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The association between adverse childhood experiences and alcohol use disorder: probing risk and protective factors

Inauguraldissertation
zur Erlangung des Doctor scientiarum humanarum
der
Medizinischen Fakultät Mannheim
der Ruprecht-Karls-Universität
zu
Heidelberg

vorgelegt von
Çağdaş Türkmen
aus
Oberhausen
2024

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In memory of my beloved pedagogy teacher Klaus K. Stephan.
Your passion for learning and teaching will always remain with me.

Preface

This work is a cumulative dissertation based on four empirical studies, and part of the results have already been published as peer-reviewed articles in scientific journals. Therefore, certain sections, tables, or figures of this thesis will be identical to these publications. Please find the list of the articles below.

Article 1:

Türkmen, C.*, Tan, H.*, Gerhardt, S., Bougelet, E., Bernardo, M., Machunze, N., Grauduszus, Y., Sicorello, M., Demirakca, T., Kiefer, F., & Vollstädt-Klein, S. (2024). The association between adverse childhood experiences and alterations in brain volume and cortical thickness in adults with alcohol use disorder. *Addiction Biology*, *29*(9), e13438. https://doi.org/10.1111/adb.13438

*Shared first authorship.

Article 2:

Türkmen, C., Lee, A., Tan, H., Gerhardt, S., Kiefer, F., & Vollstädt-Klein, S. The association between adverse childhood experiences and inhibitory control in heavy-drinking adults: a functional MRI study. Submitted to *Child Abuse & Neglect*.

Article 3:

Türkmen, C., Brunborg, G. S., Lund, I. O., Kiefer, F., Vollstädt-Klein, S., & Burdzovic Andreas, J. (2024). Sports participation moderates the risk of family-specific negative life events on alcohol use among adolescents: Evidence from the longitudinal MyLife study. *Addictive Behaviors*, *155*, 108041. https://doi.org/10.1016/j.addbeh.2024.108041

Article 4:

Türkmen, C., Martland, R., Grilli, M., Stubbs, B., Roessler, K. K., & Hallgren, M. (2024). Can high-intensity interval training improve health outcomes among people with substance use disorders? A systematic review and preliminary meta-analysis. *Mental Health and Physical Activity*, *27*, 100622. https://doi.org/10.1016/j.mhpa.2024.100622

For **Article 1**, the corresponding chapter in the dissertation is **Empirical Studies 2.1 Study I**. For **Articles 2, 3 and 4**, the corresponding chapter in the dissertation is **Empirical Studies 2.2 Study II, Empirical Studies 2.3 Study III and Empirical Studies 2.4 Study IV, respectively**. The detailed description of the personal contribution to each of the publication is provided in the table on the next page.

Work steps	Article 1	Article 2	Article 3	Article 4
Conception (%)	70	100	80	80
Literature search (%)	100	95	100	90
Ethics proposal (%)	0	35	0	N/A
Animal experimentation proposal (%)	N/A	N/A	N/A	N/A
Data collection (%)	30	100	0	N/A
Data analysis (%)	60	75	0	100
Interpretation of results (%)	80	80	80	90
Manuscript writing (%)	95	90	70	90
Revision (%)	90	N/A	75	95
Indicate which figures and tables resulted from your dissertation work.	All tables and figures.	All tables and figures.	All tables and figures.	All tables and figures.
Detail which data/figures/tables are based on research by others.	None.	None.	None.	None.

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ABBREVIATIONS

ACE	Adverse childhood experiences
ADS	Alcohol Dependence Scale
AU	Alcohol use
AUD	Alcohol use disorder
AUDIT-C	Alcohol Use Disorders Identification Test-Concise
BDI-II	Revised Beck Depression Inventory
BDNF	Brain-derived neurotrophic factor
BIS-11	Barratt Impulsiveness Scale, 11^{th} version
BOLD	Blood oxygenation level dependent
CERT	Consensus on Exercise Reporting Template
CIMH	Central Institute of Mental Health
CT	Cortical thickness
CTQ	Childhood Trauma Questionnaire
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, fifth edition
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, fourth edition
EPHPP	Effective Public Health Practice Project
FD	Framewise displacement
FDR	False discovery rate
fMRI	Functional magnetic resonance imaging
FWE	Family-wise error rate
GLM	General linear model
GMV	Gray matter volume
HC	Healthy control
HIIT	High-intensity interval training
HPA	Hypothalamic-pituitary-adrenal
HR_{peak}	Peak heart rate
ICD	International Classification of Diseases
ICTRP	International Clinical Trials Registry Platform
IFG	Inferior frontal gyrus
KERF-40-I	Brief German version of the Maltreatment and Abuse Chronology of Exposure

MACE	Maltreatment and Abuse Chronology of Exposure
MD	Mean difference
MICT	Moderate-intensity continuous training
MNI	Montreal Neurological Institute
MRI	Magnetic resonance imaging
NLE	Negative life events
NRCT	Non-randomized controlled trial
OR	Odds ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International prospective register of systematic reviews
RCT	Randomized controlled trial
ROI	Region of interest
RT	Reaction time
SBM	Surface-based morphometry
SCID-I	Structured Clinical Interview for DSM-IV Axis I disorders
SMD	Standardized mean difference
sMRI	Structural magnetic resonance imaging
SP	Sports participation
SPM12	Statistical Parametric Mapping Software 12
SSD	Stop-signal delay
SSRT	Stop-signal reaction time
SST	Stop-Signal Task
SUD	Substance use disorder
TE	Echo time
TI	Inversion time
TIDieR	Template for Intervention Description and Replication
TIV	Total Intracranial Volume
TR	Repetition time
VBM	Voxel-based morphometry
VO_{2max}	Maximal oxygen uptake
WFU	Wake Forest University
WHO	World Health Organization

1 INTRODUCTION

Development is a lifelong process that is particularly dynamic and vulnerable during childhood and adolescence, a period marked by profound brain development that coincides with behavioral changes, most notably increased risk-taking behaviors (Casey et al., 2008; Spear, 2000). The experiences encountered during this highly "plastic" period can present opportunities for growth or expose individuals to potential vulnerabilities (Kolb & Gibb, 2011; Tierney & Nelson, 2009). Thus, the environment in which a child grows up plays a crucial role, either promoting healthy development or posing risks that may undermine it (National Research & Institute of Medicine Committee on Integrating the Science of Early Childhood, 2000). Among these risks, adverse childhood experiences have received growing interest in research due to their high prevalence and long-term impact on brain development as well as physical and mental health (Herzog & Schmahl, 2018; Teicher & Samson, 2016).

1.1 Adverse childhood experiences (ACE)

Adverse childhood experiences (ACE), defined as "potentially traumatic events that occur in childhood (0-17 years)" (Centers for Disease Control and Prevention, 2024a), remain an important public health issue, contributing significantly to the global burden of disease (Gilbert et al., 2009). ACE, including maltreatment (i.e., abuse and neglect) and household dysfunction, are highly prevalent in the general population, with a recent meta-analysis estimating that globally approximately 60% of adults have reported experiencing at least one ACE (Madigan et al., 2023). This aligns with a recent report based on the Behavioral Risk Factor Surveillance System (BRFSS) data, indicating that 63.9% of U.S. adults have reported experiencing at least one ACE (Swedo et al., 2023). Among individuals exposed to ACE, around 16-18% have reported experiencing four or more ACE, which was especially prevalent in women and minoritized racial/ethnic groups (Madigan et al., 2023; Swedo et al., 2023).

Exposure to multiple ACE has been found to be a major risk factor for somatic diseases (e.g., heart disease, cancer), mental health disorders (e.g., depression and anxiety disorders), low life satisfaction, engaging in violence, as well as problematic drug and alcohol use (Amos et al., 2023; Gilbert et al., 2009; Madigan et al., 2023; Witt

et al., 2019). It is also important to note that studies have found a cumulative effect of ACE such that the risk of adverse mental and physical health consequences increases as the number of ACE increases (Felitti et al., 1998; Hashemi et al., 2021; Merrick et al., 2017). The chronicity of maltreatment (i.e., prolonged or repeated exposure) is also important consider, as chronically maltreated children have been found to exhibit more externalizing and internalizing problems, compared to children exposed to transitory maltreatment (Jaffee & Maikovich-Fong, 2011).

ACE contribute to premature mortality and account for much of the economic burden of ACE-related health conditions in adulthood (Gilbert et al., 2009; Hughes et al., 2021; Peterson et al., 2023). In Germany, ACE-attributable costs have been estimated to equal around 129 billion USD (Hughes et al., 2021). Harmful alcohol use, in particular, represents one of the highest ACE-attributable costs across many countries (Hughes et al., 2021). Indeed, individuals with harmful alcohol/drug use, particularly those diagnosed with substance use disorders, represent an important target for public health efforts, as they are among those facing the highest mortality risk, with approximately 9 to 24 years of life lost (Chesney et al., 2014). Among substance use disorders, alcohol use disorder is the most prevalent among German adolescents, with approximately 20.000 of those below the age of 20 receiving treatment for acute alcohol intoxication in emergency inpatient settings (Arnaud et al., 2023; Thomasius et al., 2022)

1.2 Alcohol use disorder (AUD)

Alcohol use disorder (AUD) is a widespread public health issue, affecting approximately 283 million people worldwide (World Health Organization, 2018). AUD, along with other substance use disorders (SUD), is characterized by a “problematic pattern of substance use leading to clinically significant impairments or distress” (American Psychiatric Association, 2013). The diagnostic criteria for SUD were revised in the fifth version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), merging the previously separate diagnoses of abuse and dependence into a single SUD diagnosis (American Psychiatric Association, 2013). A clinical diagnosis requires at least two out of eleven criteria to be met within a 12-month period (American Psychiatric Association, 2013). Notably, the DSM-5 introduced severity levels for SUD based on the number of diagnostic criteria met (2–3 criteria = mild; 4–5 = moderate; ≥

6 = severe) (American Psychiatric Association, 2013). While legal problems were removed as a criterion from the DSM-5, craving for substances, an important predictor for relapse (Vafaie & Kober, 2022), has been added as a diagnostic criterion (Hasin et al., 2013)

Given the significant global burden of disease associated with AUD (GBD 2016 Alcohol and Drug Use Collaborators, 2018), there is an urgent need to improve intervention and prevention programs. Although available treatments such as contingency management and cognitive behavioral therapy offer moderate effectiveness (Dutra et al., 2008), relapse rates among individuals with AUD remain high, affecting up to two-thirds of patients (Moos & Moos, 2006; Nguyen et al., 2020; Witkiewitz et al., 2019). Risk factors for a heightened risk of relapse include polysubstance use, psychiatric comorbidities, as well as drug craving (Andersson et al., 2019; Domino et al., 2005; Kabisa et al., 2021; Vafaie & Kober, 2022). Individuals with AUD frequently face physical health issues (e.g., liver disease, tuberculosis, ischemic stroke) and cognitive impairments, which are also predictive of relapse (Sliedrecht et al., 2019; Teixeira et al., 2024)

As noted above, a key challenge in the management of AUD is relapse (Moos & Moos, 2006). Indeed, AUD is often described as a chronically relapsing disorder characterized by periods of heavy drinking, withdrawal, and cravings, frequently followed by cycles of relapse after abstinence attempts (Koob et al., 1998; Leshner, 1997; Volkow & Li, 2005). Compounding the issue, only 20% of individuals with AUD pursue treatment (Rehm et al., 2015), with barriers such as stigma, shame, and the severity of AUD hindering access to care (Venegas et al., 2021). Addressing these challenges requires not only improving access to and encouraging AUD treatment but also focusing on preventing the onset of AUD. One promising avenue is to target ACE, which comprise a well-established risk factor for the development of AUD (Broekhof et al., 2023; Felitti et al., 1998; Leza et al., 2021).

1.3 Relationship between ACE and AUD

The relationship between ACE and AUD was first empirically supported in the seminal ACE study led by Felitti et al. (1998) who found that individuals with four or more ACE had a 4- to 12-fold higher risk of developing alcohol or drug abuse problems, compared to those without ACE exposure. This risk association has since been corroborated by

extensive evidence from reviews and meta-analyses indicating a higher prevalence of ACE in adults with SUD, compared to the general population (Leza et al., 2021), as well as a high prevalence of four or more ACE in those with addiction (Madigan et al., 2023). More recently, Broekhof et al. (2023) provided prospective evidence that individuals with a history ACE are approximately four times more likely to develop SUD. This study also revealed sex-specific risk profiles, with women being 5.9 times more likely to develop AUD and men being 5 times more likely to develop illicit drug use disorders (Broekhof et al., 2023). Additionally, research suggests that emotional abuse, in particular, may contribute to an earlier onset of AUD among women (Schückher et al., 2018).

While a risk association between ACE and AUD has been well-established, the pathways through which ACE may contribute to the development of AUD remain to be elucidated. One potential mechanism is emotion dysregulation, which has been identified as a key factor in ACE-related psychiatric sequelae (Dvir et al., 2014). For example, one study has demonstrated that maladaptive cognitive emotion regulation strategies may be a mechanism through which ACE could exert effects both on dependence and alcohol craving among treatment-seeking individuals with AUD (Khosravani et al., 2019). These findings align with the results from a previous study suggesting that emotion regulation difficulties mediate the relationship between childhood maltreatment and alcohol problems in patients with AUD (Dutcher et al., 2017).

Another potential mechanism underlying the association between ACE and AUD is stress sensitivity (Hall et al., 2022). Both ACE and AUD have been associated with dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, which plays a crucial role in the body's stress response (Blaine et al., 2016; Kalmakis et al., 2015). This dysregulation, particularly alcohol-induced, has been shown to sensitize dopaminergic reward pathways, which can influence craving and contribute to the development of AUD (Blaine et al., 2016). Notably, both stress and alcohol activate overlapping pathways, particularly within the reward system of the brain (Koob, 2008). Additionally, chronic alcohol consumption can impair prefrontal executive control over stress and reward systems, increasing craving and vulnerability to relapse (Heinz et al., 2009).

While these findings offer valuable insights into potential mechanisms underlying the association between ACE and AUD, there has been a growing interest

in cognitive functioning as a potential mechanism in understanding this risk association (Edalati & Krank, 2016).

1.3.1 The role of cognitive functioning

Cognitive functioning plays an important role in the context of ACE and AUD, with accumulating evidence indicating that it is impeded by both factors (Hawkins et al., 2021; Lund et al., 2020; Ramey & Regier, 2019; Su et al., 2019). Recent research efforts have extended this evidence by conceptualizing cognitive functioning as a potential mediator in the relationship between ACE and AUD (Bounoua & Sadeh, 2022; Edalati & Krank, 2016). Building on the dual process model (Tversky & Kahneman, 1981), Edalati and Krank (2016) have developed a model of cognitive pathways through which ACE may contribute to the development of AUD. In their model, they propose that impairments in two systems, namely automatic, nonconscious processes (System 1) and controlled, conscious processes (System 2), mediate the association between ACE and SUD.

According to this model, impairments in different cognitive functions such as behavioral inhibition and attention (System 2) can interfere with reasoning abilities, leading to irrational responses to stressful situations, which, in turn, may ultimately contribute to the development of AUD (Edalati & Krank, 2016). On the other hand, dysfunctional automatic memory associations (System 1), which connect negative self-associations to the soothing effects of substance use, may promote maladaptive coping strategies aimed at alleviating tension in response to stressful situations or negative emotions, thereby increasing the risk of developing AUD (Edalati & Krank, 2016). Indeed, a recent systematic review based on 88 studies has supported this line of reasoning, indicating that maladaptive coping strategies explain the association between ACE and alcohol use (Sebalo et al., 2023).

In line with this cognitive framework of vulnerability, a recent study has found that inhibitory control deficits mediate the relationship between ACE and increased alcohol use among adolescents (Kim & Bruce, 2022). Interestingly, ACE were not directly associated with higher alcohol use in mid-adolescence, but the association was mediated by inhibitory control deficits from early adolescence (Kim & Bruce, 2022). Similarly, a longitudinal study revealed that individuals who experienced sexual abuse before age ten showed atypical neurophysiological development in the frontal brain during tasks involving behavioral inhibition, suggesting disruptions in synaptic pruning

and cortical maturation, which were linked to alcohol use problems in emerging adulthood (Meyers et al., 2019).

