

ABSTRACT

Title of Dissertation: THE INTERGENERATIONAL
TRANSMISSION AND IMPACTS OF
ADVERSE CHILDHOOD EXPERIENCES

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Evidence that adverse childhood experiences (ACEs) are associated with a wide range of adverse health and behavioral outcomes, including poor behavioral outcomes, and increased substance use, has been expanded to demonstrate that ACEs may be a determinant in adverse health and behavioral outcomes across generations as well. To disentangle the intergenerational impacts of ACEs on select health and behavioral outcomes and inform future intergenerational research and practice, three separate studies were conducted as part of this investigation. The first is a systematic review assessing whether ACEs predict earlier age of initiation differently depending on substance, conducted to inform timing of ACE screening and substance use intervention within generations. Given evidence to suggest that maternal ACEs predict related behavioral outcomes, the association between ACEs and earlier age of substance use may extend across generations as well. Informed by the first study, the second study in this investigation assesses the association between maternal ACEs and

offspring age of alcohol initiation. Because offspring concordant for higher intergenerational ACE exposure may be most susceptible to the intergenerational impacts of adversity, this study also assesses whether the association between maternal ACEs and offspring age of alcohol initiation is different depending on offspring ACE exposure. The third study of this investigation assesses the association between maternal ACEs and internalizing and externalizing behavior. Importantly, the well-established intergenerational continuity of adversity was considered conceptually and methodologically for the latter two studies. If there is a direct association of maternal ACEs on offspring outcomes independent of offspring ACEs, then ACE screening and intervention efforts should be expanded to include and consider maternal ACEs in addition to offspring ACEs. Therefore, the controlled direct effect of maternal ACEs, not through offspring ACEs, was estimated.

Findings from the first study suggest that while ACEs are associated with earlier age of alcohol, nicotine, marijuana, and opioid initiation, often in a dose-dependent manner, ACEs may predict earlier initiation of alcohol and nicotine relative to other substances assessed. Three or more ACEs were associated with initiation of alcohol across multiple studies, with effect sizes (OR) ranging from 1.9 (95% CI: 1.7, 2.1) to 6.2 (95% CI: 4.6, 8.3). Among the youngest samples included in this review (aged 9-10), ACEs were positively associated with use of alcohol at the time of interview OR=1.3 (95% CI: 1.1, 1.5). Studies that assessed the association between ACEs and nicotine used thresholds between 15-17 to define early initiation and reported a range of effect sizes (OR) from 1.6 (95% CI: 1.2, 2.2) after exposure to more than one ACE to 5.2 (95% CI: 2.9, 9.3) after exposure to more than two ACEs.

Exposure to two or more ACEs was associated with initiating vaping before age 11 (OR=3.4 (95% CI: 2.2, 5.4)).

While not rising to statistical significance ($p < 0.05$), findings from the second study suggest there is a small inverse relationship between maternal ACEs and offspring age of alcohol initiation among the full sample. However, among offspring exposed to >2 ACEs themselves, 2 maternal ACEs are associated with $\beta = -1.4$ (95% CI: -2.7, -0.1) and >2 maternal ACEs are associated with $\beta = -2.1$ (95% CI: -3.8, -0.5) earlier age of alcohol initiation. These findings suggest that offspring exposed to high levels of intergenerational ACE exposure are at greatest risk for early alcohol initiation.

Findings from the third study suggest that maternal ACEs are associated with offspring internalizing and externalizing behavior in a dose-dependent manner, independent of offspring ACE exposure. Specifically, 1, 2, and >2 maternal ACEs were independently associated with a 1.8 (95% CI: 0.9, 2.8), 2.1 (95% CI: 0.7, 3.4), and 2.7 (95% CI: 1.0, 4.4) increase in internalizing score and a 1.8 (95% CI: 0.8, 2.7), 3.1 (95% CI: 1.7, 4.4), and 3.3 (95% CI: 1.4, 5.1) increase in externalizing score, respectively.

Taken together, findings from this investigation suggest that universal ACE screening in pediatric settings, particularly prior to onset of puberty, may identify youth for service provision prior to substance initiation and that maternal ACEs should be screened for and considered in addition to offspring ACE exposure to inform interventions related to adolescent substance use and internalizing and externalizing behavior. To that end, the prenatal period may be an opportune time for

maternal ACE screening. Conclusions from these investigations may apply to the impact of maternal ACEs on other relevant offspring outcomes across the life course. Future directions for research, including assessment of relevant biological and psychosocial mechanisms, and potential moderators of identified associations are discussed.

THE INTERGENERATIONAL TRANSMISSION AND IMPACTS OF
ADVERSE CHILDHOOD EXPERIENCES

by

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Table of Contents

Acknowledgements.....	ii
Table of Contents.....	iii
List of Tables	v
List of Figures	vi
List of Abbreviations	vii
Chapter 1: Introduction.....	1
Overview.....	1
Substance Use Behaviors.....	3
Internalizing and Externalizing Behaviors.....	5
ACE Measurement Considerations.....	6
ACE Screening.....	7
ACEs and Adverse Health Outcomes Across Generations.....	8
Biological Pathways.....	9
Psychosocial Pathways	11
Methodological Considerations	13
Intergenerational ACE Concordance vs. Discordance.....	14
Chapter 2: Adverse Childhood Experiences and Age of Substance Initiation: A Systematic Review.....	16
Introduction.....	16
Methods.....	19
Information Sources and Search Strategy.....	19
Eligibility Criteria	20
Selection and Data Collection.....	20
Results.....	21
Study Selection	21
Study Characteristics	22
Risk of Bias in Studies.....	31
ACEs and Age of Initiation Measurement Across Studies.....	31
Substance-Specific Associations Between ACEs and Age of Initiation	35
Alcohol.....	35
Marijuana	36
Nicotine.....	36
Opiates	37
Illicit Substance Use	38
Moderators	38
Discussion.....	39
Limitations	46
Conclusion	47
Chapter 3: Intergenerational Adverse Childhood Experiences and Offspring Age of Alcohol Initiation.....	49
Introduction.....	49
Methods.....	53
Study Sample	53
Measures	54

Analysis.....	56
Results.....	59
Discussion.....	60
Limitations	63
Conclusion	66
Chapter 4: Disentangling the Impacts of Intergenerational Adversity on Offspring Internalizing and Externalizing Behavioral Outcomes	72
Introduction.....	72
Epidemiological Evidence	74
Methods.....	77
Study Sample	77
Measures	78
Analysis.....	82
Results.....	84
Discussion.....	86
Limitations	92
Conclusion	94
Chapter 5: Summary and Conclusions.....	101
Summary	101
Conclusions.....	105
Implications for Public Health Interventions and Practice	105
Future Directions for Research	108
Appendices.....	111
Appendix A. PRISMA Guidelines Checklist.....	111
Appendix B. Coding of Variables Included in Studies that Used NLSY Data.....	112
Appendix C. HOME-SF Items.....	113
Appendix D. ACE Battery Items	116
Appendix E. Behavior Problem Index Items	117
Appendix F. CESD Short Form Items	118

List of Tables

Table 1. Review of Epidemiologic Studies of ACEs and Age of Substance Initiation 1990-December 2023	24
Table 2. G2 characteristics and associations with mean age of alcohol initiation, NLSYCYA (n=3,068)	67
Table 3. Adjusted estimates of the association between ACEs and offspring age of alcohol initiation, NLSYCYA (n=3,068).....	68
Table 4. Controlled direct effect of maternal ACEs on offspring age of alcohol initiation stratified by offspring ACE exposure, NLSYCYA n=3,068	68
Table 5a. Characteristics and associations with mean internalizing scores, NLSYCYA (n=5,445)	96
Table 5b. Characteristics and associations with mean externalizing scores, NLSYCYA (n=5,445).....	97
Table 6. Adjusted estimates of the association between ACEs and offspring internalizing behavior scores, NLSYCYA (n=5,445)	98
Table 7. Adjusted estimates of the association between maternal ACEs and offspring externalizing behavior scores, NLSYCYA (n=5,445)	98
Table 8. Adjusted estimates of the association between maternal ACEs and offspring internalizing behavior quartiles, NLSYCYA (n=5,445)	98
Table 9. Adjusted estimates of the association between ACEs and offspring externalizing behavior quartiles, NLSYCYA (n=5,445)	99

List of Figures

Figure 1. PRISMA flow diagram for study review process	22
Figure 2. Directed Acyclic Graphs illustrating the potential mechanisms underlying maternal (G1) ACEs and offspring (G2) age of alcohol initiation via G2 ACEs.....	69
Figure 3. Directed Acyclic Graph illustrating the potential mechanisms underlying maternal (G1) ACEs and offspring (G2) age of alcohol initiation via G2 ACEs and/or confounders of the association between G2 ACEs and G2 age of alcohol initiation.....	70
Figure 4. Estimate of the association between maternal ACEs and offspring age of alcohol initiation stratified by offspring ACE exposure.....	71
Figure 5. Directed Acyclic Graphs illustrating the potential mechanisms underlying maternal (G1) ACEs and offspring (G2) behavior via G2 ACEs	99
Figure 6. Directed Acyclic Graph illustrating the potential mechanisms underlying maternal (G1) ACEs and offspring (G2) behavior via G2 ACEs and/or confounders of the association between G2 ACEs and G2 behavior.....	100

List of Abbreviations

ACEs Adverse childhood experiences

SUD Substance use disorder

AUD Alcohol use disorder

G1 Generation 1 (mothers)

G2 Generation 2 (offspring)

NLSY National Longitudinal Survey of Youth

NLSYCYA National Longitudinal Survey of Youth Child and Young Adult

Chapter 1: Introduction

Overview

Adverse childhood experiences (ACEs) are traumatic events or experiences that occur in childhood (aged 0-17) and are broadly categorized as experiencing maltreatment including violence, abuse, or neglect; and/or household dysfunction, including witnessing violence in the home or community, having a family member attempt or die by suicide, or growing up in a household with substance use problems, mental health problems, or instability due to parental separation or incarceration (CDC, 2022). Approximately 61% of adults report experiencing at least one ACE, while almost 17% report experiencing four or more ACEs, with the latter group at greatest risk of long-term negative impacts across the life course, including substance use disorder (SUD) and poor behavioral outcomes (CDC, 2022). There is also increasing evidence that maternal ACEs may predict these health and behavioral outcomes across generations in a similar dose-dependent manner (Zhang et al., 2022).

Evidence that ACEs predict earlier initiation of substance use and that early initiation predicts SUD in adolescence and adulthood (Dawson et al., 2008; Liang & Chikritzhs, 2015; Lynskey et al., 2003; Richmond-Rakerd et al., 2015) suggests that age of initiation may be a particularly important and relatively unexplored mediator of the relationship between ACEs and SUD across the life course. Preventing initiation in the first place may disrupt the pathway from ACEs to SUD. In the general population, adolescents engage in alcohol and marijuana use prior to nicotine and opioid use (CDC,

2022; Hoots, 2023), a pattern that may be even more prevalent among those using substances to cope with adversity. Therefore, it is possible that associations between ACEs and early age of initiation may be substance specific. Identifying substance-specific associations between ACEs and age of initiation may inform the most appropriate and effective timing of interventions aimed at preventing initiation to disrupt the sequelae from ACE exposure to progression to SUD.

Beyond the well-known association between ACEs and adverse health and behavioral outcomes across the life course, the intergenerational impact of ACEs, in which maternal ACEs are associated with offspring outcomes, is supported by two lines of evidence: 1) substantial evidence supports the intergenerational continuity of adversity, meaning that maternal ACE exposure often predicts offspring ACE exposure (Madigan et al., 2019; Narayan et al., 2017; Schofield et al., 2013; Smith et al., 2021; Negriff, 2020) and 2) a large and growing body of evidence supports an association between maternal ACEs and adverse offspring health and behavioral outcomes (Zhang et al, 2022). Given that offspring ACEs independently predict many of the same adverse health and behavioral outcomes within generations that have been identified across generations (e.g., internalizing, externalizing behavior) (Appleyard et al., 2005; Baglivio et al., 2014; Flouri & Panourgia, 2011), it is possible that the association between ACEs and early age of alcohol initiation within generations may extend across generations as well.

It is also possible that the mechanism behind the impact of intergenerational ACEs is actually through offspring ACEs. Elucidating the mechanism behind the intergenerational impact of ACEs is critical to informing ACE screening and

intervention efforts. If there is a direct association between maternal ACEs on offspring outcomes independent of offspring ACEs, then ACE screening and intervention efforts should be expanded to include and consider maternal ACEs in addition to offspring ACEs.

This holistic investigation is comprised of three separate studies that, taken together, inform ACE screening and intervention within and across generations.

Specifically, I:

- 1) Systematically reviewed existing literature to determine whether associations between ACEs and age of initiation differ depending on substance.
- 2) Determined the controlled direct effect of maternal ACEs on offspring internalizing and externalizing behavior not through offspring ACEs.
- 3) a) Determined the controlled direct effect of maternal ACEs on offspring age of alcohol initiation not through offspring ACEs
b) Assessed whether this association is different depending on offspring ACE exposure.

ACEs & Adverse Health Outcomes Within Generations

Substance Use Behaviors

Existing evidence supports an association between total number of ACEs and substance use frequency and severity in adolescence (Affi et al., 2020; Gomez et al., 2017, Kelly et al., 2023). Given evidence that age of substance use initiation predicts substance use disorder (SUD) (Dawson et al., 2008; Liang & Chikritzhs, 2015; Lynskey

et al., 2003; Richmond-Rakerd et al., 2015), age of initiation may mediate the relationship between ACEs and SUD across the life course.

Among a sample of 14–17-year-old participants, ACE exposure was associated with all substance use indicators assessed, including lifetime and past-30-day use of cigarettes and electronic vapor products, as well as alcohol and cannabis use in the last 12 months and last 30 days (Affi et al., 2020). In a sample of high schoolers, total number of ACEs were strongly associated with past-month alcohol and cannabis use frequency (Kelly et al., 2023). In a sample of youth in Singapore, total number of ACEs was associated with increased risk of drug-related SUDs in a dose-dependent manner (Gomez et al., 2017).

The most cited explanation for the association between ACEs and earlier initiation of substance use is that youth use substances as a coping mechanism to avoid negative feelings arising from childhood adversity (Agnew & Brezina, 1992; Grummitt et al., 2021; Teixeira et al., 2017). Other hypotheses emphasize the underlying neurophysiology; chronic exposure to stressors disturbs cortisol regulation, alters DNA methylation involved in the regulation of gene expression, and impacts several neurological structures, including a reduction in neurogenesis and synaptic activity (Somaini et al., 2011). Functional and structural changes resulting from chronic exposure to stressors are associated with behavioral, cognitive, and mood disorders that can increase the likelihood of maladaptive coping behaviors like earlier initiation of substance use (Enoch, 2011; Tervo-Clemmens et al., 2020; Walters & Kosten, 2019).

There is evidence that, in the general population marijuana and alcohol use may precede cigarette and opioid use (Fiellin et al., 2013; CDC, 2022; Hoots, 2023). It is

possible that adolescents using substances to cope with adversity may be even more likely to use certain substances earlier than others. Therefore, strength of associations between ACEs and early initiation of substance use may depend on the substance assessed. If ACEs are more strongly associated with earlier age of initiation of certain substances compared to others, that is the average age of initiation is substantively earlier for certain substances, that can have important implications for prevention and intervention efforts. Identifying substance-specific associations between ACEs and age of initiation can thus inform the age at which specific interventions should be implemented to maximize benefits as current adolescent substance use interventions may be implemented too late, particularly for the large swath of the population exposed to ACEs (Felitti et al., 1998). While assessing current and lifetime use, as well as severity of use, is important to establish the association between ACEs and substance use in adolescence, these outcomes do not inform the most appropriate and effective timing of interventions aimed at preventing initiation in the first place—an important precursor to progression to SUD. Understanding the association between ACEs and age of initiation, specifically, can fill this gap and inform public health interventions aimed at reducing adolescent and adult SUD.

Internalizing and Externalizing Behaviors

There is also substantial evidence suggesting that ACEs are associated with child and adolescent behavioral problems, including externalizing behaviors like hyperactivity and conduct problems (Appleyard, Egeland, van Dulmen, & Alan Sroufe, 2005; Baglivio et al., 2014) and internalizing behaviors (Flouri & Panourgia, 2011), such as antisocial behavior, social withdrawal, anxiety, or depression, which may

increase risk of adolescent suicide (Borges, Angst, Nock, Ruscio, & Kessler, 2008; Goodday, Shuldiner, Bondy, & Rhodes, 2019). These associations are often dose-dependent, with higher cumulative ACE exposure predicting worse behavioral outcomes. The same physiological adaptations resulting from ACE exposure that are implicated in adolescent substance use behaviors are implicated in adolescent mental health outcomes as well. These include disrupted cortisol regulation, altered DNA methylation involved in the regulation of gene expression, and impacts on several neurological structures, including a reduction in neurogenesis and synaptic activity (Somaini et al., 2011), which are associated with behavioral, cognitive, and mood disorders (Enoch, 2011; Tervo-Clemmens et al., 2020; Walters & Kosten, 2019).

ACE Measurement Considerations

Importantly, underlying pathophysiology implicated in both substance use and behavioral outcomes varies as a function of both cumulative experience (i.e., number) and type of adversities. While certainly not exhaustive, ACEs that fall under maltreatment are generally considered to be experiences of violence, abuse, or neglect, whereas individual ACEs that fall under household dysfunction often include growing up in a household with someone with an alcohol problem, substance problem or mental illness, or instability due to parental separation or incarceration. ACE measures are generally operationalized as cumulative, encompassing the total number of ACEs one is exposed to, or individual measures of adversity—each subject to limitations. Cumulative ACE scores cannot provide potentially valuable information regarding how specific adversities are related to the outcome of interest. For example, experience of abuse may be more strongly associated with earlier substance initiation as a way to

cope with maltreatment than experience of parental separation due to divorce. Further, cumulative ACE scores may represent different constructs depending on the adversities included, which can vary greatly from study to study. While ACE batteries are often modeled on the original ACE study (Felitti et al., 1998), there is no universally agreed upon ACE battery and the number and type of early life adversities varies greatly (Holden, Gower, & Chmielewski, 2020). There are also calls to include a broader range of early life adversities in ACE batteries, including those related to systemic or structural oppression, immigration, and community dysfunction (Helton et al., 2022). Yet, most ACE batteries include more proximal household-level adversities. It is possible that early life adversity is underestimated when using traditional ACE batteries, particularly for marginalized youth.

In spite of limitations, the use of cumulative ACE scores that include measures of both maltreatment and household dysfunction acknowledges the high level of co-occurrence of different childhood adversities (Felitti et al., 1998; CDC, 2023) and allows for the assessment of dose-dependent associations that have been reported in similar literature (Grummitt et al., 2021; Shin, McDonald, & Conley, 2018) in a way that studies that assess individual ACEs cannot. Therefore, cumulative ACE exposure is the independent variable of interest in this investigation.

ACE Screening

Given the well-established association between ACEs and adverse health and behavioral outcomes across the life course, many public health scholars, and health practitioners, including the American Academy of Pediatrics, have called for the routine screening of early life adversity (AAP, 2012). While evidence suggests that

ACE screening is generally well-received by patients (Flanagan et al., 2018), there are a number of barriers to routine prenatal ACE screening, including lack of time and confidence by healthcare providers, lack of training on ACEs, lack of professional guidelines for screening, lack of privacy, lack of information to patients about ACEs ahead of screening, and lack of cultural competency (Tran et al., 2022). Enhanced funding for training could reduce many of these barriers. California, for example, has successfully launched the first statewide initiative (ACEs Aware) to screen for ACEs, including in the prenatal period (Watson, Mateo, & Vetter, n.d.). Beyond the intended benefit of informing prenatal care utilization and birth outcomes (Van Roessel, Racine, Dobson, Killam, & Madigan, 2021), prenatal ACE screening may also be used to inform pediatric care of the offspring given increasing evidence of the intergenerational transmission of early adversity.

ACEs and Adverse Health Outcomes Across Generations

There is growing evidence that cumulative maternal ACE exposure predicts a host of adverse offspring outcomes, including poor birth outcomes, infant developmental outcomes, and behavioral outcomes, with the largest body of literature assessing the intergenerational impact of ACEs on internalizing and externalizing behaviors (Zhang et al., 2022). Given evidence to suggest that pathways between ACEs and behavioral outcomes like internalizing and externalizing behaviors are similar to those involved in the association between ACEs and substance use outcomes within generations (Enoch, 2011; Tervo-Clemmens et al., 2020; Walters & Kosten, 2019), it is possible that the association between ACEs and earlier age of alcohol initiation

extends to the intergenerational level as well. However, no study to date has assessed whether maternal ACEs predict earlier age of alcohol initiation.

Additionally, the pathways behind intergenerational transmission of adversity, even among the established associations between maternal ACEs and elevated offspring internalizing and externalizing behavior, remain unclear. There is evidence to suggest that biological and postnatal environmental mechanisms may be plausibly implicated in these associations (Zhang et al., 2023). Disentangling potential mechanisms is imperative to fully understand and address the intergenerational transmission of ACEs.

Biological Pathways

The HPA axis is comprised of endocrine pathways involving the hypothalamus, pituitary gland, and adrenal gland and is responsible for stress response and regulation (Sheng et al., 2021). There is evidence that past experiences of stress (i.e., ACEs), may leave a “signature” of stress within the HPA axis, both within individuals who directly experience them directly and intergenerationally (Thomas-Argyriou et al., 2021). Chronic exposure to stress both in-utero and postnatally is associated with dysregulated HPA axis functioning, including increased cortisol, alteration in gene expression, and a reduction in neurogenesis and synaptic activity (Somaini et al., 2011). These adaptations to HPA axis functioning are associated with a host of adverse outcomes including behavioral, cognitive, and mood disorders (Enoch, 2011; Tervo-Clemmens et al., 2020; Walters & Kosten, 2019).

In pregnancy, maternal cortisol and placental corticotropin-releasing hormone (CRH) are key stress hormones that may program fetal HPA axis functioning, with

excess hormones in the presence of chronic stress predicting dysregulated fetal HPA functioning (Howland, Sandman, and Glynn, 2019). Prenatal exposure to stress is associated with increased reactivity to stress at later stages of development, decreased hippocampal volume, and epigenetic changes in the offspring (Acosta et al., 2019; Loman & Gunnar, 2016; McEwen, 2019; Lupien et al., 2009) that appear to modulate the association of prenatal stress and adverse child behavioral outcomes. As the association between in-utero stressors and dysregulated fetal HPA functioning is well-established, it is hypothesized that the association between maternal ACEs and adverse offspring outcomes may be due to similar mechanisms, though evidence is much more limited. Maternal early life adversity has been demonstrated to be associated with increased placental CRH toward the end of gestation (Moog et al., 2016) and increased cortisol concentrations after wakening among pregnant individuals even after accounting for proximal stressors (Thomas et al., 2018), suggesting that the impact of maternal ACEs may persist across the life course, including during pregnancy. These persistent changes to the maternal HPA axis may then influence fetal development and offspring HPA functioning in ways similar to what is seen in response to acute stress and may play a key role in the intergenerational transmission of adversity. However, future studies that longitudinally assess the sequelae from maternal ACEs to functional and structural adaptations to the fetal HPA axis to offspring behavior, and that adequately address timing of stress exposure (distally experienced stressors vs. proximal stressors) are needed to support fetal programming as a pathway of intergenerational transmission of adversity.

