	
2.5	5.30%	8.90%	
3 (Most frequent)	12.50%	7.10%	

Supplementary Table 2-5 Robustness checks for the associations between cortisol parameters and presence of chronic pain at MIDUS 3 among respondents who did not report chronic pain at baseline†

	Late post-wake DCS (after 15 hours)
No pain vs presence of chronic pain at MIDUS 3	**OR (95% CI)**
Main analysis†	**1.26 (1.03, 1.55)***
Multiple imputation for all	1.20 (0.99, 1.45)
Inverse probability of attrition weighting	**1.29 (1.02, 1.62)***
Bonferroni correction	1.26 (1.03, 1.55)
Excluding respondents with anxiety, depression in the past 12 months	**1.32 (1.04, 1.67)***
Excluding steroid inhaler, oral steroid, other hormonal, anti-depressant or anxiety, and birth control medication user	1.27 (0.99, 1.63)
Additionally controlling for daily stressor severity	1.14 (0.88, 1.47)

Statistical significance markers: * p<0.05; ** p<0.01; *** p<0.001

† Adjusted for age, race, sex assigned at birth, income-to-needs ratio, education, marital status, physical activity index, smoking and drinking status, multimorbidity, BMI, childhood experiences of parental emotional and physical abuse, and medication intakes (e.g., steroid inhalers, oral steroids, antidepressants, anti-anxiety medications, birth control pills, and other hormonal medications). A random intercept at the family level was included, to allow for correlations between individuals from the same family.

Note that cortisol parameters were standardized. An increase of one standard deviation in CAR indicates a steeper CAR, whereas an increase of one standard deviation in DCSs indicates flatter DCSs. One standard deviation increase in CDR indicates a wider CDR, while one standard deviation increase in AUC indicates a larger AUC.

Supplementary Table 2-6 Robustness checks for the associations between cortisol parameters and high interference pain at MIDUS 3 among respondents who did not report chronic pain at baseline†

	Early post-wake DCS (30 mins-4.5 hours)	Mid post-wake DCS (4.5 hours-15 hours)
No pain vs high interference pain at MIDUS 3	**OR (95% CI)**	**OR (95% CI)**
Main analysis‡	**1.85 (1.09, 3.16)***	**1.82 (1.09, 3.02)***
Multiple imputation for all	**1.40 (1.02, 1.92)***	**1.47 (1.08, 2.01)***
Inverse probability of attrition weighting	**2.88 (1.23, 6.74)***	**2.58 (1.17, 5.67)***
Bonferroni correction	1.85 (1.09, 3.16)	1.82 (1.09, 3.02)
Excluding respondents with anxiety, depression in the past 12 months	2.66 (0.99, 7.13)	**2.44 (1.32, 4.51)****
Excluding steroid inhaler, oral steroid, other hormonal, anti-depressant or anxiety, and birth control medication user	**2.59 (1.12, 5.61)***	**2.09 (1.03, 4.24)***
Additionally controlling for daily stressor severity	1.84 (0.93, 3.64)	**2.12 (1.04, 4.33)***

Statistical significance markers: * p<0.05; ** p<0.01; *** p<0.001

† Adjusted for age, race, sex assigned at birth, income-to-needs ratio, education, marital status, physical activity index, smoking and drinking status, multimorbidity, BMI, childhood experiences of parental emotional and physical abuse, and medication intakes (e.g., steroid inhalers, oral steroids, antidepressants, anti-anxiety medications, birth control pills, and other hormonal medications). A random intercept at the family level was included, to allow for correlations between individuals from the same family.

‡ The proportional odds assumption was violated for early and mid post-wake DCSs.

Note that cortisol parameters were standardized. An increase of one standard deviation in CAR indicates a steeper CAR, whereas an increase of one standard deviation in DCSs indicates flatter DCSs. One standard deviation increase in CDR indicates a wider CDR, while one standard deviation increase in AUC indicates a larger AUC.

Supplementary Table 2-7 Robustness checks for the associations between cortisol parameters and pain at 3 or more regions at MIDUS 3 among respondents who did not report chronic pain at baseline†

No pain vs chronic pain with 3 or more sites at MIDUS 3	Early post-wake DCS (30 mins-4.5 hours)	Mid post-wake DCS (4.5 hours-15 hours)	Late post-wake DCS (after 15 hours)
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Main analysis‡	**2.16 (1.41, 3.32)*** **	**1.93 (1.28, 2.90)** **	**1.58 (1.03, 2.43)***
Multiple imputation for all	**1.52 (1.10, 2.10)***	**1.52 (1.11, 2.10)***	1.39 (0.98, 1.97)
Inverse probability of attrition weighting	**2.26 (1.37, 3.71)** **	**2.04 (1.25, 3.32)** **	1.62 (0.97, 2.71)
Bonferroni correction	**2.16 (1.41, 3.32)***	**1.93 (1.28, 2.90)***	1.58 (1.03, 2.43)
Excluding respondents with anxiety, depression in the past 12 months	**2.36 (1.40, 3.97)** **	**2.20 (1.33, 3.64)** **	1.52 (0.91, 2.56)
Excluding steroid inhaler, oral steroid, other hormonal, anti-depressant or anxiety, and birth control medication user	**2.14 (1.28, 3.59)** **	**1.80 (1.13, 2.86)***	1.41 (0.87, 2.30)
Additionally controlling for daily stressor severity	**2.07 (1.20, 3.57)***	**1.90 (1.11, 3.23)** **	1.50 (0.85, 2.62)

Statistical significance markers: * p<0.05; ** p<0.01; *** p<0.001

† Adjusted for age, race, sex assigned at birth, income-to-needs ratio, education, marital status, physical activity index, smoking and drinking status, multimorbidity, BMI, childhood experiences of parental emotional and physical abuse, and medication intakes (e.g., steroid inhalers, oral steroids, antidepressants, anti-anxiety medications, birth control pills, and other hormonal medications). A random intercept at the family level was included, to allow for correlations between individuals from the same family.

‡ The proportional odds assumption was violated for early and mid post-wake DCSs, and CDR. The assumption was not violated for late post-wake DCS, but it was not significant in the ordinal logistic regression.

Note that cortisol parameters were standardized. An increase of one standard deviation in CAR indicates a steeper CAR, whereas an increase of one standard deviation in DCSs indicates flatter DCSs. One standard deviation increase in CDR indicates a wider CDR, while one standard deviation increase in AUC indicates a larger AUC.

Supplementary Table 2-8 Robustness checks for associations of cortisol parameters with pain interference (low vs. high) and pain multisite status (chronic non-multisite vs. chronic multisite) at MIDUS 3[†]

	No baseline chronic pain			Adjusting for chronic pain at baseline		
	Low interference pain vs high interference pain at MIDUS 3	Chronic pain with 1-2 sites vs Chronic pain with 3 or more sites at MIDUS 3		Low interference pain vs high interference pain at MIDUS 3	Chronic pain with 1-2 sites vs Chronic pain with 3 or more sites at MIDUS 3	
	Early post-wake DCS (30 mins-4.5 hours)	Early post-wake DCS (30 mins-4.5 hours)	Mid post-wake DCS (4.5 hours-15 hours)	Early post-wake DCS (30 mins-4.5 hours)	Early post-wake DCS (30 mins-4.5 hours)	AUC
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Main analysis[‡]	**2.60 (1.44, 4.70)****	**2.73 (1.49, 4.99)****	**2.21 (1.24, 3.91)****	**1.37 (1.04, 1.81)***	**1.33 (1.01, 1.75)***	**0.76 (0.58, 0.98)***
Multiple imputation for all	**1.68 (1.12, 2.53)***	**2.02 (1.24, 3.28)****	**1.92 (1.20, 3.06)****	1.17 (0.94, 1.45)	1.12 (0.87, 1.43)	**0.78 (0.61, 1.00)***
Inverse probability of attrition weighting	**4.36 (1.32, 14.44)***	**5.84 (1.69, 20.19)****	5.76 (0.96, 34.41)	**2.10 (1.18, 3.74)***	1.77 (0.98, 3.21)	**0.53 (0.29, 0.96)***
Bonferroni correction	**2.60 (1.44, 4.70)***	**2.73 (1.49, 4.99)***	2.21 (1.24, 3.91)	1.37 (1.04, 1.81)	1.33 (1.01, 1.75)	0.76 (0.58, 0.98)
Excluding respondents with anxiety, depression in the past 12 months	4.37 (0.95, 20.15)	**3.08 (1.46, 6.50)****	**2.67 (1.30, 5.47)****	**1.40 (1.01, 1.96)***	**1.51 (1.08, 2.11)***	**0.65 (0.47, 0.89)****
Excluding steroid inhaler, oral steroid, other hormonal, anti-depressant or anxiety, and birth control medication user	3.02 (0.15, 61.85)	**2.62 (1.27, 5.42)****	**2.12 (1.06, 4.21)***	**1.47 (1.03, 2.10)***	**1.45 (1.00, 2.09)***	0.88 (0.63, 1.24)
Additionally controlling for daily stressor severity	2.70 (0.87, 8.32)	**2.66 (1.15, 6.15)***	**2.74 (1.10, 6.86)***	1.45 (0.91, 2.29)	1.32 (0.95, 1.84)	0.89 (0.67, 1.19)

Statistical significance markers: * p<0.05; ** p<0.01; *** p<0.001

† Adjusted for age, race, sex assigned at birth, income-to-needs ratio, education, marital status, physical activity index, smoking and drinking status, multimorbidity, BMI, childhood experiences of parental emotional and physical abuse, and medication intakes (e.g., steroid inhalers, oral steroids, antidepressants, anti-anxiety medications, birth control pills, and other hormonal medications). A random intercept at the family level was included, to allow for correlations between individuals from the same family.

‡ The proportional odds assumption was violated for early and mid post-wake DCSs.

Note that cortisol parameters were standardized. An increase of one standard deviation in DCSs indicates flatter DCSs.

Supplementary Table 2-9 Interacting chronic pain at baseline and diurnal cortisol rhythms as robustness checks for the subgroup analyses

		Interaction (cortisol * pain at baseline)		
No pain vs presence of chronic pain at MIDUS 3	**N**	**Cortisol * no pain**	**Cortisol * pain**	**P-value for interaction**
CAR (0-30 mins)	920	0.92 (0.75, 1.14)	1.00 (0.81, 1.23)	0.585
Early post-wake DCS (30 mins-4.5 hours)	920	0.98 (0.81, 1.19)	1.12 (0.88, 1.42)	0.411
Mid post-wake DCS (4.5 hours-15 hours)	920	1.04 (0.85, 1.26)	1.14 (0.89, 1.45)	0.565
Late post-wake DCS (after 15 hours)	920	1.21 (0.99, 1.48)	1.06 (0.83, 1.37)	0.423
CDR	920	0.91 (0.74, 1.12)	0.87 (0.69, 1.10)	0.779
AUC	920	1.08 (0.87, 1.34)	0.98 (0.79, 1.21)	0.508
No pain vs low interference pain at MIDUS 3	**N**	**Cortisol * no pain**	**Cortisol * pain**	**P-value for interaction**
CAR (0-30 mins)	792	1.12 (0.89, 1.40)	0.98 (0.77, 1.24)	0.336
Early post-wake DCS (30 mins-4.5 hours)	792	1.20 (0.96, 1.50)	0.91 (0.69, 1.21)	0.103
Mid post-wake DCS (4.5 hours-15 hours)	792	1.12 (0.90, 1.39)	0.89 (0.68, 1.18)	0.326
Late post-wake DCS (after 15 hours)	792	0.86 (0.69, 1.07)	0.93 (0.70, 1.23)	0.170
CDR	792	1.05 (0.84, 1.31)	1.13 (0.88, 1.46)	0.666
AUC	792	0.91 (0.72, 1.16)	1.00 (0.78, 1.27)	0.605
No pain vs high interference pain at MIDUS 3	**N**	**Cortisol * no pain**	**Cortisol * pain**	**P-value for interaction**
CAR (0-30 mins)	680	1.03 (0.70, 1.52)	0.92 (0.66, 1.29)	0.884
Early post-wake DCS (30 mins-4.5 hours)	680	**1.59 (1.08, 2.34)***	1.06 (0.75, 1.48)	0.020
Mid post-wake DCS (4.5 hours-15 hours)	680	**1.55 (1.07, 2.26)***	1.02 (0.72, 1.44)	0.022
Late post-wake DCS (after 15 hours)	680	1.35 (0.91, 2.00)	0.89 (0.62, 1.28)	0.130
CDR	680	0.84 (0.59, 1.20)	0.78 (0.54, 1.11)	0.762
AUC	680	1.07 (0.72, 1.60)	0.85 (0.60, 1.20)	0.376