A recent review suggests that inhibitory control deficits are more pronounced in early adolescence for trauma-exposed youth but tend to diminish by late adolescence (van der Bij et al., 2020). A similar trajectory has been observed among adolescents at risk for substance use (Quach et al., 2020). However, for both trauma-exposed adolescents and those at-risk of substance use, compensatory mechanisms, as reflected in distinct brain activity patterns, may account for these changes in late adolescence (Quach et al., 2020; van der Bij et al., 2020). Indeed, adolescence, which is characterized by significant neurobiological changes and an increased tendency for risk-taking behaviors, represents a critical period for understanding how ACE affect inhibitory control (Crews et al., 2007). Therefore, further investigation into the neural mechanisms underlying ACE-related changes in inhibitory control is essential.

1.3.2 Magnetic resonance imaging (MRI) as a tool for understanding neurobiological pathways

Significant advances in neuroimaging over the past decades have greatly progressed our understanding of the neurobiological underpinnings of ACE and AUD (Hakamata et al., 2022; Parvaz et al., 2011). For example, magnetic resonance imaging (MRI), one of the most commonly used neuroimaging methods, offers a non-invasive technology to study both the structure and function of the brain using structural MRI (sMRI) and functional MRI (fMRI), respectively.

sMRI provides high-resolution images of the brain's structure (with resolution varying based on magnetic field strength), allowing for the analysis of structural changes in specific brain regions that may arise due to ACE and AUD. To analyze such changes, brain morphometric techniques such as voxel-based morphometry (VBM) (Ashburner & Friston, 2000) and surface-based morphometry (SBM) (Dale et al., 1999; Fischl et al., 1999) can be employed. While VBM is primarily used to estimate gray matter volume, SBM offers a range of applications, such as measuring cortical volume, thickness and surface area (Goto et al., 2022). For instance, a meta-analysis based on VBM studies has found that adults with a history of ACE exhibit reduced grey matter in prefrontal-limbic brain regions, including the right dorsolateral prefrontal cortex and right hippocampus (Paquola et al., 2016). Identifying such structural changes can

inform further research aimed at clarifying the functional significance of these brain regions in the relationship of ACE and AUD using fMRI.

fMRI allows for the examination of brain activity and functional connectivity patterns. It indirectly measures neuronal activity by detecting changes in blood flow, operating on the principle that when a brain region is more active, it consumes more oxygen, leading to an increase in blood flow to that area (Chen & Glover, 2015; Ogawa et al., 1992). Different contrast mechanisms can be used to detect changes in metabolic activity, including the most widely used blood-oxygen-level-dependent (BOLD) signal, which reflects the ratio of oxygenated to deoxygenated hemoglobin (Chen & Glover, 2015). This enables researchers to infer which brain regions are active at rest or during specific tasks, such as in task-based fMRI studies (Gore, 2003). For instance, task-based fMRI studies have shown that alcohol craving is associated with neural cue reactivity, which can be provoked by alcohol-related cues such as images of alcoholic beverages (H. Tan et al., 2023; Vollstädt-Klein et al., 2012). This line of research holds promise for identifying relevant biomarkers and potential therapeutic targets in AUD (Addiction Cue-Reactivity Initiative Network, 2024).

Both sMRI and fMRI provide exciting opportunities for elucidating the role of certain neural structures in the relationship between ACE and AUD, which may ultimately be translated into targeted prevention and intervention strategies.

1.3.3 Neurobiology of ACE and AUD: the role of the type and timing of ACE

Given the susceptibility of the developing brain to neurobiological changes following traumatic experiences (Jeong et al., 2021; Lim et al., 2014), it is crucial to elucidate alterations in neural structures and functions which may predispose affected individuals to increased addiction vulnerability. Certain brain regions, particularly the hippocampus and amygdala, have frequently been investigated in ACE research (Teicher et al., 2016). Both the hippocampus and amygdala also hold clinical significance in the context of AUD, given their role in memory formation (Anand & Dhikav, 2012) and in emotion regulation (Davis & Whalen, 2001), respectively.

Van Dam et al. (2014) have demonstrated that childhood maltreatment is associated with lower brain volume in the amygdala, hippocampus and other limbic structures, which were found to predict the severity of substance use relapse among adult patients with cocaine-, alcohol- and cannabis use disorders. In adolescents with

AUD, a study has found an association between increased ACE severity and reduced brain volumes in the hippocampus and in the right precentral gyrus (Brooks et al., 2014). These findings suggest that it may be relevant to consider the potential impact of ACE in research assessing neurobiological changes in AUD. Such research could benefit from a targeted focus on neuropsychological mechanisms, particularly inhibitory control, which is vulnerable to the effects of both ACE and heavy alcohol use / AUD (Hawkins et al., 2021; López-Caneda et al., 2013; Lund et al., 2020; Ramey & Regier, 2019; Su et al., 2019).

The (bilateral) inferior frontal gyrus (IFG), which plays a key role in inhibitory control (Garavan et al., 1999; Hampshire et al., 2010; Swick et al., 2008), has been shown to be affected by ACE and AUD, with studies showing that both ACE and AUD are associated with reduced gray matter volume and cortical thickness in this brain region (Momenan et al., 2012; Pollok et al., 2022; Wiers et al., 2015; Yang et al., 2023). Recent research suggests that ACE can also have potential effects at a functional level on the neural circuitry underlying inhibitory control among adults (Sacu et al., 2024). In their study, Sacu et al. (2024) have found greater ACE severity to be associated with increased activation in the bilateral IFG, insula, anterior cingulate cortex and middle temporal gyri during behavioral inhibition in adults. This suggests a potential long-term impact of ACE on the neural circuitry underlying behavioral inhibition as well as potential ACE-related compensatory mechanisms in adulthood.

While these studies provide valuable neurobiological insights, merely assessing the occurrence and severity of ACE may not capture the complexity of the dynamic developmental changes accompanying these experiences. Brain development is an intricate and dynamic process with non-linear maturation that may introduce age-specific sensitive periods during which the developing brain is particularly vulnerable to early life stress (Andersen & Teicher, 2008). The theory of sensitive periods posits that there are developmental windows of vulnerability (e.g., early childhood) during which the developing brain is differentially susceptible to the effects of ACE (Knudsen, 2004). Adolescence, in particular, is a key developmental period, as the prefrontal cortex undergoes significant maturation during this period (Arain et al., 2013). Findings from human brain imaging and animal studies suggest that bottom-up limbic systems, involved in emotional processing, mature earlier than top-down control systems, resulting in “less mature” prefrontal areas relative to subcortical areas (Casey et al., 2008). This developmental imbalance may potentially increase the susceptibility to

risk-taking behaviors such as risky alcohol use, which in turn may disrupt brain development and executive functioning (Lees et al., 2020).

In line with the framework of sensitive periods, previous research has found differential neurobiological effects that were contingent on the type and timing of ACE (e.g., abuse or neglect) (Herzog & Schmahl, 2018; Teicher & Samson, 2016). Studies on the amygdala, for example, have found that neglect during childhood is associated with an increase in amygdala volume (Lupien et al., 2011; Pechtel et al., 2014), while abuse in later stages is associated with a decrease in amygdala volume (Schmahl et al., 2003; Van Dam et al., 2014). With respect to the hippocampus, sensitive periods were identified for early childhood as well as early and late adolescence (Andersen et al., 2008; Herzog et al., 2020; Teicher et al., 2018). There also appear to be ACE type- and sex-specific effects such that male hippocampal volumes were predicted by neglect during the first seven years of life, while abuse at ages 10 and 11 predicted female hippocampal volumes (Teicher et al., 2018). More recent studies have also shown that the volume of the anterior cingulate cortex may be differentially sensitive to the effects of neglect during early childhood (Grauduszus et al., 2024; Herzog et al., 2020).

While these findings are encouraging, it is important to note that sensitive periods are inconsistent and heterogeneous across studies, especially regarding the hippocampus and amygdala (Grauduszus et al., 2024; Pechtel et al., 2014). In addition, varying types and degrees of psychopathology may account for the heterogeneity across observed volumes (Teicher & Samson, 2016). Overall, these findings highlight the value of further elucidating neurobiological mechanisms and developmental windows of vulnerability to inform targeted prevention and intervention efforts. Yet, exploring ways in which resilience processes can be promoted, particularly by identifying protective factors that could moderate adverse outcomes, represents an equally important and promising avenue of research.

1.4 Potential protective factors in the relationship between ACE and AUD

Growing evidence suggests that one particularly important aspect in preventing the onset of AUD is the age at which individuals first consume alcohol (Dawson et al., 2008; Hingson et al., 2006). Studies have shown that those who begin drinking before the age of 15 are at an increased risk of developing alcohol-related problems and

engaging in earlier hazardous drinking compared to those who delay the initiation of alcohol use until after age 15 (Gardner et al., 2024; Livingston et al., 2023). Moreover, research has shown that those who begin drinking before the age of 15 are significantly more likely to develop AUD compared to those who delay alcohol use, with one study suggesting that this risk decreases when alcohol use is postponed until age 21 or later (Hingson et al., 2006). These findings highlight the need to better understand the factors that might help to offset an early onset of alcohol use.

ACE are a well-established risk factor for both the development of AUD (Broekhof et al., 2023; Felitti et al., 1998) and for early initiation of alcohol use (Enstad et al., 2019). Growing evidence suggests that ACE increase the risk of initiating alcohol use during early adolescence (Dube et al., 2006; Rothman et al., 2008), with many individuals using alcohol as a coping mechanism for their problems (Rothman et al., 2008). Moreover, there appears to be a cumulative effect such that the risk of early alcohol use initiation increases as the number of ACE increases (Alvanzo et al., 2020; Dube et al., 2006). In one study, common ACE associated with an early initiation of alcohol use included parental separation and substance abuse at home (Rothman et al., 2008), emphasizing the importance of familial stressors. Consequently, identifying modifiable factors that can reduce the impact of early life stressors is crucial in efforts to prevent early alcohol involvement.

The risk-protective model (Fergus & Zimmerman, 2005; Rutter, 1985) offers a valuable framework for enhancing our understanding in this area of research. According to this model, protective factors act as moderators of the risk-outcome relationship, attenuating the negative outcome (e.g., alcohol misuse) at higher levels of the protective factors (e.g., parental monitoring, exercise) among the risk-exposed group (e.g., adolescents exposed to a high number of ACE) (Fergus & Zimmerman, 2005; Rutter, 1985). It is particularly important for the protective factor to be modifiable and easily translatable into prevention strategies.

Previous research has found that increased individual, family, and community-level assets are prospectively associated with lower odds of binge drinking among youth experiencing multiple negative life events (Lensch et al., 2020). However, it is challenging to translate many of these assets (e.g., general self-confidence, school connectedness) into prevention strategies. Similarly, factors such as low shyness and conduct problems, which are associated with an early onset of intoxication (Enstad et al., 2019), are also not easily translatable. In contrast, physical exercise, particularly

participation in sports, has emerged as a promising modifiable and non-stigmatizing approach to improving both the psychosocial and physical health of adolescents and adults (Bjørnarå et al., 2021; Eather et al., 2023; Eime et al., 2013), warranting further investigation as a potential protective resource in those exposed to early life stressors.

1.4.1 Physical exercise as a promising protective factor

There is a plethora of evidence indicating that increased physical activity offers both physical and mental health benefits, and can help to prevent chronic diseases (e.g., cardiovascular disease, cancer) as well as premature death (Warburton et al., 2006; World Health Organization, 2024). Despite these benefits, physical activity levels remain low in the general population, with recent reports estimating that globally 31% of adults and 81% of adolescents do not meet the recommended levels of physical activity (Guthold et al., 2020; Strain et al., 2024). The WHO recommends regular physical activity, including 150-300 minutes of moderate-intensity physical activity and 75-150 minutes of vigorous-intensity physical activity per week for adults to achieve health benefits (Bull et al., 2020). For children and adolescents, the WHO recommends an average of 60 minutes of moderate-to-vigorous physical activity per day across the week (Bull et al., 2020). Thus, promoting physical activity represents a key focus for intervention and prevention programs.

Physical exercise, a planned, structured and repetitive subset of physical activity, has received growing interest as an adjunct treatment in clinical AUD research (Hallgren, Vancampfort, Giesen, et al., 2017; Hallgren, Vancampfort, Schuch, et al., 2017; Lardier et al., 2021; Søgaard Nielsen et al., 2016). This is especially relevant for patients with AUD who have been found to be more sedentary compared to matched healthy controls (Vancampfort et al., 2019), which aligns with findings in individuals with major psychiatric disorders (Vancampfort et al., 2017). While the ultimate or intermediate goal of exercise is to improve or maintain one’s physical fitness (Caspersen et al., 1985), growing evidence suggests that moderate-intensity exercise can also reduce alcohol craving – an important predictor for relapse (Schneekloth et al., 2012) – in patients with AUD (Brown et al., 2016; Hallgren et al., 2021; Ussher et al., 2004). This highlights the potential of exercise as a relapse prevention strategy in AUD treatment, though the role of exercise intensity warrants further investigation.

While exercise shows promise as an adjunct treatment for AUD (Hallgren, Vancampfort, Giesen, et al., 2017), it may also play an important role in prevention strategies, as earlier research has shown that ACE affect physical activity levels (Felitti et al., 1998). This area of research has recently gained renewed interest, with findings from the large-scale Adolescent Brain Cognitive Development (ABCD) study indicating a cumulative impact of ACE on physical activity levels among adolescents such that those with four or more ACE were found to be less physically active (Al-shoaibi et al., 2024). Notably, emotional abuse was associated with 719 fewer steps, followed by physical neglect which was associated with 424 fewer steps (Al-shoaibi et al., 2024). These findings are consistent with earlier evidence indicating that exposure to ACE is associated with higher physical inactivity and reduced odds of participating in sports (Felitti et al., 1998; Noel-London et al., 2021). This poses a significant issue, as a recent review suggests that physical inactivity may moderate the association between ACE and poor physical health outcomes (obesity, inflammation), depressive symptoms, psychological functioning and health-related quality of life (Hadwen et al., 2022). Consistent with this, recent studies have demonstrated that higher physical activity levels are associated with improved health-related quality of life (Moon & Han, 2022) among adults with ACE, and may mitigate the effect of ACE on depression among adults (Royer & Wharton, 2022).

1.5 Research gaps and aims of the present work

While an association between ACE and the development of AUD has been established, there is a paucity of research exploring potential mechanisms underlying this association. Cognitive functioning, in particular, may be a promising candidate explaining this association (Edalati & Krank, 2016), although the neurobiological underpinnings are not well understood. Similarly, it remains unclear whether this association could be potentially moderated by protective resources. In particular, it remains unclear if exercise – especially sports, a subset of exercise that can be done individually or in teams – can mitigate adolescent alcohol use and misuse (e.g., binge drinking) related to early life stress. Another promising research direction is to assess whether a time-efficient form of exercise, namely high-intensity interval training, could be utilized to enhance AUD treatment. Lastly, further research is needed to identify

sensitive developmental periods. This dissertation aimed to address these gaps, which will be outlined below.

Study I aimed to investigate the association between self-reported ACE and structural brain changes in adults with AUD, compared to healthy controls, in a continuous manner. The following hypotheses were tested:

Hypothesis 1: Relative to healthy controls, adults with AUD have reduced voxel-wise grey matter volume (GMV) and cortical thickness (CT), and at a region of interest (ROI) level, namely within the amygdala and hippocampus.

Hypothesis 2: Within the AUD group, higher ACE severity is associated with a decrease in GMV and CT in relevant clusters – that is, brain regions showing AUD-related alterations based on the whole-brain voxel-wise analyses from hypothesis 1 – as well as in the ROIs (amygdala and hippocampus).

Hypothesis 3: There is an interaction between ACE and AUD such that those in the AUD group with higher AUD severity show a stronger association between ACE severity and reduction in GMV and CT in relevant clusters and in the ROIs (amygdala and hippocampus), compared to those with lower AUD severity.

Additionally, an exploratory research question was examined using machine learning:

Exploratory research question: Are specific types and timings of ACE associated with a decrease in GMV and CT in relevant clusters and in the ROIs (amygdala and hippocampus) within the AUD group?