Psychosocial Pathways

Mechanisms linking maternal ACEs to offspring outcomes may also be explained by postnatal environmental factors. Several studies have found that the associations between maternal ACEs and offspring outcomes are mediated by maternal mental health and parenting characteristics (Cooke et al., 2019; Dennis et al., 2019; Khoury et al., 2022; Yoon et al., 2019; Zhang, Mersky, & Lee, 2023; Hanetz-Gamliel & Dollberg, 2022). Importantly, many of these exposures directly translate to the offspring's cumulative ACE exposure. Consistent with the life course health and development framework, the intergenerational continuity of ACEs is well-documented among the mother-child dyad (Madigan et al., 2019; Narayan et al., 2017; Schofield, Lee, & Merrick, 2013; Smith et al., 2021; Negriff, 2020), which may in part explain the intergenerational continuity of outcomes like substance use disorder and behavioral disorders.

There is evidence that early life stress impacts brain development, epigenetics, and physiological reactivity, leading to maladaptive endocrine and neurophysiological responses, poor developmental and cognitive outcomes, as well as difficulty with emotional regulation (Loman & Gunnar, 2010; McEwen, 2019; Lupien et al., 2009)—all of which are strongly associated with both increased risk of adult adversity and poor parenting practices (Madigan et al., 2019). Consistent with family systems and attachment theories, evidence suggests that maltreated individuals are more likely than others to maltreat their own children. There is also evidence that mothers exposed to ACEs are more likely to experience mental health issues, domestic violence, substance use disorder, and socioeconomic insecurity in adulthood, which can translate to the

offspring's cumulative experience of childhood adversity via household dysfunction (Narayan et al., 2017; Schofield, Lee, & Merrick, 2013; Smith et al., 2021; Negri, 2020). Given what is known about the intergenerational continuity of ACE exposure and that ACEs independently predict a host of adverse health and behavioral outcomes within generations, it is possible that associations between maternal ACEs and offspring outcomes are actually via offspring ACE exposure or factors that predict the intergenerational continuity of adversity like poor parenting practices, intergenerational poverty and/or low socioeconomic status, or other psychosocial risk factors such as young motherhood, single parent households, and poor mental and physical health (Schoon & Melis, 2019). Interventions aimed at supporting mothers, including parenting interventions, reducing psychosocial stressors, etc. may be particularly salient to reducing the intergenerational transmission of adversity.

Determining the direct association between maternal ACEs on offspring outcomes not through offspring ACEs is imperative to inform ACE screening and intervention efforts, regardless of whether the direct association is via biological or psychosocial risk factors. If the mechanism behind the association between maternal ACEs and offspring outcomes is through offspring ACEs then the standard approach to screening, prevention, and intervention efforts will suffice to understand and address the impact of ACEs. If, however, there is a direct association between maternal ACEs and offspring outcomes independent of offspring ACE exposure, this suggests that a two-generation paradigm to practice, in which ACE screening is conducted among the dyad and intervention efforts account for the intergenerational exposure to ACEs, may be necessary to fully understand and ameliorate the impact of ACEs on adverse

offspring outcomes. Initiatives like California's ACEs Aware and other initiatives that follow suit may play an important role in understanding and addressing the intergenerational impact of ACEs.

Methodological Considerations

It is not only necessary to conceptually consider the intergenerational continuity of ACEs when assessing the intergenerational impact of ACEs, but also to use appropriate methodological approaches that can elucidate pathways behind associations and provide more precise estimates of the association between maternal ACEs and offspring outcomes. Methodological approaches, such as marginal structural modeling, can provide more robust and precise estimates of associations than traditional regression approaches (VanderWeele, 2009). In traditional mediation analysis between an exposure X and an outcome Y , estimation of the direct effect of X on Y is estimated after adjustment for the mediator M ; however, this estimate may be biased if Z is a confounder between M and Y , and is also affected by X (Lepage, Dedieu, Savy, & Lang, 2016). In this investigation, traditional regression approaches would allow for the estimation of the direct effect of maternal ACEs on offspring outcomes that is not through offspring ACEs or any of the measured confounders between offspring ACEs and offspring outcomes, though it is possible that the pathway between maternal ACEs and offspring outcomes is through these measured factors (e.g., home environment, maternal depression). The marginal structural model circumvents this issue by using two inverse probability of treatment weights, one to account for measured confounding of the association between maternal ACEs and offspring outcomes and one to account for the confounding of the association between

offspring ACEs and offspring outcomes. The marginal structural model estimates the controlled direct effect of maternal ACEs on offspring outcomes not mediated by offspring ACEs.

Intergenerational ACE Concordance vs. Discordance

Importantly, the intergenerational continuity of ACEs is not deterministic and there are known buffers against the intergenerational continuity of ACEs including positive childhood experiences and appropriate parenting interventions (Crouch et al., 2018; Harper, 2014; Thornberry et al., 2013). Familial emotional support, for example, has been separately identified as a protective factor that may disrupt the intergenerational continuity of ACEs (Schofield et al., 2013) and may buffer against the negative consequences of maternal ACEs on offspring outcomes (Hatch, Swerbenski, & Gray, 2020). Therefore, intergenerational adversity is not a monolith and there will be maternal-child dyads who are both concordant and discordant for ACE exposure. For those discordant for ACE exposure, there will be some offspring whose mothers are exposed to a higher number of ACEs but have lower or no exposure to ACEs themselves; and some offspring who are exposed to lower number or no exposure to maternal ACEs but are exposed to a higher number of ACEs themselves. For those concordant for ACE exposure, there will be offspring who are exposed to low or no ACEs at both generational levels; and finally, offspring who are exposed to a high number of maternal ACEs and a high number of ACEs themselves. The latter group, concordant for high intergenerational ACE exposure may be most vulnerable to adverse health and behavioral outcomes. It is possible that there is a “double-whammy” of ACE exposure, which may predict heightened vulnerability to the biological and

psychosocial risk factors associated with intergenerational adversity. Conversely, protective factors known to disrupt intergenerational adversity, including parental warmth and emotional support (Hatch, Swerbenski, & Gray, 2020; Dishion & McMahon, 1998; Donaldson, Nakawaki, & Crano, 2016) and parental involvement (Donaldson, Nakawaki, & Crano, 2016; Parker & Benson, 2005) may buffer against the impact of intergenerational ACE exposure. Examining how intergenerational ACE exposure operates among those concordant vs. discordant for high ACE exposure may inform future research efforts aimed at identifying protective psychosocial factors involved in disrupting the intergenerational transmission of adversity.

In conclusion, there is substantial evidence that early adversity predicts adverse health and behavioral outcomes within and across generations. Taken together, this investigation 1) informs timing of ACE screening and intervention to prevent adolescent substance use initiation as a way to disrupt the path from ACEs to SUD within generations and 2) informs ACE screening and intervention efforts aimed at understanding and addressing the impacts of ACEs on adverse health and behavioral outcomes, including internalizing and externalizing behavior and early age of alcohol initiation, across generations. Given the increasing opportunity for routine ACE screening and the simultaneously growing interest in the intergenerational transmission of early life adversity by researchers and practitioners alike, this investigation is particularly salient. Findings from this novel investigation may inform future intergenerational ACE research and practice.

Chapter 2: Adverse Childhood Experiences and Age of Substance Initiation: A Systematic Review

Introduction

Adverse childhood experiences (ACEs) have been consistently linked with elevated risk of substance use disorders (SUD), including alcohol, nicotine, marijuana, and opioid use disorders, across the life course, often in a dose-dependent manner (Affi et al., 2020; Dowling et al., 2022; Leza et al., 2021; Rogers et al., 2022; Shin, McDonald, & Conley, 2018). Given evidence that ACEs predict substance use in adolescence (Affi et al., 2020; Gomez et al., 2017; Kelly et al., 2023) and age of substance use initiation predicts SUD (Dawson et al., 2008; Liang & Chikritzhs, 2015; Lynskey et al., 2003; Richmond-Rakerd et al., 2015), age of initiation may be a salient mediator of the relationship between ACEs and SUD. There is evidence that, in the general population alcohol and marijuana use may precede cigarette and opioid use (Fiellin et al., 2013; CDC, 2022; Hoots, 2023). Therefore, strength of associations between ACEs and early initiation of substance use may depend on the substance assessed. Identifying substance-specific associations between ACEs and age of initiation can thus inform the age at which interventions should be implemented to maximize benefits as current adolescent substance use interventions may be implemented too late, particularly for the large swath of the population exposed to ACEs (Felitti et al., 1998).

The most cited explanation for the association between ACEs and earlier initiation of substance use is that youth use substances as a coping mechanism to avoid negative feelings arising from childhood adversity (Agnew & Brezina, 1992; Grummitt et al., 2021; Teixeira et al., 2017). Other hypotheses emphasize the underlying neurophysiology; chronic exposure to stressors disturbs cortisol regulation, alters DNA methylation involved in the regulation of gene expression, and impacts several neurological structures, including a reduction in neurogenesis and synaptic activity (Somaini et al., 2011). Functional and structural changes resulting from chronic exposure to stressors are associated with behavioral, cognitive, and mood disorders that can increase the likelihood of maladaptive coping behaviors like earlier onset of substance use (Enoch, 2011; Tervo-Clemmens et al., 2020; Walters & Kosten, 2019).

Importantly, underlying pathophysiology varies as a function of both cumulative experience (e.g., number) and type of adversities. While certainly not exhaustive, ACEs that fall under maltreatment are generally considered to be experiences of violence, abuse, or neglect, whereas individual ACEs that fall under household dysfunction often include growing up in a household with someone with an alcohol problem, substance problem or mental illness, or instability due to parental separation or incarceration. ACE measures are generally either cumulative, encompassing the total number of ACEs one is exposed to, or individual measures of adversity assessed separately from other adversities—each subject to limitations. Cumulative ACE scores, for example, cannot provide information regarding how specific adversities are related to age of substance initiation. For example, it is possible that experience of abuse may be more strongly associated with earlier substance

initiation as a way to cope with maltreatment than experience of parental separation due to divorce. Further, cumulative ACE scores may represent different constructs depending on the adversities included, which can vary greatly from study to study. The use of cumulative ACE scores that include measures of both maltreatment and household dysfunction, however, acknowledges the high level of co-occurrence of different childhood adversities (Felitti et al., 1998; CDC, 2023) and allows for the assessment of dose-dependent associations that have been reported in similar literature around ACEs and substance use (Grummitt et al., 2021; Shin, McDonald, & Conley, 2018) in a way that studies that assess individual ACEs cannot.

Existing evidence supports an association between total number of ACEs and substance use frequency and severity in adolescence. Among a sample of 14–17-year-old participants, ACE exposure was associated with all substance use indicators assessed, including lifetime and past-30-day use of cigarettes and electronic vapor products, as well as alcohol and cannabis use in the last 12 months and last 30 days (Affi et al., 2020). In a sample of high schoolers, total number of ACEs were strongly associated with past-month alcohol and cannabis use frequency (Kelly et al., 2023). In a sample of youth in Singapore, total number of ACEs was associated with increased risk of drug-related SUDs in a dose-dependent manner (Gomez et al., 2017). While assessing current and lifetime use, as well as severity of use, is important to establish the association between ACEs and increased risk of substance use in adolescence, these outcomes do not inform the most appropriate and effective timing of interventions aimed at preventing initiation in the first place—an important precursor to progression to SUD. Understanding the association between ACEs and age of initiation,

specifically, can fill this gap and inform public health interventions aimed at preventing initiation as a way to disrupt the path from ACEs to SUD.

It is currently unclear if the strength of associations between ACEs and earlier onset of substance use varies across substances. If ACEs are more strongly associated with earlier age of initiation of certain substances compared to others, that can have important implications for prevention and intervention efforts. Adolescents in the general population tend to use alcohol and marijuana earlier than nicotine and opioids (CDC, 2022; Hoots, 2023) and these trends may be more apparent among adolescents exposed to ACEs (Grummitt et al., 2021). Finally, it is imperative to evaluate factors that may ameliorate associations between ACEs and earlier age of initiation, which can inform prevention and intervention strategies. This systematic review advances the state of science by determining whether associations between ACEs and age of initiation differ depending on substance, as well as evaluating the role of potential moderators of the association between ACEs and age of initiation.

Methods

Information Sources and Search Strategy

The methodology for this study followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021). The 27-item checklist was considered in each phase of the process. Search terms included: (ACEs*[Title] OR "adverse chi*" [Title]) AND (age [Title] OR initiation[Title] OR "age of initiation"[Title/Abstract] OR "age at initiation" [Title/abstract] OR "alcohol use"[Title/Abstract] OR alcoh* [Title/Abstract] OR "substance use"[Title/Abstract] OR "substance"[Title/Abstract] OR

“opiate”[Title/Abstract] OR marij*[Title/Abstract] OR “opioids”[Title/Abstract] OR “nicotine”[Title/Abstract] OR “smoking”[Title/Abstract] OR smok*[Title/Abstract]). All search terms were entered into the Pubmed database. 613 articles were identified based on search terms.

Eligibility Criteria

Initial criteria included peer-reviewed empirical, quantitative studies, published in English from 1990- 2023. Abstracts of articles that met initial criteria were assessed for relevance by two study team members. Final criteria included 1) ACEs (including exposure to both maltreatment and household dysfunction) as independent variable(s), and 2) age of initiation of alcohol, marijuana, nicotine, and/or opioids as outcome. Studies that included samples of adolescents <14 that asked about use but did not specifically operationalize age of initiation were also included since initiation before age 14 can reasonably be defined as early initiation.

Selection and Data Collection

Data were extracted for organization and information synthesis using a spreadsheet that included authors, title, & year of publication; country/state; setting/population; type of study design; age of initiation operationalization; statistical models used; operationalization of ACE exposure; individual ACEs assessed; covariates including confounders, mediators, and moderators; sample size; and effect size. The study team assessed study risk of bias based on the Newcastle-Ottawa Scale (0-10) (Modesti et al., 2016). Components of this critical appraisal tool include whether the sample was representative of the target population; whether sample size was justified or not; quality of data on non-respondents; ascertainment of the exposure; whether confounding

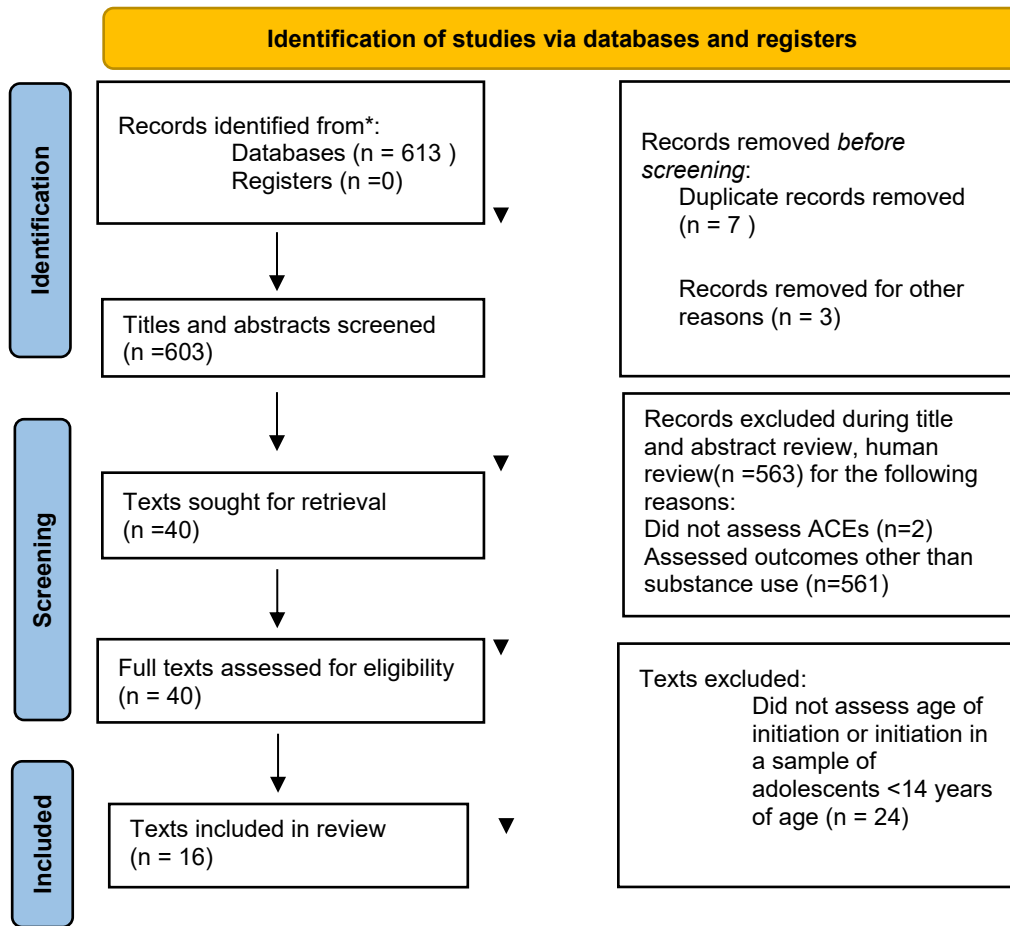
factors were controlled for; assessment of the outcome; and whether the statistical test was clearly described and appropriate. For studies that operationalized age of initiation as a binary or categorical variable, summary measures include the odds ratio (OR), risk ratio (RR), hazard ratio (HR), or prevalence ratio (PR) (95% CI). For studies that operationalized age of initiation as a continuous variable, β (95% CI) were obtained. The data were abstracted and reviewed by two reviewers to ensure consistency. All review assessments, including quality assessments, were consistent across reviewers. Confidence in the body of evidence for the association between ACEs and earlier age of initiation of each substance was determined by both quantity and quality of studies assessed.

Results

Study Selection

Figure 1 presents the flow diagram of the study selection. Of the 613 studies that populated after search terms were entered, 603 articles met initial criteria after removal of duplicates (n=7) and studies that were not quantitative in nature (n=3). After reviewing titles and abstracts for relevance, 563 articles were excluded. Of these, two studies did not examine ACEs, and the rest assessed outcomes unrelated to substance use (i.e., obesity, sexual behaviors) (n=561). Forty texts were sought for retrieval and were given full-text review. Sixteen articles met final inclusion criteria.

Figure 1. PRISMA flow diagram for study review process



Study Characteristics

Table 1 presents the characteristics of the 16 studies identified within our criteria. All but one study collected data on ACE exposure and age of substance initiation cross-sectionally, while one study collected data longitudinally (Gajos et al., 2023). Three studies (19%) included elementary, middle, or high school samples (Chatterjee et al., 2018; Nagata et al., 2023; Williams et al., 2020); two studies (12%) included samples enrolled in higher education (Woloshchuk et al., 2022; Hughes et al., 2019); three studies (19%) included birth cohort samples (Hines et al., 2023; Joannes & Kelly-Irving, 2022; Goncalves et al., 2016); and the remainder were community or

clinic-based samples (50%). Twelve (75%) of the studies were conducted in the United States. Remaining studies were conducted in Brazil (Goncalves et al., 2016), the UK (Joannes & Kelly-Irving, 2022; Hines et al., 2003) and in 10 European countries that aggregated their data (Hughes et al., 2019). Three studies assessed gender differences (Chatterjee et al., 2018; Gajos et al., 2023; Goncalves et al., 2016). Sample sizes ranged from $n=107$ to $n=79,339$.

