Do Cognitive Processes Mediate the Relationship Between Adverse Childhood Experiences and Health Related Outcomes?

by

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Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

Adverse childhood experiences (ACEs) are stressful life events that occur during development. It is well-established that ACE exposure has negative downstream implications for a broad range of health-related behaviors, ultimately hastening mortality. Underlying mechanisms linking the experience of early life adversity with poor health remain less understood, however, and thus potential targets for intervention remain elusive. This work seeks to fill an important theoretical gap in the ACE literature by evaluating whether executive function (EF) constitute a biologically-plausible mediating mechanism in this causal pathway. To do so, two separate studies were conducted. In Study 1, undergraduate students completed measures of ACE exposure, EF, health-risk behaviors (e.g., smoking, drug and alcohol use, unsafe sexual practices), and psychopathology (e.g., anxiety, depression). Multivariate modeling determined that executive dysfunction in daily life mediated the relationship between childhood adversity exposure and current mental health concerns. EF did not mediate the effect between ACEs and health-risk behaviours. Study 2 sought to replicate and extend this work by narrowing the focus of health-risk behaviours to those most relevant for an undergraduate population (i.e., risky alcohol-related behaviours), and incorporating behavioural measures of EF in addition to self-report questionnaires. EF difficulties in daily life, but not on in-lab tasks, mediated the relationship between ACEs and psychopathology symptoms. The relationship between ACEs and risky alcohol use was not mediated by EF. These results partially support a neurodevelopmental model of ACE exposure vis-à-vis future health, focusing on the role of EF.

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Introduction

Adverse Childhood Experiences

Background.

Adverse childhood experiences (ACEs) are stressful life events that occur early in development. They can encompass intensely traumatic experiences, such as abuse and neglect, as well as household dysfunction (e.g., parental divorce, incarceration, mental illness). A seminal study conducted by Felitti et al. (1998) first examined the long-term effects of a wide range of negative early experiences. Using a retrospective self-report design, this study surveyed over 60 000 respondents regarding ACE history, and evaluated medical records to assess current health status. This large-scale study revealed that ACEs were quite prevalent amongst the general population, and that exposure to early adversity is strongly associated with wide-ranging negative health outcomes that ultimately hasten mortality (Felitti et al, 1998). This formative study underscored the extent to which ACEs present a public health concern and represented a shift in the literature towards evaluating the effect of a variety of adverse experiences in aggregate. Similar frameworks developed later on (e.g., cumulative risk) similarly review the additive impact of a diverse set of early life risk factors and further demonstrate the adverse downstream consequences of exposure to multiple environmental risk factors early in development (Evans, Li, & Whipple, 2013). In subsequent years, several studies have assessed the prevalence of ACEs at the population level and evaluated their long-term consequences. More recently, some work has attempted to understand the mechanisms linking ACE exposure with poor health outcomes.

Prevalence.

Following in the tradition of the initial project conducted by the Center for Disease Control and Prevention (CDC), several large-scale epidemiological studies in the United States have assessed the prevalence of ACEs at the population level (e.g., Merrick, Ford, Ports, & Guinn, 2018). Due to the existence of such large-scale public health initiatives, a wealth of data exists on ACE prevalence amongst the general population, as well as several health-related factors that follow from ACE exposure. With respect to ACE prevalence, results typically mirror findings from the original Felitti (1998) study, indicating that ACEs are relatively common in the general population. Most recently, the Behavioral Risk Factor Surveillance System (BRFSS) collected ACE-related data in 23 U.S states from 2011 through 2014 (Center for Disease Control and Prevention, 2019). This CDC initiative utilized randomly administered telephone surveys to collect data on adversity and health-related factors from a nationally representative sample. This study employed the traditional ACE questionnaire, asking participants to report on the experience of abuse and a range of household challenges prior to age 18. ACEs surveyed include sexual, verbal, and physical abuse; intimate partner violence in the home; parental divorce; incarceration of a parent; substance abuse in the household; and mental illness in the household (Center for Disease Control and Prevention, 2019). Findings from over 200 000 respondents revealed that more than 60% of individuals report at least one ACE, while almost 25% report three or more (Merrick et al., 2018). Emotional abuse was the most commonly reported ACE, occurring in over 30% of the sample, followed by household substance abuse (27.6%) and parental divorce (27.6%). The least prevalent ACEs were sexual abuse (11.6%) and incarcerated member of the household (7.9%). Moreover, certain demographic characteristics predicted the likelihood of experiencing adversity, including gender, race, sexual orientation, income, and

education. Higher ACE scores were identified in females relative to males; Black, Hispanic, and multiracial participants relative to White participants; and those who identified as gay/lesbian or bisexual relative to heterosexual. ACE score decreased as income increased, and those with less than a high school education reported more ACEs than college graduates (Merrick et al., 2018). Despite these tendencies, it is important to note that ACEs are not solely predicted by socioeconomic status, race, or related social factors, and instead represent a universal phenomenon that cut across social strata.

While large-scale studies impressively capture rates and patterns of ACE exposure at the population level, they also possess certain limitations. Specifically, these epidemiological studies assess ACEs using self-report measures and require retrospective reporting of events that may have occurred decades prior to the time of the study. Flaws of this methodology include the possibility that certain events may have been forgotten in the intervening years, and that participants may not want to disclose information on sensitive topics. Some empirical evidence validates this concern, indicating that retrospective recall of childhood events leads to underreporting when objective data is available for comparison (Della Femina, Yeager, & Lewis, 1990). Further, a recent meta-analysis comparing retrospective recall of childhood maltreatment with prospective measures identifies low agreement between the two methods, particularly when self-report questionnaires are utilized (Baldwin, Reuben, Newbury, & Danese, 2019). However, the authors note that some prospective measures may lack sensitivity relative to retrospective self-reporting, as mining data from official records may only produce reports of severe cases of maltreatment. On the other hand, some studies comparing prospective recordings of ACEs obtained while following participants longitudinally with retrospective reporting from the same individuals later on identify good to excellent agreement between the two measurement methods

(Reuben et al., 2016). In order to mitigate some concerns regarding the most commonly used methodology in the ACE literature, one study assessed the reliability of retrospective ACE reporting on a subsample of participants from the original ACE study. Overall, test-retest reliability was good, and there was very little discordance between responses at different time points, suggesting that people are consistent in their reporting (Dube, Williamson, Thompson, Felitti, & Anda, 2004). More recent work also identifies good to excellent reliability across all ACE categories and confirms that the presence of psychopathology symptoms at the time of reporting does not cause reporting of ACEs to change at different time points (Pinto, Correia, & Maia, 2014). Overall, the evidence regarding the reliability of retrospective, self-report measures of childhood adversity is mixed, with results from the most recent meta-analysis showing discordance between measurement methods. However, despite these limitations, employing self-report questionnaires that ask participants to retrospectively report on ACE exposure is the most feasible method for the collection of large-scale data of ACE prevalence at the population level.

Despite the availability of large amounts of data from epidemiological studies, results are often additionally limited by the exclusive sampling of American participants. Research on various adverse experiences in isolation suggests that prevalence can vary substantially across nations. For example, one meta-analysis comparing the prevalence of childhood sexual abuse internationally found significant variability depending on country, ranging from less than 1% to over 70% (Stoltenborgh, Van Ijzendoorn, Euser, & Bakermans-Kranenburg, 2011). It clearly cannot be assumed that early adverse events occur at consistent rates internationally, and therefore American data cannot be exclusively referenced, especially when working outside of the United States. Large-scale studies utilizing data from the Brain Research International Database (BRID) find that total ACE prevalence is similar across three continents (North

America, Europe, Australia), and this is generally mirrored when looking at prevalence of specific ACEs (Cohen et al., 2006). Data from a Canadian study conducted by the Ontario Ministry of Health found that 72% of respondents experienced at least one ACE, while 37% reported two or more, prevalence rates that are similar to those identified in American samples (Chartier, Walker, & Naimark, 2010). Though these results suggest consistency internationally, these data still represent findings from high-income countries. More recently, large-scale studies assessing ACE prevalence have been launched in low- and middle-income countries. Results from one such study in the Philippines identify that 75% of respondents report at least one ACE, while 23% report three or more (Ramiro, Madrid, & Brown, 2010). Data from a Brazilian birth cohort find that over 80% of individuals report at least one ACE, a number exceeding what is typically found in North American and European samples (Soares et al., 2016). However, the authors attribute this discrepancy to the relatively high rate of parental separation (42%), and prevalence from most other categories of ACEs remain similar, and at times lower, to those seen in other large-scale international studies (Soares et al., 2016). Overall, despite some methodological limitations, several large-scale studies conducted internationally and in North America converge to identify relatively high rates of ACE exposure in the general population, making it clear that ACEs present a severe international public health concern, especially when considering their relation to important life outcomes.

Health-related outcomes.

The relationship between ACEs and disease is a robust finding in the literature; prior research has demonstrated that early adversity predicts all of the leading causes of death in the United States (Felitti et al., 1998). Studies show that ACE history is associated with increased risk of ischemic heart disease, chronic obstructive pulmonary disease, cancer, stroke, diabetes,

autoimmune disease, and more (e.g., Dong et al., 2004; Dube et al., 2009; Brown et al., 2010; Campbell, Walker, & Egede, 2016). Data from the BRFSS suggest that ACE exposure is related to elevated risk of being diagnosed with all cancers in adulthood, and high levels of ACE exposure is related to increased risk of myocardial infarction (Brown, Thacker, & Cohen, 2013; Campbell et al., 2016). ACEs are also found to increase the risk of health-related disability, impacting mental health and reducing quality of life (Campbell et al., 2016). Overall, it is clear that adverse early experiences exert a significant negative effect on physical health, with some consequences only emerging years following exposure to the events.

ACEs additionally negatively impact health via their relationship with health-risk behaviours. Health-risk behaviours refer to a collection of activities that directly cause, or significantly increase the risk for, negative physical health outcomes. They include cigarette smoking, illicit drug use, risky alcohol use, sedentary behaviour, and unsafe sexual behaviours. Studies consistently find that those who experience early adversity are more likely to engage in a wide range of health-risk behaviours (e.g., Campbell et al., 2016; Ramiro, Madrid, & Brown, 2010). In young adults, ACE exposure is associated with illicit drug use, particularly amongst those with a substantial ACE burden (Schilling et al., 2007). ACEs are also linked to earlier initiation of illicit drug use, drug use problems, and drug addiction (Dube et al., 2003). Other findings suggest that ACE history strongly predicts various cigarette smoking risk factors, including early initiation of cigarette smoking (age 14 or younger), current smoking, lifetime smoking, and heavy smoking (Anda et al., 1999). Finally, risky sexual practices (e.g., early age of onset of sexual intercourse, unprotected sex, and having a high number of sexual partners) are related with ACE exposure, and ACEs increase both self-perception of AIDS risk and objectively determined HIV risk (Campbell et al., 2016; Hillis, Anda, Felitti, & Marchbanks,

2001). Taken together, significant evidence confirms the link between adversity history and engagement in several behaviours that impact health in the long term, offering insight into one mechanism via which environmental experiences determine physical health outcomes.

Substantial evidence further indicates that mental health is additionally negatively impacted by ACE exposure. While disease states more commonly emerge with advanced age, mental health may be impacted more proximally to the adverse event(s). Research suggests that ACE exposure is associated with increased incidence of depressive symptoms (Schilling, Aseltine, & Gore, 2007; Chapman et al., 2004). This relationship is present in both young adults and across the lifespan, indicating that ACEs increase risk for depression in both the short- and long-term. ACEs are also found to increase risk for a wide-range of psychiatric illnesses. One large-scale meta-analysis of over 30 years of research suggests that childhood adversity increases risk for psychosis, with other work suggesting that ACEs are linked with a history of hallucinations (Varese et al., 2012; Whitfield, Dube, Felitti, & Anda, 2005). ACEs are additionally associated with higher prevalence rates of anxiety disorders, as well as earlier age of onset and increased symptom severity (Young, Abelson, Curtis, & Nesse, 1997). Finally, several personality disorders in adulthood are strongly linked with childhood adversity, most notably borderline personality disorder. Childhood abuse and neglect are associated with elevated symptoms across personality disorders (Afifi et al., 2011; Tyrka, Wyche, Kelly, Price, & Carpenter, 2009). Transdiagnostically, ACEs exert a clear negative impact on mental health and wellbeing.