Study II aimed to examine associations between self-reported ACE and neural and behavioral correlates of inhibitory control in adults with heavy alcohol use using fMRI. The following pre-registered hypotheses (Türkmen et al., 2022) were tested:

Hypothesis 4: ACE severity modulates activation in prefrontal regions during a response inhibition task (stop-signal task).

Hypothesis 5: ACE severity modulates performance on the stop-signal task.

Post-hoc region of interest (ROI) analyses were performed to explore the association between ACE severity and activation in the left and right IFG, given the large body of evidence linking the IFG to both ACE and inhibitory control (Hampshire et al., 2010; Pollok et al., 2022; Swick et al., 2008; Yang et al., 2023).

Study III originated from a collaboration with researchers from the Norwegian Institute of Public Health, who led the longitudinal Monitoring Young Lifestyles (MyLife) study (Brunborg et al., 2019). We assessed adolescent alcohol use trajectories in relation to family-specific negative life events, organized sports participation, and their interaction using the risk-protective model as a framework (Fergus & Zimmerman, 2005; Rutter, 1985). This study aimed to test the following hypotheses:

Hypothesis 6: Accumulated family-specific negative life events are associated with greater alcohol use among adolescents over the five-year period.

Hypothesis 7: Sports participation moderates this association to reduce alcohol use among adolescents with a high number of family-specific negative life events over the five-year period.

Study IV was a systematic review and preliminary meta-analysis that aimed to synthesize the state of the evidence regarding high-intensity interval training (HIIT) an intervention to improve health outcomes among individuals with SUD. While this study did not consider the aspect of ACE, it extended Study III by shifting from a preventive perspective to an interventive perspective, while also considering the aspect of exercise intensity. The following research questions were assessed:

Research question 1: What are the effects of HIIT on physical health outcomes (e.g., cardiorespiratory fitness, cardiometabolic risk factors) in people with SUD?

Research question 2: What are the effects of HIIT on mental health/psychological outcomes (e.g., depressive/anxiety symptoms, cognitive functioning) in people with SUD?

Research question 3: How feasible, safe and acceptable is HIIT among people with SUD?

The studies presented in this dissertation may contribute to a better understanding of the neurobiological mechanisms underlying ACE and AUD, the role of inhibitory control and sensitive developmental periods, as well as physical exercise as a potential resource in prevention and intervention programs. Please note that while Study II is unpublished Status: Submitted), the results of the other three studies (Studies I, III and IV) (Türkmen, Brunborg, et al., 2024; Türkmen, Martland, et al., 2024; Türkmen, Tan, et al., 2024) have already been published. Therefore, certain sections, tables, or figures of this thesis will be identical to those in these publications.

2 EMPIRICAL STUDIES

2.1 Study I: The association between adverse childhood experiences and alterations in brain volume and cortical thickness in adults with alcohol use disorder[1]

2.1.1 Abstract

Background: Previous studies have established a connection between adverse childhood experiences (ACE) and alcohol use disorder (AUD), both of which are associated with alterations in grey matter volume (GMV) and cortical thickness (CT). The current study aimed to assess the neurobiological impact of ACE specifically in the context of AUD, as well as the role of maltreatment type (i.e., abuse or neglect) and timing.

Methods: Structural MRI data were collected from 35 adults with AUD (mean age: 40; 31% female) and 28 healthy controls (mean age: 36; 61% female). ACE were assessed retrospectively using the Childhood Trauma Questionnaire, and the Maltreatment and Abuse Chronology interview. Global and regional GMV and CT were estimated using voxel- and surface-based morphometry.

Results: Relative to the healthy controls, the AUD group had significantly reduced CT in the left inferior frontal gyrus, left circular sulcus of the insula and subcentral gyrus and sulci (cluster C1), and in the central sulcus and precentral gyrus (cluster C2). Within the AUD group, a reduction of CT in cluster C1 was significantly associated with higher severity of ACE and AUD. Type and timing analyses revealed a significant association between higher levels of abuse at ages 13 to 15 and reduced CT in cluster C1 within the AUD group.

Conclusions: In adults with AUD, abuse experienced during early adolescence is associated with reduced CT in regions involved in inhibitory control, indicating the potential relevance of cognitive pathways in the association between ACE and AUD. Longitudinal studies are needed to confirm and expand upon current findings.

[1] **Published as:** Türkmen, C., Tan, H., Gerhardt, S., Bougelet, E., Bernardo, M., Machunze, N., Grauduszus, Y., Sicorello, M., Demirakca, T., Kiefer, F., & Vollstädt-Klein, S. (2024). The association between adverse childhood experiences and alterations in brain volume and cortical thickness in adults with alcohol use disorder. Addiction Biology, 29(9), e13438. https://doi.org/https://doi.org/10.1111/adb.13438

2.1.2 Introduction

Adverse childhood experiences (ACE), including emotional, sexual and physical abuse, as well as emotional and physical neglect and household dysfunction, remain a prevalent public health problem with a significant impact on premature mortality and socioeconomic burden (Brown et al., 2009; Ferrara et al., 2015). ACE are common in the general population and have short- and long-term lasting consequences on physical and mental health (Herzog & Schmahl, 2018; Madigan et al., 2023). Notably, ACE increase the risk of developing substance use disorders (SUD) which rank among the psychiatric disorders with the highest mortality rates (Chesney et al., 2014; Enoch, 2011; Kisely et al., 2020).

Alcohol use disorder (AUD) has recently been reported to be the most prevalent SUD among German adolescents (Arnaud et al., 2023). The relationship between ACE and AUD was first studied by Felitti et al. (1998) who found that adolescents who had experienced four or more ACE were at a 4- to 12-fold increased risk of developing alcohol or drug abuse problems. In addition, a review of 12 retrospective studies found a higher prevalence of ACE in adults with SUD, compared to the general population (Leza et al., 2021). More recently, Broekhof et al. (2023) have presented longitudinal evidence that adults with any history of ACE are approximately four times more likely to develop an SUD, confirming previous retrospective findings. This study also found sex-specific risk profiles, showing that women were 5.9 times more likely to develop an AUD, whereas men were 5 times more likely to develop an illicit drug use disorder (Broekhof et al., 2023). Another study highlighted that particularly emotional abuse could explain an earlier onset of AUD among women (Schückher et al., 2018). A history of childhood maltreatment is clinically significant in relation to AUD, as it can have an indirect impact on alcohol problems via emotion regulation difficulties (Dutcher et al., 2017). Moreover, research shows that women with AUD and a history of abuse exhibit lower abstinence rates than those without a history of abuse (Schückher et al., 2019). Together, these findings highlight the need for clinical attention to AUD subgroups with exposure to ACE.

Although a risk association between ACE and AUD has been well-established, potential mechanisms underlying this association remain to be elucidated. Given the susceptibility of the developing brain to neurobiological changes as a result of potentially traumatic experiences (Jeong et al., 2021; Lim et al., 2014), it is crucial to

elucidate alterations in neural structures which may predispose affected individuals to increased addiction vulnerability. Previous studies have focused on the hippocampus and amygdala as particularly vulnerable regions to the deleterious effects of both early life stress and heavy alcohol use (Calem et al., 2017; Phillips et al., 2021; Soravia et al., 2022). Both the hippocampus and amygdala hold clinical significance in the context of AUD, given their role in memory formation (Anand & Dhikav, 2012) and in emotion regulation (Davis & Whalen, 2001), respectively.

Both ACE and AUD have been associated with a reduced volume in hippocampal subfields (De Bellis et al., 2000; Teicher et al., 2012). Regarding the amygdala, there appears to be a differential impact of ACE which is dependent upon type and timing (Teicher & Samson, 2016). While neglect during childhood is associated with an increased amygdala volume (Lupien et al., 2011; Pechtel et al., 2014), abuse in later stages is associated with a decrease in amygdala volume (Schmahl et al., 2003; Van Dam et al., 2014). In addition, previous studies assessing amygdala volume have been conducted in samples with varying types and degrees of psychopathology, which may account for differences in observed volumes (Teicher & Samson, 2016). In the context of SUD, Van Dam et al[28] have demonstrated that childhood maltreatment is associated with lower brain volume in the amygdala, hippocampus and other limbic structures, which were found to predict the severity of substance use relapse among patients with cocaine-, alcohol- and cannabis use disorders.

The impact of ACE specifically in the context of AUD has been investigated in a study involving South African adolescents with AUD and healthy controls (Brooks et al., 2014). The findings indicated that increased ACE severity was associated with reduced brain volumes in the right precentral gyrus and bilateral hippocampus in the AUD group, suggesting that the potential impact of ACE should be taken into account when studying neurobiological alterations in individuals with AUD (Brooks et al., 2014). More recently, Soravia et al. (2022) have demonstrated that childhood maltreatment is associated with decreased structural connectivity of the amygdala in patients with AUD. To build upon the current body of evidence, the aim of this cross-sectional research was to investigate the neurobiological impact of retrospectively reported ACE in a sample of adults with AUD while exploring the role of ACE type (abuse or neglect) and timing using a machine learning approach. While prospective research better explains changes over time, the current research could provide

valuable insights into relevant neural structures and sensitive developmental periods that may play a role in the development and maintenance of AUD. Such insights could guide future prospective studies. The following hypotheses and explorative research question were assessed:

Hypotheses:

1. Relative to healthy controls, adults with AUD have reduced voxel-wise grey matter volume (GMV) and cortical thickness (CT), and at a region of interest (ROI) level, namely within the amygdala and hippocampus.
2. Within the AUD group, higher ACE severity is associated with a decrease in GMV and CT in relevant clusters from hypothesis 1 and in the ROIs (amygdala and hippocampus).
3. There is an interaction between ACE and AUD such that those in the AUD group with higher AUD severity show a stronger association between ACE severity and reduction in GMV and CT in relevant clusters from hypothesis 1 and in the ROIs (amygdala and hippocampus), compared to those with lower AUD severity.

Explorative research question:

4. Are specific types and timings of ACE associated with a decrease in GMV and CT in relevant clusters from hypothesis 1 and in the ROIs (amygdala and hippocampus) within the AUD group?

2.1.3 Methods and materials

2.1.3.1 Participants and procedures

Structural magnetic resonance imaging (MRI) data were acquired at the Central Institute of Mental Health (CIMH), Mannheim, Germany, between January 2019 and March 2021. The study was prospectively registered on ClinicalTrials.gov (Identifier: NCT03758053). The primary research questions and analysis intentions were not pre-registered. The results should thus be considered exploratory. The ethics committee of the Medical Faculty Mannheim of the University of Heidelberg evaluated and approved the conduct of this study (ethics approval number: 2018-560N-MA). All study

procedures were conducted in accordance with the Declaration of Helsinki. Written informed consents were obtained from all participants prior to data collection.

The sample comprised a healthy control (HC) group and an AUD group, including individuals with a diagnosis of AUD or heavy alcohol use, aged 18 to 65. Participants were recruited from public announcements mainly within the vicinity of Mannheim, Germany. In- and outpatients with AUD were recruited from the addiction ward and day clinic of the CIMH. Potential participants were screened by telephone to assess study eligibility, after which they were invited to complete two measurements, one baseline measurement and one MRI measurement.

During the baseline measurement, participants provided written informed consent, underwent a drug and pregnancy screening, and had their breath alcohol measured using a breathalyser. Sociodemographic as well as behavioural data (see Section 2.1.3.2) were collected. A diagnostic assessment was performed using the Structured Clinical Interview (4th version) of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) to assess psychiatric comorbidities, while the severity of AUD was assessed using the diagnostic criteria from the DSM-V. Individuals were categorised into the AUD group if they either met the criteria for at least a mild AUD diagnosis or reported heavy alcohol use (alcohol consumption per day: ≥ 40 g (female), 60 g (male) on min. 5 days/week). A maximum of 28 consecutive days of abstinence was allowed within the AUD group. Exclusion criteria are specified in **Table S1**.

2.1.3.2 Measures

The severity of alcohol dependence was measured using the Alcohol Dependence Scale (ADS) (Skinner et al., 1984), a well-established tool with supported validity and reliability (Doyle & Donovan, 2009). ADS scores range from 0 to 47, with scores of ≤ 13 indicating a low level of dependence, 14 to 21 an intermediate level, 22 to 30 a substantial level and 31 to 47 a severe level of dependence.

To retrospectively assess exposure to ACE, two measures were utilised, namely the Childhood Trauma Questionnaire (CTQ), a valid and reliable 28-item self-report questionnaire (Bernstein & Fink, 1998), as well as an adapted brief German version of the Maltreatment and Abuse Chronology of Exposure (MACE; German: KERF-40-I) (Isele et al., 2014; Teicher & Parigger, 2015), which was administered in an interview setting. The CTQ assesses five subscales of ACE, namely emotional, physical and

sexual abuse, as well as emotional and physical neglect. Participants provided responses to each item on a five-point Likert scale, ranging from “not at all” to “very often”, leading to sum scores between 5 (indicating no trauma) and 25 (indicating severe trauma) for each subscale. The KERF-40-I is a structured interview, which additionally considers the timing of ACE (i.e., age at occurrence of ACE between the ages of 3 and 17). A recent study has provided evidence supporting the validity and reliability of this adapted version of the instrument (Seitz et al., 2022). Ten different ACE types were assessed, including emotional neglect and physical neglect, which make up the neglect score, while the abuse score comprises parental physical abuse, sibling physical abuse, parental emotional abuse, sibling emotional abuse, sexual abuse, peer abuse, witnessing interparental violence and witnessing violence to siblings. The scores for the single life years are the sums across different ACE events at a given age. Total ACE severity was calculated as the average score across these life years. ACE was quantified by a) an averaged KERF-40-I severity score indicating ACE across childhood and adolescence (i.e. global ACE severity), and b) by a KERF-40-I average for each year of life, respectively (i.e. time-specific ACE severity). Both scores range from 0 to 100. Abuse is represented by collapsing all abuse subscales, while neglect is represented by collapsing all neglect subscales. The scores have been averaged across childhood and adolescence, i.e. global abuse severity, and global neglect severity, as well as for each year of life respectively, i.e. time-specific abuse severity, and time-specific neglect severity. The neglect and abuse scores each range from 0 to 20.

2.1.3.3 MRI acquisition and preprocessing

Structural MRI data were collected with a 3 Tesla whole-body tomograph (Siemens PrismaFit, Erlangen, Germany). Images were obtained using a transaxial T1-weighed image acquisition (voxel size 1x1x1 mm^3, FoV 232 x 256 mm^2, TR = 2000 ms, TE = 3.03 ms, TI 900 ms, flip angle = 9°). Voxel-wise and regional GMV and CT were estimated using voxel and surface-based morphometry (VBM and SBM) in the SPM12 software (The Wellcome Centre for Human Neuroimaging, at University College, London, UK) and its extension CAT12 (Christian et al., 2023) within the MATLAB environment (R2021, MathWorks Inc., Natick, Massachusetts). CT was estimated based on the projection-based thickness (PBT) method (Dahnke et al.,

2013). Preprocessing was performed using CAT12. All brain images underwent quality checks. Specifically, the ratio between the weighted overall image quality (IQR) and the mean correlation was examined using a boxplot. IQR combines measurements of noise and spatial resolution before preprocessing, while mean correlation assesses data homogeneity and image quality after preprocessing. This analysis was conducted separately for the AUD and HC groups and for volume and surface data, ensuring that anatomical differences from alcohol misuse did not skew mean correlation values. Low mean correlation by itself did not lead to exclusion, provided that image quality was sufficient. For surface data, the Euler number (indicating topology defects) and defect size, were additionally assessed. Based on findings from existing research (Calem et al., 2017; Phillips et al., 2021; Soravia et al., 2022), we defined bilateral amygdala and hippocampus as regions of interest (ROIs) in addition to whole-brain voxel-wise analyses.

2.1.3.4 Statistical analyses

Sixty-nine individuals participated in the study. The analytical sample comprised $N = 63$ participants; $N = 35$ in the AUD group and $N = 28$ in the HC group. $N = 6$ participants were excluded from the analyses due to incidental neurological findings ($N = 1$), image quality concerns ($N = 1$), dropout before MRI assessment ($N = 1$), exclusion criteria ($N = 1$), MRI termination due to claustrophobia ($N = 1$) and MRI termination due to technical problems ($N = 1$). An overview of the study flow is provided in **Figure S4**. Psychometric data were analysed using SPSS (Statistics for Windows, Version 27.0., IBM Corp., Armonk, NY). Descriptive analyses as well as chi-squared tests and *t*-tests were applied to describe the sample and perform statistical analyses regarding group differences. CTQ scores were missing for one participant in the HC group.