Table 1. Review of Epidemiologic Studies of ACEs and Age of Substance Initiation 1990-December 2023

Author	Sample (mean age/age range); Location, Years (N)	Analytic Study Type	Measures: ACEs; Age of initiation; Mediators/Moderators	Association between ACEs and Age of alcohol initiation OR/RR/HR (95% CI), β (95% CI)	New Castle Ottawa Scale Rating*
<i>Alcohol</i>					
Dube et al., 2006	Representative sample of US adults (30.1) 2006 N=3,592	Cross-sectional	10-item ACE questionnaire 0,1,2,3,>3 Initiation of alcohol categorical 14, 15-17, 18-20, >20	<u>Early Initiation by 14</u> 1 ACE: 1.1 (0.7, 1.9) 2 ACEs: 1.7 (0.8, 3.2) 3 ACEs: 2.1 (1.0, 4.2) >3 ACEs: 3.6 (2.0, 6.4) <u>Initiation 15-17</u> 1 ACE: 1.4 (1.0, 1.9) 2 ACEs: 1.4 (0.9, 2.0) 3 ACEs: 1.8 (1.1, 2.9) >3 ACEs: 1.8 (1.2, 2.8)	8 Retrospective recall of ACEs
Chatterjee et al., 2018	Representative sample of students enrolled in public high schools (15.5) MN, US 2013 (N = 79,339)	Cross-sectional	Physical, sexual, emotional abuse Household dysfunction (parental drug/alcohol abuse, domestic violence) Initiation of alcohol <15 years Moderator: gender	<u>Among boys</u> Any abuse: 1.43 (1.29, 1.59) Any household dysfunction: 1.34 (1.20,1.49) Both: 2.04 (1.83, 2.29) <u>Among girls</u> Any abuse: 1.49 (1.35, 1.64) Any household dysfunction: 1.47 (1.32, 1.64) Both: 1.91 (1.73, 2.10)	8 Retrospective recall of ACEs
Hughes et al., 2019	Representative sample of students enrolled in higher	Cross-sectional	10-item ACE questionnaire 0,1,2-3, >3	1 ACE: 1.44 (1.29, 1.60) 2-3 ACEs: 1.92 (1.71, 2.16)	8

	education (18-25 years) 10 European countries 2010-2017 N=14,381		Initiation of alcohol <15 years	>3 ACEs: 2.25 (1.89, 2.68)	Retrospective recall of ACEs
Gajos et al., 2023	Sample of adolescents representative of non-marital births (15.5); Large US cities (>=200,000), 1998-2017 N=2,455	Longitudinal cohort	Physical and psychological abuse, neglect, parental substance abuse, parental mental illness and criminal behavior parentally reported from birth-age 5 continuous Initiation of alcohol <15 years Moderator: gender	<u>Among boys</u> 0.93 (0.73, 1.10) <u>Among girls</u> 1.07 (0.91, 1.26)	8 Retrospective recall of ACEs
Nagata et al., 2023	Representative sample of elementary school students (9-10 years) US 2016-2018 N=10,853	Cross-sectional	Physical abuse, sexual abuse, household violence, household alcohol abuse, household mental illness, parental divorce/separation, emotional neglect, physical neglect, household criminal justice system involvement summed, 0,1,2,3, >3 Ever drank alcohol by interview (9-10 years old)	1 ACE: 1.06 (0.96, 1.18) 2 ACEs: 1.16 (1.04, 1.31) 3 ACEs: 1.16 (1.01, 1.34) >3 ACEs: 1.27 (1.11, 1.45)	8 Retrospective recall of ACEs
Rothman et al., 2008	Convenience sample of adults (56.1) CA, US 1997 N=8,417	Cross-sectional	Emotional, physical, sexual abuse Household dysfunction (battered mother, parental discord/divorce, mentally ill household member, substance abuse in home, incarcerated household member) 0,1,2,3, >3 Initiation of alcohol <15 years	1 ACE: 1.5 (1.1, 2.1) 2 ACEs: 2.4 (1.7, 3.3) 3 ACEs: 3.9 (2.8, 5.6) >3 ACEs: 6.2 (4.6, 8.3)	7 Retrospective recall of ACEs Not representative of target population
Goncalves et al., 2016	Subsample of a population-based birth cohort (b. 1993) Sao Paulo Brazil 2008 N=4,230	Cross-sectional	Physical abuse, sexual abuse, physical neglect, emotional neglect, and domestic violence 0,1,2,>2 Initiation of alcohol <16 years	Prevalence Ratio (95% CI) <u>Among boys</u> 1 ACE: 1.5 (1.2, 1.9) 2 ACEs: 1.8 (1.3, 2.5) >2 ACEs: 2.0 (1.3, 3.1)	7 Retrospective recall of ACEs

			Moderator: gender	<u>Among girls</u> 1 ACE: 1.7 (1.4, 2.0) 2 ACEs: 1.8 (1.4, 2.3) >2 ACEs: 2.4 (1.8, 3.1)	Not representative of target population
Woloshchuk et al., 2022	Convenience sample of Latinx university students (20.8); a Mexico/US border town, N/A N=382	Cross-sectional	10 items + early life stressors (foster care, bullying, deceased parent, deportation/immigration issues, serious illness, neighborhood violence, arrest/detainment, discrimination, IPV 0-19 Age of alcohol initiation continuous Moderators: attachment style, familism, machismo beliefs, bicultural self-efficacy	$r=0.27 <0.001$ For female participants, bicultural self-efficacy moderated the association. Scores below 247 strengthened association	5 Retrospective recall of ACEs Not representative of target population Sample size not justified No information on non-respondents
<i>Marijuana</i>					
Chatterjee et al., 2018	Representative sample of students enrolled in public high schools (15.5) MN, US 2013 (N = 79,339)	Cross-sectional	Physical, sexual, emotional abuse Household dysfunction (parental drug/alcohol abuse, domestic violence) Initiation of marijuana <15 years Moderator: gender	<u>Among boys</u> Any abuse: 1.21 (1.03, 1.42) Any household dysfunction: 1.64 (1.43, 1.92) Both: 2.02 (1.83, 2.49) <u>Among girls</u> Any abuse: 1.24 (1.04, 1.43) Any household dysfunction: 1.47 (1.24, 1.74) Both: 1.71 (1.54, 2.00)	8 Retrospective recall of ACEs

Hines et al., 2023	Subsample of a population-based birth cohort (b. 1991-1992); Avon, UK, 2005-2016 N=5,212	Cross-sectional	Physical, sexual, emotional abuse, emotional neglect, bullying, parental substance use or abuse, inter-partner violence between parents, parental mental health problems or suicide, parental separation, parent convicted of criminal offense before age 13 0,1,2-3, >3 Early initiation of regular use of marijuana	>3 ACEs: 3.15 (1.81, 5.50)	8 Retrospective recall of ACEs
Meadows et al., 2023	Clinical sample of adults with active substance use disorder (36.6) Lexington, KY N=107	Cross-sectional	Standard 10-item ACE questionnaire (1, 2, 3, 4+)	1 ACE: 1.07 (0.58, 1.98) 2 ACEs: 0.91 (0.47, 1.79) 3 ACEs: 1.06 (0.49, 2.26) 4+ ACEs: 1.24 (0.7, 2.21)	5 Retrospective recall of ACEs Not representative of target population Sample size not justified No information on non-respondents
Nicotine					
Williams et al., 2020	Representative sample of middle school students (11-14) N=5,464	Cross-sectional	Physical abuse, verbal abuse, forced sex, household domestic violence, household mental illness, household substance use 0,1,2,>2 Initiation of vaping <11 years old	1 ACE: 1.60 (0.99, 2.59) 2 ACEs: 2.29 (1.33, 3.93) >2 ACEs: 3.43 (2.20, 5.36)	8 Retrospective recall of ACEs
Joannes & Kelly-Irving., 2022	Subsample of a population-based birth cohort (b. 1958); England, Wales, and Scotland UK	Cross-sectional	Foster care stay, physical neglect, lived in a household with offenders, parental separation, mental illness (child), alcohol abuse in the home 0,1,>1	1 ACE: 1.50 (1.27, 1.77) >1 ACE: 1.61 (1.20, 2.15)	8 Retrospective recall of ACEs

	1974 N=7,414		Initiation of nicotine <17 years Mediation: family factors and conscientiousness	Partial mediation by family factors and conscientiousness	
Anda et al., 1999	Convenience sample of adults (56.1) CA, US 1997 N=9,215	Cross-sectional	Emotional, physical, sexual abuse Household dysfunction (battered mother, parental discord/divorce, mentally ill household member, substance abuse in home, incarcerated household member) 0,1,2,3,4, >4 Initiation of nicotine <15 years	1 ACE: 1.2 (1.0, 1.3) 2 ACEs: 1.3 (1.1, 1.6) 3 ACEs: 1.6 (1.3, 2.0) 4 ACEs: 1.7 (1.3, 2.2) >4 ACEs: 1.6 (1.3, 2.2)	7 Retrospective recall of ACEs Not representative of target population
Goncalves et al., 2016	Subsample of a population-based birth cohort (b. 1993) Sao Paulo Brazil 2008 N=4,230	Cross-sectional	Physical abuse, sexual abuse, physical neglect, emotional neglect, and domestic violence 0,1,2,>2 Initiation of tobacco by <16 Moderator: gender	Prevalence Ratio (95% CI) <u>Among boys</u> 1 ACE: 2.3 (1.4, 3.8) 2 ACEs: 0.9 (0.3,2.7) >2 ACEs: 2.0 (0.5, 8.3) <u>Among girls</u> 1 ACE: 3.1 (2.0, 4.8) 2 ACEs: 4.5 (2.7, 7.3) >2 ACEs: 5.2 (2.9, 9.3)	7 Retrospective recall of ACEs Not representative of target population
Meadows et al., 2023	Clinical sample of adults with active substance use disorder (36.6) Lexington, KY N=107	Cross-sectional	Standard 10-item ACE questionnaire (1, 2, 3, 4+)	<i>Nicotine</i> 1 ACE: 1.52 (0.69, 3.35) 2 ACEs: 1.85 (0.81, 4.21) 3 ACEs: 0.99 (0.37, 2.65) 4+ ACEs: 2.12 (1.02, 4.43)*	5 Retrospective recall of ACEs Not representative of target population

					Sample size not justified No information on non-respondents
Opiates					
Stein et al., 2017	Clinical sample of adults seeking opioid detoxification at an inpatient treatment center (32.2) MA, US 2015 N=457	Cross-sectional	Standard 10-item ACE questionnaire Age of opioid initiation, continuous	B=-0.50 (-0.70, -0.29)	5 Retrospective recall of ACEs Not representative of target population Sample size not justified No information on non-respondents
Guarino et al., 2021	Chain-referral sample of opioid-using adults (24.5) NY, US 2014-2016 N=539	Cross-sectional	10-item ACE questionnaire, ordinal 0-10 Early initiation of opioids bottom 25 th percentile compared to top 75 th percentile	<u>Non-medical PO use</u> 1.23 (1.12, 1.43) <u>Regular PO use</u> 1.22 (1.10, 1.36) <u>Heroin use</u> 1.17 (1.03, 1.32) <u>Regular heroin use</u> 1.14 (1.03, 1.25)	5 Retrospective recall of ACEs Not representative of target population Sample size not justified No information on non-respondents
Meadows et al., 2023	Clinical sample of adults with active substance use disorder (36.6)	Cross-sectional	Standard 10-item ACE questionnaire (1, 2, 3, 4+)	1 ACE: 0.88 (0.31, 2.48) 2 ACEs: 0.90 (0.32, 2.61) 3 ACEs: 1.46 (0.51, 4.15)	5 Retrospective recall of ACEs

	Lexington, KY N=107			4+ ACEs: 1.13 (0.45, 2.79)*	Not representative of target population Sample size not justified No information on non-respondents
<i>Illicit Substance Use</i>					
Goncalves et al., 2016	Subsample of a population-based birth cohort (b. 1993) Sao Paolo Brazil 2008 N=4,230	Cross-sectional	Physical abuse, sexual abuse, physical neglect, emotional neglect, and domestic violence 0,1,2,>2 Illicit drug initiation <16 years Moderator: gender	Prevalence Ratio (95% CI) <u>Among boys</u> 1 ACE: 3.0 (1.2, 7.4) 2 ACEs: 4.0 (1.4, 11.7) >2 ACEs: 5.3 (1.5, 19.4) <u>Among girls</u> 1 ACE: 3.3 (1.2, 9.2) 2 ACEs: 3.7 (1.0, 13.0) >2 ACEs: 25.5 (10.5, 61.8)	7 Retrospective recall of ACEs Not representative of target population
Garrido et al., 2018	All foster care placements due to maltreatment (10.3); Large metro area Western US 2002-2011 N=515	Cross-sectional	Physical abuse, sexual abuse, removal from a single parent household, exposure to community violence, number of caregiver transitions, number of school transitions summed 0-6 Any substance use by time of interview (9-11 years)	Any substance use initiation: 1.59 (1.27, 1.98)	5 Retrospective recall of ACEs Sample size not justified No information on non-respondents

* Includes reasons for point deductions

Risk of Bias in Studies

All studies were deemed “satisfactory” (score >4; range 0-10) based on the Newcastle Ottawa criteria. A risk common to all included studies, and indeed studies of adversity in general, is that ACEs are retrospectively reported based on recall, which automatically deducts two possible points from the total score. Six of the studies (Rothman et al., 2008; Anda et al., 1999; Woloshchuk et al., 2022; Guarino et al., 2021; Stein et al., 2017; Meadows et al., 2023) were not representative of the target population. Findings from studies that are not representative of the source population may be less generalizable. Three studies (Meadows et al., 2023; Stein et al., 2017; Woloshchuk et al., 2022) included sample sizes <500, potentially limiting power to detect statistically significant differences among those exposed to ACEs compared to those exposed to low or no ACEs. Table 1 presents individual risk assessment scores for all included studies, including reasons for point deductions.

ACEs and Age of Initiation Measurement Across Studies

Five studies (Dube et al., 2006; Hughes et al., 2019; Guarino et al., 2021; Stein et al., 2017; Meadows et al., 2023) used the original 10-item ACE Questionnaire (Felitti et al., 1997) assessing seven types of adversity (abuse: psychological, physical, sexual; and household dysfunction: substance abuse, mental illness, mothers treated violently, criminal behavior in the household). Others used various modified ACE batteries. The number of adverse experiences assessed ranged from five (Chatterjee et al., 2018) to 19 (Woloshchuk et al., 2022). Extra items not included in the original 10-item battery

included foster care placement, deceased parent, deportation/immigration issues, serious childhood illnesses, discrimination, arrest/detainment, and IPV (Woloshchuk et al., 2022), witnessing community/neighborhood violence (Woloshchuk et al., 2022; Garrido et al., 2018), bullying (Hines et al., 2023), number of school and caregiver transitions (Garrido et al., 2018), and removal from a single parent household (Garrido et al., 2018). All studies included at least three items from the original 10-item battery.

Five studies assessed total number of ACEs as continuous measures (Woloshchuk et al., 2022; Garrido et al., 2018; Gajos et al., 2023; Guarino et al., 2021; Stein et al., 2017), while the remainder assessed number of ACEs categorically. Of the studies that assessed ACEs categorically, one study assessed any abuse, any household dysfunction, or both (Chatterjee et al., 2018), one study used a threshold of two ACEs as the highest level of exposure (Joannes & Kelly-Irving, 2022), regardless of the type of ACE exposure, and the remainder used a threshold of three or more ACEs as the highest level of exposure, which is commonly cited among ACE literature investigating dose-dependent associations as higher thresholds can better detect dose-dependent associations (citations). Five studies included in this review found non-significant associations between ACEs and age of initiation using a threshold of one ACE, but found significant associations at higher thresholds (i.e., 2, 3, >3 ACEs) (Anda et al., 1999; Dube et al., 2006; Nagata et al., 2023; Williams et al., 2020; Meadows et al., 2023). All studies included in the review used a reference value of “0” to indicate no ACE exposure.

All but one study assessed ACEs and age of initiation retrospectively. Eight studies (50%) inquired about ACE exposure and age of initiation among adult samples

(Rothman et al., 2008; Anda et al., 1999; Dube et al., 2006; Woloshchuk et al., 2022; Hughes et al., 2019; Guarino et al., 2021; Stein et al., 2017; Meadows et al., 2023), while the rest included adolescent samples. Studies that included adult samples asked participants to report on ACE exposure from birth to age 18. Because most studies using an age threshold define early age of initiation between 11-17 years old, a limitation to these studies is the inability to establish temporality in the association between ACEs and substance use. It is possible that age of initiation precedes ACE exposure. In studies among adolescent samples, one study assessed ACEs only until the age of 13 to reduce temporality limitations (Hines et al., 2017), while the remainder assessed ACE exposure up until the time of the interview. Of these studies, two assessed ACE exposure among samples of youth around the age of 10 (Garrido et al., 2018; Nagata et al., 2023), one between 11-14 years of age (Williams et al., 2020), and three between 14-16 years of age (Chatterjee et al., 2018; Goncalves et al., 2016; Johannes & Kelly. 2022). One study included parents' reports of ACEs from birth to age 5 (Gajos et al., 2023) and children's report of age of initiation at a mean age of 15.5. However, parental-report of ACEs from birth to age 5 may be a fundamentally different construct than self-report of ACEs from birth to age 18.

For studies that only included participants <14 years old (Garrido et al., 2018; Nagata et al., 2023), any report of substance use was categorized as early initiation. The remainder of the studies operationalized age of initiation as continuous (Stein et al., 2017; Meadows et al., 2023; Woloshchuk et al., 2022) or based on a threshold. Among the studies with a threshold for early initiation, one used <17 years (Joannes & Kelly-Irving, 2022), 6 studies used <15 years (Chatterjee et al., 2018; Rothman et al.,

2008; Anda et al., 1999; Dube et al., 2006; Gajos et al., 2023; Hughes et al., 2019), 1 study used <16 years (Goncalves et al., 2016), 1 study used <11 years (Williams et al., 2020) and the remainder used latent class analysis (Hines et al., 2023) or bottom 25th percentile of age (mean age 15 for non-medical prescription opioid use-age 18 for regular heroin use) (Guarino et al., 2021). Of the 11 studies that used thresholds for age at initiation, all but one reported a significant association between ACEs and early initiation of each substance assessed. Significant findings from studies that use lower thresholds may be more informative regarding intervention, as the earliest initiation likely represents the riskiest substance use. Thresholds to define early age of initiation are likely based on typical adolescent substance use patterns, which may differ across study populations and/or substances. For example, there is no legal age to misuse licit or use illicit opioids in the United States, while there are varying legal ages to use marijuana (dependent on U.S. state residence), alcohol, and nicotine. Additionally, the availability and stigma of substances may vary, which may lead to differential use patterns. According to recent US data, approximately 47.4% of high schoolers reported lifetime use of alcohol, 27.8% reported lifetime use of marijuana, 12.2% reported lifetime use of opioids (Hoots et al., 2023), and 12.6% reported use of a tobacco product (CDC, 2022). Similar patterns hold for many European countries (Kraus et al., 2018). Therefore, what constitutes as early initiation for alcohol and marijuana in the United States and Europe may be substantively different, and earlier, than what constitutes as early initiation for opioids or tobacco products. Adolescent substance use patterns may be different in other countries or contexts where social norms, availability, and laws around substances are different.

Substance-Specific Associations Between ACEs and Age of Initiation

Despite significant variation in study design, sample/population, and operationalization of ACEs and age of initiation, all but two studies found a significant association between ACEs and earlier age of initiation across substances assessed, and most reported a dose-response association.

Alcohol

Of the eight studies that examined age of initiation of alcohol, seven studies, using different methodologies, found that increasing ACE score was associated with earlier age of alcohol initiation. Among two U.S. samples (Chatterjee et al., 2018; Rothman et al., 2008) and a representative European sample (Hughes et al., 2019), ACEs predicted the risk of initiating alcohol use by age 15 in a dose-dependent manner. Among a representative sample of U.S. adults, ACE score was associated with increased risk of initiating alcohol use before age 14 in a dose-dependent manner and was associated with initiation during mid-adolescence (15-17 years) as well (Dube et al., 2006). Compared with respondents who did not report a history of ACEs, respondents with ACEs were significantly more likely to report that they drank to cope during the first year that they used alcohol. Among a representative sample in Brazil, a dose-response association between ACEs and risk of initiating alcohol before the age of 16 was reported (Goncalves et al., 2016). Among a representative sample of US elementary school students, each category of ACEs was associated with a relatively stable increase in risk of reporting ever-use of alcohol (Nagata et al., 2023). Although age of initiation was not operationalized in this study, given the age of participants

(<11), any reported use can reasonably be classified as early initiation. Among a convenience sample of college students, ACEs were inversely associated with age of first alcohol use (Woloshchuk et al., 2022). The only study to report null findings assessed ACEs by maternal report from birth to age 5 (Gajos et al., 2023).

Marijuana

Three studies examined marijuana use. Among a representative U.S. sample, findings support a positive association between ACE scores and risk of initiating marijuana use by age 15 (Chatterjee et al., 2018). Among a representative UK sample, participants who experienced >3 ACEs were over three times more likely to be classified as early initiators of regular marijuana use (Hines et al., 2023). Among a clinical sample, no association between ACEs and age of initiation of cannabis was reported (Meadows et al., 2023), although the study may have been underpowered to detect a true association (n=107), as the two other studies in this category had larger sample sizes (n=5,212 and n=79,339) .

Nicotine

Of the five studies that examined nicotine initiation, all reported a significant association between ACEs and earlier age of initiation. Among two representative samples in the UK (Joannes & Kelly-Irving, 2022) and Brazil (Goncalves et al., 2016), findings support positive association between increasing number of ACEs and increased risk of initiating cigarette smoking before the age of 17, though among the Brazilian sample, a dose-dependent association only existed for females. For males, compared to those reporting no ACEs, one ACE was associated with initiating nicotine

early, but higher exposures were not. This study adjusted for cigarette smoking at age 11, which may underestimate the true association between ACEs and age of initiation among males, particularly if males with higher ACE scores initiated smoking before age 11 at a higher rate than females. It is possible that cigarette smoking at age 11 mediates the association between ACEs and cigarette smoking before the age of 17. Among a clinical sample, ACEs were associated with earlier age of initiation of tobacco in a dose-dependent manner (Meadows et al., 2023). Among a convenience sample, each category of ACEs (1-4) was associated with earlier initiation compared to those not exposed to ACEs (Anda et al., 1999). Among a representative sample of U.S. middle school students, ACEs were associated with increased risk of initiating vaping <11 years old in a dose-dependent manner (Williams et al., 2020).

Opiates

Three studies of opioid initiation found that among samples of opioid users, ACEs were associated with earlier opioid initiation. In the first study, each increase in ACE was associated with an increased risk of early initiation (bottom 75th percentile for age) of prescription opioid misuse and heroin use (Guarino et al., 2021). In the second, ACEs were inversely associated with earlier age of initiation (Stein et al., 2017). In the third, a survival analysis revealed that exposure to ≥ 4 ACEs was associated with earlier initiation of opioid use compared to those experiencing < 4 ACEs (Meadows et al., 2023).

Illicit Substance Use

Both studies that considered any illicit substance use reported an inverse association between ACEs and age of initiation. Among a U.S. sample of youth, each additional ACE predicted a 59% increase in the odds of substance use (Garrido et al., 2018). Although this study did not assess age of initiation, given that the sample was limited to 9-11-year-olds, any reported substance use can be classified as early initiation. Substances assessed included nicotine, marijuana, alcohol (full drink), inhalants, and methamphetamines. Among a representative Brazilian sample, a dose-response association between ACEs and initiating illicit drug use before the age of 16 was reported (Goncalves et al., 2016). Illicit drug use was classified as any substance not including tobacco, alcohol, or marijuana.

Moderators

Among the four studies testing moderation (25%), the most assessed moderator was gender (n=3), with mixed findings. One study assessed internal assets, as measured by the developmental assets profile of social competency and positive identity, by gender (Chatterjee et al., 2018). This study found that internal assets reduced the association between ACEs and earlier initiation of marijuana and alcohol among girls, but not boys. For girls with high internal assets scores ($\geq 75^{\text{th}}$ percentile), there was no association between experiencing both abuse and household dysfunction and early initiation of marijuana use, while for girls with low internal assets scores (5^{th} percentile), odds of initiating alcohol and marijuana use were more than twice the odds compared to girls who did not experience either abuse or household dysfunction.

Higher internal assets did not reduce the association between experiencing both abuse and household dysfunction among boys. The one study that did not find an association between ACEs and age of alcohol use initiation reported no moderation by gender (Gajos et al., 2023). In contrast, one study reported significant moderation by gender, but only for those with higher adversity profiles (Goncalves et al., 2016). Specifically, this study reported that risk of early initiation of illicit drugs was nearly 5 times higher and risk of early initiation of tobacco was over 2 times higher for girls who had experienced 3 or more ACEs compared to girls who had experienced fewer than 3 ACEs. No significant association between ACEs and early initiation of tobacco was found among boys. This study found no gender moderation for alcohol age of initiation.

One study assessed attachment style (anxious/avoidant), familism (Attitudinal Familism Scale), machismo beliefs (20-item scale), and bicultural self-efficacy (Bicultural Self-efficacy Scale) as moderators (Woloshchuk et al., 2022). This study found that bicultural self-efficacy (BSE) significantly moderated the association between ACEs and earlier age of initiation of alcohol. Lower BSE scores strengthened the association between ACEs and earlier age of initiation of alcohol. There was no moderation by attachment style, familism, or machismo beliefs.

Discussion

This review is the first to evaluate the association between ACEs and earlier age of initiation by substance. All studies included for review were satisfactory based on quality assessment, though findings from studies that include large representative samples may be more generalizable. Despite variation in study design and study

characteristics, all but two studies reported positive associations between ACEs and earlier age of initiation of all substances assessed, with the majority reporting a dose-response association. Effect sizes were relatively consistent between studies among each substance assessed, with effect sizes generally increasing as the number of ACEs increased, ranging from 6%-300% increased risk for exposure to one ACE, up to 80-620% for the highest number of ACEs. The reviewed evidence generally suggests that individuals who experience higher numbers of ACEs are at higher risk of earlier initiation of substance use compared to those with none or lower levels of ACE exposure.

