UNIVERSITY OF CALIFORNIA

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Adverse Childhood Experiences and Mental Health Over the Life Course Among Men Who Have Sex with Men in Los Angeles County

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Community Health Sciences

by

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ABSTRACT OF THE DISSERTATION

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by

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Professor Michael L. Prelip, Chair

Early life adversity exposing vulnerable individuals to potential harm during the first 18 years of life increases the risk for a wide range of adverse physical and mental health outcomes. Childhood adversity is an example of a public health problem that requires "systems thinking" through consideration of social, environmental, familial, psychological, and biological/genetic factors. Understanding the mechanisms of these complex concepts and synthesizing this information into a comprehensive model is necessary.

The widely accepted Adverse Childhood Experience (ACE) measure captures exposure to childhood maltreatment and household dysfunction. ACEs have been shown to associate with nonspecific risk for a wide range of adverse mental health conditions across all socioeconomic groups. Using a social determinants of health framework, ACEs can be viewed as a consequence of upstream vulnerability factors that are structural (i.e., rooted in cumulative disadvantage when

families face socioeconomic and relational adversity). ACEs can also be viewed as a psychosocial risk factor impacting mental health independent of other social patterns (e.g., among those with higher socioeconomic status).

Although sexual minority groups appear disadvantaged concerning both ACE exposure and mental health outcomes, the literature describing links between ACEs and mental health is limited among men who have sex with men (MSM), particularly those of low-income and minoritized status. The primary research aim in this dissertation is to investigate if exposure to ACEs (recalled from the first 18 years of life) predict poor mental health outcomes (drug use, depressive and anxiety symptoms) among mostly Black and Latino low-income MSM in adulthood, adjusting for a wide range of sociodemographic and behavioral factors. This research question was explored in three separate studies, based on a Life Course Perspective. Each study examined the cumulative ACE score, dimensional approaches (separating ACEs into categories of childhood maltreatment and household dysfunction), and selective approaches (considering individual ACEs) on these mental health outcomes. All studies investigated whether specific resilience factors (i.e., perceived social support, and sleep quality) buffer the hypothesized associations between ACEs and mental health through effect modification (i.e., moderation).

Data for this dissertation comes from the mSTUDY (Men Who Have Sex with Men and Substance Use Cohort at UCLA Linking Infections, Noting Effects [MASCULINE]), a longitudinal study of HIV-positive and HIV-negative MSM with varied substance use behaviors. Participants were assigned male sex at birth, English-speaking, ages 18-45; and if HIV-, reported having sex with men in the past twelve months (n=297). Multilevel commands using participant ID were used for mixed effects in random intercept logistic and ordinal regression models.

The results of this research suggest that ACEs have significant associations with mental health during adulthood among mostly Black and Latino low-income MSM in Los Angeles. While relationships between ACEs and mental health are well documented, evidence linking these among MSM is sparse, particularly among those with multiple forms of cumulative disadvantage. In this research, the total ACE score predicted depressive and anxiety symptoms, and the outcome of self-reported drug use trended toward significance. The dimension of childhood maltreatment predicted depressive and anxiety symptoms, but not drug use. Selective approaches identified that childhood sexual abuse predicts depressive symptoms; and emotional neglect predicts anxiety. Only the association between childhood sexual abuse and depressive symptoms survived adjustment for the other nine ACEs.

Perceived social support emerged as a buffering factor for drug use in the cumulative and selective approaches. Sleep quality did not emerge as a resilience factor (moderator) for any outcomes of depressive and anxiety symptoms, suggesting that the association between ACEs and these outcomes did not differ by sleep quality. This dissertation's findings contribute to our understanding of how ACEs might impact mental and behavioral health outcomes among socially disadvantaged MSM. One limitation is that the sample was not randomly selected. Several recommendations for future research (including ACE measurement) are proposed.

The dissertation of David Andrew Wiss is approved.

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Bray, B., Rodríguez-Martín, B. C., Wiss, D. A., Bray, C. E., & Zwickey, H. (2021). Overeaters Anonymous: An overlooked intervention for binge eating disorder. *International Journal of Environmental Research and Public Health*, *18*(14), 7303. doi:10.3390/ijerph18147303

Wiss, D., Javanbakht, M., Li, M., Prelip, M., Bolan, R., Shoptaw, S., & Gorbach, P. (2021). Food insecurity partially mediates the association between drug use and depressive symptoms among men who have sex with men in Los Angeles, California. *Public Health Nutrition, 24*(13), 1-9. doi:10.1017/S1368980021002494

Wiss, D. A., Avena, N., & Gold, M. (2020). Food addiction and psychosocial adversity: Biological embedding, contextual factors, and public health implications. *Nutrients, 12*(11), 3521. doi:10.3390/nu12113521

Wiss, D. A., Russell, L., & Prelip, M. (2020). Staff-perceived barriers to nutrition intervention in substance use disorder treatment. *Public Health Nutrition, 24*(11), 3488-3497. doi:10.1017/S1368980020003882

Wiss, D. A. & Brewerton, T. D. (2020). Separating the signal from the noise: How psychiatric diagnoses can help discern food addiction from dietary restraint. *Nutrients, 12*(10), 2937. doi:10.3390/nu12102937

Wiss, D. A. & Brewerton, T. D. (2020). Adverse childhood experiences and adult obesity: A systematic review of plausible mechanisms and meta-analysis of cross-sectional studies. *Physiology & Behavior, 223*(112964). doi:10.1016/j.physbeh.2020.112964

Wiss, D. A. (2019). The relationship between alcohol and glychohemoglobin: A biopsychosocial perspective. *Bioresearch Open Access, 8*(1), 146-154. doi:10.1089/biores.2019.0009

Wiss, D. A. (2019). A Biopsychosocial overview of the opioid crisis: Considering nutrition and gastrointestinal health. *Frontiers in Public Health, 7*(193). doi:10.3389/fpubh.2019.00193

Wiss, D. A., Avena, N., & Rada, P. (2018). Sugar addiction: From evolution to revolution. *Frontiers in Psychiatry, 9*(545). doi:10.3389/fpsyt.2018.00545

Wiss, D. A., Schellenberger, M., & Prelip, M. L. (2018). Rapid assessment of nutrition services in Los Angeles substance use disorder treatment centers. *Journal of Community Health, 44*(1), 88-94. doi:10.1007/s10900-018-0557-2

Wiss, D. A., Schellenberger, M., & Prelip, M. L. (2018). Registered dietitian nutritionists in substance use disorder treatment centers. *Journal of the Academy of Nutrition and Dietetics, 118*(2), 2217-2221. doi:10.1016/j.jand.2017.08.113

Wiss, D. A., Criscitelli, K., Gold, M., & Avena, N. (2017). Preclinical evidence for the addiction potential of highly palatable foods: Current developments related to maternal influence. *Appetite, 115*, 19-27. doi:10.1016/j.appet.2016.12.019

Wiss, D. A., & Brewerton, T. B. (2016). Incorporating food addiction into disordered eating: The disordered eating and food addiction nutrition guide (DEFANG). *Eating and Weight Disorders, 22*(1), 49-59. doi:10.1007/s40519-016-0344-y

BOOK CHAPTERS

Wiss, D. A., Avena, N. (2020). Food addiction, binge eating, and the role of dietary restraint: Converging evidence from animal and human studies. In Frank, G. K. W., Berner, L. A. *Binge Eating: A Transdiagnostic Psychopathology* (pp.193-209). Springer, Cham.

Wiss, D. A. (2019). The role of nutrition in addiction recovery: What we know and what we don't. In Danovitch, I., & Mooney L. J., *The Assessment and Treatment of Addiction* (pp. 21-42). St. Louis, MO: Elsevier Publishing.

Wiss, D. A., & Waterhous, T. S. (2014). Nutrition therapy for eating disorders, substance use disorders, and addictions. In Brewerton, T. D., & Dennis, A. B., *Eating disorders, substance use disorders, and addictions* (pp. 509-532). Heidelberg, Germany: Springer Publishing.

Specter, S. E., & Wiss, D. A. (2014). Muscle dysmorphia: Where body image obsession, compulsive exercise, disordered eating, and substance abuse intersect in susceptible males. In Brewerton, T. D., & Dennis, A. B., *Eating disorders, substance use disorders, and addictions* (pp. 439-457). Heidelberg, Germany: Springer Publishing.

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Introduction: Why is Childhood Adversity an Important Public Health Issue?

Life experiences during developmental periods can have a profound impact on adult health. Challenges faced by children that may have once been viewed as "harmless" are increasingly understood as capable of influencing later health. The saying "what doesn't kill you makes you stronger" is not always the case. The sequela of childhood adversity can be enduring over the lifespan, which is particularly concerning given that many exposures can be prevented.

The early life adversity (ELA) framework stems from the broader context of the life stress paradigm [1] and is often viewed through a life course lens [2]. The term ELA represents the widest ranging category of adversity exposure, including various stressors, traumas, and forms of deprivation experienced in any setting during the first 18 years of life, known to increase the risk for a wide range of physical and mental health outcomes. The broad domain of ELA can also include factors not discussed herein such as poor nutrition, toxin exposure, or lack of cognitively stimulating experiences.

The most well-known forms of ELA are Adverse Childhood Experience (ACEs) [3], which traditionally include the categories of childhood maltreatment (emotional abuse, physical abuse, sexual abuse, emotional and physical neglect) and household dysfunction (mother treated violently, household substance abuse, household mental illness, incarcerated household member, and parental separation or divorce). The term ELA subsumes the term ACEs, and they are often used interchangeability. Here, ACE-specific studies are identified to be more specific about the instrument, wherever possible (referred to as ACEs). Meanwhile, literature from the broader domain of ELA is cited to be more comprehensive, wherever possible (referred to as ELA).

The long-term consequences of ELA have been well documented. In North America, 23.4% of individuals have one ACE, and 35.0% have two or more [4]. Exposure to multiple

ACEs is a major risk factor for a variety of health conditions. Associations of multiple ACEs have been determined as weak/modest for diabetes, physical inactivity, overweight/obesity; moderate for smoking, heavy alcohol use, poor self-rated health, heart disease, cancer, and respiratory disease; strong for sexual risk-taking, problematic alcohol use, mental ill-health; and the strongest for problematic drug use and interpersonal and self-directed violence [5]. Of all the risk factors, illicit drug use had the highest population attributable fraction (defined as the fraction of all cases in the population attributable to ACEs). According to one meta-analysis, ACEs contributed to about 40% of depression cases and 30% of anxiety cases [4].

The total annual costs attributable to ACEs (based on studies published between 1990 and 2018) have been estimated to be $748 billion in North America, suggesting that a 10% reduction in ACE prevalence could equate to an annual savings of $105 billion [4]. Economic estimates follow a similar pattern in Europe [6]. These estimates do not include intergenerational effects. It has been established that outcomes associated with multiple ACEs such as illicit drug use and mental health disorders can increase risk for ACEs in the next generation, indicating intergenerational effects that can fasten families into cycles of adversity and disadvantage [5]. ACEs represent profound societal burden globally that only recently has begun to receive adequate attention.

In public health, the predominant conceptual approach is based on upstream Social Determinants of Health that fundamentally impact downstream determinants [7,8]. The World Health Organization has defined social determinants as the "conditions in which people are born, grow, live, work, and age." Thus, childhood adversity is an example of a public health problem that requires "systems thinking" utilizing social, environmental, and familial factors, then moving to the mechanisms and potential consequences, and finally synthesizing all the

information into a comprehensive model. Two key reviews summarized the social determinants of mental health [9,10]. It was suggested that while people are made vulnerable to mental illness by deep-rooted poverty, social inequality, and discrimination, mental health disorders affect everyone not only the poorest or most disadvantaged [9]. Other examples of social determinants of mental health include ACEs, poor and unequal education, food insecurity, housing instability, unemployment and underemployment, and limited access to health care [10]. Thus, there are many challenges with disentangling the impact of ELA from other forms of adversity associated with low socioeconomic status (SES).

In the mental health literature, some researchers focus on the most upstream social determinants such as SES [11,12], while others focus on midstream factors such as ELA. The link between ELA and mental health outcomes has shown that "time does not heal all wounds" [13]. Indeed, both SES and ELA are important drivers of mental ill-health. Using a social determinants of health framework, ELA can be viewed as a consequence of upstream vulnerability factors that are structural in nature (i.e., rooted in cumulative disadvantage when families face multiple forms of socioeconomic adversity), but can also be viewed as risk factors operating independently of SES. Current evidence suggests that ELA is strongly correlated with social and environmental factors (including multiple forms of parental adversity as well as neighborhood factors) but can occur across all levels of SES [14]. The social determinants of mental health framework will necessitate investigation into cumulative disadvantage, driven by contextual factors such as SES as well as exposure to stress, trauma, and adversity.

Other known consequences associated with ELA include unemployment, disability, and homelessness. Individuals with ACEs are more likely to have difficulties maintaining employment in adulthood [15,16]. Links between ACE exposure and worker performance have

been mediated by interpersonal relationship problems, emotional distress, and substance use [17]. In one sample of primarily Black low-income community dwellers, drug problems along with depressive symptoms helped explain the link between ACEs and employment barriers [18]. There is a strong graded relationship between multiple forms of adversity and self-reported disability in adulthood, after adjusting for demographic factors and potentially mediating chronic conditions [19]. Finally, data have shown a high prevalence of each ACE among individuals experiencing lifetime homelessness [20,21].

To address the question "why is childhood adversity an important public health issue?" it is important to summarize findings on the risk for all-cause mortality, including suicide. Several lines of research have shown that ELA increases the risk for premature mortality for both women and men [22–24], in some cases independent of adult lifestyle factors [23]. One noteworthy contributor to increased mortality is suicide, which may be mediated by alcohol use disorder (AUD), depressed affect, and illicit drug use [25]. The odds of suicide behaviors following combined abuse (i.e., multiple forms) is increased by over 3-fold [26]. It has been suggested that the link between ACEs and suicidality is due to multi-varied pathways, including unique stressors associated with later life [27], for example substance use disorders (SUDs) [28].

This dissertation starts with an overview of ELA, discusses its measurement, summarizes social determinants including vulnerability factors, known correlates of childhood adversity, and then transitions into a discussion of the potential consequences within the domain of mental health, as well as potential resilience factors. The literature review starts with a discussion of ELA (section 1.1), mostly referring to research using the ACE measure [3], which is described in section 1.2. Theories utilized to conceptualize the studies are described in Chapter Two. Chapter Three introduces the aims, research questions, and hypotheses for each study. Chapter Four

covers the methods including a description of the study sample and instruments utilized. Chapters Five through Seven include the findings and discussion from each study. Chapter Eight integrates the findings from all three studies into a broader discussion, including recommendations for future research, strengths, and limitations.

1 CHAPTER 1: BACKGROUND AND SIGNIFICANCE

Section 1.1 provides an overview of ELA, including various ways it has been measured across different disciplines, known social correlates including antecedents and outcomes, and relations to race and ethnicity. This section is not specific to studies using the ACE measure. A historical recap of the ACE measure (since 1998) including recently expanded versions of the instrument is then described in section 1.2. In section 1.3, literature linking both ACEs and the broader domain of ELA to mental health outcomes (post-traumatic stress disorder [PTSD], substance use disorder [SUD], depression and depressive symptoms, and anxiety as well as anxiety symptoms) are summarized. Section 1.4 introduces the concept of vulnerability to ELA, including parental adversity and neighborhood factors. Section 1.5 introduces the concept of biological embedding across multiple physiological systems and is included to provide mechanistic elaboration for the deleterious life course impact of ELA. The concept of resilience (following childhood adversity) is described in section 1.6, with emphasis on perceived social support and sleep quality. Finally, studies using the ACE measure among men who have sex with men (MSM) is introduced in section 1.7, with an emphasis on HIV and HIV-risk as well as various mental health outcomes. Chapter One is then summarized in section 1.8.

1.1 Early Life Adversity Overview

The pediatric medical literature often uses the term “toxic stress” to describe the consequences of early unfavorable conditions and environments [29]. Toxic stress has been defined as the excessive or prolonged activation of the physiological stress response systems in the absence of the buffering protection afforded by stable, responsive relationships [30]. Toxic stress during critical periods of development can disrupt brain circuitry and other regulatory systems in ways that negatively influence health behaviors later in life. While biomedical

approaches are sometimes criticized for overlooking the broader social and contextual factors that contribute to disease, the American Academy of Pediatrics has recognized the need for the pediatric community to move beyond the medical office or hospital setting and expand into the larger ecology of the community, state, and society [30].

Importantly, ELA amplifies health risks associated with stress in adulthood, thereby increasing the likelihood for multiple negative health outcomes [31]. Thus, stress can accumulate and multiply over the lifespan, reinforcing the need for a quality start in life. Furthermore, research has shown that ELA can restrict an individuals' sense of purpose in life, subsequently associated with poorer subjective health and increased likelihood of functional limitations [32]. It has recently been suggested that psychopathology emerges as a function of the subjective rather than objective childhood maltreatment experience [33]. Recent evidence suggests that mental ill-health is more likely associated with the subjective rather than objective experience of childhood maltreatment [34]. It has been recommended that ACE instruments should include a question about the perception of how upsetting each experience was [35]. The PEARLS ACE screener recently introduced in California has added a question about subjective health impact.

In this paragraph, research linking ELA to mental health outcomes will be introduced briefly, and in section 1.2, the focus will switch exclusively to the 23-year legacy of ACE research (with differences further specified in section 1.1.1). Several lines of research have identified that childhood maltreatment associates with common psychiatric disorders through latent liabilities to internalizing (e.g., anxiety, depression, PTSD, dissociation, intrusive experiences, phobia, and panic disorder) and externalizing (e.g., antisocial personality disorder, anger, irritability, SUD/AUD) psychopathology [36,37]. Among children with documented physical and sexual abuse before the age of 12 (n=496), earlier onset of maltreatment predicted

more anxiety and depression symptoms in adulthood, controlling for gender, race, current age, and other abuse reports [38]. Among adults with anxiety and/or depression (n=221), physical or sexual abuse was associated with less coherence (the quality of being logical and consistent) in the present day (similar to dissociative disorders, discussed in PTSD section) [39]. Finally, exposure to interpersonal violence has contributed to greater resistance to mental health treatment efforts [40].

1.1.1 Early Life Adversity Measurement

Human research on ELA can be conceptually traced back decades, identifying a "life stress-distress paradigm" (where stressful life events lead to negative symptoms) to capture this phenomenon [1]. ELA broadly represents multiple forms of childhood maltreatment (e.g., physical or sexual abuse) experienced in the home, deprivation including poverty and low SES, and any other stressors (e.g., insecure attachment or rejection) experienced in or outside of the home. Instruments such as the Childhood Trauma Questionnaire [41,42] and several others generally capture this construct. The adversity can be reported by the victim/child, by a parent/caregiver, or from a third party (i.e., record review). Assessment can be in the form of a self-report questionnaire, clinical interview, record review, or a combination.

The most common instrument for capturing ELA is the ACE measure [3] (see section 1.2 for detailed discussion). For clarity, data generated from the ACE measure, including expanded versions of the instrument will be identified as ACEs throughout this dissertation. While the original ACE measure captures specific exposures in the household, several expanded ACEs have been operationalized, including but not limited to low SES, single-parent home, parents always arguing, exposure to community violence, the experience of discrimination, peer victimization/bullying, below-average grades, and others. There appears to be no real consensus

about what constitutes an ACE, as several studies have modified the original scale to best fit their sample under study. Therefore, ACE screening tools are consistently far from uniform. Some investigators have removed some of the original ACE items from the household dysfunction dimension (parental separation or divorce, mother treated violently, household substance abuse, household mental illness, and incarcerated household member) to accommodate community- and school-level ACEs (e.g., bullying, violence) [43].

1.1.2 Social Correlates of Early Life Adversity

In the late 1990s, it was proposed that unhealthy environments, such as those that threaten safety, are conflictual or abusive, and undermine the creation of meaningful social ties can get "under the skin" to create health disorders [44]. Integration of stress, trauma, and adversity into conceptual models have been referred to as the "psychosocial determinants of health" by social epidemiologists [45]. The term "psychosocial" pertains to the influence of social factors on an individual's mind, brain, and behavior, as well as the interrelation of behavioral and social factors. Psychosocial factors are thought to mediate the effects of social structural factors on individual-level health outcomes [45]. These factors should not be equated with structural characteristics of societies however, they can modify social context and have long-lasting consequences at the individual level. It has been suggested that social and biological factors are inextricably linked, and that many false dichotomies between them exist [46]. The concept known as the "Biological Embedding of Adversity" will be reviewed in section 1.5, but first, emphasis will be placed on the social factors which can drive vulnerability to ELA.

Many facets of the human experience can be viewed as being socially patterned (predicted by social factors). For example, traumatized children often have significant pre-existing vulnerabilities (e.g., low SES) that entangle explanatory models. Childhood adversity

occurs within social contexts that can alleviate or exacerbate its negative impact [47]. ELA often originates from an accumulation of contextual risk factors beyond a child's control. Therefore, it is important not to always assume that group differences in health measures across ELA are simply attributable to direct changes caused by the adversity [48].

To illustrate, in a study of Finnish middle-aged men (n=2,674), many adult behaviors (e.g., alcohol, smoking) and psychosocial dispositions detrimental to health (e.g., depression) were consistently related to poor childhood conditions (e.g., low education, blue-collar employment) [49]. A cohort study from a Midwestern metropolitan county showed that adults with documented ELA histories had lower levels of education, employment, earnings, and fewer assets as adults, compared to matched controls [50]. In a longitudinal study of urban minority young adults, increased adversity was associated with poorer health by age 24 [51], but this may be because adversity is also associated with lower odds of being insured and receiving a physician checkup within the last year [52].

Thus, differentiating between the impact of low SES and ELA has created some methodological challenges since they frequently co-occur, and both predict adult disadvantage. Lower childhood SES is consistently associated with greater risk of ELA [53]. We know that SES and ELA are linked, but it is less clear how they interact dynamically over time, requiring a Life Course Perspective [54,55]. It has been consistently shown that ELA decreases the probability of employment in middle age, adjusting for background factors such as accumulated property and wealth [50]. Most authors acknowledge that there are multiple pathways by which SES determines health, with psychosocial determinants viewed as midstream factors [56].

In nationally representative data from the US, the proportion of children experiencing ACEs follows a steep income gradient, with those at the bottom having a higher likelihood of

experiencing adversity [14]. However, higher income was not necessarily found to be a protective factor, suggesting that ACEs are distributed across the income ladder. Specifically, ACEs in the dimension of household dysfunction (e.g., divorce, parental drug/alcohol use) are fairly evenly distributed across all but the highest income groups [14]. According to one study (n=6,320), child abuse exists in approximately 12% of affluent families [57]. These findings suggest that low SES is not necessarily an antecedent of all ACEs. Literature reviewed in sections 1.3 and 1.5 demonstrate that ACEs can impact mental health independently of SES.

More recently, ACEs have been framed as variables that interact with childhood household income in their association with adult SES. Using the Panel Study of Income Dynamics data, investigators have shown that ACE exposure was negatively correlated with household income, and that increases in income are associated with reduced exposure to specific ACEs: physical abuse, domestic violence, parental depression, and parental drug use [58]. Taken together, there appears to be a need to better understand several specifics (e.g., directionality of associations and their interactions) that link ELA with SES.

Studies support the concept that childhood economic adversity should be considered an ACE. In a longitudinal study of students K-12, the timing of maltreatment (abuse and neglect) was a significant predictor of cognitive impairment (i.e., knowledge, comprehension, analysis) over time, however the addition of poverty into the model resulted in nonsignificant effect of maltreatment timing [59]. Women's hardships (e.g., food and housing insecurity) during and just before pregnancy have been identified as a neglected issue in ACE research [60]. Among pregnant women ages 16-40 (n=1,503), a Socioeconomic Adversity Index (SAI) which included marital status, household structure, annual income, education, and health insurance, significantly

contributed to ELA [61]. This study found the highest potential for child abuse among the lowest SAI group. Thus, there is strong evidence to suggest that ELA frequently stems from low SES.

To study antecedents of ACEs further, Women, Infants, and Children (WIC) Supplemental Food Program data from Los Angeles suggest that a severe housing cost burden (an indicator of low SES) is associated with an increase in the odds of each ACE, however directionality remains unclear in cross-sectional data [62]. Longitudinal data from Alaska showed that the number of household challenges reported during the 12 months before or during pregnancy predicted ACEs in a graded, dose-response manner [63]. These findings suggest that prevention of ACEs should begin before birth.

A recent systematic review of global ACE data identified the following antecedents: 1) social/environmental: being part of a historically underserved population, having low social status, living in a dysfunctional environment, having poor life circumstances, and living in unfortunate environments; 2) familial: lack of parental resources, maternal mental health problems, excessive parental alcohol intake, and parental divorce; and 3) economic: poverty, and living in low-income communities [64].

To understand the causal chain further, longitudinal data from the UK found that 18% of the total effect of childhood disadvantaged SES on socioemotional behavioral problems was mediated through ACEs [65]. Thus, ACEs can be viewed as a midstream psychosocial factor in life course models but can also be seen as an upstream predictor of mental health outcomes, a concept which will be developed further throughout Chapters One and Two.

1.1.2.1 Race/Ethnicity

In this section, race/ethnicity will be introduced as a correlate to both SES and ELA in the context of mental health outcomes. A landmark paper found that Black-White differences in

self-reported measures of physical and mental health can be explained by racial differences in SES, social class, and acute and chronic indicators of perceived discrimination, as well as general measures of stress [66]. Observed Black-White differences were markedly reduced after adjusting for education and income. Nationally representative data have shown that economic status moderates the differences in ACE scores between White adolescents and adults and many racial/ethnic minority groups [67]. Findings emphasize that race/ethnicity are social constructs and do not by themselves put a child at more risk of abuse or neglect [68].

Mental health outcomes following ELA do not follow predictable patterns by race/ethnicity. Qualitative research has found that Black men describe much more persistent childhood adversity than White men [69]. The authors propose that ELA may constrain men's relationships, contributing to racial inequalities in family dynamics across the life span. A nationally representative study showed that Black children were more likely to experience all ACEs, except for parental drug use, compared to both White and Latinx children [70]. Interestingly, in a longitudinal study of high school seniors of diverse SES (n=1,093), the impact of ACEs on mental health (depressive symptoms, drug use, and antisocial behavior) was consistently worse for White young adults compared to Black and Latinx/Hispanic young adults [71]. In this study, White young adults exhibited greater vulnerability to ACEs particularly with respect to externalizing behaviors (e.g., SUDs).

It is likely that inconsistent findings related to ACEs and race/ethnicity are due to which ACEs are included in the study. Expanded ACEs that include community-level stressors such as experiencing racism disproportionately affect ethnic minorities [72]. In a sample of primarily Black children from Chicago (n=1539), nearly 20% reported only expanded ACEs, which are

often not measured when assessing ACEs [73]. In this study, males reported higher rates of expanded ACEs, particularly related to violent crime.

A limitation in the ACE framework is a lack of inclusion of immigration-related threat and deprivation, particularly psychological violence inflicted on children through increasing anti-immigration policy and rhetoric [74]. Among Hispanic children and adolescents (n=223), the likelihood of binge drinking was higher for the household dysfunction ACE of parental separation compared to childhood maltreatment ACEs when they also perceived discrimination in emerging adulthood [75]. Thus, it is important to acquire knowledge regarding specific types of victimization that different racial/ethnic minority groups may experience relative to their peers, and how this may dynamically interact with other factors.

While significant interactions between ACEs and race/ethnicity emerge for physical health outcomes in national studies, none of the interactions between ACE scores and race/ethnicity are significant for mental health outcomes [76]. Taken together, race/ethnicity appears to correlate with exposure to ACEs however does not appear to be a consistent confounder in the overall relationship between ELA and mental health. However, race/ethnicity should be accounted for in explanatory models, contextually situated in layers of structural adversity woven from threads of historically and culturally embedded inequities [77].

1.2 Adverse Childhood Experiences: History and Measurement

The original ACE measure (1998) is a seven-category (17-item) questionnaire introduced in a large managed care population at Kaiser San Diego [3]. The instrument included yes/no questions which investigate the presence of abuse (emotional, physical, sexual) and household dysfunction (mother treated violently, household substance abuse, household mental illness, and incarcerated household member) experienced during the first 18 years of life. Shortly after,

questions related to emotional and physical neglect were added to the abuse category and renamed childhood maltreatment, and parental separation or divorce were added to the household dysfunction category. A major limitation of the original study was that the sample was not representative, being predominantly White and middle-to-upper class insured patients.

The widely accepted ACE questionnaire originally showed that individuals who had experienced four or more categories of childhood adversity had a 4-12-fold increased risk for alcohol use disorder (AUD), illicit drug use, depression, and suicide attempts, compared to those who had none [3]. During the first twenty years of ACE research (1998-2018), 789 peer-reviewed articles on ACEs appeared in 351 different academic journals [78]. The category of mental health has been the most common outcome studied. A recent review of ACE trends in the US suggested that rates of parental drug abuse, incarceration, and divorce are worsening (with drug abuse being the worst) whereas all other ACEs appear to be improving [79].

The ACE measure has also been criticized for its incomplete capture of the ELA construct. It has been recommended that investigators consider weighting ACEs differentially, and incorporate the severity, frequency, duration, and timing of events [80], as well as perception, ascribed meaning, and the role of the perpetrator [81]. A recent review suggested new theoretical approaches to measuring ACEs, including weighting ACEs with more known pathology (e.g., maltreatment), considering their timing (including discontinuity of the exposure), and severity/chronicity (e.g., neglect as an event versus ongoing condition) [80]. Methodological advances in ACE research are likely to elucidate novel findings. For example, recent studies have investigated ACEs with ordinal response scales (i.e., Likert-type) to capture the frequency and intensity rather than binary yes/no [81–83]. Likert ACE scores consistently outperform (increased explained variance) traditional ACEs on most mental health outcomes.

While there are differential influences of ACE components on risky behavior, morbidity, and disability, most research validates the adverse effect of cumulative exposure (sum score) [84]. The most used cut-point (where all ACEs above are lumped into a highest exposure category) is four or more ACEs, compared to the reference group of none [3]. Other authors have used other cut-points for various statistical and substantive reasons [15,85,86]. Cumulative scoring frequently emerges rather than analysis of specific ACEs, and often along a dose-response continuum [87]. While the cumulative risk approach has proven informative when it comes to prediction, it lacks clear specification when it comes to identifying mechanistic processes which might influence diverse features of development [88].

Cumulative scoring challenges notions about what is a more severe traumatic event and assumes a single mechanism by which all ACEs lead to a specific outcome. Results suggests that pathways to poor health differ by types of ACEs, with child physical, emotional, and sexual abuse being the worst [89]. While using a scoring system remains a potent predictor of many mental health outcomes, using sum scores can obscure information about individual adversities' importance. For example, one study of youths ages 12-25 (n=243) found that physical abuse imposed the greatest risk for serious mental illness [90]. In a longitudinal study (n=454), the overall category of childhood maltreatment (which includes physical abuse) predicted the development of mental health disorders [35].

Focusing on the specific categories of ACEs has been referred to as the dimensional approach, compared to the cumulative (total) and selective (single ACE) approaches [91]. The dimensional approach combines the comprehensiveness of the cumulative approach and the distinctiveness of a selective approach. The selective approach may introduce missing variable problems since ACEs are highly intercorrelated [92]. Many researchers agree that the dose-

response method as well as examining ACEs in clusters (rather than selectively) is the best practice [93]. Meanwhile, understanding individual ACEs remains important for designing interventions. For example, it has been shown that childhood sexual abuse is a significant risk factor for sexual revictimization in adulthood [94], suggesting a need for specific psychoeducation within this exposure subgroup.

Multiple studies have relied on the use of expanded ACEs, which add additional questions, typically tailored to their population (sometimes referred to as Community Level ACEs and/or Adverse Family Experiences). For example, focus groups with low-income urban youth in Philadelphia aimed to capture stressors that emerge which are not captured by the original ACE measure (e.g., single-parent homes, criminal behavior, discrimination, among others) [95]. This led to an expansion of questions used by ACE research and clinical screening tools. Community Level Adverse Experiences were added in recent years to include acts of racism, violence, bullying, and foster care, which disproportionately affect ethnic minorities [72]. Other ACE questions have been tailored for specific populations and used worldwide (ACE-International Questionnaire [ACE-IQ]) [96].

Research in the last ten years supports extending the conventional ACE measure to more accurately represent the level of adversity experienced across various sociodemographic groups [97]. In a study of children ages 10-17 (n=1,949), additional measures (i.e., peer victimization, peer isolation/rejection, and community violence) added significantly to the prediction of mental health symptoms [98]. To illustrate the importance of expanded ACEs further, community-level stressors among Philadelphia adults (n=1,784) were associated with health risk behaviors (e.g., sexual behaviors that increase risk for sexually transmitted infection, substance misuse) and mental illness, but not with physical health outcomes [99]. Other expanded ACEs include

satisfaction with the neighborhood, low social class, and social support [100]. In summary, omitting certain adversities such as community violence and extreme poverty may underestimate mental health disparities in specific groups.

A major criticism of ACE research is recall bias [101]. However, a longitudinal study assessed the temporal stability of self-reported ACEs at three different time points [102]. Data show adequate stability in the report of maltreatment toward the individual (abuse and physical neglect) and in specific aspects of household dysfunction. While using the original ACE measure allows for comparing findings across the breadth of ACE research, it is likely to miss out on many exposures early in life that significantly impact mental health.

1.3 Adverse Childhood Experiences and Mental Health

In this section, links between ACEs and mental health are introduced broadly, while in subsequent sections, specific mental health diagnoses (i.e., PTSD, SUD, depression, and anxiety) will be discussed in greater detail. In section 1.7, the focus is on sexual minority men.

The damaging effect of ACEs have been described as nonspecific since they affect a variety of brain structures and functions [103]. There are multiple mechanisms by which ACEs can impact mental wellbeing, highlighting the need for a biopsychosocial approach. While the disease manifestations of ACEs can take decades, many impairments likely begin at a young age. Among children ages three to five, ACEs were associated with compromised social development [104]. Among adolescents aged 12-17, higher ACE scores were associated with worse reported emotional wellbeing [105]. Young adults with any ACEs (n=321) were more likely to seek help for anxiety, stress, and depression, however they were less likely to find interventions helpful and were more likely to drop out of treatment [106].

Large studies have highlighted the persistence of social, emotional, and behavioral problems among the ACE-exposed, despite having received mental health services [107]. According to a national study, having experienced any ACEs was associated with more than double the odds of having any past-year psychiatric diagnosis [108]. Thus, ACEs can be enduring over the life course, and are likely mediated by processes of biological embedding (described in section 1.5).

In the original ACE research, a dose-response relationship was identified between the number and types of maltreatment reported and mental health scores (including both depression and anxiety) [109]. More recent research has shown significant associations between ACEs and mental health disorders in later life [110]. This study found that the association between physical abuse, sexual abuse, emotional neglect, and parental separation or divorce and mental health disorders was stronger in men. In a longitudinal study (n=391) of mostly Black children, childhood maltreatment that spanned several developmental periods predicted a cascade of both internalizing and externalizing psychopathology that led to greater symptoms of depression, anxiety, SUD, and antisocial personality disorder during emerging adulthood [111]. In support of the need to expand ACE measures, evidence suggests that childhood maltreatment plus peer victimization (an expanded ACE) is additive on mental health outcomes [112].

It has been suggested that executive functioning (self-regulatory cognitive processes that enable individuals to engage in goal-oriented behaviors) mediates the relationship between ACE scores and mental health problems [113]. These findings can be corroborated by strong links between ACEs and attention deficit hyperactivity disorder (ADHD) [114–116], which can be considered a disorder of executive functioning (specifically inattention-disorganization) [117].

While associations between ACEs and general mental health outcomes have been adequately described, there is a need to disentangle the impact of individual ACEs using dimensional (categories) and/or selective approaches. For example, one study used an expanded ACE measure that included being spanked as a child [118]. Investigators found that being spanked was significantly associated with all self-reported mental health outcomes. Results stress the importance of examining the effects of cumulative ACE scores, categories of ACEs, and individual ACEs. In a longitudinal study (n=352), investigators reevaluated a meaningful cut-off for the number of ACEs needed to predict mental health outcomes (i.e., depression, anxiety, trauma, and externalizing behaviors) [119]. In their study, results suggest that a cut-off of one may be a useful proxy for risk in this population. ACE cut-points may depend on the group under study and is likely to differ across groups with lower versus higher baseline risk for the outcome.

ACEs can also be studied in clusters (i.e., dimensions) to further understand which ACE categories specifically link to mental health outcomes. Concerning four mental health outcomes: depression, anxiety, trauma, and externalizing behaviors, assessment of childhood maltreatment (emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect) was more salient than household dysfunction (parental separation or divorce, mother treated violently, household substance abuse, household mental illness, and incarcerated household member) [119]. After controlling for household dysfunction, maltreatment had significant main effects on all four outcomes. Other longitudinal research (n=10,784) has also identified that household dysfunction did not predict depression, anxiety, and PTSD, whereas childhood maltreatment did [120]. Estimates from this study suggest that childhood maltreatment increased the odds of depression (odds ratio [OR]: 1.56; 95% CI: 1.26-1.92), anxiety (OR: 1.3; 95% CI: 1.06-1.62), and PTSD (OR: 1.97; 95% CI: 1.35-2.87) compared to the low adversity class. Cleary, ACEs can

impact multiple forms of mental health, and are not all equal in their impact, therefore may require nuanced analysis of ACE dimensions (clusters) and selective (individual) ACEs.

1.3.1 Post-Traumatic Stress Disorder (PTSD)

PTSD is a potential consequence of ACEs known to have a wide range of impacts on an individual's life course trajectory. Trauma (distinct from PTSD) is a lived experience and not a clinical disorder. Although some traumatized children develop trauma-related psychopathology, others do not [48], which supports the concept of resilience among certain individuals. This section is relevant because PTSD can hinder mental health resilience. PTSD is diagnosed when symptoms such as hypervigilance, avoidance, dissociation, anxiety, anhedonia, sleep disturbance, and intrusive thoughts are present [121]. From a recent meta-analysis, children exposed to ELA had greater cognitive deficits than controls, and the greatest deficits were associated with PTSD [122]. Thus, PTSD can alter physiology and exacerbate mental ill-health.

Compared to individuals without a diagnosis, those with PTSD were more likely to assess risk for aversive events as higher [123], often referred to as threat vigilance. Being hypervigilant to threats can impair social ties and may impact one's perception of social support [124]. In a longitudinal study from the UK (n=2,332), 7.8% of the study group had experienced PTSD by age 18, however only 20.6% of those with PTSD ever received help from a mental health professional [125]. These findings suggest that PTSD may impair help-seeking behavior and thereby hinder resilience resources. For example, the pathway from ACEs to avoidant personality disorder (characterized by feelings of extreme social inhibition, inadequacy, and sensitivity to negative criticism and rejection) can be mediated by PTSD [126]. Thus, those with PTSD appear less likely to seek and benefit from mental health services.

Notwithstanding, it has been shown that positive childhood experiences and relationships can buffer the adverse effects of extensive childhood adversity [127]. Despite the optimism offered by resilience studies (reviewed in section 1.6), the overwhelming body of literature suggests that cumulative childhood adversity (e.g., poly-victimization) in conjunction with adult adversity creates the highest vulnerability to mental illness (e.g., hyperarousal, suicidal ideation) [128–131], including the co-occurrence of PTSD and depression [132].

Another well-known co-occurrence is PTSD and SUD. A recent systematic review of 29 studies described a state of anhedonia, where a reduced hedonic (pleasure) response was consistently observed in PTSD patients compared to healthy controls [133]. Anhedonia has been described as both a cause and consequence of SUDs, which is characterized by substance-seeking behavior in the face of negative consequences. A person's response to traumatic experiences, particularly given a lack of resources to process such experiences (i.e., resilience), may facilitate unhealthy coping through substance use, which may increase the risk for new traumatizing experiences. SUD will be discussed in more detail in the next section, but the following paragraph will highlight its relevance in the context of PTSD.

One proposed pathway linking ELA to SUDs is through externalizing psychopathology. Numerous studies have described the transition from ELA to SUD/AUDs [108,134–140], discussing various mediating and moderating factors such as PTSD. Among people with co-occurring AUD-PTSD, ELA was a primary predictor of unremitted PTSD [141], further exemplifying how ELA can impact resilience. Known correlates of comorbid PTSD-SUD include anxiety, depression, and suicidal ideation [142,143]. Correlates of PTSD include earlier age of first drug use [142], reward dysfunction (e.g., altered motivational processes) [144], and higher levels of impulsivity [145]. The biology of reward is discussed briefly in section 1.5.5.

Other biological indicators of PTSD, such as elevated inflammatory markers can increase risk for mental ill-health [146,147]. Biomarker data point to bidirectional associations, as there is no distinct biological signature of PTSD. In summary, pathways from ELA to PTSD are direct yet cluster and co-occur with several of the outcomes and resilience resources investigated by the current studies (i.e., drug use, depressive symptoms, anxiety, social support, and sleep quality).

1.3.2 Substance Use Disorders (SUDs)

In the original ACE study, people with five or more ACEs (compared to people with none) were 7-10-fold more likely to report illicit drug use, addiction, and intravenous use [136]. In a systematic review and meta-analysis, the OR of illicit drug use following four or more ACEs was 5.62 (95% CI: 4.46-7.07) [5]. The findings can be seen across different ELA measures and different drug-related outcomes. For example, in a national survey of adolescents ages 13-18, a potentially traumatic event before the age of eleven nearly tripled the risk of cocaine use [148]. Among methamphetamine-dependent patients undergoing detox (n=110), the age of first-time drug use was negatively correlated with emotional and physical abuse [149]. Recent results from a longitudinal study (n=2,880) link ACEs to increased risk of polysubstance abuse [150]. Numerous studies have indicated a strong graded relationship to the risk of drug initiation and associated problems from early adolescence into adulthood following ACEs [136,151,152].

Links between ACEs and alcohol/drug use were described in a nationally representative Canadian sample after adjusting for depression, anxiety, smoking, pain, social support, gender, and SES [153]. In another Canadian study, peer victimization (e.g., bullying) is one ACE that potentiates the ACE-SUD relationship [154]. In a European study, the presence of supportive childhood relationships was independently associated with moderating the risks of smoking and problematic drinking among those with elevated ACE scores [155], suggesting that resilience

factors can have profound implications for SUD risk. Resilience research linking ACEs to SUDs is sparse. One potential resilience factor is perceived social support, discussed in section 1.6.1.

Several recent reviews have summarized important biological mechanisms along the pathway between ELA and later-life addiction. Some authors have identified changes in reward processing (stronger responses to drugs), executive functioning (compromised ability for self-regulation) and affect processing (increased likelihood of self-medication in response to internal aversive states) that interact to increase the risk for SUD following ELA [156]. While some authors focus on the molecular and neuroendocrine pathways (i.e., dopamine, oxytocin, and glucocorticoid) [157], other focus on the cognitive processes (e.g., impaired memory and reasoning) [135] that increase the risk for SUD following ELA.

The neuropsychoanalytic addiction model suggests that the link between ELA and SUD is mediated by dispositions for anger and sadness [138]. Clearly, there are numerous biopsychosocial domains by which explanatory mechanisms have been investigated and described. Another example is the hypothalamic-pituitary-adrenal (HPA) axis (see section 1.5.2), which appears to be a critical factor by which chronic stress reinforces drugs' effects [158]. Other known pathways by which ELA increases SUD risk include delay discounting (preference for smaller rewards sooner over larger rewards later), which is closely linked to impulsivity (the tendency to act rash when distressed) [159–162]. In the following section, data linking SUDs to depression will be summarized, and then links between ACEs and depression will be described.

1.3.3 Depression and Depressive Symptoms

There are bidirectional associations between SUDs and depressive symptoms, including major depressive disorder (MDD), with multiple mechanisms likely to be active simultaneously [163,164]. For example, a higher frequency and intensity of ELA predicted AUD/SUD stronger

than it did for depression [165], while longitudinal data suggests that MDD becomes a consequence of AUD/SUD [166,167]. Other research has viewed depressive symptoms as a possible mediator between SES and substance use [168], whereas others have shown mediation by depressive symptoms between ACEs and SUDs [169]. Depressive symptoms moderate the positive association between community violence victimization and alcohol/tobacco use [170]. Taken together, depressive symptoms have been used as an outcome, mediator, or moderator in ACE and mental health (SUD) research. Directionality may depend on individual-level factors.

Models from Canada have failed to detect socioeconomic predictors of SUD-MDD comorbidity [171]. Meanwhile, socioeconomic disadvantage within these contexts should not be ignored, as multiple reports have documented socioeconomic gradients in long-term depression trajectories [172–175]. In line with the Life Course Perspective, early life exposure affects social development risk factors in emerging adulthood. The Acceleration Maturation Model suggests that for individuals raised in environments with multiple sources of threat and deprivation, "developmental reprioritization" manifests as earlier emergence of adult-like phenotypes [176]. Among Black men ages 19-25 in a rural setting (n=505), ACEs predicted additional adverse adult exposures, which placed them at higher risk for developing substance use and depressive symptoms [177]. Findings have been replicated in a longitudinal study of Black children and youth (n=265), where ACEs (time one) predicted depressive symptoms (time two) which in turn predicted substance use (time four) [178]. Taken together, SUD and depressive symptoms cluster and co-occur, and this is an area that has been well researched.

It is important to distinguish between a clinical diagnosis of depression, and the presence of depressive symptoms, as measured by tools such as the Center for Epidemiological Studies Depression (CESD), which has 20 questions (see section 4.2) [179]. There are a wide range of

assessment tools used for depression and depressive symptoms (e.g., the Patient Health Questionnaire [PHQ]-9 with nine questions, and brief screener PHQ-2 with only two questions).

The original ACE data demonstrated a strong, dose-response relationship between ACE score and probability of lifetime and recent depressive disorders [180]. The authors concluded that exposure to multiple ACEs increases the risk for depressive disorders decades after their occurrence. Longitudinal results from China (n=11,639) confirm a significant dose-response relationship between ACEs and adult depression [181]. Enduring emotional consequences (i.e., depression) of ACEs are not always explained by concurrent risk factors such as socioeconomic disadvantage [182]. While ELA is more common in deprived environments, reducing childhood poverty alone may be insufficient to reduce abnormalities (e.g., increased inflammatory markers) that may contribute to depressive symptoms [182]. A recent umbrella review of meta-analyses found that the presence of any ACEs doubles the odds of depression (95% CI: 1.86-2.32) [183].

Another recent umbrella review of 19 meta-analyses focused specifically on childhood sexual abuse and depression reported an OR of 2.7 (95% CI: 2.4-3.0), suggesting that childhood sexual abuse confers specific risk [184]. In a French cohort of individuals with treatment-resistant depression (n=256), depression was correlated with physical and sexual abuse, but not other forms of childhood trauma [185]. In a nationally representative sample from the US, family history of mental illness had the highest likelihood of predicting a depression diagnosis [186]. Those with a combination of family history of mental illness and childhood sexual abuse had the highest odds of depression (OR: 2.8; 95% CI: 2.7-3.0).

Links between physical abuse and major depression is stronger for men than women, despite an overall lower risk of depression among men [187]. Meanwhile, one meta-analysis found that psychological abuse and neglect were most strongly association with depression,

highlighting the potential impact of more "silent" types of maltreatment (other than physical and sexual abuse) on depressive symptoms [188]. In summary, associations between ELA and depression have been well described, and findings linking depressive symptoms to specific dimensions of ACEs are somewhat mixed. However, the strongest evidence suggests that the dimension of childhood maltreatment confers the highest risk of depressive symptoms compared to the other ACE group (e.g., household dysfunction) [189]. According to the recent umbrella review, the pooled OR for depression following exposure to any ACEs in the childhood maltreatment dimension was 2.02 (95% CI: 1.79-2.29), which is nearly identical to estimates when all ACEs (>1) were combined [183].

Several biological pathways linking ELA to depressive symptoms have been proposed and will be expanded in later sections. To introduce briefly, alteration in the neural circuitry that support reward processing may influence the emergence of depression following ELA, which is also closely related to SUDs. Investigators have identified the ventral striatum (limbic structure implicated in reward processing) as a possible mechanism by which individuals can experience reduced ability to feel pleasure (anhedonia) [190]. Stress-induced alterations to the ventral striatum may mediate the link between ELA and depression, as well as increase the risk for other forms of adversity throughout development. A recent systematic review and meta-analysis identified cortisol dysfunction as a potential predictor of MDD [191]. Taken together, biopsychosocial models of depression allow for a comprehensive understanding of the causes and consequences of depression following ELA. More research is needed on the biological mechanisms of depression. To date, no single marker has been agreed upon.

An important resilience factor in the context of outcomes following ELA is social support, which can buffer mental health disorders such as depression. In an Irish cohort

(n=2,047), exposure to ACEs (including the sum score, category score, or individual experience) was associated with higher odds of depressive symptoms, but only among individuals with poor perceived social support [192]. These findings suggest that higher levels of social support attenuate this association, therefore may be an important mental health resilience factor. Childhood maltreatment has been associated with a lack of remission during treatment for depression (those exposed were twice as likely to develop recurrent and persistent depressive episodes), indicating a reduction in resilience capacity [193]. Research investigating novel resilience factors (e.g., sleep quality) and established ones (self-esteem, self-efficacy, coping) may prove beneficial for interventions related to depression-related outcomes following ELA.

1.3.4 Anxiety and Anxiety Symptoms

Diagnostic criteria for anxiety include the presence of excessive worrying that is challenging to control [121]. According to a recent meta-analysis, ACEs can be attributed to about 30% of anxiety cases in North America [5]. According to this study, the pooled relative risk for anxiety following two or more ACEs is 2.25 (95% CI: 1.43-3.56) compared to individuals with no ACEs. Estimates from the most recent umbrella review of meta-analyses are slightly less (OR:1.94; 95% CI: 1.82-2.22) with the childhood maltreatment dimension even lower (OR: 1.86; 95% CI: 1.62-2.14) [183]. In a large study of children (n=39,929), anxiety estimates following exposure to multiple ACEs are even lower (OR: 1.7; 95% CI: 1.4-2.1), suggesting that anxiety symptoms can accumulate over the life course following other known risk trajectories. Meanwhile, anxiety disorders are more likely to emerge during childhood than most other psychiatric disorders [194].

ELA, PTSD, SUDs, depression, and anxiety frequently cluster and co-occur, with impairment greatest among patients with multiple disorders [195,196]. A review article that

discussed comorbid anxiety and SUD described a mutual maintenance pattern wherein each condition perpetuates the other [197]. General anxiety disorder and panic disorder (which includes panic attacks) have the strongest associations with SUDs [197]. According to these authors, pathways capturing the co-occurrence can include: 1) self-medication where anxiety leads to SUD, 2) substance-induced anxiety disorder pathway, and 3) a third variable pathway via genetic predisposition to both or through anxiety sensitivity, which may also serve as shared vulnerability to both.

Anxiety sensitivity (fear of anxiety and arousal-related sensation) has been described as a malleable cognitive-affective factor that holds relevance in both SUD and PTSD. Findings from a recent systematic review (n=35 studies) suggest that anxiety sensitivity may moderate or mediate the association between PTSD and SUDs [198]. Among individuals diagnosed with a social anxiety disorder, those with co-occurring AUD reported higher levels of ELA, lower levels of maternal care, and lower cooperativeness (indicating externalizing psychopathology) [199]. In line with the Life Course Perspective, ACEs predict adverse adult experiences, indicating general revictimization and increasing psychiatric comorbidity with anxiety [196].

In a smaller study of adults (n=264), negative affect and trait anxiety have been shown to independently mediate the relationship between ACEs and health anxiety in adulthood [200]. Among primary care patients (n=4,606), each type of ACE was significantly associated with increased anxiety symptoms in adulthood [201]. The indirect effect of ACEs on anxiety via emotional dysregulation among those with lower levels of psychological resilience only held for emotional abuse and household dysfunction [201]. Results suggest that certain types of ACEs may be more profound in the development of anxiety. It has been shown that ACEs may lead to

increased repetitive negative thinking (sometimes referred to as rumination in PTSD context), leading to increased anxiety symptoms [202].

Consistent with a biopsychosocial approach, a brief overview of biological factors associated with anxiety will be reviewed here. In a longitudinal study of non-medicated adolescents (n=240), a prior anxiety diagnosis was associated with higher levels of IL-6 (pro-inflammatory cytokine) at follow-up, suggesting that anxiety in childhood could alter inflammatory markers [203]. Additionally, amygdala function can be affected by ELA, increasing fear and anxiety including reduced efficacy of the caregiver as a "safe haven" [194]. Multiple pathways link ELA to anxiety, but less is known about potential resilience resources. For example, no studies have documented the moderating effects of sleep quality (see section 1.6.2) on anxiety symptoms following exposure to childhood adversity.

1.4 Vulnerability Factors

Why do individuals who have experienced similar patterns of ELA have different outcomes? Vulnerability has been described as a "state of heightened sensitivity to a stressor by mounting inappropriate or ineffective defense mechanisms that also implies a lack of resistance and absent or impaired resilience" [204]. Models of vulnerability draw from the Diathesis-Stress Theory [205]. Diathesis refers to a tendency for a medical condition, latent weakness, or vulnerability to manifest once the individual is exposed to certain risks or stress. Thus, adverse environments can activate a latent diathesis in the form of behavioral, physiological, or genetic predispositions. Simply put, this theory views some people as particularly vulnerable to adversity. Vulnerability is thus viewed from social, psychological, and biological domains. This section is included as important context for the integrated conceptual model described in section 2.5, and because vulnerability is closely related to resilience (covered in section 1.6).

The Differential Susceptibility Model was developed to advance the Diathesis-Stress Theory by considering that susceptibility to environmental influences can work "for better and for worse" [206]. The very same individual attributes (e.g., genotype) that compromise development or function under adverse conditions can also predispose one to develop or function well under positive or supportive circumstances [207–209]. The theory incorporates an evolutionary perspective that suggests humans have evolved to produce variability not only in the heritability of externalizing behavior but in susceptibility to environmental influences [210]. The dual risk designation derives from the synergistic effect of inherent individual risk interacting with environmental risk, often understood as Gene x Environment (GxE) interactions, including the concept of polygenic plasticity (GxG and GxGxE interactions) [211,212]. To illustrate the concept of differential susceptibility, a study of 1,364 families showed that 15-year-olds who were considered highly negative as infants reported more externalizing behavior if they experienced low-quality childcare, but fewer if they experienced high-quality care, relative to those with less difficult temperaments in infancy [213]. Thus, vulnerability relates to resilience.