Low interference pain vs high interference pain at MIDUS 3	N	Cortisol * no pain	Cortisol * pain	P-value for interaction
CAR (0-30 mins)	328	1.18 (0.7, 1.97)	0.87 (0.66, 1.16)	0.312
Early post-wake DCS (30 mins-4.5 hours)	328	**2.15 (1.35, 3.42)***	1.04 (0.74, 1.46)	0.013
Mid post-wake DCS (4.5 hours-15 hours)	328	**2.06 (1.30, 3.27)****	0.95 (0.68, 1.32)	0.008
Late post-wake DCS (after 15 hours)	328	1.23 (0.81, 1.85)	0.82 (0.59, 1.16)	0.145
CDR	328	0.82 (0.51, 1.33)	0.91 (0.68, 1.22)	0.716
AUC	328	0.96 (0.58, 1.57)	0.82 (0.61, 1.11)	0.606
No pain vs chronic pain with 1-2 sites at MIDUS 3	**N**	**Cortisol * no pain**	**Cortisol * pain**	**P-value for interaction**
CAR (0-30 mins)	784	1.12 (0.89, 1.40)	0.86 (0.65, 1.14)	0.331
Early post-wake DCS (30 mins-4.5 hours)	784	1.19 (0.96, 1.47)	0.92 (0.69, 1.23)	0.116
Mid post-wake DCS (4.5 hours-15 hours)	784	1.08 (0.88, 1.34)	0.91 (0.67, 1.22)	0.463
Late post-wake DCS (after 15 hours)	784	0.84 (0.68, 1.05)	0.93 (0.70, 1.24)	0.125
CDR	784	1.09 (0.88, 1.36)	1.00 (0.75, 1.34)	0.641
AUC	784	0.90 (0.71, 1.14)	0.86 (0.65, 1.13)	0.807
No pain vs chronic pain with 3 or more sites at MIDUS 3	**N**	**Cortisol * no pain**	**Cortisol * pain**	**P-value for interaction**
CAR (0-30 mins)	703	0.98 (0.68, 1.41)	0.83 (0.63, 1.10)	0.914
Early post-wake DCS (30 mins-4.5 hours)	703	**1.74 (1.18, 2.55)*****	1.02 (0.75, 1.38)	0.005
Mid post-wake DCS (4.5 hours-15 hours)	703	**1.56 (1.08, 2.24)***	1.03 (0.76, 1.40)	0.018
Late post-wake DCS (after 15 hours)	703	1.33 (0.91, 1.93)	0.97 (0.70, 1.35)	0.140
CDR	703	0.89 (0.63, 1.26)	0.76 (0.56, 1.01)	0.463
AUC	703	0.95 (0.66, 1.36)	0.76 (0.56, 1.02)	0.330
Chronic pain with 1-2 sites vs Chronic pain with 3 or more sites at MIDUS 3	**N**	**Cortisol * no pain**	**Cortisol * pain**	**P-value for interaction**
CAR (0-30 mins)	343	1.33 (0.79, 2.23)	0.77 (0.57, 1.04)	0.070
Early post-wake DCS (30 mins-4.5 hours)	343	**2.21 (1.37, 3.56)****	1.00 (0.72, 1.40)	0.008

Mid post-wake DCS (4.5 hours-15 hours)	343	**1.77 (1.13, 2.78)***	0.98 (0.72, 1.35)	0.038
Late post-wake DCS (after 15 hours)	343	1.10 (0.73, 1.64)	0.92 (0.66, 1.27)	0.504
CDR	343	1.05 (0.64, 1.71)	0.79 (0.59, 1.06)	0.329
AUC	343	0.92 (0.56, 1.52)	0.70 (0.51, 0.96)	0.350

Statistical significance markers: * p<0.05; ** p<0.01; *** p <0.001

† Adjusted for age, race, sex assigned at birth, income-to-needs ratio, education, marital status, physical activity index, smoking and drinking status, multimorbidity, BMI, childhood experiences of parental emotional and physical abuse, and medication intakes (e.g., steroid inhalers, oral steroids, antidepressants, anti-anxiety medications, birth control pills, and other hormonal medications). A random intercept at the family level was included, to allow for correlations between individuals from the same family.

Note that an increase of one standard deviation in CAR indicates a steeper CAR, whereas an increase of one standard deviation in DCSs indicates flatter DCSs.

Supplementary Table 2-10 Supplementary analysis of the cross-sectional associations between cortisol parameters and 3 or more regions at baseline†

Pain status at baseline (No pain VS.)	Chronic pain with 3 or more sites
Cortisol parameters	**OR (95% CI)**
CAR (0-30 mins)	**0.80 (0.65, 0.99)***
Early post-wake DCS (30 mins-4.5 hours)	0.92 (0.74, 1.16)
Mid post-wake DCS (4.5 hours-15 hours)	0.92 (0.73, 1.16)
Late post-wake DCS (after 15 hours)	0.95 (0.75, 1.20)
CDR	0.85 (0.69, 1.04)
AUC	**0.77 (0.62, 0.96)***

Statistical significance markers: * p<0.05; ** p<0.01; *** p<0.001

† Adjusted for age, race, sex assigned at birth, income-to-needs ratio, education, marital status, physical activity index, smoking and drinking status, multimorbidity, BMI, childhood experiences of parental emotional and physical abuse, and medication intakes (e.g., steroid inhalers, oral steroids, antidepressants, anti-anxiety medications, birth control pills, and other hormonal medications). A random intercept at the family level was included, to allow for correlations between individuals from the same family.
Note that cortisol parameters were standardized. An increase of one standard deviation in CAR indicates a steeper CAR, whereas an increase of one standard deviation in DCSs indicates flatter DCSs. One standard deviation increase in CDR indicates a wider CDR, while one standard deviation increase in AUC indicates a larger AUC.

Supplementary Table 2-11 Characteristics of non-standardized baseline cortisol parameters by chronic pain interference and by widespreadness of pain in follow-up period, stratified by chronic pain outcomes at baseline

	Subgroup A.1: respondents with low interference chronic pain at baseline			Subgroup A.2: respondents with chronic pain with 1-2 sites at baseline		
Pain status at follow-up	**No Pain**	**Low interference pain**	**High interference pain**	**No Pain**	**Low interference pain**	**High interference pain**
Cortisol parameters	*N=118*	*N=111*	*N=43*	*N=111*	*N=75*	*N=41*
CAR (0-30 mins)	0.49 (0.34)	0.51 (0.41)	0.49 (0.34)	0.50 (0.33)	0.48 (0.45)	0.53 (0.25)
Early post-wake DCS (30 mins-4.5 hours)	-0.13 (0.05)	-0.13 (0.04)	-0.13 (0.05)	-0.13 (0.05)	-0.13 (0.05)	-0.13 (0.05)
Mid post-wake DCS (4.5 hours-15 hours)	-0.16 (0.04)	-0.15 (0.03)	-0.15 (0.04)	-0.16 (0.04)	-0.15 (0.03)	-0.15 (0.03)
Late post-wake DCS (after 15 hours)	-0.13 (0.04)	-0.13 (0.03)	-0.13 (0.03)	-0.13 (0.04)	-0.13 (0.03)	-0.13 (0.03)
CDR	2.46 (0.44)	2.40 (0.59)	2.37 (0.61)	2.47 (0.46)	2.35 (0.64)	2.40 (0.48)
AUC	4.83 (0.38)	4.84 (0.43)	4.82 (0.43)	4.85 (0.35)	4.84 (0.45)	4.85 (0.28)
Pain status at follow-up	**No Pain**	**Chronic pain with 1-2 sites**	**Chronic pain with 3 or more sites**	**No Pain**	**Chronic pain with 1-2 sites**	**Chronic pain with 3 or more sites**
Cortisol parameters	*N=118*	*N=94*	*N=75*	*N=111*	*N=86*	*N=41*
CAR (0-30 mins)	0.49 (0.34)	0.55 (0.33)	0.46 (0.42)	0.50 (0.33)	0.51 (0.36)	0.49 (0.43)
Early post-wake DCS (30 mins-4.5 hours)	-0.13 (0.05)	-0.13 (0.04)	-0.13 (0.05)	-0.13 (0.05)	-0.13 (0.05)	-0.13 (0.05)

Mid post-wake DCS (4.5 hours-15 hours)	-0.16 (0.04)	-0.15 (0.03)	-0.15 (0.03)	-0.16 (0.04)	-0.15 (0.03)	-0.15 (0.04)
Late post-wake DCS (after 15 hours)	-0.13 (0.04)	-0.13 (0.03)	-0.13 (0.03)	-0.13 (0.04)	-0.13 (0.03)	-0.13 (0.03)
CDR	2.46 (0.44)	2.45 (0.51)	2.34 (0.67)	2.47 (0.46)	2.40 (0.57)	2.33 (0.60)
AUC	4.83 (0.38)	4.89 (0.37)	4.78 (0.46)	4.85 (0.35)	4.85 (0.38)	4.84 (0.41)

	Subgroup B.1: respondents with high interference chronic pain at baseline			**Subgroup B.2: respondents with chronic pain with 3 or more sites at baseline**		
Pain status at follow-up	**No Pain**	**Low interference pain**	**High interference pain**	**No Pain**	**Low interference pain**	**High interference pain**
Cortisol parameters	*N=24*	*N=19*	*N=55*	*N=34*	*N=58*	*N=58*
CAR (0-30 mins)	0.36 (0.45)	0.47 (0.31)	0.35 (0.45)	0.35 (0.45)	0.53 (0.29)*/**	0.32 (0.47)
Early post-wake DCS (30 mins-4.5 hours)	-0.13 (0.05)	-0.14 (0.08)	-0.14 (0.06)	-0.13 (0.05)	-0.14 (0.05)	-0.14 (0.06)
Mid post-wake DCS (4.5 hours-15 hours)	-0.15 (0.04)	-0.16 (0.06)	-0.16 (0.05)	-0.16 (0.04)	-0.16 (0.04)	-0.16 (0.05)
Late post-wake DCS (after 15 hours)	-0.12 (0.03)	-0.14 (0.06)	-0.13 (0.04)	-0.14 (0.04)	-0.14 (0.04)	-0.13 (0.04)
CDR	2.36 (0.70)	2.26 (0.75)	2.19 (0.66)	2.32 (0.56)	2.42 (0.58)/*	2.16 (0.72)
AUC	4.73 (0.40)	4.76 (0.27)	4.68 (0.43)	4.64 (0.46)	4.82 (0.34)	4.66 (0.50)