Findings suggest that ACEs may predict earlier initiation of alcohol and nicotine relative to other substances assessed. ACEs were found to predict earlier age of initiation of alcohol across seven studies, the majority of which had the highest quality ratings included in the review (Chatterjee et al., 2018; Dube et al., 2006; Hughes et al., 2019; Nagata et al., 2023) and were found to predict earlier age of initiation of nicotine across five studies, many of which also had the highest quality ratings included in the review (i.e., 7 or 8) (Williams et al., Johannes & Kelly-Irving, 2022; Anda et al., 1999; Goncalves et al., 2016).

Three or more ACEs were associated with initiation of alcohol across multiple studies, with effect sizes (OR) ranging from 1.91 (95% CI: 1.73, 2.10) to 6.2 (95% CI: 4.6, 8.3). Positive findings from studies that use relatively lower thresholds (<14 years of age) (Williams et al., 2020) or assess ever-use in populations <14 years of age (Garrido et al., 2018; Nagata et al., 2023) may be less sensitive and more specific for adolescent substance use that would qualify as “early” initiation and support

implementing interventions prior to pubertal adolescence. Among the youngest samples included in this review (aged 9-10), ACEs were positively associated with use of alcohol at the time of interview OR=1.27 (95% CI: 1.11, 1.45). (Nagata et al, 2023). Most studies that assessed the association between ACEs and nicotine used thresholds between 15-17 to define early initiation and reported a range of effect sizes (OR) from 1.6 (95% CI: 1.20, 2.15) after exposure to more than one ACE to 5.2 (95% CI: 2.9, 9.3) after exposure to more than two ACEs. One study found that exposure to more than two ACEs was associated with initiating vaping before age 11. Therefore, interventions aimed at vaping may need to be implemented prior to pubertal adolescence as well.

While reviewed evidence generally supports an association between total number of ACEs and earlier initiation of all substances assessed, findings of ACEs and earlier initiation of opioids, marijuana, and general substance misuse should be viewed within the context of limited literature and in light of individual study limitations, including ACE and age of initiation measurement precision and other methodological limitations. For example, though all three studies assessing ACEs and age of opioid initiation found a statistically significant association, there was no consistency for what constituted early initiation. One study assessed early initiation as initiating in the bottom 25th percentile compared to top 75% percentile. Effect size (OR) for this study was marginal, ranging from 1.14 (95% CI: 1.03, 1.25) for regular heroin use to 1.22 (95% CI: 1.10, 1.36) for regular prescription opioid use with each additional ACE experienced. The other two studies assessed age of initiation as continuous or with a survival analysis, both of which are less informative for intervention timing than studies that use early and specific thresholds. Only two studies found an association between

ACEs and earlier age of marijuana, though effect sizes (OR) ranged from 2.02 (95% CI: 1.83, 2.49) to 3.15 (1.31, 5.50) for initiating marijuana before age 15 suggests that there may be an association between ACEs and early initiation of marijuana. More and higher quality studies assessing the relationship between ACEs and age of initiation of opioids, marijuana, and other substances are needed to ensure findings from this review are valid and reliable. Studies should consider using thresholds to inform timing of prevention and intervention efforts.

The balance of extant evidence suggests that gender does not moderate the association between ACEs and age of substance initiation, though confidence in these conclusions is low because gender has been rarely tested. Only one study included mediation analysis to evaluate potential pathways (Joannes & Kelly-Irving et al., 2022). This study suggested that sibling order and/or parental smoking, as well as personality factors, may at least partly mediate the association between ACEs and earlier age of initiation of nicotine use. Future studies should assess theoretically and practically plausible mediators and moderators to inform tailored prevention and intervention strategies. Given the sequelae of early adversity leading to dysregulated and maladaptive behavior, potential mediators include behavioral disorders like anxiety and depression. Plausible moderators include factors known to protect against dysregulated and maladaptive behaviors in adolescence such as internal resilience (e.g., positive acceptance of change and trust in one's instincts) and external assets like family communication, school connectedness, peer role models, and non-parental adult role models (Lensch et al., 2021; Brown & Shillington, 2017). Findings may inform

intervention strategies aimed at disrupting involved mechanisms and promoting protective factors.

Findings from this review should be interpreted based on limitations of studies included. Whereas most studies chose threshold ages for early initiation based on conceptual and empirical considerations, findings may be substantively different if other potentially plausible thresholds were utilized. For example, most studies assessing ACEs and early initiation of alcohol use picked thresholds below 15-17 years of age. This is likely due to normative drinking patterns in the study populations or context and the fact that all studies were conducted in countries where the legal drinking age ranges from 18-21. Thresholds may be relatively arbitrary when applied to other contexts where availability, social norms, and laws around substance use may differ. While thresholds provide insight into early initiation that may be distinct from normal initiation patterns, testing multiple thresholds may better inform intervention efforts. For example, evidence to suggest that ACEs predict substance initiation before age 15 is informative, but less informative than testing increasingly earlier ages to determine at what age this increased risk begins.

A limitation common to ACE studies, including the ones presented in this review, are that ACEs are retrospectively self or parentally reported. Among the eight studies that assess ACE exposure prior to age 18, it is possible that age of substance initiation may precede ACE exposure. However, we reason that individuals with high ACE scores have experienced multiple ACEs across childhood rather than isolated ACEs at limited time points beyond the age of initiation. One study in this review that reported an association between increasing ACEs and earlier marijuana initiation

retrospectively collected ACE exposure up to age 13 as a way to minimize temporality limitations (Hines et al., 2023). Future studies examining ACEs and age of initiation should account for timing in their study designs or in analyses to allow for more robust inference.

Another limitation common to ACE studies relates to the measurement of ACEs themselves. While the conceptual basis for ACEs is predicated on experience of maltreatment and/or household dysfunction (Felitti, 1998), how these exposures are measured vary between studies and may not capture duration, frequency, or type of adversity in a way that adequately informs severity of adversity. For example, it is possible that the risk profile for someone who experienced a very brief period of time living with someone with depression or other mental illness is distinct from someone who lived their entire childhood with someone with severe depression or other mental illness. Analogous arguments can be made for other household dysfunction and maltreatment indicators based on duration and/or frequency. A related limitation is that grouping people into a binary of whether they experienced an adversity or not obfuscates how severely that experience impacted the individual based on their perception of the experience. It is possible that abuse by a loved one is distinct from abuse by a stranger in terms of perceived severity and impact on subsequent health and behavioral outcomes (Westermair et al., 2018). Beyond the issue of temporality already raised, timing of ACE exposure, either individually or cumulatively, may also lead to differential impacts. Given what is known about critical periods of development in childhood and adolescence, there may be periods of development that are particularly vulnerable to adverse exposures (Hawes et al., 2021).

Further, there are certain types of adversities that some groups experience that are not well captured in the current literature. An increasingly common criticism of the ACE literature is that adversity related to systemic and structural oppression is often overlooked (Helton et al, 2022). Adversity associated with societal risks like minority status, nativity status, and community dysfunction are often neglected in favor of more proximal household exposures. While ACE research is often based on Felitti's original ACE study, this review's findings of a wide range of ACE measurement and operationalization support that there is no universally agreed upon ACE battery. While it is likely that other ACEs beyond those included in the original 10-item battery are important to include, there needs to be greater conceptual and/or empirical justification for their inclusion.

Null findings from two studies included in the review should be interpreted in light of methodological limitations. Among a sample of adolescents representative of non-marital births where no association between ACEs and age of alcohol initiation was found, ACEs were obtained based on maternal report from birth to age five. Parents may be less likely to truthfully report their child's exposure to adversity given that they are likely to be implicated, and depending on the nature of adversity, potentially reported to child protective services. Therefore, findings may be subject to social desirability bias. It is also possible that ACE exposure from birth to age 5 is not comparable to cumulative ACE exposure over a broader time period across childhood. Among a small clinic-based sample (n=107) of adults with active substance use disorder, ACEs were significantly associated with earlier opioid and nicotine initiation, but not cannabis (Meadows et al., 2023). Despite there being a trend toward earlier

initiation of cannabis with increasing ACE exposure, the association did not rise to statistical significance. While 94% of the sample reported lifetime cannabis use, there is evidence that cannabis-use disorder is undertreated in the United States (Bonn-Miller et al., 2012). It is possible that there were too few regular cannabis users in this small sample to identify statistically significant differences, particularly when stratifying by dose of exposure.

Finally, while two studies assessed aggregate substance use (Garrido et al., 2018; Goncalves et al, 2016) no study assessed age of initiation of poly-substance use, specifically. Earlier age of poly-substance use may be a particularly salient risk factor for progression to SUD (Olthuis, Darredeau, & Barrett, 2013). Future studies should evaluate the association between ACEs and polysubstance use to further inform timing of needed interventions.

Limitations

Our conclusions should be considered in light of limitations of this review. First, this review was limited to peer-reviewed studies published between 1990 and 2023 in English using the PubMed search engine. Relevant studies may have been missed if they were published outside of this frame, including “gray” literature, or in a language other than English. This review is also limited to studies that included cumulative ACE exposure. Therefore, this search is likely not exhaustive for all types of individual adversity that may be relevant to age of initiation. It is possible that specific adversities may be differentially associated with earlier age of initiation, which may inform prevention and intervention strategies further. However, the use of

cumulative ACE scores acknowledges the high level of co-occurrence of different childhood adversities and that dose-dependent associations have been commonly reported in similar literature around ACEs and substance use (Grummitt et al., 2021; Shin, McDonald, & Conley, 2018).

All but one study reported statistically significant ($p < 0.05$) findings for at least one substance assessed. It is possible that studies with null findings were excluded from publication and therefore not included in this review. Although not all psychoactive substances are represented in this review, we reviewed the most prevalent substances used in the United States. The substances included in this review may not generalize to other countries/populations where substance use patterns differ.

Conclusion

There is growing evidence that ACEs predict earlier age of initiation of substance use, including alcohol, marijuana, nicotine, and opioids, in a dose-dependent manner. Given evidence that earlier age of substance initiation may mediate the association between ACEs and substance use disorders in adulthood (Dawson et al., 2008; Liang & Chikritzhs, 2015; Lynskey et al., 2003; Richmond-Rakerd et al., 2015), substance use intervention and prevention strategies should consider the potential impact of ACEs on adolescent initiation of substance use to inform timing and approach. Findings that ACEs are associated with prepubescent and pubescent initiation of substance use, particularly alcohol use, suggest that prevention interventions may be most effective if implemented in early childhood rather than in adolescence, though future studies identifying specific ages at which increased risk

begins are necessary to inform intervention efforts. Additionally, more studies that address temporality limitations related to ACEs and adolescent substance use are needed. Despite these limitations, evidence suggests that adequate and routine ACE screening in both pediatric and adolescent settings may identify youth at greatest risk of early initiation and subsequent substance use disorder to be targeted for service provision prior to substance initiation. Future research should also examine potential mediators and moderators of the association between ACEs and specific substance use patterns in adolescents to inform public health initiatives.

Chapter 3: Intergenerational Adverse Childhood Experiences and Offspring Age of Alcohol Initiation

Introduction

Approximately 10-15% of harmful alcohol use can be attributed to adverse childhood experiences (ACEs) (Grummitt, Barrett, & Newton, 2022). ACEs traditionally include experiencing violence, abuse, or neglect; witnessing violence in the home or community; having a family member attempt or die by suicide; or growing up in a household with substance use problems, mental health problems, or instability due to parental separation or incarceration (CDC, 2023). Evidence suggests that age of alcohol initiation, specifically, may mediate the association between ACEs and alcohol use disorder (AUD) across the life course (Dawson et al., 2008; Liang & Chikritzhs, 2015; Lynskey et al., 2003; Richmond-Rakerd et al., 2015). Several studies have found an association between ACEs and earlier age of alcohol initiation (Chatterjee et al., 2018; Rothman et al., 2008; Hughes et al., 2019; Dube et al., 2006; Goncalves et al., 2016; Nagata et al., 2023; Woloshchuk et al., 2022), with most reporting a dose-response association. There is also growing evidence that ACEs predict health and behavioral outcomes across generations (Zhang, Gruber, & Kim, 2022). The intergenerational impact of ACEs is supported by two bodies of evidence—the first is that there is often intergenerational continuity of ACEs, in which maternal ACE exposure predicts offspring ACE exposure; the second is that there is growing evidence

that maternal ACEs may independently predict many of the same adverse health and behavioral outcomes among offspring that are found within generations. Yet, current literature assessing the association between maternal ACEs and offspring outcomes are primarily limited to psychological outcomes in early childhood, such as internalizing and externalizing behaviors (Zhang et al., 2022). There is currently a dearth of literature assessing the intergenerational impact of ACEs on other plausible offspring behavioral outcomes, like offspring age of alcohol initiation.

While evidence suggests that adolescents exposed to adversity themselves may engage in earlier alcohol use as a way to cope with negative feelings (Agnew & Brezina, 1992; Grummitt et al., 2021; Teixeira et al., 2017), offspring of mothers exposed to early adversity may be vulnerable to a host of biological and psychosocial factors that independently predict earlier age of alcohol use. Emerging evidence suggests that the association between maternal ACEs and offspring outcomes may be modulated by persistent alterations in the maternal HPA-axis, which is responsible for regulating stress response, that occur in response to early childhood adversity and that these adaptations may be transmitted to the fetus in a similar way that acute stress is transmitted to the fetus in-utero. Maternal early life adversity has been demonstrated to be associated with increased placental CRH toward the end of gestation (Moog et al., 2016) and increased cortisol concentrations after waking among pregnant individuals even after accounting for proximal stressors (Thomas et al., 2018), suggesting that the impact of maternal ACEs may persist across the life course, including during pregnancy, independent of present stressors. Increased placental CRH and fetal cortisol levels have been found to be associated with increased risk of mood disorders and

substance use (Enoch, 2011; Somaini et al., 2010; Tervo-Clemmens et al., 2020; Walters & Kosten, 2019).

It is also possible that maternal ACEs predict earlier offspring age of alcohol initiation via postnatal environmental factors associated with intergenerational ACE exposure. Because maternal ACEs predict offspring ACEs, and offspring ACEs predict earlier age of alcohol initiation, it is reasonable to assume that offspring ACE exposure or confounders between offspring ACE exposure and age of initiation (e.g., home environment, parenting attributes), may mediate the association between maternal ACEs and offspring age of alcohol initiation. Marginal structural models can estimate the controlled direct effect of maternal ACEs on offspring age of initiation not through offspring ACE exposure, while correctly accounting for confounders between offspring ACE exposure and age of initiation that are impacted by maternal ACE exposure. Estimating the controlled direct effect of maternal ACEs on offspring age of alcohol initiation not through offspring ACEs can potentially elucidate important mechanisms behind the impact of intergenerational adversity on age of alcohol initiation, and subsequent risk of AUD.

While the intergenerational continuity of ACEs is well established, continuity across generations is not determinative. There are both dyads who are concordant and discordant for ACE exposure—that is to say, there will be dyads who have similar levels of ACE exposure and those who have different levels of ACE exposure. Therefore, the association between maternal ACEs and offspring age of alcohol initiation may be different depending on offspring ACE exposure. Offspring who are exposed to high maternal ACE exposure and high ACE exposure themselves may be

most vulnerable to initiating alcohol use early, as this population may be subject to greater HPA axis dysfunction (e.g., higher cortisol) in-utero, the effects of which may be compounded by postnatal exposure to stress (e.g., ACEs). Individuals concordant for high ACE exposure may also be subject to higher exposure to adverse postnatal environmental factors known to be associated with maternal ACEs, such as poor parenting practices, poverty, and other psychosocial risk factors. Conversely, offspring exposed to high maternal ACEs, but low ACEs themselves may benefit from protective factors that are known to disrupt the intergenerational continuity of ACEs and that may buffer against the intergenerational impact of ACEs on adverse health outcomes. For example, familial emotional support has been identified as one such protective factor in related intergenerational ACE literature. Higher emotional support is associated with reduced intergenerational continuity of adversity (Schofield et al., 2013) and has been separately identified as being a protective factor against the impact of maternal ACEs on elevated offspring behavioral problems (Hatch, Swerbenski, & Gray, 2020; Dishion & McMahon, 1998; Donaldson, Nakawaki, & Crano, 2016). Parental involvement, including helping with homework, assigning chores, and limiting TV watching, has been identified as another important factor in disrupting intergenerational ACEs and protecting against adolescent substance use (Donaldson, Nakawaki, & Crano, 2016; Parker & Benson, 2005).

Examining how intergenerational ACE exposure operates among dyads concordant vs. discordant for elevated ACE exposure may inform future intergenerational ACE research and intervention efforts. It is likely that the impact of intergenerational ACEs is not a monolith and may depend on complex factors involved

in the intergenerational continuity and transmission of adversity. The present study seeks to 1) estimate the controlled direct effect of maternal ACEs on offspring age of alcohol initiation; and 2) assess whether controlled direct effects of maternal ACEs on offspring age of alcohol initiation depend on offspring ACE exposure. Findings may inform interventions aimed at identifying adolescents at risk of earlier initiation of alcohol use and interventions aimed at preventing AUD.

Methods

Study Sample

We analyze data from the National Longitudinal Survey of Youth (NLSY) (Bureau of Labor Statistics, 2019)— a biennial survey of a nationally representative sample of American youth born between 1957-1964 starting in 1979 (NLSY79) and female NLSY79 respondents' offspring who were enrolled in a separate biennial survey starting in 1986, the National Longitudinal Survey of Youth 1979 Child and Young Adult cohort (NLSCYA) (Bureau of Labor Statistics, 2019). The sample for this study is comprised of female respondents of the NLSY and their children enrolled in the NLSYCYA. As of 2018, 6,283 NLSY79 mothers had 11,545 offspring enrolled in the NLSYCYA study. The NLSY provides analogous childhood adversity data on both generations. Offspring were excluded from the sample if they were too young (<14 years old) at the latest interview round (n=456), if they reported never drinking through latest interview round (n=1,788), were lost to follow-up (n=4,055), or they had missing data (n=2,178). Missing data included missing maternal ACE exposure (n=722), offspring ACE exposure (n=445), or covariates including poverty status (n=412), and

maternal age of alcohol initiation (n=599). The final analytic sample included 3,068 offspring born to 1,454 mothers who provided data on all identified covariates.

Measures

Age of initiation of alcohol use is measured, starting at age 14, by an item asking about the age of respondents when they first drank alcohol at least once a month or more, consistent with literature defining once a month or more as “regular use” (Sartor et al., 2016). This measure is more sensitive to potentially problematic drinking than asking when they first drank a sip or more than a sip of alcohol.

ACEs are measured using NLSY’s childhood adversity battery, administered to both mothers and their offspring in either 2012, 2014, or 2016. This 4-item battery inquires 1) whether respondents ‘lived with a household member who was depressed, mentally ill, suicidal’ (0=no, 1=yes), 2) ‘lived with someone who was a problem drinker or alcoholic before age 18’ (0=no, 1=yes), 3) ‘how often they were hit or physically abused as a child beyond spanking’ (0=never or once, 1=more than once), and 4) ‘how much parental love and affection they received before age 18’ as a measure of emotional neglect (reverse coded as 1=none at all or a little, 0= quite a lot or a great deal). While the 4-item ACE battery included in the NLSY is not validated, all items except for the item measuring parental love and affection are included in traditional ACE batteries that have been validated (Felitti et al., 1998). The parental love and affection question is intended to capture emotional abuse and neglect, which is a concept included in most ACE batteries and has been included in other literature that uses the NLSY Childhood Adversity Battery (Williams & Finch, 2019; Ports et al.,

2021). All items were first summed to create an ACE composite score (0-4). ACEs were included in analysis as indicator variables (0 ACEs, 1 ACE, 2 ACEs, >2 ACEs). Dose-dependent associations between ACEs and health and behavioral outcomes are often identified in the literature, with >3 ACEs often used as a threshold for “high” ACE exposure. In this sample, most offspring were born to mothers who reported no adversity (59.0%), while 23.3% reported experiencing 1 ACE, 11.0% reported experiencing 2 ACEs, and 6.7% reported experiencing >2 ACEs. Given the distribution, and that the ACE battery in this study was limited to four measures, not including the most common ACEs experienced in the general population (e.g., parental divorce), >2 ACEs was chosen as the “high” threshold of ACE exposure.

Covariates were chosen a priori based on extant literature assessing ACEs and age of alcohol initiation (Chatterjee et al., 2018; Rothman et al., 2008; Hughes et al., 2019; Dube et al., 2006; Goncalves et al., 2016; Nagata et al., 2023; Woloshchuk et al., 2022). Variables known to be associated with ACEs and age of alcohol initiation include race/ethnicity, poverty status, maternal marital status and educational attainment, and home environment. Race/ethnicity was parameterized in the NLSY survey and in this study as non-Black, non-Hispanic (includes White, “other” or neither Black nor Hispanic), Black, or Hispanic. Offspring are assigned the same race/ethnicity as their mothers. Poverty status was coded as a dichotomous variable based on year-specific poverty thresholds and obtained within +/- 3 years of birth. Maternal marital status was parameterized as never married, married vs. other; maternal educational attainment as < high school, high school graduate, some college, or college graduate. The HOME-SF is a validated survey of the home environment (i.e., degree of emotional

support and cognitive stimulation provided to the child) based on maternal report and interviewer observation (e.g., interviewer observed mother spontaneously vocalize to/converse with child at least twice during interview; Caldwell & Bradley, 1984).

In order to estimate the controlled direct effect of maternal ACEs on offspring age of alcohol initiation, we distinguish between confounders of the association between maternal ACEs and offspring age of alcohol initiation (race/ethnicity, poverty status), and confounders of the association between offspring ACEs and offspring age of alcohol initiation (sex, birth order, maternal age of alcohol initiation, home environment, maternal marital status, maternal educational attainment, maternal age at birth). See figures 2 and 3 for directed acyclic graphs illustrating potential mediating mechanisms. Figure 2 represents traditional regression approaches to assess direct effects. Figure 3 represents the marginal structural modeling approach to assess controlled direct effects, accounting for each set of confounders.

Analysis

Descriptive statistics were computed (means, frequencies) for the independent variable (maternal ACEs) and all covariates. We then estimated the total association between maternal ACEs and offspring age of alcohol initiation by fitting linear regression models adjusted for confounders of the association between maternal ACEs and offspring age of alcohol initiation using PROC GENMOD (link=identity) (Total Effects Model). Robust standard errors based on a working exchangeable correlation matrix were used to correct for dependence in the risk of early age of alcohol initiation across multiple offspring born to the same mother. This model is

akin to traditional regression approaches that are found in current intergenerational ACE literature. In order to account for selection bias caused by loss-to-follow-up inverse probability weights (IPW) for age of alcohol initiation were estimated (Narduzzi et al., 2014) and multiplied by NLSYCYA survey weights and included in all models. The IPW was calculated using the eligible population of study and predicting the probability of non-missingness using a logistic regression model, where the response was the non-missingness and the covariates were its possible predictors. The weight of each subject was given by the inverse of the predicted probability. Including these weights in the models is akin to estimating the associations had all eligible offspring provided information on age of alcohol initiation. Predictors of non-missingness included sex, race/ethnicity, poverty status, maternal education, and marital status.