Regarding the primary analyses, a two-sample *t*-test was used to assess voxel-wise and regional differences in GMV and CT between the HC and AUD groups, controlling for age, gender and transcranial volume (TIV, only for GMV) (voxel-wise-$p < .001$ with cluster corrections by SPM random field theory, corresponding to pFWE $< .05$). The association between ACE and GMV/CT in the ROIs and relevant clusters from the voxel-wise analysis was assessed using partial correlation, correcting for age, gender and TIV. In line with recommendations for MRI studies, only GMV (and not CT)

was corrected for TIV (Barnes et al., 2010). The Destrieux 2009 Atlas (Destrieux et al., 2010) was used for the labelling of brain regions.

To identify sensitive life years for the effects of different ACE types (abuse or neglect) on neurobiological changes, we employed the same machine learning approach as Herzog et al. (2020), namely random forest regression with conditional inference trees. As our study incorporated 15 strongly correlated predictors (ages 3 to 17) into the same model, conditional random forest regression is particularly suited, given that it takes into account multicollinearity among predictor variables (Strobl et al., 2009), and it has been frequently used in previous studies on sensitive periods for early adversity (Herzog et al., 2020; Sicorello et al., 2021; Teicher et al., 2018). For the analyses, we used the “cforest” function in the R package party (Strobl et al., 2008; Strobl et al., 2009) within the R software environment (Version 4.2.3, R Development Core Team 2022, Vienna, Austria). We ran the conditional random forest regressions for each ROI and extracted means from relevant clusters identified from the voxel-wise analysis using randomly generated seeds to ensure the reproducibility of the results. Each ROI was corrected for age and TIV and then z-transformed. Each random forest model consisted of 1,000 trees with four randomly selected variables at each split. To evaluate the predictive accuracy (performance) of each model, we present the explained variance and variable importance based on the out-of-bag samples. Each model was run separately for abuse and neglect (ACE type analysis). Models with a positive predictive accuracy were further used for permutation tests to identify predictors with statistically significant variable importance using 1,000 permutations. Given the exploratory nature, the *p*-values in the permutation test were not corrected for multiple testing. For predictors with statistically significant variable importance, we performed follow-up correlation analyses. The significance levels of all analyses were $p < .05$.

2.1.4 Results

2.1.4.1 Descriptives

An overview of descriptive statistics can be found in **Table 1**. The AUD group, relative to the healthy control group, had a greater severity of alcohol dependence (ADS) and higher alcohol consumption in the past three months (FORM-90). We also noted significant group differences in depression scores (BDI), gender ratio, years of

education, smoking status and ACE severity (KERF-40 and CTQ). Further details about the KERF-40 subscales and an illustration of the average severity for abuse, neglect and overall KERF-40 scores from the ages 3 to 17 are provided in **Table S2** and **Figure S1**, respectively. An illustration of the distribution for CTQ subscore severities in both groups can be found in **Figures S2 and S3**.

Table 1. Sample description of AUD and healthy control (HC) groups.

	HC Mean (SD)	**AUD Mean (SD)**	**Statistics**
N	28	35	
Gender (male:female)	11:17	24:11	**$\chi^2(1) = 5.4$, p = .020**
Age (years)	36.3 (12.6)	46.5 (12.7)	T(61) = 1.32, p =
Marital status (married:divorced:single)	7:3:18	5:8:22	$\chi^2(2) = 2.26$, p = .324
Living status (alone:together with others)	7:21	14:21	$\chi^2(1) = 1.57$, p = .209
Years of education	15.8 (2.3)	14.3 (3.0)	**T(61) = -2.13, p =**
Smoker (yes:abstinent:no)	3:0:25	10:3:22	**$\chi^2(2) = 6.26$, p =**
KERF-40 sum	5.1 (7.2)	19.3 (15.5)	**T(50.2) = -4.84, p <**
Abuse	0.5 (0.8)	1.8 (1.5)	**T(43.8) = -3.86, p <**
Neglect	0.5 (0.9)	2.2 (2.5)	**T(52.8) = -4.73, p <**
CTQ sum	32.1 (8.8)	39.4 (14.6)	**T(57) =2.44, p =**
CTQ Emotional abuse	8.8 (4.9)	6.5 (2.8)	**T(55.5) =2.36, p =**
CTQ Physical abuse	5.4 (1.1)	6.4 (2.5)	T(48) =1.98, p =
CTQ Sexual abuse	5.1 (0.5)	5.5 (1.9)	T(38.7) =1.15, p =
CTQ Emotional neglect	9.0 (5.0)	11.4 (5.5)	T(60) = 1.79, p =
CTQ Physical neglect	6.1 (2.0)	7.3 (3.3)	T(57.2) =1.75, p =
ADS	2.4 (2.3)	11.9 (6.7)	**T(43.8) =7.78, p <**
BDI	1.7 (3.2)	10.7 (8.8)	**T(43.5) =5.52, p <**
FORM-90 alcohol per day (g)	25.2 (19.3)	136.5 (125.8)	**T(35.9) =5.16, p < .001**

Note: significant group differences are highlighted in bold. SD = Standard Deviation; g = grams; N = sample size; ADS = Alcohol Dependence Scale; CTQ = Childhood Trauma Questionnaire; FORM-90 = amount of alcohol consumption per day over the last 90 days; KERF-40 = Brief German version of the Maltreatment and Abuse Chronology of Exposure (MACE) interview; BDI = Beck´s Depression Inventory

2.1.4.2 Hypothesis 1

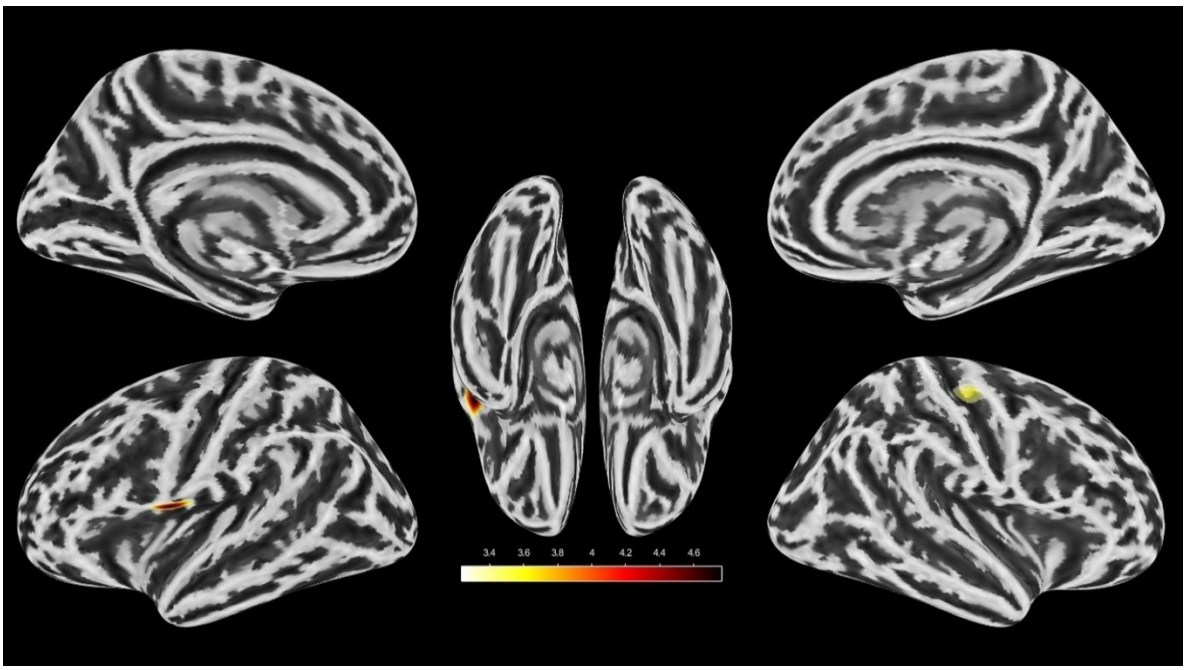
The two-sample *t*-test indicated significantly reduced CT in the AUD group, relative to the HC group, in two clusters (see **Figure 1**); one cluster (C1) comprising the left

inferior frontal gyrus (IFG), left circular sulcus of the insula and subcentral gyrus and sulci (cluster size 163 voxels, Peak T: 4.8, MNI: −42, 10, 5, $p < .05$) and a second cluster (C2) comprising the central sulcus and precentral gyrus (cluster size 136 voxels, Peak T: 3.5, MNI: 42, −23, 40, $p < .05$). No differences in GMV or in the ROIs were found.

2.1.4.3 Hypotheses 2 and 3

There was a significant positive correlation between the CTQ sum score and KERF sum score in all participants ($r = 0.765$, $p < .001$). Total ACE severity was significantly higher in the AUD group compared to the HC group, as indicated by the CTQ sum score ($t(57) = 2.44$, $p < .05$) and the KERF-40 sum score ($t(50.2) = -4.84$, $p < .001$). In the AUD group, there was a significant negative correlation between CT in cluster C1 and CTQ sum scores ($r = -0.319$, $p < .05$) as well as ADS scores ($r = -0.346$, $p < .05$; see **Figure 2**). There was no interaction between CTQ sum scores and ADS scores on CT in the clusters or in the predefined ROIs. No significant associations between CTQ sum scores and the ROIs or the other cluster (C2) were found.

Figure 1. Significant clusters in the AUD group, relative to the HC group.



Note. A two-sample t-test was used with cluster corrections (voxel-wise p < .001, cluster pFWE < .05). Reduced CT in the left inferior frontal gyrus, left circular sulcus of

insula, and subcentral gyrus and sulci (cluster C1; size: 163 voxels, Peak T: 4.8, MNI: −42, 10, 5, p < .05) and in the right central sulcus and precentral gyrus (cluster C2; size 136 voxels, Peak T: 3.5, MNI: 42, −23, 40, p < .05).

2.1.4.4 Explorative research question (type and timing)

The random forest regression revealed a low albeit positive predictive accuracy for a model with age-specific and overall abuse severities (KERF-40) as predictors and CT in the C1 cluster as an outcome (R^2 = 0.01). The permutation test of this model indicated statistically significant variable importance for abuse at the ages 13, 14 and 15 in the AUD group (p < .05, see **Figure 3**). Follow-up correlation analyses revealed a significant association between higher abuse in these life years and reduced CT in the C1 cluster (age 13, r = −0.315, p < .05; age 14, r = −0.335, p < .05; age 15, r = −0.332, p < .05; FDR-corrected). All other models had a negative predictive accuracy and thus were not used for further analyses.

Figure 2. Partial correlation between CT in cluster C1 (see Figure 1) and ADS scores (left) and CTQ scores (right), controlling for age and gender.

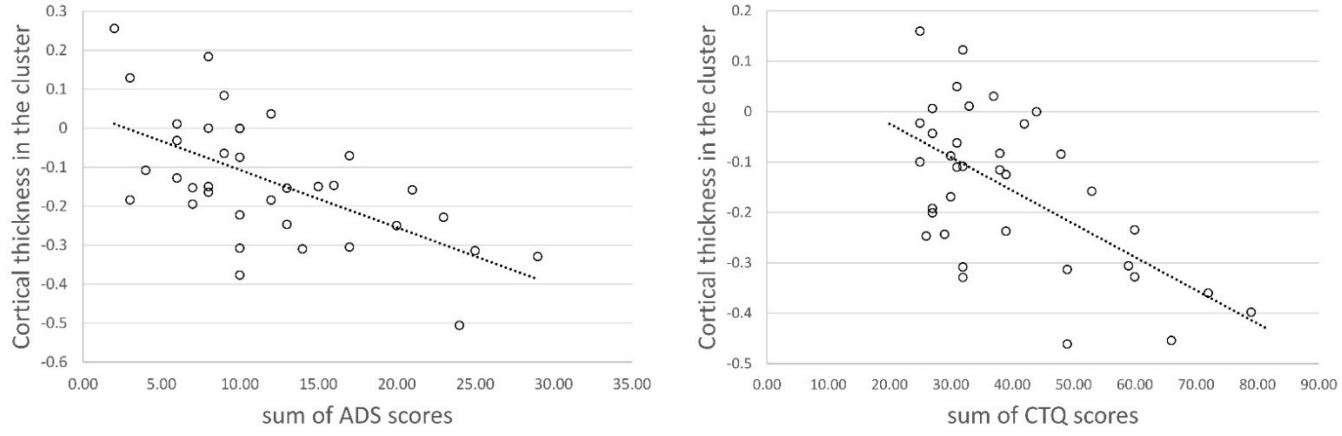
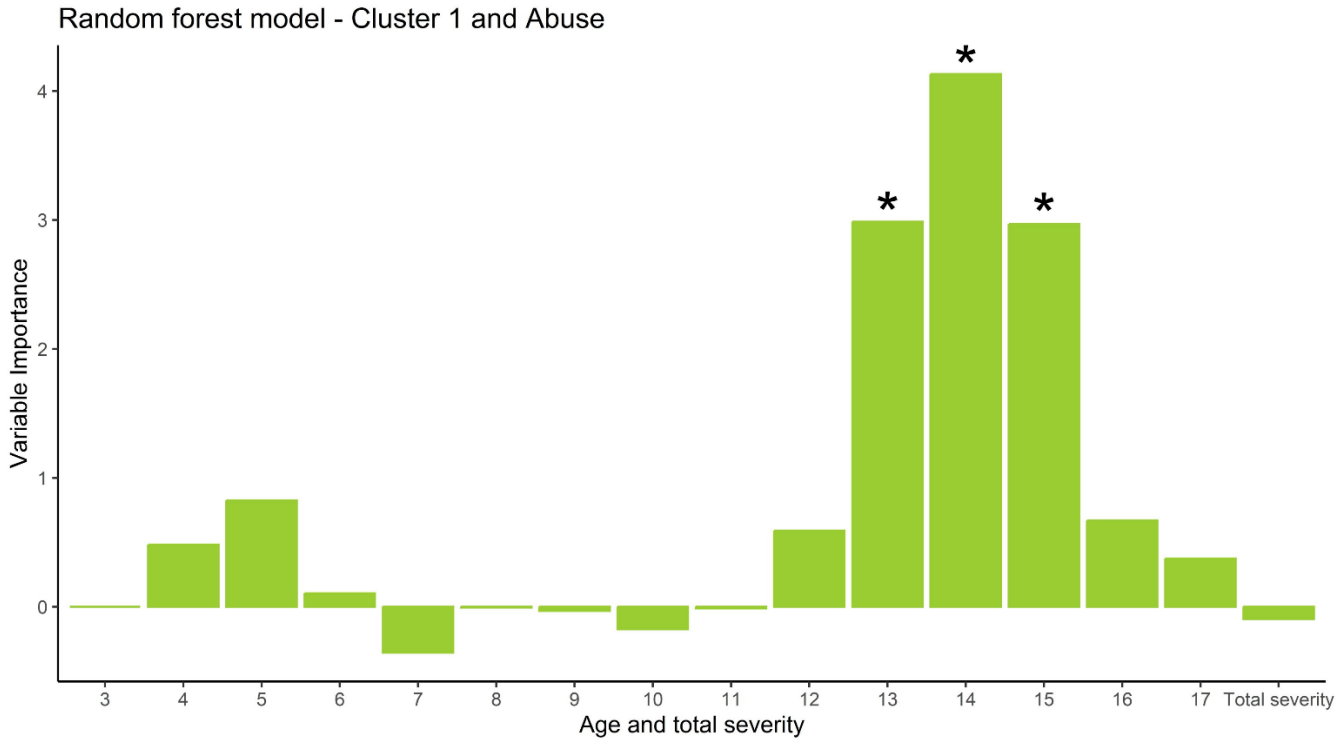


Figure 3. Random forest regression indicating the importance of time-specific abuse severity from 3 to 17 years of age on cluster C1.