Pain status at follow-up	**No Pain**	**Chronic pain with 1-2 sites**	**Chronic pain with 3 or more sites**	**No Pain**	**Chronic pain with 1-2 sites**	**Chronic pain with 3 or more sites**
Cortisol parameters	*N=24*	*N=25*	*N=51*	*N=34*	*N=36*	*N=86*
CAR (0-30 mins)	0.36 (0.45)	0.43 (0.35)	0.36 (0.44)	0.35 (0.45)	0.56 (0.29)*/**	0.38 (0.42)
Early post-wake DCS (30 mins-4.5 hours)	-0.13 (0.05)	-0.13 (0.06)	-0.14 (0.07)	-0.13 (0.05)	-0.14 (0.04)	-0.14 (0.06)

Mid post-wake DCS (4.5 hours-15 hours)	-0.15 (0.04)	-0.16 (0.05)	-0.16 (0.05)	-0.16 (0.04)	-0.16 (0.04)	-0.16 (0.04)
Late post-wake DCS (after 15 hours)	-0.12 (0.03)	-0.13 (0.06)	-0.13 (0.04)	-0.14 (0.04)	-0.13 (0.04)	-0.13 (0.04)
CDR	2.36 (0.70)	2.30 (0.63)	2.18 (0.69)	2.32 (0.56)	2.48 (0.44)/*	2.25 (0.72)
AUC	4.73 (0.40)	4.77 (0.31)	4.67 (0.42)	4.64 (0.46)	4.92 (0.30)*/**	4.68 (0.45)

Statistical significance markers: * p<0.05; ** p<0.01; *** p<0.001 (ANOVA; before the '/', columns "No pain" and "Low interference pain" or "Chronic pain with 1-2 sites" were compared; after the '/', the columns "Low interference pain" or "Chronic pain with 1-2 sites" and "High interference pain" or "Chronic pain with 3 or more sites" were compared)

Supplementary Materials for the Biomarker Project Stream Sample in the Mediation Analysis Chapter

Supplementary Table 3-1 High-risk values for AL biomarkers

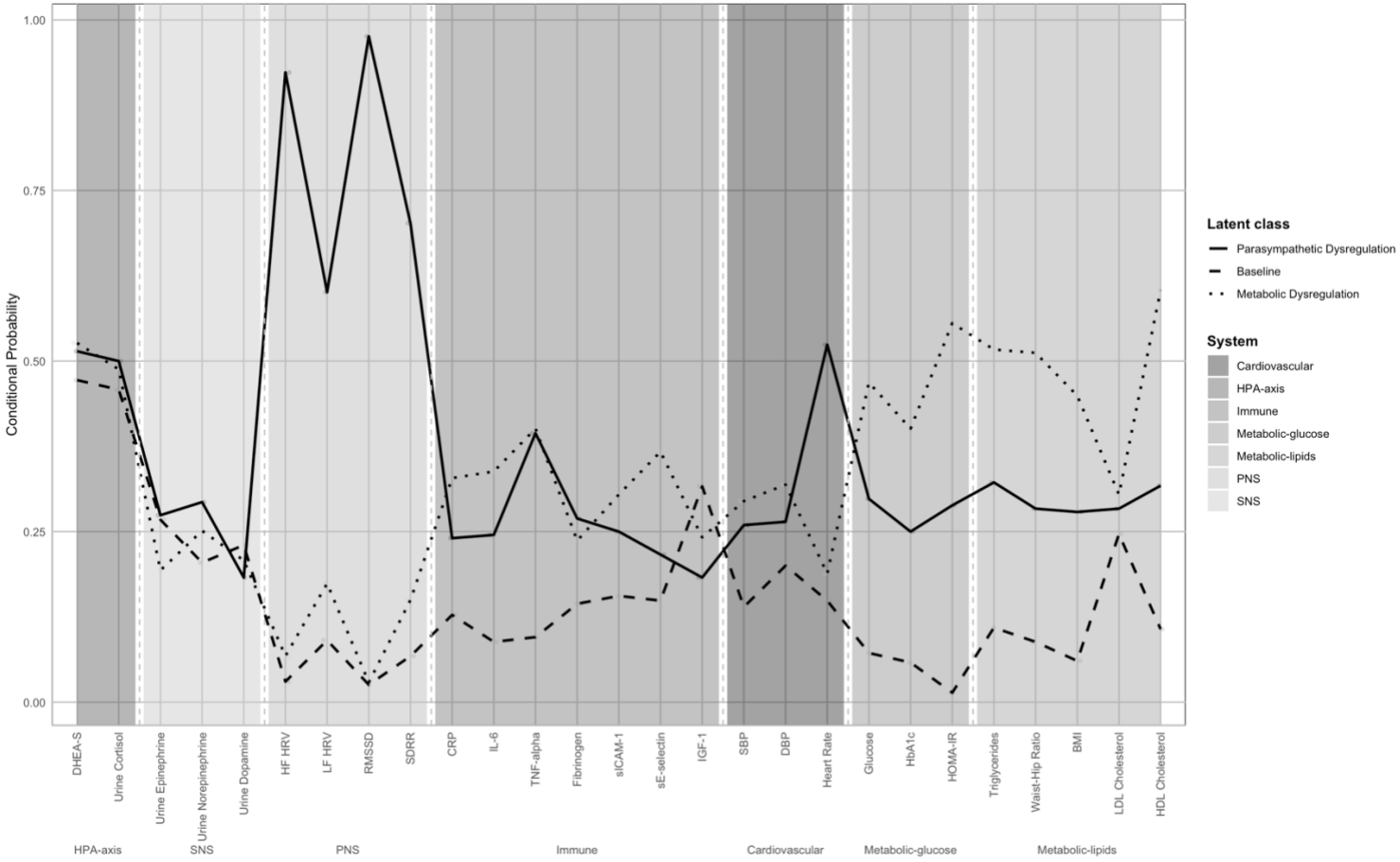
Biomarker	Simple High Risk Quartile
Hypothalamic Pituitary Adrenal Axis	
DHEA-s (ug/dL)	≤54 or ≥146
Urine cortisol (µg/g)	≤7.3 or ≥21
Sympathetic Nervous System	
Urine epinephrine (µg/g)	≥2.5
Urine norepinephrine (µg/g)	≥33
Urine Dopamine (µg/g)	≥175
Parasympathetic Nervous System	
High-frequency HRV	≤54
Low-frequency HRV	≤111
RMSSD	≤12
SDRR (m s)	≤24
Cardiovascular	
Resting heart rate (bpm)	≥80
Resting SBP (mmHg)	≥142
Resting DBP (mmHg)	≥82
Metabolic-glucose	

Fasting glucose	≥104
Hemoglobin A1c%	≥6.1
HOMA-IR	≥4
Metabolic-lipids	
Triglycerides (mg/dL)	≥159
WHR	≥0.96
BMI	≥32
LDL cholesterol (mg/dL)	≥129
HDL cholesterol (mg/dL)	≤42
Inflammation	
CRP (mg/L)	≥3.1
IL6 (pg/mL)	≥1.1
TNF-α (pg/mL)	≥2.5
Fibrinogen (mg/dL)	≥386
E-Selectin (ng/mL)	≥326
ICAM-1 (ng/mL)	≥50
Blood Fasting IGF1 (Insulin-like Growth Factor 1) ng/mL)	≥159

Supplementary Table 3-2 Fit statistics for latent class analysis of AL

Model	LogLikelihood	AIC	BIC	Gsq	SABIC	Entropy	%						
1	-12602.86	25259.72	25387.68	13975.38	25205.72	NaN	1.000						
2	-11963.06	24036.11	24296.77	12695.77	23926.11	85.1%	0.626	0.374					
3	-11688.87	23543.74	23937.10	12147.40	23377.74	85.2%	0.246	0.497	0.257				
4	-11571.45	23364.90	23890.96	11912.56	23142.90	84.4%	0.462	0.226	0.179	0.132			
5	-11467.10	23212.20	23870.96	11703.86	22934.20	84.1%	0.157	0.134	0.099	0.429	0.181		
6	-11386.33	23106.66	23898.13	11542.32	22772.66	81.9%	0.265	0.102	0.202	0.180	0.128	0.123	
7	-11319.70	23029.41	23953.58	11409.07	22639.41	NaN	0.255	0.137	0.106	0.050	0.176	0.188	0.088

Supplementary Figure 3-1 Identified phenotypes of AL



Supplementary Table 3-3 Fit indices of test for measurement invariance

Model	Degree of freedom	AIC	BIC	Chisq	Chisq diff	RMSEA diff	Df diff	Pr(>Chisq)
Configural invariance model	65	18759	19157	158.22				
Metric invariance model	70	18762	19137	171.17	12.95	0.047255	5	0.024
Scalar invariance model	75	18819	19171	238.44	67.27	0.132255	5	0.000
Strict invariance model	81	18924	19248	354.72	116.28	0.160673	6	0.000

Supplementary Table 3-4 Analytic sample characteristics of Covariates, stratified by CP conditions

Pain interference	No pain			Low interference pain			High interference pain			
Variable	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**Test**
Childhood covariates										
Live with biological parents until 16	548			208			113			X2=5.677
No	99	18%		46	22%		31	27%		
Yes	449	82%		162	78%		82	73%		
Parental emotional abuse	509	2.5	1.3	103	3	1.5	193	2.7	1.4	F=5.067***
Parental physical abuse	512	2.2	1.3	105	2.6	1.4	196	2.3	1.3	F=6.541***
Sociodemographics - time invariant										
Sex	548			208			113			X2=9.516***
Male	261	48%		91	44%		36	32%		
Female	287	52%		117	56%		77	68%		
Ethnicity	540			204			109			X2=0.037
White	507	94%		192	94%		102	94%		
non-White	33	6%		12	6%		7	6%		
MIDUS 1 covariates										
Age in MIDUS 1	548	45	11	208	46	11	113	44	10	F=1.235
Marital status in MIDUS 1	548			208			113			X2=0.739
Not married	160	29%		55	26%		30	27%		
Married	388	71%		153	74%		83	73%		
Multimorbidity in MIDUS 1	540			204			109			X2=35.997***
No	293	54%		95	47%		25	23%		
Yes	247	46%		109	53%		84	77%		

Marital status in MIDUS 2	547			208			113			X2=1.835
Not married	151	28%		51	25%		25	22%		
Married	396	72%		157	75%		88	78%		
MIDUS 2 covariates										
Age in MIDUS 2	548	54	11	208	55	11	113	53	10	F=1.099
Multimorbidity in MIDUS 2	548			208			113			X2=44.861***
No	295	54%		79	38%		25	22%		
Yes	253	46%		129	62%		88	78%		
Chronic pain in MIDUS 2	540			205			113			X2=110.082***
No	421	78%		110	54%		35	31%		
Yes	119	22%		95	46%		78	69%		
Health insurance in MIDUS 2	543			208			112			X2=5.431*
Yes	516	95%		195	94%		100	89%		
No	27	5%		13	6%		12	11%		
Physical activity in MIDUS 2	520	30	10	193	30	10	102	30	11	F=0.004
Smoking status in MIDUS 2	548			208			113			X2=5.99
Current smoker	50	9%		20	10%		18	16%		
Ex-smoker	331	60%		130	62%		68	60%		
non-Smoker	167	30%		58	28%		27	24%		
Drinking status in MIDUS 2	548			208			113			X2=7.862*
Moderate + Drinker	180	33%		83	40%		34	30%		
Light Drinker	172	31%		55	26%		28	25%		
non-Drinker or Rarley Drink	196	36%		70	34%		51	45%		
Medications										
Antihyperlipidemic agents	547			113			208			X2=0.968
No	380	69%		83	73%		142	68%		
Yes	167	31%		30	27%		66	32%		