In traditional mediation analysis between an exposure X and an outcome Y , estimation of the direct effect of X on Y is estimated after adjustment for the mediator M ; however, this estimate may be biased if Z is a confounder between M and Y , and is also affected by X (Lepage, Dedieu, Savy, & Lang, 2016). In this case, traditional regression approaches would allow one to estimate the direct effect of maternal ACEs on offspring age of initiation that is not through offspring ACEs or any of the measured confounders between offspring ACEs and offspring age of initiation, though it is possible that the pathway between maternal ACEs and offspring age of initiation is through these measured factors (e.g., maternal age of alcohol initiation, home environment). The marginal structural model circumvents this issue by estimating the controlled direct effect of maternal ACEs on offspring age

of alcohol initiation. To account for potential mediation of offspring ACEs in the association between maternal ACEs and offspring age of initiation, we estimated the controlled direct effect of maternal ACEs on offspring age of alcohol initiation by fitting marginal structural models (VanderWeele, 2009). The marginal structural model is a weighted linear regression model that accounts for potential confounding with two stabilized inverse probability of treatment weights (IPTW), one accounting for the measured confounding between maternal ACEs and offspring age of alcohol initiation (w_i^M) and one accounting for the measured confounding between offspring ACEs and offspring age of alcohol initiation (w_i^C). The coefficient from the weighted model provides an estimate of the direct effect of maternal ACEs not mediated by offspring ACEs provided that the two sets of confounders are sufficient to control for confounding between maternal ACEs and offspring age of alcohol initiation and between offspring ACEs and offspring age of alcohol initiation.

To assess whether there was a difference in association between maternal ACEs and offspring age of initiation by level of offspring ACE exposure, a dichotomous variable for high offspring ACE exposure (>2) was created. An interaction term with this dichotomous variable was included for each category of maternal ACE exposure in the marginal structural model. Separate estimates of the controlled direct effect of maternal ACEs on offspring age of alcohol initiation were fit for offspring exposed to ≤ 2 ACEs and offspring exposed to >2 ACEs.

Results

Characteristics of the sample and bivariate associations with means age of alcohol initiation are presented in table 2. Offspring were primarily female (51.6%), not in poverty (76.0%), whose mothers had at least a high school education (76.9%) and were married (61.3%). Most offspring reported no adversity themselves (65.5%), with 21.8% reporting exposure to 1 ACE, 8.3% reporting exposure to 2 ACEs, and 4.4% reporting exposure to >2 ACEs. Maternal and offspring ACE scores were significantly correlated ($r=0.17$, $p<0.001$).

Results from both the total effects model and the marginal structural model are presented in table 3. Results from the total effects model show that there is an inverse relationship between maternal ACEs and offspring age of alcohol initiation. Specifically, 1 maternal ACE is associated with $\beta=-0.3$ (95% CI: 0.6, -0.1) years, 2 ACEs are associated with $\beta=-0.2$ (95% CI: -0.6, -0.1) years, and >2 ACEs are associated with $\beta=-0.6$ (95% CI: -1.0, -0.1) years earlier age of alcohol initiation. In the marginal structural model, associations are significantly attenuated. Specifically, 1 maternal ACE is associated with $\beta=-0.2$ (95% CI: -0.5, 0.0), 2 ACEs are associated with $\beta=-0.1$ (95% CI: -0.5, 0.2), and >2 ACEs are associated with $\beta=-0.4$ (95% CI: -0.9, 0.1) earlier age of alcohol initiation. While not rising to statistical significance ($p<0.05$), these models show that there is a small inverse relationship between maternal ACEs and offspring age of alcohol initiation.

The model assessing moderation of the association between maternal ACEs and offspring age of alcohol initiation by offspring ACE exposure revealed that the

controlled direct effect of maternal ACEs depends on offspring ACE exposure. The interaction term was significant ($p=0.01$), with >2 maternal ACEs associated with significantly earlier age of initiation among offspring similarly exposed to >2 ACEs compared to offspring exposed to ≤ 2 ACEs (see figure 4). Results from models assessing the association between maternal ACEs and offspring age of alcohol initiation stratified by offspring ACE exposure is presented in table 4. Among offspring exposed to >2 ACEs, 2 maternal ACEs are associated with $\beta=-1.4$ (95% CI: -2.7, -0.1) years earlier age of initiation, and >2 maternal ACEs are associated with $\beta=-2.1$ (95% CI: -3.8, -0.5) years earlier age of alcohol initiation. No direct effect of maternal ACEs was found among offspring exposed to ≤ 2 ACEs.

Discussion

Findings from the total effects model suggests that maternal ACEs are associated with earlier offspring age of alcohol initiation. However, attenuated findings from the marginal structural model suggests that this association is not independent of offspring ACEs. While formal mediation analysis is beyond the scope of this study, the attenuation of significant findings in the total effects model to non-significance in the marginal structural model suggest that, among the full sample, the association between maternal ACEs and offspring age of initiation may be mediated by offspring ACEs or the confounders between offspring ACEs and offspring age of alcohol initiation (e.g., home environment, maternal age of alcohol initiation). However, this assumption may not hold true if there is an interaction between the effects of maternal ACEs and offspring ACEs on offspring age of initiation; in this

case, the controlled direct effect may differ from the total effect even if maternal ACEs are not a cause of offspring age of initiation (VanderWheele, 2011). Moderation analysis suggests that the controlled direct effect of maternal ACEs on offspring age of alcohol initiation depends on offspring ACE exposure. While no linear trend between increasing maternal ACEs and earlier age of alcohol initiation was found in the total effects or marginal structural models among the full sample, a dose-dependent association was found among offspring exposed to >2 ACEs themselves, with >2 maternal ACEs being associated with the earliest initiation. Among offspring exposed to lower levels of adversity, no association between maternal ACEs and earlier age of alcohol initiation was found. These findings suggest that the intergenerational impact of ACEs on earlier age of initiation are strongest for offspring concordant for high intergenerational ACE exposure.

This study's finding of an association between maternal ACEs and earlier age of initiation among offspring exposed to similarly high levels of ACEs may be supported by both biological and psychosocial mechanisms. Offspring of mothers with high ACE exposure may be vulnerable to greater HPA axis dysfunction (e.g., higher cortisol) (Moog et al., 2016; Thomas et al., 2018). These impacts may be further compounded, leading to greater HPA axis dysfunction, as a result of postnatal ACE exposure—the sequelae of which may predict risk of earlier age of alcohol initiation via increased cortisol and reactivity to stress (Enoch, 2011; Somaini et al., 2010; Tervo-Clemmens et al., 2020; Walters & Kosten, 2019). Offspring with high intergenerational ACE exposure may be subject to a number of psychosocial risk factors, including poverty, housing insecurity, and low educational attainment, as well

as socioemotional risk factors like poor maternal attachment and low emotional support, none of which are adequately captured by offspring ACE measures used in this, or any other ACE study. Conversely, offspring with high maternal ACE exposure and low ACE exposure themselves may be exposed to protective psychosocial factors like increased familial emotional support and parental involvement that explain the discordance in adversity (high maternal ACE exposure, low offspring ACE exposure).

Regardless of the underlying mechanisms, our findings suggest that offspring intergenerationally concordant for high ACE exposure may be at greatest risk of early alcohol initiation. Screening for maternal ACEs in addition to offspring ACEs may identify these youth for targeted service provision earlier in the life course. While maternal ACEs are not yet routinely screened for, there are initiatives, like California's ACEs Aware, that are attempting to routinely screen for ACEs across the prenatal, pediatric, and adult primary care settings (Watson, Mateo, & Vetter, N.D.). The prenatal period has been identified as an important period for ACE screening for other health outcomes (Flanagan, Alabaster, McCaw, Stoller, Watson, & Young-Wolff, 2018), and in this context, may play an important role in informing pediatric practice as well. While a number of barriers to routine prenatal ACE screening have been identified, including lack of time and confidence by healthcare providers, lack of training on ACEs, lack of professional guidelines for screening, lack of privacy, lack of information to give patients about ACEs ahead of screening, and lack of cultural competency (Tran et al., 2022), funding for training as part of comprehensive initiatives like ACEs Aware could reduce these barriers.

This study has several strengths. While few studies have conceptually or methodologically accounted for the intergenerational continuity of ACEs when assessing the intergenerational impact of ACEs on offspring outcomes (Deardorff, Borgen, Rauch, Kogut, & Eskenazi, 2024), this study addresses this gap by using parallel self-reported cumulative ACE measures for each member of the dyad to estimate the controlled direct effect of maternal ACEs on offspring age of alcohol initiation among a large population-based sample. This study also substantively contributes to the literature by expanding on outcomes besides behavioral ones at limited timepoints in early childhood. Finally, this is the first study to assess whether impacts of maternal ACEs on offspring outcomes are different depending on offspring ACE exposure. This study provides evidence that the intergenerational impact of ACEs extends to outcomes across the life course and that intergenerational impacts of ACEs may depend on concordance of ACE exposure across generations.

Limitations

This study is also subject to several limitations, several of which pertain to ACE measurement. First, the measurement of adversity among mothers & offspring is limited to only 4 items, one of which is not included in more traditional ACE batteries. It is possible that the item measuring emotional abuse or neglect does not actually measure that construct, as it has not been validated. Because some of the more commonly reported ACEs (i.e., parental separation, economic hardship) are not included in the NLSY adversity battery, there is a small sample of offspring exposed to both high (>2) maternal ACEs and high ACEs themselves. While not generally a

threat to our study's inference, other important adversities related to offspring age of initiation may not be included in this battery. There is no universally agreed upon ACE battery and the number and type of early life adversities varies greatly from study to study (Holden, Gower, & Chmielewski, 2020). There are also calls to include a broader range of early life adversities in ACE batteries, including those related to systemic or structural oppression, immigration, and community dysfunction (Helton et al., 2022). It is possible that early life adversity is underestimated when using traditional ACE batteries, including the one in this study, particularly for marginalized youth (Helton et al., 2022). It is also possible that certain adversities are more strongly related to early initiation, which is something that is not captured with the use of cumulative ACE scores in this study. For example, it is possible that offspring living with a problem drinker or alcoholic before age 18 is more predictive of early alcohol initiation than living with someone with a mental illness. However, the use of cumulative ACE scores acknowledges the high co-occurrence of different childhood adversities and allows for the assessment of dose-dependent associations, which are commonly reported in similar literature examining ACEs and substance use outcomes. Due to social desirability concerns, ACEs may be underreported, again potentially leading to the underestimation of associations. It is also possible that offspring ACEs occurred after age of alcohol initiation since ACEs are retrospectively reported and no information on timing of ACEs is provided. However, we reason that it is unlikely that the offspring's cumulative exposure to adversity would be substantively different across childhood and adolescence (i.e., before

initiation vs. after initiation) and therefore, issues around temporality are unlikely to substantively alter the inferences from this study.

While the majority of the non-Black, non-Hispanic category of participants self-identified as White, this category includes some traditionally marginalized races/ethnicities. Despite this, the non-Black, non-Hispanic category is used as the reference category in analysis. Our findings, therefore, may not generalize to specific races/ethnicities.

It is also possible that the two sets of confounders are not sufficient to adequately estimate the controlled direct effect of maternal ACEs on offspring age of initiation. While this study accounts, conceptually and methodologically, for a broad range of measured confounders between maternal ACEs and offspring age of initiation and between offspring ACEs and offspring age of initiation, it is possible that unmeasured confounders of either or both of these associations exist. Any unmeasured confounding between maternal ACEs and offspring age of initiation or between offspring ACEs and offspring age of initiation threatens causal inference from the controlled direct effect models, as no unmeasured confounding is a requirement of these models to avoid biased estimates. Future studies assessing the direct effect of maternal ACEs on offspring age of alcohol initiation that include expansive measures of potential confounders are needed to support our novel study's findings.

Conclusion

To conclude, offspring with higher ACE exposure (>2 ACEs) may be most vulnerable to the impacts of maternal ACEs compared to offspring exposed to no or low ACE exposure. Offspring with lower ACE exposure relative to their mother's may be exposed to protective factors that are simultaneously associated with the disruption of intergenerational continuity of adversity and amelioration of the association between maternal ACEs and offspring age of alcohol initiation. Screening and intervention efforts should consider both maternal exposure to ACEs and offspring exposure to ACEs in order to fully understand and address the impact of ACEs on adolescent alcohol use. Identification of specific protective factors and investigation of plausible biological and psychosocial mechanisms involved in the continuity and transmission of adversity are salient areas of future research, as findings may better inform tailored interventions aimed at reducing risky alcohol use in adolescence and beyond.

Table 2. G2 characteristics and associations with mean age of alcohol initiation, NLSYCYA (n=3,068)

Characteristic	Total N (%), M (SD)	Age of alcohol initiation M (SD)	P-value
	3,068	17.1 (2.7)	
Sex			<0.01
Female	1,583 (51.6)	17.3 (2.8)	
Male	1,485 (48.4)	16.9 (2.6)	
Poverty			0.97
No	2,332 (76.0)	17.1 (2.7)	
Yes	736 (24.0)	17.1 (2.9)	
Maternal age at birth			0.14
<20	664 (21.6)	17.2 (3.1)	
21-24	895 (29.2)	17.1 (2.9)	
25-28	866 (28.2)	17.2 (2.6)	
29-46	643 (30.0)	16.9 (2.3)	
Race/ethnicity			<0.01
Hispanic	600 (19.6)	16.7 (2.8)	
Black	912 (29.7)	17.7 (2.9)	
Non-Black, non-Hispanic	1,556 (50.7)	16.9 (2.5)	
Home environment	46.8 (29.1)	17.11 (2.7)	<0.01
Birth order			<0.05
First	1,375 (44.8)	17.3 (2.8)	
Second	1,023 (33.3)	17.0 (2.6)	
Third	473 (15.4)	16.3 (2.9)	
Fourth+	197 (6.5)	16.8 (2.9)	
Offspring ACEs			<0.01
0	2,009 (65.5)	17.3 (2.6)	
1	669 (21.8)	16.9 (2.9)	
2	256 (8.3)	16.7 (2.9)	
>2	134 (4.4)	16.3 (3.0)	
Maternal marital status			<0.01
Never married	903 (29.4)	17.4 (3.0)	
Married	1,882 (61.3)	17.1 (2.6)	
Other	283 (9.3)	16.7 (2.6)	
Maternal education			0.08
Less than HS	709 (23.1)	16.9 (2.9)	
HS graduate	1,420 (46.2)	17.1 (2.7)	
Some college	860 (28.0)	17.3 (2.6)	
College graduate	79 (2.6)	17.0 (2.2)	
Maternal ACEs			<0.01
0	1,809 (59.0)	17.3 (2.7)	
1	715 (23.3)	16.9 (2.7)	
2	339 (11.0)	17.0 (2.7)	
>2	205 (6.7)	16.6 (2.9)	

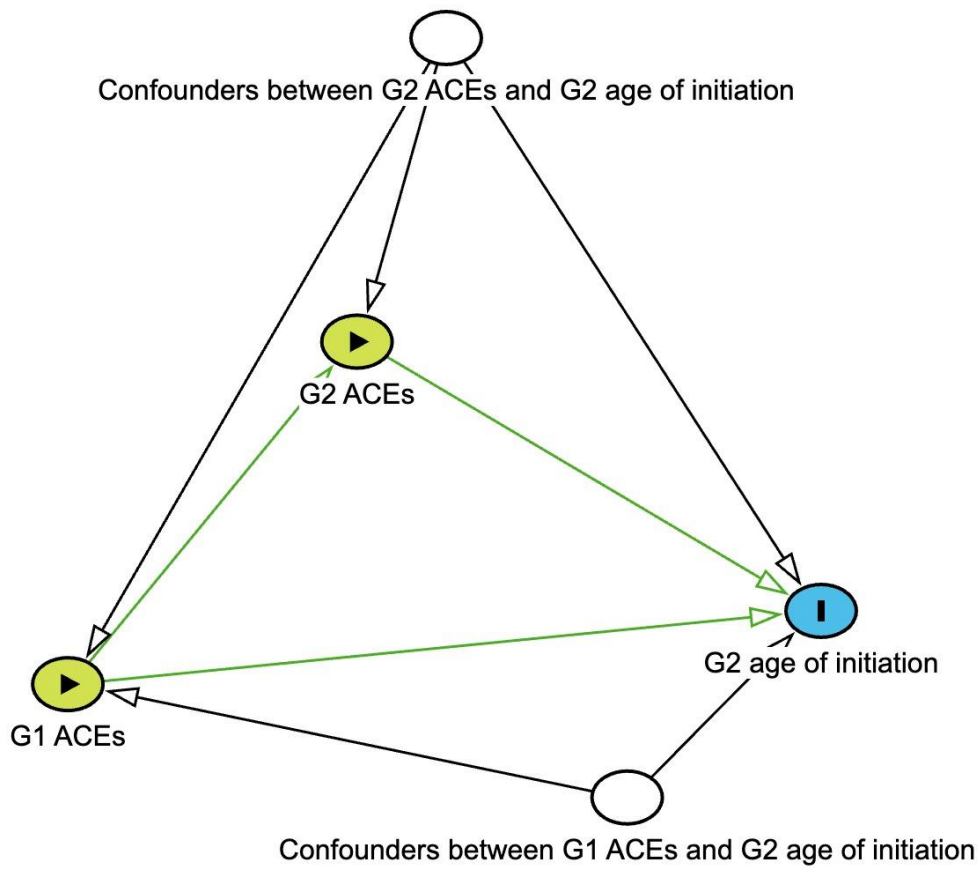
Table 3. Adjusted estimates of the association between ACEs and G2 age of alcohol initiation, NLSYCYA (n=3,068)

Parameter	Total Effects Model, Estimate β (95% CI)	Marginal Structural Model, Estimate β (95% CI)
Intercept	15.6	15.4
Maternal ACEs		
0	ref	ref
1	-0.3 (-0.6, -0.1)	-0.2 (-0.5, 0.0)
2	-0.2 (-0.6, -0.1)	-0.1 (-0.5, 0.2)
>2	-0.6 (-1.0, -0.1)	-0.4 (-0.9, 0.1)

Table 4. Controlled direct effect of G1 ACEs on G2 age of alcohol initiation stratified by G2 ACE exposure, NLSYCYA n=3,068

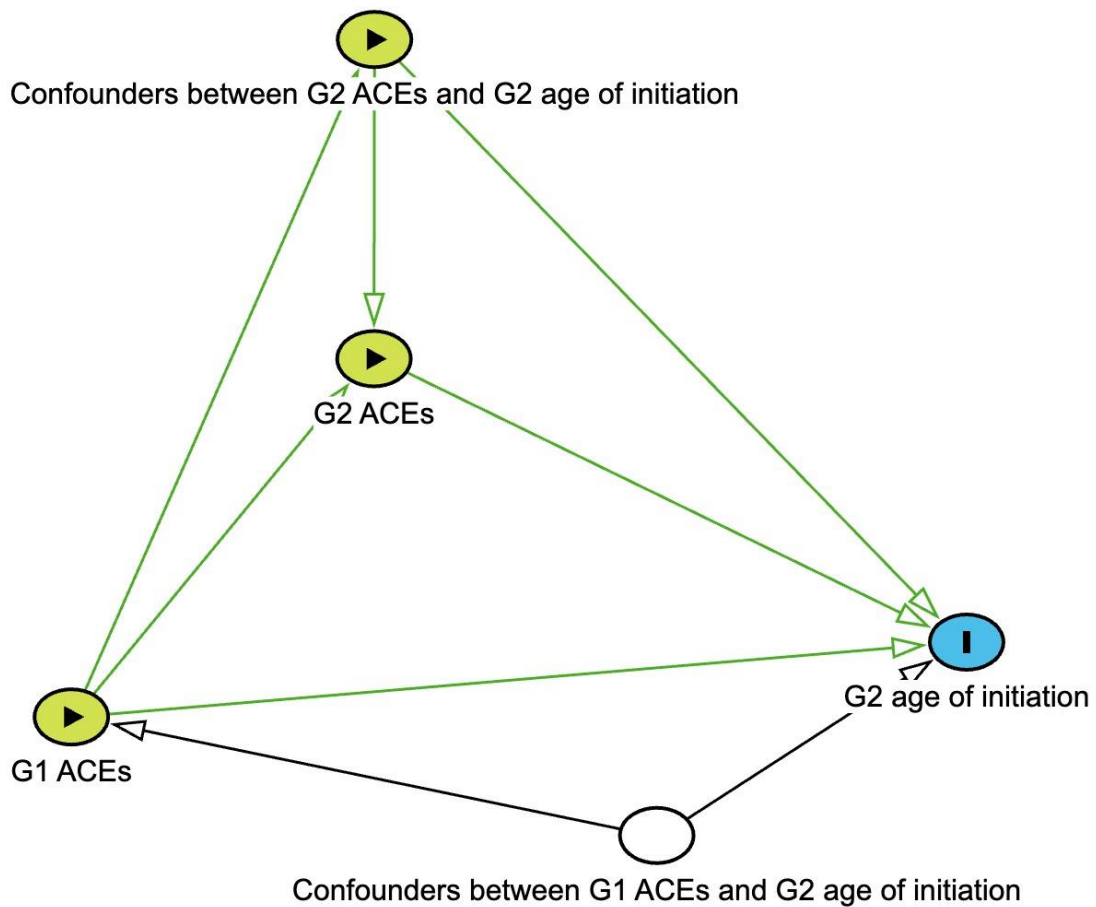
Parameter	G2 with ≤ 2 G2 ACEs n=2,934	G2 with > 2 G2 ACEs n=134
Intercept	15.64	11.87
G1 ACEs		
0	ref	ref
1	-0.2 (-0.5, 0.0)	-0.2 (-1.5, 1.1)
2	-0.1 (-0.4, 0.3)	-1.4 (-2.7, -0.1)
>2	-0.3 (-0.8, 0.1)	-2.1 (-3.8, -0.5)

Figure 2. Directed Acyclic Graphs illustrating the potential mechanisms underlying maternal (G1) ACEs and offspring (G2) age of alcohol initiation via G2 ACEs*



*Confounders of G1 ACEs and G2 age of initiation: race/ethnicity, poverty
 Confounders of G2 ACEs and G2 age of initiation: maternal educational attainment, age at birth, age of alcohol initiation, offspring sex, birth order, and home environment