Note. N trees = 1,000; N randomly selected variables = 4. Permutation test: *p < .05; N permutations = 1,000.

2.1.5 Discussion

The aim of this study was to assess the neurobiological impact of retrospectively reported ACE in adults with AUD and to explore the role of the ACE type and timing using a machine learning approach. The current results partially confirm our hypotheses, indicating that in the AUD group, CT was reduced and associated with higher ACE severity, whereas GMV analyses did not yield significant results. We found significantly reduced CT in a cluster comprising the left IFG, left circular sulcus of the insula and subcentral gyrus and sulci (C1), which was associated with a higher ACE severity. The random forest regression further revealed that greater abuse severity during early adolescence (ages 13 to 15) was significantly associated with reduced CT in this cluster. In addition, we found a second significant cluster with reduced CT in the AUD group, encompassing the central sulcus and precentral gyrus (C2). Unlike C1, reduced CT in this cluster was not associated with higher ACE severity. We found no

interaction between ACE and AUD with respect to changes in the significant clusters or in the predefined ROIs.

Among the observed changes in CT, the finding that the AUD group exhibited reduced CT in the left IFG may be of particular importance with respect to the development and maintenance of AUD. This finding builds upon a previous study indicating that patients with alcohol dependence, relative to healthy controls, have reduced CT in the right IFG (Momenan et al., 2012). While neuroimaging studies have indicated right-hemispheric IFG dominance in inhibitory control (Garavan et al., 1999; Hampshire et al., 2010), there is evidence suggesting that the left IFG is also critical for response inhibition (Swick et al., 2008). In addition, the current results indicate that greater severity of alcohol dependence is associated with reduced CT in the IFG, consistent with a previous study that found a higher alcohol dependence severity to be strongly related to CT reductions in the inferior frontal region (Fortier et al., 2011). This is further supported by findings from the Human Connectome Project showing that a greater drinking quantity and higher frequency of heavy drinking were associated with reduced CT in the IFG in young adult drinkers (Morris et al., 2019).

Consistent with the findings related to AUD, recent meta-analyses indicated that ACE are associated with decreased GMV and CT in the left IFG (Pollok et al., 2022; Yang et al., 2023), indicating the possible relevance of cognitive functioning in the association between ACE and AUD. This idea is supported by Edalati and Krank's model of cognitive pathways proposing that impairments in cognitive functions (e.g., response inhibition, working memory) mediate the relationship between ACE and SUD (Edalati & Krank, 2016). As our type and timing analyses revealed that abuse during early adolescence is associated with reduced CT in the left IFG, it is possible that early adolescence represents a sensitive developmental period for abuse-related cortical thinning, which may increase the risk of developing AUD. This possibility is supported by a review proposing that cortical development during adolescence is a crucial vulnerable period for addiction (for an overview, see review by Crews and Hodge, 2007). In addition, the current findings converge with those of a recent longitudinal study showing that family-specific negative life events were associated with increased alcohol use during middle school years (Türkmen, Brunborg, et al., 2024). This supports the view that early adolescence may be a sensitive period for early life adversity-related AUD development, as starting to drink before the age of 15 is associated with higher odds of developing AUD (Dawson et al., 2008). Importantly,

cognitive functioning could play an important role in this increased vulnerability. Indeed, a study by Gold et al. (2016) reported deleterious effects of childhood abuse on CT in the parahippocampal gyrus in a sample of adolescents which, in turn, was associated with higher levels of externalizing psychopathology. This suggests that reduced CT in regions involved in cognitive functioning may serve as a risk factor for AUD in later life, although the underlying mechanisms remain to be elucidated. One line of explanation may lie in cognitive development being delayed following exposure to abuse (Carrey et al., 1995) and triggering a series of neurobiological alterations associated with cognitive deficits in adulthood (Gould et al., 2012).

These findings hold clinical significance, as they underscore the potential relevance of cognitive deficits in the treatment of patients with AUD and a history of ACE. Previous research has indicated that cognitive deficits can arise during childhood following ACE and persist into adulthood, which may increase the risk of developing psychiatric disorders (Majer et al., 2010). These deficits align with cognitive impairments observed in individuals with AUD (Bernardin et al., 2014). Among the cognitive domains, executive functioning has emerged as a particularly relevant domain, as highlighted by a study revealing that deficits in response inhibition predict relapse in patients with alcohol dependence (Czapla et al., 2016). In the context of ACE, Jankowski et al. (2017) have provided initial support that maltreatment in early childhood is associated with changes in neural activation patterns underlying response inhibition during early adolescence. Moreover, their findings suggest that engaging in a preventive intervention could potentially mitigate the effects of maltreatment on the neural circuitry related to successful response inhibition. Thus, prevention and intervention programs should start early, and aim to incorporate response inhibition as a treatment target. Likewise, future longitudinal studies should incorporate cognitive functioning as an outcome, and assess changes at a neural level over time using neuroimaging-based cognitive paradigms. Importantly, these studies should utilise treatments such as cognitive training and remediation interventions (Verdejo-Garcia et al., 2023), and assess whether these interventions are associated with improved response inhibition or accompanied by structural changes in relevant brain regions.

In the present study, we did not replicate findings from a previous study by Van Dam et al. (2014) indicating an association between higher ACE severity and reduced GMV in the amygdala and hippocampus in patients with SUD. Previous findings regarding the effects of ACE on GMV volumes in the amygdala and hippocampus have

been mixed (Calem et al., 2017; Yang et al., 2023). The AUD sample in the present research included many cases of minimally traumatised individuals, which is likely to have resulted from employing strict exclusion criteria with respect to psychiatric comorbidities. This might have led to range restriction with regard to ACE severity and thus diminished correlations. Indeed, in the study by Van Dam et al. (2014), SUD patients with childhood maltreatment had, on average, a considerably higher CTQ score compared to our AUD sample. In addition, several other limitations should be noted. First, this study had a modest sample size, which may have led to underpowered analyses to detect smaller effects of retrospectively reported ACE on GMV. It is unclear whether CT, relative to GMV, is a more sensitive outcome measure for assessing the influence of retrospectively reported ACE in AUD samples. Future prospective, longitudinal studies with larger sample sizes are needed to confirm and expand upon current findings. Second, while retrospective designs combined with machine learning techniques represent a fruitful approach to detect sensitive periods for ACE-related addiction vulnerability, it should be noted that a recent meta-analysis has reported low agreement between prospective and retrospective measures of ACE, raising concerns about whether these two measurement approaches capture different groups of individuals (Baldwin et al., 2019). Although retrospective designs introduce potential biases embedded within this methodology, studies employing prospective designs are likely to primarily include more severe cases of traumatisation. Third, due to the modest sample size, we did not examine potential sex differences regarding changes in GMV and CT. Given that different types of ACE have varying predictive values for developing SUD among men and women (Broekhof et al., 2023), future research should further elucidate potential sex- and ACE-type-dependent volumetric and cortical changes and their roles in the development and maintenance of AUD. In addition, while there were significant differences between the AUD and HC groups regarding years of education and smoking status, these were not incorporated as covariates of no interest. Specifically, due to the association of lower educational attainment and smoking with AUD and heavy drinking, this may remove AUD-related variance and influence the effect of interest (Grucza & Bierut, 2006; Murakami & Hashimoto, 2019; National Center for Health Statistics (US), 2012; Weinberger et al., 2015). In our sample, it was not possible to disentangle the differential effects of education and smoking on the results. Finally, given the cross-sectional nature of this study, there is no certainty regarding the directionality or causality of the findings.

2.1.6 Conclusions

In adults with alcohol use disorder, retrospectively reported abuse during early adolescence is associated with reduced cortical thickness in brain regions involved in inhibitory control, providing support for the potential relevance of cognitive pathways in the association between adverse childhood experiences and the development and maintenance of alcohol use disorder. Prevention and intervention programs should incorporate inhibitory control as a treatment target in individuals with alcohol use disorder and a history of adverse childhood experiences.

2.2 Study II: The association between adverse childhood experiences and inhibitory control in heavy-drinking adults: a functional MRI study[2]

2.2.1 Abstract

Background: Deficient inhibitory control is associated with adverse childhood experiences (ACE) and heavy alcohol use, with recent evidence suggesting that it may mediate the relationship between ACE and adolescent alcohol use. However, its role in adulthood after ACE exposure remains unclear.

Objective: This study aimed to assess the association between ACE and inhibitory control among heavy-drinking adults with self-reported ACE.

Participants and Setting: A non-probability sample of 32 heavy-drinking individuals (43.75% women; 12.5% treatment-seeking) from Germany.

Methods: This cross-sectional functional MRI study assessed inhibitory control using the stop-signal task and retrospectively reported ACE with the Childhood Trauma Questionnaire (CTQ). A linear regression model was used to estimate task-related whole-brain activation, with CTQ sum score as a predictor. Additionally, the correlation between activation in the left/right inferior frontal gyrus (IFG) and ACE severity was explored in region of interest (ROI) analyses.

Results: Increased ACE severity was significantly associated with shorter stop-signal reaction times ($r(25)= -0.55$, $p = 0.003$). The whole-brain analyses showed no significant association between brain activation and ACE severity. Exploratory post-hoc ROI analyses indicated that higher emotional neglect was associated with lower left IFG activation in the “Stop success > Stop error” contrast ($r(24) = -0.49$, $p = 0.011$, uncorrected), whereas higher emotional abuse was associated with higher activation ($r(24) = 0.55$, $p = 0.004$, uncorrected).

Conclusions: Greater ACE severity might be associated with better inhibitory control among heavy-drinking adults. While neural efficiency after more severe emotional neglect may partly explain this observation, the interpretation regarding the directionality of brain activation warrants further investigation.

[2] Türkmen, C., Lee, A., Tan, H., Kiefer, F., Gerhardt, S., & Vollstaedt-Klein, S. The association between adverse childhood experiences and inhibitory control in heavy-drinking adults: a functional MRI study. Status of manuscript: Submitted.

2.2.2 Introduction

Adverse childhood experiences (ACE), including maltreatment (i.e., abuse and neglect) and household dysfunction, remain a prevalent public health issue with a high economic burden (Peterson et al., 2023). A recent meta-analysis estimates that approximately 60% of adults across 22 countries have reported having experienced at least one ACE (Madigan et al., 2023). ACE significantly contribute to premature mortality and have both short- and long-term physical and mental health consequences, while also accounting for a considerable portion of the economic burden of ACE-related health conditions in adulthood (Gilbert et al., 2009; Herzog & Schmahl, 2018; Peterson et al., 2023). Of note, ACE increase the risk of substance misuse, particularly problematic alcohol use, which may contribute to many of the negative health outcomes observed in individuals with ACE (Gilbert et al., 2009; Hamburger et al., 2008; Lippard & Nemeroff, 2020; Zhu et al., 2023).

Recent prospective evidence indicates that those with any history of ACE are four times more likely to develop substance use disorders (SUD) (Broekhof et al., 2023). In addition, the presence of four or more ACE has been found to be especially prevalent in populations with substance misuse and addiction (Gerhardt, Eidenmueller, et al., 2022; Madigan et al., 2023). There also appears to be a gender-specific pattern such that women with ACE are around six times more likely to develop an alcohol use disorder (AUD) (Broekhof et al., 2023). ACE are also associated with an increased risk of psychiatric comorbidities among individuals with SUD, which may negatively affect the clinical course of SUD (Stocchero et al., 2024). Notably, women with AUD and a history of abuse exhibit lower abstinence rates than those without such a history (Schückher et al., 2019), highlighting the need to identify and elucidate potential mechanisms underlying the association between ACE and AUD.

Accumulating evidence suggests that cognitive functioning may play an important role in linking ACE to substance use and the development of SUD (Bounoua & Sadeh, 2022; Edalati & Krank, 2016). Based on the dual process model , Edalati and Krank (2016) have developed a model of cognitive pathways proposing that impairments in automatic, nonconscious processes (System 1) and controlled, conscious processes (System 2) mediate the association between ACE and SUD. According to this model, impairments in cognitive functions such as behavioral inhibition and working memory (System 2) can undermine reasoning abilities, leading

to irrational responses to stressful situations which may contribute to the development of SUD (Edalati & Krank, 2016). Additionally, dysfunctional automatic memory associations (System 1) that link negative self-associations to the soothing effects of substance use may promote maladaptive coping strategies aimed at alleviating tension in response to stressful situations or negative emotions, thereby increasing the risk of developing SUD (Edalati & Krank, 2016).

In line with this cognitive framework of vulnerability, a recent study has found that inhibitory control deficits mediate the relationship between ACE and increased alcohol use among adolescents (Kim & Bruce, 2022). Interestingly, the presence of ACE was not directly but only indirectly associated with increased alcohol use in middle adolescence via inhibitory control deficits during early adolescence . In addition, a longitudinal study has found that individuals who experienced sexual abuse before age ten exhibited atypical frontal neurophysiological development during behavioral inhibition, potentially reflecting disruptions in synaptic pruning and cortical maturation related to inhibitory control throughout adolescence and emerging adulthood, which were associated with alcohol use problems in emerging adulthood (Meyers et al., 2019). The current body of literature suggests that inhibitory control deficits are more apparent during early adolescence, but seem to disappear by late adolescence in trauma-exposed youth (van der Bij et al., 2020). A similar pattern has been observed among adolescents at-risk for substance use . Nevertheless, it is possible that compensatory mechanisms reflected by distinct patterns of brain activity may explain the observed changes in late adolescence (Quach et al., 2020; van der Bij et al., 2020). Indeed, adolescence represents a sensitive developmental stage marked by dynamic neurobiological changes which are accompanied by high levels of risk-taking behaviors. Thus, it is important to elucidate the neural mechanisms underlying ACE-related changes in inhibitory control.

At a structural level, a recent study using a machine learning approach has found that abuse during early adolescence (ages 13-15) is associated with reduced cortical thickness in brain regions implicated in inhibitory control, notably in the left inferior frontal gyrus (IFG), in adults with AUD (Türkmen, Tan, et al., 2024). This finding aligns with recent meta-analyses indicating that ACE are associated with reduced brain volume and cortical thickness in the left IFG (Pollok et al., 2022; Yang et al., 2023). It is important to note that although neuroimaging studies have highlighted right-hemispheric dominance of the IFG in inhibitory control (Garavan et al., 1999;

Hampshire et al., 2010), there is evidence that the left IFG also plays a crucial role in inhibitory control . At a functional level, ACE have been associated with increased activation in the bilateral IFG, insula, anterior cingulate cortex and middle temporal gyri during behavioral inhibition in adults, suggesting a potential long-term impact of ACE on the neural circuitry underlying behavioral inhibition as well as ACE-related compensatory mechanisms in adulthood (Sacu et al., 2024). However, the long-term impact of ACE on inhibitory control in the context of alcohol misuse and AUD remains unclear.

To build upon the current body of evidence, the aim of the present study was to investigate the association between ACE and inhibitory control among heavy-drinking adults both at a behavioral and neural level using functional magnetic resonance imaging (fMRI). Although prospective research is better suited to establish causality regarding the mechanisms underlying the relationship between ACE and heavy alcohol use, the present cross-sectional study may provide valuable insights into relevant neurobiological mechanisms to guide such research efforts. The following a priori hypotheses (Türkmen et al., 2022) were assessed:

Hypothesis 1: ACE severity modulates activation in prefrontal regions during a response inhibition task (stop-signal task).

Hypothesis 2: ACE severity modulates performance on the stop-signal task.

Given the large evidence base indicating the importance of the IFG both in relation to ACE and inhibitory control (Hampshire et al., 2010; Pollok et al., 2022; Swick et al., 2008; Türkmen, Tan, et al., 2024; Yang et al., 2023), we additionally assessed the association between ACE severity and activation in the left and right IFG in post-hoc region of interest (ROI) analyses.

2.2.3 Methods and materials

2.2.3.1 Procedures and participants

The present study was conducted at the Central Institute of Mental Health (CIMH), Mannheim, Germany, between November 2021 and September 2023. The ethics committee of the Medical Faculty Mannheim of the University of Heidelberg evaluated and approved the conduct of this study (ethics approval number: 2018-560N-MA). All study procedures were conducted in accordance with the Declaration of Helsinki. Written informed consents were obtained for all participants prior to data collection.

This study was prospectively registered on ClinicalTrials.gov (Identifier: NCT05048758).