Poor mental health further predisposes individuals with ACE history to an additional leading cause of death: suicide. Suicidal behaviours, non-suicidal self-injury, and suicidal ideation are strongly linked with ACE exposure (Cluver, Orkin, Boyes, & Sherr, 2015;

Isohookana, Riala, Hakko, & Räsänen, 2013). Amongst one sample of adolescents, suicide attempts jumped from a baseline rate of 1.9% in those with no ACEs to 6.3% in adolescents with 5 or more ACEs during a one year period (Cluver et al., 2015). Across the lifespan, ACEs continue to significantly increase the risk of suicide attempts 2- to 5-fold (Dube et al., 2001). Evidence suggests that the relationship between ACEs and suicidality is mediated by mental health status, indicating that the increased risk for the development of psychopathology following ACEs directly impacts subsequent suicide risk and associated mortality (Cluver et al., 2015).

Early adversity experiences increase engagement in a host of risky behaviours that predispose individuals to disease, chronic illness, and overall poor health. When additionally considering increased risk of psychopathology, it is unsurprising that ACE exposure is associated with reduced quality of life and, ultimately, earlier mortality (Corso, Edwards, Fang, & Mercy, 2008; Felitti et al., 1998). Via longitudinal tracking of mortality records of respondents from the original ACE study, empirical evidence supports the notion that ACEs hasten mortality, especially amongst those with the highest ACE burden (Felitti et al., 1998; Brown et al., 2009). Results indicate that individuals with six or more ACEs are at risk of dying 20 years earlier than those with no ACE history, and are over two times more likely to die prior to age 65 than those with no ACEs (Brown et al., 2009). When further examining risk for premature mortality (defined in this study as death prior to age 50), those with two or more ACEs are at a 57% (males) to 80% (females) higher risk (Kelly-Irving et al., 2013). This evidence underscores the severity of ACE exposure on life outcome, highlighting the robust relationship between early experiences and mortality.

Several large-scale ACE projects converge to demonstrate that ACEs enact an effect on health in a dose-response manner (e.g., Felitti et al., 1998, Campbell et al., 2016; Chartier et al., 2010; Ramiro, Madrid, & Brown, 2010). With each additional ACE exposure, risk for negative health-related outcomes increases proportionally. For example, ACE exposure shows a graded relationship with suicide risk, such that one increase in ACE score is found to be associated with up to a 60% increase in suicide attempt risk (Dube et al., 2001). Similar patterns are seen for several health-risk behaviours, including use of illicit drugs, early initiation of smoking, and risky sexual practices (Ramiro, Madrid, & Brown, 2010). A strong graded relationship also exists between number of ACEs and several disease states, including ischemic heart disease and cancer (Felitti et al., 1998). The dose-response nature of the relationship between adversity and outcome demonstrates that individuals with low levels of adversity exposure are at some increased risk for poor health, while those who have experienced substantial adversity face significant risk. Despite substantial evidence indicating that ACEs predispose individuals to engage in risky behaviours and contribute to the development of psychopathology, ultimately leading to increased morbidity and mortality, little evidence exists to explain the underlying biological mechanisms linking the experience of environmental factors early in life with physical health many years later.

Underlying mechanisms.

There is growing recognition of the complex interplay between genetic and environmental factors in determining health-related outcomes. The literature on epigenetics has exploded in recent years, and its emphasis on the role of environmental factors in determining the timing and pattern of gene expression underscores the importance of assessing experiences such as ACE exposure when evaluating physical health outcomes. Further, by enhancing our

understanding of the impact of adverse environmental experiences on underlying biological maturation and development, we can begin to develop targeted interventions that address the physiological and psychological processes disrupted by ACE exposure, with the ultimate goal of remediating them prior to the onset of illness and disease. A tentative model initially proposed by Felitti and colleagues (1998) links ACE exposure to early mortality via disrupted social, emotional, and/or cognitive development, subsequent engagement in health-risk behaviours, and, accordingly, deteriorating mental and physical health. However, this model does not identify a precise mechanism and fails to create an identifiable target for intervention.

Thus far, work examining underlying mechanisms between adversity and health outcomes mainly focuses on the role of the stress response. The stress response refers to the body's physiological response to perceived and actual stressors in the environment. It involves an intricate cascade of events, including activation of the sympathetic nervous system (triggering the "fight or flight" response), and the release of stress-related hormones into the bloodstream (Stephens & Wand, 2012). Critical to the latter process is the hypothalamic-pituitary-adrenal (HPA) axis, the central neuroendocrine component of the stress response. In response to a stressor, the amygdala signals to the HPA axis to release glucocorticoids, the body's stress hormones, into the bloodstream. Glucocorticoids, including cortisol, enter the brain and bind with receptors in order to return the body to homeostasis. In the short term, the release of glucocorticoids is protective and adaptive, allowing the body to return to baseline once the stressor has dissipated (Danese & McEwan, 2012). However, repeated exposure to environmental stressors necessitates chronic activation of the physiological compensatory mechanisms that respond to stress. This has been demonstrated amongst those with a history of early life adversity, indexed by elevated levels of cortisol which indicates over-activation of the

HPA axis (Danese & McEwan, 2012). Chronic activation of the HPA axis been demonstrated to exert toxic effects on several bodily systems, including neuroendocrine, immune and central nervous system functioning, that are ultimately related to increased morbidity and mortality (Solís et al., 2015). Thus, it is suggested that the inherent stressful nature of ACEs leads to chronic activation of the HPA axis, ultimately causing physiological distress and initiating the deleterious health outcomes known to follow from ACE exposure. Relatedly, allostatic load has been proposed as a framework that offers insight into how chronic stressful environmental experiences get 'under the skin' to impact health. Allostatic load refers to physiological wear and tear on the body due to exposure to chronic stress, recognizing the toxic effect of chronic stress on several bodily systems (McEwen & Stellar, 1993). Prospective studies evaluating allostatic load longitudinally confirm that ACEs are associated with greater allostatic load, which is in turn visible via markers of physiological dysregulation, inducing a multisystem predisease state that ultimately leads to many of the same consequences known to follow from ACEs (Solís et al., 2015).

Inflammatory processes have also been proposed as a potential biological mediator in the ACE-health outcome relationship (Danese & McEwan, 2012; Danese, Pariante, Caspi, Taylor, & Poulton, 2007). The inflammatory response is an integral component of the stress response that activates in the face of harmful stimuli including toxins, pathogens, and psychosocial stressors. It is thus vulnerable to environmental influences, and indeed several components of the inflammatory response demonstrate alterations following childhood maltreatment (Danese et al., 2007). In fact, it has been proposed that early adversity is so detrimental to the inflammatory response that those exposed to stressful early environments express a proinflammatory phenotype, whereby stress becomes biologically embedded within immune cells (Miller & Chen,

2010). This framework proposes that the biological embedding of early life stress results in within heightened sensitivity of the immune response to stressors and, ultimately, increased vulnerability to chronic illness. Support for this proposal has been demonstrated empirically, and evidence further suggests that the proinflammatory phenotype is uniquely related to early life adversity and does not simply represent a response to acute social stressors (Ehrlich, Ross, Chen, & Miller, 2016). Despite these promising findings, a systematic review of the literature ultimately found inconsistent results regarding the immune response, concluding that there is not yet sufficient evidence to support the role of inflammation as a clear underlying mechanism linking early adversity with poor health later in life (Coelho, Viola, Walss-Bass, Brietzke, & Grassi-Oliveira, 2014).

To date, efforts to understand the underlying physiological and psychological mechanisms whereby early adversity transfers increased risk for maladaptive health outcomes largely focus on the role of the stress response. While results are promising, there is a need for a broader review of the biological factors relevant for understanding the mechanistic processes. Specifically, reviews suggest that directing attention towards the central nervous system as an additional potential mediator is warranted, especially in light of findings confirming the widespread effects of early life stress on brain development.

Impact on neurodevelopment.

It has been widely demonstrated that early adversity exerts a widespread and lasting impact on the structure and function of the developing brain. Review of the literature surrounding the influence of early stress on neurodevelopment may elucidate the underlying mechanisms that link early experiences with health-related outcomes by identifying specific

brain areas, especially those of relevance for mental and physical health, that are particularly impacted by environmental stress during development.

Studies examining the impact of early life stress on neurodevelopment typically identify several alterations in brain structure and function following early adversity both globally (i.e., across the entire brain) and locally (i.e., within specific brain regions). While some evidence demonstrates reductions in cortical volume across all four lobes of the brain following early life stress, other work points to certain regions that are particularly vulnerable to the effects of early life stress (Hodel et al., 2015). Teicher and colleagues (2003) propose three distinct characteristics of brain regions that enhance vulnerable to early environmental stress, including (1) a protracted postnatal development period; (2) high density of glucocorticoid receptors; and (3) some degree of postnatal neurogenesis. Prominent regions possessing some or all of these features include limbic structures, most notably the hippocampus and amygdala, and the prefrontal cortex (PFC; Hodel et al., 2015). These three regions also serve as integral components of a highly interconnected network responsible for detecting and responding to psychosocial stressors, enhancing their relevance to the present review (McEwan, 2007).

Limbic regions are likely prone to disruption by environmental factors because they play a central role in the stress response and are closely related to the HPA axis (Tottenham & Sheridan, 2009). The hippocampus features all three vulnerability factors described above, and, despite some mixed findings, volumetric reductions are often demonstrated following early adversity (Andersen et al., 2008; Teicher et al., 2003). Further work identifies highly localized volumetric reductions in specific hippocampal subfields relevant for neurogenesis following ACEs (Teicher, Anderson, & Polcari, 2012). Evidence also indicates that repeated exposure to stress hormones can cause hippocampal atrophy, can be neurotoxic to hippocampal pyramidal

cells, and can cause reduced dendritic branching within the hippocampus (Andersen & Teicher, 2004). Animal models converge to support the notion that hippocampal development is altered in the face of early adversity. In rodents, chronic early stress leads to lower hippocampal volume and reduced dendritic arborization (Ivy et al., 2010; Fenoglio, Brunson, & Baram, 2006). The amygdala is also central to the stress response because of its sensitivity to emotional stimuli and high density of glucocorticoid receptors. Increased amygdala volume has been demonstrated following exposure to early adverse environments, however these effects were apparent secondary to severe early life deprivation, and alterations to amygdala development following milder adversity remain unclear (Tottenham et al., 2010; Mehta et al., 2009). In animal models, however, rearing in environments mirroring early life stress causes alterations in amygdala development, including volumetric increases (Cohen et al., 2013; Tottenham & Sheridan, 2009).

The prefrontal cortex (PFC) is characterized by a relatively high density of glucocorticoid receptors and a protracted period of development (Teicher et al., 2003; Hodel et al., 2015). The PFC is highly reactive in response to acute stressors throughout the lifespan, demonstrating its overall vulnerability to psychosocial stress (Arnsten, 2009). This vulnerability to stress in general, combined with the extended window of ongoing development, culminates in overall extreme susceptibility to environmental stress occurring early in life. Indeed, several alterations to PFC structure and function have been identified following early adversity. Smaller volumes of the orbitofrontal cortex (OFC), superior frontal gyrus, dorsolateral prefrontal cortex (DLPFC), and anterior cingulate cortex (ACC) have all been documented following early adversity (De Brito et al., 2013; Hanson et al., 2010; Cohen et al, 2006). In animal models, early life stress results in a loss of dendrites and dendritic spines in the PFC (Arnsten, Raskind, Taylor, & Connor, 2015). Connectivity of the PFC is also affected by early life stress. Alterations of

connections between the amygdala and PFC regions, specifically the ventromedial PFC (VMPFC), following early life stress are evident (Tottenham & Sheridan, 2009). VMPFC – amygdala connections are of particular importance for self-regulatory processes in response to environmental stressors, so alterations to their connectivity in the face of early adversity are notable (Pakulak, Stevens, & Neville, 2018). Finally, following early adversity, the PFC demonstrates atypical patterns of activation during laboratory tasks, demonstrating aberrant functioning during cognitive processing (Hart & Rubia, 2012).

White matter (WM) tracts connect distant regions of the brain, allowing for communication and integration between brain areas that are physically far apart. Following childhood adversity, WM tracts demonstrate alterations in myelination, an additional implication of early life stress on neurodevelopment. The brain's largest WM tract, the corpus callosum, is smaller amongst children who experienced abuse and neglect (Teicher et al., 2004). Other WM tracts including the cingulum, arcuate fasciculus, and fornix have been found to shown significantly reduced fractional anisotropy (FA), a measure of WM tract integrity, following childhood verbal abuse (Choi, Jeong, Rohan, Polcari, & Teicher, 2009). Notably, the uncinate fasciculus, the WM tract that connects limbic and frontal regions, shows reduced FA in children following early adversity (Hodel et al., 2015). Additionally, alterations to WM microstructure and organization in the PFC following early neglect have been identified, and these alterations are associated with deficits on cognitive tasks (Hanson et al., 2013). Atypical development of WM pathways has negative consequences for brain connectivity, and alterations to WM tracts resulting from adversity are of significance for neurocognitive performance.