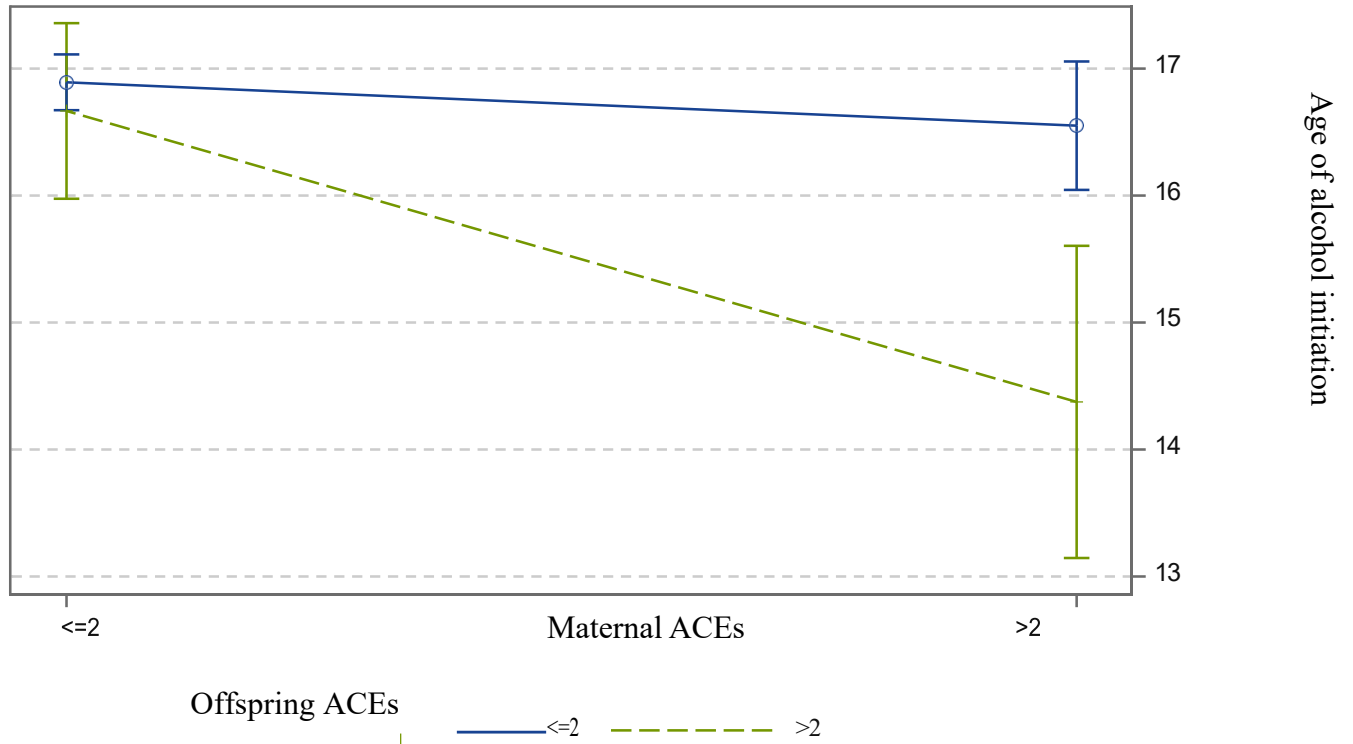
Figure 3. Directed Acyclic Graph illustrating the potential mechanisms underlying maternal (G1) ACEs and offspring (G2) age of alcohol initiation via G2 ACEs and/or confounders of the association between G2 ACEs and G2 age of alcohol initiation *



*Confounders of G1 ACEs and G2 age of initiation: race/ethnicity, poverty
 Confounders of G2 ACEs and G2 age of initiation: maternal educational attainment, age at birth, age of alcohol initiation, offspring sex, birth order, and home environment

Figure 4. Estimate of the association between G1 ACEs and G2 age of alcohol initiation stratified by G2 ACE exposure

Interaction Plot for Maternal ACE Exposure Stratified by Offspring ACE Exposure
With 95% Confidence Limits



Chapter 4: Disentangling the Impacts of Intergenerational Adversity on Offspring Internalizing and Externalizing Behavioral Outcomes

Introduction

A large and growing body of evidence supports a positive association between maternal adverse childhood experiences (ACEs) and poor behavioral problems, including internalizing and externalizing behavior (Cooke et al., 2019; Deardorff, Borgen, Rauch, Kogut, & Eskenazi, 2024; Doi & Isumi, 2021; Fredland, McFarlane, Symes, & Maddoux, 2018; Greenfield et al., 2019; Hatch, Swerbenski, & Gray, 2020; Hetherington, Racine, Madigan, McDonald, & Tough, 2020; Hanetz-Gamliel & Dolberg, 2022; Zhu, Zhan, Anme, & Zhang, 2023; Kang et al., 2021; Khan & Renk, 2019; Khoury et al., 2022; Kumar et al., 2018; Min, Singer, Minnes, Kim, & Short, 2013; Letourneau, et al., 2019; McDonald et al., 2019; Ochoa, Fernandez, Lee, & Estrada, 2022; Plant, Jones, Pariante, & Pawlby, 2017; Schickendanz, Halfon, Sastry, & Chung, 2018; Rieder et al., 2019, Stepleton, Bosk, Duron, Greenfield, Ocasio, & Mackenzie, 2018; Stargel & Easterbrooks, 2020; Sauve et al., 2022; Thomas-Argyriou, Letourneau, Dewey, Cambell, and Gielsbrecht, 2021; Thomas-Giyer & Keesler, 2021; Van de Ven, Van den Heuvel, Bhogal & Thomason, 2020; Wang, Lee, & Camille, 2022; Wang et al., 2022; Yoon, Cederbaum, Mennen, Traube, Chou, & Lee, 2019; Zhang, Mersky, & Lee, 2023) and depression (Dennis, Clehessy, Stone, Darnall, &

Wilson, 2019; Haynes, Crouch, Probst, Radcliff, Bennett, & Glover, 2020), often in a dose-dependent manner. There is also ample evidence of the intergenerational continuity of ACEs, in which maternal ACE exposure predicts offspring ACE exposure (Madigan et al., 2019; Narayan, Kalstabakken, Labella, Nerenberg, Monn, & Masten, 2017; Schofield, Lee, & Merrick, 2013; Smith, Brumage, Zullig, Claydon, Smith, & Kristijansson, 2021; Negriff, 2020). Given evidence of the intergenerational continuity of ACEs and that offspring ACEs independently predict internalizing (Flouri & Panourgia, 2011) and externalizing behavior (Appleyard, Egeland, van Dulmen, & Alan Sroufe, 2005; Baglivio et al., 2014) it is reasonable to question whether offspring exposure to ACEs is a determinant in the association between maternal ACEs and offspring behavioral outcomes. Yet no study to date has assessed the controlled direct effect of cumulative maternal ACEs on offspring behavior independent of offspring ACEs.

In traditional mediation analysis between an exposure X and an outcome Y , estimation of the direct effect of X on Y is estimated after adjustment for the mediator M ; however, this estimate may be biased if Z is a confounder between M and Y , and is also affected by X (Lepage, Dedieu, Savy, & Lang, 2016). In this study, traditional regression approaches would allow one to estimate the direct effect of maternal ACEs on offspring behavior that is not through offspring ACEs or any of the measured confounders between offspring ACEs and offspring behavior, though it is possible that the pathway between maternal ACEs and offspring behavior is through these measured factors (e.g., home environment, maternal depression). The marginal structural model circumvents this issue by estimating the controlled direct

effect of maternal ACEs on offspring outcomes using two inverse probability of treatment weights, one to account for measured confounding of the association between maternal ACEs and offspring outcomes and one to account for the confounding of the association between offspring ACEs and offspring outcomes. Estimating the controlled direct effect of maternal ACEs on offspring behavior not through offspring ACEs can potentially elucidate important mechanisms behind the impact of intergenerational adversity on behavioral outcomes that can be used to inform intervention. The present study seeks to estimate the controlled direct effect of maternal ACEs of offspring internalizing and externalizing behavior.

Epidemiological Evidence

Extant studies assessing the association between maternal ACEs and offspring behavioral outcomes include cumulative measures of maternal ACEs (≥ 4 measures of adversity) that encompass both maternal maltreatment (e.g., sexual, physical, emotional abuse) and household dysfunction (e.g., living with someone with a mental illness or substance use disorder) (Zhang, Gruber, & Kim, 2022). Importantly, the intergenerational continuity of ACEs includes both the continuity of maltreatment and the continuity of household dysfunction. Consistent with family systems and attachment theories, evidence suggests that maltreated individuals are more likely than others to maltreat their own children (Madigan et al., 2019). There is also evidence that mothers exposed to ACEs are more likely to experience mental health issues, domestic violence, substance use disorder, and socioeconomic insecurity in adulthood, which can translate to the offspring's cumulative experience of childhood

adversity via household dysfunction (Narayan, Kalstabakken, Labella, Nerenberg, Monn, & Masten, 2017; Schofield, Lee, & Merrick, 2013; Smith, Brumage, Zullig, Claydon, Smith, & Kristijansson, 2021; Negriff, 2020). ACEs, including those associated with maltreatment and household dysfunction, often co-occur. Evidence suggests that the impact of ACEs often vary as a function of the total number of ACEs experienced. It is reasonable to assume that the mechanisms behind intergenerational transmission of ACEs may vary as a function of total number of ACEs as well. Therefore, including parallel measures of cumulative offspring ACE exposure is necessary when assessing the independent association between maternal cumulative ACEs and offspring outcomes.

While no study to date has assessed the controlled direct effect of cumulative maternal ACEs on offspring behavioral outcomes, one study used structural equation modeling to determine whether the association between cumulative maternal ACEs and offspring internalizing and externalizing behavior was mediated by cumulative offspring ACE exposure among Latino families (Deardorff, Borgen, Rauch, Kogut, & Eskenazi, 2024). Results from this study found that maternal ACEs were directly associated with maternal reported internalizing and externalizing behaviors, but that maternal ACEs were only indirectly associated with youth-reported internalizing behaviors via the combined effect of maternal depression and offspring ACEs. Several other studies have assessed the mediating role of maternal mental health and parenting attributes in the association between maternal ACEs and offspring behavior—both of which can be experienced as adversity by the offspring. Of the studies that assessed maternal mental health (Cooke, Racine, Plamondon, Tough, &

Madigan, 2019; Letourneau et al., 2019; Ochoa, Fernandez, Lee, & Estrada, 2022; Plant, Jones, Pariante, & Pawlby, 2017; Schickendanz, Halfon, Sastry, & Chung, 2018; Dennis, Clohessy, Stone, Darnall, & Wilson, 2019; Khoury et al., 2022; Kumar et al., 2018; Min, Singer, Minnes, Kim, & Short, 2013; Rieder et al., 2019; Zhang, Mersky, & Lee, 2023; Hetherington, Racine, Madigan, McDonald, & Tough, 2020; Hanetz-Gamliel & Dollberg, 2022; Zhu, Zhan, Anme, & Zhang, 2023) and/or parenting attributes (Cooke, Racine, Plamondon, Tough, & Madigan, 2019; Ochoa, Fernandez, Lee, & Estrada, 2022; Plant, Jones, Pariante, & Pawlby, 2017; Schickendanz, Halfon, Sastry, & Chung, 2018; Thomas-Giyer & Keesler, 2021; Khoury et al., 2022; Yoon, Cederbaum, Mennen, Traube, Chou, & Lee, 2019; Hetherington, Racine, Madigan, McDonald, & Tough, 2020; Hanetz-Gamliel & Dollberg, 2022) as mediating pathways between maternal ACEs and offspring behavioral outcomes, half found evidence of mediation of at least one offspring outcome by maternal mental health (Cooke, Racine, Plamondon, Tough, & Madigan, 2019; Dennis, Clohessy, Stone, Darnall, & Wilson, 2019; Zhang, Mersky, & Lee, 2023), physical discipline and parenting stress (Yoon, Cederbaum, Mennen, Traube, Chou, & Lee, 2019), maternal psychopathology and hostile parenting (Hanetz-Gamliel & Dollberg, 2022), and the combination of maltreatment, maternal mental health and positive parenting (Khoury et al., 2022). In two studies, poor maternal health fully mediated the association between maternal ACEs and offspring internalizing behaviors (Cooke, Racine, Plamondon, Tough, & Madigan, 2019), and depression (Dennis, Clohessy, Stone, Darnall, & Wilson, 2019), but not between maternal ACEs and externalizing behaviors.

Overall, epidemiological evidence suggests that maternal ACEs predict elevated internalizing and externalizing symptomatology in a dose-dependent manner and that this association may, in part, be mediated by factors that translate to the offspring's cumulative experience of childhood adversity. Assessing the controlled direct effect of maternal ACEs on offspring internalizing and externalizing behaviors not through cumulative offspring ACEs may provide a more nuanced understanding of the pathways involved and a more precise estimation of the magnitude of the association between maternal ACEs and offspring internalizing and externalizing behavior than what is currently found in the literature.

If the mechanism behind the association between maternal ACEs and offspring behavior is through offspring ACEs then the standard approach of screening, prevention, and intervention efforts at the intra-generational level will suffice to understand and address the impact of ACEs on behavioral outcomes. If, however, there is a direct association between maternal ACEs and offspring behavior this suggests that a two-generation paradigm to practice, in which ACE screening is conducted among the dyad and intervention efforts account for the intergenerational exposure to ACEs, may be necessary to fully understand and ameliorate the impact of ACEs on behavioral outcomes.

Methods

Study Sample

We analyze data from the National Longitudinal Survey of Youth (NLSY) (Bureau of Labor Statistics, 2019)— a biennial survey of a nationally representative

sample of American youth born between 1957-1964 starting in 1979 (NLSY79) and female NLSY79 respondents' offspring who were enrolled in a separate biennial survey starting in 1986, the National Longitudinal Survey of Youth 1979 Child and Young Adult cohort (NLSCYA) (Bureau of Labor Statistics, 2019). The sample for this study is comprised of female respondents of the NLSY and their children enrolled in the NLSYCYA. As of 2018, 6,283 NLSY79 mothers had 11,545 offspring enrolled in the NLSYCYA study. Approximately 98% of offspring respondents completed more than six Child and Young Adult interviews through 2018 (Bureau of Labor Statistics, 2019). The NLSY provides analogous childhood adversity data on both generations as well as data on offspring behavioral outcomes using validated measures.

Offspring were excluded from the sample if they were older than 14 years old at the first interview or younger than 4 years old at the last interview round (n=1,652), lost to follow-up (n=124) or they had missing data (n=4,324). Missing data included missing maternal ACE exposure (n=1,943), offspring ACE exposure (n=1,306), or covariates including poverty status (n=469), maternal depression (n=146), and home environment (n=460). The final analytic sample included 5,445 offspring with data on all covariates born to 2,792 mothers.

Measures

The Behavior Problem Index (BPI) was used to estimate internalizing (i.e., depression, anxiety, dependence, withdrawal) and externalizing (i.e., aggression, conduct disorders, and attention deficit hyperactive disorder) scores based on maternal report from age 4-14 (Baker & Mott, 1989). The BPI uses items derived from the

validated Child Behavior Checklist (Achenbach & Edelbrock, 1981) to assess behavior in children over the age of four. The BPI assessment is among the most commonly used of the NLSY79 child assessments, both as an outcome and as a robust predictor of a wide range of child attitudes and behaviors and has been used to test the reliability and validity of other behavioral scales (Baker & Mott, 1989). The 28-item BPI is composed of six subscales: antisocial behavior, anxiousness/depression, headstrongness, hyperactivity, immature dependency, and peer conflict/social withdrawal, which are aggregated into internalizing and externalizing scales (see appendix E for full items). Scores from ordinal variables (not true (0), sometimes true (1), often true (2)) were summed and then averaged across all available years to minimize the influence of outlier scores. These scores were standardized (mean 100, standard deviation of 15) based on 1981 National Health Interview Survey administration (Baker & Mott, 1989). Quartiles (Q) of internalizing and externalizing scores were also calculated to assess the association between maternal ACEs and odds of scoring in the highest quartile of internalizing and externalizing behavior. While assessing the association between ACEs and linear changes in symptomatology provides a more comprehensive picture of how maternal ACEs are associated with offspring behavior changes, assessing the association between ACEs and odds of scoring in the highest quartile of behavioral scores allows us to infer whether intergenerational ACEs predict potentially problematic behavior. These findings may have more clinical or practical relevance than assessing linear changes alone. For example, in a study using scores derived from the BPI to predict school outcomes, children scoring in the highest quartile were

significantly more likely to have the poorest school outcomes two years later compared to children in the lowest quartile (Kahn, Wilson, & Wise, 2005).

ACEs are measured using NLSY's Childhood Adversity battery, administered to both mothers and their offspring in either 2012, 2014, or 2016. This 4-item battery inquires whether respondents 1) 'lived with a household member who was depressed, mentally ill, suicidal before age 18' (0=no, 1=yes), 2) 'lived with someone who was a problem drinker or alcoholic before age 18' (0=no, 1=yes), 3) 'were hit or physically abused as a child beyond spanking' (0=never or once, 1=more than once), and 4) 'received parental love and affection before age 18' (reverse coded as 1=none at all or a little, 0= quite a lot or a great deal). While the 4-item ACE battery included in the NLSY is not validated, all items included except for the item measuring parental love and affection are included in traditional ACE batteries (Felitti et al., 1998). The parental love and affection question is intended to capture emotional abuse and neglect, which is a concept included in most ACE batteries and has been included in other literature that uses the NLSY Childhood Adversity Battery (Williams & Finch, 2019; Ports et al., 2021). All items were first summed to create an ACE composite score (0-4) and then operationalized as indicator variables (0 ACEs, 1ACE, 2 ACEs, >2 ACEs).

Covariates were selected for inclusion based on extant literature assessing the association between maternal ACEs and offspring behavioral outcomes (Zhang, Mersky, Gruber, & Kim, 2022). Variables known to be associated with ACEs and behavioral outcomes include race/ethnicity; poverty status; maternal marital status, educational attainment, depression; and offspring home environment. Race/ethnicity was parameterized in the NLSY as non-Black, non-Hispanic (includes White, "other"

or neither Black nor Hispanic), Black, or Hispanic. Offspring are assigned the same race/ethnicity as their mothers. Poverty status was coded as a dichotomous variable based on year-specific poverty thresholds and obtained within +/- 3 years of birth. Maternal marital status was parameterized as never married, married vs. other; maternal educational attainment as < high school, high school graduate, some college, or college graduate. Maternal depression was assessed in 1992 using the 20-item CES-D (Radloff, 1977). Consistent with guidelines, respondents with a score of >15 were identified to be at elevated risk of major depressive disorder. The HOME-SF is a validated survey of the home environment (i.e., degree of emotional support and cognitive stimulation provided to the child) based on maternal report and interviewer observation (Baker & Mott, 1989; Caldwell & Bradley, 1984).

To estimate the controlled direct effect, we distinguish between confounders of the association between maternal ACEs and offspring behavioral outcomes (race/ethnicity, poverty status, maternal marital status, educational attainment, and age at birth) and confounders between offspring ACEs and offspring behavioral outcomes (sex, maternal depression, and home environment). See figures 5 and 6 for directed acyclic graphs illustrating potential mediating mechanisms. Figure 5 represents traditional regression approaches to assess direct effects. Figure 6 represents the marginal structural modeling approach to assess controlled direct effects, accounting for each set of confounders.

Analysis

Descriptive statistics were computed (means, frequencies) for the independent variable (maternal ACEs) and all covariates for internalizing and externalizing separately. We then estimated the total association between maternal ACEs and standardized offspring internalizing and externalizing scores by fitting linear regression models adjusted for confounders of the association between maternal ACEs and offspring behavioral outcomes using PROC GENMOD (link=identity) (Total Effects Model). Robust standard errors based on a working exchangeable correlation matrix were used to correct for dependence in the risk of internalizing/externalizing behaviors across multiple offspring born to the same mother. This model is akin to traditional regression approaches that are found in current intergenerational ACE literature. In order to account for selection bias caused by loss-to-follow-up, inverse probability weights (IPW) for behavioral outcomes were estimated (Narduzzi et al., 2014) and multiplied by NLSYCYA survey weights and included in all models. The IPW was calculated by considering the eligible population of study, and then calculating the probability of non-missingness using a logistic regression model, where the response was the non-missingness and the covariates were its possible predictors. The weight of each subject was given by the inverse of the predicted probability. The analysis was then performed only on the non-missing observations using a weighted model. Including these weights in the models is akin to estimating the associations had all eligible offspring provided information on behavioral outcomes. Predictors of non-missingness included sex, race/ethnicity, poverty status, maternal depression, maternal education, and marital status.

To consider the possibility that offspring ACEs mediate the association between maternal ACEs and offspring behavior, we fit marginal structural models (VanderWeel, 2009) to estimate the controlled direct effect of maternal ACEs on offspring internalizing and externalizing behavior. We fit weighted linear regression models (Marginal Structural Models) and accounted for potential confounding with two stabilized inverse probability of treatment weights (IPTW), one accounting for the measured confounding between maternal ACEs and offspring behavior ($w_i M$) and one accounting for the measured confounding between offspring ACEs and offspring behavior ($w_i C$). The coefficient from the weighted model provides an estimate of the direct effect of maternal ACEs on offspring behavior provided that the two sets of confounders are sufficient to control for confounding between maternal ACEs and offspring behavior and between offspring ACEs and offspring behaviors. Two marginal structural models using inverse probability of treatment weighting were fit for internalizing and externalizing separately.

A sensitivity analysis using quartiles of internalizing and externalizing behavior was undertaken to confirm results from the models that included internalizing and externalizing parameterized as continuous outcomes. In these models, the PROC GENMOD distribution was binomial, and the link was logit instead of normal and identity, respectively. We calculated E values based on results from the fully adjusted model to determine how readily our findings could be explained by unmeasured confounding (VanderWeele & Ding, 2017).

Results

Characteristics of the sample and bivariate associations with internalizing scores and externalizing scores are presented in tables 5a and 5b, respectively. Approximately half of offspring respondents identified as female (50.7%), most were not in poverty (74.0%), and a little more than half identified as either Black (32.3%) or Hispanic (21.6%). Most respondents were born to mothers who were primarily married (62.6%), with at least a high school education (75.3%). Approximately 60% of offspring respondents were born to mothers who reported no ACE exposure, 23.2% were born to mothers who reported exposure to one ACE, 10.4% who reported exposure to 2 ACEs, and 6.5% exposed to 3 or more ACEs. Approximately 68% of offspring respondents reported no ACE exposure themselves, 20.7% reported exposure to one ACE, 7.8% reported exposure to two ACEs, and 3.8% reported exposure to 3 or more ACEs. Maternal and offspring cumulative ACE scores were significantly correlated ($r=0.2$, $p<0.0001$). Internalizing scores ranged from 86.0 to 172.0 (μ (SD)=103.0 (11.9) with 1st, 2nd, 3rd, and 4th quartile ranges of <94.0, 94.0 to <100.0, 100.0 to 109.0, and >109.0, respectively. Externalizing scores ranged from 83.0 to 161.0 (μ (SD)=103.5 (12.6) with quartile ranges of <94.0, 94.0 to <101.3, 101.3 to 110.8, and >110.8, respectively. Internalizing and externalizing scores were strongly correlated ($r=0.80$, $p<0.0001$). Risk factors, such as ACE exposure and other known determinants of behavior, can simultaneously increase the chance for developing more than one disorder, which makes it difficult to examine internalizing behavior independent of externalizing behavior and vice versa (Pesenti-Gritti et al., 2008). Disentangling the mechanisms behind each of these outcomes is beyond the

scope of this study, therefore, internalizing, and externalizing behavior were modeled separately and do not control for concurrent behavior. Using the highest quartiles of behavioral scores, as described previously, we determined that almost 69% of the sample had neither high internalizing nor externalizing behavior scores, followed by 17% who had both high internalizing and externalizing behavior scores, and approximately 8% who had only high internalizing or only high externalizing scores.