Figure 4 provides an overview of the study flow, including the number of participants and reasons for exclusion at each stage of the study. Overall, 47 participants completed the baseline assessment, with n = 32 and n = 29 ultimately included in the fMRI and behavioral analyses, respectively. The sample comprised both individuals with heavy alcohol use, defined as moderate drinking risk level according to the World Health Organization (WHO) (Knox et al., 2019), and patients diagnosed with AUD aged 18 to 65. Heavy-drinking individuals were recruited from public announcements mainly within the vicinity of Mannheim, Germany, while patients with AUD were recruited from the residential addiction clinic and addiction day unit of the CIMH. Potential participants were screened in person or by telephone to assess study eligibility. Eligible individuals were invited to complete one baseline measurement and one fMRI measurement.

During the baseline measurement, participants provided written informed consent, underwent urine drug and pregnancy screenings, and had their breath alcohol levels measured using a breathalyzer. In addition, a diagnostic assessment was conducted using the Structured Clinical Interview (4^{th} version) of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) to assess psychiatric comorbidities, while the severity of AUD was determined using the diagnostic criteria from the DSM-5. Participants had to meet the diagnostic criteria for either mild AUD or heavy alcohol use (alcohol consumption per day: ≥ 40 g (female), 60 g (male) on min. 5 days/week). The inclusion and exclusion criteria are specified in **Table S1** in the **Supplementary Materials**.

Sociodemographic as well as behavioral data were collected and managed using REDCap electronic data capture tools hosted at the CIMH (Harris et al., 2019; Harris et al., 2009). The main questionnaire of the present study was the Childhood Trauma Questionnaire (CTQ, Cronbach's alpha (α) = 0.80), a valid and reliable 28-item self-report questionnaire (Bernstein & Fink, 1998; Klinitzke et al., 2012) which was used to retrospectively assess ACE. The CTQ consists of five subscales, namely emotional, physical and sexual abuse, as well as emotional and physical neglect, all of which contribute to an overall sum score. Participants provided responses to each question on a 5-point Likert scale, ranging from "not at all" to "very often", leading to

sum scores between 5 (indicating no trauma) and 25 (indicating severe trauma) for each subscale.

Besides the CTQ, the Alcohol Dependence Scale (ADS, α = 0.92) (Skinner et al., 1984), a well-established tool with supported validity and reliability (Doyle & Donovan, 2009), was used to measure the severity of alcohol dependence, with total scores ranging from 0 to 47. Impulsiveness was measured using the revised form of the Barrat Impulsiveness Scale (BIS-11) (Patton et al., 1995), with scores ranging from 30 to 120. The BIS-11 has demonstrated adequate internal consistency (α = 0.79) in patients with SUD (Patton et al., 1995). In the general population, total scores between 52 and 72 are considered within normal limits for impulsiveness, while total scores of ≥ 72 indicate high impulsiveness (Stanford et al., 2009). The Beck Depression Inventory-II (BDI-II) was used to measure the severity of depressive symptoms, with total scores ranging from 0 to 63 (Beck et al., 1961; Kühner et al., 2007). Drinking behaviors over the 90 days before the baseline measurement were examined using the Form-90 interview (Miller & Del Boca, 1994). Further details on the study design can be found in the published study protocol (Türkmen et al., 2022).

2.2.3.2 Neuroimaging paradigm

The stop-signal task (SST) (Lappin & Eriksen, 1966; Logan & Cowan, 1984) was utilized as a neuroimaging paradigm to measure inhibitory control. The task description and results are reported following the recommendations from a consensus guide for the SST (Verbruggen et al., 2019). A shortened version of that used in Gan et al. (2014) was implemented in the present study. Participants responded to the direction of white arrows pointing left or right (go-signal) by pressing the left or right buttons on a four-button response box (Current Designs, Philadelphia, PA, USA) with the thumb of their dominant hand. The SST consisted of 300 trials, 20% of which were so-called stop trials, in which an upward-pointing arrow (stop-signal) was presented after a delay following the go stimulus (stop-signal delay [SSD]), prompting participants to inhibit their motor response.

The SSD, initially set at 200 ms, dynamically adjusted by ± 50 ms based on the performance in the preceding stop trial, following a tracking algorithm (Logan et al., 1997; Williams et al., 1999). This adjustment allowed the probability of inhibition (PI: successful stops/total stop trials) to converge to around 50% after 10 to 15 stop trials.

The stop-signal reaction time (SSRT), which reflects the latency of response inhibition, was estimated by rank ordering the Go reaction times (RTs) and subtracting the mean SSD from the nth Go RT, which corresponds to the percentile of response probability in stop trials (Verbruggen & Logan, 2009). Trials were separated by short, jittered inter-trial intervals with a mean duration of 900 ms (range: 700–1100 ms). The Go stimuli remained visible until a response was recorded or for a maximum of 1000 ms (in the case of no response). In stop trials, the go stimulus was displayed for the duration of the SSD, followed by the stop-signal for 300 ms in successful stop trials or until a response was recorded in failed trials. The SST included stop trials every 2 to 7 go trials for clear hemodynamic separation between stop trials. For a visual representation of the task, please refer to Gan et al. (2014).

Quality checks were performed to ensure that participants' probability of responding on a stop trial did not substantially deviate from 50%; those with a probability below 25% or above 75% were excluded from the analyses (Congdon et al., 2012). We also examined whether the so-called independence assumption was seriously violated by comparing the mean RT on unsuccessful trials with that on go trials, as SSRT estimates become unreliable if the RT on unsuccessful trials exceeds that of go trials (Verbruggen et al., 2019). To balance statistical power, only participants with a serious violation of this assumption (difference ≥ 100 ms) were excluded from the behavioral analyses.

The SST lasted 10:39 minutes and was presented using the Presentation® software (Neurobehavioral Systems, Albany, USA). All participants completed a practice session on a laptop outside the MRI scanner. Details regarding the practice session and instructions for both the practice and main sessions can be found in **Supplement 1**.

2.2.3.3 fMRI acquisition and preprocessing

Functional MRI data were acquired with a 3 Tesla whole-body tomograph (Siemens PrismaFit, Erlangen, Germany). A total of 725 T2*-weighted multi-band transversal echo planar images (mb-EPI) using a multi-band acceleration factor 6, encompassing the whole brain, were obtained (TR = 869 ms, TE = 38 ms, flip angle = 58°, 60 slices, slice thickness = 2.4 mm, 0 mm gap, FoV = 210 x 210 mm^2, 88 x 88 in-plane resolution, 64-channel head coil) 20° clockwise to AC-PC-line. To correct for geometric distortions

caused by magnetic field inhomogeneities, fieldmaps were collected (TR = 698 ms, TEs = 5.19 ms/7.65 ms, flip angle = 54°). Scanner sequences were provided by the Center for Magnetic Resonance Research (CMRR), University of Minnesota, Minneapolis, MN, USA (https://www.cmrr.umn.edu/multiband/).

Preprocessing was performed using Statistical Parametric Mapping 12 (SPM12, The Wellcome Centre for Human Neuroimaging, at University College, London, UK) within the MATLAB environment (R2021, MathWorks Inc., Natick, Massachusetts). The scans were corrected for residual geometric distortion by utilizing the acquired magnetic fieldmap. In addition, several other preprocessing steps were applied, including slice-timing correction, spatial realignment, and normalization to an MNI template (Montreal Neurological Institute, Quebec, Canada). The processed images were then smoothed with an isotropic Gaussian kernel of 8 mm full width at half maximum.

Quality checks were performed at the first level (after preprocessing). Participants were excluded from the second-level (group-level) analyses if they had more than 30% of volumes with framewise displacement (FD) exceeding 0.5 mm or if any other artifacts were detected (Patel et al., 2014; Power et al., 2012).

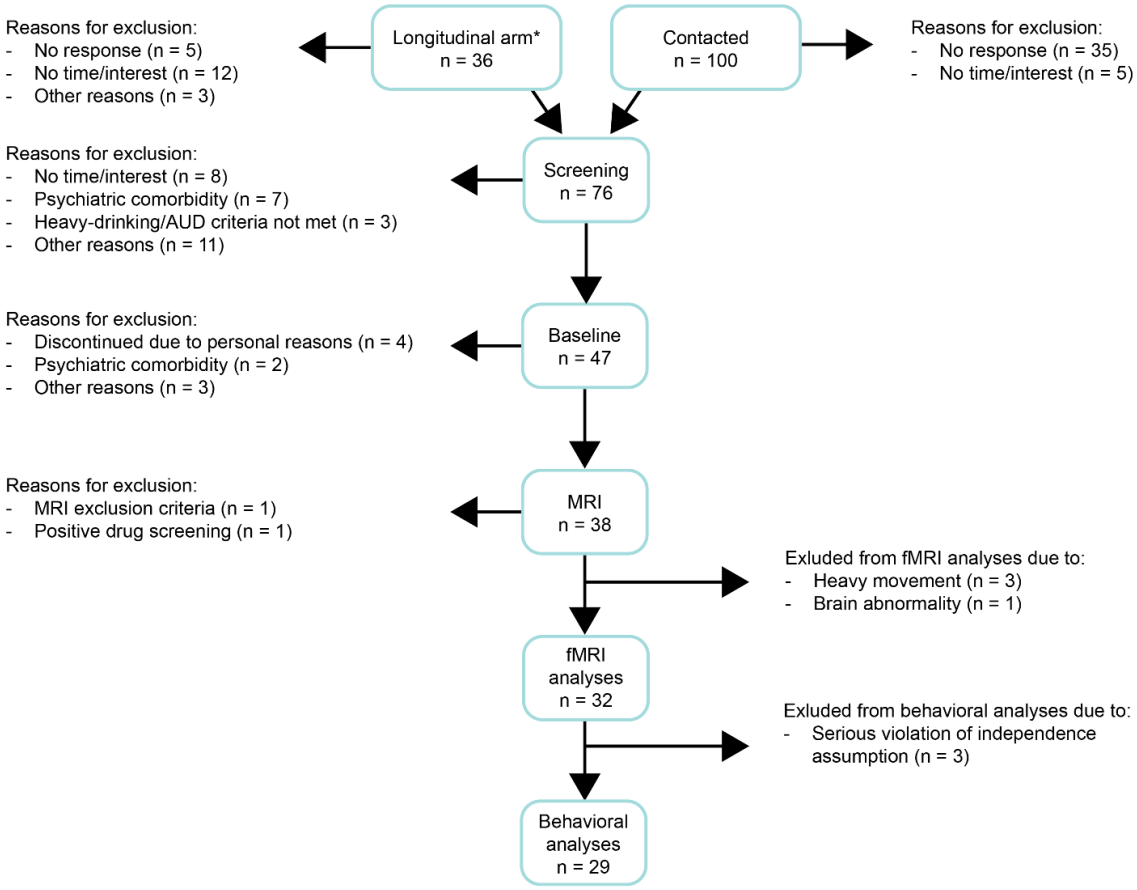
2.2.3.4 Statistical analyses

The analytical sample comprised N= 32 and N = 29 for the fMRI and behavioral analyses, respectively (see **Figure 4** for reasons of exclusion).

2.2.3.4.1 fMRI analyses

The fMRI analyses followed a two-level procedure. At the first level, a general linear model (GLM) was applied to successful (Stop success) and failed (Stop error) stop trials as well as go error trials, which were modeled as separate events. Head motion parameters (numerical) were included in the design matrix as nuisance covariates, and the volumes with FD > 0.5 mm were excluded by dummy covariates. At the second level, following the approach of , an initial whole-brain conjunction analysis of “Stop success” and "Stop error” was performed (as a proof of concept) using one sample t-tests to confirm activation in relevant motor inhibition-related brain regions during stop trials, regardless of the outcome. Additionally, brain activity between "Stop success" and "Stop error" trials was compared.

Figure 4. Study flow chart



Note. *This is a follow-up study that additionally reassessed participants from the previous study (NCT03758053). However, the stop-signal task was newly added to this study and, therefore, was not included in the longitudinal assessments.

The first-level contrasts “Stop success” and “Stop error” were used in a 1x2 full-factorial linear regression model, including the within-subject factors stopping (Stop success, Stop error) and ACE. ACE severity (CTQ sum score) served as the substantive predictor of interest across all analyses. Age and gender were added as covariates of no interest. In addition, the association between activation in the left and right IFG and ACE global and subtype severity (sum score as well as subscales for exploratory analyses) were examined in post-hoc ROI analyses using partial correlation (corrected for age and gender and for the other ACE subtypes in the exploratory subtype analyses). The ROI extraction tool from Reinhard et al. (2015) in combination with the WFU-PickAtlas for masks were used to obtain ROI activation estimates in the left and right IFG. The sums of t-values exceeding an individually

defined thresholds were used as estimates. The partial correlations were conducted using SPSS (Statistics for Windows, Version 27.0., IBM Corp., Armonk, NY).

Brain activation was visualized using the MRIcroGL tool (Rorden et al., 2007). A voxel-wise-threshold of $p < 0.001$ in combination with a cluster-extent threshold determined with random field theory in SPM12 was used for a corresponding cluster-level family-wise error (FWE) significance threshold of $p < 0.05$. The post-hoc ROI analyses were exploratory in nature and thus not corrected for multiple comparisons.

2.2.3.4.2 Behavioral analyses

A partial correlation analysis, controlling for age and gender, was performed to assess the association between ACE severity (CTQ sum score) and SSRT. We also performed exploratory partial correlation analyses assessing the association between ACE subtype severity and SSRT, while controlling for age and gender as well as the effect of the other intercorrelated subtypes. The analyses were conducted using SPSS (Statistics for Windows, Version 27.0., IBM Corp., Armonk, NY).

2.2.4 Results

2.2.4.1 Sample description

An overview of the sample characteristics is provided in **Table 2**. Most participants were men (56.25%) and not in treatment for AUD (87.5%). The sample was characterized by mild-to-moderate ACE severity across all subscales of the CTQ, based on the severity classification by Häuser et al. (2011). Visualizations of the distributions for CTQ subscale scores can be found in the **Figure S1** and **Figure S2** in the **Supplementary Materials**. A visual inspection indicated low variance for both sexual and physical abuse, and non-normal distributions for all subscales except for emotional neglect. Given the low variance for physical and sexual abuse, both subscales were excluded as predictors from the exploratory analyses (but included as covariates in the exploratory subtype analyses). On average, participants had minimal or no depression (based on BDI), moderate AUD severity (mean, DSM-5 criteria fulfilled = 5.91 ± 3.01), and were within the normal range of impulsiveness.

Table 2. Sample characteristics.

	Mean (SD)
N	32
Gender	18:14:0
Age (years)	45.7 (12.1)
Marital status (married:divorced:single)	9:6:17
Living status (alone:together with	18:14
Years of education	15.6 (2.2)
Current smoker (yes:no)	12:20
CTQ (sum score)	49.1 (16.2)
CTQ Emotional abuse	12.0 (6.0)
CTQ Physical abuse	8.2 (4.3)
CTQ Sexual abuse	6.3 (3.4)
CTQ Emotional neglect	14.2 (5.7)
CTQ Physical neglect	8.4 (3.0)
ADS (sum score)	13.8 (8.8)
BDI (sum score)	11.3 (10.6)
BIS-11 (sum score)	62.8 (9.6)
Form-90 at baseline, alcohol per day (g)[a]	118.4 (99.5)

Note. ADS = Alcohol Dependence Scale; BDI = Beck's Depression Inventory; BIS-11 = Barratt Impulsiveness Scale - Version 11 (BIS-11); CTQ = Childhood Trauma Questionnaire; Form-90 = amount of alcohol consumption per day over the last 90 days; g = grams; N = sample size; SD = Standard Deviation; [a]missing data for one participant.