While stressful events across the lifespan exert negative effects on the brain, there is evidence to suggest that alterations in response to stressors in adulthood are reversible and are

perhaps not as critical as those that occur while maturation is ongoing (Chen & Baram, 2016). Alterations occurring during crucial developmental stages are of particular concern because they interrupt the natural developmental sequence. Based on evidence demonstrating the presence of sensitive periods for the development of some specific cognitive processes (e.g., vision and language), researchers propose that similar periods exist for other neurodevelopmental factors, including neurogenesis, synaptic overproduction and pruning, and myelination (Teicher et al., 2003). Interruptions to development during the sensitive period by factors such as environmental stress alter the developmental trajectory and exert irreversible changes. These changes can be long-lasting even in the absence of further environmental stress, and alterations during early developmental periods may not manifest until years later (Andersen & Teicher, 2004). Ultimately, the exact timing of adverse experiences will differentially impact different regions, because of their different developmental trajectories. However, regions with the most prolonged developmental stages are susceptible for the longest period of time, suggesting that the PFC is among the brain's most vulnerable regions.

Overall, different methods ranging from human neuroimaging to animal models converge to suggest that ACEs induce widespread disruption of neurodevelopment. Stressful events occurring early in development are of particular relevance, as their disruption of the brain's maturation process appears to permanently alter the course of neurodevelopment, resulting in irreversible changes with widespread implications. Research suggests that the PFC is particularly vulnerable to these environmental stressors because of its protracted period of immaturity during which external factors can irreversibly alter the course of its development. Because of the importance of the PFC for core cognitive skills that are important for coping and regulation (which ultimately impact health-related factors), the PFC's particular vulnerability to early stress

represents a notable finding in the search to further understand the link between adversity and poor health.

Executive Function

Considerable debate exists regarding the exact conceptualization of executive function (EF). While it has at times been considered to be a single, unitary construct, it is more commonly viewed as an umbrella term for a set of several inter-related higher-order cognitive constructs that work together to allow individuals to engage in purposeful, goal-oriented behaviours (Lezak, 1995). Central skills typically include planning, self-regulation, attention, and task initiation, though, since the concept was first defined in the 1970s, over 30 separate skills have been attributed to the construct of EF (Goldstein, Naglieri, Princiotta, & Otero, 2014). Despite the inclusion of so many distinct abilities in some conceptualizations of EF, Miyake and colleagues (2001) identify three core EF constructs that, while related, represent distinct cognitive abilities. These include the ability to hold and manipulate goal-relevant information in mind (working memory), inhibit prepotent but inappropriate responses (response inhibition), and switch between different actions or mental sets in order to achieve a goal (cognitive flexibility). Working memory requires careful coding of incoming information in order to assess relevance for current goals; continuous, active updating and monitoring of mental representations; replacement of information that is no longer task relevant; and online manipulation of mental representations (Morris & Jones, 1990). Response inhibition refers to deliberate and controlled suppression of automatic or dominant responses when not situationally appropriate, or no longer relevant (Nigg, 2000). Cognitive flexibility, also referred to as task shifting, encompasses the ability to switch between a set of mental tasks, and is characterized by a cost in performance immediately

following a shift (Monsell, 1993). This framework for EF is utilized to conceptualize EF skills in the present work.

EF measurement.

While the study of EF has a long and well-established tradition in the field of neuropsychology, debate regarding optimal operationalization and measurement of EF persists (Toplak, West, & Stanovich, 2013). Typically, methods have been divided into two categories: performance-based and rating scales. Performance-based measures involve the administration of a cognitive task under standardized conditions. Response times and/or accuracy are typically measured and can be compared to norms in order to assess performance relative to peers. While performance-based measures allow for consistency, optimize experimenter/clinician control, and provide objective outcomes, they offer information about only a limited subset of behaviour (tasks typically take between 5-30 minutes to complete, and are conducted in highly controlled environments), and results may be confounded with other cognitive processes (e.g., processing speed; Barkley & Murphy, 2011). Rating scales, on the other hand, evaluate the application of executive skills to everyday life. They serve as more ecologically valid measures of EF that capture capabilities in problem-solving, emotion-regulation, and other complex real-life tasks that rely heavily executive skills (Barkley & Murphy, 2010). Though different methods may purport to measure the same broad construct (i.e., EF), evidence suggests that results from the two do not tend to correlate (Toplak et al., 2013). Instead, following meta-analysis of several studies evaluating EF using both methods, Toplak and colleagues conclude that there is in fact little to no relationship between the two measurement methods, indicating that they may be capturing separable constructs. It is hypothesized that performance-based measures capture cognitive efficiency, assessing availability of EF skills and their integrity. Rating scales, on the

other hand, incorporate the real-world aspect of goal pursuit, and evaluate whether individuals are able to tap their available EF resources and apply them in everyday situations in order to accomplish goals. Thus, type of measurement is an important consideration when assessing EF, and the correct choice will depend on the specific question at hand. However, in order to get a comprehensive understanding of both available EF skills and their application to everyday life, it is evident that both tasks and questionnaires are necessary, as they each provide unique information.

Neural substrates and EF development.

It is widely recognized that the frontal lobes serve as the neural substrates underlying EF; several studies utilizing a range of methods converge to identify the frontal lobes, specifically the PFC, as the key neural underpinnings of executive control. Multiple meta-analyses demonstrate that patients with frontal lobe lesions perform worse than those with non-frontal lesions and healthy controls on several well-validated neuropsychological tests of EF, including the Wisconsin Cart Sorting Task (WCST), the Stroop colour-word interference task, and verbal fluency tasks (Alvarez, & Emory, 2006; Demakis, 2003; Henry & Crawford, 2004; Stuss, Floden, Alexander, Levine, & Katz, 2001). Functional neuroimaging studies further identify activation in bilateral prefrontal areas during several EF tasks (Alvarez, & Emory, 2006; Leung, Skudlarski, Gatenby, Peterson, & Gore, 2000). Though specific EF tasks recruit unique regions, three PFC regions have been identified as particularly important across EF domains (Collette et al., 2005). These include the DLPFC, ventrolateral PFC (VLPFC) and ACC, which all demonstrate reliable activation on neuroimaging scans during inhibition, working memory, and cognitive flexibility tasks (Nee, Wager, & Jonides, 2007; Wager, Jonides, & Reading, 2004; Wager & Smith, 2003). While the PFC in general, and these three regions more specifically, are

thought to be of particular importance for EF, the brain functions as a network, and therefore they cannot be considered in isolation.

While evaluating the integrity of the frontal lobes provides insight into their role in supporting EF, more recent perspectives suggest that it is necessary to also take an integrative, network-based approach towards understanding how the brain supports behaviour. In this light, several important cortical and subcortical projections from the PFC have been identified as integral aspects of an integrated executive system (Alvarez & Emory, 2006). These include posterior portions of the cerebral cortex, mainly the parietal lobe, and subcortical structures such as the nucleus accumbens and caudate nucleus (Alvarez & Emory, 2006; Collette, Hogge, Salmon, & Van der Linden, 2006). As well, functional connectivity analyses identify a set of brain regions, collectively known as the executive control network, that consistently activate in unison during EF tasks (Niendam et al., 2012). This network recruits several regions of the PFC and parietal cortex bilaterally, and includes the thalamus, caudate, and putamen subcortically. Together, evidence suggests that although the PFC represents the central neural architecture underlying EF, recruitment and integration of widespread brain areas is necessary in order to complete tasks of cognitive control.

A central principle of neurodevelopment is born out of recapitulation theory, stating that ontogeny recapitulates phylogeny (Pechtel & Pizzagalli, 2011). Thus, brain regions that are the "youngest" evolutionarily are the latest to mature in the course of development. These structures, most notably the PFC, typically support higher-order cognitive functions such as EF. Within prefrontal regions, maturation continues throughout adolescence, with changes to the structure of the DLPFC and OFC seen until age 20, and myelination continuing throughout the PFC until the third decade of life (Toga, Thompson, & Sowell, 2006; Hodel et al., 2015). Others have

characterized the developmental trajectory of executive skills based on their emergence at the behavioural level, where EF demonstrates a similarly prolonged period of maturation (McAuley & White, 2011; Stuss, 1992). While EF skills initially emerge during infancy, they improve rapidly during the preschool years (Huizinga, Dolan, & van der Molen, 2006). Refinement continues throughout adolescence and early adulthood, in tandem with myelination and enhancement of the underlying neural architecture. Taken together, it is evident that the maturation of executive skills and their underlying neural substrates is a prolonged process that occurs throughout the first three decades of life. This protracted period of development results in an extended window of vulnerability to environmental factors. In combination with the PFC's characteristics that enhance its vulnerability to stressors, it is not surprising that robust evidence supports the notion early adversity exerts a deleterious effect on EF maturation, resulting in poorly developed EF skills after exposure to stressful environments early in life.

EF following early adversity.

EF is thought to be particularly important amongst those who experience early adversity due to its importance for effective emotion regulation and coping. Unfortunately, considerable evidence suggests that EF development is disrupted in the case of early adversity, ultimately manifesting in poor EF skills (e.g., Hostinar, Stellern, Schaefer, Carlson, & Gunnar, 2012). In fact, one comprehensive review paper concludes that executive dysfunction is the most frequently reported and severe neurocognitive sequelae of childhood maltreatment (Kavanaugh, Dupont-Frechette, Jerskey, & Holler, 2017). This is supported by several studies evaluating different types of early adversity. Children facing extreme early life deprivation, including being raised in institutional settings, demonstrate EF deficits across several domains (Hostinar et al., 2012; Bos, Fox, Zeanah, & Nelson, 2009). As well, children exposed to familial trauma (e.g.,

witnessing domestic abuse) demonstrate relatively poor EF skills on neuropsychological testing (DePrince, Weinzierl, & Combs, 2009). These deficits following early adversity are apparent across several core EF constructs. On tests of inhibitory control, individuals with a history of childhood trauma perform worse than controls (Marshall et al., 2016). Cognitive flexibility is further shown to be impacted; adolescents with a history of childhood maltreatment exhibit deficits on the WCST (Spann et al., 2012). Early life stress further relates to depleted verbal and visual working memory, and alterations in neural activation during working memory tasks (Philip et al., 2016; Majer, Nater, Lin, Capuron, & Reeves, 2010; Philip et al., 2013). Additionally, parents report poorer EF skills amongst children exposed to early life adverse conditions on rating-scale measures of EF, suggesting recognizable difficulties exist both in the integrity of cognitive skills and in their application to daily life (Merz & McCall, 2011). It is important to note that contradictory evidence does exist. Some studies find that children reared in unpredictable environments actually perform better on certain cognitive flexibility tasks, suggesting an enhancement effect of early adversity on EF (Mittal, Griskevicius, Simpson, Sung, & Young, 2015). This is attributed to the adaptiveness of flexibility in environments fraught with unpredictability. However, this finding only emerges under very specific conditions, and ultimately, overwhelming evidence points towards depleted EF amongst those with early adverse experiences. It is clear that the cognitive deficits that emerge following early adversity are long-lasting; not only do children and adolescents display impairments, evidence suggests that adults with a history of early adversity continue to display executive dysfunction later in life (e.g., Navalta, Polcari, Webster, Boghossian, & Teicher, 2006).

In order to further understand this robust finding, different approaches have been taken to better explain why ACEs disrupt cognitive development. One approach focuses on contextual

factors necessary for the development of EF, specifically examining the role that parents play in the maturation of a child's executive skills (Sameroff, 2010; Fay-Stammbach, Hawes, & Meredith, 2014). This framework posits that supportive environmental factors, most notably sensitive parenting and parental responsivity, are required early in life in order to support the emergence of self-regulation skills. This is further demonstrated empirically, with research showing that the absence of maternal sensitivity and presence of family risk factors lead to delayed EF skills in early childhood (Browne, Wade, Prime, & Jenkins, 2018). Overall, this line of research suggests that chaotic early environments fraught with stress lack familiar supports necessary for the healthy development of EF. Other approaches draw on work from animal models to elucidate the relationship between adverse environments and EF development. Doing so yields further evidence for the directionality and causal nature of the relationship between environmental factors and neurocognitive performance emerges, because animal work allows researchers to control the timing and conditions of adversity, and disentangle potential confounding factors (e.g., genetics) that cannot be separated in humans. Substantial evidence demonstrates that inducing stressful early life environments in rodents leads to poor performance on tasks designed to mirror human EF skills. For example, one study finds that animals reared in environments mimicking early adversity demonstrate deficits in attention, inhibition and set shifting, while other work demonstrates that stressful events early in life leads to poorer performance on set-shifting tasks in rats (Lovic & Fleming, 2004; Liston et al., 2006). Such evidence of poorly developed EF skills following early adversity is unsurprising, given the extensive evidence discussed earlier demonstrating that early life environmental stress disrupts the underlying neural architecture that supports higher level cognitive skills. Overall, executive dysfunction represents a serious cognitive deficit that is highly linked with poor educational and

occupational attainment. It is therefore of significant concern that adversity disrupts EF development, and unsurprising that negative health consequences ensue.