Beta adrenergic blocking agents	547			113			208			X2=7.943*
No	489	89%		92	81%		174	84%		
Yes	58	11%		21	19%		34	16%		
Antihypertensive combinations	547			113			208			X2=0.796
No	505	92%		103	91%		188	90%		
Yes	42	8%		10	9%		20	10%		
Analgesics	547			113			208			X2=22.966***
No	287	52%		35	31%		82	39%		
Yes	260	48%		78	69%		126	61%		
Anxiolytics sedatives and hypnotics	547			113			208			X2=18.987***
No	493	90%		85	75%		179	86%		
Yes	54	10%		28	25%		29	14%		
Antidiabetic agents	547			113			208			X2=3.214
No	507	93%		99	88%		191	92%		
Yes	40	7%		14	12%		17	8%		
Sex hormones	547			113			208			X2=1.851
No	490	90%		100	88%		179	86%		
Yes	57	10%		13	12%		29	14%		
Thyroid hormones	547			113			208			X2=1.871
No	493	90%		104	92%		182	88%		
Yes	54	10%		9	8%		26	12%		
Antidepressants	547			113			208			X2=18.813***
No	481	88%		82	73%		182	88%		
Yes	66	12%		31	27%		26	12%		
Pain locations	**0**			**1-2**			**3+**			
Variable	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**Test**
Live with biological parents until 16	548			208			127			X2=4.385

No	99	18%		49	24%		31	24%		
Yes	449	82%		159	76%		96	76%		
Parental emotional abuse	509	2.5	1.3	193	2.7	1.3	115	2.8	1.5	F=3.482**
Parental physical abuse	512	2.2	1.3	197	2.3	1.3	117	2.6	1.4	F=6.488***
Sex	548			208			127			X2=19.124***
Male	261	48%		99	48%		34	27%		
Female	287	52%		109	52%		93	73%		
Ethnicity	540			203			124			X2=0.454
White	507	94%		192	95%		115	93%		
non-White	33	6%		11	5%		9	7%		
Age in MIDUS 1	548	45	11	208	45	11	127	47	11	F=2.054
Marital status in MIDUS 1	548			208			127			X2=1.714
Not married	160	29%		51	25%		37	29%		
Married	388	71%		157	75%		90	71%		
Multimorbidity in MIDUS 1	540			203			124			X2=27.731***
No	293	54%		89	44%		36	29%		
Yes	247	46%		114	56%		88	71%		
Marital status in MIDUS 2	547			208			127			X2=2.62
Not married	151	28%		46	22%		36	28%		
Married	396	72%		162	78%		91	72%		
Age in MIDUS 2	548	54	11	208	54	11	127	56	11	F=2.192
Multimorbidity in MIDUS 2	548			208			127			X2=42.763***
No	295	54%		79	38%		31	24%		
Yes	253	46%		129	62%		96	76%		

Chronic pain in MIDUS 2	540			204			127			X2=107.868***
No	421	78%		108	53%		43	34%		
Yes	119	22%		96	47%		84	66%		
Health insurance in MIDUS 2	543			207			127			X2=15.78***
Yes	516	95%		197	95%		109	86%		
No	27	5%		10	5%		18	14%		
Physical activity in MIDUS 2	520	30	10	190	31	10	113	29	11	F=1.881
Smoking status in MIDUS 2	548			208			127			X2=12.558**
Current smoker	50	9%		17	8%		23	18%		
Ex-smoker	331	60%		132	63%		77	61%		
non-Smoker	167	30%		59	28%		27	21%		
Drinking status in MIDUS 2	548			208			127			X2=3.941
Moderate + Drinker	180	33%		73	35%		47	37%		
Light Drinker	172	31%		58	28%		29	23%		
non-Drinker or Rarley Drink	196	36%		77	37%		51	40%		
Antihyperlipidemic agents	547			208			127			X2=0.059
No	380	69%		145	70%		87	69%		
Yes	167	31%		63	30%		40	31%		
Beta adrenergic blocking agents	547			208			127			X2=8.172**
No	489	89%		175	84%		103	81%		
Yes	58	11%		33	16%		24	19%		
Antihypertensive combinations	547			208			127			X2=3.693
No	505	92%		193	93%		111	87%		

Yes	42	8%	15	7%	16	13%	
Analgesics	547		208		127		X2=23.791***
No	287	52%	78	38%	42	33%	
Yes	260	48%	130	62%	85	67%	
Anxiolytics sedatives and hypnotics	547		208		127		X2=13.251***
No	493	90%	177	85%	100	79%	
Yes	54	10%	31	15%	27	21%	
Antidiabetic agents	547		208		127		X2=1.607
No	507	93%	187	90%	116	91%	
Yes	40	7%	21	10%	11	9%	
Sex hormones	547		208		127		X2=1.043
No	490	90%	181	87%	112	88%	
Yes	57	10%	27	13%	15	12%	
Thyroid hormones	547		208		127		X2=0.086
No	493	90%	186	89%	114	90%	
Yes	54	10%	22	11%	13	10%	
Antidepressants	547		208		127		X2=8.198**
No	481	88%	173	83%	100	79%	
Yes	66	12%	35	17%	27	21%	

Statistical significance markers: * p<0.05; ** p<0.01; *** p<0.001

Supplementary Table 3-5 Baseline sample characteristics

	Attrtition			Retention			
Variables in MIDUS 1	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**Test**
Sex	6161			945			X2=6.68***
Male	3020	49%		420	44%		
Female	3141	51%		525	56%		
Ethnicity	5331			923			X2=15.757***
White	4781	90%		867	94%		
non-White	550	10%		56	6%		
Age	6104	47	13	945	45	11	F=8.056***
Marital status in MIDUS 1	5353			831			X2=19.132***
Married	3988	75%		678	82%		
Not married	1365	25%		153	18%		
Parental emotional abuse	4847	2.6	1.4	868	2.6	1.4	F=0.062
Parental physical abuse	4921	2.4	1.3	878	2.3	1.3	F=3.647*
Live with biological parents until 16	6158			945			X2=2.452
No	1402	23%		193	20%		
Yes	4756	77%		752	80%		
Multimorbidity	5386			922			X2=3.696*
<2	2395	44%		442	48%		
2+	2991	56%		480	52%		

Fathers education	5227		874		X2=10.87***
less than high school	2123	41%	308	35%	
high school/GED/some college	2186	42%	383	44%	
bachelor's degree or more	918	18%	183	21%	
Mother education	5698		920		X2=29.904***
less than high school	1994	35%	246	27%	
high school/GED/some college	3066	54%	533	58%	
bachelor's degree or more	638	11%	141	15%	
Financial level growing up	5365		922		X2=13.704**
A lot better off	189	4%	23	2%	
Somewhat better off	631	12%	120	13%	
A little better off	709	13%	148	16%	
Same as average family	2287	43%	362	39%	
A little worse off	941	18%	176	19%	
Somewhat worse off	421	8%	70	8%	
A lot worse off	187	3%	23	2%	
Father's occupation	5387		870		X2=30.695***
Managerial And Professional Specialty Occupations	1298	24%	258	30%	
Technical, Sales, And Administrative Support Occupations	765	14%	146	17%	
Service Occupations	250	5%	35	4%	
Farming, Forestry, And Fishing Occupations	681	13%	123	14%	
Precision Production, Craft, And Repair Occupations	1292	24%	157	18%	

Operators, Fabricators, And Laborers	981	18%		130	15%		
Experienced Unemployed Not Classified By Occupations	120	2%		21	2%		
Rate current financial situation	5317	6.1	2.2	914	6.3	2.2	F=3.89**
Money to meet needs	5331			921			X2=21.442***
More than enough money	825	15%		192	21%		
Just enough money	3019	57%		519	56%		
Not enough money	1487	28%		210	23%		
How difficult to pay monthly bills	5328			921			X2=9.011**
Not at all difficult	1455	27%		288	31%		
Not very difficult	2016	38%		351	38%		
Somewhat difficult	1540	29%		229	25%		
Very difficult	317	6%		53	6%		
Education	6151			944			X2=121.443***
less than high school	647	11%		34	4%		
high school/GED/some college	3745	61%		488	52%		
bachelor's degree or more	1759	29%		422	45%		
Income-to-needs ratio	5199			911			X2=56.353***
Affluent	3152	61%		666	73%		
Adequate-income	1207	23%		164	18%		
Low-income	447	9%		47	5%		
Poor	128	2%		12	1%		
Extreme poverty	265	5%		22	2%		

Occupation	5902		919		X2=54.144***
Managerial And Professional Specialty Occupations	2057	35%	422	46%	
Technical, Sales, And Administrative Support Occupations	1629	28%	239	26%	
Service Occupations	528	9%	77	8%	
Farming, Forestry, And Fishing Occupations	117	2%	20	2%	
Precision Production, Craft, And Repair Occupations	664	11%	70	8%	
Operators, Fabricators, And Laborers	584	10%	61	7%	
Experienced Unemployed Not Classified By Occupations	323	5%	30	3%	

Statistical significance markers: * p<0.05; ** p<0.05; *** p<0.01

Supplementary Table 3-6 Sensitivity analyses for the significant associations between lifecourse SES and CP conditions in the main analyses

AL Stream	Main results	Complete-case analysis	Estimator = "MLR"
High pain interference vs no pain	**P-value**	**P-value**	**P-value**
Childhood SES -> MIDUS 1 SES	**0.000**	**0.000**	**0.000**
Childhood SES -> MIDUS 2 SES	**0.000**	**0.000**	**0.000**
MIDUS1 SES -> MIDUS 2 SES	**0.000**	**0.000**	**0.000**
Childhood SES -> CP	0.485	0.648	0.519
MIDUS 1 SES -> CP	0.552	0.892	0.613
MIDUS 2 SES -> CP	**0.001**	**0.003**	**0.003**
Childhood SES -> MIDUS 1 SES -> MIDUS 2 SES	**0.000**	**0.000**	**0.000**
Childhood SES -> MIDUS 1 SES -> CP	0.554	0.892	0.618
Childhood SES -> MIDUS 1 SES -> MIDUS 2 SES -> CP	**0.013**	**0.026**	**0.020**
Childhood SES -> MIDUS 2 SES -> CP	**0.005**	**0.009**	**0.009**
MIDUS1 SES -> MIDUS 2 SES -> CP	**0.002**	**0.005**	**0.005**
	Main results	**Complete-case analysis**	**Estimator = "MLR"**
Pain with 3 or more locations vs no pain	**P-value**	**P-value**	**P-value**
Childhood SES -> MIDUS 1 SES	**0.000**	**0.000**	**0.000**
Childhood SES -> MIDUS 2 SES	**0.000**	**0.000**	**0.000**
MIDUS1 SES -> MIDUS 2 SES	**0.000**	**0.000**	**0.000**
Childhood SES -> CP	0.528	0.694	0.540
MIDUS 1 SES -> CP	0.064	0.227	0.124
MIDUS 2 SES -> CP	**0.040**	0.064	0.069

Childhood SES -> MIDUS 1 SES -> MIDUS 2 SES	**0.000**	**0.000**	**0.000**
Childhood SES -> MIDUS 1 SES -> CP	0.087	0.248	0.143
Childhood SES -> MIDUS 1 SES -> MIDUS 2 SES -> CP	0.076	0.110	0.098
Childhood SES -> MIDUS 2 SES -> CP	0.057	0.080	0.079
MIDUS1 SES -> MIDUS 2 SES -> CP	**0.044**	0.069	0.074

	Main results	**Complete-case analysis**	**Estimator = "MLR"**
Pain with 1-2 locations vs no pain	**P-value**	**P-value**	**P-value**
Childhood SES -> MIDUS 1 SES	**0.000**	**0.000**	**0.000**
Childhood SES -> MIDUS 2 SES	**0.000**	**0.000**	**0.000**
MIDUS1 SES -> MIDUS 2 SES	**0.000**	**0.000**	**0.000**
Childhood SES -> CP	0.176	0.135	0.187
MIDUS 1 SES -> CP	0.221	0.202	0.208
MIDUS 2 SES -> CP	**0.028**	**0.018**	**0.028**
Childhood SES -> MIDUS 1 SES -> MIDUS 2 SES	**0.000**	**0.000**	**0.000**
Childhood SES -> MIDUS 1 SES -> CP	0.231	0.217	0.204
Childhood SES -> MIDUS 1 SES -> MIDUS 2 SES -> CP	0.056	**0.045**	0.052
Childhood SES -> MIDUS 2 SES -> CP	**0.043**	**0.027**	**0.040**
MIDUS1 SES -> MIDUS 2 SES -> CP	**0.033**	**0.021**	**0.031**