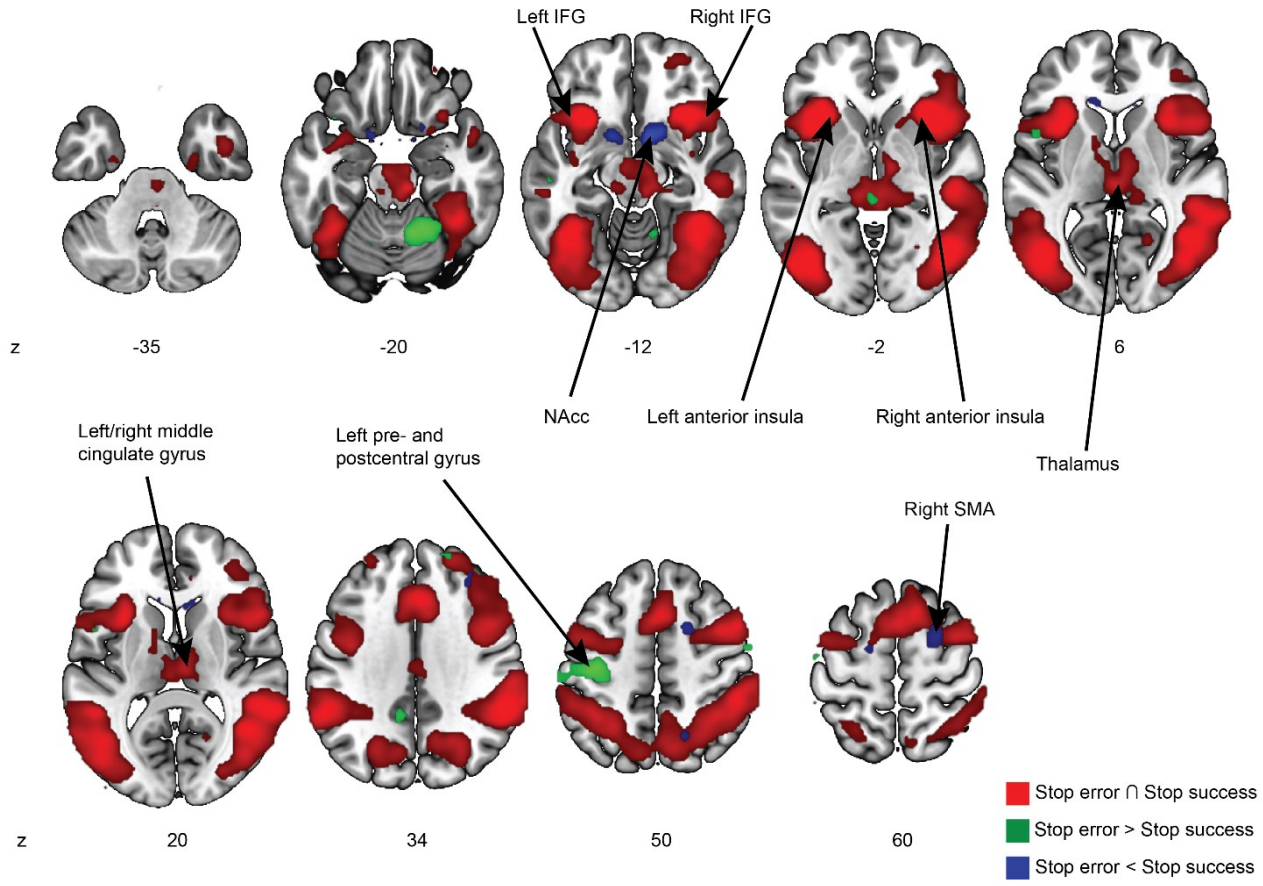
2.2.4.2 fMRI results

Inhibition-related brain activation

The whole-brain conjunction analysis of "Stop error" and "Stop success" indicated increased brain activation in an inhibition-related network, encompassing the bilateral IFG, anterior insula, thalamus and middle cingulate gyrus, confirming that the task was adequately executed. In the contrast of "Stop success > Stop error", increased activation was observed in the right supplementary motor cortex. On the other hand, in the "Stop error > Stop success" contrast, there was increased activation in the left pre- and postcentral gyrus. **Table S2** provides an overview of the results from the one

sample t-tests assessing general inhibition-related brain activation, while **Figure 5** presents a visualization of the activation in the relevant regions.

Figure 5. Activation of the inhibition network during stop trials.



Note. IFG, inferior frontal gyrus; SMA, supplementary motor area. Brain areas that were active across both stopping conditions (conjunction of stop success and stop error) are highlighted in red. Brain areas with increased activation for the condition "Stop error > Stop success" is shown in green, while increased activation for the condition "Stop success > Stop error" is shown in blue. Voxel-wise significance threshold: $p < 0.001$, uncorrected.

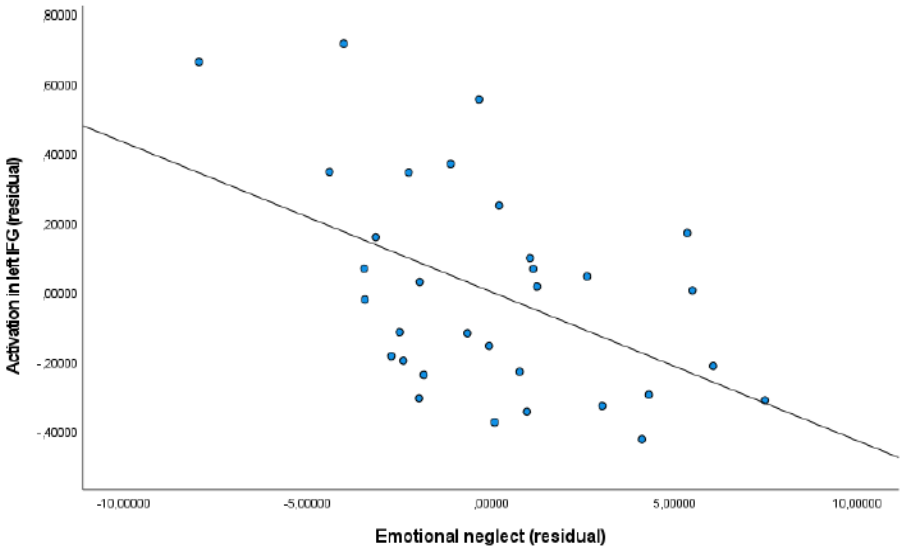
Association between ACE and inhibition-related brain activation

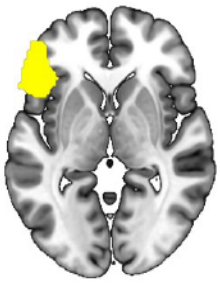
The whole-brain analyses did not yield significant results for the association between CTQ sum score and alterations in brain activation for any of the contrasts in the second-level analyses. Across the exploratory ROI analyses, we did not observe a

significant association between CTQ sum score and activation in the left or right IFG. However, in the exploratory CTQ subgroup analyses, we found that higher levels of emotional neglect were significantly associated with lower activation in the left IFG in the "Stop success > Stop error" contrast (r(24) = -0.49, p = 0.011, uncorrected; see **Figure 6a**). In contrast, we found a significant positive association between emotional abuse and activation in the left IFG in the same contrast (r(24) = 0.55, p = 0.004, uncorrected; see **Figure 6b**).

Figure 6. Partial correlation between emotional abuse/neglect and activation in the left inferior frontal gyrus in the "Stop success > Stop error" contrast, controlling for age, gender and other CTQ subscales.

a)





b)

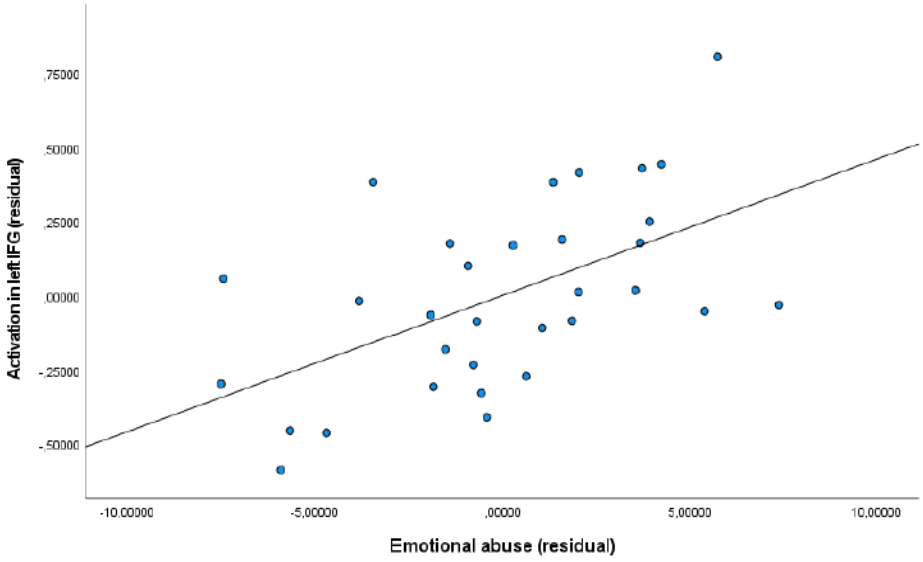
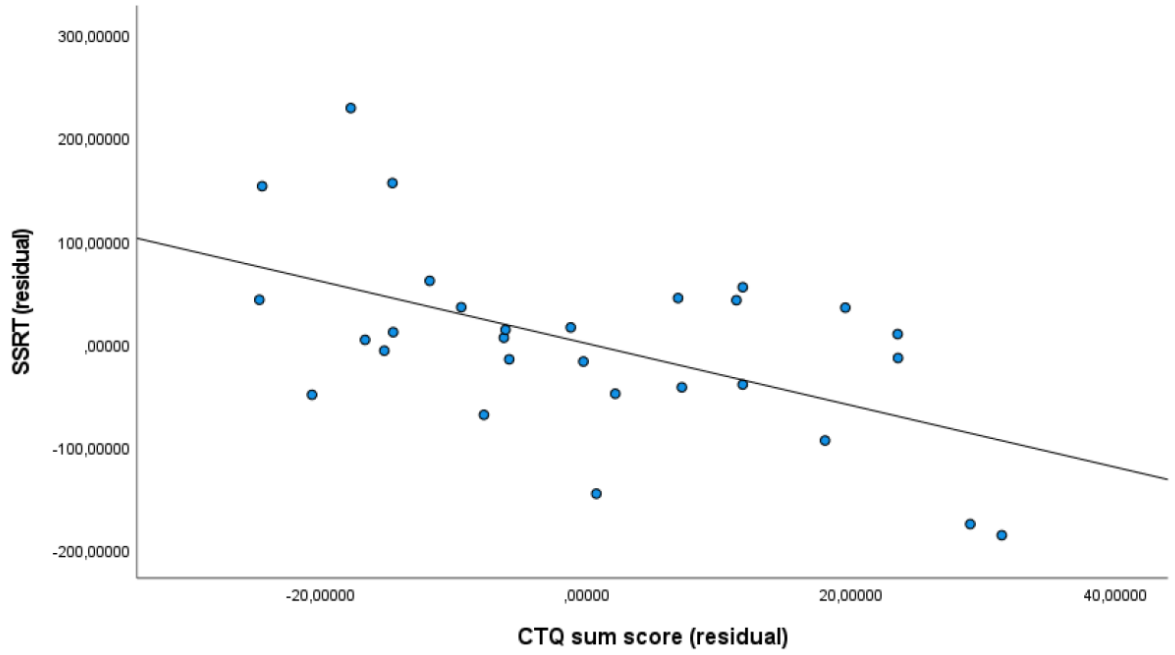


Figure 7. Partial correlation between CTQ sum score and stop-signal reaction time (SSRT), controlling for age and gender.



Note. CTQ = Childhood Trauma Questionnaire; SSRT = stop-signal reaction time.

2.2.4.3 Behavioral results

On average, participants had an SSRT of 272.26 (± 91.47) ms. Additional descriptive statistics for the stop-signal task can be found in **Table S3** in the **Supplementary Materials**. The partial correlation analyses indicated that lower mean SSRTs were significantly associated with higher CTQ total severity (r(25)= -0.55, p = 0.003, see **Figure 7**). In the exploratory analyses, a higher emotional neglect severity was associated with lower mean SSRTs (r(21)= -0.42, p = 0.045, uncorrected). No statistically significant correlation between mean SSRT and emotional abuse (r(21)= -0.06, p = 0.78) as well as physical neglect (r(21)= 0.13, p = 0.56) was found.

2.2.5 Discussion

The aim of the present study was to assess the association between ACE and inhibitory control among heavy-drinking adults with retrospectively reported ACE at a

behavioral and neuroimaging level. While the whole-brain analyses yielded no significant associations between ACE severity and changes in brain activation, the exploratory post-hoc ROI analyses revealed significant associations between ACE subtypes and activation in the left IFG. Specifically, higher levels of emotional neglect were associated with lower activation in the left IFG during successful inhibition, whereas a higher severity of emotional abuse was associated with higher activation in the same brain region during successful inhibition, in line with the first hypothesis, which predicted changes in prefrontal regions. The behavioral results indicated that greater ACE severity was associated with better inhibitory control, confirming the second hypothesis although we did not put forward a specific hypothesis on the direction of the association. This association appeared to be primarily driven by emotional neglect.

The finding that greater ACE severity is associated with better response inhibition in heavy-drinking individuals contrasts with findings in maltreated adolescents who have been found to have worse inhibitory control (Kim & Bruce, 2022; van der Bij et al., 2020). However, at the same time, it is consistent with evidence indicating that inhibitory control issues seem to diminish by late adolescence among trauma-exposed adolescents and those at-risk for substance use (Quach et al., 2020; van der Bij et al., 2020). Thus, the relationship between ACE and inhibitory control may be more complex in nature and potentially contingent on the developmental stage. It is possible that impaired inhibitory control is a potent vulnerability factor for ACE-related increases in alcohol use during sensitive developmental periods such as early adolescence in those with early life adversities . This aligns with longitudinal evidence demonstrating that early adolescence is a sensitive developmental period for increases in alcohol use related to negative life events (Cheney et al., 2018; Türkmen, Brunborg, et al., 2024). By late adolescence and emerging adulthood, however, these studies have also found that increased alcohol use may no longer be a response to negative life events (Cheney et al., 2018; Türkmen, Brunborg, et al., 2024). Similarly, inhibitory control issues appear to subside by this developmental stage, possibly due to compensatory mechanisms developed throughout adolescence (Quach et al., 2020; van der Bij et al., 2020).

Potential compensatory mechanisms may persist into adulthood, as shown by a recent study which found ACE to be associated with increased activation in inhibition-related brain areas, including the bilateral IFG, among adults, suggesting that ACE

may have lasting effects on the neural circuitry underlying inhibitory control (Sacu et al., 2024). The exploratory ROI analyses partially align with these results such that higher levels of emotional abuse were associated with increased activation in the left IFG during successful inhibition. However, at the same time, higher levels of emotional neglect were associated with lower activation in the IFG during successful inhibition. In addition, the behavioral suggested that higher levels of emotional neglect might be associated with improved inhibitory control. Thus, the interpretation of the directionality of brain activation as well as the role of ACE subtype remain uncertain. Neural efficiency might explain the findings related to emotional neglect, though it is essential to recognize that this effect may vary across developmental stages. Taken together, future longitudinal studies are needed to further elucidate sensitive developmental periods and how neural changes underlying inhibitory control issues may contribute to the relationship between ACE and heavy alcohol use during such periods and beyond.

While the present study indicated that higher levels of ACE severity were associated with better inhibitory control, it is important to note that this association does not provide insights into the actual performance of the group itself due to the absence of a control group. Compared to a study utilizing the same paradigm among social drinkers, our sample had a considerably higher SSRT (274 ms vs 226 ms). However, this difference may be influenced by a substantial age gap, as the other study included younger individuals (18.9 ± 0.4 vs 45.7 ± 12.1 years). Incorporating a non-maltreated control group in future longitudinal research may help to better disentangle the effects of ACE and build upon the framework of cognitive vulnerability proposed by Edalati and Krank (2016). The effects of sex and a family history of AUD should also be considered. A recent study has found a three-way interaction effect such that men with higher levels of both ACE and a family history of AUD showed better response inhibition, while those with ACE but less family history of AUD exhibited poorer inhibition (Elton et al., 2023). In contrast, women with higher ACE and less family history of AUD demonstrated better inhibitory control, whereas those with higher levels of both had worse inhibitory control (Elton et al., 2023). Elton et al. (2023) also found that higher levels of ACE were associated with reduced brain activation during behavioral inhibition in an inhibition-related network, including the medial prefrontal cortex, bilateral middle frontal gyrus, left IFG, posterior cingulate cortex, and angular gyrus, in men with less and women with more family history of AUD. In contrast, men with more family history showed greater activation.