Executive dysfunction and health.

Pathophysiology of frontal lobes, manifested behaviourally through EF deficits, is widely associated with psychopathology. Because EF is central for effective emotion regulation, problem solving, and coping, it has obvious implications for mental health (Snyder, Miyake, & Hankin, 2015). Specifically, deficits in cognitive flexibility contribute to perseveration and rigid thinking styles, with consequences for rumination and mood and anxiety disorders (Whitmer & Banich, 2007). Deficits in inhibitory control relate to externalizing behaviours, substance use, and addiction (e.g., Young et al., 2009). Accordingly, evidence suggests that diffuse EF deficits characterize several neuropsychiatric disorders, including depression, anxiety disorders, OCD, and schizophrenia (e.g., Snyder et al., 2015, Snyder, 2013). EF has further been conceptualized as a transdiagnostic risk factor for psychopathology more generally (McTeague, Goodkind, & Etkin, 2016; Goschke, 2014). Though debate remains concerning the direction of this relationship (i.e., do EF deficits lead to psychopathology or vice versa), some evidence does support the notion that executive dysfunction is not merely a symptom of psychopathology, but rather a risk factor for and contributor to its development. Prospective longitudinal studies identify EF deficits prior to the onset of symptoms. In one sample, EF at age 13 predicted development of schizophreniform disorder in adulthood, while another study suggests that EF skills in early elementary school predicted internalizing and externalizing symptoms later on (Cannon et al., 2006; Riggs, Blair, & Greenberg, 2004; Parslow & Jorm, 2007). Further, EF deficits appear to be present in individuals even when disorders are in remission, perhaps indicating that they are not just an additional symptom of the disorder (Kurtz & Gerraty, 2009).

EF and mental health are tightly linked: several mental illnesses are characterized by executive dysfunction, with further evidence suggesting a causal role for EF in the development of psychopathology.

Executive dysfunction has also been linked with increased engagement in health-risk behaviours. From a theoretical perspective, avoiding certain behaviours that may be desirable in the short-term but present health risks in the long-term requires complex executive skills, including inhibition and impulse control. Temporal self-regulation theory (TST) proposed by Hall and Fong (2013) posits that executive control is one of the main determinants of engagement in health-related behaviour. Since health-promoting behaviours (e.g., physical activity, adoption of a healthy diet, etc.) require short-term consequences for long-term gains, they rely on the ability to inhibit prepotent responses. Evidence does support this, showing that stronger executive skills predict greater engagement in health-promoting behaviours (Allan, McMinn, & Daly, 2016). Further in line with TST, evidence indicates that EF is an important determinant of propensity to engage in health-risk behaviours. Risky alcohol-related behaviours, including earlier age of onset of alcohol use and binge drinking, have been identified as consequences of poorer EF (Peeters et al., 2015). EF has also been associated with unhealthy eating behaviours, overweight status, and sedentary behaviour (Limbers & Young, 2015; Stautz, Pechey, Couturier, Deary, & Marteau, 2016). Overall, EF is thought to be an important determinant of health-related behaviours, as strong EF skills increase engagement in health-promoting behaviours and lower the likelihood of engagement in health-risk behaviours.

Finally, executive dysfunction has been linked with chronic illness and physical health. One prospective study identified EF deficits as a predictor of coronary heart disease and stroke amongst older adults. Over a 3-year follow-up period, individuals in the lowest third of EF

scores demonstrated a significantly increased risk for stroke and coronary heart disease relative to those with above average EF (Rostamian et al., 2015). EF may also relate to physical health conditions by impacting their severity. Executive dysfunction may lead to difficulties managing chronic illnesses that involves complex medical considerations. In diabetes, for example, poorer EF is associated with reduced glycemic control (Duke & Harris, 2014). Taken together, physical and mental health, and engagement in risky health-related behaviours that predispose individuals to subsequent health challenges, are all related to executive skills. Specifically, executive dysfunction serves as a risk factor for the development of several neuropsychiatric illnesses, increased engagement in various health-risk behaviours, and poorer physical health via increased risk of illness and poorer management of existing chronic illnesses. Overall, EF demonstrates a clear relationship to health status.

Present Studies

The present work seeks to assess and refine a biologically plausible model of ACE exposure developed in our lab focusing on the role of EF (Figure 1). It is well-established that early life adversity predicts several maladaptive health-related outcomes that ultimately combine to reduce quality of life and hasten mortality. However, after review of the literature, it remains evident that gaps exist in our understanding of the underlying biological mechanisms that link ACE exposure with poor health outcomes. Careful examination of the detrimental effect of ACEs on neurodevelopment offers new insights about the neurobiological avenues through which ACEs exert a deleterious impact on health. Specifically, it is well documented that early adverse experiences disrupt the development of PFC-mediated neural networks that support complex cognitive skills subsumed under the umbrella of EF. Executive dysfunction further relates to many of the same health outcomes known to follow from ACE exposure, including

increased engagement in health-risk behaviours, psychopathology, and disease states. The sum of this evidence suggests that EF is a biologically and behaviorally plausible candidate for mediating the effects of ACE exposure on subsequent health. Therefore, we propose that ACEs disrupt the development of PFC-mediated neural networks, resulting in behaviourally evident EF deficits. In turn, executive dysfunction predicts poor health outcomes, both directly and indirectly via engagement in health-risk behaviour, culminating in early mortality.

Here, we present the findings from two separate samples of undergraduate research volunteers. Participants were asked to retrospectively report on ACE exposure. After assessment of EF and several health-related factors, mediation models were used to test the idea that EF serves as an underlying mechanism linking ACE exposure with poor physical and mental health. Specifically, we examined the relationship between ACE exposure, performance-based and rating-scale measures of EF, engagement in health-risk behaviours, and mental health distress. Because chronic illnesses and disease states that are known to follow early adversity are unlikely to emerge in young adulthood, we focussed specifically on mental health and risky behaviour in this work with undergraduates. We hypothesize that (1) individuals with greater levels of ACE exposure will exhibit relatively poor health in young adulthood, evidenced by greater engagement in health-risk behaviours and more mental health distress; (2) ACE history will predict EF, such that higher levels of ACE exposure will lead to poorer performance on in-lab tasks of EF and more symptoms of executive dysfunction in everyday life; (3) in turn, EF deficits will predict greater engagement in health-risk behaviours and poorer mental health; and (4) EF will significantly mediate the relationship between ACEs and health-related outcomes.

Study 1

Methods

Participants.

Participants were 86 undergraduate students from the University of Waterloo who were recruited from the Department of Psychology volunteer participant pool and completed the study in exchange for course credit. The final sample (N = 84) consisted of 48 women (57%), 34 men (40%), and two participants who self-identified their gender as other (2%). Participants ranged in age from 18-35 years of age (M = 20.68, SD = 2.91). Almost half (43%) of participants identified as Caucasian, while 26% identified as Asian and 17% identified as East Indian. In all, 73 (87%) participants spoke English as their first language and 64 (76%) had been exposed to English since birth. No exclusion criteria were utilized.

Materials.

Adverse Childhood Experience Questionnaire (ACE-Q; Felitti et al., 1998). This 10-item questionnaire assesses the occurrence of adverse life experiences, including abuse (psychological, physical, sexual) and household dysfunction (substance abuse, mental illness, domestic violence, criminal behaviour). Participants were asked to indicate whether or not they experienced each ACE prior to age 18. Consistent with the ACE literature, items were summed to create a total ACE score (Felitti et al., 1998). Internal consistency in our sample was 0.75.

Barkley Deficits in Executive Functioning Scale – Short Form: Self-Report (BDEFS-SF:SR; Barkley, 2011). This scale consists of 20 items that assess EF-related difficulties in daily life. Participants were asked to select 1 (*never or rarely*), 2 (*sometimes*), 3 (*often*) or 4 (*very often*) to indicate how often they experienced each problem during the past 6 months. Using the scoring system developed by Barkley (2011), all items rated “often” or “very often” were scored

as symptoms of executive dysfunction. The number of symptoms each participant endorsed were summed to create a total symptom score. Internal consistency of responses in our sample was 0.90.

Brief Symptom Inventory (BSI; Derogatis & Melisaratos, 1983). This 53-item scale was administered in order to assess our first health-related outcome variable: mental health distress. The BSI assesses symptoms of a range of psychopathologies (e.g., depression, anxiety). Participants were asked to select 0 (*not at all*), 1 (*a little bit*), 2 (*moderately*), 3 (*quite a bit*), or 4 (*extremely*) in response to problems that have bothered them in the seven days prior. Items were summed to create a composite score of mental health distress. Internal consistency in our sample was 0.96.

Health Behaviours Questionnaire (HBQ; in-house). To measure engagement in health-risk behaviours, this in-house questionnaire was developed based on items from the Canadian National Longitudinal Survey of Children and Youth. Health-risk behaviours selected for inclusion in our questionnaire pertain to regular smoking, illicit drug use, binge drinking, engaging in unprotected sex, and obesity. Items were summed to create an aggregate health-risk index. Internal consistency in our sample was .50.

Undergraduate Stress Questionnaire (USQ; Crandall, Preisler & Aussprung, 1992). This 83-item life events checklist was used to assess the occurrence of stressful life events in the previous month. This questionnaire has been normed on undergraduate U.S. college students and has been found to capture current stress levels in this population in a valid and reliable manner (Crandall et al., 1992). The number of stressful items that participants endorsed were summed to create a total stress score. Internal consistency in our sample was 0.86.

Perceived Stress Scale (PSS; Cohen, Kamarck, & Mermelstein, 1983). The PSS was administered in order to assess stress perception. This measure includes 10 items that ask participants to reflect upon their subjective level of stress during the month prior to the assessment. Participants are asked to choose 0 (*never*), 1 (*almost never*), 2 (*sometimes*), 3 (*fairly often*), or 4 (*very often*) in response to questions about how often they thought or felt certain things during the last month (e.g., "In the last month, how often have you been able to control irritations in your life?). These questions focus on individual perceptions of control over one's own life. The PSS has been validated for use in non-clinical settings with college students (Roberti, Harrington, & Storch, 2006). Items were summed to create a total perceived stress score. Internal consistency in our sample was 0.36. Because the stress response is known to be an important factor in the ACE-health relationship, data on the occurrence of stressful events and stress perception were collected. However, because the scope of the present work focused on evaluating the core components of our EF-centric model, stress data were not analyzed further for the current project.

Procedure.

Participants were informed that the purpose of the study was to assess associations amongst negative childhood experiences, life stress, thinking skills and mental/physical health for the end goal of understanding why exposure to early adversity has a long-term negative impact on wellbeing later in development. Based on this information, participants were then able to self-select into the study. After signing up online, students attended a one-hour session in the lab where they were presented with an informed consent letter by a trained research assistant. After reading and signing the consent letter, participants worked with the research assistant in a separate room of the lab where distractions were minimized. Instructions were given by the

researcher for all six questionnaires administered online using Qualtrics. Since the study used an individual differences design, the order of administration was standardized across participants in the following order: Background Questionnaire, ACE-Q, BDEFS-SF:SR, HBQ, USQ, PSS, BSI. Paper-based copies of questionnaires were available to students upon request, however no requests for paper-based copies were made. After completing the questionnaires, students received 1 course credit. This research protocol was approved by the Office of Research Ethics at the University of Waterloo.

To minimize the impact of missing data, participants missing more than 10% of data on any scale ($N = 2$) were dropped from analysis. For participants missing less than 10% of data on a scale, data were imputed via single imputation with the expectation-maximization algorithm to compute missing values[1]. To test mediation relationships, the PROCESS 3 macro for SPSS was used (Hayes, 2017). This method uses bootstrapping to establish the significance of the indirect relationship between the predictor and the outcome via the mediator, while also evaluating the paths from the predictor to the mediator, the mediator to the outcome, and the predictor to the outcome. All predictor variables were mean-centred prior to being entered into mediation models.