Miller et al. (2011) described a Biological Embedding of Childhood Adversity Model where childhood stress becomes "programmed" into cells that will subsequently show an increased inflammatory response when exposed to a challenge, with decreased capacity for modulating this response [214]. Behaviorally, the model assumes that ELA gives rise to excessive threat vigilance, mistrust of others, difficulty forming deep social ties, impaired self-regulation, and unhealthy lifestyle choices. Heightened awareness of potentially threatening situations leads to abrasive exchanges creating difficulties garnering social support from others [214]. The notion inherent in life course trajectory models is that adversity begets adversity. In a nationally representative sample, higher levels of ACEs had stronger associations to adult life

stress and transdiagnostic psychopathology [215]. Thus, ELA itself is a vulnerability factor, but there are important antecedents of ELA that link biological sensitivity to context. These include familial, psychological, social, and environmental factors.

Behavioral indicators of susceptibility are grounded in neurobiology and maintained by natural selection. It has been suggested that individuals of all ages vary in neurobiological susceptibility to environmental influences and that this susceptibility varies across the life span [216]. Daskalakis et al. (2013) introduced a three-hit concept of vulnerability, which includes: 1) multigenic inputs, 2) early life environmental inputs and experience-related factors, and 3) programmed phenotypes with differential susceptibility to later-life challenges [217]. When all three hits are present, mental functioning can become compromised, leading to a higher risk of psychiatric symptoms. The Theory of Latent Vulnerability contends that altered threat processing is a potential consequence of early neglectful or maltreating environments [218]. Hypervigilance to threat reduces attentional resources that would otherwise be allocated to other domains of functioning, including wider social and academic achievement. Ignoring these factors may lead to missed opportunities to target interventions for the most vulnerable children, offsetting risk trajectories before psychiatric disorders emerge.

1.4.1 Parental Adversity

In this section, research suggesting that psychiatric disability can occur through parental adversity will be discussed. This perspective introduces the potential for biological/genetic factors to play a role, in addition to the social and environmental determinants. Not surprisingly, adversity can reverberate across generations, therefore familial legacies of disadvantage remain likely and relevant to ACE research. In a German cohort of children ages 7-17 (n=2,111), investigators found a significant interaction between parental education and stressful life

situations (i.e., parental accident, mental illness, or severe financial crisis) in predicting children's mental health problems after adjusting for control variables [219].

In a US cohort of children and parents living in urban poverty (n=2,750), exposure to three or more ACEs before age three was significantly associated with the top-risk behavior category at age five [220]. Low SES in childhood also exacerbates substance use problems, including drug-related mortality and long-term unemployment [221,222]. A seminal review article proposed that risky families characterized by conflict, aggression, neglect, cold and unsupportive relationships create vulnerabilities that disrupt psychosocial functioning and lead to risky health behaviors (e.g., substance use) and subsequent mental health problems [223]. Thus, many mental health problems can be viewed as socially constructed and patterned through vulnerability factors, including parental adversity.

A study of children in an urban environment (n=1,815) suggested a relationship between parental psychopathology and childhood sexual abuse [224]. These authors proposed that parental physical and psychiatric impairment, stress, neglect, or decreased monitoring of child behavior may have contributed to this outcome. The study emphasizes the need to incorporate upstream vulnerability factors into conceptual models, although they are not easily modifiable. To illustrate further, cohort data from Finland found that both parents' psychiatric issues and the mother's receipt of psychiatric disability pension increased the risk for offspring disability pension due to mental disorders [225]. These findings highlight the importance of childhood determinants of mental health outcomes, which may also be due to genetic predispositions.

Furthermore, in a representative German sample (n=2,531), mental illness in a household member was associated with a nearly 5-fold increase in the risk for all types of childhood maltreatment [226]. Authors have identified several biological embedding pathways by which

stress can be transferred to the fetus during the prenatal period [227]. This concept has also been described in a recent longitudinal study (n=185), showing a significant indirect effect of parent maltreatment exposure on offspring maltreatment exposure and mental health, through parental emotional stressors and adversities [228]. These findings suggest that intervening with the parent to provide support and resources to meet basic needs and better cope with emotional stressors may reduce risk for generational and intergenerational transmission of adversity.

1.4.2 Neighborhood Factors

To further introduce potential vulnerability factors for ELA, neighborhood factors are described as important considerations. However, the original ACE measure did not capture any. Even when families can provide safety at home, children can experience adversity outside the home. This includes neighborhood or school violence, bullying, and denigration in many forms, resulting from prejudice and/or "othering," as well as stress caused by continuous exposure to discrimination and marginalization based on race/ethnicity and/or sex/gender [229]. A longitudinal study showed that lower neighborhood cohesion and higher neighborhood stress was associated with greater depressive symptoms in children/adolescents [230]. Child protective services are disproportionately experienced as a life event in children from poor and non-White neighborhoods [231]. Meanwhile, it remains unclear how the home environment mediates the links between neighborhood conditions and adverse adolescent outcomes.

A study of 4,898 US children and their mothers (64% living in poverty) found that neighborhood collective efficacy was indirectly associated with delinquency, behavior problems, and social skills by age 15, through family processes (i.e., parenting stress and exposure to ACEs) [232]. Specifically, ACEs significantly mediated the link to adolescent delinquency and behavior problems, but not social skills. This work showed that neighborhood structural

disadvantage and collective efficacy have direct impacts on ACEs, bullying victimization, and social emotional development, as well as indirect impacts on adolescents' depressive symptoms [233]. Taken together, neighborhood factors should not be ignored in ELA frameworks that attempt to identify streams of causation, often requiring multilevel modeling approaches.

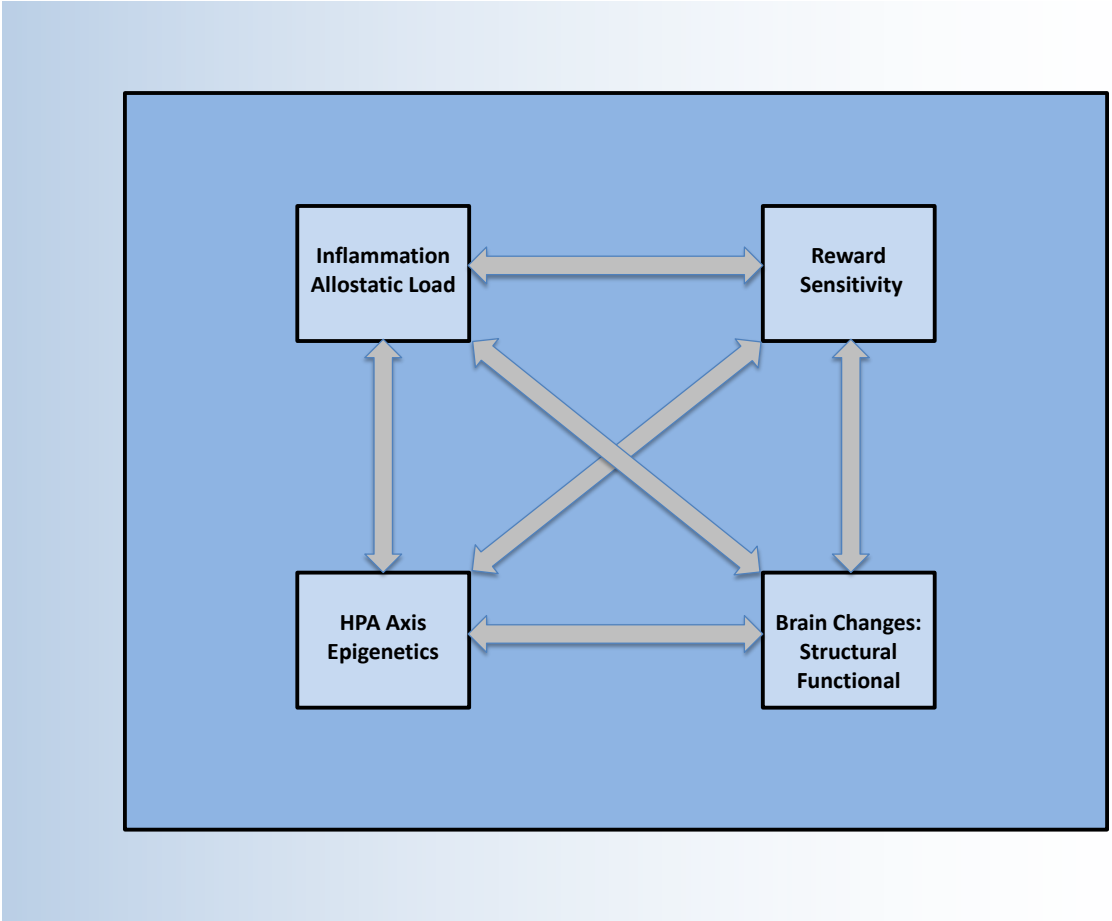
1.5 Biological Embedding of Adversity Overview

The Biological Embedding of Adversity includes multiple pathways by which early life social conditions can alter physiology, cross-associate with other vulnerability factors, hinder resilience resources, and increase the risk for psychiatric conditions. ELA can disrupt biopsychosocial development in children in various ways, weaving into their neurobiological infrastructure and negatively impacting developmental trajectories. The idea that early life conditions and circumstances can become directly embedded into human biology is a relatively new topic. This section is included because the mechanisms help to make sense out of the psychological and behavioral manifestations that link ELA to mental ill-health. ACEs have been shown to impact multiple body systems, and the following sections briefly focus on: proinflammatory cascades (i.e., inflammation), the HPA axis, epigenetic modification, and structural, functional, and morphological brain changes, including impaired reward sensitivity (i.e., the mesolimbic dopaminergic pathway).

The Developmental Origins of Health and Disease proposed by Barker focuses on how fetal programming translates into later pathology [234–236]. Hertzman emphasized how SES gradients sustain processes that lead to differing levels of mortality among social classes, stating that "socioeconomic differences in the quality of early life experiences contribute to subsequent gradients in health status" via cumulative disadvantage [237,238]. Biological pathways underlie the social gradient in health, leading to the hypothesis of biological embedding based on four

criteria: 1) experiences alter biological and developmental processes, 2) systematic differences in experience in different social environments across society lead to systematically different bio-developmental states, 3) differences are stable and long-term, and 4) differences have the capacity to influence health, well-being, learning, or behavior over the life course [239]. Many of the effects of adversity accumulate over time, therefore a Life Course Perspective is needed. An important premise is that the "hidden wounds" described below help explain the long-term impact of ELA on mental health, although more research is needed. Figure 1.1 represents a roadmap for the following brief sections, originally published elsewhere [240]. More evidence on the cross-associations between these pathways is needed and is outside the current scope.

Figure 1.1: Interconnected Biological Embedding of Childhood Adversity Pathways



1.5.1 Inflammation and Allostatic Load

The immune system regulates the inflammatory cascade. Immune dysregulation may be one pathway that explains the link between ELA and elevated rates of morbidity and mortality. Early life immune activation sensitizes traumatized individuals to the effects of subsequent stressors [241]. Thus, greater stress sensitivity resulting from ELA may put people at greater risk for multiple forms of immune dysregulation [242]. Specifically, epigenetic changes following ELA have been proposed to increase the production of monocytes and macrophages with strong pro-inflammatory tendencies [214]. Along with many other roles, these immune cells are a primary source of cytokines, which are immunomodulating agents. Common examples include interleukins (IL) and tumor necrosis factors (TNF).

In a meta-analysis of 36 studies, trauma exposure was associated with elevated levels of C-reactive Protein (CRP), IL-1-beta, IL-6, and TNF-α [243]. In this report, the presence of psychiatric symptoms was a significant predictor of increased effect sizes for IL-1-beta and IL-6. In a New Zealand birth cohort (n=1,037) followed for 32 years, maltreated children had graded increases in the risk for clinically relevant CRP 20 years later, independent of co-occurring early life risks, stress in adulthood, smoking, and physical activity [244].

Early stress research by Bruce McEwen identified “allostatic load” (AL) as the cost of chronic exposure from repeated environmental challenges, as a biological mechanism leading to a wide range of diseases [245]. A later definition described AL as the “price of adaption that can lead to disease over long periods” [246]. Social environments have major impacts on human physiology by influencing the process of adaptation or allostasis. The original AL study used ten parameters (e.g., blood pressure, total cholesterol, glycosylated hemoglobin, cortisol, epinephrine, norepinephrine), which were dichotomized based on clinical cut-offs to determine

an index score based on out-of-range values [247]. Longitudinal research (n=1,189) supports the concept of AL as a measure of biological burden [248]. Thus, AL may be a suitable indicator of the physiological wear-and-tear embodied over the life course [249] and has been used in many studies, often using different biomarkers (e.g., various cytokines).

In a longitudinal study from Scotland (n=4,488), higher AL scores were not associated with an increased risk of all-cause mortality after five years however became significant after ten [250]. These investigators also found that AL was not associated with specific causes of death, suggesting broad wear-and-tear across multiple physiological systems. To corroborate these findings, a longitudinal study of adults (n=157) showed that those who experienced any type of abuse in childhood demonstrated steeper rises in inflammation over time [251].

Prolonged influences on the biological stress system during development may increase individual susceptibility to later mental health disorders. Several recent reviews have proposed that gut-based immune responses leading to inflammation are likely to play a role in altered reward processing and reactivity, suggesting a potential role of neuroinflammation in both depression and addictions [252–254]. More specifically, inflammatory mediators can act on cortico-amygdala (threat) and cortico-basal ganglia (reward) circuitries in a manner that predisposes individuals to self-medicating behaviors such as smoking and drug use [255].

In line with the concept of vulnerability factors presented in section 1.4, potentially important antecedents and social patterns of inflammation will be reviewed. A recent meta-analysis of 43 studies concluded that proinflammatory pathways are likely an important mechanism translating SES inequalities to mental health disparities [256]. Lower education levels consistently emerge as important predictors of AL [257–259]. Meanwhile, other associations between SES and AL are not totally accounted for by variations in adult SES and

stress exposure, supporting the conclusion that ELA is not always redeemable by subsequent experience [260]. In summary, ACEs predict increased inflammatory processes over time in conjunction with other social factors that frequently cluster with ACEs, lending credence to the Biological Embedding of Childhood Adversity framework [214].

1.5.2 Hypothalamic-Pituitary-Adrenal (HPA) Axis

The HPA axis is a major neuroendocrine system that governs stress-reactivity throughout the body. The stress response is a complex, multilevel mechanism largely dependent on feedback regulation. The hypothalamus is part of the limbic system partly responsible for regulating the autonomic nervous system, with input from the hippocampus (which is associated with memory). In the paraventricular region of the hypothalamus, corticotrophin-releasing hormone (CRH) is produced, traveling to the anterior pituitary gland, stimulating the production of adrenocorticotropic hormone (ACTH), which in turn stimulates the adrenal cortex to produce glucocorticoids (cortisol in humans) [261]. Alterations in any of the organ systems along the HPA axis following exposure to ELA has the potential to impact the stress response, and such impacts may persist over the life course, with implications for mental health outcomes.

The glucocorticoid receptor (NR3C1) is present in cells throughout the body where cortisol and other glucocorticoids bind. While glucocorticoids are primarily recognized as the main hormone secreted in response to stress, they are also known to exert their effects throughout the body and brain, affect learning and memory, cognition and reward-related behaviors, and other processes [262]. It has been shown that the first 1,000 days of life are a critical period for long-term developmental programming, and the NR3C1 gene is key for epigenetic regulation (i.e., methylation, reviewed in section 1.5.3) in response to ELA [263].

In a meta-analysis of 30 studies, investigators reported an association between ELA and blunted cortisol response to social stress [264]. Cortisol suppresses the immune system by preventing the release of proinflammatory mediators, therefore a blunted response can be considered suboptimal. Cortisol is a primary outcome in many stress- and adversity-related studies and is often viewed as the simplest way to document abnormal HPA axis function. Many investigators create cumulative markers of the HPA axis by combining cortisol awakening response, evening cortisol, and dexamethasone suppression cortisol. In a study from the Netherlands (n=2,778), individuals with severe ELA had significantly higher levels of cumulative HPA axis markers, partially explained by higher rates of smoking, BMI, and chronic diseases [265]. In summary, the HPA axis and fluctuating cortisol levels represent an important biological pathway which may help describe the effect of embodiment following psychosocial adversity. This is one of the many mechanisms which interact with other physiological systems to increase the risk for compromised mental health (e.g., anxiety) over the life course.

1.5.3 Epigenetic Modification

Epigenetics is the study of how various facets of the environment regulate the genome, best described as changes in gene function without gene sequence changes. In contrast to genetic sequences, epigenetic alterations are potentially reversible [266]. For this reason, early childhood may be a "sensitive" rather than "critical" period (reviewed in section 2.2) since epigenetic mechanisms can be realtered in later life, leading to stable positive outcomes [267]. While epigenetic mechanisms are temporally dynamic, adjusting in the short- and long-term to various environmental influences [268], some authors point toward the relative stability of epigenetic marks even years after the exposure was experienced [269]. Longitudinal data suggest that exposures before three years of age explain more variability in epigenetic modification than the

accumulation or recency of exposure [270]. Thus, epigenetics represents an important bridge between the social and biological sciences. Following ELA, specific epigenetic alterations linked to psychiatric outcomes are likely dependent on multiple individual factors, consistent with the concept of differential susceptibility.

The focus of this section is on DNA methylation, which is an enzymatically catalyzed modification of DNA affecting long-term phenotypes [271], therefore one plausible mechanism through which ELA can become biologically embedded. DNA methylation involves adding a methyl group to the fifth carbon on the pyrimidine ring [269]. DNA methylation at gene promoter sites is generally associated with some form of a repressed response, but hypomethylation also has important consequences, requiring further research. It has been found that both DNA methylation and demethylation mechanisms are induced by ELA [272].

The epigenetic regulation of the hippocampal glucocorticoid expression (increased cytosine methylation at NR3C1) has been shown in humans [273]. A systematic review of 40 ELA studies in both animal and human (including in-utero adversity) found that most studies reported increased methylation at the exon 1_F variant of the NR3C1 gene [274]. While most studies in humans demonstrate increased NR3C1 methylation following childhood maltreatment, others do not [275]. Concerning psychiatric outcomes, several papers indicate that NR3C1 methylation levels correlate with depression [276–279]. Other methylation sites such as the serotonin transporter gene (SLC6A4), brain-derived neurotrophic factor (BDNF), and oxytocin receptors (OXTR) have relevance for both depression and anxiety [276–279]. Collectively, this data demonstrates the diverse and complex epigenetic alterations associated with ELA. While epigenetic research is still in its infancy, data reviewed herein suggest a mechanism relevant to ELA, providing strong support for biological embedding.

1.5.4 Structural/Functional/Morphological Brain Changes

ELAs effect on brain structure, function, and size provide convincing biological evidence for many of the documented health and social problems related to childhood adversity. Integration of neuroscience research has helped uncover mechanisms by which ELA places individuals at risk for mental and behavioral health problems. In this section, neuroimaging data following ELA will be reviewed, including the prefrontal cortex (PFC), responsible for executive functioning; the hippocampus, largely responsible for memory; and the amygdala, which plays a primary role in the processing memory, decision-making, and emotional responses. These systems do not work in isolation, but rather communicate through various pathways that may depend on gray and white matter as well as other brain systems outside of the current scope.

Functional magnetic resonance imaging (fMRI) techniques best capture metabolic activity, whereas structural (sMRI) captures anatomical features. Positron emission tomography (PET) is a functional imaging technique. Finally, voxel-based morphometry (VBM) is used to measure volumetric brain changes.

A recent review covered three processes by which ELA can influence brain and behavioral development in ways that are adaptive in the short-term but may break down over the long-term: 1) threat detection processes, 2) reward-related processes, and 3) cognitive control [280]. The authors identified four primary psychological and behavioral consequences: 1) emotional reactivity (threat vigilance in the amygdala), 2) reward responsivity (reward processing in the ventral striatum), 3) emotion regulation (modulation of the amygdala by the PFC), and 4) delay discounting (the tendency to select smaller sooner rewards over larger later ones). All four can be considered trans-disease processes, which helps explain why health-risk behaviors frequently cluster among individuals [280].

Among adolescents (n=58) exposed to ELA, VBM revealed a reduction in gray matter volume, which may be involved in increased risks for mental health problems later in life [281]. Structural MRI data on individuals in SUD treatment (n=79 compared to 98 healthy controls) revealed that ELA-related gray matter volume reductions predicted relapse severity [282]. Among deprived adoptees (n=67 compared to 21 non-deprived adoptees), total brain volume was strongly associated with deprivation duration (between 3-41 months), after accounting for potential environmental and genetic confounders [283]. This study also found that smaller brain volume was associated with lower IQ and more ADHD symptoms. The authors concluded that time-dependent severe deprivation in the first years of life was related to brain structure alterations, despite extended enrichment in adoptive homes in subsequent years [283].

ELA has been shown to impair executive functioning (mental skills that include working memory, flexible thinking, and self-control), which may be one explanation of why maltreated children are at higher risk for academic, psychological, behavioral, and social problems relative to their peers. A recent systematic review of 36 studies revealed a strong relationship between maltreatment and executive functioning deficits among children [284]. This association is stronger for deprivation than threat [285]. Family member illness (particularly maternal depression) has also been associated with poor executive functioning [284], highlighting the need to investigate vulnerability factors whenever possible. These findings implicate the importance of biological and genetic factors that are often overlooked in social science research.

There is an increasing body of literature documenting decreased hippocampal volumes following ELA. A meta-analysis of 15 articles found that those with ELA had lower hippocampal volumes [286]. The consequences of reduced hippocampal volumes may include broad associative memory difficulties. In an fMRI study of children and adolescents ages eight to

19 (n=59), violence-exposed children showed selective disruption of associative memory for threat cues, regardless of age, likely contributing to poor life outcomes through multiple pathways [287]. In one study of children who experienced ELA (n=128), smaller hippocampal volumes were noted in children who were physically abused or from low SES households [288]. These findings strengthen the argument that low SES can, in many cases, be considered a form of adversity with enduring consequences over the lifespan. Research is needed on the resilience of hippocampal volume following ELA but will be difficult to adjust for other contextual factors.

Morphological research on the amygdala remains inconclusive. A meta-analysis of individuals exposed to ELA showed no strong evidence of differences in amygdala volume [286]. Individual studies introduce more nuance to these findings. In one longitudinal sample of adolescents (n=117) using MRI, childhood maltreatment predicted accelerated growth of the left amygdala over time [289]. A recent study concluded that investigation of total amygdala volume may not provide an adequate index of the link between the amygdala and stress-related mental illness [290]. A better understanding may come from the study of amygdala reactivity and connectivity. Among low-income boys followed for nearly 19 years (n=310), fMRI revealed that harsher parenting and greater neighborhood deprivation as a toddler predicted clinically significant symptoms of antisocial behavior via decreased amygdala reactivity [291].

1.5.5 Reward Sensitivity

In this final section, evidence linking ELA to altered reward sensitivity is summarized. ELA is a common antecedent of adolescent and adult affective disorders involving reward circuitry, with relevance for SUD. The primary neurotransmitter associated with addictions is dopamine, which contributes to various addictions through its differentiated roles in reinforcement, motivation, and self-regulation [292]. The mesolimbic pathway transports

dopamine from the ventral tegmental area (VTA) to the nucleus accumbens (NAc), amygdala, and hippocampus. In the context of SUD and PTSD, three major neural systems have been identified: 1) motivational reward (the "wanting" that drives the motivation necessary to claim the reward), 2) consummatory reward (the experience of pleasure when a reward is received), and 3) reward learning (adaption of behavior based on reward history) [144]. Early experiences of maltreatment have a long developmental reach, resulting in reward-related neural alterations [293] with profound implications for substance-seeking behavior.

Brain sensitization in PTSD (e.g., diminished corticolimbic response to pleasant and aversive psychosocial stimuli) may interfere with reward valuation [294]. Individuals with PTSD have been shown to have increased dopamine transporter density, which may reflect a higher dopamine turnover and potentiate exaggerated fear responses to cues associated with past trauma [295]. The overlaps between stress and reward neurobiology suggest that any changes in stress neurobiology are likely to influence reward [296]. It is not necessarily positive or negative reinforcement to avoid withdrawal symptoms that drive SUDs, but rather the learned association of relief from an aversive mental state that drives cravings in susceptible individuals [297]. Such learned associations may be established for life. Altered functioning of key reward-related frontostriatal circuits is most pronounced when maltreatment and depression co-occur [298].

As discussed throughout, ELA alters core aspects of affect and cognition that subsequently increase the risk for additional pathology. ELA results in deficits in ventral-striatum-related functions of reward responsiveness and approach motivation, particularly when the stressor is experienced in early development [296]. The ventral striatum includes the NAc and is associated with the limbic system, implicated as a critical part of decision-making in the context of reward-related behavior. Among 20 individuals exposed to a high degree of

psychosocial stressors (including ethnic minority status and living in an urban environment), resting-state MRI showed increased corticostriatal connectivity between the ventral striatum and brain regions implicated in salience, compared to controls (n=22) [299]. Salience can be understood as the assignment of value, which works with the memory to "learn" behaviors. Among children ages 9-12 (n=40), MRI suggested that ELA is associated with alterations in the brain's sensitivity to rewards [300]. Findings suggest that the link between ELA and reward processing could be explained, in part, by differences in the ventral striatal response to rewards.

Impulsivity refers to an individual's propensity to have a compromised ability to engage in top-down inhibitory control in the face of reward anticipation [301]. Impulsivity is a multidimensional construct spanning several psychological domains with links to both dopamine and serotonin [302]. According to this review, key frontostriatal circuits may link multiple forms of adversity to drug use and other addiction-related behaviors. Impulsivity has been negatively correlated with dopamine in the PFC: higher impulsivity levels relate to lower concentrations of dopamine, which creates a positive feedback loop leading to increased impulsivity [303].

A final construct linking ELA to SUDs is delay discounting, which is related to impulsivity and may be a consequence of brain-related changes. Delay discounting describes the process by which individuals discount temporally displaced rewards more steeply in favor of immediate rewards. It has been suggested that elevated temporal discounting rates are a predisposing factor rather than a consequence of compulsive behavior [304]. A recent meta-analysis of neuronal correlates of delay discounting found that reduced ventral striatum activity was associated with an impaired valuation process [305]. In summary, the effect of ELA on reward sensitivity can be captured by a range of behavioral processes, but the most notable outcome is SUD, implicating biological embedding in the pathway between ACEs and drug use.

1.6 Resilience Factors

Most of the original theories on resilience came from developmental psychologists and psychiatrists during the 1970s. Resilience is not just the inverse of an individual's vulnerability [306], nor is it the absence of psychopathology [307]. Resilience factors can be defined as characteristics, skills, and resources that reduce the risk of mental problems following ELA. Although ELA is a powerful predictor of psychopathology, the relationship is not deterministic, as a significant proportion of individuals exposed to ELA function better than expected [308], which may be due to differential susceptibility as well as various resilience factors. Because resilience in relation to ELA may stem from positive adult experiences, a life course trajectory approach is needed that measures risk and protective factors over time. Resilience continues to be difficult to measure because of its broad definition, and difficulty comparing findings given that numerous instruments have been utilized.

Early contributions to resilience concepts came from Michael Rutter [309–312]. Rutter described a "steeling effect" where the experience of stress or adversity can sometimes strengthen resistance to later stress [313]. Such concepts can be inferred from observing individual variations in outcomes among individuals exposed to ELA. Resilience starts with the assumption that given the same dose of stress, trauma, or adversity, there will always be marked heterogeneity in response [314]. In some cases, appropriate experience in adult life can counter the effects of ELA. While individual differences in response to adversity may reflect biological pathways influenced by genes, there is always the need to consider the social context of possible influences [315]. Ungar (2019) stated that resilience is "best understood as the process of multiple biological, psychological, social, and ecological systems interacting in ways that help individuals to regain, sustain, or improve their mental wellbeing when challenged by one or more

risk factors" [316]. Culture and context will influence what resilience looks like and the processes by which individuals manage situations when stress levels are heightened.

Resilience is a dynamic process (not a trait) that operates through the lifespan- before, during, and after adversity. It encompasses several interacting features, including emotion regulation abilities, flexibility, coping strategies, health behaviors, self-esteem, prosocial skills, and a positive outlook. Mental health resilience describes the process of effective adaptation, naturally linked to the question of preventing stress-related disorders. Among young Black gay and bisexual men in New York City (n=228), the resilience factor of self-efficacy emerged as more important than social support in promoting resilience to distress, depression, and anxiety [317]. These findings suggest there is not a single way resilience plays out across various groups.

Resilience represents a category of protective factors among people who have experienced ELA. In a community-based longitudinal study from the UK (n=571 adolescents and their parents), resilience (defined as the absence of mental health problems in adulthood) following childhood maltreatment was related to perceived parental care, adolescent peer relationships, the quality of adult love relationships, and personality [318]. In another study linking ACEs to school-related outcomes, the strongest protective factor was a parent who could communicate with their child about things that matter and share ideas [319]. A cross-sectional study from China found that the impact of ACEs on depression and anxiety can be buffered by high levels of resilience (as measured by the Connor-Davidson Resilience Scale) [320]. Meanwhile, in an Irish longitudinal study of older adults, the investigators found no evidence that resilience (as measured by the Resilience Scale) mediated the association between ACEs and depressive symptoms [321]. Findings suggest that other ACE-related factors (e.g., poverty,

biological embedding) may make individuals less responsive to the protective influence of resilience, necessitating an examination of the larger socioecological context.

Most research suggests that childhood adversity hinders resilience. Among 14-year-olds exposed to ELA, there were significantly lower levels of resilience factors compared to those unexposed [322]. Among children ages 6-17, ACEs decrease resilience in a dose-dependent manner after controlling for child, family, and community factors [323]. A study of a community-based sample of Black adults (n=1,962) found lower resilience capacity associated with maltreatment, with no differential influences due to developmental timing [324].

The importance of socio-contextual factors (e.g., supportive relations, community resources) continues to emerge in resilience literature [308,325]. Community-level resilience factors can include neighborhood safety, neighborhood amenities (e.g., libraries, parks), access to mentorship, and others. Actions that strengthen community resilience assets may partially offset the immediate harms of ACEs [326]. More research is needed to understand mechanisms by which resilience factors buffer the impact of ACEs on mental health, and how this may vary across different sociodemographic groups.

Given the growing importance of resilience in the context of ELA, it has been suggested that a combined assessment of positive childhood experiences together with ACEs may better target needs and interventions, which may enable strategies to promote wellbeing [327]. In a South Carolina study, it was suggested that urban children may be less likely than rural children to have positive childhood experiences (social connections with family and community) [328]. Some investigators have referred to these prosocial connections as counter-ACEs, which have been shown to diminish ACEs negative effect on young adult health and independently contribute to better health outcomes [329]. A recently published Resilience Protective Factors

Checklist includes individual, family, and community level buffers to ELA known to contribute to positive outcomes [330]. Future ACE research should incorporate these variables into models to better capture factors known to interact and counteract with adversity over the life course. Specific focus on how resilience may manifest across generations is needed.

Below is a summary of resilience's neurobiological markers, drawn from key articles published within the last few years. Individual differences in inflammatory reactivity (often measured by cytokines such as IL-6 or CRP) may explain why certain individuals exhibit differing susceptibility to the impact of stress [331,332]. The ability to modulate negative emotions (via the amygdala) using cognitive control strategies may be a resilience marker. Other factors that become increasingly important during adolescence include reward processing, affective learning, and self-regulation, all governed by neurobiological processes which are influenced by contextual factors (e.g., family, peers, social environment) [333]. A recent review suggested that the resilient brain's development seems closely tied to the emergence of intact social networks [334]. Other mechanisms of resilience have been found in the HPA axis [335].

1.6.1 Perceived Social Support

One important resilience resource in the context of ELA is perceived social support. Pioneering work on social support initially described it as information rather than the provision of services and material aid [336]. Later work described social support as a characteristic of the interaction between the recipient and the provider [337]. Hupcey (1998) defined social support as a "well-intentioned action that is given willingly to a person with whom there is a personal relationship and that produces an immediate or delayed positive response in the recipient" [337]. The studies reviewed below use a wide range of instruments to capture the construct of social support, ranging from the Multidimensional Scale of Perceived Social Support (MSPSS),

Perceived Social and Emotional Support, Social Provisions Scale, ENRICH Social Support Index, Interpersonal Support Evaluation List, and several unvalidated questionnaires. Other disciplines have used the concept of social capital [338,339] and social networks [340,341] to capture the importance of social relationships in health.

Findings linking low levels of social support to poor mental health outcomes have been described. In a nationally representative Swedish sample, poor social support was independently associated with mental ill-health [342]. This relationship has been explored in the context of exposure to ELA. In a representative German sample, ELA was associated with reduced social support [343]. Childhood maltreatment may compromise the capacity to build or utilize supportive relationships [214]. Meanwhile, among adults (n=7,047), the life course impact of ACEs on mental health was mitigated by always having support from a trusted adult during childhood [344]. Younger age individuals tend to identify family members as their strongest sources of support whereas older individuals identify friends and community members [345].

Recently, investigators have attempted to define "complete mental health" as the absence of mental illness in combination with almost daily happiness and/or life satisfaction, as well as high levels of psychological and social wellbeing [346]. In their study of Canadians adults (n=17,665), complete mental health among survivors of childhood sexual abuse was related to social support and lifetime history of favorable mental health conditions.

Multiple studies have shown that social support and social networks partially mediate links between ELA and mental health outcomes [341,347–349]. Furthermore, among adults with at least one ACE (n=12,487), individuals who reported that they usually/sometimes received social support were 87% less likely to report current depression, compared to those who rarely/never received it [350]. Other studies have demonstrated that lack of social support, as

well as low-income and adult adversity, are conduits for which ACEs exert their detrimental influence on mental health in adulthood [351]. These authors conclude that social support is a critical resource in buffering the effects of life stressors on mental health, but it is vulnerable to erosion by the adversities that spawn the stress. Perceived social support has shown to be protective of anxiety in cross-sectional data [352] and identified as a mechanism by anxiety symptoms improve in an intervention study [353]. However, there is a lack of data examining social support as a protective factor between ELA and drug use.

1.6.2 Sleep

One of the known consequences of ELA is impaired sleep over the lifespan. Sleep disturbances are both a mediator and moderator linking ACEs to a wide range of mental health outcomes. They may contribute to consequences of ELA that modulate later quality of life [354].

It has been recently proposed that sleep quality might be an important resilience resource. In a large cohort of adults (n=19,333), the authors found that sufficient sleep was consistently associated with fewer days of poor mental health and had significant interactions with ACEs for all but the oldest age group [355]. This reinforces the potential for sleep and other health behaviors to buffer the vestiges of ELA. In a longitudinal study of adolescents (n=2,280), resilience significantly mediated the effects of all family dysfunction trajectories on sleep quality [356]. Most of the research linking ACEs to sleep disturbance is not adversity-specific, however some studies have linked childhood sexual abuse to sleep in adulthood [357,358]. Childhood sexual abuse may be a nonspecific risk factor for sleep disorders above and beyond the impact of depression and PTSD.

There is a graded inverse relationship between sleep quality and cumulative ACE score [359,360]. Using the original ACE study sample (n=17,377), those with five or more ACEs were

over twice as likely to report trouble falling or staying asleep, compared to those with no ACEs [360]. In a nationally representative study, each ACE increased the odds of short sleep duration by 20% and was not explained by symptoms of poor mental or physical health, suggesting unique causal mechanisms [359]. One potential pathway is through nightmares [361,362], which is also correlated with PTSD. Among trauma-exposed adults (n=349), sleep difficulties played a key role in explaining PTSD, with links through physical factors (e.g., inflammation) and psychological factors (e.g., cognition) [363].

Sleep complaints after exposure to ELA can persist even in old age. In a national sample of adults ages 60 and older, early parental emotional abuse was associated with impaired sleep through hindered development of supportive social relationships later in life [364]. This in turn was associated with more emotional distress and ultimately decreased subjective sleep quality. Life course models investigating sleep patterns following ELA may elucidate mechanisms by which adversity impacts mental health (e.g., depression) in older age.

An important correlate of sleep disruption is depressive symptoms. Insomnia or hypersomnia is part of the diagnostic criteria for Major Depressive Disorder [121]. While the relationship is likely bidirectional, evidence supports sleep disturbance as predictive of future mood disorders [365–367]. In a meta-analysis of 21 longitudinal studies, the odds of depression following insomnia increased by 260% [367]. Research on US military personnel (n=759) showed an indirect effect of ACEs on depressive symptoms through sleep disturbance [368]. Other research in college students (n=399) documented sleep quality as a mediator between ACEs and depressive and anxiety symptoms [369].

Statistical models should account for the U-shaped association between sleep duration and incident depression [370]. A nationally representative study has shown that when sleep

duration is less than eight hours, increased sleep is associated with lower risk of incident depression, whereas when sleep duration is more than eight hours, depression risk increased with longer sleep [370]. Taken together, impaired sleep appears to be one sequelae of the life course trajectory following ELA that is less documented in the context of mental health research. However, given that links between sleep and depressive symptoms are not straight-forward, a nuanced approach to modeling this relationship is required.

While most studies have focused on poor sleep as an outcome, mediator, or effect modifier, fewer studies have investigated sleep as a protective resource. In a longitudinal study (n=715) starting from ages three to five through early adulthood (ages 21-26), good sleep emerged as a resilience factor in young adults [371]. Adequate sleep could be conceptualized as a resilience factor that moderates the link between ACEs to both depressive and anxiety symptoms, however this has not yet been shown.

1.7 Men Who Have Sex with Men (MSM) Overview

The purpose of this section is to highlight health disparities among MSM and other sexual minority groups, defined as non-heterosexual, transgender, or non-binary individuals. Being transgender and gender nonconforming has been associated with worse mental health when compared to cisgender lesbian, gay, and bisexuals [372]. Other groups of people who identify as “mostly heterosexual” or “unsure of sexual identity” rather than MSM have higher rates of victimization as well as suicide attempts [373,374].

According to a recent systematic review of 16 US studies, the prevalence of MSM among men ranges from 3.8-6.4% [375]. However, fewer people identified as MSM than reported sexual experience or attraction with other men, suggesting that stigma associated with sexual identity could downwardly bias this estimate.

Multiple studies have documented higher rates of ACEs among sexual minority groups [376–380]. Sexual minority groups have more frequent SUD/AUD and psychiatric comorbidity, which is exacerbated in the presence of ACEs [379,381]. Sexual minority populations exposed to household dysfunction as children (parent/adult incarcerated or has SUD or other psychiatric condition) had much higher likelihood of an early sexual debut [382], which can open the door for other forms of vulnerability and adversity. According to this study, eight in ten respondents reporting sexual debut before age 13 were exposed to ACEs.

In a sample of MSM adults (n=2,590), nearly 80% reported exposure to at least one ACE [383], which is over three times higher than the general population [4]. ACE exposures are more likely to cluster with other forms of childhood adversity rather than occur in isolation. For example, one study indicated that ACEs and peer bullying explained the health disparities between sexual minorities and heterosexuals [377]. In a longitudinal study of 16-29-year-olds assigned male at birth who identify as sexual and gender minorities, pre-trauma inflammation amplified the effect of incident trauma exposure on perceived stress at follow-up [384]. These findings corroborate with the biological embedding processes described in section 1.5.1.

At the intersection of two minority statues, several studies have investigated health outcomes among Black MSM, who experience high rates of both HIV and incarceration [385]. In a study of low-income Black MSM (n=542), participants were more likely to engage in transactional sex if they did not complete high school, suggesting that HIV risk behavior (see section 1.7.1) may be linked to undereducated neighborhoods [386]. Black men testing positive for HIV (n=99) had significantly more sexual partners, condom-less sex, and more transactional sex when PTSD was present [387]. In another investigation (n=536), almost 90% of Black MSM experienced at least one ACE, and all ACEs were significantly associated with adult mental

health [388]. The presence of multiple marginalized identities contributes to cumulative disadvantage which necessitates life course models to capture collective and accruing risk.

Finally, MSM status has also been associated with unstable housing in the presence of ACEs [389,390], which supports a social determinants of health framework for explaining MSM health disparities. These findings are particularly relevant for the group under study (see section 4.1). In summary, MSM (especially Black MSM) appear disadvantaged with respect to ACE exposure, experiencing higher prevalence of ACEs than non-MSM. Disparities in mental health outcomes among MSM are discussed in section 1.7.2, but first, data on HIV will be reviewed.

1.7.1 MSM & HIV

HIV incidence decreased by 14.8% between 2008 and 2015, among all transmission risk groups except for MSM [391]. According to this study, the percentage of undiagnosed HIV infections remains higher among Black and Hispanic/Latinx persons than White persons. According to a systematic review and meta-analysis (n=12 studies), MSM with a history of childhood sexual abuse were more likely to be HIV+ and to engage in recent condom-less anal intercourse [392]. In one sample of older adults (n=131, ages 54+) at an outpatient HIV clinic, 40% reported experiencing sexual abuse in childhood [393]. Individuals with childhood sexual abuse histories had higher cytokine levels than those without, suggesting that the physiological sequelae of childhood trauma may persist into older adulthood among those living with HIV.

Investigators have also found that MSM with a history of childhood sexual abuse were more likely to report substance use and sex under the influence of alcohol and drugs [392]. Intravenous drug users are at high risk of HIV infection [394]. Of all the drugs, crystal meth appears to associate with the most risk. A systematic review (n=61 studies) reported that compared to HIV+ MSM who do not use crystal meth, HIV+ MSM who do are more likely to

report high-risk sexual behaviors, incident STIs, and condom-less anal intercourse [395]. Frequent meth use has been consistently associated with HIV-related outcomes [396].

For males, the odds of HIV risk increased significantly following exposure to at least one ACE [397]. According to a recent systematic review and meta-analysis of 19 studies pooled across multiple populations, the proportion of STIs attributable to childhood adversity was 33% [398]. Other research has suggested that the cumulative impact of ACEs best characterizes HIV risk-taking behavior [399]. One example of high-risk sexual behaviors is transactional sex. Global data suggests that transactional sex is associated with a significant elevation in HIV prevalence [400]. Among MSM enrolled in the mSTUDY (n=511; current study sample, described in section 4.1), HIV viral load was significantly associated with transactional sex [401]. More research is needed to understand the life course trajectories by which ACEs may confer increased risk for HIV among socially disadvantaged MSM. In national data, the effect of ACEs on HIV/STIs was fully explained through PTSD and intimate partner violence perpetration among men [402].

1.7.2 MSM & Mental Health

Mental health and other psychosocial problems such as substance use, depression, anxiety, and violence frequently cluster and co-occur for many MSM. The presence of multiple risk factors for poor health has been described as "syndemic" [403–405]. Associations between urban MSM and anxiety and depressive symptoms are consistent in the literature, particularly among those who are HIV+ [406,407]. It has been suggested that HIV diagnosis often precedes depressive symptoms [408]. Two recent meta-analyses suggested that the pooled prevalence of depression and depressive symptoms among MSM in China is between 38.9-47.5% [409,410].

Approximately one-third of MSM report anxiety, while one in five report suicidal ideation [410]. In the presence of ACEs, significant associations with anxiety and worse mental health quality of life have been reported [411]. In one sample of MSM (n=304), models showed an indirect effect of ELA on adult psychological distress through dysfunctional thoughts toward oneself [412]. ACEs are associated with poor mental health outcomes, and marginalized groups such as MSM are at higher risk for ACEs, exemplifying cumulative disadvantage over the life course. Meanwhile, evidence reviewed above suggests that other experiences associated with being MSM (e.g., stigma) can also predict poor mental health outcomes in the absence of ACEs.

MSM have higher rates of SUD [413]. Among Black and Latino MSM reporting childhood sexual abuse before the age of 16, nearly half (46%) scored at or above the diagnostic cut-off for harmful drug use or dependence [414], which is approximately five times higher than SUD rates in the general population [415]. In meth-using MSM (n=286), nearly a quarter met the criteria for antisocial personality disorder [416]. Among MSM enrolled in the mSTUDY (n=534), meth was the most influential predictor of depressive symptoms as well as an inability to improve over time [417]. Among persons living with HIV in New York City (n=7,986), persistent drug users were more likely to have an unsuppressed viral load compared to non-users [418]. “Chemsex” has been described as using specific drugs during planned sexual activity to sustain or enhance sexual functioning [419]. A recent systematic review found frequent reports of adverse mental health outcomes and documents of chemsex-related inpatient admission [420].

Like other ACE research, there is a growing interest in identifying mental health resilience factors among MSM exposed to multiple forms of adversity. Among MSM in China (n=714), the effect of ACEs on depressive symptoms has been shown to be moderated and buffered by resilience [421]. Recent mSTUDY data (n=379) suggest that increasing social

capital resources may impact the HIV-prevention continuum [422]. It has been suggested that social support can play a protective role regarding HIV risk [423]. A recent systematic review of interventions for sexual minority groups found that all interventions improved mental health outcomes [424], suggesting that investment into resilience and recovery factors among MSM can be productive.

1.8 Chapter One Summary

ELA has a pronounced impact on an individual's mind, brain, and behavior over the life course, giving rise to excessive threat vigilance, mistrust of others, difficulty forming deep social ties, impaired self-regulation, and unhealthy lifestyle choices. Childhood adversity usually originates from an accumulation of contextual risk factors beyond a child's control. Antecedents include socioeconomic disadvantage, parental mental health (which includes biological/genetic predispositions), family structure, education, neighborhood safety, and other environmental exposures. It is important to consider both vulnerability and resilience factors including supportive relations, community resources, and positive childhood experiences. ELA can impair resilience resources such as the perception of social support, which has been linked to poor mental health outcomes. Research investigated the moderating effect of resilience resources (e.g., social support, sleep quality) following ACEs is limited among mental health outcomes.

ACEs represent a major health and financial burden globally. An accumulation of risk by multiple forms of stress, trauma, adversity, and social disadvantage increases the likelihood of poor mental health outcomes, particularly in the absence of resilience factors. ACEs have been shown to confer nonspecific risk for a wide range of adverse health conditions across all socioeconomic groups. A significant body of literature shows that ACEs predict PTSD, SUD, depression, anxiety, and poor sleep. All sexual minority groups appear disadvantaged concerning

both ACE exposure and mental health outcomes. Psychosocial problems such as substance misuse and depressive symptoms frequently cluster and co-occur for many MSM (the group under study). Research linking ACEs to mental health outcomes is limited among MSM.

The Biological Embedding of Adversity describes multiple pathways by which early life social conditions can alter physiology, cross-associate with other vulnerability factors, and increase the risk for psychiatric conditions. Biological embedding pathways lead to inflammation and allostatic load, alterations in the HPA axis, epigenetic modifications, as well as structural, functional, and morphological brain changes, including impaired reward sensitivity. The Biological Embedding of Adversity framework can help to elucidate the social determinants of specific health outcomes and may identify pathways of risk across the life course.

Embodiment of ELA disrupts physiology and alters differential susceptibility by way of cumulative disadvantage, compromising mental health at all socioeconomic levels. Emerging individual-level biological evidence on ELA suggests that childhood adversity is an important and often overlooked upstream risk factor, which is noteworthy given that these exposures are somewhat preventable. When stressors accumulate and multiply over the lifespan through biological, psychological, social, and environmental factors, they reinforce the need to reduce ACEs to promote quality starts in life, particularly among socially marginalized groups. In the next chapter, foundational theories which drive the research questions will be described.

2 CHAPTER TWO: THEORY

2.1 Theory Overview

A theory summarizes the cumulative knowledge used to explain, predict, and influence behavior across different populations and contexts. At present, no single theory can fully explain the complexity and pathways that give rise to ELA as well as describe potential long-term consequences. This chapter summarizes three theories from various disciplines to propose an integrated conceptual framework linking ELA to adult mental health outcomes. This chapter discusses the Life Course Perspective, the Biopsychosocial Model, and the Fundamental Cause Theory, separately, and then conjunctively.

2.2 Life Course Perspective

The Life Course Perspective (LCP) was pioneered by sociologists and has since been used in medicine and more recently, by public health researchers. Medical perspectives influenced by the Development Origins of Health and Disease and the Biopsychosocial Model (see section 2.3) overlook the potential for later life interventions to alter disease progression. This created a need for updated models to consider that health may be adaptive with changing environmental contexts over time [425,426]. Thus, life course research shifted the time frames of interest from months and years to decades and even the entire life span. Although many diseases and disorders are diagnosed in older age, these conditions generally reflect injury incurred from exposures earlier in life. This is particularly relevant for the current dissertation which aims to capture associations between childhood adversity and adult mental health outcomes.

Simply collecting exposure data across time is not synonymous with a life course model for disease causation [427]. The LCP also considers how widespread social change (e.g., political, economic) can alter developmental paths of both individuals and groups. The LCP has

been utilized across several possible models, including latency and pathway (or trajectory) models, which are discussed below. All hypothesize streams of causation that can be direct and/or indirect, biological and/or psychosocial, and occur across the domains of space and time.

The core constructs of LCP include: 1) *Early Programming* (discussed previously in the Biological Embedding of Adversity section 1.5), 2) *Sensitive and Critical Periods*, 3) *Cumulative Impact*, and 4) *Risk and Protective Factors* [428]. A primary objective in each of these constructs is to understand how health develops and how disparities are created and perpetuated over time. LCP calls for greater investment in community health by improving the social conditions that can be considered fundamental causes of health inequities (see section 2.4).

Sensitive and Critical Periods. Exposure to various types of adversities can cause long-term, gradual damage to health in separate and independent ways, or they may cluster in socially patterned ways [427]. Timing matters. Latency models describe how discrete events that tend to occur early in life can have a strong independent effect later in life, whereas pathway models look at their cumulative effect along developmental trajectories [238]. Latency models recognize "sensitive" periods- windows of time during which an exposure is extremely influential and outside of that window becomes less relevant [429]. A "critical" period of exposure must occur during a specific window to have its effect, as originally proposed by the fetal origins of adult disease hypothesis [234], later renamed the Developmental Origins of Health and Disease.

Cumulative Impact. The LCP highlights the complex inter-relationships and arbitrary differentiation between social and biological mechanisms [427,430]. A primary premise is that these mechanisms influence health and disease independently, cumulatively, and interactively [431]. Cumulative biological models consider how each additional period of risk exposure can induce lasting physiological harm [429]. An example would be brain changes following ELA in

the context of persistently low SES throughout childhood and adolescence (see section 1.5.4). Trajectories describe sequences of experiences which can include various life transitions over time [55]. Social trajectory models emphasize "sticky" exposures such as social position, which tend to have long-lasting effects on health [429]. For example, if education is a mechanism through which class-based inequalities are reproduced, then education-based stratification in early childhood can be expected to amplify across the life course [432]. Thus, childhood disadvantage can be compounded across the life course with chains of further adversities [433].

Since individual lives are embedded in larger contexts, LCP incorporates constructs such as social ties, which are known to change over time and contribute to both positive and negative health behaviors [340]. The Cumulative Inequality Theory proposed by Ferraro (2009) incorporated knowledge from the Biological Embedding of Adversity framework to consider how various social factors get "under the skin" and accelerate aging [434]. This theory focuses on how social systems generate inequality that reverberate over the life course. As disadvantage accumulates, trajectories can be altered, which can in turn impact anticipated consequences (for example incarceration). Thus, personal trajectories are shaped by the accumulation of risk factors, available protective resources, and an individuals' perception of these trajectories [434].

Risk and Protective Factors. Pathway models have also been called "chains of risk" models, considering various mediators and moderators at points along the causal chain [430]. An example would be an investigation of potential resilience factors following exposure to ACEs in the context of mental health outcomes (see section 1.6). Fortunately, some unfavorable risk trajectories can be mitigated by the magnitude, onset, and duration of protective resources [435].

The LCP also considers how socioeconomic advantage over a lifespan can be protective of better health in elderly years, consistent with the concept of resilience resources. As advantage

continues to grow over time, it can be conceptualized in terms of increasing return on resources such as education [436]. While individuals are faced with many choices and paths to follow, these choices are constrained by the opportunities structured by social institutions (e.g., culture, community) [55]. Unfortunately, many health behaviors and psychosocial characteristics change little over generations [49], and in some cases, upward social mobility does not mitigate or reverse the adverse effects of early life SES on adult health [437]. Some contend that adult health is the cumulative outcome of childhood circumstances plus adult socioeconomic resources and lifestyles [438]. Clearly, social disadvantage early in life perpetuates throughout the life course.

Concerning ELA, many of its effects appear "sticky" but to date, there is a shortage of longitudinal resilience research in the context of mental health. Importantly, the effects of ELA should be considered in conjunction with, as well as independent of, SES in life course models. Because the studies herein link exposures in early life to outcomes in adulthood, the LCP is the primary theory driving the research questions, conceptualized as a trajectory model. Meanwhile, it is unlikely that any single life course model will adequately account for the widespread associations of ELA to neurodevelopment, behavioral health, and adult mental health outcomes. Therefore, additional theories are needed for mechanistic explanation.

2.3 Biopsychosocial Model

Engel's Biopsychosocial (BPS) model (1977) proposed an update to the prevalent biomedical model at that time to include psychosocial components of illness, with the hope of creating better patient understanding and care [439,440]. Reductionistic medical models assume only physiological processes are causally relevant. Thus, the BPS is seen as a patient-centered model that incorporates a broader context, to reflect the social responsibilities of disciplines such as psychiatry (which has become increasingly cross-disciplinary due to ACE research).

However, in this dissertation the BPS will not be invoked as a clinical model, but rather used to conceptualize the physiological mechanisms by which ELA can impact mental health trajectories, particularly among marginalized groups.

The BPS model substantiates the relevance of biological embedding pathways (reviewed in section 1.5) and provides important theoretical context for life course trajectories following childhood adversity. First, the strengths of the BPS model relevant to this dissertation will be summarized, then several shortcomings and critiques will be discussed.

Health is not simply about biology, which is in many ways structured by an individual's psychology and the societal context. Engel advocated for physicians to evaluate all the potential factors contributing to illness, as well as the experience of being a patient. The BPS model is grounded in General Systems Theory, which contends that all levels of organization are linked to one another in a hierarchical relationship: changes in one level affect change in others [439]. General Systems Theory orders the world into a hierarchy from the most elementary particles to the individual person, to social phenomenon, and the universe.

The primary strength of the BPS model is the effort to investigate the multilevel interactions that contribute to health and illness. This includes genetic susceptibility, harmful biological exposures, childhood and adolescent experiences, SES, personality, acute and chronic stressors, lifestyle behaviors, social networks, and their combined effects on physiological functioning [441]. The BPS provided the groundwork for the intersystem communication among the neural, immune, and endocrine systems in the context of psychopathology and related outcomes. The BPS framework has been referred to as a "revolution" bridging science and humanism, while recognizing that medicine has been slow to incorporate psychosocial components such as emotions, family, and community contexts [442]. Thus, BPS can be viewed

as an integrative approach concerned with the intersection of disciplines, which is a primary strength but also limiting in its implementation.