Results from the models estimating the association between maternal ACEs and offspring internalizing and externalizing appear in tables 6 and 7, respectively. Results from the total effects models for both internalizing and externalizing show all levels of maternal ACEs (1, 2, >2) are associated with elevated scores. Specifically, 1, 2, and >2 maternal ACEs were associated with a 2.5 (95% CI: 1.5, 3.5), 3.2 (95% CI: 1.8, 4.6) and 4.8 (95% CI: 3.0, 6.5) increase in G2 internalizing score and a 2.6 (95% CI: 1.6, 3.6), 4.2 (95% CI: 2.8, 5.6) and 5.1 (95% CI: 3.1, 7.1) increase in externalizing score, respectively. Results from the marginal structural model for both internalizing and externalizing show an attenuated association but confirm that all levels of maternal ACE exposure are independently associated with elevated behavior scores. 1, 2, and >2 maternal ACEs were independently associated with a 1.8 (95% CI: 0.9, 2.8), 2.1 (95% CI: 0.7, 3.4), and 2.7 (95% CI: 1.0, 4.4) increase in internalizing score and a 1.8 (95% CI: 0.8, 2.7), 3.1 (95% CI: 1.7, 4.4), and 3.3 (95% CI: 1.4, 5.1) increase in externalizing score, respectively.

Results of the models estimating the association between maternal ACES and odds of offspring scoring in the highest quartile for internalizing and externalizing appear in tables 8 and 9, respectively. A similar trend was found regarding an

attenuated, but still significant association, from the total effects models to the marginal structural models. Specifically, 1, 2, and >2 maternal ACEs were associated with a 50% (OR: 1.5, 95% CI: 1.2, 1.8), 40% (OR: 1.4, 95% CI: 1.1, 1.8), and 80% (OR: 1.8, 95% CI: 1.3, 2.5) increased risk of G2 scoring in the highest internalizing quartile, respectively. The E-values for these effects are 2.4 (95% CI: 1.7, 3.0), 2.2 (1.4, 3.0), and 3.0 (1.9, 4.4), respectively, and shows the minimum strength of an unmeasured confounder that would have rendered these effects null. 1, 2, and >2 maternal ACEs were associated with a 50% (OR: 1.5, 95% CI: 1.2, 1.8), 60% (OR: 1.6, 95% CI: 1.3, 2.1), and 60% (OR: 1.6, 95% CI: 1.2, 2.3) increased risk of G2 scoring in the highest externalizing quartile, respectively. E-values for these effects are 2.4 (1.7, 3.0), 2.8 (1.9, 3.6), and 2.8 (1.7, 4.0), respectively.

Discussion

Among a large population-based sample of mother-child dyads residing in the U.S., we observed a positive, independent direct association between maternal ACEs and elevated offspring mean internalizing and externalizing scores, as well as 40-70% increased odds of scoring in the highest quartiles for both internalizing and externalizing scores, which may confer the highest risk for subsequent adverse outcomes (Kahn, Wilson, & Wise, 2005). While findings were attenuated from the total effects models to the marginal structural models, our results provide evidence of a direct pathway between maternal ACEs and offspring behavioral outcomes, not through offspring ACEs. Additionally, we found that the association between maternal ACEs and offspring internalizing and externalizing behavior was

independent of maternal depression. Findings support the need to consider intergenerational exposure to ACEs in order to fully understand and address the impact of ACEs on behavioral outcomes, including screening for maternal ACE exposure.

Currently, screening for maternal ACEs has not been largely adopted. While evidence suggests that prenatal ACE screening would be well-received by pregnant individuals (Flanagan, Alabaster, McCaw, Stoller, Watson, & Young-Wolff, 2018), there are a number of barriers to routine prenatal ACE screening, including lack of time and confidence by healthcare providers, lack of training on ACEs, lack of professional guidelines for screening, lack of privacy, lack of information to patients about ACEs ahead of screening, and lack of cultural competency (Tran et al., 2022). We note that funding for training could reduce these barriers. California, for example, has successfully launched the first- statewide initiative (ACEs Aware) to screen for ACEs, including in the prenatal period (Watson, Mateo, & Vetter, N.D.). This initiative and others that are likely to follow may play an important role in informing pediatric interventions addressing intergenerational effects of adversity.

This study's findings are in line with extant epidemiological evidence of a positive association between maternal ACEs and offspring behavior independent of offspring ACEs (Deardorff, Borgen, Rauch, Kogut, & Eskenazi) and factors that may translate to offspring adversity, including poor maternal mental health (Cooke, Racine, Plamondon, Tough, & Madigan, 2019; Letourneau et al., 2019; Ochoa, Fernandez, Lee, & Estrada, 2022; Plant, Jones, Pariante, & Pawlby, 2017; Schickendanz, Halfon, Sastry, & Chung, 2018; Kumar et al., 2018; Min, Singer,

Minnes, Kim, & Short, 2013; Rieder et al., 2019; Zhu, Zhan, Anme, & Zhang, 2023, child maltreatment (Plant, Jones, Pariante, & Pawlby, 2017; Khoury et al., 2022), and physical discipline (Yoon, Cedarbaum, Mennen, Traube, Chou, & Lee, 2019).

While two studies found that maternal depression fully mediated the association between maternal ACEs and offspring internalizing behavior (Cooke, Racine, Plamondon, Tough, & Madigan, 2019; Letourneau et al., 2019) and depressive symptoms (Dennis, Clohessy, Stone, Darnall, & Wilson, 2019) the current study found that the association between maternal ACEs and offspring internalizing behavior is independent of maternal depression. It is possible that this study was better able to detect independent associations between maternal ACEs and internalizing behavior given the large sample size and longitudinal assessment of internalizing behaviors across childhood and early adolescence. The first study that reported full mediation of the association between maternal ACEs and elevated internalizing behaviors by maternal depression, conducted among a Canadian birth cohort, assessed internalizing behaviors at a singular timepoint at 5 years of age (Cooke, Racine, Plamondon, Tough, & Madigan, 2019). Evidence suggests that many internalizing behaviors do not become apparent until the age of 6 years old (Acosta et al., 2019; Basten et al., 2016). Further, internalizing behaviors that are directly associated with maternal ACEs may not manifest until later in childhood. Evidence suggests that adaptations to brain structure and function as a result of early adversity may be protective against adverse outcomes in the short term (DiPietro, Novak, Costigan, & Atella, 2006), at the expense of extended brain plasticity (Lebel, Walton, Letourneau, Giesbrecht, Kaplan, & Dewey, 2016). Connections that may be

important for behavioral outcomes in later childhood may be prematurely pruned, which supports the need for studies of maternal ACEs and offspring behavioral outcomes to include longitudinal behavior assessments across timepoints in childhood and adolescence (Lebel, Walton, Letourneau, Giesbrecht, Kaplan, & Dewey, 2016). This theory is further supported by epidemiological evidence of an association between maternal ACEs and offspring behavioral outcomes among an older cohort (aged 6-18), but not among a younger cohort (aged 1.5-5) (Greenfield, Wills-Butler, Fay, Duron, Bosk, Stepleton, & Mackenzie, 2019). The second study that reported full mediation of the association between maternal ACEs and offspring depressive symptoms among a clinical sample assessed offspring depressive symptoms using the PROMIS pediatric short form, comprised of eight questions that assess depressive symptoms over the last 7 days, a relatively shorter scale and time period than what is used in most other studies to assess internalizing behavior (Dennis, Clohessy, Stone, Darnall, & Wilson, 2019). These findings may also be subject to limited generalizability.

While assessing specific pathways involved in the direct association of maternal ACEs on offspring behaviors independent of offspring ACEs is beyond the scope of this study, a number of potential biological and psychosocial mechanisms provide support for our study's findings. Maternal early life adversity has been demonstrated to be associated with increased stress hormones during pregnancy, including placental CRH toward the end of gestation (Moog et al., 2016) and increased cortisol concentrations after wakening among pregnant individuals even after accounting for proximal stressors (Thomas et al., 2018). Though evidence is

preliminary, it is possible that these changes to the maternal HPA axis may then influence fetal development and offspring HPA functioning in ways similar to what is typically seen in response to acute stress. Changes that appear to modulate the association of prenatal stress and adverse behavioral outcomes and are hypothesized to play a role in the intergenerational transmission of adversity include increased reactivity to stress at later stages of development, decreased hippocampal volume, and epigenetic changes (Acosta et al., 2019; Lom & Gunnar, 2010; McEwen, 2019; Lupien, McEwen, Gunnar, & Haim, 2009). More studies accounting for timing of stressors (distally experienced maternal ACEs vs. proximal stressors experienced during pregnancy) and that longitudinally assess how maternal ACEs are related to offspring behavioral outcomes via fetal programming are needed to support the role of HPA dysfunction as a plausible mechanism. It is also possible that the mechanism behind the association between maternal ACEs and offspring behavior is via psychosocial risk factors that are not adequately captured by offspring ACE measures or other measures included in this study, including poor parenting practices (e.g., poor maternal attachment, low emotional support) (Schofield et al., 2013), or socioeconomic factors that are implicated in the intergenerational continuity of adversity including poverty, housing insecurity, and single parenthood (Schoon & Melis, 2019). For example, there is evidence to suggest that maternal ACEs may predict poor maternal attachment behaviors (Khan & Renk, 2020) and that poor maternal-child attachment (e.g., insecure and/or dysregulated attachment patterns) may predict internalizing and externalizing behaviors (Dagan et al., 2022).

Future studies assessing the role of biological and postnatal environmental factors are necessary to further elucidate these complex pathways and inform interventions. If, for example, the direct association is through maternal-child attachment, interventions aimed at promoting positive attachment and parenting practices may be necessary to ameliorate the effect of maternal ACEs on offspring behavior. Though it is likely that these associations are through a combination of biological and environmental factors. Regardless of the mechanisms behind the association between maternal ACEs and offspring behavior, findings of a positive direct effect suggest that maternal ACEs should be screened for to inform appropriate interventions.

This study has several strengths. First, this study uses a large and diverse population-based sample, which provides more generalizable evidence than smaller samples. Second, this study's categorical operationalization of ACEs allows us to assess dose-response associations compared to studies that only assess any ACE exposure. Although the confidence intervals overlap, a linear trend between maternal ACEs and offspring behavioral symptomatology is suggested. Further, our study assesses behavioral outcomes longitudinally across childhood from age 4-14, making it less likely that behavioral outcome measures are anomalous, or that important changes in behavior were missed. Most significantly, we accounted for the intergenerational continuity of ACEs in a way that is lacking in the literature to date. Only one study to date considered the intergenerational continuity of cumulative ACE exposure in their analysis (Deardorff, Borgen, Rauch, Kogut, & Eskenazi, 2024), while the remainder assess narrow measures that may or may not be perceived as

adversity by the offspring. Our study is the first to assess the controlled direct effect of maternal ACEs on offspring behavioral outcomes among dyads that provided parallel self-reported measures of cumulative ACE exposure, encompassing both maltreatment and household dysfunction. Findings suggest that the association between maternal ACEs and offspring behavioral outcomes is not confounded by or mediated by oft-correlated offspring ACEs. Based on E-values calculated in sensitivity analyses, it is unlikely that an unmeasured confounder exists that would render these findings null.

Limitations

This study is also subject to several limitations. First, the measurement of adversity among the dyad is limited to only 4 items, one of which is not included in more traditional ACE batteries. It is possible that the item measuring emotional abuse or neglect is not a valid or reliable measure, as it has not been validated. It is also possible that there are other important adversities that are not included in this battery that are related to offspring behavior. A related limitation is that there is a relatively small sample of dyads exposed to the highest level of adversity—some of the more commonly reported ACEs (e.g., parental separation) are not included in the NLSY adversity battery, which leads to wide confidence intervals for the highest level of adversity. Given the positive findings in spite of the limited adversity battery and small sample of participants exposed to the highest number of adversities, it is likely this study's findings are underestimated. Another limitation common to studies of ACEs is that social desirability concerns may have led to under-reporting of ACEs

and therefore, underestimation of the associations. Additionally, it is possible that ACEs occurred after behavioral outcomes were assessed, which threatens our ability to make causal inference around observed associations. However, we reason that it is unlikely that cumulative offspring ACE exposure would differ drastically across childhood and early adolescence. While the majority of the non-Black, non-Hispanic category of participants self-identified as White, this category includes some traditionally marginalized races/ethnicities. Despite this, the non-Black, non-Hispanic category is used as the reference category in analysis. Our findings, therefore, cannot be extrapolated to specific races/ethnicities.

Additionally, maternal report of child behavior is subject to limitations. There is evidence to suggest that depressed mothers report higher internalizing and externalizing behaviors among their children (Gartstein et al., 2009), while other studies find little evidence for maternal psychopathology biasing reports of child behavior problems (Olino, Michelini, Mennies, Kotov, & Klein, 2021). It is unclear if higher maternal report of offspring behaviors among mothers with psychopathology is due to environmental and genetic transmission of mental illness from mother to child, or whether mothers' perception of child behavior is overinflated as a symptom of her depression. It is also possible that depressed mothers may be more sensitive to their child's internalizing behaviors, and therefore maternal report may be more accurate. Relatively low agreement across different reporters (e.g., fathers, teachers, researchers) suggests that maternal report may be overinflated, but also may be explained by differences in child behavior in different contexts (Gartstein et al., 2009). Epidemiological evidence of a direct association between maternal ACEs and

maternal reported internalizing and externalizing behavior, but not among youth reported internalizing behavior (Deardorff, Borgen, Rauch, Kogut, & Eskenazi, 2024) suggests that associations may differ depending on who is reporting on offspring behavior (i.e., mothers vs. offspring). In the context of the current study's findings, if mothers exposed to a higher number of ACEs are more likely to overreport on their children's behavior, it is possible that the association between maternal ACEs and offspring behavior is overestimated. Given the current study's findings of a strong association between maternal ACEs and elevated internalizing and externalizing symptoms independent of offspring ACEs and maternal depression, it is unlikely that bias related to maternal report is driving these findings. However, future studies should build on whether maternal ACEs and/or depression are associated with variation in maternal and youth reported mental health outcomes and if so, how this may impact how intergenerational adversity is studied.

Conclusion

Children born to mothers with a history of ACEs, particularly higher levels of ACEs, may be especially vulnerable to experiencing ACEs themselves, and to the intergenerational effects of their mothers' adversity. Findings suggest a two-generation approach, in which both maternal and child ACEs are screened for and considered in pediatric practice, may be necessary to fully understand and ameliorate detrimental impacts of ACEs.

The prenatal period is identified as an opportune time for ACE screening, as ACEs predict pregnancy outcomes and pregnancy provides an ideal opportunity for

supportive intervention (Watson, Mateo, & Vetter, n.d.; van Roessel, Racine, Dobson, Killam, & Madigan, 2021). In light of evidence that maternal ACEs independently predict elevated internalizing and externalizing behaviors, prenatal ACE screening may identify at-risk offspring earlier in the life course so that protective interventions may be implemented before onset of adverse behavioral outcomes. More studies that assess potential biological and psychosocial pathways involved in the intergenerational transmission of adversity and offspring behavioral outcomes are needed to tailor interventions.

Table 5a. Characteristics and associations with mean internalizing scores, NLSYCYA (n=5,445)

Characteristic	Total N (%), M (SD)	BPI Internalizing Score	P-value
	5,445	103.0 (11.9)	
Age	7.9 (1.5)	103.0 (11.9)	<0.0001
Sex			0.53
Female	2,761 (50.7)	103.1 (11.6)	
Male	2,684 (49.3)	102.8 (12.2)	
Poverty			<0.0001
Yes	1,416 (26.0)	105.1 (12.3)	
No	4,029 (74.0)	102.2 (11.6)	
Maternal age at birth			<0.0001
<20	1,145 (21.0)	105.3 (12.5)	
21-24	1,428 (26.2)	104.7 (12.1)	
25-28	1,417 (26.0)	101.9 (11.4)	
29-46	1,455 (26.7)	100.4 (10.9)	
Race/ethnicity			<0.0001
Hispanic	1,175 (21.6)	103.5 (11.9)	
Black	1,760 (32.3)	104.09 (11.8)	
Non-Black, non-Hispanic	2,510 (46.1)	101.9 (11.8)	
Home-SF	45.0 (29.3)	103.0 (11.9)	<0.0001
Maternal ACEs			<0.0001
0	3,266 (60.0)	101.6 (11.3)	
1	1,261 (23.2)	104.2 (12.0)	
2	565 (10.3)	105.2 (12.9)	
>2	353 (6.5)	106.9 (13.0)	
Maternal marital status			<0.0001
Never married	1,530 (28.1)	104.7 (11.9)	
Married	3,410 (62.6)	101.9 (11.6)	
Other	505 (9.3)	104.5 (12.6)	
Educational attainment			<0.0001
Less than HS	1,343 (24.7)	106.3 (13.0)	
HS graduate	2,365 (43.4)	102.8 (11.7)	
Some college	1,551 (28.5)	100.7 (10.7)	
College graduate	186 (3.4)	99.9 (9.1)	
Offspring ACEs			<0.0001
0	3,687 (67.7)	102.0 (11.5)	
1	1,125 (20.7)	104.5 (12.0)	
2	426 (7.8)	104.8 (12.7)	
>2	207 (3.8)	108.3 (13.8)	

Table 5b. Characteristics and associations with mean externalizing scores, NLSYCYA (n=5,445)

Characteristic	Total N (%), M (SD)	BPI Externalizing Score	P-value
	5,445	103.5 (12.6)	
Age	7.9 (1.5)	103.5 (12.6)	<0.0001
Sex			<0.0001
Female	2,761 (50.7)	101.7 (11.5)	
Male	2,684 (49.3)	105.4 (13.5)	
Poverty			<0.0001
Yes	1,416 (26.0)	102.6 (12.4)	
No	4,029 (74.0)	106.2 (13.0)	
Maternal age at birth			<0.0001
<20	1,145 (21.0)	106.9 (13.0)	
21-24	1,428 (26.2)	105.9 (12.8)	
25-28	1,417 (26.0)	101.8 (12.0)	
29-46	1,455 (26.7)	100.3 (11.7)	
Race/ethnicity			<0.0001
Hispanic	1,175 (21.6)	103.8 (12.7)	
Black	1,760 (32.3)	104.7 (12.4)	
Non-Black, non-Hispanic	2,510 (46.1)	102.6 (12.6)	
Home-SF	45.0 (29.3)	103.5 (12.6)	<0.0001
Maternal ACEs			<0.0001
0	3,266 (60.0)	102.0 (12.2)	
1	1,261 (23.2)	104.8 (12.4)	
2	565 (10.3)	106.7 (13.5)	
>2	353 (6.5)	107.9 (13.9)	
Maternal marital status			<0.0001
Never married	1,530 (28.1)	105.8 (12.8)	
Married	3,410 (62.6)	102.3 (12.2)	
Other	505 (9.3)	105.2 (13.5)	
Educational attainment			<0.0001
Less than HS	1,343 (24.7)	107.4 (13.6)	
HS graduate	2,365 (43.4)	103.6 (12.5)	
Some college	1,551 (28.5)	100.5 (11.2)	
College graduate	186 (3.4)	99.6 (9.9)	
Offspring ACEs			<0.0001
0	3,687 (67.7)	102.4 (12.2)	
1	1,125 (20.7)	105.3 (12.6)	
2	426 (7.8)	106.2 (13.9)	
>2	207 (3.8)	108.9 (14.0)	

Table 6. Adjusted estimates of the association between maternal ACEs and offspring internalizing behavior scores, NLSYCYA (n=5,445)

Parameter	Total Effects Model, Estimate β (95% CI)	Marginal Structural Model β , Estimate (95% CI)
Intercept	106.6	111.1
G1 ACEs		
0	ref	ref
1	2.5 (1.5, 3.5)	1.8 (0.9, 2.8)
2	3.2 (1.8, 4.6)	2.1 (0.7, 3.4)
>2	4.8 (3.0, 6.5)	2.7 (1.0, 4.4)

Table 7. Adjusted estimates of the association between maternal ACEs and offspring externalizing behavior scores, NLSYCYA (n=5,445)

Parameter	Total Effects Model, Estimate β (95% CI)	Marginal Structural Model β , Estimate β (95% CI)
Intercept	111.11	119.49
G1 ACEs		
0	ref	ref
1	2.6 (1.6, 3.6)	1.8 (0.8, 2.7)
2	4.2 (2.8, 5.6)	3.1 (1.7, 4.4)
>2	5.1 (3.1, 7.1)	3.3 (1.4, 5.1)

Table 8. Adjusted odds ratios of the association between maternal ACEs and offspring internalizing behavior quartiles, NLSYCYA (n=5,445)

Parameter	Total Effects Model, OR (95% CI)	Marginal Structural Model, OR (95% CI)
G1 ACEs		
0	ref	ref
1	1.6 (1.4, 2.0)	1.5 (1.2, 1.8)
2	1.7 (1.3, 2.1)	1.4 (1.1, 1.8)
>2	2.4 (1.8, 3.2)	1.8 (1.3, 2.5)

Table 9. Adjusted estimates of the association between maternal ACEs and offspring externalizing behavior quartiles, NLSYCYA (n=5,445)

Parameter	Total Effects Model, Estimate (95% CI)	Marginal Structural Model, Estimate (95% CI)
G1 ACEs		
0	ref	ref
1	1.7 (1.4, 2.0)	1.5 (1.2, 1.8)
2	1.8 (1.4, 2.3)	1.6 (1.3, 2.1)
>2	1.9 (1.4, 2.8)	1.6 (1.2, 2.3)

Figure 5. Directed Acyclic Graphs illustrating the potential mechanisms underlying maternal (G1) ACEs and offspring (G2) behavior via G2 ACEs