Results

Descriptive statistics for ACEs, executive dysfunction, mental health distress and health-risk behaviours indicated that all data were approximately normally distributed, with skew less than 3 and kurtosis less than 10 (see Table 1). No univariate outliers were detected in the executive dysfunction or health-risk variables, with all observations falling within 3 standard

[1] Data were confirmed to be missing completely at random using Little's MCAR test. Less than 5% of data were missing.

deviations of the mean. ACEs and mental health distress each contained one univariate outlier. Data were winsorized to reduce the extremity of the outliers, allowing for extreme cases to be retained while minimizing their impact on results. Extreme values were adapted such that they fell at exactly 3 standard deviations away from the mean. To test for multivariate outliers, the Mahalanobis distance was calculated at the $p = .001$ level on 5 degrees of freedom. Using this cut-off, no multivariate outliers were detected.

Next, zero order correlations between all variables were evaluated using Pearson correlations (see Table 2). Results revealed that ACEs were significantly positively correlated with executive dysfunction, $r(82) = .22$, $p = .044$, mental health distress, $r(82) = .35$, $p = .001$, and health-risk behaviours, $r(82) = .35$, $p = .001$. Further, executive dysfunction symptoms were positively correlated with mental health distress, $r(82) = .61$, $p < .001$, but were not significantly related to health-risk behaviours, $r(82) = .17$, $p = .133$. Due to the poor reliability identified in the in-house questionnaire used to assess engagement in health-risk behaviour ($\alpha = .50$), the correlation between EF and health-risk behaviours was re-examined after correcting for unreliability, resulting in an attenuated correlation of $r = .31$.

A basic mediation model (PROCESS model 4) was used to test the hypothesis that EF mediates the relationship between ACEs and mental health distress. Results revealed a significant total path (*c* path) in the positive direction from ACEs to mental health distress, $b = 6.05$, $SE = 1.76$, $t(81) = 3.43$, $p < .001$. Intermediate pathways from ACEs to executive dysfunction (*a* path), $b = 0.46$, $SE = 0.22$, $t(81) = 2.04$, $p = .044$, and executive dysfunction to mental health distress (*b* path), $b = 4.61$, $SE = 0.71$, $t(81) = 6.54$, $p < .001$, were also both significant in the positive direction. Lastly, the indirect effect of ACEs on mental health distress

mediated by executive dysfunction (*ab* path) was significant, $b = 2.12$, $SE = 1.14$, 95% CI [0.15, 4.58], $p < .05$ (see Figure 2).

In the next analysis, a second mediation model (PROCESS model 4) was run to evaluate whether executive dysfunction mediates the relationship between ACEs and engagement in health-risk behaviours. Results revealed a significant, positive total path (*c* path) from ACEs to health-risk behaviours, $b = 0.20$, $SE = 0.06$, $t(81) = 3.40$, $p = .001$. As reported above, the *a* path from ACEs to executive dysfunction was significant, while the *b* path from executive dysfunction to health-risk behaviours was not significant, $b = 0.03$, $SE = 0.03$, $t(81) = 0.87$, $p = .387$. The *ab* path was not significant, $b = 0.01$, $SE = 0.01$, 95% CI [-0.01, 0.05], $p > .05$, indicating that the relationship between ACEs and health-risk behaviour was not mediated by EF (see Figure 3).

Discussion

The above analyses sought to identify preliminary empirical support for a proposed model explaining the neurobiological mechanism behind the relationship between early adversity and negative health outcomes later in life. To do so, we first evaluated the bivariate relationship between model components and then utilized statistical models to test whether EF mediates the relationship between ACEs and two health related outcome measures.

Results from bivariate correlations indicated consistencies between our data and many relationships frequently reported in the literature. Increased ACE exposure was associated with higher levels of both mental health distress and engagement in health-risk behaviours, as well as more symptoms of executive dysfunction. Further, poorer EF was related to elevated symptoms of psychopathology. Surprisingly, EF was not significantly related to engagement in health-risk behaviours, despite theoretical predictions that greater difficulties with EF would be associated

with increased engagement in risky behaviours. To further investigate this unexpected finding, the reliability of the HBQ, the in-house scale developed to measure engagement in health-risk behaviours, was examined, revealing that this questionnaire failed to produce acceptable reliability. The correlation between executive dysfunction and health-risk behaviours was thus re-examined after correcting for unreliability, revealing an attenuated correlation much greater than the original uncorrected correlation. Therefore, the scale's poor reliability perhaps explains the null findings in regard to a predicted relationship between poor executive functioning and propensity to engage in risky behaviours like binge drinking and illicit drug use, as the attenuated correlation indicates that the variables would be more strongly linked had there been less unreliability in the measurement of health-risk behaviour.

In the first mediation model, results provided support for our proposed theoretical model. Results revealed that EF significantly mediated the relationship between ACE exposure and current mental health distress, indicating that experiencing early life adversity leads to increased EF difficulties in daily life, which in turn leads to higher levels of mental health distress. While an exact *p*-value cannot be ascertained via bootstrapping, this method produced confidence intervals that do not pass through zero, indicating a significant mediation. In accordance with recent trends in the literature, we chose to rely on bootstrapping methods to examine indirect effects as this method optimizes statistical power (MacKinnon, Lockwood, Hoffman, West & Sheets, 2002). In addition to a significant mediation, this model revealed significant positive relationships between ACEs and executive dysfunction, ACEs and mental health distress, and executive dysfunction and mental health distress. These findings indicate that exposure to greater levels of adversity early in life results in more difficulties with EF and mental health. As well, poorer EF predicts higher levels of psychopathology. Taken together, results suggest that the

relationship between ACEs and mental health distress is partially mediated by executive dysfunction. However, this finding is limited by the fact that EF was measured solely be rating-scale methods, and thus only provides information about the ability to apply executive skills to daily life situations.

Results from the second mediation model did not support our proposed model, as no significant mediated pathway from ACEs to health-risk behaviours was detected via executive dysfunction. While the lack of a significant mediation may indicate a failure to prove the proposed theoretical model, some methodological shortcomings were identified that may have contributed to the null results. Specifically, the measurement of health-risk behaviours failed to produce acceptable levels of reliability, as discussed above. Additionally, endorsement of health-risk behaviours was quite low throughout the sample, with some behaviours (e.g., risky sexual behaviours, illicit drug use) demonstrating particularly low prevalence rates. This restricted the range of the health-risk behaviour variable and may have reduced our ability to detect differences related to ACEs and EF. Despite overall low endorsement, one particular health-risk behaviour, binge drinking, did illicit higher rates of reporting. This likely reflects a unique feature of undergraduate samples who may be less likely to engage in some behaviours while still exhibiting high rates of risky alcohol use. Despite these limitations with the measurement, results did reveal a significant direct relationship between ACEs and health-risk behaviour, indicating that higher levels of early adversity predict increased engagement in risky behaviours. However, due to the unreliability in the measurement of health-risk behaviour, this result should be interpreted with caution.

Overall, this preliminary investigation lends partial support to our proposed model whereby EF mediates the relationship between ACEs and health-related outcomes. While this

relationship was demonstrated for mental health, it was not replicated for measures of physical health risk. In light of the limitations that emerged in relation to measurement of health-risk behaviours and EF, a follow-up study was undertaken in order to replicate and extend the present findings while addressing issues with operationalization of variables.

Study 2

Methods

Participants.

128 undergraduate students from the University of Waterloo participated in this study. Participants were recruited via the department participant pool and voluntarily participated in this experiment in exchange for course credit. The final sample (N = 119) consisted of 96 women (81%) and 23 men (19%). Participants ranged in age from 17-25 years of age (M = 19.87, SD = 1.72) at time of testing. Of the students in the sample, 33% of participants identified as Caucasian, while 28% identified as East Asian and 18% identified as East Indian. 65% of participants reported that English was their primary language, while 77% of participants reported being exposed to English since birth. No exclusion criteria were utilized.

Materials.

The ACE-Q, USQ, PSS, and BDEFS:SF-SR were once again administered to assess ACE exposure, current life stress, perceived stress, and executive dysfunction in daily life, respectively. In order to refine the assessment of health-related outcomes to be of maximal relevance for an undergraduate sample, scales assessing both mental health distress and health-risk behaviour were updated for this study.

Depression, Anxiety, and Stress Scale (DASS-42; Lovibond & Lovibond, 1995). The DASS was used to assess current symptoms of psychopathology. As this scale focuses specifically on symptoms related to depression, anxiety, and stress, it was selected to reflect the mental health concerns that are most prevalent among undergraduates. This 42-item measure asked participants to rate how much each statement applied to their life over the previous week on a scale from 0 (*did not apply to me at all*) to 4 (*applied to me very much or most of the time*).

The DASS-42 demonstrates excellent reliability and has been validated for use in non-clinical samples (Antony, Bieling, Cox, Enns, & Swinson, 1998). Internal consistency of the DASS in our sample was 0.97.

Young Adult Alcohol Consequences Questionnaire (YAACQ; Read, Kahler, Strong, & Colder, 2006). Because binge drinking was identified as the most prevalent health-risk behaviour in Study 1 while others were very rarely endorsed, it was determined that narrowing the scope of health-risk behaviours to focus specifically on those with most relevance to the population at hand was warranted. Thus, the YAACQ was administered to assess risky alcohol use. This self-report questionnaire is well-validated for use in an undergraduate sample and focuses on a health-risk behaviour with specific relevance for this population. The YAACQ consists of 48 items that ask participants to report whether or not they have experienced a range of consequences associated with alcohol use in the previous year. Consequences include academic and occupational impairment, physiological dependence, and interpersonal problems as a result of alcohol consumption. Responses were summed to create a risky alcohol use total score. Internal consistency in our sample was 0.94.

As previously mentioned, research indicates that rating-scale measures of EF (e.g., BDEFS) do not correlate with performance on laboratory tasks designed to capture EF-related cognitive abilities, and in fact capture different aspects of the construct of EF (Toplak et al., 2013). In order to measure the integrity of EF skills, three in-lab EF tasks were administered to assess each of the core executive skills: response inhibition, working memory, and cognitive flexibility.

Stop Signal Task (SST; Logan, Cowan, & Davis 1984). The SST is a computerized task that has been demonstrated to reliably measure response inhibition (Wöstmann et al., 2013). This

choice reaction time task requires a speeded response to stimuli on a computer screen, except on 25% of trials in which appearance of the stimulus is followed by an auditory 'stop' signal, requiring participants to inhibit the prepotent motor response. Timing of the signal is determined using a dynamic tracking algorithm such that responses are inhibited on 50% of trials. Following practice, participants completed 128 trials, 32 of which featured the auditory tone following stimulus presentation and were thus classified as stop trials (trials without a stop signal are referred to as go trials). Response inhibition was indexed using stop signal reaction time (SSRT), which is the difference between the mean delay of the stop signal and the average latency to correctly respond to stimuli on go trials. Internal consistency on go trials was 0.98.

Symmetry Span Task (Foster et al., 2015). To assess working memory, the shortened Symmetry Span Task was administered. This task requires memory of a spatial location on a 4x4 grid interleaved with a distraction task involving symmetry judgements of abstract designs. The memory-judgement sequence is repeated 2 to 5 times each trial. At the end of each trial, the sequence of spatial locations must be recalled in the same order of presentation. Following practice on memory and symmetry judgment tasks, participants completed 3 blocks of 14 trials. Working memory was indexed by the symmetry span partial score (i.e., total number of spatial locations correctly recalled across trials). Internal consistency of partial score across blocks was 0.76.

Letter Number Task (Rogers & Monsell, 1995). Cognitive flexibility was assessed using the Letter Number Task. In this task, participants are presented with a 4x4 grid where a number-letter combination (e.g., 3A) appear in a square of the grid. The task is either to determine whether the number is a vowel or a consonant or the number is even or odd depending on the location of the stimuli within the grid. Stimuli in the top squares of the grid required number

judgments, while those in the lower squares required letter judgments. Stimuli first appeared in the top left square of the grid and progressed around the grid in a clockwise fashion. Thus, on every second trial, participants were required to switch judgment type (i.e., from number judgment to letter judgment, or vice versa). Trials where participants make the same judgment as the previous trial are considered 'non-switch' trials, and trials where they must switch judgments are referred to as 'switch' trials. Following practice of number and letter judgments separately and together, participants completed 3 blocks of 24 trials (50% non-switch trials, 50% switch trials). Cognitive flexibility was indexed by reaction time switch cost, calculated by taking the difference in average reaction time between correct switch and non-switch trials. Internal consistency on non-switch trials was 0.89.