One criticism of BPS models in health psychology is the failure to incorporate culture, which informs and influences all aspects of the model [443]. Viewing the BPS model as a dynamic (rather than hierarchical) system would permit broader patterns of shared culture, norms, policies, and values [444]. Others have argued that better collaboration with neuroscience is essential to understanding causal chains by which social circumstances and psychological processes link to disease through specific neurobiological mechanisms [445]. Others criticize the BPS model for being epistemologically naïve with respect to the way research into illness, disability, and wellbeing is conducted [446]. For example, critical explorations about professional power and status are needed in the context of capitalistic sub-systems that reinforce them [446]. Such arguments are posed by the social determinants of health framework (see section 2.4), which are underrepresented in BPS models, as well as in medical training.

The most common criticism of the BPS model is on the issue of mental health. Surprisingly, psychiatry is the only branch of medicine lacking a well-formulated theoretical basis with logically derived models with true predictive power [447]. Unfortunately, psychiatry often ignores social determinants such as migration, poverty, illiteracy, and inequitable distribution of resources [448]. Although the BPS provides a holistic approach to the conceptualization of psychiatric illness and has theoretical potential in clinical science, it fails to translate into measurable clinical outcomes [449]. It is likely that Engel did not intend for it to be a clinical decision-making model, but rather a starting point for further development. While a BPS model may be one way to form a rounded, multidimensional view of mental disorders, the downside is that the levels proposed by Engel make it hard to envision specifically how the

unique systems interact. Despite criticisms, the potential for complex, multifactorial top-down and bottom-up directions of influence are important for psychiatry [450], as well as for the comprehensive conceptualization of the dissertation studies.

While it is common knowledge that both illness and health results from interactions between biological, psychological, and social factors, true integration has not been achieved [451]. Recently, an updated theoretical model called the BPS pathways has been proposed [452]. This breaks down the model into testable pathways that can assess subjective well-being as well as objective health outcomes, with the goal of advancing the field of personalized medicine.

Importantly, subjective psychological experiences are particularly relevant for understanding individual differences in response to various exposures [453]. ELA is one example of how subjective interpretation (of its meaning and impact) can especially matter for mental health outcomes [34]. Despite its shortcomings, the importance of biological pathways in the trajectory from ELA to adult mental health necessitate application of the BPS model. For example, childhood adversity can alter immune function which can in turn impact brain development, with implications for the formation of prosocial bonds as well as risky health behaviors, that all impact mental health outcomes [214,241]. Meanwhile, additional theories that focus explicitly on social factors are also required.

2.4 Fundamental Cause Theory

The Fundamental Cause Theory (FCT) [454] has been recognized as one of the leading theories in the social determinants of health [455]. FCT contends that public health initiatives focusing on specific diseases are futile if fundamental causes such as SES are still at play. Link and Phelan (1995) argue that exposures and risk factors commonly identified in medical and epidemiological research need to be contextualized into people's life circumstances. The FCT

focuses on why people are exposed to risk in the first place, de-emphasizing mediators identified in causal pathways because intervention strategies become the new and exciting "next step" and thereby neglect the importance of social factors. Such consequences can be unintended, for example, when an original interest in studying social support as a moderator of stress becomes overshadowed by higher impact research focusing on the biological consequences of stress [454]. Social placement and structural forces are viewed as mechanism-generating and should receive more attention by researchers and advocates for social change. FCT does not ignore mechanisms but rather aims to identify their origins.

There are four key components to the FCT which are required to define a fundamental cause: *1) Affects Multiple Disease Outcomes.* The identified cause is nonspecific and therefore not limited to one or a few health problems. For example, low SES has been linked to mortality through a wide range of causes, which have been explained through health-damaging behaviors [456] as well as cumulative risk [457]. *2) Affects Disease Outcomes Through Multiple Mechanisms.* There will be several pathways by which a fundamental cause can translate into disease over the lifespan. For example, low SES has been associated with increased allostatic load [458–460]. Meanwhile, other mechanisms such as living in less socially cohesive neighborhoods could similarly be used to explain the pathway between low SES and poor health [461,462]. *3) Associations Will Reemerge Even When Intervening Mechanisms Change.* Simply tracing the mechanisms that link fundamental social causes to disease will not fully capture the underlying associations to SES. Basic social conditions (e.g., low SES including low levels of education) will reproduce various mediating mechanisms, therefore efforts to elucidate pathways can be misleading by failing to recognize the importance of the underlying conditions needing to be explained [454]. Furthermore, higher SES groups will be better positioned to take advantage

of new knowledge, innovations, and technology. *4) Embodies Access to Resources.* This component considers how limited access to resources and different forms of deprivation harm health, but also how access to resources can be used to minimize risk and address the consequences of disease once it occurs. The deliberate use of flexible resources such as money, power, knowledge, prestige, and beneficial social conditions is essential in maintaining the enduring association between SES and mortality [463]. Applying the conditions of FCT to the ELA construct, it is proposed here that ELA meets all four criteria:

Affects Multiple Disease Outcomes. ACEs increase the risk for SUD, depression, suicide, smoking, risky sexual behavior, and severe obesity, even among socially advantaged groups [3]. Noteworthy findings that childhood trauma increases the risk of suicide have recently been replicated [273]. Multiple ACEs are a major risk factor for a wide range of health conditions [5] that drive the recent decrease in life expectancy, particularly since 2014 [464]. This has been attributed to increased mortality from drug overdoses, suicides, and organ system diseases among young and middle-aged adults from all racial/ethnic groups. Pathways to embodiment are likely to be moderated by vulnerability factors and certainly confounded by social factors, which further contextualize risk, consistent with "multiple causation" [465].

Affects Disease Outcomes Through Multiple Mechanisms. ACE data combines epidemiological and neurobiological evidence, where functional alterations in the brain affect psychological and psychosocial mechanisms known to contribute to a wide range of mental disorders [466]. The damaging effect of ACEs is nonspecific. This nonspecific risk pattern may increase vulnerability to numerous psychiatric disorders, which frequently cluster and co-occur with ELA. Perhaps the most convincing pathway is through illicit drug use. For example, among adolescents, exposure to any potentially traumatic event before age eleven years nearly tripled

the risk of cocaine use [148]. Any alterations in the reward system are likely to interfere with one's ability to goal-direct their decision-making behavior.

Associations Will Reemerge Even When Intervening Mechanisms Change. Epigenetic changes associated with childhood trauma create widespread associations with neurodevelopment [467] (section 1.5.3), including changes in the mesolimbic dopaminergic circuit (section 1.5.5), which predict overall poor self-regulation and impulsive behavior [134]. To illustrate, an fMRI study showed that ELA predicts subjective responses to reward-related cues as well as a weaker response in brain regions implicated in learning and motivation [468]. Alterations in the mesolimbic reward circuitry can interfere with an individual's ability to recruit executive functioning processes [156]. Not discounting the importance of contextual and structural factors, human behavior is largely influenced by individual capacity for reasoning and decision-making, which is negatively impacted by ELA. For example, an individual predisposed to addiction-like behaviors who dodges dependence on alcohol or drugs may develop a "food addiction" leading to obesity [469–471], or gambling [472], or risky sexual behavior [473].

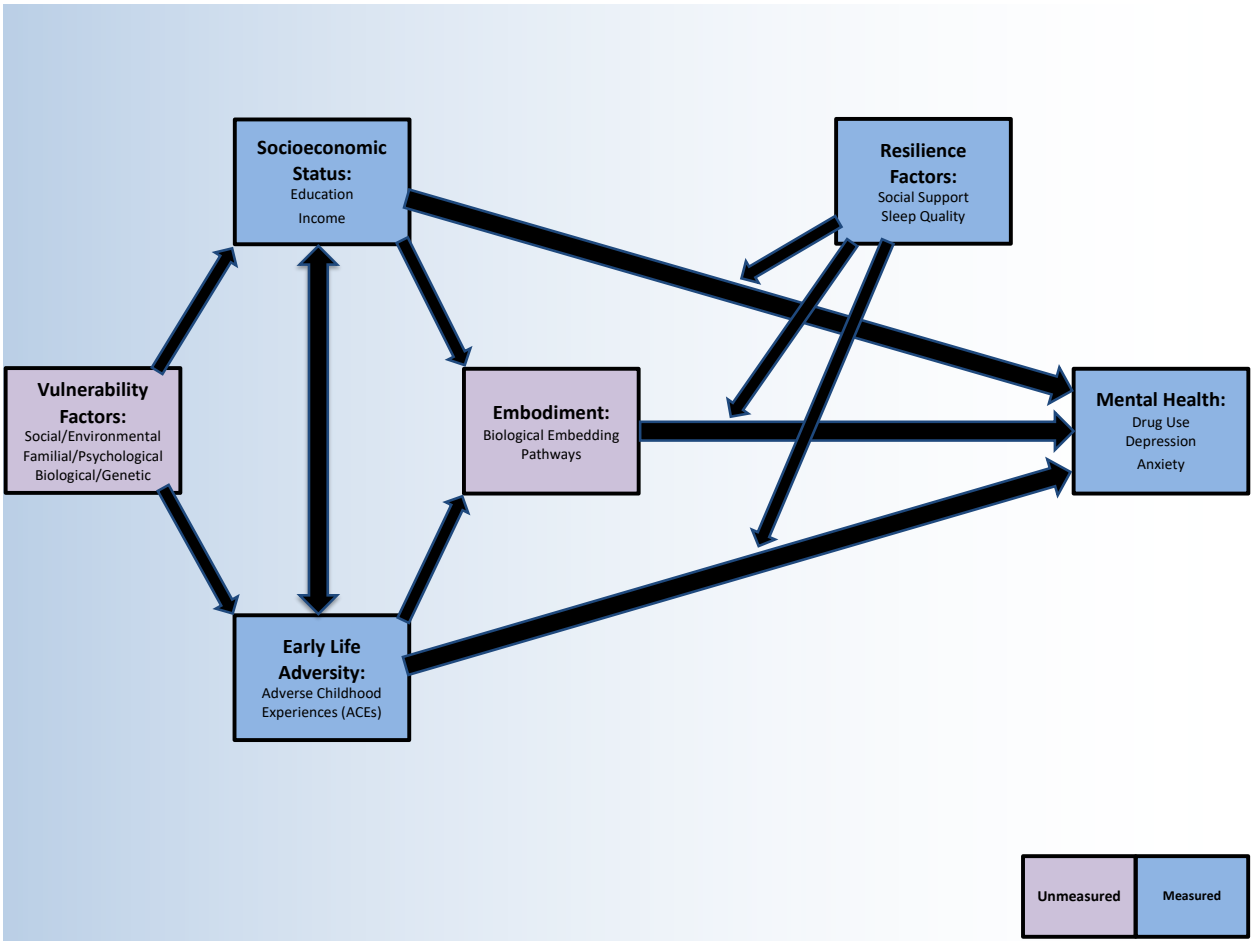
DNA methylation is only one plausible mechanism through which ELA becomes embedded [269], but may predict the reproduction of health problems (see section 1.5.3). Other molecular mechanisms include disrupted central neural networks, neuroendocrine stress dysregulation, and chronic inflammation, as reviewed throughout Chapter One. With multiple mechanisms of embodiment, associations to mental disorders are reproducible, and there is limited evidence to suggest that protective factors (e.g., resilience) are transportable across all domains of ELA. New treatment innovations (e.g., eye-movement desensitization and reprocessing) are likely to benefit only those with access (e.g., knowledge, health insurance) to such resources, leaving those with ELA from low SES with less resilience resources.

Embodies Access to Resources. While a rise in SES from childhood to adulthood should have a protective effect on health outcomes, ELA may be a special case. ACEs impact resilience [323] (see section 1.6). Impairment by ACE disrupts and inhibits access to social, psychological, and emotional resources across the lifespan. For example, juvenile offenders with higher ACE scores were more likely to have early onset of offenses and recidivism [474]. Not surprisingly, adults with documented histories of child abuse and/or neglect have lower levels of education, employment, earnings, and fewer assets [50]. The experience of child abuse by parents has been associated with fewer adult social resources (low family support, high family strain, and personal control) and lifestyle risks (i.e., smoking, obesity) [475]. In line with the concept of cumulative disadvantage described in the LCP, low childhood SES coupled with frequent abuse by parents lead to fewer adult resources [475].

In summary, ELA meets all the established criteria for a fundamental cause of mental health disparities, an argument that has not been previously proposed. The FCT in conjunction with the LCP and the BPS model provides sufficient theoretical basis for the various components of the integrated conceptual model, which is described next.

2.5 Integrated Conceptual Model

Figure 2.1: Elaboration Model Linking Early Life Adversity to Mental Health Outcomes



No single theory can fully explain the complexity of pathways that give rise to the mental health inequalities described herein. Neither biological, psychological, or social theories by themselves provide adequate frames for understanding human developmental processes. Rather, development is a concept that pertains to the property of an ecosystem [476,477]. Childhood adversity is an example of a public health problem that requires "systems thinking" by considering social, environmental, familial, psychological, and biological/genetic factors, then moving on to the mechanisms, and finally synthesizing into a comprehensive model.

The purple boxes represent factors not measured in the current study, whereas blue boxes represent constructs in the dataset. The purple box on the left "Vulnerability Factors" represents antecedents of ACEs via parental factors, utilizing a generational life course model. While ACEs themselves can be considered a vulnerability factor, there are important antecedents that link biological sensitivity to context, as suggested by the FCT. Findings reviewed herein highlight the importance of childhood determinants of mental health outcomes via parental adversity, which may also be due to biological/genetic predispositions as well as potential interactions between genes and environment, as suggested by the BPS model. A more comprehensive understanding of parents' childhood experiences is needed to inform prevention of ACEs in their children [478]. Other important antecedents include living in a dysfunctional environment, including unfortunate neighborhood and community circumstances, consistent with the social production of disease [465]. Neighborhood factors should not be ignored in ACE frameworks that attempt to identify streams of causation, requiring multilevel modeling approaches (albeit not conducted in this study due to data limitations).

Using a social determinants of health framework, ACEs can be viewed as consequence to upstream vulnerability factors that are structural in nature and can also be viewed as a psychosocial risk factor operating independently of other social risk factors. Even when families provide safety at home, children can experience adversity outside the home. Thus, both low SES and ACEs are viewed as fundamental causes of mental health inequality over the lifespan. Literature differentiating between the impact of low SES and ACEs has led to the conclusion that both can contribute to poor mental health, but those outcomes are worse when combined. This is consistent with the LCP concept of cumulative disadvantage and inequality [433,434]. Given that low SES is not necessarily an antecedent of all forms of adversity, these constructs are

conceptualized on the same "level" with bidirectional interactions. Both have been independently linked to embodiment through biological embedding pathways. Embodiment of childhood adversity disrupts physiology (subject to differential susceptibility) by cumulative disadvantage that reverberates across life course processes, thereby creating the novel argument that ACEs can be viewed as a fundamental cause of mental health inequalities.

Arrows between SES and ACEs are bidirectional, acknowledging that ACEs are more common in low SES groups and that ACEs can impact educational attainment, thereby influencing income. Importantly, ACEs are measured in the first 18 years of life when people are less likely to generate income, therefore lower income could even be seen as consequential to ACEs in the context of life course processes. The integrated conceptual model highlights the importance of ACEs as a primary predictor of poor mental health outcomes. Meanwhile, it will be important to consider contributions from all potential drivers, therefore interpretation of any findings will be made in the light of the range of theories invoked herein.

Clearly, there are multiple mechanisms by which ACEs can impact mental wellbeing. One pathway is through imprint on multiple body systems, including proinflammatory cascades, the HPA axis, epigenetic modification, and structural, functional, and morphological brain changes, including impaired reward sensitivity. Such constructs are not measured in the current study but have been identified as important pathways linking ACEs to mental health. The BPS model emphasizes biological embedding at the individual level, contextualized among other forms of psychosocial risk. Furthermore, ACEs have been shown to decrease resilience factors. This may be linked to ACEs biological consequences (i.e., the BPS model) or other contextually situated factors (i.e., FCT), and certainly both (i.e., the LCP).

The primary theory driving the elaboration model is the LCP, given that adult mental health outcomes will be investigated as consequence to childhood adversity. Specifically, a pathway model will examine "chains of risk" by considering the moderating effect of various resilience factors. Meanwhile, the integrated conceptual model oversimplifies the dynamic and interactive picture of ELA. However, simplifications are required to add a feasible quantitative approach to the theoretical underpinnings driving the research questions. Specific resilience factors under investigation have been reviewed throughout Chapter One and will be explained in the next chapter outlining each study. Concepts of resilience will be viewed from a life course trajectory perspective.

3 CHAPTER THREE: RESEARCH AIMS & HYPOTHESES

This chapter provides an overview of the three dissertation studies, including the aims, research questions, and hypotheses. The purpose of these studies is to investigate the link between ACE scores and potential life course processes that generate mental health inequalities among mostly Black and Latino low-income MSM in Los Angeles, California. Mental health outcomes include drug use (which may be considered a proxy for SUD and a correlate of other mental health disorders but is a behavioral rather than mental health outcome), depressive symptoms, and anxiety symptoms. While links between ACEs and these mental health outcomes have been previously described, they have not been adequately described among MSM. Furthermore, no mental health research on MSM has investigated the moderating effects of social support and sleep quality as potential resilience factors following ACEs.

Primary Research Question: Does exposure to ACEs, as recalled from the first 18 years of life, predict poor mental health outcomes among MSM in adulthood, after adjusting for a wide range of sociodemographic and behavioral factors?

The primary question is explored in three separate studies, based on a Life Course Perspective. Each study examines the cumulative ACE score, as well as use a dimensional approach (separating ACEs into categories of childhood maltreatment and household dysfunction), and a selective approach (which considers the impact of individual ACEs). The category of childhood maltreatment is investigated in each of the studies because it has been shown to be associated with worse mental health outcomes than household dysfunction [35,80,89,119]. All three studies investigate whether resilience factors buffer the hypothesized associations between ACEs and mental health through effect measure modification (i.e., moderation).

3.1 Study One

Study One: Does the Association Between ACEs and Self-Reported Drug Use Differ by Perceived Social Support?

Study Aim: To investigate the association between ACEs and self-reported drug use during the past six months, and whether this is moderated by perceived social support. This study uses data collected in the mSTUDY since cohort conception in August 2014. To address this aim, several research questions were investigated:

Research Question 1.1: Does the cumulative ACE score predict self-reported drug use during the past six months, after adjusting for a range of sociodemographic and behavioral factors? Factors include race/ethnicity, age, income, education, BMI, depressive symptoms, alcohol use, cigarette/vape use, and HIV status. Covariates are defined and described in Chapter Four.

Research Question 1.2: Does the association between cumulative ACE score and drug use differ by social support, after adjusting for a range of sociodemographic and behavioral factors?

Research Question 1.3: Does the ACE category of childhood maltreatment (emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect) associate with drug use more so than the category of household dysfunction (parental separation or divorce, mother treated violently, household substance abuse, household mental illness, and incarcerated household member) after adjusting for a range of sociodemographic and behavioral factors?

Research Sub-Question 1.3.1: Does the association between childhood maltreatment and drug use differ by social support, after adjusting for a range of sociodemographic and behavioral factors?

Research Question 1.4: Does a history of household substance abuse (single ACE, part of the household dysfunction category) predict drug use, after adjusting for a range of sociodemographic and behavioral factors?

This question is motivated by the concept of parental adversity as a vulnerability factor, reviewed in section 1.4.1. There is evidence that parental substance use can be traumatic for children and heighten the risk of drug use in adolescence and young adulthood [479].

Research Sub-Question 1.4.1: Does the association between history of household substance abuse and drug use differ by social support, after adjusting for a range of sociodemographic and behavioral factors?

Research Question 1.5: Are any of the findings in this study changed after adjustment with a time variable indicating COVID-19?

Research questions will be tested based on the following research hypotheses:

Hypothesis 1.1: The cumulative ACE score will have an independent association with self-reported drug use, following a dose-response continuum.

Hypothesis 1.2: The association between the cumulative ACE score and drug use will be attenuated in those who report a higher level of perceived social support.

Hypothesis 1.3: The ACE category of childhood maltreatment will have a stronger association with drug use than the category of household dysfunction.

Hypothesis 1.3.1: The association between childhood maltreatment and drug use will be attenuated in those who report a higher level of perceived social support.

Hypothesis 1.4: The single ACE of household substance abuse history will have an independent association with drug use.

Hypothesis 1.4.1: The association between household substance abuse history and drug use will be attenuated in those who report a higher level of perceived social support.

Hypothesis 1.5: None of the findings from any of these hypotheses will differ after adjustment for a time variable indicating COVID-19.

3.2 Study Two

Study Two: Does the Association Between ACEs and Depressive Symptoms Differ by Sleep Quality?

Study Aim: To investigate the association between ACEs and self-reported depressive symptoms, and whether this differs by sleep quality. This study was restricted to data collected from study conception in August 2014 until March 13, 2020, when in-person visits were stopped due to COVID-19. To address this aim, several research questions are investigated:

Research Question 2.1: Does the cumulative ACE score predict self-reported depressive symptoms, after adjusting for a range of sociodemographic and behavioral factors? Factors include race/ethnicity, age, income, education, BMI, drug use, alcohol use, cigarette/vape use, and HIV status.

Research Question 2.2: Does the association between cumulative ACE score and depressive symptoms differ by level of sleep quality, after adjusting for a range of sociodemographic and behavioral factors?

Research Question 2.3: Does the ACE category of childhood maltreatment associate with depressive symptoms more so than the category of household dysfunction, after adjusting for a range of sociodemographic and behavioral factors?

Research Sub-Question 2.3.1: Does the association between childhood maltreatment and depressive symptoms differ by level of sleep quality, after adjusting for a range of sociodemographic and behavioral factors?

Research Question 2.4: Does childhood sexual abuse (single ACE, part of the childhood maltreatment category) predict depressive symptoms, after adjusting for a range of sociodemographic and behavioral factors?

This research question is motivated by data that suggests childhood sexual abuse confers additional (i.e., independent) specific risk for depression [184,185].

Research Sub-Question 2.4.1: Does the association between childhood sexual abuse and depressive symptoms differ by level of sleep quality, after adjusting for a range of sociodemographic and behavioral factors?

This research question is motivated by data that suggests childhood sexual abuse disturbs sleep in adulthood [357,358].

Research questions will be tested based on the following research hypotheses:

Hypothesis 2.1: The cumulative ACE score will have an independent association with self-reported depressive symptoms, following a dose-response continuum.

Hypothesis 2.2: The association between the cumulative ACE score and depressive symptoms will be attenuated in those who report a higher level of sleep quality.

Hypothesis 2.3: The ACE category of childhood maltreatment will have a stronger association with depressive symptoms than the category of household dysfunction.

Hypothesis 2.3.1: The association between childhood maltreatment and depressive symptoms will be attenuated in those who report a higher level of sleep quality.

Hypothesis 2.4: The single ACE of childhood sexual abuse will have an independent association with depressive symptoms.

Hypothesis 2.4.1: The association between childhood sexual abuse and depressive symptoms will be attenuated in those who report a higher level of sleep quality.

3.3 Study Three

Study Three: Does the Association Between ACEs and Anxiety Symptoms Differ by Sleep Quality?

Study Aim: To investigate the association between ACEs and self-reported anxiety symptoms, and whether this differs by sleep quality. This study was restricted to data collected from study conception in August 2014 until March 13, 2020, when in-person visits were stopped due to COVID-19. To address this aim, several research questions are investigated:

Research Question 3.1: Does the cumulative ACE score predict self-reported anxiety symptoms, after adjusting for a range of sociodemographic and behavioral factors? Factors include race/ethnicity, age, income, education, BMI, drug use, alcohol use, cigarette/vape use, and HIV status.

Research Question 3.2: Does the association between cumulative ACE score and anxiety symptoms differ by level of sleep quality, after adjusting for a range of sociodemographic and behavioral factors?

Research Question 3.3: Does the ACE category of childhood maltreatment influence anxiety symptoms more so than the category of household dysfunction, after adjusting for a range of sociodemographic and behavioral factors?

Research Sub-Question 3.3.1: Does the association between childhood maltreatment and anxiety symptoms differ by level of sleep quality, after adjusting for a range of sociodemographic and behavioral factors?

Research Question 3.4: Does emotional neglect (single ACE, part of the childhood maltreatment category) predict anxiety symptoms, after adjusting for a range of sociodemographic and behavioral factors?

This research question has not been previously explored in ACE research among MSM and is motivated by psychological research which suggests individuals with insecure attachment to their caregiver have higher anxiety [480].

Research Sub-Question 3.4.1: Does the association between emotional neglect and anxiety symptoms differ by level of sleep quality, after adjusting for a range of sociodemographic and behavioral factors?

Research questions will be tested based on the following research hypotheses:

Hypothesis 3.1: The cumulative ACE score will have an independent association with self-reported anxiety symptoms, following a dose-response continuum.

Hypothesis 3.2: The association between the cumulative ACE score and anxiety symptoms will be attenuated in those who report higher levels of sleep quality.

Hypothesis 3.3: The ACE category of childhood maltreatment will have a stronger association with anxiety symptoms than the category of household dysfunction.

Hypothesis 3.3.1: The association between childhood maltreatment and anxiety symptoms will be attenuated in those who report higher levels of sleep quality.

Hypothesis 3.4: The single ACE of emotional neglect will have an independent association with anxiety symptoms.

Hypothesis 3.4.1: The association between emotional neglect and anxiety symptoms will be attenuated in those who report higher levels of sleep quality.

3.4 Chapter Three Summary

All three studies are informed by the conceptual model in section 2.5 (Figure 2.1). To summarize, cumulative ACEs (sum scores), the category of childhood maltreatment, and a single ACE for each study are investigated as risk factors for mental health outcomes: drug use, depressive symptoms, and anxiety symptoms. Each study adjusts for SES indicators (i.e., education and income) as well as other relevant factors: race/ethnicity, age, BMI, alcohol use, cigarette/vape use, and HIV status. Study One (drug use) additionally adjusts for depressive symptoms, and Studies Two (depressive symptoms) and Three (anxiety symptoms) adjust for drug use. All three studies investigate whether potential resilience factors (perceived social support for Study One and sleep quality for Studies Two and Three) buffer the observed associations. In Chapter Four, the data source, study sample, statistical methods, and measurement instruments used are introduced and described.

4 CHAPTER FOUR: METHODS

This chapter describes the data and study sample, as well as the statistical methods for testing hypotheses described in Chapter Three. A detailed summary of how each variable is measured is included before each study is described. After the instruments are described, the timeline for variable collection is displayed. Techniques that were employed to create a full dataset of overlapping variables for statistical analysis are described in section 4.3.

4.1 Data Source and Study Sample

Data for the present study comes from the mSTUDY (Men Who Have Sex with Men and Substance Use Cohort at UCLA Linking Infections, Noting Effects [MASCULINE]) an ongoing National Institute on Drug Abuse (NIDA) sponsored longitudinal study of HIV-positive and HIV-negative MSM with varied substance use behaviors (NIDA project U01 DA036267). The mSTUDY was approved by the University of California, Los Angeles (UCLA) Institutional Review Board (IRB) and all individuals provided written informed consent at study entry. Because the current studies use data from a previously approved study, UCLA IRB determined this research exempt.

Eligible participants were assigned male sex at birth, English-speaking, ages 18-45; if HIV-, reported having sex with men in the past twelve months, and were recruited from two community clinics in Los Angeles, CA (The Los Angeles LGBT Center and the UCLA Vine Street Clinic). Sample recruitment occurs through these sites where staff determine if an individual qualifies and is interested in participating. Participants are remunerated for study participation ($75 per study visit), as well as get access to free and confidential STI testing every six months, HIV risk-reduction counseling, testing and referral for care (if needed) including referrals to SUD treatment (if desired). By design, half of the sample is HIV+, and the other half

HIV-. The mSTUDY investigates questions related to sexual health among Black and Latino MSM and is designed to ascertain information about (and improve prevention and treatment) of HIV and other STIs. Study enrollment began in August 2014 and is ongoing.

Participants complete assessments every six months, including a comprehensive physical exam and medical history, urine drug panel, clinical laboratory tests, and computer-assisted detailed behavioral questionnaire. Physical exams and urine drug tests have not occurred during remote visits since March 31, 2020. The current studies used data from study conception (August 2014) until October 8, 2021. ACE questions were added to the battery of behavioral data collected as part of the computer-assisted self-interviews on December 15, 2020, during remote (online) visitation. More specifics on data restriction by time ranges (before and during COVID-19) will be described in each study.

4.2 Measurement Summary

Adverse Childhood Experiences (Key Independent Variable). The ACE measure is a ten-question instrument that was originally introduced in a large managed care population at Kaiser San Diego [3]. As mentioned previously, this sample was not representative (data linking ACEs with MSM including MSM of color are reviewed in section 1.7).

Yes/no questions investigate the presence of childhood maltreatment (emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect) and household dysfunction (parental separation or divorce, mother treated violently, household substance abuse, household mental illness, and incarcerated household member) experienced during the first 18 years of life. The most common cut-point is four or more ACEs, compared to the reference group of none [3]. Other authors use other cut-points for various statistical and substantive reasons [15,85,86].

Cumulative scoring frequently emerges regardless of specific ACEs, as well as analysis along a dose-response continuum [87]. Cumulative scoring challenges assumptions about what is a more severe traumatic event. Data suggests that pathways to poor health differ by types of ACEs, with child physical, emotional, and sexual abuse being the worst [89]. Focusing on the specific categories of ACEs have been referred to as the dimensional approach, compared to the cumulative and selective (single ACE) approaches. While it has been shown that MSM of color experience a higher number of ACEs than the general population [388], investigations into different ACE cut-points among this population have not been conducted. In the current studies, the cumulative, dimensional, and selective approaches are all used in statistical models.

Because ACE collection began on December 15, 2020, ACE scores will be used retrospectively (based on participant ID) to conduct analysis for pre-COVID-19. This is a sound methodological approach because ACE scores are recall measures from experiences during the first 18 years of life, therefore can be assumed to be stable over time and transportable along participant ID. The original ACE questionnaire can be found in Appendix A.

Drug Use (Study One Dependent Variable). While SUD diagnoses are not in the mSTUDY dataset, there are data on self-reported drug use as well as urine drug screens. However, transition to remote visits put a hold on urine testing on March 13, 2020. There are questions about drug use in the past six months that have been collected since study conception. These questions have been adapted from the NIDA Quick Screen (https://archives.drugabuse.gov/publications/resource-guide-screening-drug-use-in-general-medical-settings/nida-quick-screen) which investigate the frequency of drug use across several categories of substances including methamphetamine, ecstasy, cocaine/crack, heroin/fentanyl, party drugs (GHB, special K, mushrooms, LSD/acid), other drugs (bath salts, PCP), and

marijuana. Participants were asked how frequently they used each substance during the past six months: daily, weekly, monthly, less often, once, or never. In the current analyses, each substance was dichotomized into any versus never, and a composite variable of all drugs indicates self-reported use of any drugs in the past six months. This variable was explored with and without the usage of marijuana, given that it is now legal in the state of California. Final analysis excludes self-reported use of marijuana.

For drug use data during time periods prior to COVID-19 (for use as a covariate in Studies Two and Three), prior data on urine drug screens were used. Urine drug screen (Fastect® II Drug Screen Dipstick Test D, Brenan Medical Corporation, Irvine, CA) was used to identify recent use of any of the following: methamphetamine, opiates, cocaine, ecstasy, marijuana, amphetamines, and fentanyl (all drugs were tested using separate drug screen tests). A single indicator variable (i.e., yes/no for any positive on any drug test) is used for Studies Two and Three when drug use is examined as a covariate (rather than an outcome). Drug use variables will not be transported across time for any analyses.

Depressive Symptoms (Study Two Dependent Variable). Depressive symptoms are measured using the CESD, a 20-item validated screening measure for depressive symptoms in the general population [179]. Scores range from 0-60, with responses indicating frequency within the last week: rarely or none of the time (less than one day) (0), some or a little of the time (1-2 days) (1), occasionally or a moderate amount of time (3-4 days) (2), or most or all the time (5-7 days) (3). Example questions include: “I was bothered by things that usually don’t bother me” and “I thought my life had been a failure” with reverse scoring for positive questions such as “I felt hopeful about the future” and “I enjoyed life.” In the validation study of the general population, Cronbach’s alpha was 0.85, indicating high internal consistency [179]. The standard

cut-point for “likely depressed” is 16, however the cut-point of <23/23+ is used to classify clinically meaningful symptoms linked with likely diagnosis of depressive disorder [481], which is used in the current studies. The CESD has previously been used in studies of MSM [409] including MSM of color [417]. The CESD questionnaire is in Appendix B.

Anxiety (Study Three Dependent Variable). Anxiety symptoms are operationalized using the GAD-7, a validated 7-item tool for screening for generalized anxiety disorder (GAD) and assessing its severity [482]. The instrument asks about symptoms in the last two weeks, with questions such as: not being able to stop or control worrying; or feeling afraid as if something awful might happen. Scoring is based on not at all (0), several days (1), more than half the days (2), and nearly every day (3). The sum score ranges from 0-21, with 0-4 indicating minimal anxiety, 5-9 mild anxiety, 10-14 moderate anxiety, and 15-21 severe anxiety. These categories are used for ordinal logistic regression, as well as the dichotomized measure (for logistic regression) which classifies those with scores 0-9 as low anxiety and 10-21 as high (sensitivity=89% and specificity=82% from the validation study of a primary care sample across twelve US states) [482]. The GAD-7 has been used in studies of MSM [411]. The GAD-7 questionnaire can be found in Appendix C, where the operational characteristics of the GAD-7 at different cut-points are also reported. The proportional odds assumption required for ordinal logistic regression is discussed in section 4.5.

Perceived Social Support (Study One Moderator). Social support is operationalized using the Multidimensional Scale of Perceived Social Support (MSPSS), which is a 12-item psychometrically sound instrument validated in 1988 [483]. A seven-point Likert-type rating scale ranges from very strongly disagree (1) to very strongly agree (7). Questions include: 1) There is a special person who is around when I am in need, 2) There is a special person with

whom I can share my joys and sorrows, 3) My family really tries to help me, 4) I get the emotional help and support I need from my family, 5) I have a special person who is a real source of comfort to me, 6) My friends really try to help me, 7) I can count on my friends when things go wrong, 8) I can talk about my problems with my family, 9) I have friends with whom I can share my joys and sorrows, 10) There is a special person in my life who cares about my feelings, 11) My family is willing to help me make decisions, and 12) I can talk about my problems with my friends. In the original study of university undergraduates, Cronbach's alpha was 0.88, indicating good internal consistency for the measure [483]. The score is dichotomized for use in moderation analysis. Because there is no universally accepted cut-point for MSPSS (it varies based on the sample), a cut-point was established based on the data (i.e., the median). This data was collected starting on August 31, 2020, during COVID-19, however, was transported retrospectively (based on a strong assumption) for analysis pre-COVID-19, which will be discussed as a limitation. The MSPSS has been used in studies of MSM [484]. The MSPSS questionnaire can be found in Appendix D.

Sleep Quality (Study Two and Three Moderator). Sleep quality is measured using the Pittsburgh Sleep Quality Index (PSQI) [485]. This self-reported questionnaire assesses sleep quality and disturbances over the course of one month. Nineteen self-rated questions are combined to form seven component scores, each of which ranges from zero to three points. A score of zero indicates no difficulty, while a score of three indicates severe difficulty. The seven components are: 1) subjective sleep quality, 2) sleep latency, 3) sleep duration, 4) habitual sleep efficiency, 5) sleep disturbances, 6) use of sleeping medication, and 7) daytime dysfunction. The seven component scores are then added to yield one global score, with a range of 0-21 points, zero indicating no difficulty and 21 indicating severe difficulties in all areas. In the validation

study, a global score above five yielded a diagnostic sensitivity of 89.6% and specificity of 86.5% for identifying cases with a sleep disorder [485]. Thus, six (and above) is used as the cut-point for moderation analyses, with lower levels of sleep quality as the reference group. The PSQI has been used in studies of MSM [486]. The PSQI questionnaire is found in Appendix E.

Race/Ethnicity (Covariate). Race/Ethnicity is categorized as Black, White, Other Race (reference), Hispanic/Latino. Other Race includes categories: American Indian or Alaskan Native, Asian, Asian Indian, Native Hawaiian Pacific Islander, which was collapsed due to small sample size (and prior experience with the dataset). Race/ethnicity is included as a covariate because it has been shown to vary by ACEs [116], drug use [487], depressive symptoms [488], and anxiety [489]. This variable was accessed retrospectively for analysis (Study One) after collection was halted (due to remote visits) and is assumed to be stable over time.

Age (Covariate). Age is measured as a continuous variable but will be categorized as 18-29, 30-39, 40-52 years. The youngest group (18-29 years) is the reference group for analyses. Age is included as a covariate because it has been shown to vary by ACEs [490], with the prevalence of ACEs often declining with increasing age [491]. Age also varies by drug use [492], depressive symptoms [493], and anxiety [494]. This variable is accessed retrospectively for analysis (Study One) after collection was halted (due to remote visits).

Income (Covariate). Income data was collected in ranges of $10,000, with the highest category being $70,000 and above. For the current analysis, income was collapsed into the categories: $0-19,999, $20,000-39,999, $40,000+ (reference). Income is included as a covariate because it has been shown to vary by ACEs [14], as well as drug use [495], depressive symptoms [172], and anxiety [496].

Education (Covariate). Education data is collected as a continuous variable reflecting the total number of years spent in school. Assumptions were made to categorize education as: did not finish high school (0-11 years), high school (12 years), some college (13-15 years), college grad+ (16 years) (reference). Education is included as a covariate because it has been shown to vary by ACEs [84], as well as drug use [497], depressive symptoms [172], and anxiety [498]. This variable was accessed retrospectively for analysis (Study One) after collection was halted (due to remote visits) and is assumed to be stable over time.

Body Mass Index (BMI) (Covariate). Height and weight are measured at each visit (by trained clinical staff using anthropometric equipment that is calibrated annually) to calculate BMI and will be categorized using the standard US definition: underweight (below 18.5), normal weight (18.5-24.99) (reference), overweight (25-29.99), and obese (30 and above). One implausible BMI (=10) was recoded to missing. BMI is included as a covariate because it has been shown to vary by ACEs [470], as well as drug use [499], depressive symptoms [500], and anxiety [501]. This variable will be accessed retrospectively for analysis (Study One) after collection was halted (due to remote visits) and is assumed to be stable over time. Meanwhile, since BMI can vary over time [502], this will be mentioned as a limitation.

Alcohol Use (Covariate). Alcohol use is collected using the National Institute on Alcohol Abuse and Alcoholism (NIAAA) recommended alcohol questions (https://www.niaaa.nih.gov/research/guidelines-and-resources/recommended-alcohol-questions). Among the three questions used in mSTUDY, a single question was used to covary alcohol use in analysis: in the past six months, how often did you have a drink containing alcohol? Answers include never; monthly or less; 2-4 times per month; 2-3 times per week; 4 or more times per week. Because “never” can include those with a history of AUD who are currently abstinent, it

may be flawed as a reference group. Thus, never, and monthly or less were collapsed to provide an adequate reference group. Alcohol use is included as a covariate because it has been shown to vary by ACEs [139], as well as drug use [503], depressive symptoms [166], and anxiety [504].

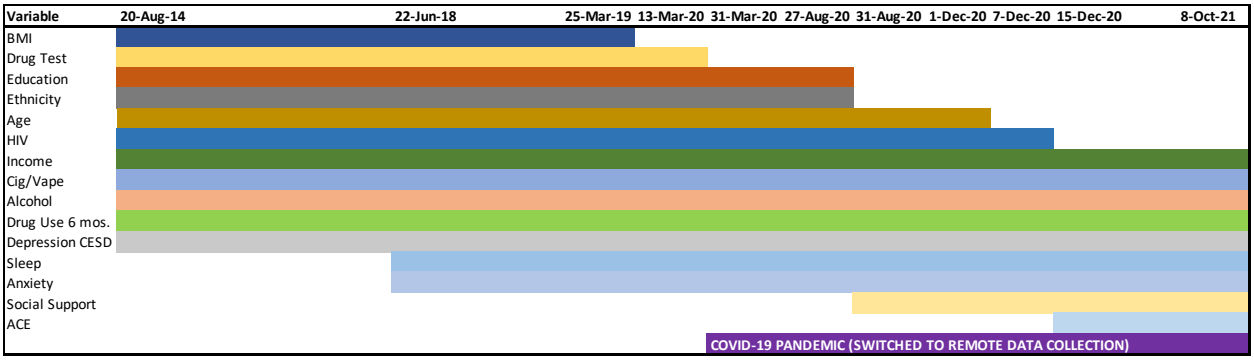
Cigarette/Vape Use (Covariate). An indicator variable was created if the participant reports current use of cigarette or e-cig/vape (combined into a single variable). Nicotine use is included as a covariate because it has been shown to vary by ACEs [505], as well as drug use [506], depressive symptoms [507], and anxiety [508].

HIV Status (Covariate). HIV status is measured using seropositive status from laboratory blood tests. HIV status is included as a covariate because it has been shown to vary by ACEs [397], as well as drug use [509], depressive symptoms [417], and anxiety [410]. This variable was accessed retrospectively for analysis (Study One) after collection was halted (due to remote visits) and is assumed to be stable over time. Meanwhile, since HIV status can change from negative to positive (particularly in this at-risk sample), this will be mentioned as a limitation.

COVID-19 (Covariate). An indicator for COVID-19 time was created for Study One where some data was collected during COVID-19 by remote visitation. This adjustment attempts to account for potential differences in data collected during versus prior to the pandemic.

Remote visits (online questionnaires only) due to COVID-19 began on March 31, 2020, at which point several new study variables were added, and some were removed (see Figure 4.1 and 4.2 below). Figure 4.1 displays the timeline that different variables were introduced, as well as stopped, during the data collection process. Time periods are not represented to scale. The purple bar in the bottom right corner represents the COVID-19 pandemic (separating the timelines used in Studies Two and Three).

Figure 4.1: Timeline of Variable Collection in the mSTUDY Cohort (August 2014-Present)



After applying data management techniques (discussed below in section 4.3) and making some assumptions (discussed above under the description of each variable) about the stability of some covariates over time, availability of the data became as shown in Figure 4.2.

Figure 4.2: Availability of Variables in the mSTUDY Cohort After Data Adjustments Using Statistical Software (August 2014-Present)

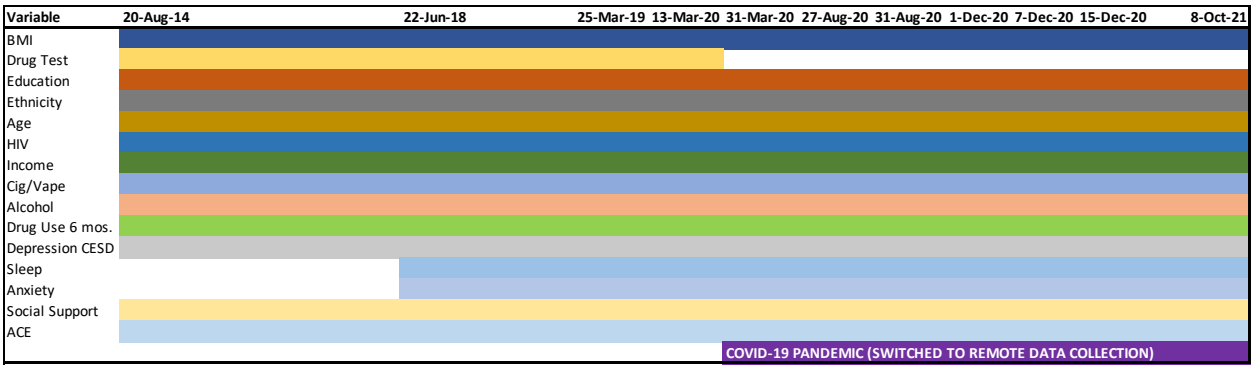


Table 4.1 summarizes the use of each variable across all three studies.

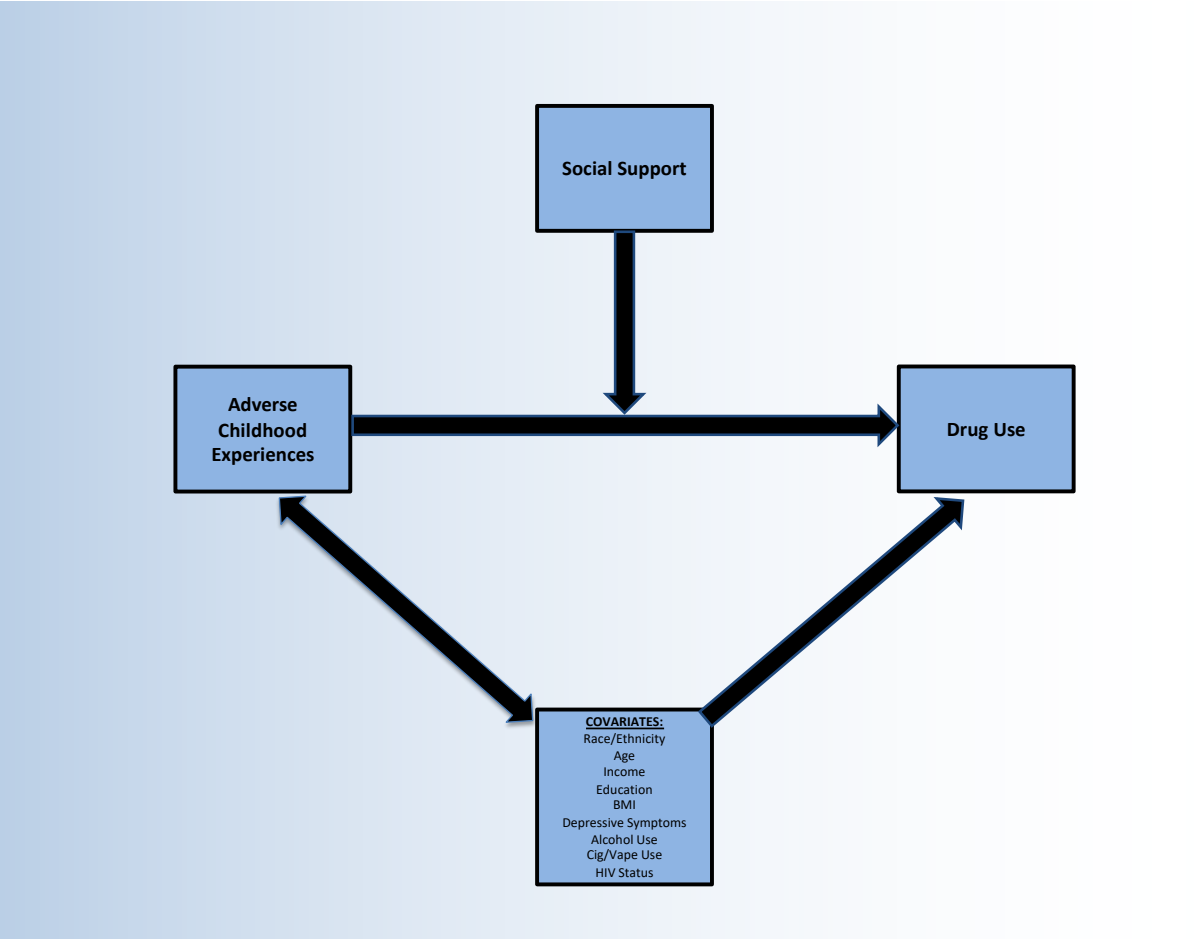
Table 4.1: Summary of Variable Application Across all Three Dissertation Studies

Variable	Study 1	Study 2	Study 3
ACE	Predictor	Predictor	Predictor
Drug Use	Outcome	Covariate*	Covariate*
CESD	Covariate	Outcome	**
GAD-7	***	***	Outcome
MSPSS	Moderator	****	****
PSQI	*****	Moderator	Moderator
Race/Ethnicity	Covariate	Covariate	Covariate
Age	Covariate	Covariate	Covariate
Income	Covariate	Covariate	Covariate
Education	Covariate	Covariate	Covariate
BMI	Covariate	Covariate	Covariate
Alcohol Use	Covariate	Covariate	Covariate
Cig/Vape Use	Covariate	Covariate	Covariate
HIV Status	Covariate	Covariate	Covariate
COVID-19	Covariate	****	****

*using urine drug test when available (Studies 2 and 3) and self-report for Study 1
**not used due to a known strong correlation with anxiety symptoms
***not used due to a known strong correlation with depressive symptoms (and time collected)
****not used because collected during COVID-19 therefore only relevant to Study 1
*****not used because analyzed pre-COVID-19 which is only relevant to Studies 2 and 3

4.3 Study One: Does the Association Between ACEs and Self-Reported Drug Use Differ by Perceived Social Support?

Figure 4.3: Study One Conceptual Model



First, descriptive univariate analysis of ACEs was conducted using a histogram and measures of central tendency and dispersion (i.e., mean and standard deviation). Sample characteristics were ascertained at the first visit where ACE data was collected (i.e., index visit for this analysis). If covariates were not collected at the same time as ACEs (remote visits), the most recent variable was accessed using Stata version 17 [510] *carryforward* command, after declaring the data as time-series (using *tsset*). As mentioned, this required some assumptions.

After using the *carryforward* command to retrieve covariates that were not collected during the remote visits, both the ACE measure and MSPSS measure were transported retrospectively along participant ID to ascertain a full dataset (of overlapping variables) since study conception. Multilevel commands using participant ID were used for mixed effects in random intercept models, where time (level one) is nested in person (level two).

Frequency measures were examined after dichotomizing ACEs at various cut-points, and the best cut-point (<6/6+) was determined based on the data (visual inspection of the marginal predicted means of the outcome drug use at each level of ACE, described further in section 5.3). Bivariate analysis examined the crude relationship between ACEs and the drug use indicator, and covariates were then added into the model one at a time. This permits investigation of the impact of each additional covariate on the focal relationship. Information criteria (AIC/BIC) were used to assess final model selection however, inclusion of covariates was determined a priori and was prioritized over model fit based on current data. Finally, perceived social support was tested as a moderator using an indicator variable dichotomized at the median (described in section 4.2), both on the bivariate association between ACEs and drug use, as well as in the fully adjusted model.

Significance levels were set to $\alpha=0.05$, and all confidence intervals are reported at 95%. All analyses were conducted using Stata version 17 [510].

Hypothesis 1.1: The cumulative ACE score will have an independent association with self-reported drug use, following a dose-response continuum.

This hypothesis was first tested using the continuous ACE score (as a categorical variable at each level of ACE) and the drug use indicator variable in mixed-effects logistic regression, adjusting for covariates. Stata's post-estimation commands *margins* and *marginsplot* were used to retrieve and visualize predicted probabilities to assess the presence of a dose-response

relationship. Once the best cut-point was determined from visual inspection of the margins plot (<6/6+), the full mixed-effects logistic model including the entire set of covariates was tested.

Hypothesis 1.2: The association between the cumulative ACE score and drug use will be attenuated in those who report a higher level of perceived social support.

This hypothesis was tested using the dichotomized ACE score (<6/6+) and the drug use indicator in mixed-effects logistic regression, adjusting for covariates. Moderation analysis was conducted three ways: 1) an interaction term between the dichotomized ACE score and the dichotomized MSPSS score (at the median) in the adjusted mixed-effects logistic regression model, followed by Stata's post-estimation command *margins* and *marginsplo*t to retrieve and visualize predicted probabilities, 2) assessment of additive interaction by the relative excess risk due to interaction (RERI), as described by VanderWeele and Kool (2014) [511], and 3) stratification by the MSPSS indicator in the fully adjusted model. Stratified models allow for comparison between ACEs and drug use at different levels of social support, however, do not establish statistical evidence of interaction.

Hypothesis 1.3: The ACE category of childhood maltreatment will have a stronger association with drug use than the category of household dysfunction.

This hypothesis was tested using a dimensional approach, where ACEs were clustered into indexes for childhood maltreatment (emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect) and household dysfunction (parental separation or divorce, mother treated violently, household substance abuse, household mental illness, and incarcerated household member). ACE dimensions (continuous variables ranging from 0-5) were added to models separately, and information criteria were used to assess which was a better fit for the data. Both ACE clusters were added into the mixed-effects logistic regression model, adjusting

for covariates. To test the significance of the difference between ACE clusters, Stata's post-estimation command *lincom* (using subtraction) determined statistical significance of the difference between estimates.

Hypothesis 1.3.1: The association between childhood maltreatment and drug use will be attenuated in those who report a higher level of perceived social support.

This hypothesis was tested using a dimensional approach, where ACEs were clustered into childhood maltreatment and household dysfunction. Both ACE indexes were added into the mixed-effects logistic regression model, using the drug use indicator outcome, adjusting for covariates. Moderation analysis was conducted three ways: 1) an interaction term between the childhood maltreatment dimension (dichotomized at <3/3+, proportional to the <6/6+ cut-point for all ten ACEs) and the MSPSS indicator in the adjusted mixed-effects logistic regression model, followed by Stata's post-estimation commands *margins* and *marginsplot* to retrieve and visualize predicted probabilities, 2) assessment of additive interaction by the relative excess risk due to interaction (RERI), and 3) stratification by MSPSS level in the fully adjusted model.

Hypothesis 1.4: The single ACE of household substance abuse history will have an independent association with drug use.

This hypothesis was tested using a selective approach, with the single ACE of household substance abuse history in the model, as well as the other nine ACEs (indexed as a continuous variable) as adjustments. The model was tested without the other nine ACEs, however, creates a missing variable problem. The drug use indicator was used as the outcome in the mixed-effects logistic regression model, adjusting for covariates.

Hypothesis 1.4.1: The association between household substance abuse history and drug use will be attenuated in those who report a higher level of perceived social support.