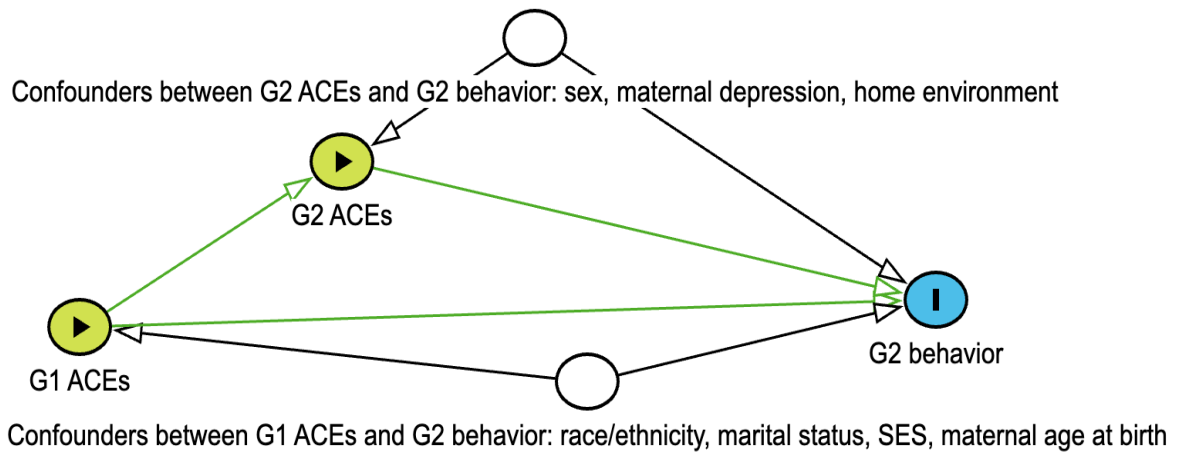
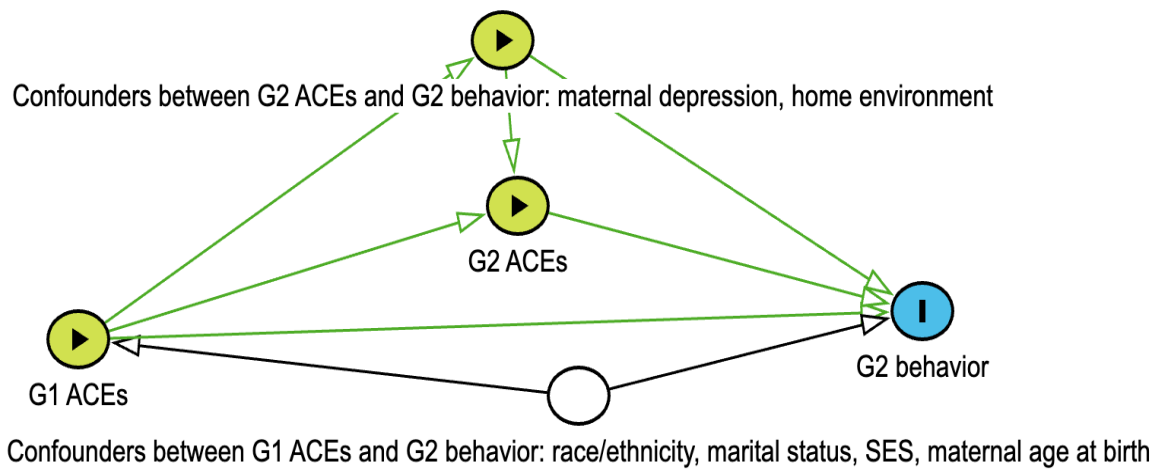


Figure 6. Directed Acyclic Graph illustrating the potential mechanisms underlying maternal (G1) ACEs and offspring (G2) behavior via G2 ACEs and/or confounders of the association between G2 ACEs and G2 behavior



Chapter 5: Summary and Conclusions

Summary

There is evidence that ACEs predict adverse health and behavioral outcomes within and across generations. To better inform ACE screening and intervention, this dissertation, comprised of three novel studies, respectively: 1) systematically reviewed existing literature to determine whether associations between ACEs and age of initiation within generations differs depending on substance, 2) determined the controlled direct effect of maternal ACEs on offspring age of initiation of alcohol, and whether these associations are different depending on offspring ACE exposure, and 3) determined the controlled direct effect of maternal ACEs on offspring internalizing and externalizing behavior. The first study found that ACEs are generally associated with earlier age of substance initiation across all substances assessed, but that ACEs predict relatively earlier alcohol and nicotine initiation compared to other substances, often in a dose-dependent manner. The second study found that the total effect of maternal ACEs on earlier offspring age of alcohol initiation was attenuated to suggest no direct effect among the full sample. However, a direct dose-dependent association between maternal ACEs and earlier offspring age of alcohol initiation was found among offspring similarly exposed to high levels of

adversity, but not among offspring exposed to low levels of adversity. This suggests that the association between maternal ACEs and offspring age of alcohol initiation depends on offspring ACE exposure. The final study found that there is a direct dose-response association between maternal ACEs and offspring internalizing and externalizing symptom count independent of offspring ACE exposure. These findings collectively suggest that consideration of both maternal and offspring ACEs is necessary to fully understand and address the impacts of ACEs. Taken together, this dissertation fills important gaps in the literature and informs future directions of intergenerational research and practice.

A key goal of this dissertation was to start to elucidate mechanisms by which ACEs predict adverse health and behavioral outcomes within and across generations. Findings suggest that maternal ACEs may predict offspring behavioral outcomes independent of offspring ACEs. These findings support the theorized role of both biological and psychosocial mechanisms in the association between ACEs and adverse health outcomes within and across generations. Positive, dose-dependent associations between ACEs and earlier age of alcohol initiation within individuals may be explained by functional and structural adaptations to the HPA axis, which is comprised of multiple endocrine pathways that respond to feedback loops involving the hypothalamus, pituitary gland, and adrenal gland, that occur as a result of chronic stress. Abnormal physiological functions as a result of exposure to chronic stress include increased cortisol, altered DNA methylation involved in the regulation of gene expression, and a reduction in neurogenesis and synaptic activity (Somaini et al., 2011). These adaptations are known to be associated with behavioral, cognitive, and mood

disorders that can increase the likelihood of maladaptive coping behaviors like earlier onset of substance use (Enoch, 2011; Tervo-Clemmens et al., 2020; Walters & Kosten, 2019). It is hypothesized that the intergenerational impact of ACEs may also be due to HPA axis dysfunction via fetal programming. There is evidence to suggest that early life adversity causes persistent alterations in the maternal HPA-axis, which may predict dysregulated fetal HPA axis functioning via increased cortisol and placental CRH in ways similar to what is seen in the presence of acute prenatal and postnatal stress (Moog et al., 2016; Thomas et al., 2018). Findings of a controlled direct effect of maternal ACEs on offspring outcomes, including earlier age of alcohol initiation among offspring exposed to high intergenerational adversity, and on elevated internalizing and externalizing behaviors, may be due to HPA axis dysregulation, though longitudinal studies assessing the role of HPA axis changes from maternal ACEs to offspring outcomes via stress hormone exposure in-utero are needed to strengthen evidence for potential fetal programming mechanisms.

Beyond biological mechanisms, psychological and psychosocial mechanisms may provide an explanation for this investigation's findings. There is evidence to suggest that adolescents exposed to early life adversity engage in substance use earlier as a way to cope with negative feelings arising from adversity (Agnew & Brezina, 1992; Grummitt et al., 2021; Teixeira et al., 2017). The fact that ACEs were found to predict earlier age of initiation across all substances assessed, but particularly among alcohol and nicotine, suggests that adolescents may be engaging in earlier substance use to cope with adversity, and that alcohol and nicotine may be substances that adolescents turn to earlier in the life course compared to other

substances. However, more studies assessing mechanisms for earlier initiation are needed to better inform intervention. Only one study included in the review assessed mediation. Further, studies assessing the association between ACEs and age of substance initiation should better control for timing of ACE exposure to ensure that ACEs precede initiation.

In terms of the intergenerational impact of ACEs, findings of attenuated associations between maternal ACEs and offspring outcomes in the marginal structural models compared to the total effects models for both age of alcohol initiation and offspring behavioral outcomes suggests that at least some of the association between maternal ACEs and offspring outcomes may be via offspring ACEs or confounders between offspring ACEs and offspring outcomes (e.g., home environment), though formal mediation analysis is beyond the scope of this investigation. This may be particularly true for the association between maternal ACEs and offspring age of alcohol initiation, as a dose-dependent direct effect of maternal ACEs on early age of initiation was only observed among offspring exposed to >2 ACEs, but not among offspring exposed to lower adversity. It is possible that offspring with high maternal ACE exposure and low personal ACE exposure may be exposed to protective psychosocial factors themselves, or have mothers exposed to protective factors, that disrupt both intergenerational continuity and transmission of ACEs, while offspring exposed to high levels of intergenerational adversity may be exposed to a greater number of psychosocial risk factors. It is also possible that the mechanisms behind observed associations in this investigation, including on dose-dependent associations between maternal ACEs and offspring internalizing and

externalizing behavior, are due to postnatal environmental factors, such as parenting factors (e.g., attachment, warmth) or socioeconomic conditions that predict intergenerational continuity of adversity (i.e., poverty). Future studies are needed to assess specific mediating pathways between ACEs and outcomes within and across generations to better inform interventions. Regardless of the mechanisms involved, evidence from this investigation points to the need to consider maternal ACEs in addition to offspring ACEs when researching and addressing the impacts of ACEs on adverse health outcomes.

Conclusions

Implications for Public Health Interventions and Practice

Findings from this investigation that ACEs are associated with substantially earlier age of substance initiation, particularly alcohol and nicotine, often in a dose-dependent manner, point to the need to routinely screen for ACEs in pediatric settings to identify youth at greatest risk of substance initiation for service provision. Evidence suggests that implementing preventive interventions prior to puberty may maximize their effectiveness. Interventions that are implemented later in adolescence may not be implemented early enough to prevent early age of initiation. As youth exposed to ACEs may be more likely to experience mood disorders that predict earlier use and may use substances as a way to cope with negative feelings around adversity, interventions targeting youth mental health (e.g., depression, anxiety, etc.) may be particularly effective at delaying the onset of substance use. Identifying youth at greatest risk of early initiation of substance use through ACE screening, as well as

optimized timing of intervention based on use patterns identified in this review, may reduce risk of SUD, particularly AUD and nicotine-dependence, in adolescence and beyond. Future studies that account for windows of risk by operationalizing early initiation in multiple ways, using different thresholds of initiation, are needed to better inform interventions. While findings generally point to earlier initiation for those exposed to high levels of adversity compared to those with little or no adversity, and that this risk may be conferred as early as 9 or 10 years old, specific ages of greatest risk are not well established in any of the studies included in the review.

Findings that maternal ACEs predict offspring age of alcohol initiation in a dose-dependent manner among offspring exposed to a similarly high number of ACEs themselves suggests that offspring concordant for high intergenerational adversity are at greatest risk of early alcohol initiation compared to offspring who experience fewer adversities than their mothers. Screening for maternal ACEs in addition to offspring ACEs may identify youth at greatest risk for early alcohol initiation, and who are therefore candidates for targeted service provision earlier in the life course. Finally, findings that maternal ACEs independently predict offspring internalizing and externalizing behavior further supports the need to screen and account for maternal ACEs in pediatric practice and intervention. While pediatric ACE screening may identify youth at risk for early age of initiation or adverse behavioral outcomes after ACEs have occurred, maternal ACE screening may identify youth at risk for behavioral health concerns prior to the onset of direct ACE exposure. Again, services aimed at addressing mental health in the offspring, as well as interventions targeting postnatal protective factors like emotional support and

parental warmth (Hatch, Swerbenski, & Gray, 2020; Dishion & McMahon, 1998; Donaldson, Nakawaki, & Crano, 2016), may be particularly useful in disrupting intergenerational continuity of ACEs and buffering against the impact of ACEs within and across generations on elevated internalizing and externalizing behavior and earlier age of alcohol initiation. Taken together, this holistic investigation supports the need to screen for ACE exposure routinely and adequately within and across generations.

While maternal ACEs are not yet routinely screened for, initiatives like California's ACEs Aware that are attempting to routinely screen for ACEs across the prenatal, pediatric, and adult primary care settings (Watson, Mateo, & Vetter, N.D.) may become more commonplace. The prenatal period has been identified as an important period for ACE screening for other health outcomes (Flanagan, Alabaster, McCaw, Stoller, Watson, & Young-Wolff, 2018), and in this context, may play an important role in informing pediatric practice as well. If providers know that there is a history of high maternal ACE exposure, interventions such as classes aimed at promoting positive parenting, as well as therapy for individual members of the family and/or family therapy, etc. may be implemented earlier in the life course, potentially disrupting intergenerational continuity of ACEs, and promoting factors that are protective against the intergenerational impact of maternal ACEs on adverse offspring outcomes.

Funding for training as part of comprehensive initiatives like ACEs Aware could reduce barriers to ACE screening that have been identified in the literature including lack of time and confidence by healthcare providers, lack of training on

ACEs, lack of professional guidelines for screening, lack of privacy, lack of information to patients about ACEs ahead of screening, and lack of cultural competency (Tran et al., 2022). Findings from this investigation should be used to inform timing and approach to ACE screening.

Future Directions for Research

This investigation highlights important limitations to ACE research more broadly, including a lack of consistency and justification around ACE measurement, as well as issues regarding temporality when assessing the association between ACEs and adolescent outcomes. More comprehensive ACE batteries that expand upon known maltreatment and household dysfunction exposures and that include adversity related to structural or systemic factors (e.g., discrimination, immigration, etc.) are needed to better understand the impact of ACEs both within and across generations. Further, studies should account for timing of ACE exposure when assessing the association between ACEs and outcomes that occur, or could potentially occur, prior to the age of 18. Temporality concerns when measuring ACE exposure and outcomes that may happen concurrently severely limits causal inference of findings. Studies should also account for severity and chronicity of ACEs to better understand the impact of early life adversity within and across generations rather than rely on cumulative ACE score alone.

Findings of a differential impact of maternal ACEs on offspring age of alcohol initiation depending on offspring ACE exposure suggests the existence of protective factors that simultaneously disrupt continuity of ACEs and buffer against the direct

association between maternal ACEs and offspring age of alcohol initiation. Future research efforts should aim to identify such factors in order to inform intervention efforts and examine whether patterns around intergenerational ACE concordance apply to other outcomes. Existing literature points to familial emotional support and parental involvement as being factors that may play an important role in disrupting the intergenerational continuity and transmission of ACEs (Schofield et al., 2013; Hatch, Swerbenski, & Gray, 2020). Other known protective factors implicated in the disruption of intergenerational continuity of adversity, including parental resilience and positive childhood experiences, such as having a trusted adult who makes the child feel safe and protected (Crouch et al., 2018; Harper, 2014) may also play a role in the intergenerational transmission of adversity and should be further explored.

As the field of intergenerational ACE research is relatively understudied, future research should continue to examine the association between maternal ACEs and other relevant and biologically plausible outcomes across the life course, including other mental health outcomes (e.g., depression in adulthood), chronic health conditions (e.g., cardiovascular disease, hypertension), and other conditions that are associated with HPA axis dysfunction and/or weathering. Importantly, this relies on comprehensive intergenerational ACE data, which is currently limited. Future studies should include robust measures of adversity among the dyad. As it is possible that the mechanisms by which maternal ACEs impact offspring health and behavioral outcomes is via biological and/or postnatal factors, future research should continue to assess plausible biopsychosocial mechanisms behind identified associations. Relevant biological mechanisms to investigate include in-utero exposure to cortisol and other

stress hormones. Relevant psychosocial mechanisms include maternal-child attachment patterns and other parent-child relationship factors (Khan & Renk, 2020; Dagan et al., 2022). Identifying pertinent mechanisms behind these relatively poorly understood intergenerational impacts of adversity may reveal opportunities for intervention. Finally, future research and programmatic initiatives should evaluate whether ACE screening among the dyad can better identify youth at risk of adverse health outcomes for service provision and tailored intervention than offspring ACE screening alone.

Appendices

Appendix A. PRISMA Guidelines Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pages 1-3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	page 4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 4
Search strategy	7	Present the full search strategies for all databases, registers, and websites, including any filters and limits used.	Page 5
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 5
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 5
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/A
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 29

Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Pages 5, 15
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Appendix B. Coding of Variables Included in Studies that Used NLSY Data

Variables	Original Coding
Maternal/child race	Hispanic Black Non-Black, non-Hispanic
Marital status	Married, spouse present Never married Other
Maternal age at birth	Continuous
Maternal highest grade completed	None-grade 11 Grade 12 (assumed HS graduate) 1 st -3 rd year college (assumed some college) 4 th -8 th year college (assumed college graduate)
Maternal age of alcohol initiation	Continuous
Child sex	Male Female
Family poverty status	Not in poverty In poverty (based on year-specific poverty thresholds)
Home environment (HOME-SF)	Continuous sum based on y/n items (see appendix C)
ACE items	Individual items (see appendix D)
Behavior problem index	Continuous, standardized with a mean of 100 and a SD of 15 (see appendix E)
Maternal depression (CESD-20)	Continuous (see appendix F)

Appendix C. HOME-SF Items

HOME-SF Item Description	Age Assessed			
	0-2 yrs	3-5 yrs	6-9 yrs	10-14 yrs
1. Child gets out of house 4 times a week or more	S	-	-	-
2. Child has 3 children's books (10 for ages 3-9 yrs; 20 for ages 10-14 yrs)**	S	S	S	S
3. Mother reads to child 3 times a week or more***	S	S	S	-
4. Child taken to grocery store (once/week or 2-3 times a month)	S	S	-	-
5. Child has one or more cuddly, soft or role-playing toys	S	-	-	-
6. Child has one or more push or pull toys	S	-	-	-
7. Mother believes parents should usually or always spend time teaching kids	S	-	-	-
8. Child eats meal with both mother and father(-figure) once a day or more	S	S	S	S
9. Mom often talks with child while working	S	-	-	-
10. Mom reports no more than 1 spank during past week	S	S	S	-
11. Mom spontaneously vocalize to/conversed with child at least twice	O	O	O	O
12. Mom responded verbally to child	O	-	-	-
13. Mom showed physical affection to child	O	O	O***	O***
14. Mom did not spank child	O	O	-	-
15. Mom did not interfere/restrict child more than 3 times	O	-	-	-
16. Mom provided appropriate toys/activities to child	O	-	-	-

17. Mom kept child in view	O	-	-	-
18. Play environment is safe (home or building for ages 36 mos +)	O	O	O	O
19. Family subscribes to at least one magazine	-	S	-	-
20. Child has use of record/CD player and at least 5 records/CDs/tapes	-	S	-	-
21. Child helped to learn numbers at home	-	S	-	-
22. Child helped to learn alphabet at home	-	S	-	-
23. Child helped to learn colors at home	-	S	-	-
24. Child helped to learn shapes and sizes at home	-	S	-	-
25. Child has some choice in foods for breakfast and lunch	-	S	-	-
26. TV is on in home less than 5 hours per day	-	S	-	-
27. Non-harsh discipline if child hits (or swears/speaks in anger ages 72mos+)	-	S	S	S
28. Child taken to museum in past year	-	S	S	S
29. Child expected to make his/her bed	-	-	S	S
30. Child expected to clean his/her room	-	-	S	S
31. Child expected to clean up after spills	-	-	S	-
32. Child expected to bathe him/herself	-	-	S	-
33. Child expected to pick up after himself/herself	-	-	S	S
34. Child expected to keep shared living areas clean and straight	-	-	-	S
35. Child expected to do routine chores such as lawn, help w/ dinner, dishes	-	-	-	S
36. Child expected to help manage his/her own time	-	-	-	S
37. Musical instrument in home child can use (see #20)	-	-	S	S

38. Family gets a daily newspaper	-	-	S	S
39. Child reads several times a week for enjoyment	-	-	S	S
40. Family encourages child to start and do hobbies	-	-	S	S
41. Child receives lessons or belongs to sports/music/art/dance/drama org	-	-	S	S
42. Child taken to musical or drama performance in past year	-	-	S	S
43. Family visits with family or friends 2-3 times a month	-	-	S	S
44. Child spends time with father(-figure) 4 times a week	-	-	S	S
45. Child spends time with father(-figure) in outdoor activities once a week	-	-	S	S
46. When watching TV, parent discusses program with child	-	-	S	S
47. Mom encouraged child to contribute to conversation	-	-	O	O
48. Mom answered child's questions or requests verbally	-	O	O	O
49. Mom introduced interviewer to child by name	-	O	O	O
50. Mom's voice conveyed positive feeling about child	-	O	O	O
51. Home is not dark	-	O	O	O
52. Home is reasonably clean	-	O	O	O
53. Home is minimally cluttered	-	O	O	O

Appendix D. ACE Battery Items

Variables	Original Coding
Lived with a household member who was depressed, mentally ill, suicidal before age 18'	Yes No
Lived with someone who was a problem drinker or alcoholic before age 18'	Yes No
Were hit or physically abused as a child beyond spanking'	Never Once More than Once
Quantity of love and affection received growing up, before age 18	A great deal Quite a lot A little None at all

Appendix E. Behavior Problem Index Items

BPI Item Description	Scale*	Subscale
Cheats or tells lies	E	Antisocial
Bullies or is cruel/mean to others	E	Antisocial
Does not seem to feel sorry after misbehaving	**	Antisocial
Breaks things deliberately (<12 yrs)	E	Antisocial
Is disobedient at school (>5 yrs)	E	Antisocial
Has trouble getting along with teachers (>5 yrs)	E	Antisocial
Has sudden changes in mood or feeling	E	Anxious/Depressed
Feels/complains no one loves him/her	I	Anxious/Depressed
Is too fearful or anxious	E/I	Anxious/Depressed
Feels worthless or inferior	I	Anxious/Depressed
Is unhappy, sad, or depressed	E/I	Anxious/Depressed
Clings to adults (<12 yrs)	I	Dependent
Cries too much (<12 yrs)	I	Dependent
Demands a lot of attention (<12 yrs)	I	Dependent
Is too dependent on others (<12 yrs)	I	Dependent
Is rather high strung, tense, and nervous	E	Headstrong
Argues too much	E	Headstrong
Is disobedient at home	E	Headstrong
Is stubborn, sullen, or irritable	E	Headstrong
Has strong temper and loses it easily	E	Headstrong
Has difficulty concentrating/paying attention	E	Hyperactive
Is easily confused, seems in a fog	E/I	Hyperactive
Is impulsive or acts without thinking	E	Hyperactive
Has trouble getting mind off certain thoughts	E	Hyperactive
Is restless, overly active, cannot sit still	E	Hyperactive
Has trouble getting along with other children	E	Peer Problems
Is not liked by other children	E	Peer Problems
Is withdrawn, does not get involved with others	I	Peer Problems

Appendix F. CESD Short Form Items

During the past week:

	Rarely or none of the time (less than 1 day) 0	Some or a little of the time (1-2 days) 1	Occasionally or a moderate amount of time (3-4 days) 2	Most or all of the time (5-7 days) 3
1. I was bothered by things that usually don't bother me.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. I did not feel like eating; my appetite was poor.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. I felt that I could not shake off the blues even with help from my family or friends.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. I felt that I was just as good as other people.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. I had trouble keeping my mind on what I was doing.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. I felt depressed.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. I felt that everything I did was an effort.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. I felt hopeful about the future.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. I thought my life had been a failure.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. I felt fearful.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11. My sleep was restless.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12. I was happy.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13. I talked less than usual.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14. I felt lonely.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
15. People were unfriendly.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16. I enjoyed life.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
17. I had crying spells.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
18. I felt sad.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
19. I felt that people dislike me.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
20. I could not get "going".	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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