Procedure.

Participant recruitment mirrored the procedure outlined above in Study 1. After obtaining informed consent, trained research assistants provided participants with instructions to each computerized task and questionnaire. All participants completed the tasks in the following order: SST, USQ, PSS, ACE-Q, DASS-42, Symmetry Span Task, YAACQ, BDEFS, Background Questionnaire, Letter Number Task. After completing the tasks, students received 1.0 course credit. This research protocol was approved by the Office of Research Ethics at the University of Waterloo.

To minimize the impact of missing data, participants missing more than 20% of data on any scale ($N = 2$) were dropped from analysis. However, as several participants ($N = 25$) reported having never previously consumed alcohol, they were unable to complete the measure of risky alcohol use, and thus data from these participants were not included in analyses of health-risk behaviour outcomes but were retained for other analyses. Data from EF tasks were subject to a

rigorous quality control protocol whereby participants with accuracy less than 70% on symmetry judgments (Symmetry Span Task; $N = 3$) and less than 50% on non-switch trials (Letter Number Task; $N = 3$) were removed from further analyses. As well, SSRT could not be calculated for 17 participants due to no correct responses on stop trials; data from these participants were not included in analyses of EF task data. To combine data from three EF tasks into one composite measure of EF skills, derived scores from the SST (SSRT), Symmetry Span Task (symmetry span partial score), and Letter Number Task (reaction time switch cost) were normalized and summed. This composite EF score ($M = 0.04$, $SD = 1.38$) was used for mediation analyses. The PROCESS 3 macro for SPSS was again used to test mediation relationships (Hayes, 2017). All predictor variables were mean-centered prior to being entered into mediation models. One basic mediation model was run for each outcome of interest (mental health distress and risky alcohol use), and everyday EF and EF skills were entered as parallel mediators.

Results

Descriptive statistics were first evaluated for data from questionnaires assessing ACEs, everyday executive dysfunction, mental health distress, and risky alcohol use (see Table 3). All data were approximately normally distributed. One univariate outlier (defined as 3 standard deviations above or below the mean) was detected from each of the ACE-Q and DASS. Two univariate outliers were detected on the BDEFS:SF-SR symptom score and YAACQ total score. To minimize the impact of univariate outliers, data were winsorized to fall exactly 3 standard deviations away from the mean. Descriptive statistics were then evaluated for EF task data (see Table 4). One extreme univariate outlier was identified in the SSRT, and data from this participant were dropped from analyses. After removal of this participant, data on all derived scores were normally distributed. To evaluate performance on the Letter Number Task, t-tests

were used to compare performance between switch and non-switch trials. Results revealed significantly better accuracy on non-switch trials relative to switch trials, $t(118) = -9.93$, $SEM = 0.01$, $p < .001$, 95%CI[-0.08, -0.06], and significantly slower reaction times on switch trials relative to non-switch trials, $t(118) = 21.70$, $SEM = 16.85$, $p < .001$, 95%CI[332.26, 398.99]. To test for multivariate outliers, the Mahalanobis distance was calculated at the $p = .001$ level on 7 degrees of freedom. Using this cut-off, one multivariate outlier was detected. Data from this participant were dropped from analyses.

Zero order correlations between questionnaire data and EF tasks were evaluated using Pearson correlations (see Table 5). Results revealed that ACEs were significantly positively correlated with everyday executive dysfunction, $r(117) = .27$, $p = .003$, mental health distress, $r(117) = .33$, $p < .001$, and risky alcohol use, $r(93) = .37$, $p < .001$. ACEs were not significantly correlated with performance on any of the three EF tasks (all ps > .281). Further, everyday executive dysfunction symptoms were positively correlated with mental health distress, $r(117) = .61$, $p < .001$, but only marginally related to risky alcohol use, $r(93) = .19$, $p = .070$. Everyday EF did not significantly relate to any EF task data (all ps > .170). Mental health distress did not relate to any tasks of EF (all ps > .106), while risky alcohol use was negatively correlated with working memory, $r(93) = -0.21$, $p = .045$, but was not significantly correlated with response inhibition, $r(84) = -0.05$, $p = .645$, or cognitive flexibility, $r(93) = -0.12$, $p = .252$. Finally, no EF tasks were significantly correlated with each other (all ps > .197).

Next, a basic mediation model (PROCESS model 4) was used to test whether EF mediates the relationship between ACEs and mental health distress. Results revealed a significant total (c) path in the positive direction from ACEs to mental health distress, $b = 5.21$, $SE = 1.36$, $t(101) = 3.84$, $p < .001$. Intermediate paths from ACEs to EF skills (a_1 path), $b = 0.08$,

SE = 0.08, *t*(101) = 0.98, *p* = .327, and EF skills to mental health distress (b_1 path), *b* = -0.72, *SE* = 1.46, *t*(101) = -0.49, *p* = .623 were not significant. Intermediate pathways from ACEs to everyday EF (a_2 path), *b* = 0.79, *SE* = 0.22, *t*(101) = 3.57, *p* < .001, and everyday EF to mental health distress (b_2 path), *b* = 3.32, *SE* = 0.52, *t*(101) = 6.39, *p* < .001, were both significant in the positive direction. The mediated pathway from ACEs to mental health distress via everyday EF was significant, *b* = 2.61, *SE* = 0.84, 95% CI [1.05, 4.41], *p* < .05, but there was no significant mediation via EF skills, *b* = -0.06, *SE* = 0.19, 95% CI [-0.50, 0.28], *p* > .05 (see Figure 4).

A second basic mediation model was used to test whether EF mediates the relationship between ACEs and risky alcohol use. Results revealed a significant total (*c*) path in the positive direction from ACEs to risky alcohol use, *b* = 1.05, *SE* = 0.40, *t*(84) = 2.66, *p* = .009. As reported above, there was no significant a_1 path from ACEs to EF skills, while the intermediate a_2 path from ACEs to everyday EF was significant in the positive direction. Neither the intermediate pathway from EF skills to risky alcohol use (b_1 path), *b* = -0.25, *SE* = 0.51, *t*(84) = -0.49, *p* = .624, nor the pathway from everyday EF to risky alcohol use (b_2 path), *b* = 0.20, *SE* = 0.19, *t*(84) = 1.04, *p* = .302, were significant. The relationship between ACEs and risky alcohol use was not significantly mediated by everyday EF, *b* = 0.18, *SE* = 0.19, 95% CI [-0.17, 0.59], *p* > .05 or EF skills, *b* = -0.02, *SE* = 0.06, 95% CI [-0.18, 0.06], *p* > .05 (see Figure 5).

Discussion

The above analyses sought to replicate and extend findings from Study 1, with the ultimate goal of lending support to the proposed model of ACE exposure. In order to address specific limitations identified in Study 1, performance-based measures of EF supplemented rating-scale measures to obtain a more complete assessment of EF, capturing both the integrity of EF skills and their application to daily life. Moreover, because endorsement of a wide variety

of health-risk behaviours was limited in Study 1, in addition to identified issues regarding psychometric properties of the in-house scale, a well-validated questionnaire designed specifically for college students focusing on risky alcohol use was selected to measure health-risk behaviour. Despite these modifications, hypotheses remained similar. Specifically, it was predicted that increased ACE exposure would lead to greater endorsement of health-risk behaviour and mental health distress, with EF mediating this relationship.

Overall, ACEs, everyday executive dysfunction symptoms, and mental health distress were reported at similar levels to Study 1, while narrowing the focus of health-risk behaviour strictly to risky alcohol use elicited greater reporting of risky behaviour. Results from bivariate correlations showed many consistencies with the literature and with the previous study. Specifically, higher levels of early adversity were linked with poorer overall health (indexed via greater endorsement of psychopathology symptoms and risky alcohol use), and poorer EF in daily life. Further, greater EF difficulties in daily life related to more psychopathology symptoms, and marginally related to higher levels of risky alcohol use. Surprisingly, performance on in-lab EF tasks did not relate to ACE exposure or health-related outcomes, with only one exception: poorer performance on an in-lab working memory task did relate to greater endorsement of risky alcohol use behaviours.

In line with previous findings, performance on in-lab EF tasks did not relate to self-reported EF difficulties in daily life on a questionnaire. Although only modest relationships between EF tasks were expected, performance across tasks was very weakly correlated. Because of this, we were prohibited from using latent variable analysis to extract a single component representing EF-specific variance from the three EF tasks. Instead, a composite measure of EF performance was created to serve as the measure of overall EF skill integrity in mediation

analyses. Despite the lack of relationships between tasks, performance on individual tasks was as expected, closely mirroring findings from the literature and our lab (Gabel & McAuley, 2018; Soveri, Rodriguez-Fornells, & Laine, 2011; Redick et al., 2012). As well, manipulation checks on the Letter Number task confirmed that performance was worse (poorer accuracy and slower reaction times) on switching vs. non-switching trials, in line with predictions based on known costs associated with switching tasks. Despite findings in line with expectations on individual tasks, bivariate relationships between performance on each task and measures of adversity, mental health, and health-risk behaviours were not detected (with the exception of a significant relationship between working memory and risky alcohol use). We hypothesize that this may relate to the nature of the undergraduate sample, discussed in depth below.

Results from our first mediation model replicated findings from Study 1, whereby EF in daily life significantly mediated the relationship between ACE exposure and mental health distress such that additional adverse experiences increased reported EF difficulties, in turn predicting higher levels of psychopathology. However, this mediation did not replicate when EF was assessed with performance-based measures. Additionally, significant intermediate relationships revealed that, while ACEs were associated with increased EF problems in daily life, they were not related to performance on in-lab EF tasks. Further, performance-based measures of EF did not predict mental health distress. Taken together, results suggest that the relationship between ACEs and mental health distress is partially mediated by executive dysfunction symptoms in daily life, but not by EF skills.

The second mediation model revealed a significant direct relationship between ACEs and risky alcohol use, such that higher levels of adversity predicted greater reporting of risky alcohol-related behaviours. EF did not mediate this relationship, and no relationships were

detected between either measure of EF and risky alcohol use. The lack of mediation between ACEs and risky behaviours via EF was consistent with findings from Study 1, despite improved measurement and range of reporting of risky behaviours.

Overall, Study 2 replicated findings from Study 1, indicating that EF difficulties in daily life mediate the relationship between ACE exposure and mental health in young adulthood. However, we did not find evidence for an intermediate role of underlying EF skills as measured on in-lab tasks; performance on all three tasks was unrelated to adversity history, and more tasks did not relate to current health status. Finally, results did not support our hypotheses regarding the role of EF in the relationship between early adversity and health-risk behaviour. Although ACEs directly predicted risky alcohol use, executive dysfunction did not mediate this relationship.

General Discussion

In order to further elucidate the relationship between early life adversity and health outcomes, this project sought preliminary empirical support for a biologically-plausible model of ACE exposure developed in our lab. Although it is well-established that early adversity is detrimental for health later in life, inducing physical and mental health problems that ultimately hasten mortality, gaps exist in our understanding of biological mechanisms linking early environmental experiences with health factors many years later. In order to address this gap in the literature, we developed a model focused on the role of EF. Development of the neural substrates that support higher-order cognitive functions (i.e., those subsumed under the umbrella of EF) continues throughout childhood and adolescence, reaching maturity only by the third decade of life. Environmental stressors timed during this protracted period interrupt the intricate maturation process, resulting in lifelong structural and functional alterations of the PFC at the neural level, and deficits in EF at the behavioural level. In order to explain the biological link between ACEs and health outcomes, we capitalized on this understanding of the detrimental effect of environmental stress on prefrontal and EF development, especially given evidence that executive dysfunction predicts many of the same health outcomes known to follow from ACE exposure. Poorly developed EF skills are linked, both theoretically and empirically, with increased engagement in health-risk behaviours. Psychopathology and chronic illness follow, and are also independently linked with executive dysfunction. Taken together, we propose a model whereby ACE exposure disrupts the development of prefrontally-mediated neural pathways, manifesting in neurocognitive deficits, specifically executive dysfunction. In turn, EF deficits predispose individuals to poor physical and mental health, both directly and indirectly via engagement in health-risk behaviours, ultimately hastening mortality.

Two studies were undertaken in order to test our proposed model. To do so, we examined the relationships between retrospectively reported early adversity experiences, EF (as assessed by both rating-scale and performance-based measures), and current health status in two independent samples of undergraduate research volunteers. Because many of the disease states known to follow from ACE exposure are age-related and unlikely to emerge in young adulthood, we selected mental health and health-risk behaviours as our outcomes of interest. We hypothesized that (1) ACE exposure would predict health status in young adulthood; (2) increased ACE exposure would predict EF deficits; (3) executive dysfunction would increase both current mental health distress and propensity to engage in risky behaviours; and (4) the relationship between ACEs and health outcomes would be mediated by EF.