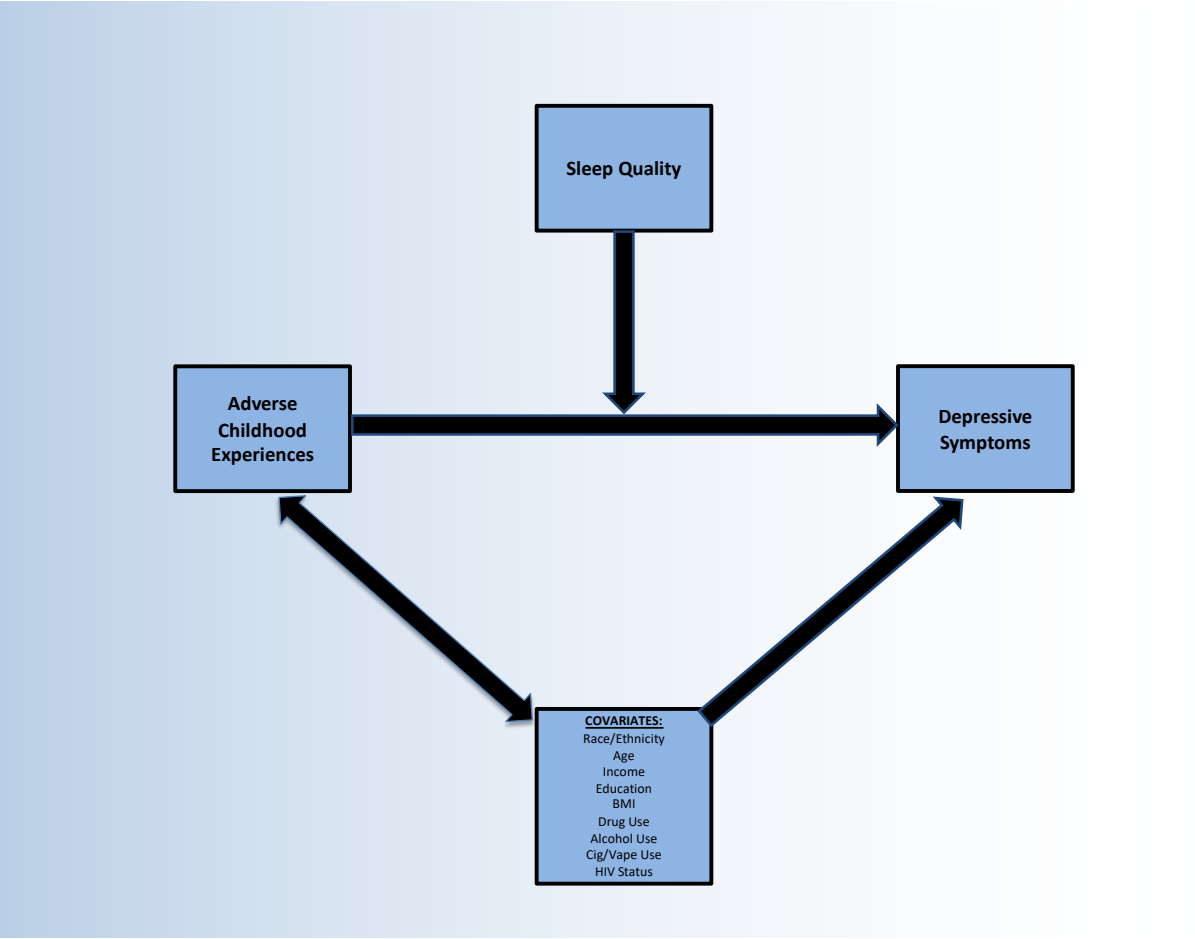
This hypothesis was tested using a selective approach, with the single ACE of household substance abuse history in the model, as well as the other nine ACEs as adjustments. The drug use indicator was used as the outcome in the mixed-effects logistic regression model, adjusting for covariates. Moderation analysis was conducted three ways: 1) an interaction term between the single ACE of household substance abuse history, and the MSPSS indicator in the adjusted mixed-effects logistic regression model, followed by Stata's post-estimation command *margins* and *marginsplot* to retrieve and visualize predicted probabilities, 2) assessment of additive interaction by the relative excess risk due to interaction (RERI), and 3) stratification by MSPSS level in the fully adjusted model.

Hypothesis 1.5: None of the findings from any of these hypotheses will differ after adjustment for a time variable indicating COVID-19.

This hypothesis was tested by adding the time covariate for COVID-19 into each model tested in this study. This covariate adjusts for potential differences in data collected during versus prior to the pandemic. These estimates were compared to the estimates from each individual hypothesis however, no formal test of significance could be conducted. All final models included the time indicator for COVID-19.

4.4 Study Two: Does the Association Between ACEs and Depressive Symptoms Differ by Sleep Quality?

Figure 4.4: Study Two Conceptual Model



First, descriptive univariate analysis of CESD and PSQI scores were conducted using histograms and measures of central tendency and dispersion (i.e., means and standard deviations). Frequency measures were examined after dichotomizing ACEs at various cut-points, and the best cut-point (<5/5+) was determined based on the data (visual inspection of the marginal predicted means of the outcome likely depressed at each level of ACE, described further in section 6.3). Bivariate analysis examined the crude relationship between ACEs and depressive symptoms, and covariates were then added into the model one at a time. This permits

investigation of the impact of each additional covariate on the focal relationship. Information criteria (AIC/BIC) were used to assess final model selection however, inclusion of covariates was determined a priori and was prioritized over model fit based on current data. Finally, sleep quality was tested as a moderator using the PSQI indicator (<6/6+), both on the bivariate association between ACEs and depressive symptoms, as well as in the fully adjusted model.

Study Two was restricted to the time range from the conception of the cohort (August 2014) until in-person visits were halted (March 13, 2020) due to COVID-19. Multilevel commands using participant ID were used for mixed effects in random intercept models, where time (level one) is nested in person (level two).

Hypothesis 2.1: The cumulative ACE score will have an independent association with self-reported depressive symptoms, following a dose-response continuum.

This hypothesis was tested using the continuous ACE score (as a categorical variable at each level of ACE) and the dichotomized CESD (<23/23+) in mixed-effects logistic regression, adjusting for covariates. Stata's post-estimation commands *margins* and *marginsplot* were used to retrieve and visualize predicted probabilities to assess the presence of a dose-response relationship. Once the best cut-point was determined from the margins plot (<5/5+), the full mixed-effects logistic model including the entire set of covariates was tested.

Hypothesis 2.2: The association between the cumulative ACE score and depressive symptoms will be attenuated in those who report a higher level of sleep quality.

This hypothesis was tested using the dichotomized ACE score (<5/5+) and the CESD indicator in mixed-effects logistic regression, adjusting for covariates. Moderation analysis was conducted three ways: 1) an interaction term between the ACE indicator and the PSQI indicator (<6/6+) in the adjusted mixed-effects logistic regression model, followed by Stata's post-

estimation command *margins* and *marginsplot* to retrieve and visualize predicted probabilities, 2) assessment of additive interaction by the relative excess risk due to interaction (RERI), as described by VanderWeele and Kool (2014) [511], and 3) stratification by PSQI level in the fully adjusted model. Stratified models allow for comparison between ACEs and depressive symptoms at different levels of sleep quality, however, do not establish statistical evidence of interaction.

Hypothesis 2.3: The ACE category of childhood maltreatment will have a stronger association with depressive symptoms than the category of household dysfunction.

This hypothesis was tested using a dimensional approach, where ACEs were clustered into indexes for childhood maltreatment (emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect) and household dysfunction (parental separation or divorce, mother treated violently, household substance abuse, household mental illness, and incarcerated household member). ACE dimensions were added to models separately, and information criteria were used to assess which was a better fit for the data. Both ACE clusters were added into the mixed-effects logistic regression model, using the CESD indicator outcome, adjusting for covariates. To test the significance of the difference between ACE clusters, Stata's post-estimation command *lincom* (using subtraction) determined statistical significance of the difference between estimates.

Hypothesis 2.3.1: The association between childhood maltreatment and depressive symptoms will be attenuated in those who report a higher level of sleep quality.

This hypothesis was tested using a dimensional approach, where ACEs were clustered into childhood maltreatment and household dysfunction. Both ACE indexes were added into the mixed-effects logistic regression model, adjusting for covariates. Moderation analysis was conducted three ways: 1) an interaction term between the childhood maltreatment dimension

(dichotomized at <3/3+) and the PSQI indicator in the adjusted logistic regression model, followed by Stata's post-estimation commands *margins* and *marginsplot* to retrieve and visualize predicted probabilities, 2) assessment of additive interaction by the relative excess risk due to interaction (RERI), and 3) stratification by PSQI level in the fully adjusted model.

Hypothesis 2.4: The single ACE of childhood sexual abuse will have an independent association with depressive symptoms.

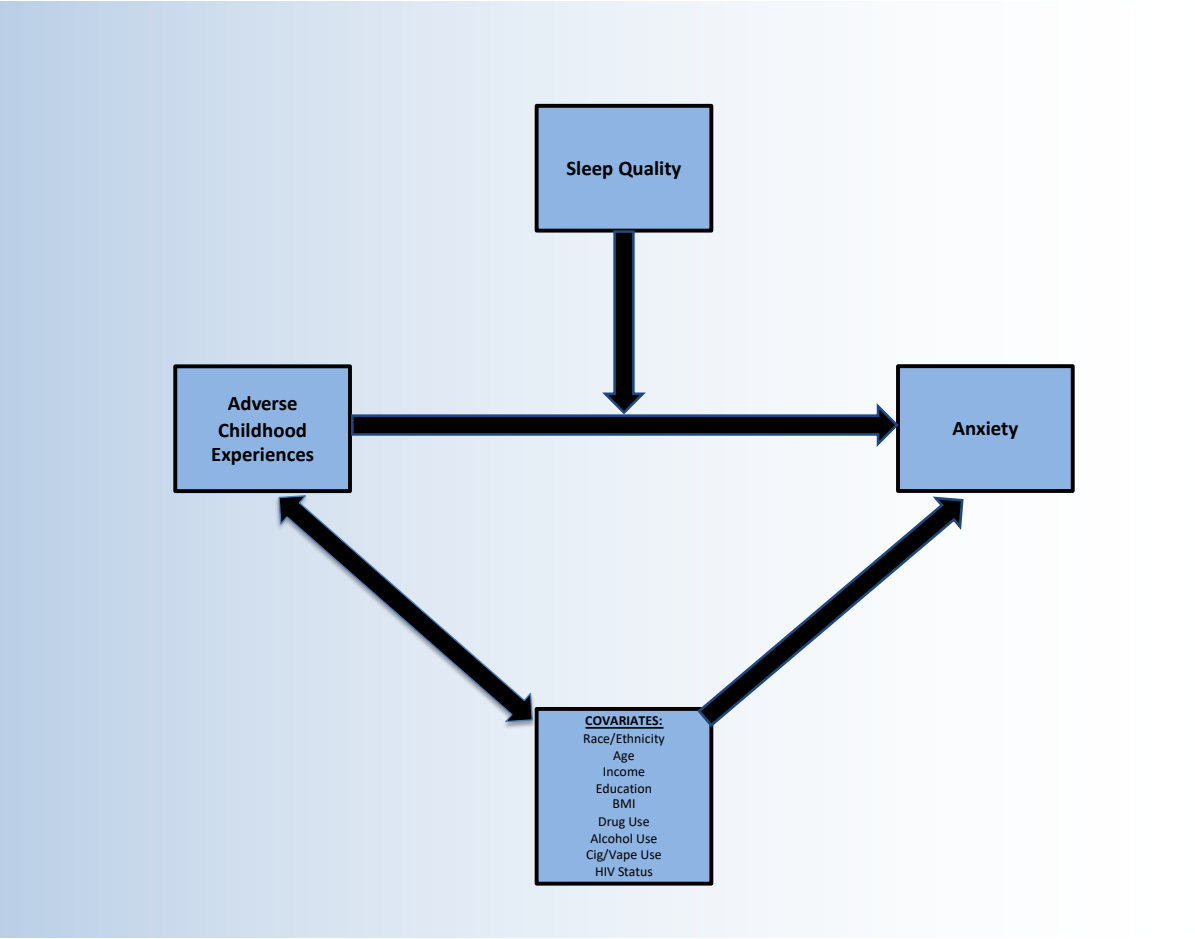
This hypothesis was tested using a selective approach, with the single ACE of childhood sexual abuse in the model, as well as the other nine ACEs (indexed as a continuous variable) as adjustments. The model was tested without the other nine ACEs, however, creates a missing variable problem. The CESD indicator was used as the outcome in the mixed-effects logistic regression model, adjusting for covariates.

Hypothesis 2.4.1: The association between childhood sexual abuse and depressive symptoms will be attenuated in those who report a higher level of sleep quality.

This hypothesis was tested using a selective approach, with the single ACE of childhood sexual abuse in the model, as well as the other nine ACEs as adjustments. The CESD indicator was used as the outcome in the mixed-effects logistic regression model, adjusting for covariates. Moderation analysis was conducted three ways: 1) an interaction term between the single ACE of childhood sexual abuse and the PSQI indicator in the adjusted mixed-effects logistic regression model, followed by Stata's post-estimation commands *margins* and *marginsplot* to retrieve and visualize predicted probabilities, 2) assessment of additive interaction by the relative excess risk due to interaction (RERI), and 3) stratification by PSQI in the fully adjusted model.

4.5 Study Three: Does the Association Between ACEs and Anxiety Symptoms Differ by Sleep Quality?

Figure 4.5: Study Three Conceptual Model



First, descriptive univariate analysis of GAD-7 scores was conducted using a histogram and measures of central tendency and dispersion (i.e., mean and standard deviation). Frequency measures were examined after dichotomizing ACEs at various cut-points, and the best cut-point (<5/5+) was determined based on the data (visual inspection of the marginal predicted means of the outcome anxiety symptoms at each level of ACE, described further in section 7.3). Bivariate analysis examined the crude relationship between ACEs and GAD-7 categories using mixed-effects ordinal logistic regression (method discussed below), and covariates were then added into

the model one at a time. This permits investigation of the impact of each additional covariate on the focal relationship. Information criteria (AIC/BIC) were used to assess final model selection however, inclusion of covariates was determined a priori and was prioritized over model fit based on current data. Finally, sleep quality was tested as a moderator using the PSQI indicator (<6/6+), both on the bivariate association between ACEs and the dichotomized GAD-7 indicator, as well as in the fully adjusted models.

Usage of ordinal logistic regression requires the proportional odds assumption [512]. Estimates are assumed to be proportional (i.e., equal) for each level of the outcome. The ordinal model can be conceptualized as a series of logistic regressions for binary dependent variables. With the 4-category GAD-7, the model combines the comparisons: minimal anxiety to the higher three levels; minimal and mild compared to moderate and severe; and minimal, mild, and moderate compared to severe; into a single estimate. While there are several methods to formally test the proportional odds assumption with single-level data, current methods using Stata do not permit a formal test of the proportional odds assumption using mixed-effects ordinal logistic regression. It is a drawback that an appropriate goodness of fit test is not available for a multilevel proportional odds assumption, but efforts are currently underway [513]. Stata technical support was contacted, but they did not yet have an accepted method. Thus, an attempt to assess the proportional odds assumption was conducted two ways:

1) A multinomial logistic regression model followed by a post-estimation Wald test comparing estimates from each level to one another. Since mixed-effects models in Stata do not permit multinomial models, the *xtset* command was used to declare data as time-series along patient ID and visit number, as has been done previously in mSTUDY research [514]. Wald tests compared the estimates from mild, moderate, and severe categories (versus minimal) in both

unadjusted and adjusted models, and a non-significant chi-square result ($p>0.05$) was used to determine if the proportional odds assumption could be satisfied.

2) A mixed-effects linear regression model using the four category GAD-7 to assess the impact of cumulative ACEs (<5/5+) on increasing level of anxiety. A significant positive estimate was used to assess if cumulative ACEs linearly predict being in a higher anxiety category.

Study Three was restricted to the time range from the introduction of the GAD-7 (June 22, 2018) until in-person visits were halted (March 13, 2020) due to COVID-19. Multilevel commands using participant ID were used for mixed effects in random intercept models, where time (level one) is nested in person (level two).

Hypothesis 3.1: The cumulative ACE score will have an independent association with self-reported anxiety symptoms, following a dose-response continuum.

This hypothesis was tested using the continuous ACE score (as a categorical variable at each level of ACE) and the dichotomized GAD-7 indicator in mixed-effects logistic regression, adjusting for covariates. Stata's post-estimation commands *margins* and *marginsplot* were used to retrieve and visualize predicted probabilities to assess the presence of a dose-response relationship. Once the best cut-point was determined from the margins plot (<5/5+), the full mixed-effects ordinal logistic model (GAD-7 four categories) including the entire set of covariates was tested.

Hypothesis 3.2: The association between the cumulative ACE score and anxiety symptoms will be attenuated in those who report higher levels of sleep quality.

This hypothesis was tested using the dichotomized ACE score (<5/5+) and the dichotomized GAD-7 indicator in mixed-effects logistic regression, adjusting for covariates. Moderation analysis was conducted three ways: 1) an interaction term between the ACE

indicator and the PSQI indicator (<6/6+) in the adjusted mixed-effects logistic regression model, followed by Stata's post-estimation command *margins* and *marginsplot* to retrieve and visualize predicted probabilities, 2) assessment of additive interaction by the relative excess risk due to interaction (RERI), as described by VanderWeele and Kool (2014) [511], and 3) stratification by PSQI level in the adjusted mixed-effects logistic regression model. Stratified models allow for comparison between ACEs and anxiety symptoms at different levels of sleep quality, however, do not establish statistical evidence of interaction.

Hypothesis 3.3: The ACE category of childhood maltreatment will have a stronger association with anxiety symptoms than the category of household dysfunction.

This hypothesis was tested using a dimensional approach, where ACEs were clustered into indexes for childhood maltreatment (emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect) and household dysfunction (parental separation or divorce, mother treated violently, household substance abuse, household mental illness, and incarcerated household member). ACE dimensions were added to models separately, and information criteria were used to assess which was a better fit for the data. Both ACE clusters were added into the mixed-effects ordinal logistic regression model, using the categorical GAD-7 outcome, adjusting for covariates. To test the significance of the difference between ACE clusters, Stata's post-estimation command *lincom* (using subtraction) determined statistical significance of the difference between estimates.

Hypothesis 3.3.1: The association between childhood maltreatment and anxiety symptoms will be attenuated in those who report higher levels of sleep quality.

This hypothesis was tested using a dimensional approach, where ACEs were clustered into childhood maltreatment and household dysfunction. Both ACE indexes were added into the

mixed-effects logistic regression model, adjusting for covariates. Moderation analysis was conducted three ways: 1) an interaction term between the childhood maltreatment dimension (dichotomized at <3/3+) and the PSQI indicator in the adjusted logistic regression model, followed by Stata's post-estimation commands *margins* and *marginsplot* to retrieve and visualize predicted probabilities, 2) assessment of additive interaction by the relative excess risk due to interaction (RERI), and 3) stratification by PSQI level in the adjusted mixed-effects ordinal logistic regression model.

Hypothesis 3.4: The single ACE of emotional neglect will have an independent association with anxiety symptoms.

This hypothesis was tested using a selective approach, with the single ACE of emotional neglect in the model, as well as the other nine ACEs (indexed as a continuous variable) as adjustments. The model was tested without the other nine ACEs, however, creates a missing variable problem. GAD-7 categories were used as the outcome in the mixed-effects ordinal logistic regression model, adjusting for covariates.

Hypothesis 3.4.1: The association between emotional neglect and anxiety symptoms will be attenuated in those who report higher levels of sleep quality.

This hypothesis was tested using a selective approach, with the single ACE of emotional neglect in the model, as well as the other nine ACEs as adjustments. The GAD-7 indicator was used as the outcome in the mixed-effects logistic regression model, adjusting for covariates. Moderation analysis was conducted three ways: 1) an interaction term between the single ACE of emotional neglect and the PSQI indicator in the adjusted mixed-effects logistic regression model, followed by Stata's post-estimation commands *margins* and *marginsplot* to retrieve and

visualize predicted probabilities, 2) assessment of additive interaction by the relative excess risk due to interaction (RERI), and 3) stratification by PSQI level in the fully adjusted model.

5 CHAPTER FIVE: STUDY ONE – RESULTS AND DISCUSSION

5.1 Overview of Aim, Hypotheses, and Methods

Section 5.1 provides a summary of the methods used to test each of the hypotheses introduced in section 3.1 and then described in detail in section 4.3. Section 5.2 displays the sample characteristics and distribution of covariates. Section 5.3 describes the results and section 5.4 is dedicated to discussing these results. Results are discussed further in section 8.1 where findings from all three studies are integrated into an overall summary and placed into a broader context, with several recommendations for future research.

Study One aimed to understand the influence of ACEs on self-reported drug use (excluding marijuana) during the past six months. First, I hypothesized the presence of a positive and linear dose-response relationship between ACEs and self-reported drug use in the unadjusted and then fully adjusted mixed-effects logistic regression models (question 1.1). This analysis provided rationale for the optimal cut-point for ACEs in model building, based on a visual inspection of the margins plot (the point where the predicted probability of drug use tended to increase, see Figure 5.1). Next, I tested if the cumulative ACE score (dichotomized at <6/6+) had an independent positive association with drug use (question 1.1). Model building included adding variables individually to assess the impact of each covariate on the focal relationship. Information criteria were examined as each covariate was added to the model, to assess each additional adjustment on model fit.

Next, I tested if there was a multiplicative and/or additive interaction between ACEs (<6/6+) and perceived social support (dichotomized at the median, as described in section 4.2), based on the hypothesis that the association between the cumulative ACE score and drug use will be attenuated in those who report a higher level of perceived social support (question 1.2). This

hypothesis was also explored in a model stratified by level of perceived social support (question 1.2), as an alternative to interaction testing.

Next, I tested the hypothesis that the ACE category of childhood maltreatment has a stronger association with drug use than the ACE category of household dysfunction (question 1.3). This hypothesis was tested by creating index scores for each ACE dimension (based on scores 0-5, as described in section 4.3). Each category was analyzed in the fully adjusted model separately, and information criteria were used to assess which model was a better fit for the data. Both indexes were then added into the fully adjusted model, and a post-estimation command was used to determine if differences between these estimates were significant. I then tested for both multiplicative and additive interactions between childhood maltreatment (dichotomized at <3/3+) and perceived social support (question 1.3.1). I chose three for the cut-point because I am using six (out of ten ACEs) for my main model; therefore, three (out of the five) was proportionate for the childhood maltreatment indicator. A dichotomized childhood maltreatment indicator for use in interaction testing is a novel and exploratory approach that I have not seen done before. A stratified model by level of perceived social support was also analyzed.

Next, I tested the hypothesis that the single ACE of household substance abuse history (part of the household dysfunction dimension) has an independent positive association with drug use (question 1.4). The single ACE was added to the logistic regression model, adjusting for covariates. The model was then adjusted for the other nine ACEs, using an index score (scores 0-9). Finally, I tested for multiplicative and additive interactions between household substance abuse history and perceived social support, based on the hypothesis that the association will be attenuated in those reporting higher levels of perceived social support (question 1.4.1). A model stratified by level of perceived social support was also analyzed.

5.2 Sample Characteristics and Covariate Distribution

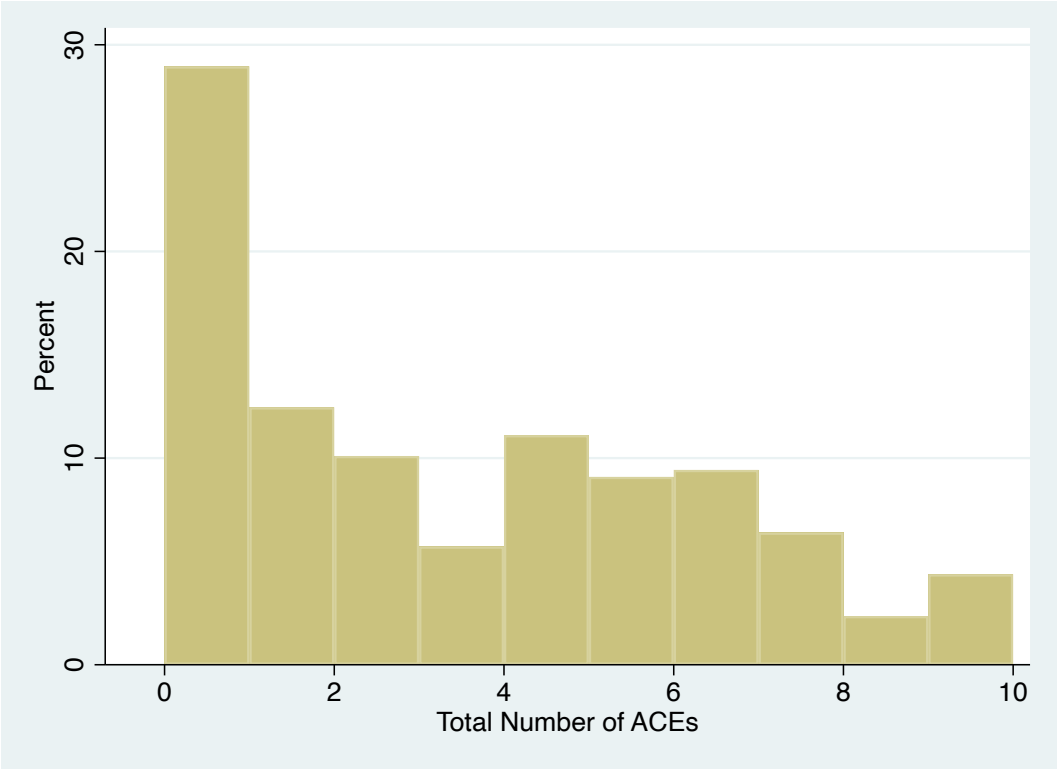
To capture sample characteristics, data was analyzed prior to using the *carryforward* command for covariate distribution at the ACE index visit, with results summarized in Table 5.1.

Table 5.1: Demographic Characteristics Based on Responses Between December 15, 2020, and October 8, 2021 (Index Visit for ACE Questionnaire; n=297)

Characteristic	n (%)
Age	
18-29 years	54 (18.2)
30-39 years	142 (47.8)
40-52 years	101 (34.0)
Race/Ethnicity	
Black	123 (41.4)
Hispanic/Latino	121 (40.7)
Other Race	16 (5.4)
White	37 (12.5)
Education	
Didn't Finish High School	30 (10.1)
High School	91 (30.6)
Some College	92 (31)
College Grad+	84 (28.3)
Income	
$0-$19,999	144 (48.5)
$20,000-$39,9999	79 (26.6)
$40,000+	74 (24.9)
HIV Status	
HIV-	131 (44.1)
HIV+	166 (55.9)
BMI	
Underweight (<18.5)	4 (1.4)
Normal (18.5-24.9)	98 (33.0)
Overweight (25-29.9)	99 (33.3)
Obese (30+)	94 (31.7)
Missing	2 (0.7)
Cigarette/Vape Use	
Not Currently	216 (72.7)
Currently	81 (27.3)
Alcohol Frequency	
Monthly or Less (Including Never)	197 (66.3)
2-4 Times/Month	39 (13.1)
2-3 Times/Week	36 (12.1)
4+ Times/Week	25 (8.4)
Depressive Symptoms	
Not Depressed	212 (71.4)
Likely Depressed	85 (28.6)

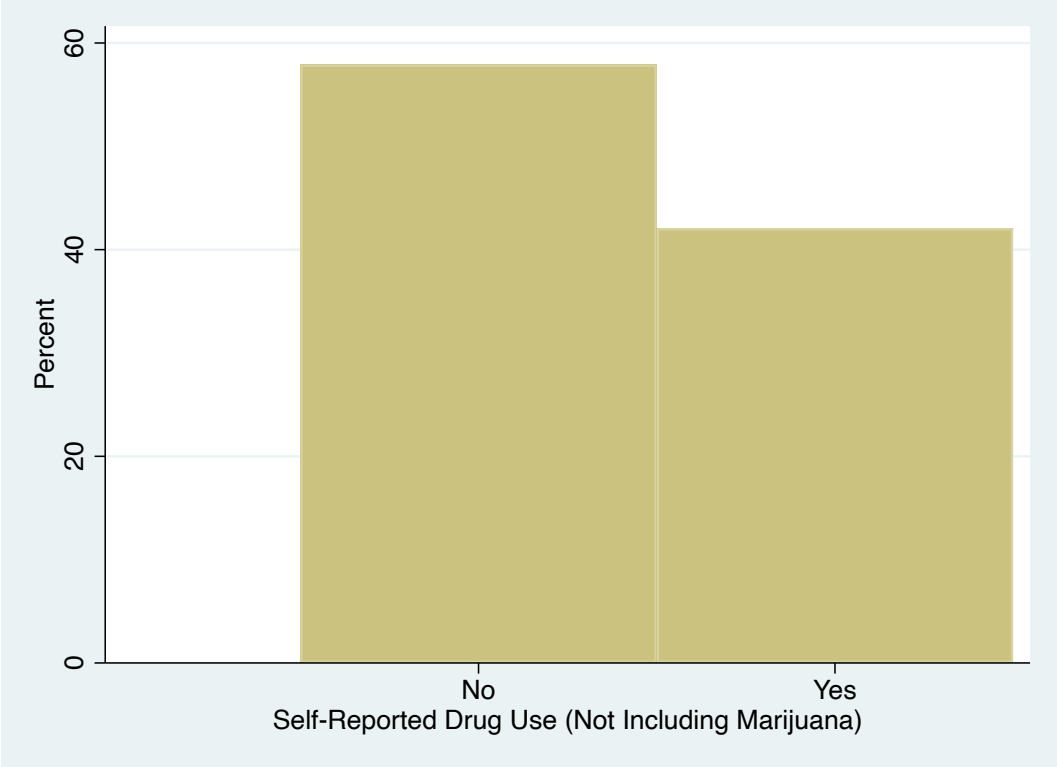
The distribution of the total ACE score at the index visit is shown in Figure 5.1. The mean ACE score in the study sample is 3.0 (SD=2.8). In this sample, 71% of participants had at least one ACE, which is slightly lower than other studies of larger MSM samples (80%) [383], including samples of Black MSM (90%) [388].

Figure 5.1: Distribution of Total Number of ACEs (Index Visit; n=297)



The distribution of self-reported drug use (outcome) at the index visit is displayed in Figure 5.2. Marijuana was the commonly used substance (with 44.4% reporting use) and was not included in this drug use indicator. Of the other drugs used for analysis, methamphetamine was the most common (with 32.7% reporting use). Among participants reporting ACEs, 42.1% report using drugs (not including marijuana) in the past six months.

Figure 5.2: Distribution of Self-Reported Drug Use Not Including Marijuana During the Past Six Months (At ACE Index Visit; n=297)

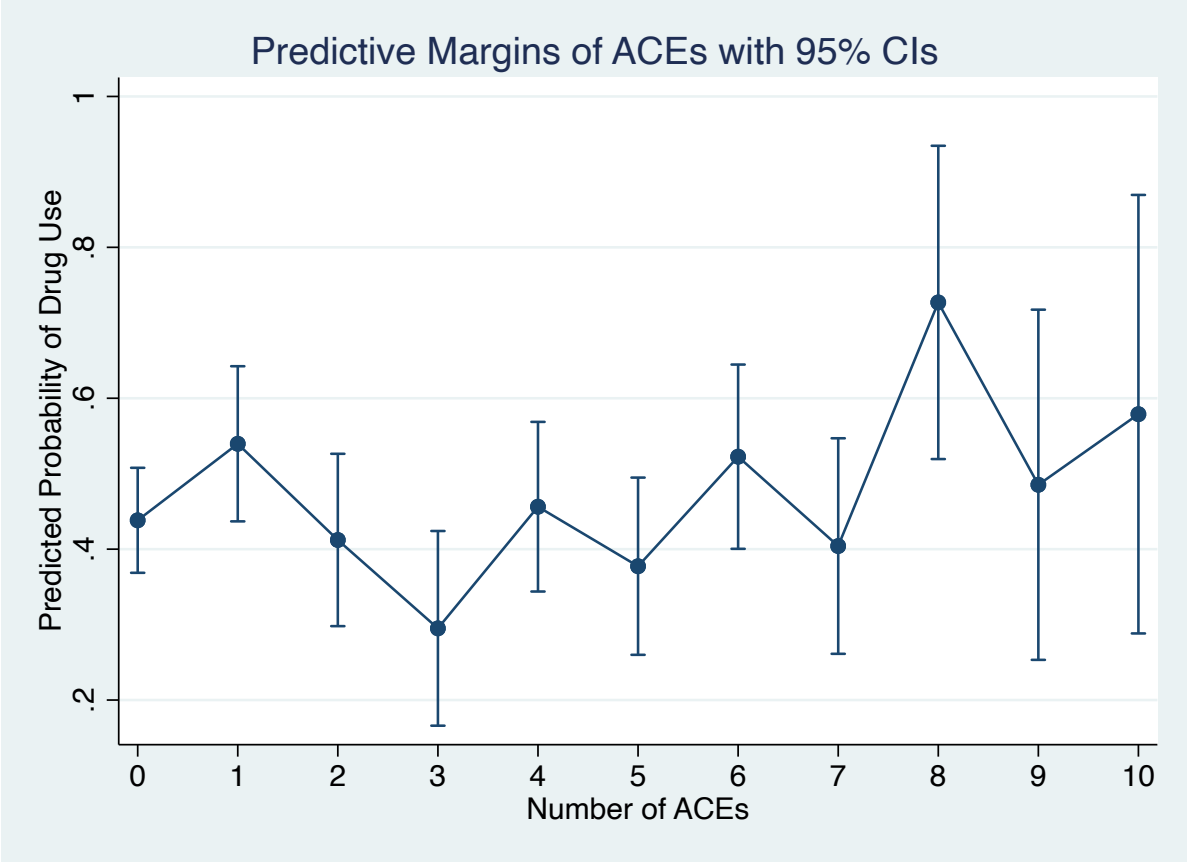


5.3 Results

Hypothesis 1.1: The cumulative ACE score will have an independent association with self-reported drug use, following a dose-response continuum.

Mixed-effects logistic regression was used to test the association of each additional ACE on the outcome of drug use. Results from testing the association of each additional ACE in the fully adjusted model are summarized by a margins plot (Figure 5.3).

Figure 5.3: Margins Plot from Fully Adjusted Mixed-Effects Logistic Regression of ACEs on Drug Use (n=295 Across 2,564 Person-Visits)



Results indicate no dose-response relationship between the number of ACEs and the predicted probability of drug use. Meanwhile, this analysis helped determine that six was the optimal cut-point for the main model. This is the point where the predicted probability of drug use tended to increase. An ACE indicator at <6/6+ was then used to investigate if the cumulative ACE score had an independent association with drug use. Crosstab indicates that 22.5% of individuals in this sample had six or more ACEs (Table 5.2).

Table 5.2: Distribution of Participants with Six or More ACEs (n= 297 Across 2,735 Person-Visits)

ACEs	Frequency	Percent
<6	2,120	77.5
6+	615	22.5

Bivariate analysis (unadjusted) found that cumulative ACEs (<6/6+) increase the odds of drug use by 1.93 (95% CI: 0.88-4.23). After adding variables one at a time and then examining model fit using information criteria at each step of model building, it was concluded that the entire set of covariates (determined a priori) was appropriate for the model. While many predictors are not significant and did not contribute to model fit, they provide sound adjustment based on previous literature. Results from the main model are summarized in Table 5.3.

Table 5.3: Mixed-Effects Logistic Regression of Six or More ACEs on Drug Use (n=295 Across 2,564 Person-Visits)

Self-Reported Drug Use	OR	95% CI	p-value
6 or More ACEs	2.04	0.87-4.82	0.10
Age	-	-	0.53
18-29 Years	-	-	-
30-39 Years	0.98	0.59-1.62	0.93
40-52 Years	0.72	0.36-1.47	0.37
Race/Ethnicity	-	-	0.27
Black	0.18	0.03-0.98	0.05
Hispanic/Latino	0.20	0.04-1.10	0.06
Other	-	-	-
White	0.20	0.03-1.29	0.09
Education	-	-	0.22
Didn't Finish HS	1.02	0.46-2.27	0.95
HS	1.46	0.79-2.72	0.23
Some College	1.71	0.97-3.02	0.06
College Grad+	-	-	-
Income	-	-	0.00**
$0-19,999	3.09	1.84-5.21	0.00**
$20,000-39,999	2.30	1.35-3.91	0.00**
$40,000+	-	-	-
HIV+	1.95	0.97-3.90	0.06
BMI	-	-	0.00**
Underweight	6.24	0.84-46.26	0.07
Normal Weight	-	-	-
Overweight	0.55	0.33-0.92	0.02*
Obese	0.19	0.10-0.37	0.00**
Current Cig/Vape Use	2.40	1.57-3.70	0.00**
Alcohol Frequency	-	-	0.00**
Monthly or Less	-	-	-
2-4 Times/Month	1.98	1.36-2.87	0.00**
2-3 Times/Week	2.86	1.75-4.70	0.00**
4+ Times/Week	2.58	1.39-4.76	0.00**
Depressive Symptoms	-	-	-
Unlikely Depressed	-	-	-
Likely Depressed	1.80	1.29-2.51	0.00**
COVID-19 Time	0.92	0.68-1.25	0.61
Constant	0.58	0.10-3.42	0.54

*p<0.05; **p<0.01; OR: odds ratio; CI: confidence interval

ACEs: Adverse Childhood Experiences; HS: High School; Cig: Cigarette

BMI: Underweight (<18.5); Normal (18.5-24.99); Overweight (25-29.99); Obese (30+)

Results indicate that the presence of six or more ACEs increases the odds of self-reported drug use by 2.04 (95% CI: 0.87-4.82) after adjusting for age, race/ethnicity, education, income, HIV status, BMI, current cig/vape use, alcohol frequency, depressive symptoms, and a time variable indicating COVID-19 (described in section 4.2). Findings suggest that being exposed to six or more ACEs during the first 18 years of life more than double the odds of reporting drug use in the past six months, however this estimate only trended toward significance (p=0.10).

Hypothesis 1.2: The association between the cumulative ACE score and drug use will be attenuated in those who report a higher level of perceived social support.

This hypothesis was tested by adding an interaction term between the ACE indicator (<6/6+) and an indicator for high levels of perceived social support (dichotomized at the median) in the fully adjusted model. Results did not indicate a statistically significant interaction, meaning that any potential buffering effects of perceived social support are not multiplicative. Additive interaction analysis using RERI was also not significant. Meanwhile, a stratified analysis did suggest that among individuals with high perceived social support, the association between ACEs and drug use was nonexistent (OR: 0.92; 95% CI: 0.23-3.69; n=172 across 1,291 person-visits), whereas among individuals with low perceived social support, ACEs (<6/6+) predicted drug use (OR: 2.89; 95% CI: 0.98-8.48; n=163 across 1,273 person-visits), albeit bordering on significance (p=0.05). Among those with low levels of perceived social support, 29.5% have six or more ACEs. Results from the model among those with low levels of perceived social support are displayed in Table 5.4. Because this analysis cuts the sample size approximately in half, CIs are high and therefore should be interpreted with caution.

Table 5.4: Mixed-Effects Logistic Regression of Six or More ACEs on Drug Use Among Individuals Perceiving Low Levels of Social Support (n=163 Across 1,273 Person-Visits)

Self-Reported Drug Use	OR	95% CI	p-value
6 or More ACEs	2.89	0.98-8.48	0.05
Age	-	-	-
18-29 Years	-	-	-
30-39 Years	1.93	0.91-4.08	0.09
40-52 Years	1.34	0.48-3.71	0.58
Race/Ethnicity			
Black	0.14	0.01-1.44	0.10
Hispanic/Latino	0.33	0.03-3.44	0.35
Other	-	-	-
White	0.51	0.03-7.51	0.62
Education	-	-	-
Didn't Finish HS	1.67	0.60-4.69	0.33
HS	2.48	1.01-6.05	0.05*
Some College	2.47	1.08-5.63	0.03*
College Grad+	-	-	-
Income	-	-	-
$0-19,999	3.21	1.46-7.03	0.00**
$20,000-39,999	2.02	0.90-4.55	0.09
$40,000+	-	-	-
HIV+	1.09	0.40-2.95	0.87
BMI	-	-	-
Underweight	35.2	1.38-902.55	0.03*
Normal Weight	-	-	-
Overweight	0.4	0.21-0.80	0.01**
Obese	0.18	0.07-0.44	0.00**
Current Cig/Vape Use	1.99	1.07-3.70	0.03*
Alcohol Frequency	-	-	-
Monthly or Less	-	-	-
2-4 Times/Month	1.52	0.90-2.56	0.11
2-3 Times/Week	2.3	1.17-4.52	0.02*
4+ Times/Week	3.73	1.57-8.83	0.00**
Depressive Symptoms	-	-	-
Unlikely Depressed	-	-	-
Likely Depressed	2.07	1.34-3.22	0.00**
COVID-19 Time	1.16	0.76-1.78	0.50
Constant	0.50	0.04-6.32	0.59

*p<0.05; **p<0.01; OR: odds ratio; CI: confidence interval

ACEs: Adverse Childhood Experiences; HS: High School; Cig: Cigarette

BMI: Underweight (<18.5); Normal (18.5-24.99); Overweight (25-29.99); Obese (30+)

Hypothesis 1.3: The ACE category of childhood maltreatment will have a stronger association with drug use than the category of household dysfunction.

First, each dimension of ACEs (continuous variables ranging from 0-5) were added separately to the fully adjusted models. Information criteria were used to determine that household dysfunction was a better fit for the data. Results are summarized in Table 5.5.

Table 5.5: Information Criteria for Each ACE Dimension in Fully Adjusted Mixed-Effects Logistic Regression with Outcome Drug Use (n=295 Across 2,564 Person-Visits)

ACE Dimension	AIC	BIC
Childhood Maltreatment	2336.1	2470.6
Household Dysfunction	2334.5	2469.1

AIC: Akaike Information Criteria; BIC: Bayesian Information Criteria

Next, both dimensions were added to the fully adjusted model. Contrary to the hypothesis, the estimate for household dysfunction was higher than childhood maltreatment, however only trended toward significance (p=0.09). Results indicate that the index score for household dysfunction trended toward being a significant predictor of drug use (OR: 1.28; 95% CI: 0.96-1.70) whereas childhood maltreatment did not. Results are shown in Table 5.6.

Table 5.6: Mixed-Effects Logistic Regression of Childhood Maltreatment on Drug Use with Adjustment for Household Dysfunction (n=295 Across 2,564 Person-Visits)

Self-Reported Drug Use	OR	95% CI	p-value
Childhood Maltreatment	0.88	0.68-1.14	0.33
Household Dysfunction	1.28	0.96-1.70	0.09
Age	-	-	0.55
18-29 Years	-	-	-
30-39 Years	0.96	0.58-1.60	0.89
40-52 Years	0.72	0.36-1.47	0.37
Race/Ethnicity	-	-	0.24
Black	0.17	0.03-0.93	0.04
Hispanic/Latino	0.20	0.38-1.11	0.07
Other	-	-	-
White	0.18	0.03-1.22	0.08
Education	-	-	0.21
Didn't Finish HS	1.06	0.48-2.35	0.89
HS	1.51	0.81-2.80	0.20
Some College	1.74	0.98-3.07	0.06
College Grad+	-	-	-
Income	-	-	0.00**
$0-19,999	3.13	1.86-5.28	0.00**
$20,000-39,999	2.31	1.36-3.93	0.00**
$40,000+	-	-	-
HIV+	2.04	1.02-4.08	0.04*
BMI	-	-	0.00**
Underweight	6.10	0.83-44.6	0.08
Normal Weight	-	-	-
Overweight	0.55	0.33-0.92	0.02*
Obese	0.20	0.10-0.38	0.00**
Current Cig/Vape Use	2.44	1.59-3.75	0.00**
Alcohol Frequency	-	-	0.00**
Monthly or Less	-	-	-
2-4 Times/Month	1.97	1.35-2.86	0.00**
2-3 Times/Week	2.84	1.74-4.63	0.00**
4+ Times/Week	2.53	1.37-4.69	0.00**
Depressive Symptoms	-	-	-
Unlikely Depressed	-	-	-
Likely Depressed	1.81	1.30-2.54	0.00**
COVID-19 Time	0.93	0.68-1.25	0.61
Constant	0.55	0.09-3.34	0.52

*p<0.05; **p<0.01; OR: odds ratio; CI: confidence interval

ACEs: Adverse Childhood Experiences; HS: High School; Cig: Cigarette

BMI: Underweight (<18.5); Normal (18.5-24.99); Overweight (25-29.99); Obese (30+)

Finally, a post-estimation command was used to test if the difference between the two predictors was statistically significant. Results indicate that the linear combination of the parameters (using subtraction) did not reach significance (p=0.12).

Hypothesis 1.3.1: The association between childhood maltreatment and drug use will be attenuated in those who report a higher level of perceived social support.

This hypothesis was tested by adding an interaction term between the childhood maltreatment indicator (<3/3+) and the indicator for high levels of perceived social support in the fully adjusted model. Results did not indicate a statistically significant multiplicative interaction, which was expected given the absence of a childhood maltreatment main effect. Additive interaction testing using RERI was also not significant. Meanwhile, in the stratified model, household dysfunction was a significant predictor of drug use (OR: 1.73; 95% CI: 1.19-2.51) among those with low levels of perceived social support, but childhood maltreatment was not.

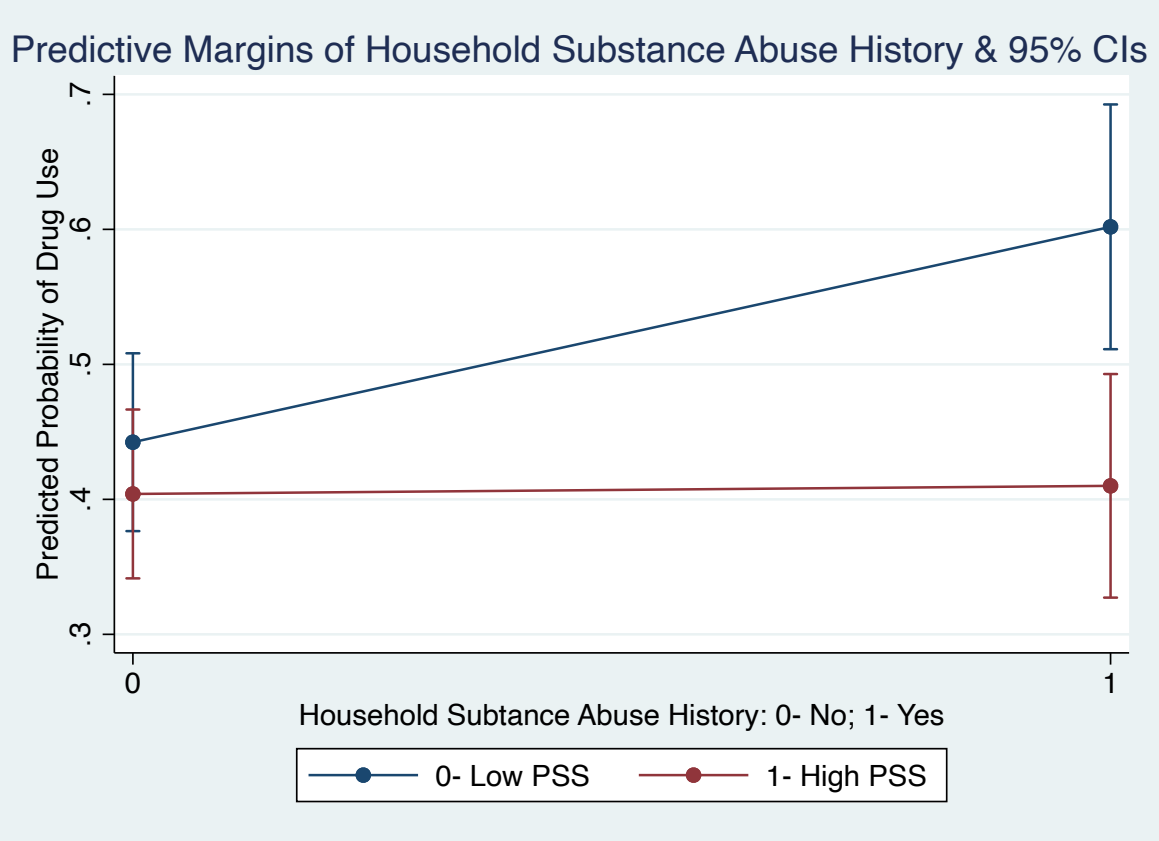
Hypothesis 1.4: The single ACE of household substance abuse history will have an independent association with drug use.

The selective approach tested if household substance abuse history (part of the household dysfunction dimension) predicts drug use using mixed-effects logistic regression, adjusting for covariates. In the model not adjusted for an index of the other nine ACEs, household substance abuse history increased the odds of drug use (OR: 1.70; 95% CI: 0.81-3.57) but was not significant (p=0.16). Next, I added an adjustment for the other nine ACEs. Not surprisingly, results indicate that household substance abuse history remained a non-significant predictor of drug use (OR: 1.82; 95% CI: 0.75-4.43; p=0.19).

Hypothesis 1.4.1: The association between household substance abuse history and drug use will be attenuated in those who report a higher level of perceived social support.

This hypothesis was tested by adding an interaction term between household substance abuse history and the indicator for high levels of perceived social support in the fully adjusted model, including adjustment for the other nine ACEs. Results indicate a significant (p=0.03) and multiplicative protective effect of high levels of perceived support on the association between household substance abuse history and drug use. Findings from testing the interaction in the fully adjusted logistic regression model are summarized by a margins plot (Figure 5.4).

Figure 5.4: Margins Plot from Fully Adjusted Mixed-Effects Logistic Regression of Household Substance Abuse History Interacting with Perceived Social Support on Drug Use (n=295 Across 2,564 Person-Visits)



A post-estimation Wald chi-squared test (*testparm*) was used to confirm statistical significance of the combined main effects plus the interaction term (p=0.00). Due to the

robustness of the findings from the multiplicative interaction model, results from the additive interaction and the stratified model are not reported.

Hypothesis 1.5: None of the findings from any of these hypotheses will differ after adjustment for a time variable indicating COVID-19.

All fully adjusted models were rerun without the time variable indicating COVID-19, and none of the main findings differed from those reported above.

5.4 Discussion

Primary Findings. While the main findings from Study One are summarized below and then findings from each hypothesis are discussed, additional discussion of the integrated findings from all three studies can be found in section 8.1.

A cumulative ACE score of six or more doubled the odds of illicit drug use in this sample of mostly Black and Latino low-income MSM in Los Angeles, however this estimate only trended toward significance (p=0.10). Because the relationship between ACEs and drug use did not follow a dose-response continuum, the chosen model compared those with six or more ACEs to those below, supporting the concept of cumulative impact. Models using ACE categories (using zero ACEs as the reference group) did not perform as well (based on AIC/BIC), which is likely due to the lack of dose-response pattern predicted by ACEs. While the original ACE study identified four or more as the best cut-point for predicting illicit drug use (compared to no ACEs), their sample was mostly White and insured patients [3]. The current study investigated a much higher-risk group subject to poverty, and likely to discrimination based on race/ethnicity, sexual orientation, and HIV status. It is not uncommon to use higher thresholds for groups with higher baseline risk.

Perceived social support emerged as a moderator between cumulative ACEs and drug use in a stratified model. Among those with low levels of perceived social support, a relationship between ACEs and drug use was present, whereas among those with high levels of perceived social support, no relationship existed. Higher levels of perceived social support can be conceptualized as a resilience factor that buffers the relationship between ACEs and drug use among mostly Black and Latino low-income MSM in Los Angeles.

The ACE dimension of childhood maltreatment did not emerge as a predictor of drug use, whereas household dysfunction trended toward significant prediction. The household dysfunction dimension might have a stronger impact because the single ACE of household substance abuse history is part of that category. The specific ACE of household substance abuse history trended toward being a significant predictor of drug use in this cohort. Findings support the notion that examining ACEs in clusters is a good practice. Meanwhile, measuring ACEs individually has the added benefit of being able to examine its unique contribution and potential interactions. In this study, the presence of a significant negative multiplicative interaction between household substance abuse history and high levels of perceived social support indicates that the presence or perception of social support may be particularly beneficial in mitigating risk for drug use among MSM who grew up in households with problematic substance use.

Hypothesis 1.1: The cumulative ACE score will have an independent association with self-reported drug use, following a dose-response continuum.

ACEs do not predict drug use in a dose-response fashion in this cohort of mostly Black and Latino low-income MSM in Los Angeles. The original ACE study showed a dose-response relationship between ACEs and illicit drug use [3] and many researchers have endorsed the practice of measuring ACEs along a dose-response continuum for mental health outcomes

[87,109]. However, drug use itself is not a mental health outcome but may be used as a proxy for SUD, which is strongly correlated with depression and anxiety (discussed in Chapter 6 and 7, respectively). Studies specifically with MSM have shown dose-response effects of ACEs on depression, anxiety, and sexual risk-taking behavior [93] but no research (to my knowledge) on MSM documents a dose-response relationship between ACEs and drug use. While several potential explanations are offered below, it is possible that the relatively small sample size made it difficult to detect a dose-response relationship that may have emerged in a larger sample. The erratic pattern of ACEs predicting the probability of drug use (Figure 5.3) supports this assertion. The fact that individuals with two, three, five, and seven ACEs have less likelihood of using drugs in adulthood compared to those with no ACEs completely diverges from prior literature.

The absence of a dose-response relationship between ACEs and drug use among MSM might be partially explained by higher rates of drug use in MSM compared to heterosexuals [413]. Drug use is often sexualized among MSM [419,420] suggesting that other unmeasured social factors can contribute to drug use among MSM. Additional factors include low SES, other substance use (i.e., nicotine and alcohol), and depressive symptoms (see Table 5.3). Furthermore, by design, approximately half of the sampled participants did not use drugs and among those, approximately 20% had six or more ACEs. Non-significant findings related to drug use might be because individuals using drugs were oversampled in the mSTUDY cohort. Findings collectively suggest that the ten ACEs from the original measure are not linearly predictive of drug use among mostly Black and Latino low-income MSM in Los Angeles. It is the presence of multiple ACEs and their cumulative impact that are more likely to have predictive power.

Furthermore, it is quite possible that mSTUDY participants experienced other ACEs such as peer-victimization and discrimination (outside of the home) that were not captured by the

current ACE instrument, downwardly biasing estimates between ACEs and drug use. In a sample of primarily Black children from Chicago, nearly 20% reported only expanded ACEs [73]. Incomplete capture of ACEs can lead to misclassification bias, discussed in section 8.2.1.

In the main model adjusted for covariates, cumulative ACEs (six or more) more than double the odds of reporting drug use in the past six months, however only trended toward significance (p=0.10). These estimates are substantially lower than has been observed in other samples. In a systematic review and meta-analysis from 2017, the OR of illicit drug use following four or more ACEs was 5.62 (95% CI: 4.46-7.07) [5]. One might expect that a higher threshold would lead to a higher likelihood of the outcome, but there are unique characteristics of this sample (i.e., multiple risk factors present) that limit its comparability to the general population. Given that men's gender is also a known risk factor for drug use [515], the current study of men only might partially explain the lower estimate.

Hypothesis 1.2: The association between the cumulative ACE score and drug use will be attenuated in those who report a higher level of perceived social support.

While the multiplicative and additive interaction models did not yield statistically significant findings, the stratified model indicated that perceived social support can be conceptualized as a resilience resource, buffering the effects of ACEs on drug use. It has been previously established that ELA reduces social support [343] which is in turn associated with mental ill-health [342]. While several studies have shown social support partially mediates links between ELA and mental health outcomes [347–349], there are a lack of data examining social support as a protective factor against drug use. This is the first study to suggest that the life course impact of ACEs on drug use might be mitigated by the presence or perception of social support among MSM.