Note: MLR denotes maximum likelihood with robust standard errors

Supplementary Table 3-7 Sensitivity analyses for the associations between lifecourse SES and AL

	Main results	Complete-case analysis	Estimator = "MLR"
Metabolic dysregulation vs baseline phenotype of AL	**P-value**	**P-value**	**P-value**
Childhood SES -> MIDUS 1 SES	**0.000**	**0.000**	**0.000**
Childhood SES -> MIDUS 2 SES	**0.000**	**0.000**	**0.000**
MIDUS1 SES -> MIDUS 2 SES	**0.000**	**0.000**	**0.000**
Childhood SES -> AL	**0.028**	**0.010**	**0.025**
MIDUS 1 SES -> AL	0.905	0.597	0.904
MIDUS 2 SES -> AL	**0.049**	**0.007**	**0.046**
Childhood SES -> MIDUS1 SES -> MIDUS 2 SES	**0.000**	**0.000**	**0.000**
Childhood SES -> MIDUS1 SES -> AL	0.905	0.601	0.349
Childhood SES -> MIDUS1 SES -> MIDUS 2 SES -> AL	0.092	**0.043**	0.069
Childhood SES -> MIDUS 2 SES -> AL	0.070	**0.018**	0.051
MIDUS1 SES -> MIDUS 2 SES -> AL	0.053	**0.009**	0.057

Note: MLR denotes maximum likelihood with robust standard errors

Supplementary Table 3-8 Sensitivity analyses for the associations between metabolic dysregulation of AL and high interference CP

	Main results	Complete-case analysis	Estimator = "MLR"
High pain interference vs no pain	**P-value**	**P-value**	**P-value**
AL - metabolic dysregulation	**0.022**	**0.038**	**0.028**

Note: MLR denotes maximum likelihood with robust standard errors

Supplementary Table 3-9 Covariate associations within the main associations between lifecourse SES and key outcomes, which remained robust following sequential sensitivity analyses

	High interference pain	1-2 pain locations	Metabolic dysregulation of AL
Covariates in MIDUS 1	**Estimate (SE)**	**Estimate (SE)**	**Estimate (SE)**
Sex (Ref: male)	**0.060 (0.027)***	-0.004 (0.033)	**-0.255 (0.037)*****
Ethnicity (Ref: white)	-0.072 (0.057)	-0.039 (0.070)	-0.013 (0.075)
Emotional abuse	0.000 (0.013)	0.010 (0.016)	0.002 (0.018)
Physical abuse	0.025 (0.013)	0.005 (0.017)	0.002 (0.019)
Live with biological parents until 16 (Ref: no)	-0.025 (0.034)	-0.054 (0.042)	-0.011 (0.045)
Age in MIDUS 1	-0.043 (0.025)	-0.016 (0.031)	0.029 (0.033)
Marital status in MIDUS 1 (Ref: married)	0.041 (0.037)	0.058 (0.045)	0.056 (0.048)
Multimorbidity in MIDUS 1 (Ref: no)	**0.086 (0.028)***	0.031 (0.034)	0.053 (0.038)
Covariates in MIDUS 2			
Age in MIDUS 2	0.042 (0.025)	0.013 (0.031)	-0.027 (0.033)
Marital status in MIDUS 2 (Ref: married)	**0.081 (0.037)***	0.044 (0.045)	0.029 (0.049)
Multimorbidity in MIDUS 2 (Ref: no)	**0.065 (0.029)***	**0.090 (0.034)****	**0.118 (0.039)****
Chronic pain in MIDUS 2 (Ref: no)	**0.245 (0.030)*****	**0.209 (0.036)*****	-0.019 (0.040)
Health insurance in MIDUS 2 (ref: yes)	0.032 (0.060)	-0.028 (0.079)	0.088 (0.078)

Statistical significance markers: * p<0.05; ** p<0.01; *** p<0.001

Supplementary Materials for the NSDE Stream Sample in the Mediation Analysis Chapter

Supplementary Table 4-1 Day level characteristics of cortisol collection

	Day-level characteristics		
Variable	**N**	**Mean**	**Sd**
Cortisol: awakening	3841	15	8.3
Cortisol: 30 mins after awakening	3841	22	11
Cortisol: lunchtime	3841	6.7	4.4
Cortisol: bedtime	3841	2.8	3.8
Collection time for awakening cortisol	3841	6.7	1.3
Collection time for 30 mins after awakening	3841	7.3	1.3
Collection time for lunch	3836	12.7	1.4
Collection time for bedtime	3841	22.5	1.3
Average waking hours	3841	17	0.86
Weekday	3841		
... Weekday	2879	75%	
... Weekend	962	25%	
Average sleeping hours	3701		
... 6-8	2776	75%	
... <6	320	9%	
... >8	605	16%	

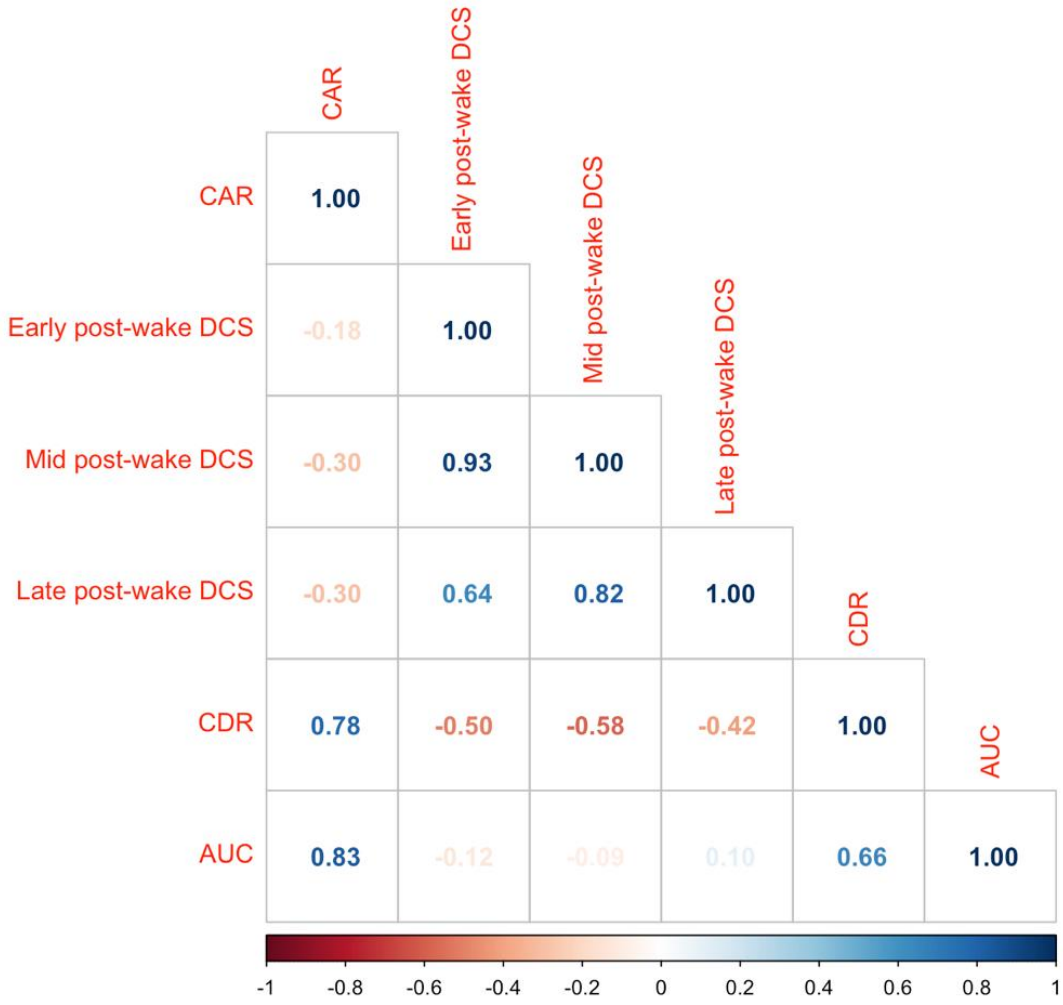
Supplementary Table 4-2 Computation for cortisol diurnal trajectory and its parameters

Fixed effects:	**Estimate**	**P-value**
(Intercept)	3.48 (0.25)	0.000
CAR (0-30mins)	0.50 (0.11)	0.000
Early post-wake DCS (30mins-4.5hours)	-0.13 (0.01)	0.000
Mid post-wake DCS (4.5mins-15hours)	-0.16 (0.00)	0.000
Evening DCS (after 15hours)	-0.13 (0.00)	0.000
Waking time	-0.04 (0.01)	0.000
Average wake-day length (individual-level)	-0.03 (0.01)	0.078
Length of sleep the previous night		
6-8 hours	Ref	
<6 hours	-0.06 (0.01)	0.000
>8 hours	-0.04 (0.02)	0.113
Weekend vs. workday status		
Weekday	Ref	
Weekend	-0.04 (0.02)	0.042
Random effects:	Variance	Std.Dev.
Between persons SD		
(Intercept)	0.146	0.383
CAR (0-30mins)	0.211	0.459
Early post-wake DCS (30mins-4.5hours)	0.009	0.095
Mid post-wake DCS (4.5mins-15hours)	0.003	0.050
Evening DCS (after 15hours)	0.002	0.046
Between days SD		
(Intercept)	0.000	0.000

Early post-wake DCS (30mins-4.5hours)	0.000	0.000
Between family SD		
(Intercept)	0.0323	0.1799
Residual SD	0.336	0.580
R^2	0.761	

†Adjusted for waking time on day of measurement, weekend vs. workday status, length of sleep the previous night, average wake-day length (individual-level).