In Study 1, we identified support for our first hypothesis, as ACE exposure directly predicted psychopathology symptomology and engagement in a range of health-risk behaviours. Hypotheses 2 and 3 were partially supported: while increased ACE exposure predicted poorer EF in daily life, those self-reported EF deficits predicted only mental health distress, but not health-risk behaviours. With regards to our fourth hypothesis, results supported the role of EF as a mediator between ACEs and mental health, but not health-risk behaviours. Limitations were identified with the measurement of health-risk behaviour, as the in-house scale did not produce adequate reliability, and included several health-risk behaviours that are rarely reported in undergraduate students. As well, EF was assessed using solely self-report questionnaires, which are known to capture only a subset of the construct of EF (Toplak et al., 2013). Study 2, designed to address the aforementioned limitations identified in Study 1 by improving measurement of health-risk behaviours and examining the integrity of EF skills on in-lab task, replicated several findings from Study 1. Firstly, ACE exposure predicted EF difficulties in daily life, mental

health distress, and health-risk behaviour. In turn, self-reported EF deficits directly predicted psychopathology symptoms, but not health-risk behaviours. Finally, symptoms of executive dysfunction in everyday life mediated the relationship between ACEs and mental health distress, but not risky behaviour. Results from Study 2 failed to identify significant relationships between performance on in-lab tasks of EF and other model components, with the exception of a significant bivariate relationship between working memory performance and risky alcohol use. No significant mediation between ACEs and health status via EF skills emerged.

Taken together, results converge to suggest that everyday EF mediates the relationship between ACEs and mental health. This finding provides preliminary empirical support for the hypothesis that exposure to environmental stress early in development disrupts the maturation of EF, resulting in EF deficits in meeting everyday life goals, in turn predicting increased psychopathology. Psychopathology, especially mood and anxiety disorders, are highly prevalent amongst undergraduate samples, and symptoms often emerge at this transitional life stage. With the psychosocial pressures of transitioning to university, the ability to use EF skills to effectively regulate emotions and cope with challenges may be especially important in order to buffer against psychopathology. On the other hand, neither everyday EF nor EF skills mediated the relationship between ACE exposure and health-risk behaviours. Initially, it was thought that measurement error and inappropriate selection of health-risk behaviours for an undergraduate population contributed to these null results. However, improvements in these factors for Study 2 ultimately did not alter the results. Once again, EF was not a significant mediator of the ACE-health-risk behaviour relationship. This finding was surprising given the theoretical and empirical links between ACEs, EF, and health-risk behaviour. The relative scarcity of health-risk behaviours amongst undergraduates may in part explain these findings. Additionally, although

risky alcohol use was more prevalent than the wider range of risky behaviours presented in Study 1 (e.g., illicit drug use, unsafe sexual practices), it might reflect a unique phenomenon in unergraduates that may be somewhat independent from the traditional conceptualization of health-risk behaviour in the ACE literature, that looks at a range of behaviours across the lifespan. In the context of an undergraduate population, alcohol use is a prevalent facet of social experience. While binge drinking is inherently risky, alcohol use at this particular life stage may not reflect the same underlying propensity to risk taking as it would in another context, and may be more influenced by social factors and peer pressures. Therefore, it may not reflect the predicted relationship with EF.

In Study 2, we were unable to find evidence for the role of EF skills in mediating the relationship between ACEs and health outcomes, nor was EF task performance related to early adversity or current health (with the exception of a significant bivariate relationship between working memory performance and health-risk behaviour). Because correlations of performance across EF tasks were meager, we were unable to extract a latent factor representing the shared variance related to the underlying construct of EF, and instead created a composite measure of scores from each task. Thus, the composite measure contained variability related to several other factors, many of which are unrelated to EF, increasing noise in the data and perhaps creating too much variance to allow predicted relationships to emerge. Further, sampling exclusively from an undergraduate population may distort distributions of performance on EF tasks, and may not be representative of performance in the general population. This may have influenced our ability to detect relationships on EF tasks specifically. Because participants were university students, cognitive skills on basic EF tasks might be quite high overall, because entrance to university typically relies on some degree of EF skill. However, differences did emerge when looking at the

ability to apply those basic skills and use them to complete complex real-world tasks and accomplish goals. Questionnaires assessing EF in daily life ask about situations that require different types of EF skills, such as self-regulation. This type of executive skill is not as necessary for performance on the types of computerized in-lab tasks we administered, but perhaps is where difference related to early adversity become most evident. Further, both of our samples consisted of young adults, with the average age falling around only 20 years old. Based on what is known about the development of EF skills, it is likely that younger participants in the sample possess immature EF skills. Therefore, it is possible that some of the variability in EF skill performance is associated with age-related differences in developmental stage, and not related to difference caused by ACE exposure, limiting the conclusions we could draw.

Several limitations exist that minimize the conclusions that can be drawn from this work. Firstly, ACEs were exclusively measured using retrospective, self-report questionnaires. Despite evidence supporting retrospective recall as an acceptable methodology that produces accurate and reliable results, more recent meta-analytic findings suggest that retrospective questionnaires may produce discrepant results from prospective tracking of maltreatment (e.g., Reuben et al., 2016; Dube et al., 2004; Baldwin et al., 2019). Thus, replication using prospective measures would be necessary in order to ensure that the present findings generalize across ACE measurement methods. Secondly, data were collected exclusively from undergraduate samples. While ACEs are still endorsed at a relatively frequent rate amongst this population, an undergraduate sample is not representative of the general population in many ways, and may especially not reflect those who have the highest early adversity burden. Further, educational attainment, specifically in a rigorous academic institution, is inherently demanding on higher level cognitive skills like EF. Because of this, our sample may not reflect the true variation of EF

skills in a general population. Thirdly, as previously discussed, self-report measures of EF represent only a subset of the construct of EF and possess certain limitations that limit the conclusions that can be drawn from these data (Toplak et al., 2013). Additionally, self-report measures may not accurately reflect real difficulties in daily life EF tasks that individuals possess because individuals can have limited insight into their own EF-related challenges. Because informant-report data were not collected as part of the present work, findings are restricted by limitations inherent in self-report methods.

Ultimately, although this project faces limitations and produced mixed results, it is significant insofar as it is the first step in a larger inter-disciplinary research program seeking to refine the proposed model of ACE exposure. In doing so, this work attempts to move beyond studies that demonstrate association between childhood adversity and behaviors that hasten mortality to elucidating how this association is established. Model building is an essential component of this undertaking as it leads to testable hypotheses that may be explored at multiple levels of analysis (e.g., biological, behavioral) using complementary methods and research designs (e.g., human and animal work, correlational studies and experiments). Ultimately, this line of work aims to contribute to the development of targeted interventions that reduce the health burden associated with ACE exposure.

Of course, in order to gain a truly comprehensive understanding of the biological mechanisms that underlie the link between adversity and health, several systems must be rigorously evaluated and subsequently integrated. In order to refine our model focused on EF, this work isolated the effect of adversity on the frontal lobes and associated cognitive processes. However, it is evident that adversity enacts a complex and widespread effect on physiological and psychological development, and disrupted development across these factors is interrelated

(e.g., Nusslock & Miller, 2016). Other proposed mechanisms (e.g., the stress response, inflammation), are highly linked with the PFC, and disruptions to their development influence PFC functions and vice versa. Indeed, several reviews attempting to integrate existing knowledge in order to gain a better understanding of underlying mechanisms all reference the PFC as one of several important pieces of the puzzle (e.g.,Nusslock & Miller, 2016; Pakulak, Stevens, & Neville, 2018; Danese & McEwen, 2012). Therefore, the present work must be understood in this context, as an attempt to validate one potential pathway in order to ultimately gain a thorough understanding the complete ACE-health relationship.

In conclusion, this study identified partial preliminary empirical support for a model seeking to elucidate underlying neurobiological mechanisms linking the experience of early life adversity with later life poor health outcomes. Further research is needed in order to better understand the role that neurocognitive factors, such as EF, play in linking ACEs with health outcomes in more diverse populations, and characterizing the complex interaction between EF and other biological systems.

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Appendix A

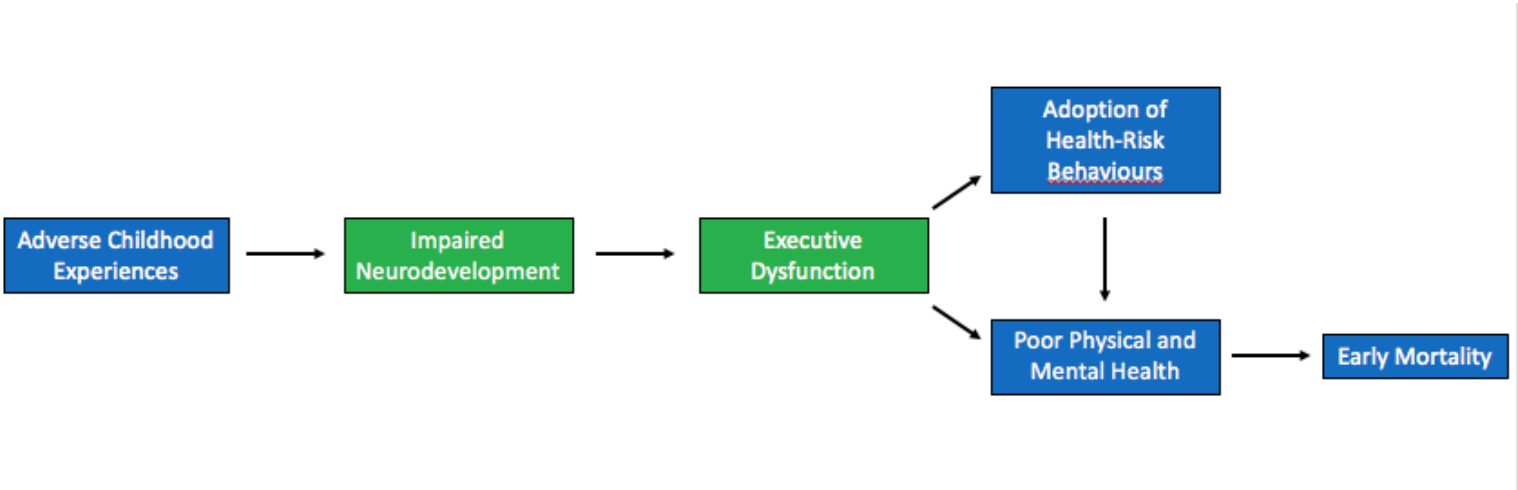

Figure 1. The proposed neurodevelopmental model connecting childhood adversity with early mortality via the presumed impact of altered brain function on executive function (EF). This model includes direct effects of EF on health, as well as indirect effects of EF on health via health-risk behaviours.