A strength of this analysis is in its potential to inform intervention strategies. Among MSM who report multiple ACEs and are at risk for drug use, promotion of social support (for example through community-based programs targeting trauma survivors) may offset the risk for transition into drug use. Longitudinal data has shown that individuals with ACEs are less likely to transition out of a riskier class and more likely to become polysubstance users [150]. Given that substance use often begins during adolescence and early adulthood, it is imperative that early interventions are implemented. First-time drug use begins at an earlier age when there is childhood trauma [149]. Among Hispanic adolescents in Southern California, those exposed to more ACEs experienced steeper inclining trajectories to substance use [516]. Given the links between ACEs and drug use in this sample, promotion of social support may be one ingredient in public health interventions designed to support the health and well-being of low-income MSM, many of whom are HIV+ or can be considered at-risk for HIV infection.

Hypothesis 1.3: The ACE category of childhood maltreatment will have a stronger association with drug use than the category of household dysfunction.

Findings from the current study did not support this hypothesis. This research question was generated from studies suggesting that childhood maltreatment is associated with worse mental health outcomes than household dysfunction [35,80,89,119]. Meanwhile, a recent analysis from the National Survey of Children's Health found that household dysfunction is a stronger predictor of substance use than childhood maltreatment [517], however these findings were only recently published (August 2021), after dissertation hypotheses were developed. In their study, the odds of SUD following three or more household dysfunction ACEs was 7.75 (95% CI: 3.45-17.39) [517]. Once again, it is possible that estimates from the current sample are

much lower than nationally representative samples due to the co-occurrence of other risk factors driving drug use, or the incomplete capture of ACEs (such as those that occur in the community).

This hypothesis was also generated from literature related to the biological embedding of adversity (reviewed in section 1.5) suggesting that childhood maltreatment is more likely to "get under the skin" and impact neural mechanisms associated with reward/dopamine. While I anticipated that links between ACEs and drug use could be partially conceptualized through biological pathways, the finding that household dysfunction is a stronger predictor of drug use support a social determinants of health framework. It is more likely that social and immediate environmental factors (in the home) contribute to drug use compared to abuse and neglect among MSM in Los Angeles. This appears to be an important finding that should be explored further.

Hypothesis 1.3.1: The association between childhood maltreatment and drug use will be attenuated in those who report a higher level of perceived social support.

This hypothesis was not supported by the data, which was expected given the absence of a childhood maltreatment main effect. No previous studies have reported buffering effects by perceived social support and the specific dimension of childhood maltreatment, therefore this research question was novel and exploratory in nature.

Hypothesis 1.4: The single ACE of household substance abuse history will have an independent association with drug use.

Household substance abuse history comes from the dimension of household dysfunction. Among those reporting ACEs in the mSTUDY cohort, 36% experienced household substance abuse history. When the single ACE was examined as a key predictor, the odds of reporting drug use in the past six months did not reach significance. Surprisingly, after adding the index of the other nine ACEs, the estimate increased (but did not reach significance) and the OR of the other

nice ACEs was less than one (0.98; 95% CI: 0.82-1.16) suggesting that this specific ACE may be predictive of drug use in this sample. A larger sample size may have contributed to statistical significance. Findings provide further support that the presence of multiple ACEs and their cumulative impact have more predictive power than single ACEs. Other potential reasons that this ACE may have predictive capacity may be due to the genetic nature of addictive disorders (see section 1.4), assuming that the household member is a biological relative.

In summary, the single ACE of household substance abuse history may be important for predicting drug use outcomes, given the evidence that parental substance use can be traumatic for children and heighten their risk of drug use later in life [479]. However, in this study the estimate did not quite reach statistical significance but became significant when interacted with perceived social support in the model (hypothesis 1.4.1).

Hypothesis 1.4.1: The association between household substance abuse history and drug use will be attenuated in those who report a higher level of perceived social support.

Data from this study support this hypothesis and is the most salient finding from Study One, given its potential policy implications and the fact that this has not been previously documented. The multiplicative interaction model with household substance abuse history and high levels of perceived social support survived adjustment for the other nine ACEs. This finding demonstrates that high levels of perceived social buffer the impact of household substance abuse history on drug use among mostly Black and Latino low-income MSM in Los Angeles. Along this line, those reporting lower levels of perceived social support are at significantly higher risk of developing drug use in adulthood, even after adjusting for covariates and the other nine ACEs.

As discussed under Hypothesis 1.2, the indication that perceived social support is a resilience factor has important public health and policy implications. Specifically, the presence

of drug use in the home may flag social services and early intervention strategies designed to promote social support and offset risk trajectories to later drug use. Given that drug use is associated with HIV infection and fatal overdose, this finding has potential to save lives. More research is needed to understand the mechanisms by which resilience factors such as social support (and others) buffer the impact of ACEs on drug use, and how this may vary across different sociodemographic groups.

Hypothesis 1.5: None of the findings from any of these hypotheses will differ after adjustment for a time variable indicating COVID-19.

The absence of any substantive changes in main estimates or significance from any of the models with versus without the time indicator for COVID-19 was expected because many of the variables were transported across time for analysis. Transportability of the data rendered the COVID-19 indicator to become somewhat of an artifact of the methodology. Thus, it was important to include this adjustment and test the hypothesis that the data collected during the COVID-19 pandemic did not differ significantly from data collected before.

Another interpretation from this analysis is that the minor associations described in Study One persisted despite an era characterized by dramatic social change and declining mental health. It is also possible that COVID-19 decreased drug use in some cases by way of limited access, or increased drug use in others along with social and emotional challenges, independent of ACE exposure. Both possibilities likely downwardly bias estimates. The fact that perceived social support was collected only during the pandemic and was assumed stable for retrospective transportation is discussed as a limitation. It is unlikely that the adjustment for COVID-19 time was sufficient to overcome this limitation.

6 CHAPTER SIX: STUDY TWO – RESULTS AND DISCUSSION

6.1 Overview of Aim, Hypotheses, and Methods

Section 6.1 provides a summary of the methods used to test each of the hypotheses introduced in section 3.2 and then described in detail in section 4.4. Section 6.3 describes the results and section 6.4 is dedicated to discussing these results. Results are discussed further in section 8.1 where findings from all three studies are integrated into an overall summary and placed into a broader context, with several recommendations for future research.

Study Two aimed to understand the influence of ACEs on depressive symptoms, analyzed prior to COVID-19. First, I hypothesized the presence of a positive and linear dose-response relationship between ACEs and depressive symptoms in the unadjusted and then fully adjusted mixed-effects logistic regression model (question 2.1). This analysis provided rationale for the optimal cut-point for ACEs in model building, based on a visual inspection of the margins plot (the point where the predicted probability of being likely depressed tended to increase, see Figure 6.3). Next, I tested if the cumulative ACE score (dichotomized at <5/5+) had an independent positive association with depressive symptoms using the Center for Epidemiological Studies Depression (CESD) dichotomized at <23/23+ (question 2.1). Model building included adding variables individually to assess the impact of each covariate on the focal relationship. Information criteria were examined as each covariate was added to the model, to assess each additional adjustment on model fit.

Next, I tested if there was a multiplicative and/or additive interactions between ACEs (<5/5+) and a sleep quality indicator (Pittsburgh Sleep Quality Index [PSQI] <6/6+), based on the hypothesis that the association between the cumulative ACE score and depressive symptoms

will be attenuated in those reporting a higher level of sleep quality (question 2.2). For sensitivity analysis, this relationship was also tested after removing the sleep question from the CESD.

Next, I tested the hypothesis that the ACE category of childhood maltreatment has a stronger association with depressive symptoms than the category of household dysfunction (question 2.3). This hypothesis was tested by creating index scores for each ACE dimension (based on scores 0-5, as described in section 4.3). Each category was analyzed in the fully adjusted model separately, and information criteria were used to assess which model was a better fit for the data. Both indexes were then added into the fully adjusted model, and a post-estimation command was used to determine if differences between these estimates were significant. I then tested for both multiplicative and additive interactions between childhood maltreatment (dichotomized at <3/3+) and the sleep quality indicator (question 2.3.1).

Next, I tested the hypothesis that the single ACE of childhood sexual abuse (part of the childhood maltreatment dimension) has an independent positive association with depressive symptoms (question 2.4). The single ACE was added to the logistic regression model, adjusting for covariates. The model was then adjusted for the other nine ACEs, using an index score (based on scores 0-9). Finally, I tested for multiplicative and additive interactions between childhood sexual abuse and sleep quality, based on the hypothesis that the association will be attenuated in those with higher levels of sleep quality (question 2.4.1).

6.2 Sample Characteristics and Covariate Distribution

Baseline characteristics are identical to Study One (Table 5.1) however Study Two also includes an adjustment for results from urine drug tests (see Table 6.1). Because this data was mostly collected during the time when marijuana was not legal for recreational use, positive

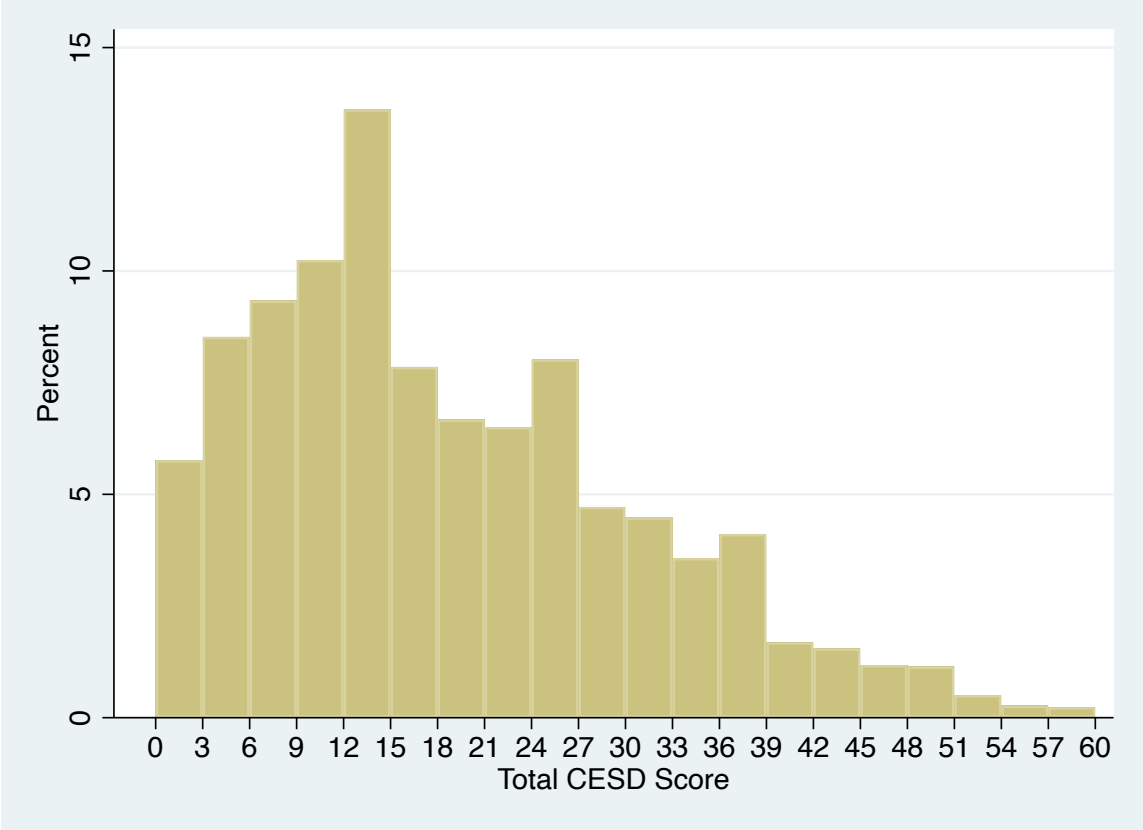
screens for marijuana are included in this covariate. The mSTUDY sampling design aimed for approximately 50% individuals who use drugs, which is consistent with data below.

Table 6.1: Positive Screens on any Drug Test for Methamphetamine, Opiates, Cocaine, Ecstasy, Marijuana, Amphetamines, and Fentanyl Between August 2014 and March 2020 (n=296 Across 2,061 Person-Visits)

Drug Test	Frequency	Percent
Positive	1,063	51.6
Negative	998	48.4

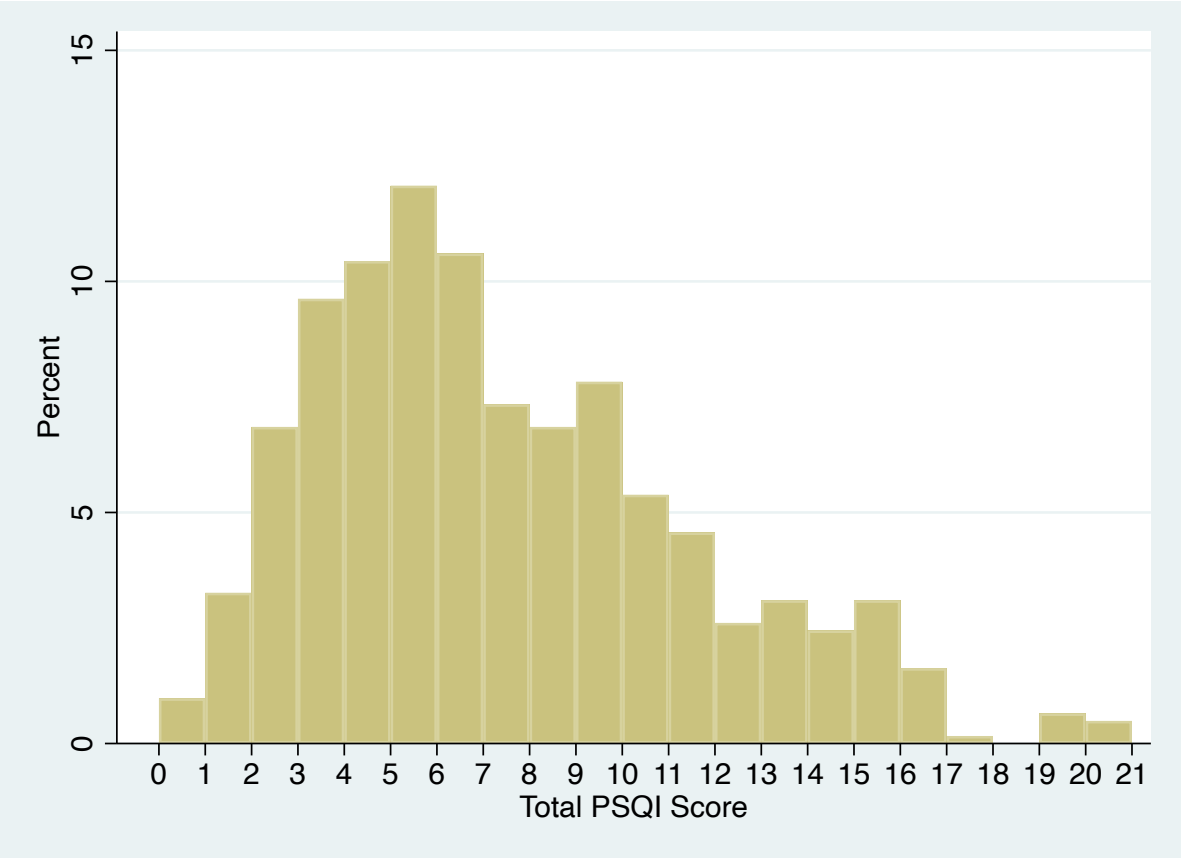
The distribution of CESD scores (outcome) is shown in Figure 6.1. The mean CESD score in the study sample is 17.9 (SD=11.9). Approximately one-third are likely depressed.

Figure 6.1: Center for Epidemiological Studies Depression (CESD) Scores Between August 2014 and March 2020 (n=557 Across 2,967 Person-Visits)



The distribution of PSQI scores (moderator) is shown in Figure 6.2. The mean PSQI score in the study sample is 6.8 (SD=4.1).

Figure 6.2: Pittsburgh Sleep Quality Index (PSQI) Scores Between August 2014 and March 2020 (n=315 Across 613 Person-Visits)

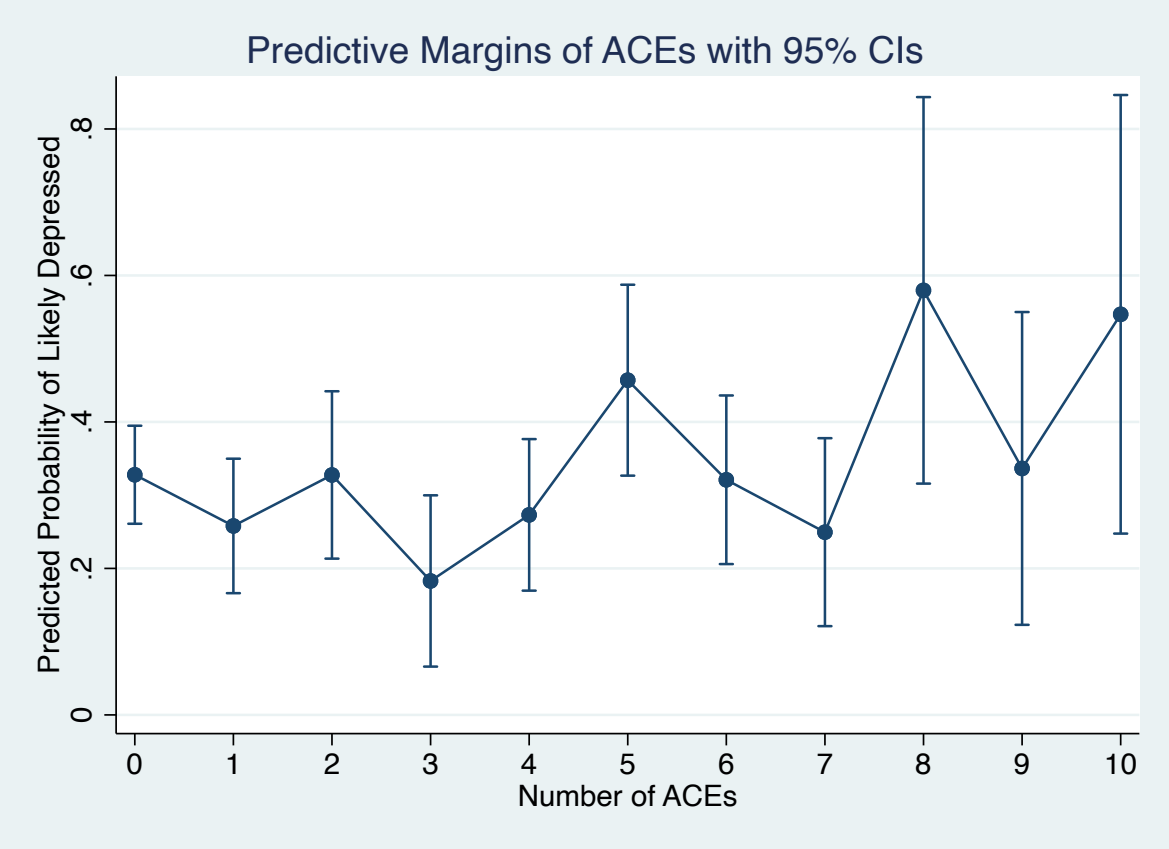


6.3 Results

Hypothesis 2.1: The cumulative ACE score will have an independent association with self-reported depressive symptoms, following a dose-response continuum.

Mixed-effects logistic regression was used to test the association of each additional ACE on the outcome of likely depressed. Results from testing the association of each additional ACE in the fully adjusted model are summarized by a margins plot (Figure 6.3).

Figure 6.3: Margins Plot from Fully Adjusted Mixed-Effects Logistic Regression of ACEs on Depressive Symptoms (n=294 Across 1,896 Person-Visits)



Results indicate no dose-response relationship between the number of ACEs and the predicted probability of likely depressed. Meanwhile, this analysis helped determine that five was the optimal cut-point for the main model. This is the point where the predicted probability of being likely depressed tended to increase. An ACE indicator at <5/5+ was then used to investigate if the cumulative ACE score had an independent association with depressive symptoms. Crosstab indicates that 31.2% of individuals in this sample had five or more ACEs.

Table 6.2: Distribution of Participants with Five or More ACEs (n=297 Across 2,734 Person-Visits)

ACEs	Frequency	Percent
<5	1,882	68.8
5+	852	31.2

Bivariate analysis (unadjusted) found that cumulative ACEs increase the odds of depressive symptoms by 1.94 (95% CI: 1.04-3.61). After adding variables one at a time and then examining model fit using information criteria at each step of model building, it was concluded that the entire set of covariates (determined a priori) was appropriate for the model. While many predictors are not significant and did not contribute to model fit, they provide sound adjustment based on previous literature. Results from the main model are summarized in Table 6.3.

Table 6.3: Mixed-Effects Logistic Regression of Five or More ACEs on Depressive Symptoms (n=294 Across 1,896 Person-Visits)

Depressive Symptoms	OR	95% CI	p-value
5 or More ACEs	1.96	1.02-3.77	0.04*
Age	-	-	0.32
18-29 Years	-	-	-
30-39 Years	0.70	0.41-1.18	0.18
40-52 Years	0.61	0.30-1.24	0.17
Race/Ethnicity	-	-	0.01*
Black	0.21	0.05-0.84	0.03*
Hispanic/Latino	0.21	0.05-0.83	0.03*
Other	-	-	-
White	0.65	0.14-3.09	0.59
Education	-	-	0.16
Didn't Finish HS	2.47	1.12-5.47	0.03
HS	1.42	0.76-2.66	0.27
Some College	1.43	0.79-2.58	0.23
College Grad+	-	-	-
Income	-	-	0.03*
$0-19,999	1.51	0.83-2.73	0.18
$20,000-39,999	0.83	0.44-1.58	0.57
$40,000+	-	-	-
HIV+	1.26	0.67-2.38	0.47
BMI	-	-	0.65
Underweight	1.02	0.26-4.01	0.98
Normal Weight	-	-	-
Overweight	0.81	0.50-1.31	0.39
Obese	0.67	0.37-1.24	0.20
Current Cig/Vape Use	1.22	0.78-1.91	0.38
Alcohol Frequency	-	-	0.99
Monthly or Less	-	-	-
2-4 Times/Month	0.96	0.64-1.44	0.86
2-3 Times/Week	0.94	0.54-1.65	0.83
4+ Times/Week	1.07	0.56-2.05	0.84
Drug Screen+	2.53	1.70-3.75	0.00**
Constant	0.39	0.08-1.82	0.23

*p<0.05; **p<0.01; OR: odds ratio; CI: confidence interval

ACEs: Adverse Childhood Experiences; HS: High School; Cig: Cigarette

BMI: Underweight (<18.5); Normal (18.5-24.99); Overweight (25-29.99); Obese (30+)

Results indicate that the presence of five or more ACEs increased the odds of being likely depressed by 1.96 (95% CI: 1.02-3.77) after adjusting for age, race/ethnicity, education, income, HIV status, BMI, current cig/vape use, alcohol frequency, and urine drug test. Findings suggest that being exposed to five or more ACEs during the first 18 years of life double the odds of being likely depressed in adulthood.

Hypothesis 2.2: The association between the cumulative ACE score and depressive symptoms will be attenuated in those who report a higher level of sleep quality.

This hypothesis was tested by adding an interaction term between the ACE indicator (<5/5+) and an indicator for high level of sleep quality in the fully adjusted model. Results did not indicate a statistically significant interaction, meaning that any potential buffering effects by higher level of sleep quality are not multiplicative. Additive interaction analysis using RERI was also not significant and therefore did not warrant stratified analysis. The sleep question was then removed from the CESD but did not change the findings.

Hypothesis 2.3: The ACE category of childhood maltreatment will have a stronger association with depressive symptoms than the category of household dysfunction.

First, each dimension of ACEs was added separately to the fully adjusted models. Information criteria were used to determine that childhood maltreatment was a better fit for the data. Results are shown in Table 6.4.

Table 6.4: Information Criteria for Each ACE Dimension in Fully Adjusted Mixed-Effects Logistic Regression with Outcome Depressive Symptoms (n=294 Across 1,896 Person-Visits)

ACE Dimension	AIC	BIC
Childhood Maltreatment	1865.2	1987.2
Household Dysfunction	1868.4	1990.4

AIC: Akaike Information Criteria; BIC: Bayesian Information Criteria

Next, both dimensions were added to the fully adjusted model. Consistent with the hypothesis, the estimate for childhood maltreatment was higher than household dysfunction. Results indicate that the index score for childhood maltreatment is a significant predictor of depressive symptoms (OR: 1.26; 95% CI: 1.01-1.57) whereas household dysfunction is not. Results are found in Table 6.5.

Table 6.5: Mixed-Effects Logistic Regression of Childhood Maltreatment on Depressive Symptoms with Adjustment for Household Dysfunction (n=294 Across 1,896 Person-Visits)

Depressive Symptoms	OR	95% CI	p-value
Childhood Maltreatment	1.26	1.01-1.57	0.04*
Household Dysfunction	0.89	0.70-1.14	0.36
Age	-	-	0.35
18-29 Years	-	-	-
30-39 Years	0.71	0.42-1.20	0.20
40-52 Years	0.62	0.30-1.26	0.19
Race/Ethnicity	-	-	0.02*
Black	0.24	0.06-1.00	0.05
Hispanic/Latino	0.23	0.06-0.94	0.04*
Other	-	-	-
White	0.75	0.16-3.56	0.72
Education	-	-	0.17
Didn't Finish HS	2.46	1.11-5.44	0.03*
HS	1.45	0.77-2.70	0.25
Some College	1.45	0.81-2.61	0.22
College Grad+	-	-	-
Income	-	-	0.02*
$0-19,999	1.50	0.83-2.71	0.18
$20,000-39,999	0.83	0.44-1.56	0.56
$40,000+	-	-	-
HIV+	1.26	0.67-2.38	0.48
BMI	-	-	0.62
Underweight	1.02	0.26-3.98	0.98
Normal Weight	-	-	-
Overweight	0.80	0.49-1.29	0.35
Obese	0.67	0.36-1.23	0.19
Current Cig/Vape Use	1.21	0.78-1.90	0.40
Alcohol Frequency	-	-	0.98
Monthly or Less	-	-	-
2-4 Times/Month	0.96	0.64-1.44	0.85
2-3 Times/Week	0.95	0.54-1.66	0.85
4+ Times/Week	1.09	0.57-2.08	0.81
Drug Screen+	2.57	1.73-3.82	0.00**
Constant	0.35	0.07-1.67	0.19

*p<0.05; **p<0.01; OR: odds ratio; CI: confidence interval

ACEs: Adverse Childhood Experiences; HS: High School; Cig: Cigarette

BMI: Underweight (<18.5); Normal (18.5-24.99); Overweight (25-29.99); Obese (30+)

Finally, a post-estimation command was used to test if the difference between the two predictors was statistically significant. Results indicate that the linear combination of the parameters (using subtraction) did not reach significance (p=0.10).

Hypothesis 2.3.1: The association between childhood maltreatment and depressive symptoms will be attenuated in those who report a higher level of sleep quality.

This hypothesis was tested by adding an interaction term between the childhood maltreatment indicator (<3/3+) and the indicator for high levels of sleep quality in the fully adjusted model. Results did not indicate a statistically significant interaction, meaning that any buffering effects by higher level of sleep quality were not multiplicative. Additive interaction analysis using RERI was also not significant and therefore did not warrant stratified analysis. Findings are consistent with previous interaction models that fail to show moderation by sleep.

Hypothesis 2.4: The single ACE of childhood sexual abuse will have an independent association with depressive symptoms.

The selective approach tested if childhood sexual abuse (part of the childhood maltreatment dimension) predicts depressive symptoms using mixed-effects logistic regression, adjusting for covariates. In the model not adjusted for an index of the other nine ACEs, childhood sexual abuse increases the odds of being likely depressed (OR: 2.26; 95% CI: 1.16-4.38). In the fully adjusted model including an index for the other nine ACEs, childhood sexual abuse survived adjustment and remained a significant predictor of depressive symptoms (OR: 2.37; 95% CI: 1.11-5.09). Results are summarized in Table 6.6.

Table 6.6: Mixed-Effects Logistic Regression of Childhood Sexual Abuse on Depressive Symptoms with Adjustment for Other Nine ACEs (n=294 Across 1,896 Person-Visits)

Depressive Symptoms	OR	95% CI	p-value
Childhood Sexual Abuse	2.37	1.11-5.09	0.03*
Index of Other 9 ACEs	0.98	0.86-1.12	0.80
Age	-	-	0.30
18-29 Years	-	-	-
30-39 Years	0.70	0.41-1.18	0.18
40-52 Years	0.60	0.30-1.22	0.16
Race/Ethnicity	-	-	0.02*
Black	0.23	0.06-0.95	0.04*
Hispanic/Latino	0.23	0.06-0.93	0.04*
Other	-	-	-
White	0.72	0.15-3.36	0.67
Education	-	-	0.13
Didn't Finish HS	2.58	1.17-5.69	0.02
HS	1.52	0.81-2.84	0.19
Some College	1.48	0.82-2.66	0.19
College Grad+	-	-	-
Income	-	-	0.03*
$0-19,999	1.52	0.84-2.76	0.17
$20,000-39,999	0.84	0.45-1.60	0.60
$40,000+	-	-	-
HIV+	1.21	0.64-2.28	0.56
BMI	-	-	0.63
Underweight	1.09	0.28-4.25	0.90
Normal Weight	-	-	-
Overweight	0.81	0.50-1.30	0.38
Obese	0.70	0.36-1.23	0.20
Current Cig/Vape Use	1.21	0.77-1.89	0.40
Alcohol Frequency	-	-	0.98
Monthly or Less	-	-	-
2-4 Times/Month	0.96	0.64-1.44	0.84
2-3 Times/Week	0.93	0.53-1.63	0.80
4+ Times/Week	1.06	0.56-2.04	0.85
Drug Screen+	2.54	1.71-3.77	0.00**
Constant	0.34	0.07-1.64	0.18

*p<0.05; **p<0.01; OR: odds ratio; CI: confidence interval

ACEs: Adverse Childhood Experiences; HS: High School; Cig: Cigarette

BMI: Underweight (<18.5); Normal (18.5-24.99); Overweight (25-29.99); Obese (30+)

Hypothesis 2.4.1: The association between childhood sexual abuse and depressive symptoms will be attenuated in those who report a higher level of sleep quality.

This hypothesis was tested by adding an interaction term between childhood sexual abuse and the indicator for high level of sleep quality in the fully adjusted model. Results did not indicate a statistically significant interaction, meaning that any buffering effects by higher level of sleep quality were not multiplicative. Additive interaction analysis using RERI was also not significant and therefore did not warrant stratified analysis. Findings are consistent with previous interaction models that fail to show moderation by sleep.

6.4 Discussion

Primary Findings. While the main findings from Study Two are summarized below and then findings from each hypothesis are discussed, additional discussion of the integrated findings from all three studies can be found in section 8.1.

A cumulative ACE score of five or more double the odds of being likely depressed in this sample of mostly Black and Latino low-income MSM in Los Angeles. Because the relationship between ACEs and depressive symptoms did not follow a dose-response continuum, the chosen model compared those with five or more ACEs to those below, supporting the concept of cumulative impact. Models using ACE categories (using zero ACEs as the reference group) did not perform as well (based on AIC/BIC), which is likely due to the lack of dose-response pattern predicted by ACEs. Sleep quality did not emerge as a moderator between ACEs and depressive symptoms in any of the models, likely because sleep quality had such a powerful main effect. A sensitivity analysis removed the sleep question from the CESD but did not change any results.

The ACE dimension of childhood maltreatment emerged as a significant predictor of depressive symptoms, whereas household dysfunction did not. Sleep quality did not moderate

this relationship. The single ACE of childhood sexual abuse (part of the childhood maltreatment dimension) emerged as a salient predictor of depressive symptoms in adulthood in the fully adjusted model including the other nine ACEs, with no evidence of moderation by sleep.

Hypothesis 2.1: The cumulative ACE score will have an independent association with self-reported depressive symptoms, following a dose-response continuum.

Consistent with the findings from Study One, ACEs do not predict depressive symptoms in a dose-response fashion in this cohort of mostly Black and Latino low-income MSM in Los Angeles. The original ACE study demonstrated a strong, dose-response relationship between ACE score and probability of lifetime and recent depressive disorders [180]. The authors concluded that exposure to multiple ACEs increases the risk for depressive disorders decades after their occurrence. Longitudinal results from China confirm a significant dose-response relationship between ACEs and adult depression [181]. It is possible that the relatively small sample size made it difficult to detect a dose-response relationship that may have emerged in a larger sample. The erratic pattern of ACEs predicting the probability of being likely depressed (Figure 6.3) supports this assertion. The fact that individuals with one, three, four, and seven ACEs have less likelihood of being likely depressed in adulthood compared to those with no ACEs completely diverges from prior literature. Findings from the main model (Table 6.3) indicate that other factors such as lower levels of education and drug use also contribute to depressive symptoms, but even in an unadjusted model, the relationship between ACEs and depression was non-linear.

Findings collectively suggest that the ten ACEs from the original measure are not linearly predictive of depressive symptoms among mostly Black and Latino low-income MSM in Los Angeles. It is the presence of multiple ACEs and their cumulative impact that have predictive

power. As mentioned in the discussion for Study One, it is possible that mSTUDY participants experienced other ACEs such as peer-victimization and discrimination that were not captured by the current ACE instrument, leading to misclassification bias and downwardly biasing estimates. As mentioned, in a sample of primarily Black children from Chicago, nearly 20% reported only expanded ACEs [73]. Future studies should include community-level ACEs to better estimate the association between ACEs and becoming likely depressed during adulthood.

In the main model adjusted for covariates, cumulative ACEs (five or more) doubled the odds of being likely depressed. Findings are consistent with large bodies of previous literature. A recent umbrella review of meta-analyses also found that ACEs double the odds of depression (pooled OR: 2.01; 95% CI: 1.86-2.32) [183]. While participants in the mSTUDY cohort have more depressive symptoms than the general population, the life course association between cumulative ACEs and being likely depressed is not unlike other groups. It is important to point out that depressive symptoms are consistently higher among women [518] suggesting that this group of MSM may be at higher risk of depressive symptoms following ACEs than some other groups. Findings substantiate a higher cut-point on the CESD (<23/23+ vs. <16/16+) for classifying clinically meaningful symptoms of likely depressed among higher-risk groups.

Results emphasize the importance of ACE prevention programs, given that inequalities are manifested over the life course and the experience of adversity during childhood increases risk for both depressive symptoms and other forms of adversity in later life [519].

Hypothesis 2.2: The association between the cumulative ACE score and depressive symptoms will be attenuated in those who report a higher level of sleep quality.

The multiplicative and additive interaction models did not yield statistically significant findings. The hypothesis was based on evidence that good sleep is a resilience factor in young

adults growing up in challenging environments [355,371]. Conceptually, it makes sense that good sleep would be protective against the effects of childhood adversity, considering both biological and psychological mechanisms of resilience (see section 1.6). Sleep disturbances contribute to some of the consequences of ELA that modulate later quality of life [354]. The main effect of ACEs on sleep quality was noteworthy and should be investigated in future mSTUDY research.

Future research should account for the U-shaped association between sleep duration and incident depression [370]. Insomnia or hypersomnia is part of the diagnostic criteria for Major Depressive Disorder [121]. While the relationship is likely bidirectional, evidence supports sleep disturbance as predictive of future mood disorders [365–367]. Nationally representative data have shown that when sleep duration is less than eight hours, increased sleep is associated with lower risk of incident depression, whereas when sleep duration is more than eight hours, depression risk increased with longer sleep [370]. Given that links between sleep and depressive symptoms are not straight-forward, a nuanced approach to modeling this relationship is required. Investigation into individual components of the PSQI: 1) subjective sleep quality, 2) sleep latency, 3) sleep duration, 4) habitual sleep efficiency, 5) sleep disturbances, 6) use of sleeping medication, and 7) daytime dysfunction may prove worthwhile, particularly the component of sleep disturbances. It might also prove worthwhile to investigate higher cut-points on the PSQI for this high-risk group.

The reason I did not investigate perceived social support as a resilience factor in the relationship between ACEs and depressive symptoms is because this study was restricted to pre-COVID-19. The Multidimensional Scale of Perceived Social Support (MSPSS) was administered only during remote visits. Because social distancing and widespread fear related to

the virus has profound implications for social support, this variable was not transported retrospectively. The PSQI was available for moderation analysis and there is a shortage of data investigating sleep quality as a resilience resource in the context of ACEs. Meanwhile, future studies should investigate perceived social support as a moderator between ACEs and depressive symptoms. This has been documented in an Irish cohort, where higher levels of social support attenuate the association between ACEs and depressive symptoms, therefore may be an important mental health resilience factor [192].

Hypothesis 2.3: The ACE category of childhood maltreatment will have a stronger association with depressive symptoms than the category of household dysfunction.

Findings from this study provided some support for this hypothesis. The estimate from the childhood maltreatment dimension was positive and significant, whereas the index for household dysfunction did not predict depressive symptoms. However, post-estimation analysis found that the difference between these predictors in the model was not significant.

This research question was generated from studies suggesting that childhood maltreatment is associated with worse mental health outcomes than household dysfunction [35,80,89,119]. This hypothesis was also generated from literature related to the biological embedding of adversity (reviewed in section 1.5) suggesting that childhood maltreatment is more likely to "get under the skin" and increase inflammatory processes [244] that have bidirectional links to depression [520–522]. In conjunction with findings from Study One, it can be concluded that different dimensions of ACEs associate with differential mental health outcomes among low-income MSM. Such findings may aid in the prediction of psychiatric outcomes following exposure to ACEs and inform early intervention programs to offset deleterious risk trajectories among highly marginalized groups.

Hypothesis 2.3.1: The association between childhood maltreatment and depressive symptoms will be attenuated in those who report a higher level of sleep quality.

This hypothesis was not supported by the data. Given the absence of moderating effects of sleep quality in the main model with all ten ACEs, it is not surprising that effect measure modification did not emerge here. The main effect of sleep on depressive symptoms was strong, and although findings suggest heterogeneity across sleep quality, data do not support moderation in either multiplicative or additive approaches.

Hypothesis 2.4: The single ACE of childhood sexual abuse will have an independent association with depressive symptoms.

Childhood sexual abuse has received a disproportionate amount of attention in research compared to other ACEs. While some representative samples suggest that only 1.8-2.3% of men report childhood sexual abuse [523], other estimates suggest the prevalence is as high as 6.9% [524]. Adult males are less likely than adult females to report childhood sexual abuse [525,526]. Stigma associated with homosexuality as well as unhelpful disclosure responses likely relate to more mental distress and may impair future disclosures. Among those reporting ACEs in the mSTUDY cohort, 29% experienced childhood sexual abuse. A higher prevalence of reported childhood sexual abuse among MSM in the mSTUDY suggests that this ACE may be particularly salient among this group and is likely not underestimated.

This hypothesis was strongly supported by the data. In the fully adjusted model including an index for the other nine ACEs, childhood sexual abuse survived adjustment and remained a significant predictor of depressive symptoms. The estimate for childhood sexual abuse was even higher than cumulative ACEs dichotomized at <5/5+. Findings are consistent with previous literature. A recent umbrella review of 19 meta-analyses focused specifically on childhood

sexual abuse and depression reported an OR of 2.7 (95% CI: 2.4-3.0), suggesting that childhood sexual abuse confers additional (i.e., independent) specific risk [184].

Meanwhile, because multiple ACEs often occur simultaneously, analysis of single ACEs may overestimate their impact [92,94]. This missing variable problem was addressed by adjustment for the other nine ACEs in the model, however future research should investigate if this single ACE survives adjustment by expanded ACEs, to further disentangle this signal from potential noise caused by missing ACEs. I hypothesize that this ACE will remain a potent predictor of depressive symptoms among MSM and suggest that it should receive a disproportionate amount of attention in the development of trauma-informed intervention programs. Because ACEs tend to cluster rather than occur in isolation, it remains important to consider how childhood sexual abuse can be socially patterned as well as increase the risk for future revictimization [93,196,376,377,427,527–529]. This appears particularly important for MSM who are at higher risk for HIV/STI infection.

Hypothesis 2.4.1: The association between childhood sexual abuse and depressive symptoms will be attenuated in those who report a higher level of sleep quality.

This hypothesis was not supported by the data. Given the absence of moderating effects of sleep quality in the main model with all ten ACEs and the model with childhood maltreatment dimension, it is not surprising that effect measure modification did not emerge. The main effect of sleep on depressive symptoms was strong, and although findings suggest heterogeneity across sleep quality, data do not support moderation in either multiplicative or additive approaches.

7 CHAPTER SEVEN: STUDY THREE – RESULTS AND DISCUSSION

7.1 Overview of Aim, Hypotheses, and Methods

Section 7.1 provides a summary of the methods used to test each of the hypotheses introduced in section 3.3 and then described in detail in section 4.5. Section 7.3 describes the results and section 7.4 is dedicated to discussing these results. Results are discussed further in section 8.1 where findings from all three studies are integrated into an overall summary and placed into a broader context, with several recommendations for future research.

Study Three aimed to understand the influence of ACEs on anxiety symptoms, analyzed prior to COVID-19. First, I hypothesized the presence of a positive and linear dose-response relationship between ACEs and anxiety symptoms in mixed-effects logistic regression models (question 3.1). This analysis provided rationale for the optimal cut-point for ACEs in model building, based on a visual inspection of the margins plot (the point where the predicted probability of anxiety symptoms tended to increase, see Figure 7.2). Next, I tested if the cumulative ACE score had an independent positive association with anxiety level, using ordinal logistic regression (question 3.1). Model building included adding variables individually to assess the impact of each covariate on the focal relationship. Information criteria were examined as each covariate was added to the model, to assess each additional adjustment on model fit.

Next, I tested if there was a multiplicative and/or additive interactions between ACEs (<5/5+) and a sleep quality indicator (<6/6+) in mixed-effects logistic regression (using dichotomized anxiety), based on the hypothesis that the association between the cumulative ACE score and anxiety symptoms will be attenuated in those who report a higher level of sleep quality (question 3.2). Logistic regression using the anxiety indicator (yes/no) allowed me to visualize the margins plot to adequately assess if effect measure modification (moderation) was present.

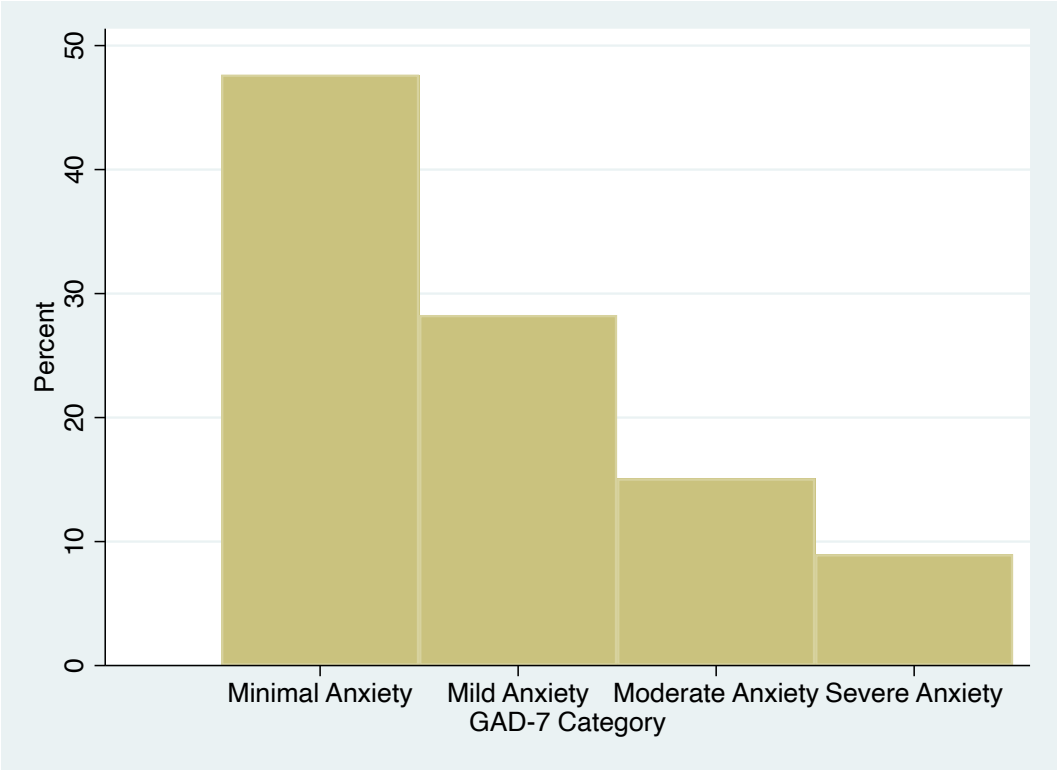
Next, I tested the hypothesis that the ACE category of childhood maltreatment has a stronger association with anxiety symptoms than the category of household dysfunction (question 3.3). This hypothesis was tested by creating index scores for each ACE dimension (based on scores 0-5, as described in section 4.3). Each category was analyzed in the fully adjusted model separately, and information criteria were used to assess which model was a better fit for the data. Both indexes were then added into the fully adjusted model, and a post-estimation command was used to determine if differences between these estimates were significant. I then tested for both multiplicative and additive interactions between childhood maltreatment (dichotomized at <3/3+) and sleep quality (question 3.3.1).

Next, I tested the hypothesis that the single ACE of emotional neglect (part of the childhood maltreatment dimension) has an independent positive association with anxiety symptoms (question 3.4). The single ACE was added to the ordinal logistic regression model, adjusting for covariates. The model was then adjusted for the other nine ACEs, using an index score (based on scores 0-9). Finally, I tested for multiplicative and additive interactions between emotional neglect and sleep quality in the logistic model, based on the hypothesis that the association will be attenuated in those with higher levels of sleep quality (question 3.4.1).

7.2 Sample Characteristics and Covariate Distribution

Baseline characteristics are identical to Study One (Table 5.1) with the same adjustment for urine drug tests as Study Two (Table 6.1). The distribution of Generalized Anxiety Disorder (GAD-7) categories (outcome) is shown in Figure 7.1. The mean GAD-7 score in the study sample is 5.8 (SD=5.8). Nearly one-quarter have moderate or severe anxiety and over half have any anxiety.

Figure 7.1: General Anxiety Disorder-7 (GAD-7) Categories Between June 2018 and March 2020 (n=390 Across 1,047 Person-Visits)



7.3 Results

Proportional Odds Assumption. As reviewed in section 4.5, usage of mixed-effects ordinal logistic regression requires a proportional odds assumption. Given limitations of formally testing this assumption using multilevel data in Stata, an attempt to assess the proportional odds assumption was conducted two ways:

1) The *xtset* command was used to declare data as time-series along participant ID and visit number. A multinomial logistic regression model using the ACE indicator (<5/5+) reported coefficients for each level of anxiety (mild, moderate, severe) compared to minimal. A post-estimation Wald test compared these estimates from each level to one another and yielded a

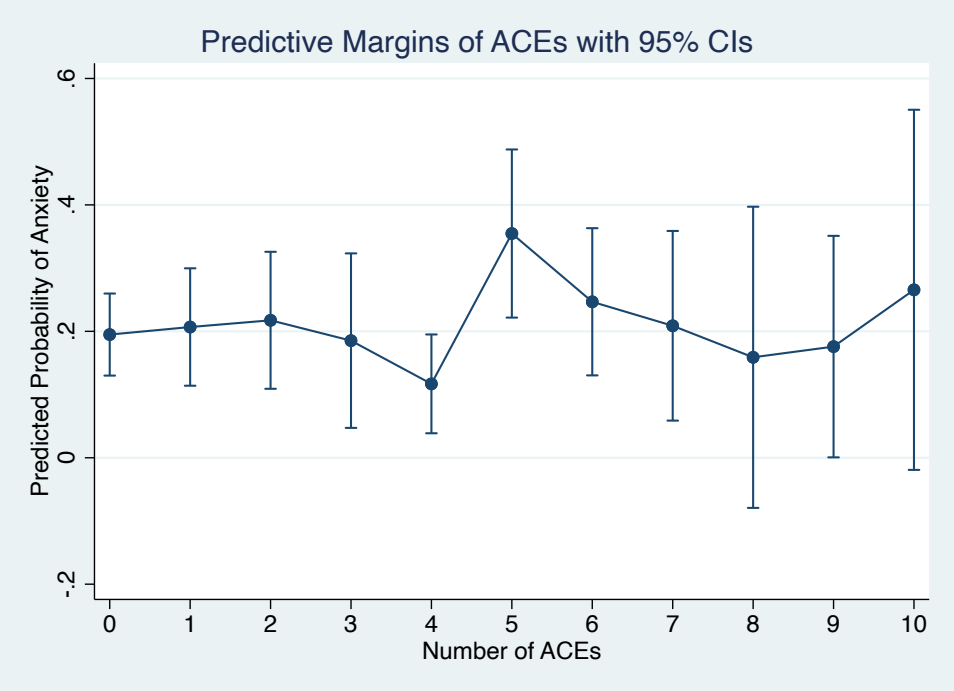
non-significant chi-square result (p=0.95 in the crude unadjusted model; p=0.50 in the fully adjusted model) and was used as support for the proportional odds assumption.

2) A mixed-effects linear regression model using the four category GAD-7 assessed the impact of cumulative ACEs (<5/5+) on increasing level of anxiety. A significant positive estimate (ß=0.29; p=0.00) determined that cumulative ACEs linearly predict a higher anxiety category. Visual inspection of the distribution of GAD-7 categories (Figure 7.1) and the ordinal nature of these levels was used to corroborate the proportional odds assumption.

Hypothesis 3.1: The cumulative ACE score will have an independent association with self-reported anxiety symptoms, following a dose-response continuum.

Mixed-effects logistic regression was used to test the association of each additional ACE on the outcome of anxiety symptoms. Results from testing the association of each additional ACE in the fully adjusted model are summarized by a margins plot (Figure 7.2).

Figure 7.2: Margins Plot from Fully Adjusted Mixed-Effects Logistic Regression of ACEs on Anxiety Symptoms (n=280 Across 789 Person-Visits)



Results indicate no dose-response relationship between the number of ACEs and the predicted probability of anxiety. Meanwhile, this analysis helped determine that five was the optimal cut-point for the main model. This is the point where the predicted probability of anxiety symptoms tended to increase. An ACE indicator at <5/5+ was then used to investigate if the cumulative ACE score had an independent association with anxiety symptoms, using the four-level GAD-7 in mixed-effects ordinal logistic regression.

Bivariate analysis (unadjusted) found that cumulative ACEs increase the odds of being in a higher anxiety category by 3.27 (95% CI: 1.62-6.61). After adding variables one at a time and then examining model fit using information criteria at each step of model building, it was concluded that the entire set of covariates (determined a priori) was appropriate for the model. While many predictors are not significant and did not contribute to model fit, they provide sound adjustment based on prior literature. Results from the main model are summarized in Table 7.1.

Table 7.1: Mixed-Effects Ordinal Logistic Regression of Five or More ACEs on Anxiety Symptoms (n=280 Across 789 Person-Visits)

Anxiety Symptoms	OR	95% CI	p-value
5 or More ACEs	3.05	1.50-6.20	0.00**
Age	-	-	0.25
18-29 Years	-	-	-
30-39 Years	0.94	0.46-1.91	0.86
40-52 Years	0.53	0.22-1.28	0.16
Race/Ethnicity	-	-	0.00**
Black	0.29	0.06-1.41	0.13
Hispanic/Latino	0.55	0.11-2.67	0.46
Other	-	-	-
White	2.11	0.37-11.96	0.40
Education	-	-	0.75
Didn't Finish HS	0.89	0.31-2.55	0.83
HS	0.85	0.40-1.80	0.67
Some College	0.69	0.34-1.38	0.29
College Grad+	-	-	-
Income	-	-	0.02*
$0-19,999	3.05	1.41-6.56	0.00**
$20,000-39,999	2.05	0.97-4.33	0.06
$40,000+	-	-	-
HIV+	1.91	0.92-3.98	0.08
BMI	-	-	0.35
Underweight	0.66	0.07-5.96	0.71
Normal Weight	-	-	-
Overweight	1.42	0.70-2.85	0.33
Obese	0.72	0.33-1.61	0.43
Current Cig/Vape Use	1.60	0.90-2.86	0.11
Alcohol Frequency	-	-	0.69
Monthly or Less	-	-	-
2-4 Times/Month	1.37	0.78-2.39	0.28
2-3 Times/Week	1.21	0.56-2.61	0.62
4+ Times/Week	1.42	0.57-3.55	0.46
Drug Screen+	2.42	1.49-4.03	0.00**
/cut1	1.12	(-)0.65-2.88	
/cut2	3.58	1.79-5.37	
/cut3	5.43	3.59-7.27	

*p<0.05; **p<0.01; OR: odds ratio; CI: confidence interval

ACEs: Adverse Childhood Experiences; HS: High School; Cig: Cigarette

BMI: Underweight (<18.5); Normal (18.5-24.99); Overweight (25-29.99); Obese (30+)

Results indicate that the presence of five or more ACEs triple the odds (OR: 3.05; 95% CI: 1.50-6.20) of being in a higher anxiety category after adjusting for age, race/ethnicity, education, income, HIV status, BMI, current cig/vape use, alcohol frequency, and urine drug test.

Hypothesis 3.2: The association between the cumulative ACE score and anxiety symptoms will be attenuated in those who report higher levels of sleep quality.

This hypothesis was tested by adding an interaction term between the ACE indicator (<5/5+) and an indicator for high level of sleep quality in the fully adjusted logistic regression model. Results did not indicate a statistically significant interaction, meaning that any potential buffering effects by higher level of sleep quality are not multiplicative. Additive interaction analysis using RERI was also not significant and therefore did not warrant stratified analysis.

Hypothesis 3.3: The ACE category of childhood maltreatment will have a stronger association with anxiety symptoms than the category of household dysfunction.

First, each dimension of ACEs was added separately to the fully adjusted ordinal models. Information criteria were used to determine that childhood maltreatment was a better fit for the data. Results are shown in Table 7.2.

Table 7.2: Information Criteria for Each ACE Dimension in Fully Adjusted Mixed-Effects Ordinal Logistic Regression with Outcome Anxiety (n=280 Across 789 Person-Visits)

ACE Dimension	AIC	BIC
Childhood Maltreatment	1619.4	1731.5
Household Dysfunction	1625.2	1737.3

AIC: Akaike Information Criteria; BIC: Bayesian Information Criteria

Next, both dimensions were added to the fully adjusted model. Consistent with the hypothesis, the estimate for childhood maltreatment was higher than household dysfunction.