Supplementary Figure 4-1 Correlation matrix of cortisol parameters



Supplementary Table 4-3 Fit indices of test for measurement invariance

Model	Degree of freedom	AIC	BIC	Chisq	Chisq diff	RMSEA diff	Df diff	Pr(>Chisq)
Configural invariance model	65	23414	23833	178.27				
Metric invariance model	70	23429	23823	202.93	24.658	0.065766	5	0.000
Scalar invariance model	75	23502	23873	286.7	83.767	0.131646	5	0.000
Strict invariance model	81	23603	23945	399.39	112.690	0.139863	6	0.000

Supplementary Table 4-4 Analytic sample characteristics of Covariates, stratified by CP conditions

CP inteference	No pain			Low interference pain			High interference pain			
Variable	**N**	**Mean**	**Sd**	**N**	**Mean**	**Sd**	**N**	**Mean**	**Sd**	**Test**
Childhood covariates										
Live with biological parents until 16	700			276			152			X2=3.182
... No	124	18%		56	20%		36	24%		
... Yes	576	82%		220	80%		116	76%		
Parental emotional abuse	655	2.4	1.3	138	2.9	1.4	253	2.7	1.4	F=6.31***
Parental physical abuse	655	2.1	1.3	139	2.5	1.3	259	2.2	1.3	F=3.39*
Sociodemographics - time invariant										
Sex	700			276			152			X2=9.12*
Male	336	48%		113	41%		55	36%		
Female	364	52%		163	59%		97	64%		
Ethnicity	693			272			147			X2=0.328
White	659	95%		261	96%		140	95%		
non-White	34	5%		11	4%		7	5%		
MIDUS 1 covariates										
Age in MIDUS 1	700	46	11	276	47	12	152	47	11	F=1.472
Marital status in MIDUS 1	700			276			152			X2=0.862

... Not married	179	26%		78	28%		38	25%		
... Married	521	74%		198	72%		114	75%		
Multimorbidity in MIDUS 1	693			272			147			X2=63.552***
... No	399	58%		117	43%		34	23%		
... Yes	294	42%		155	57%		113	77%		
MIDUS 2 covariates										
Marital status in MIDUS 2	700	55	11	276	56	12	152	56	11	F=1.565
... Not married	699			276			152			X2=0.03
... Married	178	25%		69	25%		38	25%		
Age in MIDUS 2	521	75%		207	75%		114	75%		
Multimorbidity in MIDUS 2	691			273			150			X2=46.653***
... No	356	52%		102	37%		35	23%		
... Yes	335	48%		171	63%		115	77%		
BMI in MIDUS 2	668	27	5.1	262	28	5.4	143	30	6.3	F=11.179**
Chronic pain in MIDUS 2	672			270			150			X2=141.492***
... No	525	78%		137	51%		50	33%		
... Yes	147	22%		133	49%		100	67%		
Health insurance in MIDUS 2	687			272			148			X2=8.398*
... Yes	657	96%		253	93%		133	90%		
... No	30	4%		19	7%		15	10%		
Physical activity (high scores=high levels)	659	30	11	249	29	10	131	28	11	F=1.593

Smoking status in MIDUS 2	700		276		152		X2=13.856***
... Current smoker	66	9%	26	9%	26	17%	
... Ex-smoker	413	59%	177	64%	94	62%	
... non-Smoker	221	32%	73	26%	32	21%	
Drinking status in MIDUS 2	700		276		152		X2=10.248**
... Moderate + Drinker	225	32%	92	33%	40	26%	
... Light Drinker	215	31%	76	28%	35	23%	
... non-Drinker or Rarley Drink	260	37%	108	39%	77	51%	
NSDE covariates							
Steroid inhaler in NSDE	700		276		152		X2=1.597
... No	677	97%	271	98%	147	97%	
... Yes	23	3%	5	2%	5	3%	
Oral steroid meds in NSDE	700		276		152		X2=1.35
... No	685	98%	267	97%	147	97%	
... Yes	15	2%	9	3%	5	3%	
Other hormonal meds in NSDE	700		276		152		X2=0.94
... No	685	98%	268	97%	147	97%	
... Yes	15	2%	8	3%	5	3%	
Anti-depressant or anti- anxiety meds in NSDE	700		276		152		X2=4.897*
... No	629	90%	236	86%	139	91%	
... Yes	71	10%	40	14%	13	9%	

Birth control pills in NSDE	700			276			152			X2=28.06***
... No	631	90%		235	85%		113	74%		
... Yes	69	10%		41	15%		39	26%		
CP locations	**0**			**1-2**			**3 or more**			
Variable	**N**	**Mean**	**Sd**	**N**	**Mean**	**Sd**	**N**	**Mean**	**Sd**	**Test**
Childhood covariates										
Live with biological parents until 16	700			275			178			X2=1.903
... No	124	18%		58	21%		37	21%		
... Yes	576	82%		217	79%		141	79%		
Parental emotional abuse	655	2.4	1.3	256	2.6	1.3	158	2.9	1.5	F=6.489**
Parental physical abuse	655	2.1	1.3	261	2.2	1.3	161	2.5	1.4	F=5.208**
Sociodemographics - time invariant										
Sex	700			275			178			X2=8.915**
Male	336	48%		118	43%		64	36%		
Female	364	52%		157	57%		114	64%		
Ethnicity	693			270			174			X2=0.644
White	659	95%		260	96%		166	95%		
Non-White	34	5%		10	4%		8	5%		
MIDUS 1 covariates										
Age in MIDUS 1	700	46	11	275	47	12	178	49	11	F=6.316***
Marital status in MIDUS 1	700			275			178			X2=0.144
... Not married	179	26%		71	26%		48	27%		

... Married	521	74%		204	74%		130	73%		
Multimorbidity in MIDUS 1	693			270			174			X2=66.982***
... <2	399	58%		113	42%		43	25%		
... 2+	294	42%		157	58%		131	75%		
MIDUS 2 covariates										
Age in MIDUS 2	700	55	11	275	56	12	178	58	11	F=6.819***
Marital status in MIDUS 2	699			275			178			X2=2.009
... Not married	178	25%		64	23%		52	29%		
... Married	521	75%		211	77%		126	71%		
Multimorbidity in MIDUS 2	691			271			177			X2=54.03***
... <2	356	52%		104	38%		39	22%		
... 2+	335	48%		167	62%		138	78%		
BMI in MIDUS 2	668	27	5.1	261	28	5.2	168	30	6.4	F=12.846***
Chronic pain in MIDUS 2	672			267			177			X2=168.93***
... No	525	78%		144	54%		50	28%		
... Yes	147	22%		123	46%		127	72%		
Health insurance in MIDUS 2	687			269			175			X2=33.706***
... Yes	657	96%		259	96%		148	85%		
... No	30	4%		10	4%		27	15%		
Physical activity (high scores=high levels)	659	30	11	237	31	10	160	26	11	F=10.377***
Smoking status in MIDUS 2	700			275			178			X2=11.161**

... Current smoker	66	9%	29	11%	26	15%	
... Ex-smoker	413	59%	176	64%	114	64%	
... Non-Smoker	221	32%	70	25%	38	21%	
Drinking status in MIDUS 2	700		275		178		X2=11.759**
... Moderate+ Drinker	225	32%	84	31%	53	30%	
... Light Drinker	215	31%	82	30%	36	20%	
... Non-Drinker or Rarley Drink	260	37%	109	40%	89	50%	
NSDE covariates							
Steroid inhaler in NSDE	700		275		178		X2=1.152
... No	677	97%	269	98%	174	98%	
... Yes	23	3%	6	2%	4	2%	
Oral steroid meds in NSDE	700		275		178		X2=1.101
... No	685	98%	267	97%	172	97%	
... Yes	15	2%	8	3%	6	3%	
Other hormonal meds in NSDE	700		275		178		X2=2.349
... No	685	98%	265	96%	175	98%	
... Yes	15	2%	10	4%	3	2%	
Anti-depressant or anti- anxiety meds in NSDE	700		275		178		X2=0.904
... No	629	90%	242	88%	157	88%	
... Yes	71	10%	33	12%	21	12%	
Birth control pills in NSDE	700		275		178		X2=21.361***
... No	631	90%	229	83%	139	78%	

... Yes	69	10%	46	17%	39	22%	

Statistical significance markers: * p<0.05; ** p<0.01; *** p<0.001

Supplementary Table 4-5 Baseline sample characteristics

	Attrtition			Retention			
Variables in MIDUS 1	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**Test**
Sex	5860			1246			X2=9.62***
Male	2887	49%		553	44%		
Female	2973	51%		693	56%		
Ethnicity	5029			1225			X2=44.882***
White	4479	89%		1169	95%		
Non-White	550	11%		56	5%		
Age	5803	46	13	1246	47	11	F=0.149
Marital status	5069			1115			X2=38.951***
... Married	3743	74%		923	83%		
... Not married	1326	26%		192	17%		
Parental emotional abuse	4563	2.6	1.4	1152	2.5	1.4	F=0.983
Parental physical abuse	4638	2.4	1.3	1161	2.2	1.3	F=12.32***
Live with biological parents until 16	5857			1246			X2=10.476***
... No	1359	23%		236	19%		
... Yes	4498	77%		1010	81%		
Multimorbidity	5084			1224			X2=6.889**
... <2	2245	44%		592	48%		

... 2+	2839	56%	632	52%	
Fathers education	4968		1133		X2=3.65
Less than high school	2007	40%	424	37%	
High school/GED/some college	2078	42%	491	43%	
Bachelor's degree or more	883	18%	218	19%	
Mother education	5407		1211		X2=18.477***
Less than high school	1890	35%	350	29%	
High school/GED/some college	2906	54%	693	57%	
Bachelor's degree or more	611	11%	168	14%	
Financial level growing up	5065		1222		X2=14.788**
A lot better off	183	4%	29	2%	
Somewhat better off	597	12%	154	13%	
A little better off	676	13%	181	15%	
Same as average family	2158	43%	491	40%	
A little worse off	876	17%	241	20%	
Somewhat worse off	395	8%	96	8%	
A lot worse off	180	4%	30	2%	
Father's occupation	5118		1139		X2=24.789***
Managerial And Professional Specialty Occupations	1250	24%	306	27%	
Technical, Sales, And Administrative Support Occupations	711	14%	200	18%	
Service Occupations	236	5%	49	4%	

Farming, Forestry, And Fishing Occupations	643	13%		161	14%		
Precision Production, Craft, And Repair Occupations	1221	24%		228	20%		
Operators, Fabricators, And Laborers	940	18%		171	15%		
Experienced Unemployed Not Classified By Occupations	117	2%		24	2%		
Rate current financial situation	5015	6.1	2.2	1216	6.4	2.1	F=22.804***
Money to meet needs	5031			1221			X2=43.06***
More than enough money	750	15%		267	22%		
Just enough money	2855	57%		683	56%		
Not enough money	1426	28%		271	22%		
How difficult to pay monthly bills	5028			1221			X2=22.108***
Not at all difficult	1355	27%		388	32%		
Not very difficult	1887	38%		480	39%		
Somewhat difficult	1472	29%		297	24%		
Very difficult	314	6%		56	5%		
Education	5852			1243			X2=104.747***
Less than high school	627	11%		54	4%		
High school/GED/some college	3557	61%		676	54%		
Bachelor's degree or more	1668	29%		513	41%		
Income-to-needs ratio	4899			1211			X2=64.393***
Affluent	2954	60%		864	71%		
Adequate-income	1129	23%		242	20%		

Low-income	438	9%	56	5%	
Poor	126	3%	14	1%	
Extreme poverty	252	5%	35	3%	
Occupation	5615		1206		X2=59.823***
Managerial And Professional Specialty Occupations	1938	35%	541	45%	
Technical, Sales, And Administrative Support Occupations	1544	27%	324	27%	
Service Occupations	519	9%	86	7%	
Farming, Forestry, And Fishing Occupations	113	2%	24	2%	
Precision Production, Craft, And Repair Occupations	630	11%	104	9%	
Operators, Fabricators, And Laborers	554	10%	91	8%	
Experienced Unemployed Not Classified By Occupations	317	6%	36	3%	

Statistical significance markers: * p<0.05; ** p<0.01; *** p<0.001

Supplementary Table 4-6 Sensitivity analyses for the significant associations between lifecourse SES and CP conditions in the main analyses