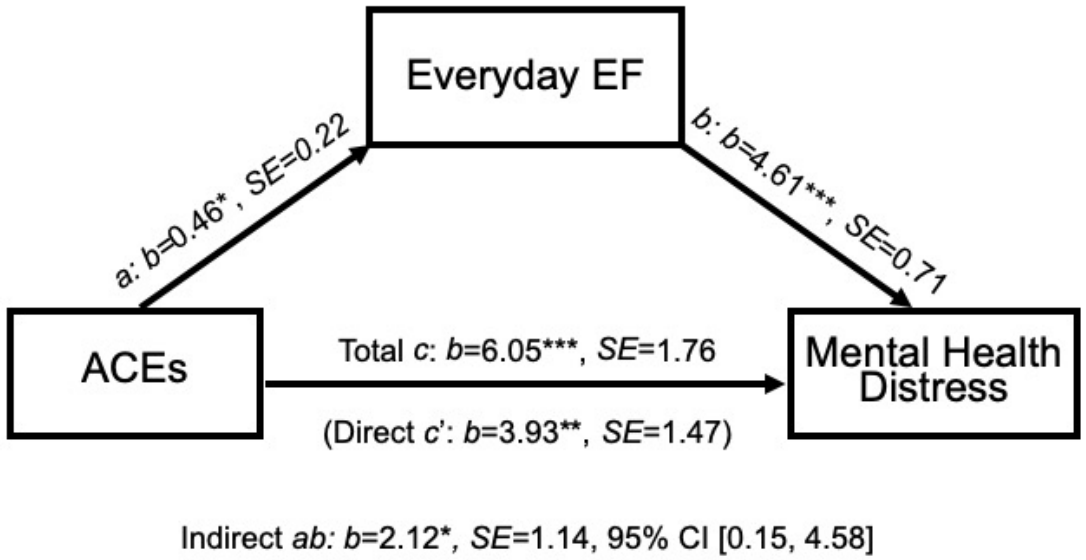

Figure 2. Mediation model depicting the relationships between ACEs and EF, ACEs and mental health distress, and EF and mental health distress, and the indirect relationship between ACEs and mental health distress via EF. Values represent unstandardized path coefficients and their standard errors. ACEs = adverse childhood experiences. EF = executive function. * $p < .05$, ** $p < .01$, *** $p < .001$

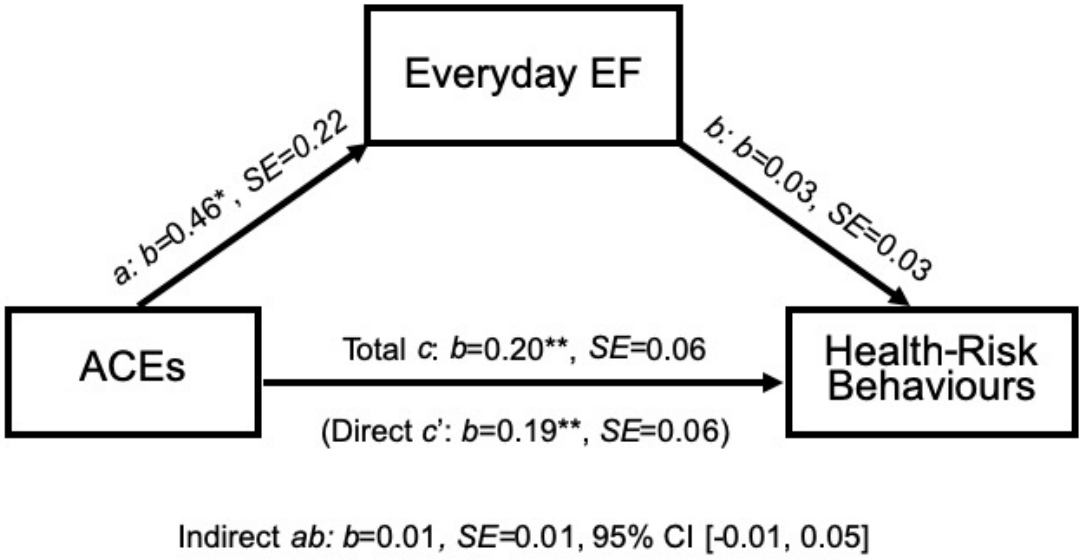

Figure 3. Mediation model depicting the relationships between ACEs and EF, ACEs and health-risk behaviours, and EF and health-risk behaviours, and the indirect relationship between ACEs and health-risk behaviours mediated by EF. Values represent unstandardized path coefficients and their standard errors. ACEs = adverse childhood experiences. EF = executive function. * $p <$ .05, ** $p <$ .01, *** $p <$ .001

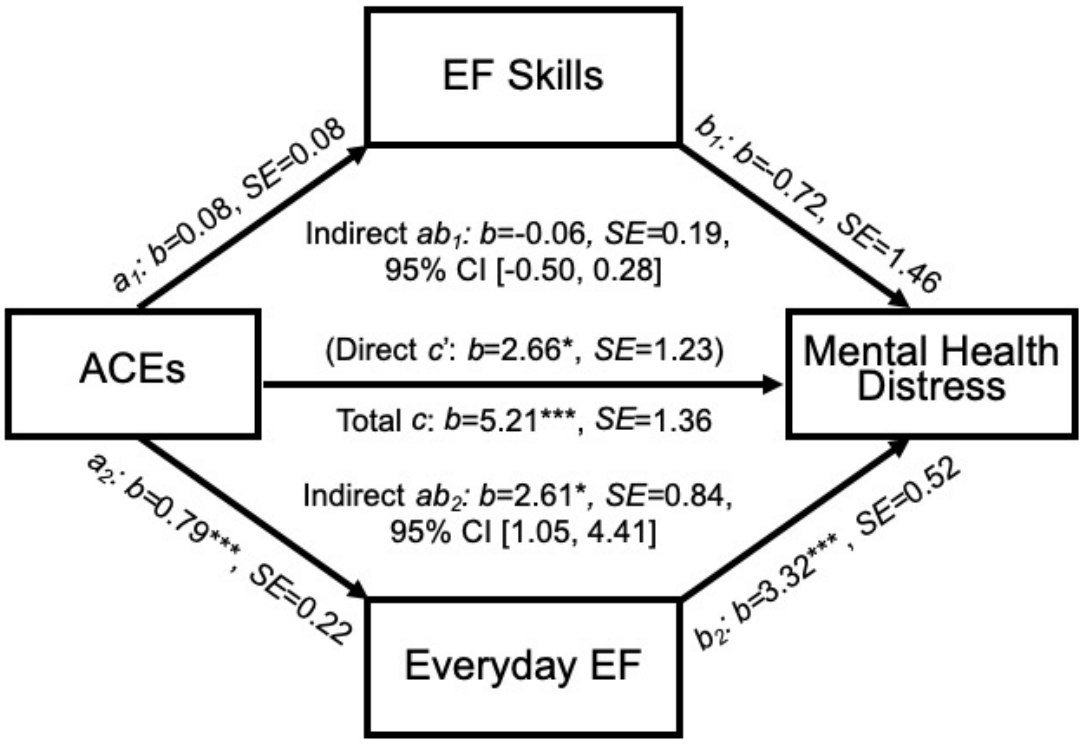

Figure 4. Mediation model depicting the direct and total relationships between ACEs and mental health distress, indirect pathways via measures of EF skills and everyday EF, and intermediate pathways between all model components. Values represent unstandardized path coefficients and their standard errors. ACEs = adverse childhood experiences; EF = executive function. * $p < .05$, ** $p < .01$, *** $p < .001$

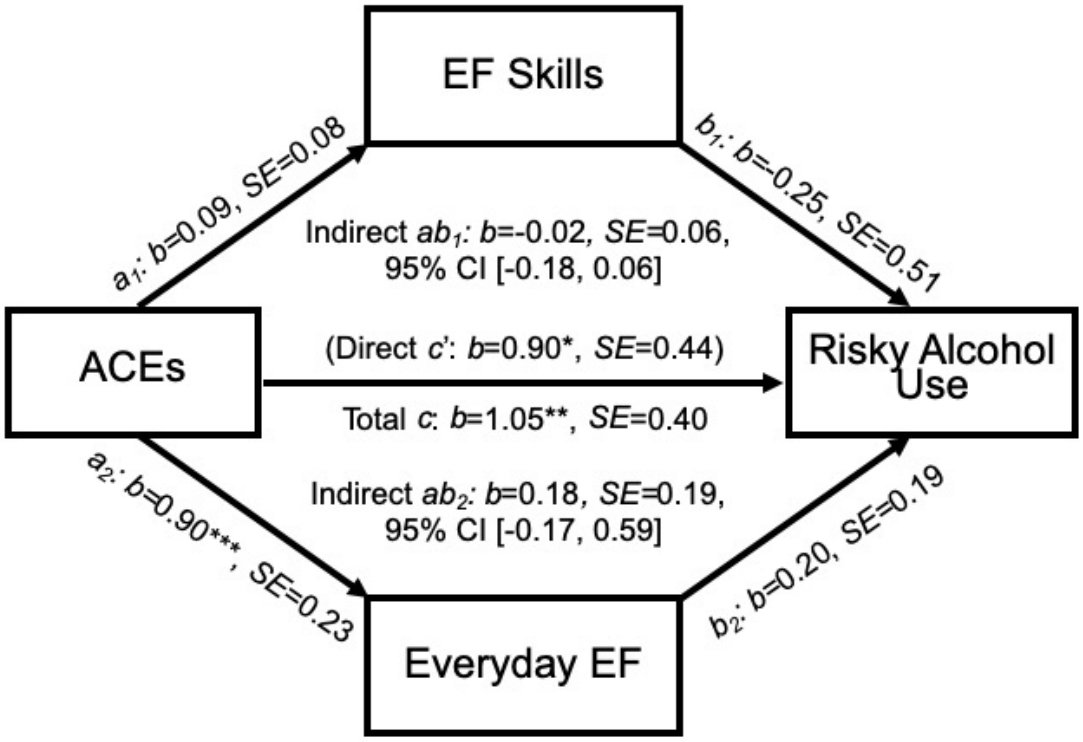

Figure 5. Mediation model depicting the direct and total relationship between ACEs and risky alcohol use, indirect pathways via measures of EF skills and everyday EF, and intermediate pathways between all model components. Values represent unstandardized path coefficients and their standard errors. ACEs = adverse childhood experiences; EF = executive function. * $p < .05$, ** $p < .01$, *** $p < .001$

Table 1. *Descriptive statistics for final variables included in Study 1 analyses (N=84)*

Measure	Mean	*SD*	Skew	Kurtosis
ACEs	1.92	2.07	1.07	0.48
Executive Dysfunction	5.01	4.32	0.54	-0.84
Mental Health Distress	53.91	35.36	0.83	0.26
Health-risk Behaviours	1.33	1.18	0.69	-0.19

Note: Statistics for ACEs and mental health distress variables are reported following winsorizing to reduce extremity of outliers. ACEs = adverse childhood experiences

Table 2. *Bivariate correlations between final variables included in Study 1 analyses (N=84)*

Measure	2	3	4
1. ACEs	.22*	.35**	.35**
2. Executive Dysfunction	-	.61**	.17
3. Mental Health Distress		-	.13
4. Health-risk Behaviours	-	-	-

Note: Statistics for ACEs and mental health distress variables are reported following winsorizing to reduce extremity of outliers. ACEs = adverse childhood experiences * $p < .05$, ** $p < .01$

Table 3. *Descriptive statistics for final questionnaire variables included in Study 2 analyses*

Measure	*N*	Mean	*SD*	Skew	Kurtosis
ACEs	119	1.48	1.81	1.30	0.97
Everyday EF	119	4.78	4.32	1.00	0.32
Mental Health Distress	119	37.88	26.64	0.60	-0.22
Risky Alcohol Use	95	6.37	7.00	1.49	1.54

Note: Statistics for all variables are reported following winsorizing to reduce extremity of outliers. ACEs = adverse childhood experiences; EF = executive function. * $p < .05$, ** $p < .01$

Table 4. *Descriptive statistics for performance-based measures of executive function*

Task	*N*	Measure	*M* (*SD*)	Range	Skew	Kurtosis
Stop Signal Task	103					
		Accuracy on go trials	0.99 (0.03)	0.79 – 1	-4.39	24.18
		Accuracy on stop trials	0.60 (0.16)	0.06 – 0.94	-0.39	0.97
		RT on correct go trials	631.30 (143.08)	285.30 – 1017.45	-0.03	-0.49
		Stop Signal RT	317.53 (56.84)	212.40 – 556.34	1.15	2.78
Symmetry Span Task	119					
		Symmetry Span Partial Score	29.44 (7.56)	9 – 42	-0.45	-0.03
Letter Number Task	119					
		Accuracy on non-switch trials	0.85 (0.13)	0.47 – 1.00	-1.11	0.40
		Accuracy on switch trials	0.94 (0.09)	0.58 – 1.00	-1.66	2.63
		RT on correct non-switch trials	1037.26 (221.87)	653.32 – 1690.61	0.76	0.38
		RT on correct switch trials	1402.88 (259.28)	813.90 – 2121.82	0.16	0.01
		RT switch cost	365.63 (183.80)	-143.72 – 1000.61	0.16	0.63

Note: RT = reaction time.

Table 5. *Bivariate correlations between final variables included in Study 2 analyses*

Measure	2	3	4	5	6	7	8
1. ACEs	.27**	-.11	-.02	.02	.10	.33**	.37**
2. Everyday EF		-.09	-.13	-.12	.06	.61**	.19
3. Response Inhibition			.11	-.05	-.33*	-.08	-.05
4. Working Memory				.12	.62**	-.15	-.21*
5. Cognitive Flexibility					-.62**	-.04	-.12
6. EF Skills Composite Score						.01	-.02
7. Mental Health Distress							.23*
8. Risky Alcohol Use							

Note: Statistics for ACEs, everyday EF, mental health distress, and risky alcohol use are reported following winsorizing to reduce extremity of outliers. ACEs = adverse childhood experiences; EF = executive function. * $p < .05$, ** $p < .01$.