Results indicate that the index score for childhood maltreatment is a significant predictor of drug use (OR: 1.34; 95% CI: 1.06-1.70) whereas household dysfunction is not (see Table 7.3).

Table 7.3: Mixed-Effects Ordinal Logistic Regression of Childhood Maltreatment on Anxiety Symptoms with Adjustment for Household Dysfunction (n=280 Across 789 Person-Visits)

Anxiety Symptoms	OR	95% CI	p-value
Childhood Maltreatment	1.34	1.06-1.70	0.02*
Household Dysfunction	0.95	0.73-1.23	0.68
Age	-	-	0.27
18-29 Years	-	-	-
30-39 Years	0.92	0.45-1.88	0.82
40-52 Years	0.53	0.22-1.29	0.16
Race/Ethnicity	-	-	0.00**
Black	0.37	0.08-1.84	0.23
Hispanic/Latino	0.67	0.14-3.31	0.63
Other	-	-	-
White	2.57	0.44-14.90	0.29
Education	-	-	0.77
Didn't Finish HS	0.86	0.30-2.49	0.79
HS	0.87	0.42-1.84	0.72
Some College	0.69	0.35-1.40	0.31
College Grad+	-	-	-
Income	-	-	0.01*
$0-19,999	3.17	1.47-6.83	0.00**
$20,000-39,999	2.02	0.95-4.27	0.07
$40,000+	-	-	-
HIV+	1.86	0.89-3.89	0.10
BMI	-	-	0.39
Underweight	0.69	0.08-6.25	0.74
Normal Weight	-	-	-
Overweight	1.36	0.68-2.74	0.40
Obese	0.70	0.32-1.57	0.39
Current Cig/Vape Use	1.55	0.86-2.77	0.14
Alcohol Frequency	-	-	0.73
Monthly or Less	-	-	-
2-4 Times/Month	1.33	0.76-2.32	0.32
2-3 Times/Week	1.23	0.57-2.65	0.60
4+ Times/Week	1.45	0.58-3.64	0.43
Drug Screen+	2.47	1.47-4.13	0.00**
/cut1	1.31	(-)0.48-3.10	
/cut2	3.77	1.95-5.59	
/cut3	5.62	3.75-7.49	

*p<0.05; **p<0.01; OR: odds ratio; CI: confidence interval

ACEs: Adverse Childhood Experiences; HS: High School; Cig: Cigarette

BMI: Underweight (<18.5); Normal (18.5-24.99); Overweight (25-29.99); Obese (30+)

Finally, a post-estimation command was used to test if the difference between the two predictors was statistically significant. Results indicate that the linear combination of the parameters (using subtraction) did not reach significance (p=0.11).

Hypothesis 3.3.1: The association between childhood maltreatment and anxiety symptoms will be attenuated in those who report higher levels of sleep quality.

This hypothesis was tested by adding an interaction term between the childhood maltreatment indicator (<3/3+) and the indicator for high level of sleep quality in the fully adjusted logistic model. Results did not indicate a statistically significant interaction, meaning that any potential buffering effects by higher level of sleep quality are not multiplicative. Additive interaction analysis using RERI was also not significant and therefore did not warrant stratified analysis. Findings are consistent with previous interaction models that fail to show moderation by sleep.

Hypothesis 3.4: The single ACE of emotional neglect will have an independent association with anxiety symptoms.

The selective approach tested if emotional neglect (part of the childhood maltreatment dimension) predicts anxiety symptoms using mixed-effects ordinal logistic regression, adjusting for covariates. In the model not adjusted for an index of the other nine ACEs, emotional neglect increased the odds of being in a higher anxiety category by over two-fold (OR: 2.42; 95% CI: 1.19-4.92). Results are summarized in Table 7.4.

Table 7.4: Mixed-Effects Ordinal Logistic Regression of Emotional Neglect on Anxiety Symptoms (n=280 Across 789 Person-Visits)

Anxiety Symptoms	OR	95% CI	p-value
Emotional Neglect	2.42	1.19-4.92	0.01*
Age	-	-	0.28
18-29 Years	-	-	-
30-39 Years	0.87	0.43-1.78	0.71
40-52 Years	0.52	0.21-1.26	0.15
Race/Ethnicity	-	-	0.00**
Black	0.36	0.07-1.75	0.20
Hispanic/Latino	0.69	0.14-3.36	0.65
Other	-	-	-
White	2.44	0.43-14.04	0.32
Education	-	-	0.79
Didn't Finish HS	0.84	0.29-2.43	0.75
HS	0.86	0.41-1.83	0.70
Some College	0.70	0.35-1.41	0.33
College Grad+	-	-	-
Income	-	-	0.01*
$0-19,999	3.16	1.47-6.80	0.00**
$20,000-39,999	1.98	0.93-4.19	0.07
$40,000+	-	-	-
HIV+	2.01	0.96-4.18	0.06
BMI	-	-	0.46
Underweight	0.75	0.08-6.80	0.80
Normal Weight	-	-	-
Overweight	1.31	0.65-2.63	0.45
Obese	0.71	0.32-1.58	0.40
Current Cig/Vape Use	1.63	0.91-2.91	0.10
Alcohol Frequency	-	-	0.69
Monthly or Less	-	-	-
2-4 Times/Month	1.31	0.75-2.30	0.34
2-3 Times/Week	1.24	0.58-2.68	0.58
4+ Times/Week	1.56	0.62-3.91	0.35
Drug Screen+	2.37	1.42-3.96	0.00**
/cut1	1.21	(-)0.58-2.99	
/cut2	3.67	1.85-5.48	
/cut3	5.52	3.66-7.37	

*p<0.05; **p<0.01; OR: odds ratio; CI: confidence interval

ACEs: Adverse Childhood Experiences; HS: High School; Cig: Cigarette

BMI: Underweight (<18.5); Normal (18.5-24.99); Overweight (25-29.99); Obese (30+)

Next, I added an adjustment for the other nine ACEs. Results indicate that emotional neglect did not survive adjustment, as defined by loss of statistical significance. Results from the fully adjusted model are displayed in Table 7.5.

Table 7.5: Mixed-Effects Ordinal Logistic Regression of Emotional Neglect on Anxiety Symptoms with Adjustment for Other Nine ACEs (n=280 Across 789 Person-Visits)

Anxiety Symptoms	OR	95% CI	p-value
Emotional Neglect	2.04	0.89-4.71	0.09
Index of Other 9 ACEs	1.06	0.91-1.24	0.46
Age	-	-	0.27
18-29 Years	-	-	-
30-39 Years	0.88	0.43-1.80	0.74
40-52 Years	0.52	0.21-1.26	0.15
Race/Ethnicity	-	-	0.00**
Black	0.35	0.07-1.70	0.19
Hispanic/Latino	0.65	0.13-3.19	0.60
Other	-	-	-
White	2.37	0.41-13.6	0.33
Education	-	-	0.77
Didn't Finish HS	0.87	0.30-2.50	0.79
HS	0.86	0.41-1.83	0.70
Some College	0.70	0.35-1.40	0.31
College Grad+	-	-	-
Income	-	-	0.01*
$0-19,999	3.18	1.47-6.85	0.00**
$20,000-39,999	2.00	0.94-4.23	0.07
$40,000+	-	-	-
HIV+	1.94	0.93-4.06	0.08
BMI -		-	0.43
Underweight	0.73	0.08-6.61	0.78
Normal Weight	-	-	-
Overweight	1.34	0.67-2.70	0.41
Obese	0.71	0.32-1.59	0.41
Current Cig/Vape Use	1.60	0.90-2.87	0.11
Alcohol Frequency	-	-	0.72
Monthly or Less	-	-	-
2-4 Times/Month	1.31	0.75-2.30	0.34
2-3 Times/Week	1.22	0.57-2.63	0.61
4+ Times/Week	1.50	0.60-3.80	0.39
Drug Screen+	2.37	1.42-3.95	0.00**
/cut1	1.27	(-)0.52-3.06	
/cut2	3.73	1.91-5.55	
/cut3	5.58	3.72-7.45	

*p<0.05; **p<0.01; OR: odds ratio; CI: confidence interval

ACEs: Adverse Childhood Experiences; HS: High School; Cig: Cigarette

BMI: Underweight (<18.5); Normal (18.5-24.99); Overweight (25-29.99); Obese (30+)

Hypothesis 3.4.1: The association between emotional neglect and anxiety symptoms will be attenuated in those who report higher levels of sleep quality.

This hypothesis was tested by adding an interaction term between emotional neglect and an indicator for high level of sleep quality in the fully adjusted logistic model. Results did not indicate a statistically significant interaction, meaning that any potential buffering effects by higher level of sleep quality are not multiplicative. Additive interaction analysis using RERI was also not significant and therefore did not warrant stratified analysis. Findings are consistent with previous interaction models that fail to show moderation by sleep.

7.4 Discussion

Primary Findings. While the main findings from Study Three are summarized below and then findings from each hypothesis are discussed, additional discussion of the integrated findings from all three studies can be found in section 8.1.

A cumulative ACE score of five or more triple the odds of being in a higher anxiety category in this sample of mostly Black and Latino low-income MSM in Los Angeles. Because the relationship between ACEs and anxiety symptoms did not follow a dose-response continuum, the chosen model compared those with five or more ACEs to those below, supporting the concept of cumulative impact. Models using ACE categories (using zero ACEs as the reference) did not perform as well (based on AIC/BIC), which is likely due to the lack of dose-response pattern predicted by ACEs. Sleep quality did not emerge as a moderator between ACEs and anxiety symptoms in any of the models, likely because sleep quality had a strong main effect.

The ACE dimension of childhood maltreatment was a significant predictor of being in a higher anxiety category, whereas household dysfunction was not. Sleep quality did not moderate this relationship. The single ACE of emotional neglect emerged as a predictor of higher anxiety

symptoms in adulthood, however only in the model that did not include the other nine ACEs as adjustments, with no evidence of moderation by sleep.

Hypothesis 3.1: The cumulative ACE score will have an independent association with self-reported anxiety symptoms, following a dose-response continuum.

Consistent with the findings from Study One and Two, ACEs do not predict anxiety symptoms in a dose-response fashion in this cohort of mostly Black and Latino low-income MSM in Los Angeles. In the published literature, there are more studies documenting dose-responses for drug use and depressive symptoms [3,5,180,181]. It seemed reasonable to hypothesize that anxiety would follow a similar pattern but is not surprising given a lack of dose-response for the other two outcomes. It is possible that the relatively small sample size made it difficult to detect a dose-response relationship that may have emerged in a larger sample. The erratic pattern of ACEs predicting the probability of being likely anxious (Figure 7.2) supports this assertion. The fact that individuals with three, four, eight, and nine ACEs have less likelihood of being anxious in adulthood compared to those with no ACEs completely diverges from prior literature. Findings from the main model (Table 7.1) indicate that other factors such as poverty and drug use also contribute to anxiety symptoms, but even in an unadjusted model, the relationship between ACEs and anxiety was non-linear.

Findings collectively suggest that the ten ACEs from the original measure are not linearly predictive of anxiety symptoms among mostly Black and Latino low-income MSM in Los Angeles. It is the presence of multiple ACEs and their cumulative impact that have predictive power. In the main ordinal model adjusted for covariates, cumulative ACEs (five or more) triple the odds of being in a higher anxiety category. Findings are slightly less than meta-analytic findings from 2017 where the odds of anxiety were reported to increase by 3.70 (95% CI: 2.62-

5.22) following multiple ACEs [5]. The estimates from representative samples are likely higher than the current study because they also include women, who have higher rates of anxiety following childhood adversity [530]. None of the studies linking ACEs to anxiety have been specific to MSM. However, analysis of five or more ACEs increased the odds of frequent anxiety by 4.19 (95% CI: 2.39-7.34) among urban, minority young adults from Chicago [51].

Many studies also use a lower GAD-7 cut-point (<5/5+) to indicate the presence of any anxiety. The most recent umbrella review of meta-analyses reported a pooled odds of anxiety at 1.94 (95% CI: 1.82-2.22) following at least one ACE [183]. Collectively, estimates reported here do not diverge much from other life course associations between multiple ACEs and anxiety symptoms. However, most analyses use an indicator for anxiety (yes/no) rather than a four-level outcome in ordinal logistic regression. The robustness of this methodological approach should be analyzed in future studies across different sociodemographic groups.

Finally, approximately a quarter (23.4%) of the study population report moderate or severe anxiety, which is slightly higher than meta-analytic findings from MSM in China when using the same GAD-7 cut-point of <10/10+ (22.5%) [410]. Given the high-risk nature of the mSTUDY cohort and the potential contribution of other factors to anxiety symptoms (e.g., excessive worrying), it may be worth exploring operating characteristics of different cut-points for classifying clinically meaningful symptoms of anxiety in this group, and in other high-risk MSM from various racial/ethnic minority backgrounds.

Hypothesis 3.2: The association between the cumulative ACE score and anxiety symptoms will be attenuated in those who report higher levels of sleep quality.

The interaction models did not yield statistically significant findings. The hypothesis was based on evidence that good sleep is a resilience factor in young adults growing up in

challenging environments [355,371]. Conceptually, it makes sense that good sleep would be protective against the effects of childhood adversity, considering both biological and psychological mechanisms of resilience (see section 1.6). Sleep disturbances contribute to some of the consequences of ELA that modulate later quality of life [354].

The reason I did not investigate perceived social support as a resilience factor in the relationship between ACEs and anxiety symptoms is because this study was restricted to pre-COVID-19, just like Study Two. Future studies should investigate perceived social support as a moderator between ACEs and anxiety symptoms during COVID-19.

Hypothesis 3.3: The ACE category of childhood maltreatment will have a stronger association with anxiety symptoms than the category of household dysfunction.

Findings from this study provided some support for this hypothesis. The estimate from the childhood maltreatment dimension was positive and significant, whereas the index for household dysfunction did not predict a higher level of anxiety. However, post-estimation analysis found that the difference between these predictors in the model was not significant.

This research question was generated from studies suggesting that childhood maltreatment is associated with worse mental health outcomes than household dysfunction [35,80,89,119]. The estimate linking the dimension of childhood maltreatment to anxiety symptoms is slightly less than reported in meta-analytic findings [183,531]. Heterogeneity of estimates is likely due to differential operationalization of ACEs and anxiety, the characteristics of the sample, and the adjustment variables used. It is also possible that the outcome of anxiety can be attributable to a host of factors other than ACEs among mSTUDY participants, such as recent housing and employment instability, which were not analyzed in the current study.

Findings provide further support that the presence of multiple ACEs and cumulative impact have the most predictive power, particularly childhood maltreatment ACEs.

Hypothesis 3.3.1: The association between childhood maltreatment and anxiety symptoms will be attenuated in those who report higher levels of sleep quality.

This hypothesis was not supported by the data. Given the absence of moderating effects of sleep quality in the main model with all ten ACEs, it is not surprising that effect measure modification did not emerge here. The main effect of sleep on anxiety symptoms was strong, and although findings suggest heterogeneity across sleep quality, data do not support moderation in either multiplicative or additive approaches.

Hypothesis 3.4: The single ACE of emotional neglect will have an independent association with anxiety symptoms.

The single ACE of emotional neglect has not received much attention in ACE research and is usually clustered with the other ACEs from the childhood maltreatment dimension. Among those reporting ACEs in the mSTUDY cohort, 31% experienced emotional neglect. Lack of data on associations following this ACE partially motivated this research question, as well as data suggesting that individuals with insecure attachment to their caregiver have higher anxiety [480]. Efforts to disentangle this specific ACE were intended to highlight the potential impact of more "silent" types of childhood maltreatment, other than physical and sexual abuse.

This hypothesis was partially supported by the data. In the adjusted ordinal model with the single ACE, emotional neglect was a significant positive predictor of being in a higher anxiety category. The estimates are consistent (but slightly lower) than meta-analytic findings examining this relationship using measures other than ACEs (OR: 1.51; 95% CI: 1.51-2.20) [473]. Emotional neglect did not survive adjustment for the other nine ACEs, suggesting that this

association does not exist independently of other ACEs. Surviving adjustment for the other nine ACEs does seem a high bar to reach, and debate exists if single ACEs should be expected to do so, given that they frequently co-occur [92,94]. Meanwhile, efforts to model this ACE individually has the added benefit of being able to examine its unique contribution to anxiety, which may prove important for targeted trauma-informed intervention programs.

Hypothesis 3.4.1: The association between emotional neglect and anxiety symptoms will be attenuated in those who report higher levels of sleep quality.

This hypothesis was not supported by the data. Given the absence of moderating effects of sleep quality in the main model with all ten ACEs and the model with childhood maltreatment dimension, it is not surprising that effect measure modification did not emerge. The main effect of sleep on anxiety symptoms was strong, and although findings suggest heterogeneity across sleep quality, data do not support moderation in either multiplicative or additive approaches.

8 CHAPTER EIGHT: CONCLUSION

8.1 Integrated Findings

This dissertation aimed to understand how ACEs associate with mental health (drug use, depressive symptoms, and anxiety symptoms) over the life course among mostly Black and Latino low-income MSM in Los Angeles. Three different approaches to operationalize ACEs were used: 1) a cumulative approach combining all ten ACEs into a sum score, 2) a dimensional approach separating the categories of childhood maltreatment and household dysfunction, and 3) a selective approach identifying a single ACE. All models included adjustments that were determined a priori, and ACE cut-points were determined based on the data (dichotomized into a higher versus lower exposure category). Integrated findings are summarized in Table 8.1.

Table 8.1: The Association of Adverse Childhood Experiences on Various Mental Health Outcomes using Mixed-Effects Logistic Regression Among Men Who Have Sex with Men in the mSTUDY Cohort

	Self-Reported Drug Use[1]			Depressive Symptoms[2]			Anxiety Symptoms[2]		
ACEs	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Cumulative									
5+[3]	-	-	-	1.96	1.02-3.77	0.04*	3.05	1.50-6.20	0.00**
6+[4]	2.04	0.87-4.82	0.10	-	-	-	-	-	-
Dimensional									
CM	1.00	0.80-1.24	0.97	1.19	0.99-1.42	0.06	1.31	1.07-1.60	0.00**
CM-adj[5]	0.88	0.68-1.14	0.33	1.26	1.01-1.57	0.04*	1.34	1.06-1.70	0.02*
Selective									
HSAH	1.70	0.81-3.57	0.16	-	-	-	-	-	-
HSAH-adj[6]	1.82	0.75-4.43	0.19	-	-	-	-	-	-
CSA	-	-	-	2.25	1.16-4.38	0.02*	-	-	-
CSA-adj[6]	-	-	-	2.37	1.11-5.09	0.03*	-	-	-
EN	-	-	-	-	-	-	2.42	1.19-4.92	0.01*
EN-adj[6]	-	-	-	-	-	-	2.04	0.89-4.71	0.09

*p<0.05; **p<0.01; OR: odds ratio; CI: confidence interval; p: p-value

ACEs: Adverse Childhood Experiences; CM: Childhood Maltreatment

HSAH: Household Substance Abuse History; CSA: Childhood Sexual Abuse; EN: Emotional Neglect

[1]adjusted for age, race/ethnicity, education, income, HIV status, BMI, current cig/vape use, alcohol frequency, depressive symptoms, and COVID-19

[2]adjusted for age, race/ethnicity, education, income, HIV status, BMI, current cig/vape use, alcohol frequency, and urine drug test

[3]compared to less than 5 ACEs; [4]compared to less than 6 ACEs

[5]adjusted for household dysfunction; [6]adjusted for an index of the other 9 ACEs

The results of this research suggest that ACEs have significant associations with mental health during adulthood among low-income MSM in Los Angeles, California. While relationships between ACEs and mental health are well documented [109,110,119,120], the evidence linking these among MSM is sparse, particularly among those with low SES and other forms of cumulative disadvantage (e.g., HIV positive). Cumulative ACEs (dichotomized into higher versus lower exposure category) predicted both depressive and anxiety symptoms in the study sample and estimates for self-reported drug use trended toward significance. Contrary to

hypotheses, none of the models demonstrated a dose-response relationship between the number of ACEs and any of the outcomes.

The dimension of childhood maltreatment predicted depressive and anxiety symptoms, but not drug use. Interestingly, the addition of household dysfunction dimension into the models for depressive and anxiety symptoms augmented the estimates, suggesting that in this sample, household dysfunction ACEs may be protective against depressive and anxiety symptoms. One possible reason that household dysfunction did not emerge as predictive of depressive and anxiety symptoms may be because these ACEs generally correlate with low SES [53]. However, post-hoc analysis removing income and education from the models did not affect estimates. Differential impacts from the two separate ACE dimensions may partially explain the absence of a dose-response relationship when all ACEs were combined across all three models. However, when a dose-response relationship was investigated for each dimension for each model, no dose-response continuum emerged. This may also be due to the small sample size, creating wide confidence intervals.

Selective (single ACE) approaches identified that household substance abuse history did not predict future drug use; childhood sexual abuse predicts depressive symptoms; and emotional neglect predicts higher anxiety, but not after adjusting for the other nine ACEs. Only the association between childhood sexual abuse and depressive symptoms remained relevant after adjustment for the other nine ACEs. This finding has noteworthy implications for the impact of childhood sexual abuse on mental health (specifically depressive symptoms) among mSTUDY participants, which may warrant targeted interventions.

Potential resilience factors were evaluated by including variables known to be negatively impacted by ACEs, as well as positively associated with the outcomes. Potential resilience

factors (i.e., perceived social support, sleep) were interacted with ACEs in mixed-effects logistic regression models to see if they attenuated associations with mental health outcomes, across the different ACE measurement strategies. Additive interactions were also tested. Perceived social support emerged as a key buffering factor for drug use in the cumulative and selective approaches. A significant multiplicative interaction between household substance abuse history and perceived social support in Study One suggests that social support may be particularly relevant for MSM growing up in households where substance use was present. Meanwhile, sleep quality did not emerge as a moderator for any outcomes of depressive and anxiety symptoms but had strong main effects.

The estimates reported in the current studies are generally lower than estimates from studies with more diverse samples and from meta-analytic findings across various populations [532]. One potential explanation is that ACE measure used in this dissertation failed to capture other forms of adversity such as bullying, racism, discrimination, etc. that can occur outside of the home (in the community), which may be particularly relevant for MSM of ethnic minority status. An incomplete capture of ELA can downwardly bias estimates through misclassification.

The non-dose-response pattern of ACEs precluded analysis along a dose-response continuum and necessitated the use of dichotomized variables. Most ACE research compares those with multiple ACEs to those who have none, which may limit comparability of the reported estimates. The ACE indicators (comparing the higher to the lower exposure category) performed better (based on prediction and model fit) than any other categorical measurement approach, which diverged from most ACE research. In all three studies, the group of participants reporting zero ACEs had a higher predicted probability of the outcomes than many of the other ACE counts. Many of the study participants had multiple ACEs and did not meet criteria for (or

appeared in some cases protected against) the mental health outcome under study. It is possible that this group experienced other forms of adversity not captured by the current ACE instrument. It is also possible that the observed pattern could change in a larger sample. However, findings from this dissertation suggest that household-level ACEs do not linearly predict drug use, depressive symptoms, or anxiety symptoms in this sample of mostly Black and Latino low-income MSM in Los Angeles, California.

Societal-level stigma and internalized shame associated with sexual minority and HIV status is particularly relevant for MSM and may lead to poor mental health outcomes [533], which may occur in the absence of ACEs. It is also possible that the presence of other social factors commonly associated with lower SES (e.g., housing and employment instability) contribute to poor mental health outcomes independent of (as well as in conjunction with) ACE exposure. Collectively, measurement limitations (discussed further in section 8.4), and specific characteristics of the study sample that may have additionally contributed to worse mental health likely dampen estimates. The study design recruited approximately 50% of MSM who use drugs, making this group higher risk at baseline. Non-significant findings related to drug use might be because individuals using drugs were oversampled in the mSTUDY cohort. Results presented herein suggest that low-income MSM are not worse off with respect to the association between ACEs and mental health outcomes than other groups, however this may be an artifact of the research methodology. Additional limitations are summarized in section 8.6.

The findings that childhood maltreatment had significant associations with depressive and anxiety symptoms but not with drug use is important. Prior published literature suggests that childhood maltreatment ACEs are more likely to impact mental health [119,120], however drug use itself may be better classified as a behavioral rather than mental health outcome. Based on

the background evidence presented in section 1.5, childhood maltreatment is more prone to become biologically embedded [275,284,287,534] which may partially explain why it has stronger effects on mental health than household dysfunction. Many of the childhood maltreatment ACEs are physical assaults to the body, which may contribute to greater effects on biological systems. Victimized children may also ascribe and internalize meaning that can impair their self-esteem and ability to form safe prosocial bonds [214]. Such disruption can be particularly damaging for individuals with multiple intersecting forms of marginalized identities (such as MSM enrolled in the mSTUDY), leading to cumulative risk over the life course.

The larger contribution of household dysfunction ACEs to adult drug use provides support for a social determinants of health framework, suggesting that the early home environment may be a key contributor to later drug use. Drug use may emerge as a coping skill or escape mechanism for dysfunction in the household. In post-hoc analysis of Study One, among those with low levels of perceived social support, household dysfunction was a significant predictor of drug whereas childhood maltreatment was not. As mentioned, the single ACE of household substance abuse history (part of household dysfunction) may have also been capturing genetic contributions to addiction, which were not measured in this dataset.

8.2 Theory Recap

Because this dissertation links exposures in early life to outcomes in adulthood, the Life Course Perspective was the primary theoretical approach driving the research questions. Although many disorders emerge in middle and late life, these conditions probably reflect injury incurred from earlier exposures. The integrated conceptual model (section 2.5) summarizes trajectories linking ACEs to mental health outcomes, including potential vulnerability factors, broad processes of biological embedding, as well as resilience (protective) factors. Childhood

disadvantage is often compounded across the life course with chains of additional adversities [433]. Many of these components were not measured in the current studies but were described for completeness.

To fully employ a life course model, data collection at multiple time points would facilitate additional analyses such as mediation using structural equation modeling. While the mSTUDY is longitudinal, this dissertation was not able to examine changing outcomes over time (due to recent addition of the ACE measure). Other recommendations for using a Life Course Perspective in future ACE research include timing of adversity (sensitive or critical periods), frequency/intensity (discussed further in section 8.4), interaction models incorporating various measures of social position and cumulative inequality, as well as the role of protective factors.

The integrated conceptual model utilized the Biopsychosocial Model to consider various physiological mechanisms by which early life adversity can impact mental health trajectories. While mechanisms of biological embedding were not measured, high quality evidence reviewed in section 1.5 was used to conceptualize streams of causation that can be both direct and/or indirect. These pathways provide important theoretical context for life course trajectories before and after childhood adversity and provide additional elaboration. Factors include genetic susceptibility, harmful biological exposures, childhood/adolescent experiences, SES, personality, acute and chronic stressors, lifestyle behaviors, social networks, and their combined effects on physiological functioning [441]. Recently, an updated Biopsychosocial Model has been proposed [452], separating components into testable pathways that can assess subjective well-being as well as objective health outcomes. Several biomarkers available in the mSTUDY dataset (e.g., inflammatory markers) should be used in future research to capitalize on this approach.

The Life Course Perspective and the Biopsychosocial Model were used to formulate an argument that ACEs are a fundamental cause of mental health disparities, based on four criteria proposed by the Fundamental Cause Theory. While the necessary supporting data was not fully analyzed in this dissertation, findings from other publications across multiple disciplines were triangulated to create this novel argument. Multiple ACEs are a known risk factor for a range of adverse mental health conditions, demonstrating that ACEs predict multiple disease outcomes. Pathways to embodiment are confounded by social factors, which further contextualize risk. The damaging effect of ACEs is nonspecific, demonstrating that ACEs can lead to adverse mental and behavioral health outcomes through multiple mechanisms. With multiple mechanisms of embodiment, associations to mental health disorders are reproducible, suggesting that associations will reemerge even after intervening mechanisms change. Impairment by ACE disrupts and inhibits access to social, psychological, and emotional resources across the lifespan, compromising access to resources that may otherwise contribute to resilience.

In summary, embodiment of childhood adversity disrupts physiology (subject to differential susceptibility) by cumulative disadvantage that reverberates across life course processes (subject to resilience resources). Empirical support for the argument that ACEs can be considered a fundamental cause of mental health disparities will necessitate inclusion of biomarkers, additional social factors such as housing and employment instability, as well as additional measures of resilience (assessed independently of the impact of COVID-19). While the estimates for poverty generally rival estimates for ACEs across all three studies (as proposed by the conceptual model in section 2.5), it is entirely possible that lower SES emerged in adulthood because of ACEs, although most likely in conjunction with low early life SES, both of which tend to be “sticky” and have long-lasting cumulative effects on health [429,433,475]. All

three theories incorporated into this dissertation will be helpful in putting this argument to the test. Longitudinal designs are needed to investigate this claim more rigorously and will necessitate the use of expanded ACEs to further explore this research question.

8.3 Public Health Implications

Childhood adversity is a leading contributor to morbidity and mortality in the US and may be considered a preventable determinant of decreased quality of life and early death. One avenue which ACEs can lead to poor health outcomes is through compromised mental health status, which is known to amplify over the life course and generate inequities that widen health gaps between advantaged and disadvantaged groups. Recent estimates suggest that a 10-25% reduction in childhood maltreatment incidence could potentially prevent 30-80 million cases of depression and anxiety worldwide [183]. When stressors accumulate and multiply over the lifespan through biological, psychological, social, and environmental factors, a life course approach is needed to adequately model cumulative risk. The findings from this dissertation reinforce the need to reduce ACEs in efforts to promote better starts in life, particularly among groups with multiple intersecting forms of disadvantage.

It is imperative that ACE prevention programs consider the perspectives of those with multiple marginalized identities to ensure that interventions are gender-sensitive and culturally inclusive. To engage youth in prevention-based intervention, it is critical to understand the contexts in which ACEs develop (at home versus in the community). It will be imperative to gain knowledge on the specific type of victimization that racial/ethnic and sexual minority youth experience relative to their peers [178]. Recently, a trauma-informed toolkit was developed to build capacity among community-based partnerships [535]. The toolkit aims to foster community connectedness and create successful linkages across a wide range of available resources.

Twenty-three years of ACE research with over a thousand publications has contributed to these recommendations. Currently, there is evidence that trauma-informed school and family-focused programs have significant positive effects on many child outcomes [536].

Most mental health problems can be viewed through a lens of social construction, patterned by vulnerability and resilience factors. ACEs operate within social contexts that alleviate or exacerbate their negative impacts [47]. Lower SES during childhood is associated with greater risk of ACEs [53]. Childhood adversity often follows generational patterns, where health inequalities become entrenched within the most vulnerable families. To go upstream, a more comprehensive understanding of parents' childhood experiences is needed to prevent ACEs in their children [478]. Mitigating the deleterious life course impact of ACEs requires an understanding of parental adversity, to break the cycle of trauma and disrupt the legacy of adversity. While the past cannot be undone, efforts to create brighter futures for ACE-exposed children should become a public health priority.

Early prevention and intervention efforts to promote positive and safe parenting are essential to decrease the burden of mental health symptoms among their offspring [111]. Focusing on resilience-promoting protective factors, specifically the quality of children's relational health in a variety of contexts may be just as effective at not only preventing ACEs, but in buffering their effects [537]. Interventions aimed at increasing social support might reduce risk for drug use later in life (Study One). Building resilience may foster adaptive skills needed to cope with future adversity in a proactive manner, without illicit drugs. A recently published Resilience Protective Factors Checklist includes individual, family, and community level buffers to ACEs known to contribute to positive outcomes [330]. Future research should incorporate such factors that are known to potentially counteract with adversity over the life course.

Understanding racial/ethnic disparities in ACE research is critical. However, race and ethnicity do not by themselves put a child at more risk of maltreatment. Differences in risk from minority groups compared to White groups has been fully explained by income, becoming nonexistent after adjustment [67,68]. In this dissertation, the Other Race category (American Indian or Alaskan Native, Asian, Asian Indian, Native Hawaiian Pacific Islander) was used as a reference group, and models consistently suggested that this group is worse off than Black and Latino groups. Although this subgroup was small (n=16) it is considered adequate for most research designs (cell size of at least five) [538], however should be interpreted with caution.

8.4 Measurement Recommendations

A key recommendation from this dissertation, together with other recent ACE research, is the inclusion of expanded ACEs to more accurately represent levels of adversity experienced across minoritized groups [97]. Omitting certain adversities such as community violence and extreme poverty may underestimate mental health disparities among specific subpopulations (misclassification bias). Using the original ACE measure allows comparison of findings across the breadth of ACE research but is likely to overlook many relevant early life exposures that can also compromise mental health, which may be particularly relevant for Black and Latino MSM.

Even when families provide safety at home, children can experience adversity in the community. This includes neighborhood or school violence, bullying, and denigration in many forms, resulting from prejudice and/or "othering," as well as stress caused by continuous exposure to discrimination and marginalization based on race/ethnicity and/or sex/gender as well as sexual orientation [229]. Thus, the experience of racism should be included as an ACE, including institutional/structural and cultural aspects, as well as interpersonal discrimination [539]. Inclusion of immigration-related threats and deprivation should be included into future

ACE frameworks [74]. Recently, an interactive workshop on racism as an ACE was effective in improving professionals comfort level with this topic and skills needed to implement antiracism efforts in clinical encounters with patients and their families [540].

Other recent studies have introduced additional dimensionality to ACE measures. For example, changing the response question from each ACE question from dichotomous to a five-point Likert scale to capture the frequency of exposure [83]. In this large and diverse sample of sexual and gender minorities, Likert ACE scores were more predictive of mental health outcomes (anxiety and PTSD, but not depression) when participants were asked how often they were exposed, rather than whether they were exposed. Modifying ACEs to have ordinal response scales have been supported by other studies. Results comparing these new measurement approaches suggest that the traditional ACE count score may significantly underestimate the amount of attributable variance in many different health outcomes [82]. The strength of observable associations may be proportional to the degree of adversity experienced.

Examination of ACEs as yes/no, whether separately or combined into a count score, limits the ability to understand the frequency in which ACEs occur and the differential impact this additional context can have on subsequent mental health outcomes. Although the cumulative risk approach has proven informative when it comes to prediction, newer dimensional models aim to link variability in adversity intensity to specific mechanistic processes across biopsychosocial domains [88]. Dimensions other than frequency include timing (including discontinuity, consistent with the Life Course Perspective), chronicity (event versus ongoing condition), perception (subjective as well as objective), and the role of the perpetrator [81]. Future research should regularly include intensity-related dimensions as a more fine-grained approach to ACE measurement.

Recommendations for researchers include communicating the nuances of different ACE domains and expanding the capacity to connect with legislative audiences for communicating evidence-based methods to address specific ACEs [541]. Recommendations for policymakers include consideration of structural contributors to ACEs (e.g., poverty, racism), recognition that ACEs vary in their deleterious effects, and emphasizing the value of ACEs to motivate policies at the state level that should consider the whole child from a trauma-informed lens [541].

8.5 Strengths

There are several novel contributions from these studies. The literature describing links between ACEs and mental health outcomes among MSM is limited, particularly those of low-income and racial/ethnic minority status. While the breadth of ACE research is vast among nationally representative samples, gaps remain among specific subgroups. A major strength of these studies is the inclusion of a wide range of sociodemographic and behavioral covariates that help establish a sound estimate of the association between ACE exposure and mental health among MSM. Validated instruments captured the various constructs analyzed in these studies, and there was virtually no missing data.

Another strength from this dissertation is consideration and analysis of potential resilience factors. While resilience factors are typically measured in the psychological domain, the current studies conceptualized resilience through the commonly used perceived social support, as well as though relevant health behaviors (i.e., sleep). Moderation analysis helped to uncover how observed effects vary across levels of another factor, potentially informing targets for intervention. Given that the association between ACEs and drug use was nonexistent among those with higher levels of social support, interventions creating social ties and building community may help reduce the burden of SUDs among those exposed to ACEs.

Another strength of this research is the sampling design. Approximately half of the participants reported drug use, and approximately half are HIV+. A balance between these variables permit comparison with a higher level of statistical efficiency, however no consistent findings related to HIV status were found across the studies. Additional strength can be found in the comprehensive use of theory to guide the research questions and interpret the findings. The results were discussed in the light of several established theories from disciplines of sociology, medicine, and public health. In social science, data needs to be interpreted through the lens of empirically supported theory to translate findings into meaningful conclusions.

This dissertation used a Life Course Perspective to investigate links between multiple forms of adversity experienced in the first 18 years of life and mental health during adulthood, contextually situated among other forms of vulnerability such as social disadvantage, drug use, and HIV status. A trajectory approach was conceptualized through examination of potential buffering factors. Finally, an argument was posed that ACEs can be considered a fundamental cause of mental health inequality, given the amount of empirical support (here and elsewhere) that ACEs can produce (and then reproduce) poor mental health outcomes independent of other social factors. Thus, ACEs can be viewed as an upstream risk factor as well as a more commonly accepted midstream psychosocial factor. However, findings from this dissertation do not fully support this assertion, likely because the full range of relevant childhood adversity exposures were not captured by the ACE instrument used.

8.6 Limitations

The findings from these studies should be viewed in the light of their limitations. The current study sample is not representative of the population. While the mSTUDY is longitudinal, the cross-sectional nature of the current analyses did not generate any causal conclusions. The

recent addition of the ACE measure into the dataset also did not permit adequate analysis of changing mental health outcomes (examined prospectively). Mixed-effects regression models accounted for repeated measures, however truly capitalizing on the longitudinal design was not possible since many variables were collected at different timepoints. For example, perceived social support could not be tested in Study Two and Three due to restriction to time periods pre-COVID-19. Changes in the questionnaires due to remote visits during COVID-19 limited transportability of some data to other time periods, necessitating some separation of data pre- and during COVID-19. Additionally, several of the variables that stopped being collected during COVID-19 remote visits were "carried forward" for statistical analyses. While most of the covariates are likely to be stable over time (e.g., education level, race/ethnicity), others may change (i.e., BMI, HIV status) therefore assumptions of stability were required for analyses.

Meanwhile, a temporal sequence can be established between ACEs and the various outcomes investigated, simply due to ACEs being a recall measure. However, ascertaining the temporal sequence between the other study variables posed some methodological challenges. Temporal sequencing was particularly relevant for the moderation analyses. For example, impaired sleep may be a consequence of depressive and anxiety symptoms in some cases. Similarly, lower levels of perceived social support may be a consequence of drug use. Additionally, moderating variables tested might also be mediators. The sample size as well as the conceptual orientation of resilience did not lend itself to any mediational analyses.

Another limitation (Study One) is the assumption of retrospective transportability of the perceived social support variable (MSPSS). While the perception of social support likely changes over time, Study One assumed its stability for analysis across the entire timespan of the dataset. Social support has emerged in several recent studies as protective of mental health

during COVID-19 [542–545], suggesting that a lack of social support during COVID-19 can be detrimental. The assumption that MSPSS measures collected during COVID-19 can be transported to periods prior to the pandemic assumes that the impact of ACEs on social support is enduring over the life course [351]. The detriment to social support can occur through embodiment [214] (e.g., hypervigilance to threat), therefore, should remain relevant for any ACE research on psychosocial outcomes.

Another possible limitation is that ACE measures are subject to recall bias [101]. Specifically, younger individuals may be better positioned to recall exposure to childhood events than older individuals. This may be particularly relevant when there is PTSD, which is associated with amnestic recall as well as impaired hippocampal function [286,287,546]. Thus, the dissertation assumed temporal stability of ACE recall over time. This limitation may be partially addressed by adjusting for age, but all potential biases cannot truly be accounted for.

Measurement limitations can lead to misclassification bias. While the use of the original ACE measure permits comparison across the breadth of ACE research, it misses many relevant exposures known to impact mental health (e.g., bullying and discrimination) particularly important for sexual minorities. Expanded ACE measures would have been more appropriate for this sample, to capture other relevant forms of adversity including historical trauma (based on race) which can embody, impact social ties, and subsequently affect life choices and chances.

Other limitations can be identified from the perspective of the theoretical underpinnings reviewed in Chapter Two. Several contextual factors shown by the elaboration model in section 2.5 are not captured by the current dataset. While the ACE measure does collect some important information on identified vulnerability factors such as parental history of substance abuse and mental illness, as well as household incarceration; genetic predisposition data are not collected.

This may be most relevant for drug use. While genes by themselves have been challenged in their ability of predict most health outcomes, gene by environment interactions (i.e., epigenetics) have consistently emerged as relevant processes in life course research [211]. Additionally, neighborhood and other related environmental factors experienced during childhood and adolescence were not captured by the dataset.

Finally, literature reviewed in section 1.5 suggests that links between ACEs and mental and behavioral health outcomes are mediated by biological embedding pathways. Understanding these biological pathways adds persuasive perspective to the hypotheses that were tested. Pathways of embodiment alter a wide range of physiological processes that are implicated in health outcomes, both directly and through impaired resilience factors. This data was not included in these analyses, limiting the ability to infer a true "chains of risk" life course model. Biological factors that are closely connected to the sociodemographic and behavioral variables used in these studies should be included in future longitudinal research. Such investigations should utilize expanded ACE measures that capture exposures to adversity most relevant to low-income Black and Latino MSM (e.g., bullying, racism, and discrimination).

8.7 Future Research in the mSTUDY Cohort

The following recommendations are made for future research with the mSTUDY cohort:

1) Investigate cumulative, dimensional, and selective ACEs as risk factors for sexual risk-taking behavior and compromised immune status that may in turn impact HIV/STI risk. Consider childhood sexual abuse (and links to future sexual revictimization) in selective ACE approaches.
2) Conceptualize some of the household dysfunction ACEs (parental separation or divorce, household substance abuse, and household mental illness) as upstream vulnerability

factors in life course models that assess chains of risk by testing mediation pathways investigating cumulative disadvantage, or in models using syndemic theory [403–405].

3) Conceptualize childhood maltreatment ACEs (e.g., physical, sexual abuse) in models of biological embedding that incorporate biomarkers (e.g., inflammatory cytokines) and assess the steepness of their trajectories over time, adjusting for other relevant factors.
4) Investigate associations and interactions between ACEs and sleep quality, using cumulative, dimensional, and selective approaches. Consider a nuanced analysis of the PSQI which investigates its specific components, particularly for depressive symptoms. Explore different cut-points for the PSQI in this high-risk group.
5) Add a measure assessing PTSD symptoms and investigate PTSD as a potential mediator in the outcomes of drug use, depressive and anxiety symptoms, poor sleep quality, and low levels of perceived social support. Conceptualize those exposed to multiple ACEs who do not display clinically significant symptoms of PTSD as a resilient group and compare differences with those who do. Investigate interactions between ACEs and PTSD symptoms in increasing risk for drug use and HIV transmission.
6) Investigate the role of perceived social support as a moderator and mediator of mental health outcomes following exposure to ACEs during COVID-19.
7) Incorporate other measures of resilience (i.e., Brief Resilience Scale) into ACE research during COVID-19 and investigate their potential buffering role in mental health outcomes. Consider factors such as self-efficacy, self-esteem, and coping as additional resilience factors that may emerge as protective against the deleterious impact of ACEs. Incorporate available data on social networks. Measures including Beneficial Childhood Experiences (or other “counter-ACEs”) may also provide insight into resilience processes

and may offset risks associated with ACEs. Investigate various ways that resilience may play out across different subgroups and for different mental health outcomes.

8) Use expanded ACEs to more adequately assess the full range of childhood adversity that mSTUDY participants may have experienced, including questions about poverty, neighborhood violence, bullying, racism, and discrimination based on sexual orientation.
9) Incorporate dimensional approaches to measuring ACEs that include ordinal responses for each ACE capturing the frequency and/or intensity of the exposure, as well as timing, and subjective interpretation.

8.8 Conclusions

This dissertation's findings contribute to our understanding of how ACEs predict mental and behavioral health outcomes among socially disadvantaged MSM in urban settings. Examination of cumulative ACEs, the dimensional approach investigating specific ACE clusters, and a selective approach helped elucidate differential impacts. Clearly, ACEs can associate with multiple mental health outcomes and are not all equal in their impact. The risk for anxiety symptoms following ACEs was higher than depressive symptoms. The childhood maltreatment dimension showed better prediction for depressive and anxiety symptoms, whereas household dysfunction was more closely associated with drug use. Household substance abuse history may be a salient ACE among those perceiving low levels of social support in life course models of drug use. Childhood sexual abuse may be a salient ACE in life course associations with depressive symptoms, and emotional neglect may be important for anxiety.

Through discovering a buffering effect of perceived social support on self-reported drug use, interventions targeting relational health should be developed among those exposed to ACEs, particularly those in the household dysfunction dimension (e.g., household substance abuse

history). Social support may be critical resource in buffering the effects of life stressors on health outcomes but is vulnerable to erosion, for example when adversity increases threat vigilance and restricts one's sense of purpose in life.

Therefore, intervention strategies are needed to improve upstream social context surrounding ACEs. There are multiple opportunities for enhancing resilience throughout the life course and will necessitate substantial allocation of public resources. By bringing trauma-informed primary care and psychological resources to vulnerable communities, ACE-exposed individuals may have greater health-promoting resources. Multidisciplinary efforts will be critical, and community-based interventions should prioritize marginalized groups at most risk.

Universal ACE-screening and trauma-informed care is warranted in public health initiatives. ACE measurement tools should be community- and culture-specific. The overwhelming weight of the evidence demonstrates the powerful effects of socioeconomic and related social factors on mental health, particularly if there is accumulation of multiple forms of psychosocial adversity and risk. The greatest opportunities for mitigating ACEs negative impact and preventing long-term adult health consequences occur during childhood and adolescence, when biological stress response systems are under development.

Newly developed policies for preventing ACEs must consider structural adversity, with strengths-based interventions aimed at cultivating mitigating forces such as positive, nurturing environments at home and in the community [77,547]. A key challenge in promoting this paradigm shift from treatment to prevention is justifying the enormous upfront costs of preventative measures, given the longer-term nature of any anticipated positive health and economic outcomes [536]. If this cannot be achieved, resource allocation for treatment should prioritize groups such as low-income minority MSM who are at risk for HIV infection.

Appendix A: The Original Adverse Childhood Experience Questionnaire [3]

Abuse by category

Psychological

(Did a parent or other adult in the household . . .)

Often or very often swear at, insult, or put you down?

Often or very often act in a way that made you afraid that you would be physically hurt?

Physical

(Did a parent or other adult in the household . . .)

Often or very often push, grab, shove, or slap you?

Often or very often hit you so hard that you had marks or were injured?

Sexual

(Did an adult or person at least 5 years older ever . . .)

Touch or fondle you in a sexual way?

Have you touch their body in a sexual way?

Attempt oral, anal, or vaginal intercourse with you?

Actually have oral, anal, or vaginal intercourse with you?

Household dysfunction by category

Substance abuse

Live with anyone who was a problem drinker or alcoholic?

Live with anyone who used street drugs?

Mental illness

Was a household member depressed or mentally ill?

Did a household member attempt suicide?

Mother treated violently

Was your mother (or stepmother)

Sometimes, often, or very often pushed, grabbed, slapped, or had something thrown at her?

Sometimes, often, or very often kicked, bitten, hit with a fist, or hit with something hard?

Ever repeatedly hit over at least a few minutes?

Ever threatened with, or hurt by, a knife or gun?

Criminal behavior in household

Did a household member go to prison?

Appendix B: The Center for Epidemiological Studies Depression (CESD) [179]

Table 1. CES-D Scale

INSTRUCTIONS FOR QUESTIONS: Below is a list of the ways you might have felt or behaved. Please tell me how often you have felt this way during the past week. HAND CARD A.

Rarely or None of the Time (Less than 1 Day)
Some or a Little of the Time (1-2 Days)
Occasionally or a Moderate Amount of Time (3-4 Days)
Most or All of the Time (5-7 Days)

During the past week:

1. I was bothered by things that usually don't bother me.
2. I did not feel like eating; my appetite was poor.
3. I felt that I could not shake off the blues even with help from my family or friends.
4. I felt that I was just as good as other people.
5. I had trouble keeping my mind on what I was doing.
6. I felt depressed.
7. I felt that everything I did was an effort.
8. I felt hopeful about the future.
9. I thought my life had been a failure.
10. I felt fearful.
11. My sleep was restless.
12. I was happy.
13. I talked less than usual.
14. I felt lonely.
15. People were unfriendly.
16. I enjoyed life.
17. I had crying spells.
18. I felt sad.
19. I felt that people dislike me.
20. I could not get "going."

Appendix C: The Generalized Anxiety Disorder (GAD-7) Questionnaire and Operating Characteristics at Different Cut-Points [482]

GAD-7

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

Total Score ___ = Add Columns ___ + ___ + ___

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Table 1. Operating Characteristics of GAD-7 at Different Cutoffs*

GAD-7 Scale Score†	Sensitivity, %	Specificity, %	PPV, %	NPV, %	LR+	Prevalence, %
8	92	76	24	99	3.8	29
9	90	79	26	99	4.3	26
10	89	82	29	99	5.1	23
11	82	85	31	98	5.5	20
12	73	89	35	98	6.5	16
13	66	91	38	97	7.7	13
14	56	92	37	96	7.2	12
15	48	95	42	96	8.7	9

Abbreviations: GAD-7, generalized anxiety disorder 7-item scale; LR+, likelihood ratio for a positive test; NPV, negative predictive value; PPV, positive predictive value.

*In 965 patients who underwent structured psychiatric interview by a mental health professional to determine the presence of generalized anxiety disorder by using *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* diagnostic criteria.

†The actual score is greater than or equal to the score shown.

Appendix D: The Multidimensional Scale of Perceived Social Support [483]

MSPSS *Items*
1. There is a special person who is around when I am in need.
2. There is a special person with whom I can share my joys and sorrows.
3. My family really tries to help me.
4. I get the emotional help and support I need from my family.
5. I have a special person who is a real source of comfort to me.
6. My friends really try to help me.
7. I can count on my friends when things go wrong.
8. I can talk about my problems with my family.
9. I have friends with whom I can share my joys and sorrows.
10. There is a special person in my life who cares about my feelings.
11. My family is willing to help me make decisions.
12. I can talk about my problems with my friends.

Appendix E: The Pittsburgh Sleep Quality Index [485]

Appendix. Pittsburgh Sleep Quality Index (PSQI)

Name _____ ID # _____ Date _____ Age _____

Instructions:

The following questions relate to your usual sleep habits during the past month *only*. Your answers should indicate the most accurate reply for the *majority* of days and nights in the past month. Please answer all questions.

1. During the past month, when have you usually gone to bed at night?
   USUAL BED TIME _____
2. During the past month, how long (in minutes) has it usually take you to fall asleep each night?
   NUMBER OF MINUTES _____
3. During the past month, when have you usually gotten up in the morning?
   USUAL GETTING UP TIME _____
4. During the past month, how many hours of *actual sleep* did you get at night? (This may be different than the number of hours you spend in bed.)
   HOURS OF SLEEP PER NIGHT _____

For each of the remaining questions, check the one best response. Please answer *all* questions.

5. During the past month, how often have you had trouble sleeping because you...

   (a) Cannot get to sleep within 30 minutes

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week

   (b) Wake up in the middle of the night or early morning

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week

   (c) Have to get up to use the bathroom

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week

   (d) Cannot breathe comfortably

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week

   (e) Cough or snore loudly

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week

   (f) Feel too cold

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week

   (g) Feel too hot

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week

   (h) Had bad dreams

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week

   (i) Have pain

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week

   (j) Other reason(s), please describe _____

   How often during the past month have you had trouble sleeping because of this?

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week

6. During the past month, how would you rate your sleep quality overall?
   - Very good _____
   - *Fairly good* _____
   - Fairly bad _____
   - Very bad _____
7. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week

8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?
   - No problem at all _____
   - Only a very slight problem _____
   - Somewhat of a problem _____
   - A very big problem _____
10. Do you have a bed partner or roommate?
    - No bed partner or roommate _____
    - Partner/roommate in other room _____
    - Partner in same room, but not same bed _____
    - Partner in same bed _____

    If you have a roommate or bed partner, ask him/her how often in the past month you have had...

    (a) *Loud snoring*

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week

    (b) Long pauses between breaths while asleep

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week

    (c) Legs twitching or jerking while you sleep

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week

    (d) Episodes of disorientation or confusion during sleep

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week

    (e) Other restlessness while you sleep; please describe _____

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week

10 REFERENCES

1. Ensel WM, Lin N. The life stress paradigm and psychological distress. J Health Soc Behav. 1991;32(4):321–41.

2. Pearlin LI, Skaff MM. Stress and the life course: A paradigmatic alliance. The Gerontological Society of America. 1996;36(2):239–47.

3. Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: The adverse childhood experiences (ACE) study. Am J Prev Med. 1998;14(4):245–58.

4. Bellis MA, Hughes K, Ford K, Rodriguez G, Sethi D, Passmore J. Life course health consequences and associated annual costs of adverse childhood experiences across Europe and North America: a systematic review and meta-analysis. Lancet Public Heal. 2019;4(10):e517-e528.

5. Hughes K, Bellis MA, Hardcastle KA, Sethi D, Butchart A, Mikton C, et al. The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis. The Lancet Public health. 2017;2(8):e356–66.

6. Hughes K, Ford K, Kadel R, Sharp CA, Bellis MA. Health and financial burden of adverse childhood experiences in England and Wales: A combined primary data study of five surveys. BMJ Open. 2020;10(6):e036374.

7. Braveman P, Egerter S, Williams DR. The social determinants of health: Coming of age. Annu Rev Publ Health. 2011;32(1):381–98.

8. Braveman P, Gottlieb L. The social determinants of health: It's time to consider the causes of the causes. Public Health Reports. 2014;129(Suppl 2):19–31.

9. Allen J, Balfour R, Bell R, Marmot M. Social determinants of mental health. International Review of Psychiatry. 2014;26(4):392–407.

10. Sederer LI. The social determinants of mental health. Psychiatric Services. 2016;67(2):234–5.

11. Miech RA, Caspi A, Moffitt TE, Wright BRE, Silva PA. Low socioeconomic status and mental disorders: A longitudinal study of selection and causation during young adulthood. Am J Sociol. 1999;104(4):1096–131.

12. Reiss F. Socioeconomic inequalities and mental health problems in children and adolescents: A systematic review. Soc Sci Med. 2013;90:24–31.

13. Raposo SM, Mackenzie CS, Henriksen CA, Afifi TO. Time does not heal all wounds: Older adults who experienced childhood adversities have higher odds of mood, anxiety, and personality disorders. The American Journal of Geriatric Psychiatry. 2014;22(11):1241–50.

14. Halfon N, Larson K, Son J, Lu M, Bethell C. Income inequality and the differential effect of adverse childhood experiences in US children. Acad Pediatr. 2017;17(7S):S70–8.