NSDE Stream	Main results	Complete-case analysis	Estimator = "MLR"
High pain interference vs no pain	**P-value**	**P-value**	**P-value**
Childhood SES -> MIDUS 1 SES	**0.000**	**0.000**	**0.000**
Childhood SES -> MIDUS 2 SES	**0.000**	**0.000**	**0.000**
MIDUS1 SES -> MIDUS 2 SES	**0.000**	**0.000**	**0.000**
Childhood SES -> CP	0.395	0.604	0.408
MIDUS 1 SES -> CP	0.131	0.302	0.182
MIDUS 2 SES -> CP	**0.001**	**0.000**	**0.002**
Childhood SES -> MIDUS_1 SES -> MIDUS 2 SES	**0.000**	**0.000**	**0.000**
Childhood SES -> MIDUS_1 SES -> CP	0.146	0.311	0.194
Childhood SES -> MIDUS_1 SES -> MIDUS 2 SES -> CP	**0.005**	**0.005**	**0.016**
Childhood SES -> MIDUS 2 SES -> CP	**0.003**	**0.001**	**0.006**
MIDUS1 SES -> MIDUS 2 SES -> CP	**0.001**	**0.000**	**0.002**
	Main results	**Complete-case analysis**	**Estimator = "MLR"**
Pain with 3 or more locations vs no pain	**P-value**	**P-value**	**P-value**
Childhood SES -> MIDUS 1 SES	**0.000**	**0.000**	**0.000**
Childhood SES -> MIDUS 2 SES	**0.000**	**0.000**	**0.000**
MIDUS1 SES -> MIDUS 2 SES	**0.000**	**0.000**	**0.000**
Childhood SES -> CP	0.367	0.280	0.375
MIDUS 1 SES -> CP	**0.026**	0.199	0.054
MIDUS 2 SES -> CP	**0.028**	**0.005**	**0.043**
Childhood SES -> MIDUS_1 SES -> MIDUS 2 SES	**0.000**	**0.000**	**0.000**
Childhood SES -> MIDUS_1 SES -> CP	**0.043**	0.217	0.067

Childhood SES -> MIDUS 1 SES -> MIDUS 2 SES -> CP	**0.048**	**0.026**	0.069
Childhood SES -> MIDUS 2 SES -> CP	**0.039**	**0.010**	**0.048**
MIDUS1 SES -> MIDUS 2 SES -> CP	**0.031**	**0.006**	**0.044**

Note: MLR denotes maximum likelihood with robust standard errors

Supplementary Table 4-7 Sensitivity analyses for the associations between lifecourse SES and cortisol parameters

	Main results	Complete-case analysis	With robust SEs
Outcome: Early post-wake DCS	**P-value**	**P-value**	**P-value**
Childhood SES -> MIDUS 1 SES	**0.000**	**0.000**	**0.000**
Childhood SES -> MIDUS 2 SES	**0.000**	**0.000**	**0.000**
MIDUS1 SES -> MIDUS 2 SES	**0.000**	**0.000**	**0.000**
Childhood SES -> Outcome	0.610	0.702	0.375
MIDUS 1 SES -> Outcome	0.947	0.736	0.054
MIDUS 2 SES -> Outcome	**0.015**	0.066	**0.043**
Childhood SES -> MIDUS1 SES -> MIDUS 2 SES	**0.000**	**0.000**	**0.000**
Childhood SES -> MIDUS1 SES -> Outcome	0.926	0.737	0.067
Childhood SES -> MIDUS1 SES -> MIDUS 2 SES -> Outcome	**0.030**	0.095	0.069
Childhood SES -> MIDUS 2 SES -> Outcome	**0.023**	0.074	**0.048**
MIDUS1 SES -> MIDUS 2 SES -> Outcome	**0.016**	0.068	**0.044**
	Main results	**Complete-case analysis**	**With robust SEs**
Outcome: Mid post-wake DCS	**P-value**	**P-value**	**P-value**
Childhood SES -> MIDUS 1 SES	**0.000**	**0.000**	**0.000**
Childhood SES -> MIDUS 2 SES	**0.000**	**0.000**	**0.000**
MIDUS1 SES -> MIDUS 2 SES	**0.000**	**0.000**	**0.000**
Childhood SES -> Outcome	0.359	0.540	0.358
MIDUS 1 SES -> Outcome	0.947	0.742	0.947
MIDUS 2 SES -> Outcome	**0.010**	**0.040**	**0.015**
Childhood SES -> MIDUS1 SES -> MIDUS 2 SES	**0.000**	**0.000**	**0.000**
Childhood SES -> MIDUS1 SES -> Outcome	0.947	0.742	0.947
Childhood SES -> MIDUS1 SES -> MIDUS 2 SES -> Outcome	**0.023**	0.069	**0.038**

Childhood SES -> MIDUS 2 SES -> Outcome	**0.017**	**0.048**	**0.024**
MIDUS1 SES -> MIDUS 2 SES -> Outcome	**0.011**	**0.042**	**0.015**
	Main results	**Complete-case analysis**	**With robust SEs**
Outcome: CDR	**P-value**	**P-value**	**P-value**
Childhood SES -> MIDUS 1 SES	**0.000**	**0.000**	**0.000**
Childhood SES -> MIDUS 2 SES	**0.000**	**0.000**	**0.000**
MIDUS1 SES -> MIDUS 2 SES	**0.000**	**0.000**	**0.000**
Childhood SES -> Outcome	0.472	0.857	0.580
MIDUS 1 SES -> Outcome	0.608	0.637	0.645
MIDUS 2 SES -> Outcome	**0.003**	**0.015**	**0.013**
Childhood SES -> MIDUS1 SES -> MIDUS 2 SES	**0.000**	**0.000**	**0.000**
Childhood SES -> MIDUS1 SES -> Outcome	0.610	0.639	0.642
Childhood SES -> MIDUS1 SES -> MIDUS 2 SES -> Outcome	**0.011**	**0.038**	**0.040**
Childhood SES -> MIDUS 2 SES -> Outcome	**0.007**	**0.021**	**0.023**
MIDUS1 SES -> MIDUS 2 SES -> Outcome	**0.003**	**0.016**	**0.015**
	Main results	**Complete-case analysis**	**With robust SEs**
Outcome: AUC	**P-value**	**P-value**	**P-value**
Childhood SES -> MIDUS 1 SES	**0.000**	**0.000**	**0.000**
Childhood SES -> MIDUS 2 SES	**0.000**	**0.000**	**0.000**
MIDUS1 SES -> MIDUS 2 SES	**0.000**	**0.000**	**0.000**
Childhood SES -> Outcome	0.834	0.911	0.837
MIDUS 1 SES -> Outcome	0.528	0.441	0.578
MIDUS 2 SES -> Outcome	**0.045**	0.102	0.090
Childhood SES -> MIDUS1 SES -> MIDUS 2 SES	**0.000**	**0.000**	**0.000**
Childhood SES -> MIDUS1 SES -> Outcome	0.531	0.447	0.573

Childhood SES -> MIDUS1 SES -> MIDUS 2 SES -> Outcome	0.063	0.131	0.131
Childhood SES -> MIDUS 2 SES -> Outcome	0.054	0.111	0.109
MIDUS1 SES -> MIDUS 2 SES -> Outcome	**0.046**	0.104	0.092

Note: MLR denotes maximum likelihood with robust standard errors

Supplementary Table 4-8 Sensitivity analyses for the associations between CDR, AUC and pain with 3 or more locations

	Main results	Complete-case analysis	Estimator = "MLR"
Pain with 3 or more locations vs no pain	**P-value**	**P-value**	**P-value**
CDR	**0.014**	**0.023**	**0.015**
AUC	**0.015**	**0.011**	**0.019**

Note: MLR denotes maximum likelihood with robust standard errors

Supplementary Table 4-9 Covariate associations within the main associations between lifecourse SES and key outcomes, which remained robust following sequential sensitivity analyses

	High interference pain	3 or more pain locations	Mid post-wake DCS	CDR
Covariates in MIDUS 1	**Estimate (SE)**	**Estimate (SE)**	**Estimate (SE)**	**Estimate (SE)**
Sex (Ref: male)	0.026 (0.025)	0.029 (0.025)	**-0.126 (0.059)***	**-0.098 (0.031)****
Ethnicity (Ref: White)	-0.040 (0.061)	-0.062 (0.059)	**0.405 (0.147)****	-0.077 (0.076)
Emotional abuse	0.016 (0.012)	0.008 (0.012)	0.022 (0.028)	-0.011 (0.015)
Physical abuse	0.008 (0.013)	0.018 (0.013)	-0.022 (0.030)	0.025 (0.016)
Live with biological parents until 16 (Ref: no)	-0.001 (0.031)	0.006 (0.032)	-0.013 (0.075)	-0.044 (0.039)
Age in MIDUS 1	-0.029 (0.021)	-0.033 (0.021)	**-0.106 (0.050)***	0.046 (0.026)
Marital status in MIDUS 1 (Ref: married)	0.048 (0.035)	0.023 (0.035)	0.125 (0.083)	-0.044 (0.043)
Multimorbidity in MIDUS 1 (Ref: no)	**0.110 (0.026)*****	**0.096 (0.026)*****	-0.013 (0.063)	-0.040 (0.032)
Covariates in MIDUS 2				
Age in MIDUS 2	0.029 (0.021)	0.036 (0.021)	**0.116 (0.050)***	-0.044 (0.026)
Marital status in MIDUS 2 (Ref: married)	0.048 (0.035)	0.042 (0.035)	**-0.181 (0.084)***	0.035 (0.043)
Multimorbidity in MIDUS 2 (Ref: no)	0.047 (0.027)	0.044 (0.027)	0.065 (0.064)	**-0.076 (0.033)***
CP in MIDUS 2 (Ref: no)	0.043 (0.057)	**0.137 (0.053)****	-0.004 (0.134)	0.109 (0.069)
Health insurance in MIDUS 2 (ref: yes)	**0.242 (0.028)*****	**0.294 (0.027)*****	0.050 (0.064)	-0.060 (0.033)

Statistical significance markers: * p<0.05; ** p<0.01; *** p<0.001

Supplementary Table 4-10 The mediating role of cortisol parameters in the association between life course SES and 3 or more pain locations among respondents without baseline CP

	3 or more pain locations		
Mediator (M): CAR	**Estimate**	**SE**	**P-value**
Childhood SES -> MIDUS 1 SES	0.190	0.041	**0.000**
Childhood SES -> MIDUS 2 SES	0.170	0.038	**0.000**
MIDUS 1 SES -> MIDUS 2 SES	0.466	0.042	**0.000**
Childhood SES -> CP	0.000	0.014	0.975
MIDUS 1 SES -> CP	0.019	0.016	0.249
MIDUS 2 SES -> CP	0.023	0.016	0.150
Childhood SES -> M	-0.002	0.044	0.959
MIDUS 1 SES -> M	0.060	0.052	0.249
MIDUS 2 SES -> M	-0.066	0.052	0.204
M -> CP	-0.020	0.013	0.126
Childhood SES -> MIDUS 1 SES -> MIDUS 2 SES	0.088	0.021	**0.000**
Childhood SES -> MIDUS 1 SES -> M	0.011	0.010	0.263
Childhood SES -> MIDUS 2 SES -> M	-0.011	0.009	0.221
Childhood SES -> MIDUS 1 SES -> MIDUS 2 SES -> M	-0.006	0.005	0.224
MIDUS 1 SES -> MIDUS 2 SES -> M	-0.001	0.020	0.959
Childhood SES -> MIDUS 1 SES -> CP	0.004	0.003	0.265
Childhood SES -> MIDUS 1 SES -> M -> CP	0.000	0.000	0.363
Childhood SES -> MIDUS 1 SES -> MIDUS 2 SES -> CP	0.001	0.001	0.190
Childhood SES -> MIDUS 1 SES -> MIDUS 2 SES -> M -> CP	0.000	0.000	0.339
Childhood SES -> MIDUS 2 SES -> CP	0.004	0.003	0.172
Childhood SES -> MIDUS 2 SES -> M -> CP	0.001	0.001	0.329
Childhood SES -> M -> CP	0.000	0.001	0.959

MIDUS 1 SES -> MIDUS 2 SES -> M -> CP	0.001	0.001	0.329
MIDUS 1 SES -> MIDUS 2 SES -> CP	0.011	0.008	0.154
MIDUS 1 SES -> M -> CP	-0.001	0.001	0.353
MIDUS 2 SES -> M -> CP	0.001	0.001	0.327
Chi-square (df)=430.668 (167); CFI=0.941; TLI=0.910; RMSEA=0.054			

Mediator (M): Early post-wake DCS	**Estimate**	**SE**	**P-value**
Childhood SES -> MIDUS 1 SES	0.190	0.041	**0.000**
Childhood SES -> MIDUS 2 SES	0.171	0.038	**0.000**
MIDUS 1 SES -> MIDUS 2 SES	0.464	0.042	**0.000**
Childhood SES -> CP	0.001	0.014	0.921
MIDUS 1 SES -> CP	0.018	0.016	0.256
MIDUS 2 SES -> CP	0.022	0.016	0.177
Childhood SES -> M	-0.021	0.047	0.661
MIDUS 1 SES -> M	-0.023	0.056	0.673
MIDUS 2 SES -> M	0.084	0.056	0.135
M -> CP	0.036	0.012	**0.004**
Childhood SES -> MIDUS 1 SES -> MIDUS 2 SES	0.088	0.021	**0.000**
Childhood SES -> MIDUS 1 SES -> M	-0.004	0.011	0.674
Childhood SES -> MIDUS 2 SES -> M	0.014	0.010	0.158
Childhood SES -> MIDUS 1 SES -> MIDUS 2 SES -> M	0.007	0.005	0.157
MIDUS 1 SES -> MIDUS 2 SES -> M	-0.010	0.022	0.661
Childhood SES -> MIDUS 1 SES -> CP	0.003	0.003	0.271
Childhood SES -> MIDUS 1 SES -> M -> CP	0.000	0.000	0.677
Childhood SES -> MIDUS 1 SES -> MIDUS 2 SES -> CP	0.001	0.001	0.213
Childhood SES -> MIDUS 1 SES -> MIDUS 2 SES -> M -> CP	0.000	0.000	0.202
Childhood SES -> MIDUS 2 SES -> CP	0.004	0.003	0.197
Childhood SES -> MIDUS 2 SES -> M -> CP	0.001	0.001	0.184

Childhood SES -> M -> CP	-0.001	0.002	0.664
MIDUS 1 SES -> MIDUS 2 SES -> M -> CP	0.001	0.001	0.184
MIDUS 1 SES -> MIDUS 2 SES -> CP	0.010	0.008	0.181
MIDUS 1 SES -> M -> CP	-0.001	0.002	0.675
MIDUS 2 SES -> M -> CP	0.003	0.002	0.182
Chi-square (df)=432.051 (167); CFI=0.940; TLI=0.910; RMSEA=0.054			
Mediator (M): Mid post-wake DCS	**Estimate**	**SE**	**P-value**
Childhood SES -> MIDUS 1 SES	0.190	0.041	**0.000**
Childhood SES -> MIDUS 2 SES	0.170	0.038	**0.000**
MIDUS 1 SES -> MIDUS 2 SES	0.464	0.042	**0.000**
Childhood SES -> CP	0.002	0.014	0.899
MIDUS 1 SES -> CP	0.019	0.016	0.237
MIDUS 2 SES -> CP	0.022	0.016	0.174
Childhood SES -> M	-0.033	0.047	0.489
MIDUS 1 SES -> M	-0.043	0.055	0.435
MIDUS 2 SES -> M	0.080	0.056	0.154
M -> CP	0.036	0.012	**0.003**
Childhood SES -> MIDUS 1 SES -> MIDUS 2 SES	0.088	0.021	**0.000**
Childhood SES -> MIDUS 1 SES -> M	-0.008	0.011	0.441
Childhood SES -> MIDUS 2 SES -> M	0.014	0.010	0.175
Childhood SES -> MIDUS 1 SES -> MIDUS 2 SES -> M	0.007	0.005	0.176
MIDUS 1 SES -> MIDUS 2 SES -> M	-0.015	0.022	0.489
Childhood SES -> MIDUS 1 SES -> CP	0.004	0.003	0.253
Childhood SES -> MIDUS 1 SES -> M -> CP	0.000	0.000	0.454
Childhood SES -> MIDUS 1 SES -> MIDUS 2 SES -> CP	0.001	0.001	0.211
Childhood SES -> MIDUS 1 SES -> MIDUS 2 SES -> M -> CP	0.000	0.000	0.217
Childhood SES -> MIDUS 2 SES -> CP	0.004	0.003	0.194

Childhood SES -> MIDUS 2 SES -> M -> CP	0.001	0.001	0.200
Childhood SES -> M -> CP	-0.001	0.002	0.499
MIDUS 1 SES -> MIDUS 2 SES -> M -> CP	0.001	0.001	0.200
MIDUS 1 SES -> MIDUS 2 SES -> CP	0.010	0.008	0.178
MIDUS 1 SES -> M -> CP	-0.002	0.002	0.448
MIDUS 2 SES -> M -> CP	0.003	0.002	0.198
Chi-square (df)=432.032 (167); CFI=0.941; TLI=0.910; RMSEA=0.054			

Mediator (M): Evening DCS	**Estimate**	**SE**	**P-value**
Childhood SES -> MIDUS 1 SES	0.190	0.041	**0.000**
Childhood SES -> MIDUS 2 SES	0.170	0.038	**0.000**
MIDUS 1 SES -> MIDUS 2 SES	0.465	0.042	**0.000**
Childhood SES -> CP	0.001	0.014	0.943
MIDUS 1 SES -> CP	0.018	0.016	0.272
MIDUS 2 SES -> CP	0.025	0.016	0.128
Childhood SES -> M	-0.029	0.049	0.549
MIDUS 1 SES -> M	-0.017	0.058	0.773
MIDUS 2 SES -> M	0.016	0.059	0.781
M -> CP	0.023	0.012	0.050
Childhood SES -> MIDUS 1 SES -> MIDUS 2 SES	0.088	0.021	**0.000**
Childhood SES -> MIDUS 1 SES -> M	-0.003	0.011	0.773
Childhood SES -> MIDUS 2 SES -> M	0.003	0.010	0.781
Childhood SES -> MIDUS 1 SES -> MIDUS 2 SES -> M	0.001	0.005	0.781
MIDUS 1 SES -> MIDUS 2 SES -> M	-0.014	0.023	0.549
Childhood SES -> MIDUS 1 SES -> CP	0.003	0.003	0.287
Childhood SES -> MIDUS 1 SES -> M -> CP	0.000	0.000	0.775
Childhood SES -> MIDUS 1 SES -> MIDUS 2 SES -> CP	0.001	0.001	0.170
Childhood SES -> MIDUS 1 SES -> MIDUS 2 SES -> M -> CP	0.000	0.000	0.783

Childhood SES -> MIDUS 2 SES -> CP	0.004	0.003	0.151
Childhood SES -> MIDUS 2 SES -> M -> CP	0.000	0.001	0.783
Childhood SES -> M -> CP	-0.001	0.001	0.565
MIDUS 1 SES -> MIDUS 2 SES -> M -> CP	0.000	0.001	0.783
MIDUS 1 SES -> MIDUS 2 SES -> CP	0.011	0.008	0.133
MIDUS 1 SES -> M -> CP	0.000	0.001	0.775
MIDUS 2 SES -> M -> CP	0.000	0.001	0.783
Chi-square (df)=433.305 (167); CFI=0.941; TLI=0.910; RMSEA=0.054			

Mediator (M): CDR	**Estimate**	**SE**	**P-value**
Childhood SES -> MIDUS 1 SES	0.190	0.041	**0.000**
Childhood SES -> MIDUS 2 SES	0.170	0.038	**0.000**
MIDUS 1 SES -> MIDUS 2 SES	0.465	0.042	**0.000**
Childhood SES -> CP	0.001	0.014	0.950
MIDUS 1 SES -> CP	0.019	0.016	0.239
MIDUS 2 SES -> CP	0.022	0.016	0.173
Childhood SES -> M	0.021	0.044	0.639
MIDUS 1 SES -> M	0.071	0.052	0.172
MIDUS 2 SES -> M	-0.117	0.052	**0.025**
M -> CP	-0.023	0.013	0.085
Childhood SES -> MIDUS 1 SES -> MIDUS 2 SES	0.088	0.021	**0.000**
Childhood SES -> MIDUS 1 SES -> M	0.014	0.010	0.190
Childhood SES -> MIDUS 2 SES -> M	-0.020	0.010	**0.046**
Childhood SES -> MIDUS 1 SES -> MIDUS 2 SES -> M	-0.010	0.005	**0.047**
MIDUS 1 SES -> MIDUS 2 SES -> M	0.010	0.020	0.639
Childhood SES -> MIDUS 1 SES -> CP	0.004	0.003	0.256
Childhood SES -> MIDUS 1 SES -> M -> CP	0.000	0.000	0.294
Childhood SES -> MIDUS 1 SES -> MIDUS 2 SES -> CP	0.001	0.001	0.210

Childhood SES -> MIDUS 1 SES -> MIDUS 2 SES -> M -> CP	0.000	0.000	0.192
Childhood SES -> MIDUS 2 SES -> CP	0.004	0.003	0.193
Childhood SES -> MIDUS 2 SES -> M -> CP	0.001	0.001	0.174
Childhood SES -> M -> CP	0.000	0.001	0.650
MIDUS 1 SES -> MIDUS 2 SES -> M -> CP	0.001	0.001	0.174
MIDUS 1 SES -> MIDUS 2 SES -> CP	0.010	0.008	0.177
MIDUS 1 SES -> M -> CP	-0.002	0.002	0.281
MIDUS 2 SES -> M -> CP	0.003	0.002	0.171

Chi-square (df)=430.499 (167); CFI=0.941; TLI=0.910; RMSEA=0.054

Mediator (M): AUC	**Estimate**	**SE**	**P-value**
Childhood SES -> MIDUS 1 SES	0.190	0.041	**0.000**
Childhood SES -> MIDUS 2 SES	0.170	0.038	**0.000**
MIDUS 1 SES -> MIDUS 2 SES	0.465	0.041	**0.000**
Childhood SES -> CP	0.001	0.014	0.953
MIDUS 1 SES -> CP	0.019	0.016	0.246
MIDUS 2 SES -> CP	0.023	0.016	0.163
Childhood SES -> M	0.017	0.044	0.701
MIDUS 1 SES -> M	0.070	0.053	0.184
MIDUS 2 SES -> M	-0.093	0.053	0.081
M -> CP	-0.018	0.013	0.181
Childhood SES -> MIDUS 1 SES -> MIDUS 2 SES	0.088	0.021	**0.000**
Childhood SES -> MIDUS 1 SES -> M	0.013	0.010	0.202
Childhood SES -> MIDUS 2 SES -> M	-0.016	0.010	0.105
Childhood SES -> MIDUS 1 SES -> MIDUS 2 SES -> M	-0.008	0.005	0.106
MIDUS 1 SES -> MIDUS 2 SES -> M	0.008	0.020	0.701
Childhood SES -> MIDUS 1 SES -> CP	0.004	0.003	0.263
Childhood SES -> MIDUS 1 SES -> M -> CP	0.000	0.000	0.353

Childhood SES -> MIDUS 1 SES -> MIDUS 2 SES -> CP	0.001	0.001	0.201
Childhood SES -> MIDUS 1 SES -> MIDUS 2 SES -> M -> CP	0.000	0.000	0.302
Childhood SES -> MIDUS 2 SES -> CP	0.004	0.003	0.184
Childhood SES -> MIDUS 2 SES -> M -> CP	0.001	0.001	0.289
Childhood SES -> M -> CP	0.000	0.001	0.711
MIDUS 1 SES -> MIDUS 2 SES -> M -> CP	0.001	0.001	0.289
MIDUS 1 SES -> MIDUS 2 SES -> CP	0.011	0.008	0.167
MIDUS 1 SES -> M -> CP	-0.001	0.001	0.343
MIDUS 2 SES -> M -> CP	0.002	0.002	0.287
Chi-square (df)=431.116 (167); CFI=0.941; TLI=0.910; RMSEA=0.054			

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