15. Dube SR, Cook ML, Edwards VJ. Health-related outcomes of adverse childhood experiences in Texas, 2002. Prev Chronic Dis. 2010;7(3):A52.

16. Metzler M, Merrick MT, Klevens J, Ports KA, Ford DC. Adverse childhood experiences and life opportunities: Shifting the narrative. Children and Youth Services Review. 2017;72:141–9.

17. Anda RF, Fleisher VI, Felitti VJ, Edwards VJ, Whitfield CL, Dube SR, et al. Childhood abuse, household dysfunction, and indicators of impaired adult worker performance. The Permanente Journal. 2004;8(1):30–8.

18. Topitzes J, Pate DJ, Berman ND, Medina-Kirchner C. Adverse childhood experiences, health, and employment: A study of men seeking job services. Child Abuse Neglect. 2016;61:23–34.

19. Rose SMS-F, Xie D, Stineman M. Adverse childhood experiences and disability in U.S. adults. PM R. 2014;6(8):670–80.

20. Roos LE, Mota N, Afifi TO, Katz LY, Distasio J, Sareen J. Relationship between adverse childhood experiences and homelessness and the impact of axis I and II disorders. American Journal of Public Health. 2013;103 Suppl 2(S2):S275-81.

21. Liu M, Luong L, Lachaud J, Edalati H, Reeves A, Hwang SW. Adverse childhood experiences and related outcomes among adults experiencing homelessness: a systematic review and meta-analysis. Lancet Public Heal. 2021;6(11):e836-e847.

22. Brown DW, Anda RF, Tiemeier H, Felitti VJ, Edwards VJ, Croft JB, et al. Adverse childhood experiences and the risk of premature mortality. Am J Prev Med. 2009;37(5):389–96.

23. Kelly-Irving M, Lepage B, Dedieu D, Bartley M, Blane D, Grosclaude P, et al. Adverse childhood experiences and premature all-cause mortality. Eur J Epidemiol. 2013;28(9):721–34.

24. Johnson J, Chaudieu I, Ritchie K, Scali J, Ancelin M-L, Ryan J. The extent to which childhood adversity and recent stress influence all-cause mortality risk in older adults. Psychoneuroendocrinology. 2019;111:104492.

25. Dube SR, Anda RF, Felitti VJ, Chapman DP, Williamson DF, Giles WH. Childhood abuse, household dysfunction, and the risk of attempted suicide throughout the life span: Findings from the adverse childhood experiences study. JAMA. 2001;286(24):3089–96.

26. Angelakis I, Austin JL, Gooding P. Association of childhood maltreatment with suicide behaviors among young people: A systematic review and meta-analysis. JAMA Netw Open. 2020;3(8):e2012563.

27. Sachs-Ericsson NJ, Rushing NC, Stanley IH, Sheffler J. In my end is my beginning: developmental trajectories of adverse childhood experiences to late-life suicide. Aging Ment Health. 2015;20(2):139–65.

28. Rajalin M, Hirvikoski T, Renberg ES, Åsberg M, Jokinen J. Exposure to early life adversity and interpersonal functioning in attempted suicide. Frontiers Psychiatry. 2020;11:552514.

29. Shonkoff JP, Garner AS, Siegel BS, Dobbins MI, Earls MF, Garner AS, et al. The lifelong effects of early childhood adversity and toxic stress. Pediatrics. 2012;129(1):e232–46.

30. Garner AS, Shonkoff JP, Siegel BS, Dobbins MI, Earls MF, Garner AS, et al. Early childhood adversity, toxic stress, and the role of the pediatrician: Translating developmental science into lifelong health. Pediatrics. 2012;129(1):e224–31.

31. Saxton K, Chyu L. Early life adversity increases the salience of later life stress: An investigation of interactive effects in the PSID. J Dev Orig Hlth Dis. 2020;11(1):25–36.

32. Homan KJ, Kong J. Longitudinal health consequences of childhood adversity: The mediating role of purpose in life. J Gerontol Soc Work. 2020;1–14.

33. Danese A, Widom CS. Objective and subjective experiences of child maltreatment and their relationships with psychopathology. Nat Hum Behav. 2020;4(8):811–8.

34. Danese A, Widom CS. The subjective experience of childhood maltreatment in psychopathology. Journal of the American Medical Association Psychiatry. 2021;78(12):1307-1308.

35. Negriff S. Childhood adversities and mental health outcomes: Does the perception or age of the event matter? Dev Psychopathol. 2020;1–14.

36. Keyes KM, Eaton NR, Krueger RF, McLaughlin KA, Wall MM, Grant BF, et al. Childhood maltreatment and the structure of common psychiatric disorders. Brit J Psychiat. 2012;200(2):107–15.

37. Roberts Y, English D, Thompson R, White C. The impact of childhood stressful life events on health and behavior in at-risk youth. Children and Youth Services Review. 2018;85:117-126.

38. Kaplow JB, Widom C. Age of onset of child maltreatment predicts long-term mental health outcomes. Journal of Abnormal Psychology. 2007;116(1):176.

39. Heinonen E, Knekt P, Härkänen T, Virtala E, Lindfors O. Associations of early childhood adversities with mental disorders, psychological functioning, and suitability for psychotherapy in adulthood. Psychiat Res. 2018;264:366–73.

40. Russell JD, Keding TJ, He Q, Li JJ, Herringa RJ. Childhood exposure to interpersonal violence is associated with greater transdiagnostic integration of psychiatric symptoms. Psychol Med. 2020;1–9.

41. Bernstein DP, Ahluvalia T, Pogge D, Handelsman L. Validity of the childhood trauma questionnaire in an adolescent psychiatric population. J Am Acad Child Adolesc Psychiatry. 1997;36(3):340–8.

42. Bernstein DP, Stein JA, Newcomb MD, Walker E, Pogge D, Ahluvalia T, et al. Development and validation of a brief screening version of the Childhood Trauma Questionnaire. Child Abuse Neglect. 2003;27(2):169–90.

43. Finkelhor D, Shattuck A, Turner H, Hamby S. Improving the adverse childhood experiences study scale. JAMA Pediatr. 2013;167(1):70.

44. Taylor SE, Repetti RL, Seeman T. Health Psychology: What is an unhealthy environment and how does it get under the skin? Psychology. 1997;48(1).

45. Martikainen P, Bartley M, Lahelma E. Psychosocial determinants of health in social epidemiology. International Journal of Epidemiology. 2002;31:1091–3.

46. Roux AV. Integrating social and biologic factors in health research: A systems view. Annals of Epidemiology. 2007;17(7):569–74.

47. Trinidad JE. Social consequences and contexts of adverse childhood experiences. Soc Sci Med. 2021;277:113897.

48. Danese A. Annual Research Review: Rethinking childhood trauma-new research directions for measurement, study design and analytical strategies. J Child Psychol Psyc. 2020;61(3):236–50.

49. Lynch JW, Kaplan GA, Salonen JT. Why do poor people behave poorly? Variation in adult health behaviours and psychosocial characteristics by stages of the socioeconomic lifecourse. Soc Sci Med. 1997;44(6):809–19.

50. Currie J, Widom CS. Long-term consequences of child abuse and neglect on adult economic well-being. Child Maltreatment. 2010;15(2):111–20.

51. Mersky JP, Topitzes J, Reynolds AJ. Impacts of adverse childhood experiences on health, mental health, and substance use in early adulthood: A cohort study of an urban, minority sample in the U.S. Child Abuse & Neglect. 2013;37(11):917–25.

52. Alcalá HEE, Valdez-Dadia A, Ehrenstein OS von. Adverse childhood experiences and access and utilization of health care. Journal of Public Health. 2018;40(4):684–92.

53. Walsh D, McCartney G, Smith M, Armour G. Relationship between childhood socioeconomic position and adverse childhood experiences (ACEs): A systematic review. J Epidemiol Commun H. 2019;73(12):1087.

54. Elder GH. The life course as developmental theory. Child Development. 1998;69(1):1–12.

55. Elder GH, Johnson MK, Cronoe R. The emergence and development of life course theory. In: Mortimer JT, Shanahan MJ, editors. Handbook of the Life Course. New York, NY: Kluwer Academic / Plenum Publishers; 2003. p. 3–19.

56. Adler NE, Ostrove JM. Socioeconomic status and health: What we know and what we don't. Annals of the New York Academy of Sciences. 1999;896(1):3–15.

57. Lee C, Ryff CD. Pathways linking combinations of early-life adversities to adult mortality: Tales that vary by gender. Soc Sci Med. 2019;240:112566.

58. Shaefer HL, Lapidos A, Wilson R, Danziger S. Association of income and adversity in childhood with adult health and well-being. Soc Serv Rev. 2018;92(1):69–92.

59. Hong S, Rhee TG, Piescher KN. Longitudinal association of child maltreatment and cognitive functioning: Implications for child development. Child Abuse Neglect. 2018;84:64–73.

60. Braveman P, Heck K, Egerter S, Rinki C, Marchi K, Curtis M. Economic hardship in childhood: A neglected issue in ACE studies? Maternal and Child Health Journal. 2018;22(3):308–17.

61. Anand KJS, Rigdon J, Rovnaghi CR, Qin F, Tembulkar S, Bush N, et al. Measuring socioeconomic adversity in early life. Acta Paediatr. 2019;108(7):1267–77.

62. Nobari TZ, Whaley SE. Severe housing-cost burden and low-income young children's exposure to adverse experiences: A cross-sectional survey of WIC participants in Los Angeles county. Matern Child Healt J. 2020;1–9.

63. Rittman D, Parrish J, Lanier P. Prebirth household challenges to predict adverse childhood experiences score by age 3. Pediatrics. 2020;e20201303.

64. Alhowaymel F, Kalmakis K, Jacelon C. Developing the concept of adverse childhood experiences: A global perspective. J Pediatric Nurs. 2021;56:18–23.

65. Straatmann VS, Lai E, Law C, Whitehead M, Strandberg-Larsen K, Taylor-Robinson D. How do early-life adverse childhood experiences mediate the relationship between childhood socioeconomic conditions and adolescent health outcomes in the UK? J Epidemiol Commun H. 2020;jech-2020-213817.

66. Williams DR, Yu Y, Jackson JS, Anderson NB. Racial differences in physical and mental health: Socio-economic status, stress and discrimination. J Health Psychol. 1997;2(3):335–51.

67. Mersky JP, Choi C, Lee CP, Janczewski CE. Disparities in adverse childhood experiences by race/ethnicity, gender, and economic status: Intersectional analysis of a nationally representative sample. Child Abuse Neglect. 2021;117:105066.

68. Rosenthal CM, Parker DM, Thompson LA. Racial disparities in child abuse medicine. JAMA Pediatr. 2022;176(2).

69. Umberson D, Thomeer MB, Williams K, Thomas PA, Liu H. Childhood adversity and men's relationships in adulthood: Life course processes and racial disadvantage. Journals Gerontology Ser B. 2016;71(5):902–13.

70. Maguire-Jack K, Lanier P, Lombardi B. Investigating racial differences in clusters of adverse childhood experiences. Am J Orthopsychiat. 2020;90(1):106–14.

71. Schilling EA, Aseltine RH, Gore S. Adverse childhood experiences and mental health in young adults: A longitudinal survey. BMC Public Health. 2007;7(1):30.

72. Thurston H, Bell JF, Induni M. Community-level adverse experiences and emotional regulation in children and adolescents. Journal of Pediatric Nursing. 2018;42:25–33.

73. Giovanelli A, Reynolds AJ. Adverse childhood experiences in a low-income black cohort: The importance of context. Prev Med. 2021;148:106557.

74. Barajas-Gonzalez RG, Ayón C, Brabeck K, Rojas-Flores L, Valdez CR. An ecological expansion of the adverse childhood experiences (ACEs) framework to include threat and deprivation associated with U.S. immigration policies and enforcement practices: An examination of the Latinx immigrant experience. Soc Sci Med. 2021;282:114126.

75. Espinosa A, Bonner M, Alexander W. The differential contribution of adverse childhood experiences and perceived discrimination on substance use among Hispanic emerging adults. J Psychoactive Drugs. 2021;1–9.

76. LaBrenz CA, O'Gara JL, Panisch LS, Baiden P, Larkin H. Adverse childhood experiences and mental and physical health disparities: The moderating effect of race and implications for social work. Soc Work Health Care. 2020;1–26.

77. Ortiz R. Contextualizing adverse childhood experiences—intersections with structural adversity and imperatives for future research. JAMA Netw Open. 2021;4(10):e2130950.

78. Struck S, Stewart-Tufescu A, Asmundson AJN, Asmundson GGJ, Afifi TO. Adverse childhood experiences (ACEs) research: A bibliometric analysis of publication trends over the first 20 years. Child Abuse Neglect. 2021;112:104895.

79. Finkelhor D. Trends in adverse childhood experiences (ACEs) in the United States. Child Abuse Neglect. 2020;108:104641.

80. Lacey RE, Minnis H. Practitioner Review: Twenty years of research with adverse childhood experience scores – Advantages, disadvantages and applications to practice. J Child Psychol Psyc. 2020;61(2):116-130.

81. Krinner LM, Warren-Findlow J, Bowling J, Issel LM, Reeve CL. The dimensionality of adverse childhood experiences: A scoping review of ACE dimensions measurement. Child Abuse Neglect. 2021;121:105270.

82. Reidy DE, Niolon PH, Estefan LF, Kearns MC, D'Inverno AS, Marker CC, et al. Measurement of adverse childhood experiences: It matters. Am J Prev Med. 2021;61(6):821-830.

83. Bond MarkA, Stone AmyL, Salcido R, Schnarrs PhillipW. How often were you traumatized? Reconceptualizing adverse childhood experiences for sexual and gender minorities. J Affect Disorders. 2021;282:407–14.

84. Campbell JA, Walker RJ, Egede LE. Associations between adverse childhood experiences, high-risk behaviors, and morbidity in adulthood. American Journal of Preventive Medicine. 2016;50(3):344–52.

85. Rehkopf DH, Headen I, Hubbard A, Deardorff J, Kesavan Y, Cohen AK, et al. Adverse childhood experiences and later life adult obesity and smoking in the United States. Ann Epidemiol. 2016;26(7):488-492.e5.

86. Kreatsoulas C, Fleegler EW, Subramanian SV. Adverse childhood events increase the risk of behavioural and cardiovascular risk factors. Can J Cardiol. 2014;30(10):S77–8.

87. Bethell CD, Carle A, Hudziak J, Gombojav N, Powers K, Wade R, et al. Methods to assess adverse childhood experiences of children and families: Toward approaches to promote child well-being in policy and practice. Acad Pediatr. 2017;17(7):S51–69.

88. McLaughlin KA, Sheridan MA, Humphreys KL, Belsky J, Ellis BJ. The value of dimensional models of early experience: Thinking clearly about concepts and categories. Perspect Psychol Sci. 2021;174569162199234.

89. Font SA, Maguire-Jack K. Pathways from childhood abuse and other adversities to adult health risks: The role of adult socioeconomic conditions. Child Abuse & Neglect. 2016;51:390–9.

90. Stowkowy J, Goldstein BI, MacQueen G, Wang J, Kennedy SH, Bray S, et al. Trauma in youth at-risk for serious mental illness. J Nerv Ment Dis. 2020;208(1):70–6.

91. Westermair AL, Stoll AM, Greggersen W, Kahl KG, Hüppe M, Schweiger U. All unhappy childhoods are unhappy in their own way—differential impact of dimensions of adverse

childhood experiences on adult mental health and health behavior. Frontiers in Psychiatry. 2018;9:198.

92. Dong M, Anda RF, Felitti VJ, Dube SR, Williamson DF, Thompson TJ, et al. The interrelatedness of multiple forms of childhood abuse, neglect, and household dysfunction. Child Abuse Neglect. 2004;28(7):771–84.

93. Noor SW, Sutherland JE, Vernon JRG, Adam BD, Brennan DJ, Hart TA. Measuring adverse childhood experiences: Comparing individual, composite, score-based and latent profile-based scoring schemas among gay, bisexual, and other men who have sex with men. Arch Sex Behav. 2020;49(5):1741–54.

94. Ports KA, Ford DC, Merrick MT. Adverse childhood experiences and sexual victimization in adulthood. Child Abuse Neglect. 2016;51:313–22.

95. Wade R, Shea JA, Rubin D, Wood J. Adverse childhood experiences of low-income urban youth. Pediatrics. 2014;134(1):e13–20.

96. World Health Organization. Adverse Childhood Experience International Questionnaire [Internet]. Adverse Childhood Experience International Questionnaire (ACE-IQ). 2018 [cited 2021 Mar 15]. Available from: https://www.who.int/violence_injury_prevention/violence/activities/adverse_childhood_experiences/en/

97. Cronholm PF, Forke CM, Wade R, Bair-Merritt MH, Davis M, Harkins-Schwarz M, et al. Adverse childhood experiences expanding the concept of adversity. American Journal of Preventive Medicine. 2015;49(3):354–61.

98. Finkelhor D, Shattuck A, Turner H, Hamby S. A revised inventory of adverse childhood experiences. Child Abuse & Neglect. 2015;48:13–21.

99. Wade R, Cronholm PF, Fein JA, Forke CM, Davis MB, Harkins-Schwarz M, et al. Household and community-level adverse childhood experiences and adult health outcomes in a diverse urban population. Child Abuse & Neglect. 2016;52:135–45.

100. Houtepen LC, Heron J, Suderman MJ, Tilling K, Howe LD. Adverse childhood experiences in the children of the Avon Longitudinal Study of Parents and Children (ALSPAC). Wellcome Open Research. 2018;3:106.

101. Reuben A, Moffitt TE, Caspi A, Belsky DW, Harrington H, Schroeder F, et al. Lest we forget: Comparing retrospective and prospective assessments of adverse childhood experiences in the prediction of adult health. Journal of Child Psychology and Psychiatry. 2016;57(10):1103–12.

102. Silva S da, Maia Â da. The stability of self-reported adverse experiences in childhood. Journal of Interpersonal Violence. 2013;28(10):1989–2004.

103. Anda R, Felitti V, Bremner J, Walker J, Whitfield Ch, Perry B, et al. The enduring effects of abuse and related adverse experiences in childhood. European Archives of Psychiatry and Clinical Neuroscience. 2006;256(3):174–86.

104. Kerker BD, Zhang J, Nadeem E, Stein R, Hurlburt MS, Heneghan A, et al. Adverse childhood experiences and mental health, chronic medical conditions, and development in young children. Academic Pediatrics. 2015;15(5):510–7.

105. Balistreri KS, Alvira-Hammond M. Adverse childhood experiences, family functioning and adolescent health and emotional well-being. Public Health. 2016;132:72–8.

106. Karatekin C. Adverse childhood experiences (ACEs) and help-seeking for health-related interventions in young adults. J Psychology. 2018;153(1):1–17.

107. Garcia AR, Gupta M, Greeson J, Thompson A, DeNard C. Adverse childhood experiences among youth reported to child welfare: Results from the National Survey of Child & Adolescent Wellbeing. Child Abuse & Neglect. 2017;70:292–302.

108. Rhee T, Barry LC, Kuchel GA, Steffens DC, Wilkinson ST. Associations of adverse childhood experiences with past-year DSM-5 psychiatric and substance use disorders in older adults. Journal of the American Geriatrics Society. 2019;67(10):2085-2093.

109. Edwards VJ, Holden GW, Felitti VJ, Anda RF. Relationship between multiple forms of childhood maltreatment and adult mental health in community respondents: Results from the adverse childhood experiences study. American Journal of Psychiatry. 2003;160(8):1453–60.

110. Choi NG, DiNitto DM, Marti CN, Choi BY. Association of adverse childhood experiences with lifetime mental and substance use disorders among men and women aged 50+ years. Int Psychogeriatr. 2017;29(3):359–72.

111. Russotti J, Warmingham JM, Duprey EB, Handley ED, Manly JT, Rogosch FA, et al. Child maltreatment and the development of psychopathology: The role of developmental timing and chronicity. Child Abuse Neglect. 2021;120:105215.

112. Goemans A, Viding E, McCrory E. Child maltreatment, peer victimization, and mental health: neurocognitive perspectives on the cycle of victimization. Trauma Violence Abus. 2021;152483802110363.

113. Trossman R, Spence S-L, Mielke JG, McAuley T. How do adverse childhood experiences impact health? Exploring the mediating role of executive functions. Psychological Trauma Theory Res Pract Policy. 2020;13(2):206-213.

114. Brown NM, Brown SN, Briggs RD, Germán M, Belamarich PF, Oyeku SO. Associations between adverse childhood experiences and ADHD diagnosis and severity. Acad Pediatr. 2017;17(4):349–55.

115. Jimenez ME, Wade R, Schwartz-Soicher O, Lin Y, Reichman NE. Adverse childhood experiences and ADHD diagnosis at age 9 years in a national urban sample. Academic Pediatrics. 2017;17(4):356–61.

116. Hunt TKA, Slack KS, Berger LM. Adverse childhood experiences and behavioral problems in middle childhood. Child Abuse Neglect. 2017;67:391–402.

117. Martel M, Nikolas M, Nigg JT. Executive function in adolescents with ADHD. J Am Acad Child Adolesc Psychiatry. 2007;46(11):1437–44.

118. Merrick MT, Ports KA, Ford DC, Afifi TO, Gershoff ET, Grogan-Kaylor A. Unpacking the impact of adverse childhood experiences on adult mental health. Child Abuse & Neglect. 2017;69:10–9.

119. Negriff S. ACEs are not equal: Examining the relative impact of household dysfunction versus childhood maltreatment on mental health in adolescence. Soc Sci Med. 2020;245:112696.

120. Lee H, Kim Y, Terry J. Adverse childhood experiences (ACEs) on mental disorders in young adulthood: Latent classes and community violence exposure. Prev Med. 2020;134:106039.

121. American Psychological Association. Diagnostic and Statistical Manual of Mental Disorders (5th ed.) [Internet]. 2013. Available from: https://dsm.psychiatryonline.org/doi/book/10.1176/appi.books.9780890425596

122. Malarbi S, Abu-Rayya HM, Muscara F, Stargatt R. Neuropsychological functioning of childhood trauma and post-traumatic stress disorder: A meta-analysis. Neurosci Biobehav Rev. 2017;72:68–86.

123. Thome J, Hauschild S, Koppe G, Liebke L, Rausch S, Herzog JI, et al. Generalisation of fear in PTSD related to prolonged childhood maltreatment: An experimental study. Psychol Med. 2018;48(13):2223–34.

124. Hawkley LC, Cacioppo JT. Perceived social isolation: Social threat vigilance and its implications for health. In: Decety J, Cacioppo JT, editors. The Oxford Handbook of Social Neuroscience. 2011.

125. Lewis SJ, Arseneault L, Caspi A, Fisher HL, Matthews T, Moffitt TE, et al. The epidemiology of trauma and post-traumatic stress disorder in a representative cohort of young people in England and Wales. The Lancet Psychiatry. 2019;6(3):247–56.

126. Rawlins B, Brooks M, Khan R. Posttraumatic stress symptoms mediate the relationship between adverse childhood experiences, avoidant personality traits and resilience. Anxiety Stress Coping. 2020;33(5):1–12.

127. Karatzias T, Shevlin M, Fyvie C, Grandison G, Garozi M, Latham E, et al. Adverse and benevolent childhood experiences in posttraumatic stress disorder (PTSD) and complex PTSD (CPTSD): Implications for trauma-focused therapies. Eur J Psychotraumato. 2020;11(1):1793599.

128. Muscatello MRA, Rizzo A, Celebre L, Mento C, Pandolfo G, Cedro C, et al. The wounds of childhood: Early trauma subtypes, salience and hyperarousal in a sample of adult psychiatric patients. Int J Soc Psychiatr. 2020;66(1):3–9.

129. Bürgin D, Boonmann C, Schmeck K, Schmid M, Tripp P, Nishimi K, et al. Compounding stress: Childhood adversity as a risk factor for adulthood trauma exposure in the health and retirement study. J Trauma Stress. 2021;34(1):124-136.

130. Charak R, Vang ML, Shevlin M, Ben-Ezra M, Karatzias T, Hyland P. Lifetime interpersonal victimization profiles and mental health problems in a nationally representative panel of trauma-exposed adults from the United Kingdom. J Trauma Stress. 2020;33(5):654–64.

131. Whiteman SE, Witte TK, Cero I, Kramer LB, Weathers FW. Posttraumatic stress disorder and suicidal ideation: The moderating effect of posttraumatic cognitions. J Trauma Stress. 2021;34(6):1178-1187.

132. Pahl K, Williams SZ, Lee JY, Joseph A, Blau C. Trajectories of violent victimization predicting PTSD and comorbidities among urban ethnic/racial minorities. J Consult Clin Psych. 2020;88(1):39-47.

133. Nawijn L, Zuiden M van, Frijling JL, Koch S, Veltman DJ, Olff M. Reward functioning in PTSD: A systematic review exploring the mechanisms underlying anhedonia. Neuroscience & Biobehavioral Reviews. 2015;51:189–204.

134. Shin SH, McDonald S, Conley D. Patterns of adverse childhood experiences and substance use among young adults: A latent class analysis. Addictive Behaviors. 2018;78:187–92.

135. Edalati H, Krank MD. Childhood maltreatment and development of substance use disorders. Trauma, Violence, & Abuse. 2016;17(5):454–67.

136. Dube SR, Felitti VJ, Dong M, Chapman DP, Giles WH, Anda RF. Childhood abuse, neglect, and household dysfunction and the risk of illicit drug use: The adverse childhood experiences study. Pediatrics. 2003;111(3):564–72.

137. Cicchetti D, Handley ED. Child maltreatment and the development of substance use and disorder. Neurobiology Stress. 2019;10:100144.

138. Fuchshuber J, Unterrainer HF. Childhood trauma, personality, and substance use disorder: The development of a neuropsychoanalytic addiction model. Frontiers Psychiatry. 2020;11:531.

139. Alvanzo AAH, Storr CL, Reboussin B, Green KM, Mojtabai R, Flair LNL, et al. Adverse childhood experiences (ACEs) and transitions in stages of alcohol involvement among US adults: Progression and regression. Child Abuse Neglect. 2020;107:104624.

140. Fitzpatrick S, Saraiya T, Lopez-Castro T, Ruglass LM, Hien D. The impact of trauma characteristics on post-traumatic stress disorder and substance use disorder outcomes across integrated and substance use treatments. J Subst Abuse Treat. 2020;113:107976.

141. Brunault P, Lebigre K, Idbrik F, Maugé D, Adam P, Barrault S, et al. Childhood trauma predicts less remission from ptsd among patients with co-occurring alcohol use disorder and PTSD. J Clin Medicine. 2020;9(7):2054.

142. Mergler M, Driessen M, Havemann-Reinecke U, Wedekind D, Lüdecke C, Ohlmeier M, et al. Differential relationships of PTSD and childhood trauma with the course of substance use disorders. J Subst Abuse Treat. 2018;93:57–63.

143. Dawson-Rose C, Shehadeh D, Hao J, Barnard J, Khoddam-Khorasani LL, Leonard A, et al. Trauma, substance use, and mental health symptoms in transitional age youth experiencing homelessness. Public Health Nurs. 2020;37(3):363–70.

144. Vujanovic AA, Wardle MC, Smith LJ, Berenz EC. Reward functioning in posttraumatic stress and substance use disorders. Current Opinion in Psychology. 2017;14:49–55.

145. Mahoney CT, Cole HE, Gilbar O, Taft CT. The role of impulsivity in the association between posttraumatic stress disorder symptom severity and substance use in male military veterans. J Trauma Stress. 2020;33(3):296-306.

146. Sumner JA, Nishimi KM, Koenen KC, Roberts AL, Kubzansky LD. Posttraumatic stress disorder and inflammation: Untangling issues of bidirectionality. Biol Psychiat. 2020;87(10):885-897.

147. Mellon SH, Gautam A, Hammamieh R, Jett M, Wolkowitz OM. Metabolism, metabolomics, and inflammation in post-traumatic stress disorder. Biological Psychiatry. 2018;83(10):866–75.

148. Carliner H, Keyes KM, McLaughlin KA, Meyers JL, Dunn EC, Martins SS. Childhood trauma and illicit drug use in adolescence: A population-based national comorbidity survey replication–adolescent supplement study. Journal of the American Academy of Child & Adolescent Psychiatry. 2016;55(8):701–8.

149. Huang C, Yuan Q, Zhang L, Wang L, Cui S, Zhang K, et al. Associations between childhood trauma and the age of first-time drug use in methamphetamine-dependent patients. Frontiers Psychiatry. 2021;12:658205.

150. Davis JP, Tucker JS, Stein BD, D'Amico EJ. Longitudinal effects of adverse childhood experiences on substance use transition patterns during young adulthood. Child Abuse Neglect. 2021;120:105201.

151. Scheidell JD, Quinn K, McGorray SP, Frueh CB, Beharie NN, Cottler LB, et al. Childhood traumatic experiences and the association with marijuana and cocaine use in adolescence through adulthood. Addiction. 2018;113(1):44–56.

152. Evans EA, Grella CE, Upchurch DM. Gender differences in the effects of childhood adversity on alcohol, drug, and polysubstance-related disorders. Soc Psych Psych Epid. 2017;52(7):901–12.

153. Fuller-Thomson E, Roane JL, Brennenstuhl S. Three types of adverse childhood experiences, and alcohol and drug dependence among adults: An investigation using population-based data. Substance Use & Misuse. 2016;51(11):1–11.

154. Afifi TO, Taillieu T, Salmon S, Davila IG, Stewart-Tufescu A, Fortier J, et al. Adverse childhood experiences (ACEs), peer victimization, and substance use among adolescents. Child Abuse Neglect. 2020;106:104504.

155. Hughes K, Bellis MA, Sethi D, Andrew R, Yon Y, Wood S, et al. Adverse childhood experiences, childhood relationships and associated substance use and mental health in young Europeans. Eur J Public Health. 2019;29(4):741-747.

156. Puetz VB, McCrory E. Exploring the relationship between childhood maltreatment and addiction: A review of the neurocognitive evidence. Current Addiction Reports. 2015;2(4):318–25.

157. Kim S, Kwok S, Mayes LC, Potenza MN, Rutherford HJ, Strathearn L. Early adverse experience and substance addiction: dopamine, oxytocin, and glucocorticoid pathways. Annals of the New York Academy of Sciences. 2017;1394(1):74–91.

158. Moustafa AA, Parkes D, Fitzgerald L, Underhill D, Garami J, Levy-Gigi E, et al. The relationship between childhood trauma, early-life stress, and alcohol and drug use, abuse, and addiction: An integrative review. Current Psychology. 2018;1–6.

159. Shin SH, McDonald S, Conley D. Profiles of adverse childhood experiences and impulsivity. Child Abuse & Neglect. 2018;85:118-126.

160. Acheson A, Vincent AS, Cohoon A, Lovallo WR. Early life adversity and increased delay discounting: Findings from the family health patterns project. Exp Clin Psychopharm. 2019;27(2):153–9.

161. Rung JM, Peck S, Hinnenkamp JE, Preston E, Madden GJ. Changing delay discounting and impulsive choice: Implications for addictions, prevention, and human health. Perspectives Behav Sci. 2019;42(3):397–417.

162. Revill AS, Patton KA, Connor JP, Sheffield J, Wood AP, Castellanos-Ryan N, et al. From impulse to action? Cognitive mechanisms of impulsivity-related risk for externalizing behavior. J Abnorm Child Psych. 2020;1–12.

163. Swendsen JD, Merikangas KR. The comorbidity of depression and substance use disorders. Clin Psychol Rev. 2000;20(2):173–89.

164. Davis L, Uezato A, Newell JM, Frazier E. Major depression and comorbid substance use disorders. Curr Opin Psychiatr. 2008;21(1):14–8.

165. Tucci AM, Kerr-Corrêa F, Souza-Formigoni MLO. Childhood trauma in substance use disorder and depression: An analysis by gender among a Brazilian clinical sample. Child Abuse Neglect. 2010;34(2):95–104.

166. Brook DW, Brook JS, Zhang C, Cohen P, Whiteman M. Drug use and the risk of major depressive disorder, alcohol dependence, and substance use disorders. Arch Gen Psychiat. 2002;59(11):1039–44.

167. Worley MJ, Trim RS, Roesch SC, Mrnak-Meyer J, Tate SR, Brown SA. Comorbid depression and substance use disorder: Longitudinal associations between symptoms in a controlled trial. J Subst Abuse Treat. 2012;43(3):291–302.

168. Goodman E, Huang B. Socioeconomic status, depressive symptoms, and adolescent substance use. Archives of Pediatrics & Adolescent Medicine. 2002;156(5):448–53.

169. Kim Y, Kim K, Chartier KG, Wike TL, McDonald SE. Adverse childhood experience patterns, major depressive disorder, and substance use disorder in older adults. Aging Ment Health. 2019;1–8.

170. Tache RM, Lambert SF, Ialongo NS. The role of depressive symptoms in substance use among African American boys exposed to community violence. J Trauma Stress. 2020;33(6):1039-1047.

171. Currie SR, Patten SB, Williams JV, Wang J, Beck CA, El-Guebaly N, et al. Comorbidity of major depression with substance use disorders. Can J Psychiatry. 2005;50(10):660–6.

172. Lorant V, Deliège D, Eaton W, Robert A, Philippot P, Ansseau M. Socioeconomic inequalities in depression: A meta-analysis. Am J Epidemiol. 2003;157(2):98–112.

173. Almeida OP, Pirkis J, Kerse N, Sim M, Flicker L, Snowdon J, et al. Socioeconomic disadvantage increases risk of prevalent and persistent depression in later life. J Affect Disorders. 2012;138(3):322–31.

174. Melchior M, Chastang J-F, Head J, Goldberg M, Zins M, Nabi H, et al. Socioeconomic position predicts long-term depression trajectory: A 13-year follow-up of the GAZEL cohort study. Mol Psychiatr. 2013;18(1):112–21.

175. Elovainio M, Vahtera J, Pentti J, Hakulinen C, Pulkki-Råback L, Lipsanen J, et al. The contribution of neighborhood socioeconomic disadvantage to depressive symptoms over the course of adult life: A 32-year prospective cohort study. Am J Epidemiol. 2020;189(7):679–89.

176. Ho TC, King LS. Mechanisms of neuroplasticity linking early adversity to depression: Developmental considerations. Transl Psychiat. 2021;11(1):517.

177. Kogan SM, Bae D, Cho J, Smith AK, Nishitani S. Pathways linking adverse environments to emerging adults' substance abuse and depressive symptoms: A prospective analysis of rural African American men. Dev Psychopathol. 2020;1–11.

178. Hicks MR, Kernsmith P, Smith-Darden J. The effects of adverse childhood experiences on internalizing and externalizing behaviors among Black children and youth. J Child Adolesc Trauma. 2021;14(1):115–22.

179. Radloff LS. The CES-D Scale. Appl Psych Meas. 1977;1(3):385–401.

180. Chapman DP, Whitfield CL, Felitti VJ, Dube SR, Edwards VJ, Anda RF. Adverse childhood experiences and the risk of depressive disorders in adulthood. Journal of Affective Disorders. 2004;82(2):217–25.

181. Chen H, Fan Q, Nicholas S, Maitland E. The long arm of childhood: The prolonged influence of adverse childhood experiences on depression during middle and old age in China. J Health Psychol. 2021;135910532110377.

182. Danese A, Moffitt TE, Harrington H, Milne BJ, Polanczyk G, Pariante CM, et al. Adverse childhood experiences and adult risk factors for age-related disease: Depression, inflammation, and clustering of metabolic risk markers. Arch Pediat Adol Med. 2009;163(12):1135–43.

183. Sahle BW, Reavley NJ, Li W, Morgan AJ, Yap MBH, Reupert A, et al. The association between adverse childhood experiences and common mental disorders and suicidality: An umbrella review of systematic reviews and meta-analyses. Eur Child Adoles Psy. 2021;1–11.

184. Hailes HP, Yu R, Danese A, Fazel S. Long-term outcomes of childhood sexual abuse: An umbrella review. Lancet Psychiatry. 2019;6(10):830–9.

185. Yrondi A, Aouizerate B, Bennabi D, Richieri R, D'Amato T, Bellivier F, et al. Childhood maltreatment and clinical severity of treatment-resistant depression in a French cohort of outpatients (FACE-DR): One-year follow-up. Depress Anxiety. 2020;37(4):365-374.

186. Giano Z, Ernst CW, Snider K, Davis A, O'Neil AM, Hubach RD. ACE domains and depression: Investigating which specific domains are associated with depression in adulthood. Child Abuse Neglect. 2021;122:105335.

187. Xiang X, Wang X. Childhood adversity and major depression in later life: A competing-risks regression analysis. Int J Geriatr Psych. 2021;36(1):215-223.

188. Infurna MR, Reichl C, Parzer P, Schimmenti A, Bifulco A, Kaess M. Associations between depression and specific childhood experiences of abuse and neglect: A meta-analysis. J Affect Disorders. 2016;190:47–55.

189. Kim Y, Lee H, Park A. Patterns of adverse childhood experiences and depressive symptoms: Self-esteem as a mediating mechanism. Soc Psych Psych Epid. 2021;1–11.

190. Goff B, Tottenham N. Early-life adversity and adolescent depression: Mechanisms involving the ventral striatum. CNS Spectrums. 2015;20(4):337–45.

191. Kennis M, Gerritsen L, Dalen M van, Williams A, Cuijpers P, Bockting C. Prospective biomarkers of major depressive disorder: A systematic review and meta-analysis. Mol Psychiatr. 2019;25(2):321–38.

192. Cheong EV, Sinnott C, Dahly D, Kearney PM. Adverse childhood experiences (ACEs) and later-life depression: Perceived social support as a potential protective factor. BMJ Open. 2017;7(9):e013228.

193. Nanni V, Uher R, Danese A. Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: A meta-analysis. American Journal of Psychiatry. 2012;(169):141–51.

194. Sullivan RM, Opendak M. Neurobiology of infant fear and anxiety: Impacts of delayed amygdala development and attachment figure quality. Biol Psychiat. 2021;89(7):641-650.

195. Olfson M, Shea S, Feder A, Fuentes M, Nomura Y, Gameroff M, et al. Prevalence of anxiety, depression, and substance use disorders in an urban general medicine practice. Arch Fam Med. 2000;9(9):876–83.

196. Feltz-Cornelis CM van der, Potters EC, Dam A van, Koorndijk RPM, Elfeddali I, Sluijs JF van E van der. Adverse childhood experiences (ACE) in outpatients with anxiety and depressive disorders and their association with psychiatric and somatic comorbidity and revictimization. Cross-sectional observational study. J Affect Disorders. 2018;246:458–64.

197. Smith JP, Book SW. Anxiety and substance use disorders: A review. Psychiatric Times. 2008;10(25):19–23.

198. Vujanovic AA, Farris SG, Bartlett BA, Lyons RC, Haller M, Colvonen PJ, et al. Anxiety sensitivity in the association between posttraumatic stress and substance use disorders: A systematic review. Clin Psychol Rev. 2018;62:37–55.

199. Rambau S, Forstner AJ, Wegener I, Mücke M, Wissussek TSC, Staufenbiel SM, et al. Childhood adversities, bonding, and personality in social anxiety disorder with alcohol use disorder. Psychiat Res. 2018;262:295–302.

200. Reiser SJ, McMillan KA, Wright KD, Asmundson GJG. Adverse childhood experiences and health anxiety in adulthood. Child Abuse Neglect. 2014;38(3):407–13.

201. Poole JC, Dobson KS, Pusch D. Anxiety among adults with a history of childhood adversity: Psychological resilience moderates the indirect effect of emotion dysregulation. J Affect Disorders. 2017;217:144–52.

202. Taylor DL, Espeleta HC, Kraft JD, Grant DM. Early childhood experiences and cognitive risk factors for anxiety symptoms among college students. J Am Coll Health. 2019;1–7.

203. Baumont A de, Bortoluzzi A, Aguiar BW de, Scotton E, Guimarães LSP, Kapczinski F, et al. Anxiety disorders in childhood are associated with youth IL-6 levels: A mediation study including metabolic stress and childhood traumatic events. J Psychiatr Res. 2019;115:43–50.

204. Karatsoreos IN, McEwen BS. Psychobiological allostasis: resistance, resilience and vulnerability. Trends in Cognitive Sciences. 2011;15(12):576–84.

205. Monroe SM, Simons AD. Diathesis–stress theories in the context of life stress research: Implications for the depressive disorders. Psychol Bull. 1991;110(3):406–25.

206. Belsky J, Jonassaint C, Pluess M, Stanton M, Brummett B, Williams R. Vulnerability genes or plasticity genes? Mol Psychiatr. 2009;14(8):746–54.

207. Belsky J. The differential susceptibility hypothesis: Sensitivity to the environment for better and for worse. JAMA Pediatr. 2016;170(4):321.

208. Belsky J, IJzendoorn MH van. Genetic differential susceptibility to the effects of parenting. Curr Opin Psychology. 2017;15:125–30.

209. Hartman S, Belsky J. An evolutionary perspective on family studies: Differential susceptibility to environmental influences. Fam Process. 2016;55(4):700–12.

210. Belsky J. Variation in susceptibility to environmental influence: An evolutionary argument. Psychol Inq. 1997;8(3):182–6.

211. Belsky J, Pluess M. Beyond diathesis stress: Differential susceptibility to environmental influences. Psychol Bull. 2009;135(6):885–908.

212. Belsky J. Differential susceptibility to environmental influences. Int J Child Care Educ Policy. 2013;7(2):15–31.

213. Belsky J, Pluess M. Differential susceptibility to long-term effects of quality of child care on externalizing behavior in adolescence? Int J Behav Dev. 2012;36(1):2–10.

214. Miller GE, Chen E, Parker KJ. Psychological stress in childhood and susceptibility to the chronic diseases of aging: Moving toward a model of behavioral and biological mechanisms. Psychological Bulletin. 2011;137(6):959–97.

215. Albott CS, Forbes MK, Anker JJ. Association of childhood adversity with differential susceptibility of transdiagnostic psychopathology to environmental stress in adulthood. JAMA Netw Open. 2018;1(7):e185354.

216. Ellis BJ, Boyce WT, Belsky J, Bakermans-Kranenburg MJ, Ijzendoorn MH van. Differential susceptibility to the environment: An evolutionary–neurodevelopmental theory. Dev Psychopathol. 2011;23(1):7–28.

217. Daskalakis NP, Bagot RC, Parker KJ, Vinkers CH, Kloet ER de. The three-hit concept of vulnerability and resilience: Toward understanding adaptation to early-life adversity outcome. Psychoneuroendocrinology. 2013;38(9):1858–73.

218. McCrory EJ, Viding E. The theory of latent vulnerability: Reconceptualizing the link between childhood maltreatment and psychiatric disorder. Development and Psychopathology. 2015;27(2):493–505.

219. Reiss F, Meyrose A-K, Otto C, Lampert T, Klasen F, Ravens-Sieberer U. Socioeconomic status, stressful life situations and mental health problems in children and adolescents: Results of the German BELLA cohort-study. PLoS One. 2019;14(3):e0213700.

220. Choi J-K, Wang D, Jackson AP. Adverse experiences in early childhood and their longitudinal impact on later behavioral problems of children living in poverty. Child Abuse Neglect. 2019;98:104181.

221. Lee J, Hill KG, Hartigan LA, Boden JM, Guttmannova K, Kosterman R, et al. Unemployment and substance use problems among young adults: Does childhood low socioeconomic status exacerbate the effect? Social Science & Medicine. 2015;143:36–44.

222. Rönkä S, Karjalainen K, Martikainen P, Mäkelä P. Social determinants of drug-related mortality in a general population. Drug and Alcohol Dependence. 2017;181:37–43.

223. Repetti RL, Taylor SE, Seeman TE. Risky families: Family social environments and the mental and physical health of offspring. Psychol Bull. 2002;128(2):330.

224. Ballard E, Eck VK, Musci R, Hart S, Storr C, Breslau N, et al. Latent classes of childhood trauma exposure predict the development of behavioral health outcomes in adolescence and young adulthood. Psychological Medicine. 2015;45(15):3305–16.

225. Merikukka M, Ristikari T, Tuulio-Henriksson A, Gissler M, Laaksonen M. Childhood determinants for early psychiatric disability pension: A 10-year follow-up study of the 1987 Finnish Birth Cohort. Int J Soc Psychiatr. 2018;64(8):715–25.

226. Clemens V, Berthold O, Witt A, Sachser C, Brähler E, Plener PL, et al. Child maltreatment is mediating long-term consequences of household dysfunction in a population representative sample. Eur Psychiat. 2019;58:10–8.

227. Barrero-Castillero A, Morton SU, Nelson CA, Smith VC. Psychosocial stress and adversity: Effects from the perinatal period to adulthood. Neoreviews. 2019;20(12):e686–96.

228. Negriff S, Molina AP, Hackman DA. Parental exposure to childhood maltreatment and offspring's mental health: Investigating pathways through parental adversity and offspring exposure to maltreatment. Child Maltreatment. 2020;25(4):422–32.

229. Bruner C. ACE, Place, race, and poverty: Building hope for children. Academic Pediatrics. 2017;17(7):S123–9.

230. Solmi F, Colman I, Weeks M, Lewis G, Kirkbride JB. Trajectories of neighborhood cohesion in childhood, and psychotic and depressive symptoms at age 13 and 18 years. Journal of the American Academy of Child & Adolescent Psychiatry. 2017;56(7):570–7.

231. Fong K. Neighborhood inequality in the prevalence of reported and substantiated child maltreatment. Child Abuse Neglect. 2019;90:13–21.

232. Wang D, Choi J-K, Shin J. Long-term neighborhood effects on adolescent outcomes: Mediated through adverse childhood experiences and parenting stress. J Youth Adolescence. 2020;1–14.

233. Choi J-K, Teshome T, Smith J. Neighborhood disadvantage, childhood adversity, bullying victimization, and adolescent depression: A multiple mediational analysis. J Affect Disorders. 2020;279:554–62.

234. Barker D. The fetal and infant origins of adult disease. British Medical Journal. 1990;301(6761):1111.

235. Barker DJP. Fetal origins of coronary heart disease. BMJ. 1995;311(6998):171.

236. Barker DJP. Developmental origins of chronic disease. Public Health. 2012;126(3):185–9.

237. Hertzman C. The biological embedding of early experience and its effects on health in adulthood. Annals of the New York Academy of Sciences. 1999;896:85–95.

238. Hertzman C, Wiens M. Child development and long-term outcomes: A population health perspective and summary of successful interventions. Soc Sci Med. 1996;43(7):1083–95.

239. Hertzman C. Putting the concept of biological embedding in historical perspective. Proceedings of the National Academy of Sciences. 2012;201202203.

240. Wiss DA, Brewerton TD, Tomiyama AJ. Limitations of the protective measure theory in explaining the role of childhood sexual abuse in eating disorders, addictions, and obesity: an updated model with emphasis on biological embedding. Eat Weight Disord - Stud Anorexia Bulimia Obes. 2021;1–19.

241. Danese A, Lewis SJ. Psychoneuroimmunology of early-life stress: The hidden wounds of childhood trauma? Neuropsychopharmacology. 2017;42(1):99–114.

242. Fagundes CP, Glaser R, Kiecolt-Glaser JK. Stressful early life experiences and immune dysregulation across the lifespan. Brain Behav Immun. 2013;27:8–12.

243. Tursich M, Neufeld RWJ, Frewen PA, Harricharan S, Kibler JL, Rhind SG, et al. Association of trauma exposure with proinflammatory activity: A transdiagnostic meta-analysis. Transl Psychiat. 2014;4(7):e413–e413.

244. Danese A, Pariante CM, Caspi A, Taylor A, Poulton R. Childhood maltreatment predicts adult inflammation in a life-course study. Proc National Acad Sci. 2007;104(4):1319–24.

245. McEwen BS, Stellar E. Stress and the individual: Mechanisms leading to disease. Archives of Internal Medicine. 1993;153(18):2093–101.

246. McEwen BS. Stress, adaptation, and disease: Allostasis and allostatic load. Annals of the New York Academy of Sciences. 1998;840(1):33–44.

247. Seeman T, Singer B, Rowe J, Horwitz R, McEwen B. Price of adaptation--allostatic load and its health consequences. MacArthur studies of successful aging. Archives of Internal Medicine. 1997;157(19):2259–68.

248. Seeman TE, McEwen BS, Rowe JW, Singer BH. Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. Proc National Acad Sci. 2001;98(8):4770–5.

249. Solís CB. Embodiment of early psychosocial adversity and allostatic load using a life course perspective: A review. ODOVTOS - Int J Dent Sci. 2015;0(16):35–46.

250. Robertson T, Beveridge G, Bromley C. Allostatic load as a predictor of all-cause and cause-specific mortality in the general population: Evidence from the Scottish Health Survey. Plos One. 2017;12(8):e0183297.

251. Renna ME, Peng J, Shrout MR, Madison AA, Andridge R, Alfano CM, et al. Childhood abuse histories predict steeper inflammatory trajectories across time. Brain Behav Immun. 2021;91:541-545.

252. Dooley LN, Kuhlman KR, Robles TF, Eisenberger NI, Craske MG, Bower JE. The role of inflammation in core features of depression: Insights from paradigms using exogenously-induced inflammation. Neurosci Biobehav Rev. 2018;94:219–37.

253. Fung TC, Olson CA, Hsiao EY. Interactions between the microbiota, immune and nervous systems in health and disease. Nat Neurosci. 2017;20(2):145–55.

254. Kohno M, Link J, Dennis LE, McCready H, Huckans M, Hoffman WF, et al. Neuroinflammation in addiction: A review of neuroimaging studies and potential immunotherapies. Pharmacol Biochem Behav. 2019;179:34–42.

255. Nusslock R, Miller GE. Early-life adversity and physical and emotional health across the lifespan: A neuroimmune network hypothesis. Biological Psychiatry. 2016;80(1):23–32.

256. Muscatell KA, Brosso SN, Humphreys KL. Socioeconomic status and inflammation: A meta-analysis. Mol Psychiatr. 2020;25(9):2189–99.

257. Tomasdottir MO, Sigurdsson JA, Petursson H, Kirkengen AL, Krokstad S, McEwen B, et al. Self reported childhood difficulties, adult multimorbidity and allostatic load. A cross-sectional analysis of the Norwegian HUNT study. PLoS One. 2015;10(6):e0130591.

258. Solís CB, Kelly-Irving M, Fantin R, Darnaudéry M, Torrisani J, Lang T, et al. Adverse childhood experiences and physiological wear-and-tear in midlife: Findings from the 1958 British birth cohort. Proc National Acad Sci. 2015;112(7):E738–46.

259. McCrory C, Fiorito G, Cheallaigh CN, Polidoro S, Karisola P, Alenius H, et al. How does socio-economic position (SEP) get biologically embedded? A comparison of allostatic load and the epigenetic clock(s). Psychoneuroendocrinology. 2019;104:64–73.

260. Turner JR, Thomas CS, Brown TH. Childhood adversity and adult health: Evaluating intervening mechanisms. Social Science & Medicine. 2016;156:114–24.

261. Hostinar CE, Sullivan RM, Gunnar MR. Psychobiological mechanisms underlying the social buffering of the hypothalamic–pituitary–adrenocortical axis: A review of animal models and human studies across development. Psychological Bulletin. 2014;140(1):256–82.

262. Lopez SA, Flagel SB. A proposed role for glucocorticoids in mediating dopamine-dependent cue-reward learning. Stress. 2020;1–41.

263. Berretta E, Guida E, Forni D, Provenzi L. Glucocorticoid receptor gene (NR3C1) methylation during the first 1000 days: A systematic review. Neurosci Biobehav Rev. 2021;125:493–502.

264. Bunea IM, Szentágotai-Tătar A, Miu AC. Early-life adversity and cortisol response to social stress: A meta-analysis. Transl Psychiat. 2017;7(12):1274.

265. Kuzminskaite E, Vinkers CH, Elzinga BM, Wardenaar KJ, Giltay EJ, Penninx BWJH. Childhood trauma and dysregulation of multiple biological stress systems in adulthood: Results from the Netherlands study of depression and anxiety. Psychoneuroendocrinology. 2020;104835.

266. McGowan PO, Szyf M. The epigenetics of social adversity in early life: Implications for mental health outcomes. Neurobiology of Disease. 2010;39(1):66–72.

267. Gershon NB, High PC. Epigenetics and child abuse: Modern-day Darwinism — The miraculous ability of the human genome to adapt, and then adapt again. Am J Medical Genetics Part C Seminars Medical Genetics. 2015;169(4):353–60.

268. Blacker CJ, Frye MA, Morava-Kozicz E, Kozicz T, Veldic M. A review of epigenetics of PTSD in comorbid psychiatric conditions. Genes (Basel). 2019;10(2):140.

269. Demetriou CA, Veldhoven K, Relton C, Stringhini S, Kyriacou K, Vineis P. Biological embedding of early-life exposures and disease risk in humans: A role for DNA methylation. European Journal of Clinical Investigation. 2015;45(3):303–32.

270. Dunn EC, Soare TW, Zhu Y, Simpkin AJ, Suderman MJ, Klengel T, et al. Sensitive periods for the effect of childhood adversity on DNA methylation: Results from a prospective, longitudinal study. Biological Psychiatry. 2019;85:838–49.

271. Szyf M. DNA methylation, behavior and early life adversity. Journal of Genetics and Genomics. 2013;40(7):331–8.

272. Lutz P-E, Turecki G. DNA methylation and childhood maltreatment: From animal models to human studies. Neuroscience. 2014;264:142–56.

273. McGowan PO, Sasaki A, D'Alessio AC, Dymov S, Labonté B, Szyf M, et al. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. Nature Neuroscience. 2009;12:342-348.

274. Turecki G, Meaney MJ. Effects of the social environment and stress on glucocorticoid receptor gene methylation: A systematic review. Biol Psychiat. 2016;79(2):87–96.

275. Parade SH, Huffhines L, Daniels TE, Stroud LR, Nugent NR, Tyrka AR. A systematic review of childhood maltreatment and DNA methylation: Candidate gene and epigenome-wide approaches. Transl Psychiat. 2021;11(1):134.

276. Chen D, Meng L, Pei F, Zheng Y, Leng J. A review of DNA methylation in depression. Journal of Clinical Neuroscience. 2017;43:39–46.

277. Bakusic J, Schaufeli W, Claes S, Godderis L. Stress, burnout and depression: A systematic review on DNA methylation mechanisms. Journal of Psychosomatic Research. 2017;92:34–44.

278. Kader F, Ghai M, Maharaj L. The effects of DNA methylation on human psychology. Behav Brain Res. 2018;346:47–65.

279. Brown A, Fiori LM, Turecki G. Bridging basic and clinical research in early life adversity, DNA methylation, and major depressive disorder. Frontiers Genetics. 2019;10:229.

280. Duffy KA, McLaughlin KA, Green PA. Early life adversity and health-risk behaviors: Proposed psychological and neural mechanisms. Ann Ny Acad Sci. 2018;1428(1):151–69.

281. Walsh ND, Dalgleish T, Lombardo MV, Dunn VJ, Harmelen A-LV, Ban M, et al. General and specific effects of early-life psychosocial adversities on adolescent grey matter volume. Neuroimage Clin. 2014;4:308–18.

282. Dam NTV, Rando K, Potenza MN, Tuit K, Sinha R. Childhood maltreatment, altered limbic neurobiology, and substance use relapse severity via trauma-specific reductions in limbic gray matter volume. JAMA Psychiat. 2014;71(8):917.

283. Mackes NK, Golm D, Sarkar S, Kumsta R, Rutter M, Fairchild G, et al. Early childhood deprivation is associated with alterations in adult brain structure despite subsequent environmental enrichment. Proc National Acad Sci. 2020;117(1):641–9.

284. Lund JI, Toombs E, Radford A, Boles K, Mushquash C. Adverse childhood experiences and executive function difficulties in children: A systematic review. Child Abuse Neglect. 2020;106:104485.

285. Johnson D, Policelli J, Li M, Dharamsi A, Hu Q, Sheridan MA, et al. Associations of early-life threat and deprivation with executive functioning in childhood and adolescence. JAMA Pediatr. 2021;175(11):e212511.

286. Calem M, Bromis K, McGuire P, Morgan C, Kempton MJ. Meta-analysis of associations between childhood adversity and hippocampus and amygdala volume in non-clinical and general population samples. Neuroimage Clin. 2017;14:471–9.

287. Lambert HK, Peverill M, Sambrook KA, Rosen ML, Sheridan MA, McLaughlin KA. Altered development of hippocampus-dependent associative learning following early-life adversity. Dev Cogn Neuros. 2019;38:100666.

288. Hanson JL, Nacewicz BM, Sutterer MJ, Cayo AA, Schaefer SM, Rudolph KD, et al. Behavioral problems after early life stress: Contributions of the hippocampus and amygdala. Biol Psychiat. 2015;77(4):314–23.

289. Whittle S, Dennison M, Vijayakumar N, Simmons JG, Yücel M, Lubman DI, et al. Childhood maltreatment and psychopathology affect brain development during adolescence. Journal of the American Academy of Child & Adolescent Psychiatry. 2013;52(9):940-952.e1.

290. Ousdal OT, Milde AM, Hafstad GS, Hodneland E, Dyb G, Craven AR, et al. The association of PTSD symptom severity with amygdala nuclei volumes in traumatized youths. Transl Psychiat. 2020;10(1):288.

291. Gard AM, Waller R, Shaw DS, Forbes EE, Hariri AR, Hyde LW. The long reach of early adversity: parenting, stress, and neural pathways to antisocial behavior in adulthood. Biological Psychiatry Cognitive Neurosci Neuroimaging. 2017;2(7):582–90.

292. Volkow ND, Wise RA, Baler R. The dopamine motive system: Implications for drug and food addiction. Nat Rev Neurosci. 2017;18(12):741–52.

293. Yang R, Yu Q, Owen CE, Aspe GI, Wiggins JL. Contributions of childhood abuse and neglect to reward neural substrates in adolescence. Neuroimage Clin. 2021;32:102832.

294. Elman I, Upadhyay J, Langleben DD, Albanese M, Becerra L, Borsook D. Reward and aversion processing in patients with post-traumatic stress disorder: Functional neuroimaging with visual and thermal stimuli. Translational Psychiatry. 2018;8(1):240.

295. Hoexter MQ, Fadel G, Felício AC, Calzavara MB, Batista IR, Reis MA, et al. Higher striatal dopamine transporter density in PTSD: an in vivo SPECT study with [99mTc]TRODAT-1. Psychopharmacology. 2012;224(2):337–45.

296. Novick AM, Levandowski ML, Laumann L, Philip NS, Price LH, Tyrka AR. The effects of early life stress on reward processing. Journal of Psychiatric Research. 2018;101:80–103.

297. Evans C, Cahill C. Neurobiology of opioid dependence in creating addiction vulnerability. F1000Res, 2016;5:F1000 Faculty Rev-1748.

298. Nagy SA, Kürtös Z, Németh N, Perlaki G, Csernela E, Lakner FE, et al. Childhood maltreatment results in altered deactivation of reward processing circuits in depressed patients: A functional magnetic resonance imaging study of a facial emotion recognition task. Neurobiology Stress. 2021;15:100399.

299. McCutcheon RA, Bloomfield MAP, Dahoun T, Mehta M, Howes OD. Chronic psychosocial stressors are associated with alterations in salience processing and corticostriatal connectivity. Schizophrenia Research. 2019;213:56-64.

300. Kamkar NH, Lewis DJ, Bos W van den, Morton JB. Ventral striatal activity links adversity and reward processing in children. Dev Cogn Neuros. 2017;26:20–7.

301. Egervari G, Ciccocioppo R, Jentsch DJ, Hurd YL. Shaping vulnerability to addiction – the contribution of behavior, neural circuits and molecular mechanisms. Neuroscience & Biobehavioral Reviews. 2018;85:117–25.

302. Jentsch DJ, Ashenhurst JR, Cervantes CM, Groman SM, James AS, Pennington ZT. Dissecting impulsivity and its relationships to drug addictions. Annals of the New York Academy of Sciences. 2017;1327(1):1–26.

303. Bosker WM, Neuner I, Shah JN. The role of impulsivity in psychostimulant- and stress-induced dopamine release: Review of human imaging studies. Neuroscience & Biobehavioral Reviews. 2017;78:82–90.

304. Kekic M, McClelland J, Bartholdy S, Chamali R, Campbell IC, Schmidt U. Bad things come to those who do not wait: Temporal discounting is associated with compulsive overeating, eating disorder psychopathology and food addiction. Frontiers Psychiatry. 2019;10:978.

305. Schüller CB, Kuhn J, Jessen F, Hu X. Neuronal correlates of delay discounting in healthy subjects and its implication for addiction: an ALE meta-analysis study. Am J Drug Alcohol Abus. 2019;1–16.

306. Kalisch R, Baker DG, Basten U, Boks MP, Bonanno GA, Brummelman E, et al. The resilience framework as a strategy to combat stress-related disorders. Nat Hum Behav. 2017;1(11):784–90.

307. King L, Jolicoeur-Martineau A, Laplante DP, Szekely E, Levitan R, Wazana A. Measuring resilience in children: A review of recent literature and recommendations for future research. Curr Opin Psychiatr. 2021;34(1):10-21.

308. Bonanno GA, Mancini AD. The human capacity to thrive in the face of potential trauma. Pediatrics. 2008;121(2):369–75.

309. Rutter M. Resilience in the face of adversity. Brit J Psychiat. 1985;147(6):598–611.

310. Rutter M. Psychosocial resilience and protective mechanisms. Am J Orthopsychiat. 1987;57(3):316–31.

311. Rutter M. Resilience: Some conceptual considerations. J Adolescent Health. 1993;14(8):626–31.

312. Rutter M. Psychosocial adversity: Risk, resilience & recovery. South Afr J Child Adolesc Ment Heal. 1995;7(2):75–88.

313. Rutter M. Implications of resilience concepts for scientific understanding. Ann Ny Acad Sci. 2006;1094(1):1–12.

314. Rutter M. Resilience: Causal pathways and social ecology. In: Ungar M, editor. The Social Ecology of Resilience, A Handbook of Theory and Practice. Springer Science+Business Media; 2011. p. 33–42.

315. Rutter M. Annual Research Review: Resilience - clinical implications. J Child Psychol Psyc. 2013;54(4):474–87.

316. Ungar M, Theron L. Resilience and mental health: How multisystemic processes contribute to positive outcomes. Lancet Psychiatry. 2020;7(5):441-448.

317. Wilson PA, Meyer IH, Antebi-Gruszka N, Boone MR, Cook SH, Cherenack EM. Profiles of resilience and psychosocial outcomes among young Black gay and bisexual men. Am J Commun Psychol. 2016;57(1–2):144–57.

318. Collishaw S, Pickles A, Messer J, Rutter M, Shearer C, Maughan B. Resilience to adult psychopathology following childhood maltreatment: Evidence from a community sample. Child Abuse Neglect. 2007;31(3):211–29.

319. Robles A, Gjelsvik A, Hirway P, Vivier PM, High P. Adverse childhood experiences and protective factors with school engagement. Pediatrics. 2019;144(2):e20182945.

320. Yu Z, Wang L, Chen W, Perrin N, Gross D. Childhood adversity and mental health among Chinese young adults: The protective role of resilience. J Adv Nurs. 2021;77(12):4793-4804.

321. Ward M, Turner N, Briggs R, O'Halloran AM, Kenny RA. Resilience does not mediate the association between adverse childhood experiences and later life depression. Findings from The Irish Longitudinal Study on Ageing (TILDA). J Affect Disorders. 2020;277:901–7.

322. Fritz J, Fried EI, Goodyer IM, Wilkinson PO, Harmelen A-L van. A network model of resilience factors for adolescents with and without exposure to childhood adversity. Sci Rep. 2018;8(1):15774.

323. Heard-Garris N, Davis MM, Szilagyi M, Kan K. Childhood adversity and parent perceptions of child resilience. BMC Pediatrics. 2018;18(1):204.

324. Nishimi K, Choi KW, Davis KA, Powers A, Bradley B, Dunn EC. Features of childhood maltreatment and resilience capacity in adulthood: Results from a large community-based sample. J Trauma Stress. 2020;33(5):665–76.

325. Woods-Jaeger BA, Cho B, Sexton CC, Slagel L, Goggin K. Promoting resilience: Breaking the intergenerational cycle of adverse childhood experiences. Health Education & Behavior. 2018;45(5):772–80.

326. Bellis MA, Hughes K, Ford K, Hardcastle KA, Sharp CA, Wood S, et al. Adverse childhood experiences and sources of childhood resilience: A retrospective study of their combined relationships with child health and educational attendance. BMC Public Health. 2018;18(1):792.

327. Bethell C, Jones J, Gombojav N, Linkenbach J, Sege R. Positive childhood experiences and adult mental and relational health in a statewide sample. JAMA Pediatr. 2019;173(11):e193007.

328. Radcliff E, Crouch E, Strompolis M. Rural–urban differences in exposure to adverse childhood experiences among South Carolina adults. Rural and Remote Health. 2018;18(1):4434.

329. Crandall A, Broadbent E, Stanfill M, Magnusson BM, Novilla MLB, Hanson CL, et al. The influence of adverse and advantageous childhood experiences during adolescence on young adult health. Child Abuse Neglect. 2020;108:104644.

330. Powell KM, Rahm-Knigge RL, Conner BT. Resilience protective factors checklist (RPFC): Buffering childhood adversity and promoting positive outcomes. Psychol Rep. 2020;33294120950288.

331. Gouin J-P, Caldwell W, Woods R, Malarkey WB. Resilience resources moderate the association of adverse childhood experiences with adulthood inflammation. Ann Behav Med. 2017;51(5):782–6.

332. Finnell JE, Wood SK. Putative inflammatory sensitive mechanisms underlying risk or resilience to social stress. Frontiers in Behavioral Neuroscience. 2018;12:240.

333. Leal ASM, Silvers JA. Neurobiological markers of resilience to early life adversity during adolescence. Biological Psychiatry Cognitive Neurosci Neuroimaging. 2021;6(2):238-247.

334. Holz NE, Tost H, Meyer-Lindenberg A. Resilience and the brain: A key role for regulatory circuits linked to social stress and support. Mol Psychiatr. 2019;25(2):379–96.

335. al'Absi M. The influence of stress and early life adversity on addiction: Psychobiological mechanisms of risk and resilience. Int Rev Neurobiol. 2020;152:71–100.

336. Cobb S. Social support as a moderator of life stress. Psychosom Med. 1976;38(5):300–14.

337. Hupcey JE. Social support: assessing conceptual coherence. Qualitative Health Research. 1998;8(3).

338. Hawe P, Shiell A. Social capital and health promotion: A review. Soc Sci Med. 2000;51(6):871–85.

339. Kawachi I, Berkman L. Social cohesion, social capital, and health. In: Berkman LF, Kawachi I, Glymour MM, editors. Social Epidemiology (2 ed.). Oxford University Press. 2014.

340. Umberson D, Crosnoe R, Reczek C. Social relationships and health behavior across life course. Annual Review of Sociology. 2010;36:139–57.

341. Schneider FD, Cook CAL, Salas J, Scherrer J, Cleveland IN, Burge SK, et al. Childhood trauma, social networks, and the mental health of adult survivors. J Interpers Violence. 2020;35(5–6):1492–514.

342. Molarius A, Berglund K, Eriksson C, Eriksson HG, Lindén-Boström M, Nordström E, et al. Mental health symptoms in relation to socio-economic conditions and lifestyle factors – a population-based study in Sweden. BMC Public Health. 2009;9(1):302.

343. Beutel ME, Tibubos AN, Klein EM, Schmutzer G, Reiner I, Kocalevent R-D, et al. Childhood adversities and distress - The role of resilience in a representative sample. PLoS ONE. 2017;12(3):e0173826.

344. Bellis MA, Hardcastle K, Ford K, Hughes K, Ashton K, Quigg Z, et al. Does continuous trusted adult support in childhood impart life-course resilience against adverse childhood experiences - a retrospective study on adult health-harming behaviours and mental well-being. BMC Psychiatry. 2017;17(1):110.

345. Heinze JE, Kruger DJ, Reischl TM, Cupal S, Zimmerman MA. Relationships among disease, social support, and perceived health: A lifespan approach. Am J Commun Psychol. 2015;56(3–4):268–79.

346. Fuller-Thomson E, Lacombe-Duncan A, Goodman D, Fallon B, Brennenstuhl S. From surviving to thriving: Factors associated with complete mental health among childhood sexual abuse survivors. Soc Psych Psych Epid. 2020;55(6):735–44.

347. Watt T, Kim S, Ceballos N, Norton C. People who need people: The relationship between adverse childhood experiences and mental health among college students. J Am Coll Heal J Ach. 2020;1–9.

348. Su Y, D'Arcy C, Meng X. Social support and positive coping skills as mediators buffering the impact of childhood maltreatment on psychological distress and positive mental health in adulthood: Analysis of a national population-based sample. Am J Epidemiol. 2020;189(5):394-402.

349. Cosco TD, Hardy R, Howe LD, Richards M. Early-life adversity, later-life mental health, and resilience resources: A longitudinal population-based birth cohort analysis. Int Psychogeriatr. 2019;31(9):1249–58.

350. Brinker J, Cheruvu VK. Social and emotional support as a protective factor against current depression among individuals with adverse childhood experiences. Preventive Medicine Reports. 2017;5:127–33.

351. Jones TM, Nurius P, Song C, Fleming CM. Modeling life course pathways from adverse childhood experiences to adult mental health. Child Abuse & Neglect. 2018;80:32–40.

352. Roohafza HR, Afshar H, Keshteli AH, Mohammadi N, Feizi A, Taslimi M, et al. What's the role of perceived social support and coping styles in depression and anxiety? J Res Medical Sci. 2014;19(10):944–9.

353. Dour HJ, Wiley JF, Roy-Byrne P, Stein MB, Sullivan G, Sherbourne CD, et al. Perceived social support mediates anxiety and depressive symptom changes following primary care intervention. Depress Anxiety. 2014;31(5):436–42.

354. Salinas-Miranda AA, Salemi JL, King LM, Baldwin JA, Berry E, Austin DA, et al. Adverse childhood experiences and health-related quality of life in adulthood: Revelations from a community needs assessment. Health and Quality of Life Outcomes. 2015;13(1):123.

355. Logan-Greene P, Green S, Nurius PS, Longhi D. Distinct contributions of adverse childhood experiences and resilience resources: A cohort analysis of adult physical and mental health. Soc Work Health Care. 2014;53(8):776–97.

356. Chang L-Y, Wu C-C, Yen L-L, Chang H-Y. The effects of family dysfunction trajectories during childhood and early adolescence on sleep quality during late adolescence: Resilience as a mediator. Soc Sci Med. 2019;222:162–70.

357. Noll JG, Trickett PK, Susman EJ, Putnam FW. Sleep disturbances and childhood sexual abuse. J Pediatr Psychol. 2006;31(5):469–80.

358. Higgs E, Drolet CE, Belicki K. The impact of childhood sexual abuse on sleep in adulthood. Child Abuse Neglect. 2020;107:104567.

359. Sullivan K, Rochani H, Huang L-T, Donley DK, Zhang J. Adverse childhood experiences affect sleep duration for up to 50 years later. Sleep. 2019;42(7).

360. Chapman DP, Wheaton AG, Anda RF, Croft JB, Edwards VJ, Liu Y, et al. Adverse childhood experiences and sleep disturbances in adults. Sleep Med. 2011;12(8):773–9.

361. Nielsen T. The stress acceleration hypothesis of nightmares. Front Neurol. 2017;8:201.

362. Nielsen T, Carr M, Picard-Deland C, Marquis L-P, Saint-Onge K, Blanchette-Carrière C, et al. Early childhood adversity associations with nightmare severity and sleep spindles. Sleep Med. 2019;56:57–65.

363. Wright LA, Roberts NP, Barawi K, Simon N, Zammit S, McElroy E, et al. Disturbed sleep connects symptoms of posttraumatic stress disorder and somatization: A network analysis approach. J Trauma Stress. 2021;34(2):375-383.

364. Poon CYM, Knight BG. Impact of childhood parental abuse and neglect on sleep problems in old age. J Gerontol B Sci Soc Sci. 2011;66(3):307–10.

365. Perlis ML, Giles DE, Buysse DJ, Thase ME, Tu X, Kupfer DJ. Which depressive symptoms are related to which sleep electroencephalographic variables? Biol Psychiat. 1997;42(10):904–13.

366. Peterson MJ, Benca RM. Sleep in mood disorders. Psychiat Clin N Am. 2006;29(4):1009–32.

367. Baglioni C, Battagliese G, Feige B, Spiegelhalder K, Nissen C, Voderholzer U, et al. Insomnia as a predictor of depression: A meta-analytic evaluation of longitudinal epidemiological studies. J Affect Disorders. 2011;135(1–3):10–9.

368. Conway MA, Cabrera OA, Clarke-Walper K, Dretsch MN, Holzinger JB, Riviere LA, et al. Sleep disturbance mediates the association of adverse childhood experiences with mental health symptoms and functional impairment in US soldiers. J Sleep Res. 2020;29(4):e13026.

369. Rojo-Wissar DM, Davidson RD, Beck CJ, Kobayashi US, VanBlargan AC, Haynes PL. Sleep quality and perceived health in college undergraduates with adverse childhood experiences. Sleep Heal. 2019;5(2):187–92.

370. Dong L, Xie Y, Zou X. Association between sleep duration and depression in US adults: A cross-sectional study. J Affect Disorders. 2022;296:183–8.

371. Wong MM, Puttler LI, Nigg JT, Zucker RA. Sleep and behavioral control in earlier life predicted resilience in young adulthood: A prospective study of children of alcoholics and controls. Addict Behav. 2018;82:65–71.

372. Schnarrs PW, Stone AL, Salcido R, Baldwin A, Nemeroff C. Differences in adverse childhood experiences (ACEs) and quality of physical and mental health between transgender and cisgender sexual minorities. J Psychiatr Res. 2019;119:1-6.

373. Zou C, Andersen JP. Comparing the rates of early childhood victimization across sexual orientations: Heterosexual, lesbian, gay, bisexual, and mostly heterosexual. PLoS One. 2015;10(10):e0139198.

374. Clements-Nolle K, Lensch T, Baxa A, Gay C, Larson S, Yang W. Sexual identity, adverse childhood experiences, and suicidal behaviors. Journal of Adolescent Health. 2018;62(2):198–204.

375. Mauck DE, Gebrezgi MT, Sheehan DM, Fennie KP, Ibañez GE, Fenkl EA, et al. Population-based methods for estimating the number of men who have sex with men: A systematic review. Sex Health. 2019;16(6):527–38.

376. Andersen JP, Blosnich J. Disparities in adverse childhood experiences among sexual minority and heterosexual adults: Results from a multi-state probability-based sample. PLoS One. 2013;8(1):e54691.

377. Andersen JP, Zou C, Blosnich J. Multiple early victimization experiences as a pathway to explain physical health disparities among sexual minority and heterosexual individuals. Soc Sci Med. 2015;133:111–9.

378. Austin A, Herrick H, Proescholdbell S. Adverse childhood experiences related to poor adult health among lesbian, gay, and bisexual individuals. Am J Public Health. 2016;106(2):314–20.

379. McCabe SE, Hughes TL, West BT, Evans-Polce RJ, Veliz PT, Dickinson K, et al. Sexual orientation, adverse childhood experiences, and comorbid DSM-5 substance use and mental health disorders. J Clin Psychiatry. 2020;81(6).

380. Giano Z, Wheeler DL, Hubach RD. The frequencies and disparities of adverse childhood experiences in the U.S. BMC Public Health. 2020;20(1):1327.

381. Evans-Polce RJ, Kcomt L, Veliz PT, Boyd CJ, McCabe SE. Alcohol, tobacco, and comorbid psychiatric disorders and associations with sexual identity and stress-related correlates. Am J Psychiat. 2020;177(11):1073–81.

382. Brown MJ, Masho SW, Perera RA, Mezuk B, Cohen SA. Sex and sexual orientation disparities in adverse childhood experiences and early age at sexual debut in the United States: Results from a nationally representative sample. Child Abuse Neglect. 2015;46:89–102.

383. Bertolino DF, Sanchez TH, Zlotorzynska M, Sullivan PS. Adverse childhood experiences and sexual health outcomes and risk behaviors among a nationwide sample of men who have sex with men. Child Abuse Neglect. 2020;107:104627.

384. Schrock JM, McDade TW, Carrico AW, D'Aquila RT, Mustanski B. Traumatic events and mental health: The amplifying effects of pre-trauma systemic inflammation. Brain Behav Immun. 2021;98:173–84.

385. Harawa NT, Brewer R, Buckman V, Ramani S, Khanna A, Fujimoto K, et al. HIV, Sexually transmitted infection, and substance use continuum of care interventions among criminal justice–involved black men who have sex with men: A systematic review. Am J Public Health. 2018;108(S4):e1–9.

386. Stevens R, Icard L, Jemmott JB, O'Leary A, Rutledge S, Hsu J, et al. Risky trade: individual and neighborhood-level socio-demographics associated with transactional sex among urban African American MSM. J Urban Heal. 2017;94(5):676–82.

387. Glover DA, Williams JK, Kisler KA. Using novel methods to examine stress among HIV-positive African American men who have sex with men and women. J Behav Med. 2012;36(3):283–94.

388. Ports KA, Lee RD, Raiford J, Spikes P, Manago C, Wheeler DP. Adverse childhood experiences and health and wellness outcomes among Black men who have sex with men. J Urban Heal. 2017;94(3):375–83.

389. Downing JM, Rosenthal E. Prevalence of social determinants of health among sexual minority women and men in 2017. Am J Prev Med. 2020;59(1):118–22.

390. Krause KD, Kapadia F, Ompad DC, D'Avanzo PA, Duncan DT, Halkitis PN. Early life psychosocial stressors and housing instability among young sexual minority men: The p18 cohort study. J Urban Heal. 2016;93(3):511–25.

391. Singh S, Song R, Johnson A, McCray E, Hall IH. HIV Incidence, prevalence, and undiagnosed infections in U.S. men who have sex with men. Ann Intern Med. 2018;168(10):685.

392. Lloyd S, Operario D. HIV Risk among men who have sex with men who have experienced childhood sexual abuse: Systematic review and meta-analysis. AIDS Educ Prev. 2012;24(3):228–41.

393. Derry HM, Johnston CD, Brennan-Ing M, Karpiak S, Burchett CO, Zhu Y-S, et al. Childhood sexual abuse history amplifies the link between disease burden and inflammation among older adults with HIV. Brain Behav Immun - Heal. 2021;17:100342.

394. Wang S-C, Maher B. Substance use disorder, intravenous injection, and HIV infection: A review. Cell Transplantation. 2019;096368971987838.

395. Rajasingham R, Mimiaga MJ, White JM, Pinkston MM, Baden RP, Mitty JA. A systematic review of behavioral and treatment outcome studies among HIV-infected men who have sex with men who abuse crystal methamphetamine. AIDS Patient Care St. 2012;26(1):36–52.

396. Quinn B, Gorbach PM, Okafor CN, Heinzerling KG, Shoptaw S. Investigating possible syndemic relationships between structural and drug use factors, sexual HIV transmission and viral load among men of colour who have sex with men in Los Angeles County. Drug Alcohol Rev. 2020;39(2):116–27.

397. Fang L, Chuang D-M, Lee Y. Adverse childhood experiences, gender, and HIV risk behaviors: Results from a population-based sample. Prev Medicine Reports. 2016;4:113–20.

398. Grummitt LR, Kreski NT, Kim SG, Platt J, Keyes KM, McLaughlin KA. Association of childhood adversity with morbidity and mortality in US adults. JAMA Pediatr. 2021;175(12).

399. Barboza GE. Latent classes and cumulative impacts of adverse childhood experiences. Child Maltreatment. 2018;23(2):111–25.

400. Oldenburg CE, Perez-Brumer AG, Reisner SL, Mimiaga MJ. Transactional sex and the HIV epidemic among men who have sex with men (MSM): Results from a systematic review and meta-analysis. AIDS Behav. 2015;19(12):2177–83.

401. Javanbakht M, Ragsdale A, Shoptaw S, Gorbach PM. Transactional sex among men who have sex with men: Differences by substance use and HIV status. J Urban Heal. 2019;96(3):429–41.

402. Brown MJ, Masho SW, Perera RA, Mezuk B, Pugsley RA, Cohen SA. Sex disparities in adverse childhood experiences and HIV/STIs: Mediation of psychopathology and sexual behaviors. AIDS Behav. 2017;21(6):1550–66.

403. Safren SA, Reisner SL, Herrick A, Mimiaga MJ, Stall RD. Mental health and HIV risk in men who have sex with men. J Acquir Immune Defic Syndromes. 2010;55:S74–7.

404. Chandler CJ, Bukowski LA, Matthews DD, Hawk ME, Markovic N, Egan JE, et al. Examining the impact of a psychosocial syndemic on past six-month HIV screening behavior of

Black men who have sex with men in the United States: Results from the POWER study. AIDS Behav. 2020;24(2):428–36.

405. Tsai AC, Burns BFO. Syndemics of psychosocial problems and HIV risk: A systematic review of empirical tests of the disease interaction concept. Soc Sci Med. 2015;139:26–35.

406. Berg MB, Mimiaga MJ, Safren SA. Mental health concerns of HIV-infected gay and bisexual men seeking mental health services: An observational study. AIDS Patient Care STDS. 2004;18(11):635–43.

407. Giano Z, Hubach RD. Adverse childhood experiences and mental health: Comparing the link in rural and urban men who have sex with men. J Affect Disorders. 2019;259:362–9.

408. Sahota PC, Cakouros BE, Russell R, Hassler M, Blank MB, Barg FK. Causal pathways between severe mental illness and behaviors related to HIV: Patient perspectives. Community Ment Hlt J. 2020;56(2):338–47.

409. Fu H, Feng T, Wang T, Wu X, Cai Y, Yang T. Reported prevalence of depression or depressive symptoms among men who have sex with men in China, 2004-2018: A systematic review and meta-analysis. J Affect Disorders. 2020;277:192–203.

410. Wei D, Wang X, You X, Luo X, Hao C, Gu J, et al. Prevalence of depression, anxiety and suicide among men who have sex with men in China: A systematic review and meta-analysis. Epidemiol Psych Sci. 2020;29:e136.

411. Young-Wolff KC, Sarovar V, Sterling SA, Leibowitz A, McCaw B, Hare CB, et al. Adverse childhood experiences, mental health, substance use, and HIV-related outcomes among persons with HIV. AIDS Care. 2019;31(10):1241–9.

412. Hart TA, Noor SW, Vernon JRG, Kidwai A, Roberts K, Myers T, et al. Childhood maltreatment, bullying victimization, and psychological distress among gay and bisexual men. J Sex Res. 2017;55(4–5):1–13.

413. Bourne A, Weatherburn P. Substance use among men who have sex with men: Patterns, motivations, impacts and intervention development need. Sex Transm Infect. 2017;93(5):342.

414. Downing MJ, Benoit E, Brown D, Coe L, Hirshfield S, Pansulla L, et al. Early sexual experiences, mental health, and risk behavior among Black Non-Hispanic and Hispanic / Latino men who have sex with men (MSM). J Child Sex Abus. 2019;29(1):1–21.

415. Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the United States: Results from the 2019 National Survey on Drug Use and Health [Internet]. Rockville, MD: Center for Behavioral Health Statistics and Quality: Substance Abuse and Mental Health Services Administration; 2020. Report No.: HHS Publication NO: PEP20-07-01-001, NSDUH Series H-55. Available from: https://www.samhsa.gov/data/

416. Fletcher JB, Swendeman D, Reback CJ. Mental health and substance use disorder comorbidity among methamphetamine-using men who have sex with men. J Psychoactive Drugs. 2018;50(3):1–8.

417. Javanbakht M, Shoptaw S, Ragsdale A, Brookmeyer R, Bolan R, Gorbach PM. Depressive symptoms and substance use: Changes overtime among a cohort of HIV-positive and HIV-negative MSM. Drug Alcohol Depen. 2019;107770.

418. Feldman MB, Kepler KL, Irvine MK, Thomas JA. Associations between drug use patterns and viral load suppression among HIV-positive individuals who use support services in New York City. Drug Alcohol Depen. 2019;197:15–21.

419. Lafortune D, Blais M, Miller G, Dion L, Lalonde F, Dargis L. Psychological and interpersonal factors associated with sexualized drug use among men who have sex with men: A mixed-methods systematic review. Arch Sex Behav. 2020;1–34.

420. Tomkins A, George R, Kliner M. Sexualised drug taking among men who have sex with men: A systematic review. Perspect Public Heal. 2019;139(1):23–33.

421. Ding C, Wang T, Chen X, Li J, Wang W, Huang D, et al. Association of adverse childhood experience and attention deficit hyperactivity disorder with depressive symptoms among men who have sex with men in China: Moderated mediation effect of resilience. BMC Public Health. 2019;19(1):1706.

422. Takada S, Gorbach P, Brookmeyer R, Shoptaw S. Associations of social capital resources and experiences of homophobia with HIV transmission risk behavior and HIV care continuum among men who have sex with men in Los Angeles. AIDS Care. 2020;1–12.

423. Bonett S, Meanley S, Stevens R, Brawner B, Bauermeister J. The role of networks in racial disparities in HIV incidence among men who have sex with men in the United States. AIDS Behav. 2020;24(10):2781–96.

424. Coulter RWS, Egan JE, Kinsky S, Friedman MR, Eckstrand KL, Frankeberger J, et al. Mental health, drug, and violence interventions for sexual/gender minorities: A systematic review. Pediatrics. 2019;144(3):e20183367.

425. Ben-Shlomo Y, Cooper R, Kuh D. The last two decades of life course epidemiology, and its relevance for research on ageing. International Journal of Epidemiology. 2016;45(4):973–88.

426. Halfon N, Larson K, Lu M, Tullis E, Russ S. Lifecourse health development: Past, present and future. Maternal and Child Health Journal. 2013;18(2):344–65.

427. Ben-Shlomo Y, Kuh D. A life course approach to chronic disease epidemiology: Conceptual models, empirical challenges and interdisciplinary perspectives. International Journal of Epidemiology. 2002;31(2):285-293.

428. Lu MC, Verbiest S, Dominguez TP. Life course theory: an overview. In: Verbiest, S, editor. Moving Life Course Theory Into Action: Making Change Happen. Washington, DC: APHA Press; 2018. p. 1–21.

429. Liu S, Jones RN, Glymour MM. Implications of lifecourse epidemiology for research on determinants of adult disease. Public Health Reviews. 2010;32(2):489–511.

430. Kuh D, Ben-Shlomo Y, Lynch J, Hallqvist J, Power C. Life course epidemiology. Journal of Epidemiology and Community Health. 2003;57(10):778–83.

431. Lynch J, Smith G. A life course approach to chronic disease epidemiology. Annual Review of Public Health. 2005;26(1):1–35.

432. Dannefer D. Cumulative advantage/disadvantage and the life course: Cross-fertilizing age and social science theory. Journals Gerontology Ser B. 2003;58(6):S327–37.

433. Seabrook JA, Avison WR. Socioeconomic status and cumulative disadvantage processes across the life course: Implications for health outcomes. Canadian Review of Sociology. 2012;49(1):50–68.

434. Ferraro KF, Shippee TP. Aging and cumulative inequality: How does inequality get under the skin? Gerontologist. 2009;49(3):333–43.

435. Ferraro KF, Shippee TP, Schafer MH. Cumulative inequality theory for research on aging and the life course. In: Bengston VL, Gans D, Pulney NM, Silverstein M, editors. Handbook of Theories of Aging. Springer Publishing Company; 2009. p. 413–33.

436. Willson AE, Shuey KM, Elder JH. Cumulative advantage processes as mechanisms of inequality in life course health. American Journal of Sociology. 2007;112(6):1886–924.

437. Poulton R, Caspi A, Milne BJ, Thomson MW, Taylor A, Sears MR, et al. Association between children's experience of socioeconomic disadvantage and adult health: A life-course study. The Lancet. 2002;360(9346):1640–5.

438. Hayward MD, Gorman BK. The long arm of childhood: The influence of early-life social conditions on men's mortality. Demography. 2004;41(1):87–107.

439. Engel GL. The need for a new medical model: A challenge for biomedicine. Science. 1977;196(4286).

440. Engel G. The clinical application of the biopsychosocial model. American Journal of Psychiatry. 1980;137(5):535–44.

441. Novack D, Cameron O, Epel E, Ader R, Waldstein S, Levenstein S, et al. Psychosomatic medicine: the scientific foundation of the biopsychosocial model. Academic Psychiatry. 2007;31(5):388–401.

442. Smith RC. The biopsychosocial revolution. Journal of General Internal Medicine. 2002;17(4):309–10.

443. Hatala AR. The status of the "biopsychosocial" model in health psychology: Towards an integrated approach and a critique of cultural conceptions. Open Journal of Medical Psychology. 2012;2012(04):51–62.

444. Lehman BJ, David DM, Gruber JA. Rethinking the biopsychosocial model of health: Understanding health as a dynamic system. Social and Personality Psychology Compass. 2017;11(8):e12328.

445. Lane RD. Is it possible to bridge the biopsychosocial and biomedical models? BioPsychoSocial Medicine. 2014;8(1):1–3.

446. Pilgrim D. The biopsychosocial model in health research: Its strengths and limitations for critical realists. Journal of Critical Realism. 2015;14(2):164–80.

447. McLaren N. A critical review of the biopsychosocial model. Australian and New Zealand Journal of Psychiatry. 1998;32(1):86–92.

448. Tripathi A, Das A, Kar SK. Biopsychosocial model in contemporary psychiatry: Current validity and future prospects. Indian J Psychological Medicine. 2019;41(6):582–5.

449. Álvarez A, Pagani M, Meucci P. The clinical application of the biopsychosocial model in mental health: A research critique. American Journal of Physical Medicine & Rehabilitation. 2012;91(13):S173.

450. Benning T. Limitations of the biopsychosocial model in psychiatry. Advances in Medical Education and Practice. 2015;6:347–52.

451. Wade DT, Halligan PW. The biopsychosocial model of illness: A model whose time has come. Clinical Rehabilitation. 2017;31(8):995–1004.

452. Karunamuni N, Imayama I, Goonetilleke D. Pathways to well-being: Untangling the causal relationships among biopsychosocial variables. Soc Sci Medicine. 2020;112846.

453. Doom JR. Mapping future directions to test biopsychosocial pathways to health and well-being. Soc Sci Medicine. 2020;258:113083.

454. Link BG, Phelan J. Social conditions as fundamental causes of disease. Journal of Health and Social Behavior. 1995;Spec No:80-94.

455. Cockerham WC, Hamby BW, Oates GR. The social determinants of chronic disease. American Journal of Preventive Medicine. 2017;52(1):S5–12.

456. Nandi A, Glymour MM, Subramanian SV. Association among socioeconomic status, health behaviors, and all-cause mortality in the United States. Epidemiology. 2014;25(2):170–7.

457. Seeman TE, Crimmins E, Huang M-H, Singer B, Bucur A, Gruenewald T, et al. Cumulative biological risk and socio-economic differences in mortality: MacArthur Studies of Successful Aging. Soc Sci Med. 2004;58(10):1985–97.

458. Upchurch DM, Stein J, Greendale GA, Chyu L, Tseng C-H, Huang M-H, et al. A longitudinal investigation of race, socioeconomic status, and psychosocial mediators of allostatic load in midlife women: Findings from the study of women's health across the nation. Psychosomatic Medicine. 2015;77(4):402.

459. Chyu L, Upchurch DM. Racial and ethnic patterns of allostatic load among adult women in the United States: Findings from the National Health and Nutrition Examination Survey 1999–2004. Journal of Women's Health. 2011;20(4):575–83.

460. Rainisch BK, Upchurch DM. Sociodemographic correlates of allostatic load among a national sample of adolescents: Findings from the National Health and Nutrition Examination Survey, 1999–2008. Journal of Adolescent Health. 2013;53(4):506–11.

461. Echeverría S, Diez-Roux AV, Shea S, Borrell LN, Jackson S. Associations of neighborhood problems and neighborhood social cohesion with mental health and health behaviors: The Multi-Ethnic Study of Atherosclerosis. Health Place. 2008;14(4):853–65.

462. Rios R, Aiken LS, Zautra AJ. Neighborhood contexts and the mediating role of neighborhood social cohesion on health and psychological distress among Hispanic and Non-Hispanic residents. Annals of Behavioral Medicine. 2012;43(1):50–61.

463. Phelan JC, Link BG, Tehranifar P. Social conditions as fundamental causes of health inequalities: Theory, evidence, and policy implications. Journal of Health and Social Behavior. 2010;51 Suppl:S28–40.

464. Woolf SH, Schoomaker H. Life expectancy and mortality rates in the United States, 1959-2017. JAMA. 2019;322(20):1996.

465. Krieger N. Epidemiology and the web of causation: Has anyone seen the spider? Social Science & Medicine. 1994;39(7):887-903.

466. Herzog JI, Schmahl C. Adverse childhood experiences and the consequences on neurobiological, psychosocial, and somatic conditions across the lifespan. Frontiers in Psychiatry. 2018;9:420.

467. Gabard-Durnam LJ, McLaughlin KA. Do sensitive periods exist for exposure to adversity? Biological Psychiatry. 2019;85(10):789–91.

468. Dillon DG, Holmes AJ, Birk JL, Brooks N, Lyons-Ruth K, Pizzagalli DA. Childhood adversity is associated with left basal ganglia dysfunction during reward anticipation in adulthood. Biol Psychiat. 2009;66(3):206–13.

469. Osadchiy V, Mayer EA, Bhatt R, Labus JS, Gao L, Kilpatrick LA, et al. History of early life adversity is associated with increased food addiction and sex-specific alterations in reward network connectivity in obesity. Obes Sci Pract. 2019;5(5):416–36.

470. Wiss DA, Brewerton TD. Adverse childhood experiences and adult obesity: A systematic review of plausible mechanisms and meta-analysis of cross-sectional studies. Physiol Behav. 2020;112964.

471. Wiss DA, Avena N, Gold M. Food addiction and psychosocial adversity: biological embedding, contextual factors, and public health implications. Nutrients. 2020;12(11):3521.

472. Poole JC, Kim HS, Dobson KS, Hodgins DC. Adverse childhood experiences and disordered gambling: Assessing the mediating role of emotion dysregulation. Journal of Gambling Studies. 2017;33(4):1187–200.

473. Norman RE, Byambaa M, De R, Butchart A, Scott J, Vos T. The long-term health consequences of child physical abuse, emotional abuse, and neglect: A systematic review and meta-analysis. PLoS Med. 2012;9(11):e1001349.

474. Wolff KT, Cuevas C, Intravia J, Baglivio MT, Epps N. The effects of neighborhood context on exposure to adverse childhood experiences (ACE) among adolescents involved in the juvenile justice system: Latent classes and contextual effects. Journal of Youth and Adolescence. 2018;47(11):2279–300.

475. Ferraro KF, Schafer MH, Wilkinson LR. Childhood disadvantage and health problems in middle and later life. Am Sociol Rev. 2016;81(1):107–33.

476. Lerner RM. The place of learning within the human development system: A developmental contextual perspective. Hum Dev. 1995;38(6):361–6.

477. Krieger N. Ecosocial theory of disease distribution: embodying societal & ecological context. In: Krieger N, editor. Epidemiology and People's Health: Theory and Context. Oxford University Press; 2011.

478. Narayan AJ, Lieberman AF, Masten AS. Intergenerational transmission and prevention of adverse childhood experiences (ACEs). Clin Psychol Rev. 2021;85:101997.

479. Parolin M, Simonelli A, Mapelli D, Sacco M, Cristofalo P. Parental substance abuse as an early traumatic event. preliminary findings on neuropsychological and personality functioning in young drug addicts exposed to drugs early. Front Psychol. 2016;7:887.

480. Bonab BG, Koohsar AAH. Relation between quality of attachment and anxiety in delinquent adolescents. Procedia - Soc Behav Sci. 2011;30:959–62.

481. Henry SK, Grant MM, Cropsey KL. Determining the optimal clinical cutoff on the CES-D for depression in a community corrections sample. J Affect Disorders. 2018;234:270–5.

482. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: The GAD-7. Arch Intern Med. 2006;166(10):1092.

483. Zimet GD, Dahlem NW, Zimet SG, Farley GK. The multidimensional scale of perceived social support. J Pers Assess. 1988;52(1):30–41.

484. Ogunbajo A, Iwuagwu S, Williams R, Biello KB, Kahler CW, Sandfort TGM, et al. Validation of depressive symptoms, social support, and minority stress scales among gay, bisexual, and other men who have with men (GBMSM) in Nigeria, Africa: A mixed methods approach. BMC Public Health. 2020;20(1):1023.

485. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. Psychiat Res. 1989;28(2):193–213.

486. Millar BM, Parsons JT, Redline S, Duncan DT. What's sleep got to do with it?: Sleep health and sexual risk-taking among men who have sex with men. AIDS Behav. 2019;23(3):572–9.

487. Evans EA, Grella CE, Washington DL, Upchurch DM. Gender and race/ethnic differences in the persistence of alcohol, drug, and poly-substance use disorders. Drug and Alcohol Dependence. 2017;174:128–36.

488. Dunlop DD, Song J, Lyons JS, Manheim LM, Chang RW. Racial/ethnic differences in rates of depression among preretirement adults. Am J Public Health. 2003;93(11):1945–52.

489. Asnaani A, Richey JA, Dimaite R, Hinton DE, Hofmann SG. A cross-ethnic comparison of lifetime prevalence rates of anxiety disorders. J Nerv Ment Dis. 2010;198(8):551–5.

490. Sonu S, Post S, Feinglass J. Adverse childhood experiences and the onset of chronic disease in young adulthood. Preventive Medicine. 2019;123:163-170.

491. Haugland SH, Dovran A, Albaek AU, Sivertsen B. Adverse childhood experiences among 28,047 Norwegian adults from a general population. Frontiers Public Heal. 2021;9:711344.

492. Poudel A, Gautam S. Age of onset of substance use and psychosocial problems among individuals with substance use disorders. BMC Psychiatry. 2017;17(1):10.

493. Stordal E, Mykletun A, Dahl AA. The association between age and depression in the general population: A multivariate examination. Acta Psychiat Scand. 2003;107(2):132–41.

494. Lenze EJ, Wetherell JL. A lifespan view of anxiety disorders. Dialogues Clin Neurosci. 2011;13(4):381–99.

495. Patrick ME, Wightman P, Schoeni RF, Schulenberg JE. Socioeconomic status and substance use among young adults: A comparison across constructs and drugs. J Stud Alcohol Drugs. 2012;73(5):772–82.

496. Sareen J, Afifi TO, McMillan KA, Asmundson GJG. Relationship between household income and mental disorders: Findings from a population-based longitudinal study. Arch Gen Psychiat. 2011;68(4):419–27.

497. Galea S, Ahern J, Tracy M, Rudenstine S, Vlahov D. Education inequality and use of cigarettes, alcohol, and marijuana. Drug Alcohol Depen. 2007;90:S4–15.

498. Bjelland I, Krokstad S, Mykletun A, Dahl AA, Tell GS, Tambs K. Does a higher educational level protect against anxiety and depression? The HUNT study. Soc Sci Med. 2008;66(6):1334–45.

499. Barry D, Petry N. Associations between body mass index and substance use disorders differ by gender: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. Addictive Behaviors. 2009;34(1).

500. Luppino FS, Wit LM de, Bouvy PF, Stijnen T, Cuijpers P, Penninx BWJH, et al. Overweight, obesity, and depression: A systematic review and meta-analysis of longitudinal studies. Arch Gen Psychiat. 2010;67(3):220–9.

501. Zhao G, Ford ES, Dhingra S, Li C, Strine TW, Mokdad AH. Depression and anxiety among US adults: Associations with body mass index. Int J Obesity. 2009;33(2):257–66.

502. NCD Risk Factor Collaboration. Trends in adult body-mass index in 200 countries from 1975 to 2014: A pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet. 2016;387(10026):1377–96.

503. Stinson FS, Grant BF, Dawson DA, Ruan WJ, Huang B, Saha T. Comorbidity between DSM-IV alcohol and specific drug use disorders in the United States: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. Drug Alcohol Depen. 2005;80(1):105–16.

504. Kushner MG, Abrams K, Borchardt C. The relationship between anxiety disorders and alcohol use disorders: A review of major perspectives and findings. Clin Psychol Rev. 2000;20(2):149–71.

505. Yeoman K, Safranek T, Buss B, Cadwell BL, Mannino D. Adverse childhood experiences and adult smoking, Nebraska, 2011. Prev Chronic Dis. 2013;10:E159.

506. Weinberger AH, Platt J, Esan H, Galea S, Erlich D, Goodwin RD. Cigarette smoking is associated with increased risk of substance use disorder relapse: A nationally representative, prospective longitudinal investigation. J Clin Psychiatry. 2017;78(02):e152–60.

507. McKenzie M, Olsson CA, Jorm AF, Romaniuk H, Patton GC. Association of adolescent symptoms of depression and anxiety with daily smoking and nicotine dependence in young adulthood: Findings from a 10-year longitudinal study. Addiction. 2010;105(9):1652–9.

508. Moylan S, Jacka FN, Pasco JA, Berk M. How cigarette smoking may increase the risk of anxiety symptoms and anxiety disorders: A critical review of biological pathways. Brain Behav. 2013;3(3):302–26.

509. Tsuyuki K, Pitpitan EV, Levi-Minzi MA, Urada LA, Kurtz SP, Stockman JK, et al. Substance use disorders, violence, mental health, and HIV: Differentiating a syndemic factor by gender and sexuality. AIDS Behav. 2017;21(8):2270–82.

510. StataCorp. Stata Statistical Software. Release 17. College Station, TX: StataCorp LLC. 2021.

511. VanderWeele TJ, Knol MJ. A tutorial on interaction. Epidemiological Methods. 2014;1(3):33–72.

512. Brant R. Assessing proportionality in the proportional odds model for ordinal logistic regression. Biometrics. 1990;46(4):1171.

513. Epasinghe N, Sooriyarachchi R. A goodness of fit test for the multilevel proportional odds model. Commun Statistics - Simul Comput. 2016;46(7):5610-5626.

514. Wiss DA, Javanbakht M, Li MJ, Prelip M, Bolan R, Shoptaw S, et al. Food insecurity partially mediates the association between drug use and depressive symptoms among men who have sex with men in Los Angeles, California. Public Health Nutr. 2021;1–26.

515. McHugh KR, Votaw VR, Sugarman DE, Greenfield SF. Sex and gender differences in substance use disorders. Clinical Psychology Review. 2018;66:12-23.

516. Rogers CJ, Forster M, Grigsby TJ, Albers L, Morales C, Unger JB. The impact of childhood trauma on substance use trajectories from adolescence to adulthood: Findings from a longitudinal Hispanic cohort study. Child Abuse Neglect. 2021;120:105200.

517. Zarei K, Xu G, Zimmerman B, Giannotti M, Strathearn L. Adverse childhood experiences predict common neurodevelopmental and behavioral health conditions among U.S. Children. Children. 2021;8(9):761.

518. Salk RH, Hyde JS, Abramson LY. Gender differences in depression in representative national samples: Meta-analyses of diagnoses and symptoms. Psychol Bull. 2017;143(8):783–822.

519. Wilson-Genderson M, Heid AR, Cartwright F, Pruchno R. Adverse childhood experiences, adult trauma, and depressive symptom trajectories. Aging Ment Health. 2021;1–9.

520. Lee C-H, Giuliani F. The role of inflammation in depression and fatigue. Front Immunol. 2019;10:1696.

521. Berk M, Williams LJ, Jacka FN, O'Neil A, Pasco JA, Moylan S, et al. So depression is an inflammatory disease, but where does the inflammation come from? BMC Med. 2013;11(1):200–200.

522. Miller AH. Beyond depression: The expanding role of inflammation in psychiatric disorders. World Psychiatry. 2020;19(1):108–9.

523. Fuller-Thomson E, Agbeyaka S. A trio of risk factors for childhood sexual abuse: Investigating exposure to parental domestic violence, parental addiction, and parental mental illness as correlates of childhood sexual abuse. Soc Work. 2020;65(3):266-277.

524. Downing NR, Akinlotan M, Thornhill CW. The impact of childhood sexual abuse and adverse childhood experiences on adult health related quality of life. Child Abuse Neglect. 2021;120:105181.

525. Easton SD. Disclosure of child sexual abuse among adult male survivors. Clin Soc Work J. 2013;41(4):344–55.

526. O'Leary PJ, Barber J. Gender differences in silencing following childhood sexual abuse. J Child Sex Abus. 2008;17(2):133–43.

527. Ackard DM, Neumark-Sztainer D. Multiple sexual victimizations among adolescent boys and girls: Prevalence and associations with eating behaviors and psychological health. J Child Sex Abus. 2002;12(1):17–37.

528. Widom CS, Czaja SJ, Dutton MA. Childhood victimization and lifetime revictimization. Child Abuse Neglect. 2008;32(8):785–96.

529. Trickett PK, Noll JG, Putnam FW. The impact of sexual abuse on female development: Lessons from a multigenerational, longitudinal research study. Dev Psychopathol. 2011;23(2):453–76.

530. Pirkola S, Isometsä E, Aro H, Kestilä L, Hämäläinen J, Veijola J, et al. Childhood adversities as risk factors for adult mental disorders. Soc Psych Psych Epid. 2005;40(10):769–77.

531. Li M, D'Arcy C, Meng X. Maltreatment in childhood substantially increases the risk of adult depression and anxiety in prospective cohort studies: Systematic review, meta-analysis, and proportional attributable fractions. Psychol Med. 2016;46(4):717–30.

532. Petruccelli K, Davis J, Berman T. Adverse childhood experiences and associated health outcomes: A systematic review and meta-analysis. Child Abuse Neglect. 2019;97:104127.

533. Xu W, Zheng L, Xu Y, Zheng Y. Internalized homophobia, mental health, sexual behaviors, and outness of gay/bisexual men from Southwest China. Int J Equity Health. 2017;16(1):36.

534. Whittle S, Simmons JG, Hendriksma S, Vijayakumar N, Byrne ML, Dennison M, et al. Childhood maltreatment, psychopathology, and the development of hippocampal subregions during adolescence. Brain Behav. 2017;7(2):e00607.

535. Gilmer TP, Center K, Casteel D, Choi K, Innes-Gomberg D, Lansing AE. Developing trauma resilient communities through community capacity-building. BMC Public Health. 2021;21(1):1681.

536. Mehta D, Kelly AB, Laurens KR, Haslam D, Williams KE, Walsh K, et al. Child maltreatment and long-term physical and mental health outcomes: An exploration of biopsychosocial determinants and implications for prevention. Child Psychiat Hum D. 2021;1–15.

537. Hambrick EP, Seedat S, Perry BD. Editorial: How the timing, nature, and duration of relationally positive experiences influence outcomes in children with adverse childhood experiences. Front Behav Neurosci. 2021;15:755959.

538. Curtis MJ, Bond RA, Spina D, Ahluwalia A, Alexander SPA, Giembycz MA, et al. Experimental design and analysis and their reporting: New guidance for publication in BJP. Brit J Pharmacol. 2015;172(14):3461–71.

539. Shonkoff JP, Slopen N, Williams DR. Early childhood adversity, toxic stress, and the impacts of racism on the foundations of health. Annu Rev Publ Health. 2021;42(1):1–20.

540. Loe IM, Froehlich TE, Edrees HH, Spinks-Franklin A. Racism as an adverse childhood experience: An interactive workshop to train pediatricians to address racism in clinical care. J Dev Behav Pediatrics. 2021;42(6):502-511.

541. Crowley DM, Connell CM, Noll J, Green L, Scott T, Giray C. Legislating to prevent adverse childhood experiences: Growth and opportunities for evidence-based policymaking and prevention. Prev Sci. 2021;1–11.

542. Li F, Luo S, Mu W, Li Y, Ye L, Zheng X, et al. Effects of sources of social support and resilience on the mental health of different age groups during the COVID-19 pandemic. BMC Psychiatry. 2021;21(1):16.

543. Szkody E, Stearns M, Stanhope L, McKinney C. Stress-buffering role of social support during COVID-19. Fam Process. 2021;60(3):1002-1015.

544. Grey I, Arora T, Thomas J, Saneh A, Tohme P, Abi-Habib R. The role of perceived social support on depression and sleep during the COVID-19 pandemic. Psychiat Res. 2020;293:113452.

545. Bareket-Bojmel L, Shahar G, Abu-Kaf S, Margalit M. Perceived social support, loneliness, and hope during the COVID-19 pandemic: Testing a mediating model in the UK, USA, and Israel. Brit J Clin Psychol. 2021;60(2):133–48.

546. O'Doherty DCM, Chitty KM, Saddiqui S, Bennett MR, Lagopoulos J. A systematic review and meta-analysis of magnetic resonance imaging measurement of structural volumes in posttraumatic stress disorder. Psychiatry Res Neuroimaging. 2015;232(1):1–33.

547. Howell KH, Miller-Graff LE, Martinez-Torteya C, Napier TR, Carney JR. Charting a course towards resilience following adverse childhood experiences: Addressing intergenerational trauma via strengths-based intervention. Children. 2021;8(10):844.