The current findings could have important implications for prevention and intervention programs targeting heavy-drinking individuals with ACE exposure. In line with research on adolescents at-risk of substance use, Jankowski et al. (2018) have provided initial evidence that ACE are associated with changes in neural activation patterns underlying response inhibition during early adolescence. Moreover, their findings suggest that engaging in a preventive intervention could help to mitigate the effects of maltreatment on the neural circuitry related to successful response inhibition. While cognitive training and remediation interventions may help to address deficits in inhibitory control (Verdejo-Garcia et al., 2023), there is preliminary evidence indicating that exercise may be an alternative engaging option for improving inhibitory control among adolescents (Browne et al., 2016; Peruyero et al., 2017). Additionally, recent evidence suggests that sports participation could mitigate the effects of negative life events on alcohol use during early adolescence (Türkmen, Brunborg, et al., 2024). Future longitudinal studies should aim to assess whether these interventions are associated with improved response inhibition among individuals with heavy alcohol use and a history of ACE, and evaluate if this is accompanied by functional changes in inhibition-related brain regions using neuroimaging-based behavioral inhibition paradigms.

2.2.5.1 Limitations and future directions

While this study offers valuable insights for guiding future longitudinal research, the present findings must be considered in light of certain limitations. Although some of the aims of this study are exploratory, the modest sample size is still a limitation, which may have resulted in insufficient power to detect smaller effects of ACE, particularly with respect to the fMRI analyses. The sample size was further reduced in the behavioral analyses (SSRT) as a result of three participants seriously violating the independence assumption in the SST. Also, the present study primarily included individuals with minimal ACE severity, particularly regarding physical and sexual abuse, which is likely due to strict exclusion criteria related to psychiatric comorbidities. While this may have contributed to range restriction in ACE severity and diminished correlations as a result, there is also increased confidence that the results were not substantially confounded by comorbid psychiatric disorders.

It is important to note that the majority of participants (87.5%) were non-treatment-seeking individuals with heavy alcohol use and, on average, had moderate AUD. This limits the ability to draw conclusions about individuals with more severe AUD. Further, the present sample was primarily characterized by emotional neglect. Different types of maltreatment (neglect vs. abuse), which may interact with developmental stages and have distinct neurobiological effects , may be important to consider. Disentangling potentially distinct effects of maltreatment is currently challenging, as evident in van der Bij et al.'s review (2020) of the effects of traumatization on inhibitory control in youth, which was limited by the inclusion of only one study that specifically focused on childhood neglect . Future longitudinal studies with larger sample sizes, encompassing the full spectrum of AUD and ACE, are needed to better disentangle the different types of maltreatment and their specific effects.

It is also important to acknowledge that the ROI and behavioral analyses per subtype were exploratory in nature and thus not corrected for multiple comparisons. Thus, these results should be considered as more preliminary and need to be confirmed in future longitudinal studies.

Lastly, it is important to note that a recent meta-analysis indicated low agreement between prospective and retrospective measures of ACE, raising concerns about whether these two measurement approaches capture different populations (Baldwin et al., 2019). Although retrospective designs introduce biases (e.g., recall bias) inherent to this methodology, studies with prospective designs may predominantly include more severe cases of trauma. Lastly, due to the cross-sectional nature of this study, the directionality and causality of the findings remain uncertain.

2.2.6 Conclusions

The present findings suggest that greater ACE severity, driven primarily by emotional neglect, might be associated with better inhibitory control among heavy-drinking individuals. While neural efficiency of inhibitory control after more severe emotional neglect may partly explain this observation, the interpretation regarding the directionality of brain activation warrants further investigation. Longitudinal studies are needed to assess ACE type- and timing-related effects on neural changes related to inhibitory control in those with heavy alcohol use.

2.3 Study III: Sports participation moderates the risk of family-specific negative life events on alcohol use among adolescents: Evidence from the longitudinal MyLife study[3]

2.3.1 Abstract

Negative life events (NLE) have been associated with increased alcohol use (AU) during adolescence. However, whether this risk association may be modified by leisure activities such as sports participation (SP) remains poorly understood. This study examined whether accumulated family-specific NLE in particular were associated with greater AU, and if so, whether SP moderated this association to reduce AU among high-NLE adolescents.

We examined five annual assessments from a nationwide cohort of 3,422 Norwegian adolescents (13–15 year-olds; 55.3 % girls at baseline) who participated in the MyLife study. At each assessment, adolescents reported their AU on the Alcohol Use Disorders Identification Test-Concise (AUDIT-C), the number of family-specific NLE in the past 12 months, SP days in the past 30 days, and multiple sociodemographic and individual-level characteristics (covariates). Changes over time in AU as a function of NLE, SP, and their interaction (NLExSP) were examined with a set of partially nested growth curve models.

AU increased non-linearly over time in all models. The fully adjusted best-fitting model showed significant NLExSP interactions (*estimate* = -0.013, 95% CI [-0.02, −0.006]), such that the initial AUDIT-C scores were lower for high-NLE adolescents with high SP and greater for high-NLE adolescents with low SP. Further, linear increases in AU over time were marginally steeper for high-NLE adolescents with high SP (NLExSPxTime *estimate* = 0.034, 95% CI [-0.0002, 0.007]). Thus, SP appeared to have a protective role in reducing AU for high-NLE youth primarily during middle school years. Prevention efforts thus may utilize organized sports for youth facing family-specific NLE as a resource early on.

[3] **Published as:** Türkmen, C., Brunborg, G. S., Lund, I. O., Kiefer, F., Vollstädt-Klein, S., & Burdzovic Andreas, J. (2024). Sports participation moderates the risk of family-specific negative life events on alcohol use among adolescents: Evidence from the longitudinal MyLife study. Addictive Behaviors, 155, 108041. https://doi.org/10.1016/j.addbeh.2024.108041

2.3.2 Introduction

Whereas alcohol use (AU) increases throughout adolescence as part of the normative transition into adulthood (Brunborg et al., 2018; Chung et al., 2018; Maggs & Schulenberg, 2004), early drinking initiation has been linked to problematic alcohol involvement, including dependence and hazardous drinking (Dawson et al., 2008; Enstad et al., 2019; Hingson et al., 2006). Given that hazardous drinking patterns remain prevalent in the Nordic region even among young drinkers (Abebe et al., 2015; ESPAD Group, 2020; Pedersen & von Soest, 2013), identifying relevant risk and protective factors for early AU remains crucial. Understanding the role of such factors could contribute to prevention strategies aimed at delaying drinking initiation or targeting the shifts from experimental to hazardous drinking among youth from societies characterized by such consumption patterns.

Accumulation of negative life events (NLE) such as parental separation, illness, or financial hardship has been associated with poorer youth health and development, including problematic AU (Cheney et al., 2018; Hoffmann & Jones, 2020; King et al., 2017; Lensch et al., 2020; Lloyd & Turner, 2008; Low et al., 2012). While the nature of negative events and stressors may vary (Low et al., 2012), those accumulating at the family level may be the most salient for developing youth (Masarik & Conger, 2017). For example, greater alcohol involvement and more problematic drinking patterns were observed among adolescents from families characterized by economic hardship (Diggs & Neppl, 2018; Hardaway & Cornelius, 2014), or by parental conflict (Bray et al., 2022) and separation (Hoffmann, 2022; Rüütel et al., 2014). Finally, the effect of NLE appears to be contingent on the developmental stage, as it was shown to affect drinking primarily during early adolescence (Cheney et al., 2018). In short, family-specific stressors outside of the child's control may be particularly relevant risks for AU, especially among the youngest adolescents.

Identifying modifiable resources with the potential to offset early familial stressors may thus be particularly relevant in efforts to reduce early alcohol involvement (Fergus & Zimmerman, 2005; Rutter, 1985). While prior studies have shown that greater individual, family, and community-level assets are prospectively associated with lower binge drinking among youth facing multiple NLE (Lensch et al., 2020), many of the identified assets – e.g., "positive peer role models" – are not easily modifiable or translatable into prevention strategies. However, sports participation

(SP), particularly *organized* SP, has been recognized as an important modifiable pathway through which adolescents' psychosocial and physical health may be improved (Bjørnarå et al., 2021; Eime et al., 2013).

Yet, the extant studies examining the relationship between SP and early AU have shown mixed results. Recent evidence from Canada showed a lower likelihood of adolescent binge drinking in neighborhoods with greater availability of sports facilities (Doggett et al., 2021), but the two systematic reviews reflecting predominantly USA-based studies concluded that sports involvement seems to be positively associated with adolescent AU (Kwan et al., 2014; Walczak et al., 2023). In contrast, Nordic studies reported either no associations between sports involvement and AU among adolescents (Brunborg et al., 2022) or concluded that the associations depended on the type of sport (Wichstrøm & Wichstrøm, 2009). Other studies from the Nordic region suggested participation in *organized sports* to be a protective factor against AU during adolescence (Kristjansson et al., 2010). Finally, previous research underscored the importance of cultural and sports contexts; for example, lower AU was associated with participation in formally *organized sports*, as opposed to participation in informal sports (Halldorsson et al., 2013) or in high school intramurals (Williams et al., 2021). It is therefore possible that SP outside the North American context – including the Norwegian model of *organized local sports teams* after school hours (Skille, 2011) – may have different cultural and individual functions and consequently have different associations with AU during adolescence.

In short, the ways in which adolescent AU may be shaped by SP remains poorly understood. For example, SP might serve a protective function for particular at-risk youth, such as those experiencing multiple family-specific NLE. In such risk-protective models (Fergus & Zimmerman, 2005; Rutter, 1985), the protective factor acts as a moderator of the known risk association, lessening the negative outcome (i.e., adolescent AU) at higher levels of protection (i.e., SP) among the risk-exposed group (i.e., high-NLE youth). However, to the best of our knowledge, no study has explored the putative protective role of SP in relation to the risk association between NLE and adolescent AU over time. There is an additional need to assess these questions in longitudinal studies to identify vulnerable developmental periods of particular relevance to prevention strategies.

To address these gaps, we used longitudinal data from a large nationwide sample of Norwegian adolescents to investigate 1) whether accumulated family-

specific NLE in particular were associated with greater and potentially hazardous levels of AU over the five-year period, and if so, 2) whether SP moderated this association in a protective manner.

2.3.3 Methods

2.3.3.1 Study design and participants

This research is based on the MyLife study (Brunborg et al., 2019), a large-scale, prospective longitudinal study of youth and substance use in Norway, which recruited a geographically and socioeconomically diverse sample of 8th, 9th, and 10th graders from 33 middle schools across the country. Details concerning the study design, recruitment, and consent procedures are provided in the study protocol (Brunborg et al., 2019). The core sample of 3,512 adolescents for whom written parental consent was obtained was invited to complete online questionnaires at five annual assessments during the fall semesters of 2017 (T1 baseline), 2018 (T2), 2019 (T3), 2020 (T4) and 2021 (T5). Adolescents assented through participation.

A total of 2,965 adolescents completed the questionnaires at T1, 2,854 at T2, 2,649 at T3, 2,327 at T4, and 1,829 at T5. However, because the entire cohort was invited to participate in each assessment, participants moved in and out of the study; specifically, only 76 (2.2 %) of the 3,512 adolescents with informed parental consent did not participate in any of the five study assessments. In addition, the remaining sample remains robust, as 417 (12.0 %) adolescents participated in two**,** 671 (19 %) in three**,** 870 (24.8 %) in four**,** and the greatest number of 1,209 (34.4 %) adolescents participated in all five assessments. Our analytic sample consisted of 3,422 adolescents (middle school grades 8–10; age range at baseline 13–15 years; 55.3 % girls) who had at least one valid assessment of alcohol consumption across the five annual study rounds.

The original study protocol was evaluated by The National Committee for Research Ethics in the Social Sciences and the Humanities (reference no.: 2016/137) and approved by the Norwegian Data Protection Authority (DPA) (reference no.: 15/01495).

2.3.3.2 Measures

Unless stated otherwise, all variables were measured at all assessments (T1-T5).

Outcome

Alcohol Use (AU) was measured using a slightly adjusted version of the 3-item Alcohol Use Disorders Identification Test – Concise (AUDIT-C) (Saunders et al., 1993). Participants were asked to indicate the frequency of their alcohol consumption in the past year, the average quantity of alcohol they typically consumed per drinking occasion, and the number of occasions they had consumed five or more alcohol units on the same day. The use of AUDIT-C in adolescents has been validated in the Nordic region, with a score of 3 or higher indicating hazardous AU (Liskola et al., 2018). The original response options capturing AU frequencies and quantities items were recoded to follow the standard AUDIT-C scoring and summed up to generate total scale scores.

Substantive predictors

Family-specific Negative Life Events (NLE) were measured using slightly modified items from the Negative Life Events Inventory (Wills et al., 1992) and additional items adopted for the Norwegian context. The current study included 10 exclusively family-related NLE as part of the broader focus on adolescents' social context. At T1 (baseline), participants indicated if they had experienced such NLE by responding with "Yes, within the last 12 months", "Yes, more than 12 months ago" (lifetime), or "No, never". From T2 to T5, the questions referred to NLE during the last 12 months and the response options changed to "Yes"/"No". Both the lifetime and past-year family-specific NLE index reflected the sum of affirmative responses. However, to prevent data loss resulting from a single baseline assessment of lifetime NLE, this indicator was categorized into "none"/"1–2"/"3 or more"/"unknown" groups.

Frequency of Sports Participation (SP) during the past 30 days was measured with the following question: "Think about the past 30 days, how often have you done sports training (e.g., soccer, handball, swimming)?". The response options ranging from "Not at all" to "5–7 days per week" were recoded as a continuous variable by selecting a mid-point value to reflect the number of SP days in the past month (i.e., 5–7 days per week = 6 days per week = 24 days past month) for ease of interpretation. Both NLE and SP were examined as continuous time-varying predictors in all growth models to follow.

Covariates

Sociodemographic covariates included *gender* (boy/girl), *grade/cohort* (Grade 8, 9, or 10 in middle school at baseline), and *immigrant background* (yes/no/not reported). Other covariates encompassed a) two additional NLE, including *lifetime history of family-specific NLE prior to T1* measured at baseline only, and *moving out of parental home* measured at T2-T5, b) a set of individual-level characteristics including *sensation seeking*, *depressive symptoms*, *conduct problems*, *involvement in unstructured leisure activities*, *positive alcohol expectancies*, and *number of close friends* measured across all five T1-T5 study rounds, and c) *COVID-19 worries* measured at T4-T5. For a complete set of measures, see **Supplement 1** and **Table 4**.

Missingness

As noted above, only 76 adolescents from the core sample of 3,512 did not complete a single study assessment. Based on the consent forms information, we know that they were more likely to be boys (OR = 1.99, 95% CI [1.5, 2.6]), and to be grade 9 (OR = 2.08, 95 % CI [1.4, 3.0]) and grade 10 (OR = 4.7, 95% CI [3.3, 6.7]) than grade 8 at baseline. No attempts were made to include these 76 cases in current analyses.

Further, two questions were asked only at T1 baseline. We thus have no information for adolescents who did not participate at that time regarding their *immigrant background* (*n* = 462) and *lifetime NLE* (*n* = 472). To prevent data loss, these variables were recoded as “No report” groups and modeled as such in all analyses. Of those with at least one assessment, small proportions did not provide any information concerning their AU/AUDIT-C (*n* = 14), NLE (*n* = 18), or SP (*n* = 17). There was a substantial overlap in these non-completers (*n* = 21) and they were excluded due to the complete missingness on either the key predictors or outcome. Finally, due to incomplete participant reporting on various covariates, our final model was reduced by an additional 48 cases. Given the robust sample size and multiple assessments, all models were estimated without utilizing advanced procedures for handling missing data.

2.3.3.3 Statistical analyses

The initial set of analyses described the sample characteristics and examined univariate associations of our key alcohol use outcome (AUDIT-C scores) with substantive predictors and covariates at study baseline using simple linear regression models.

Our primary aims concerned understanding "systematic changes over time" (Willett et al., 1998) in adolescent AU, and how such changes may differ as a function of NLE risks and SP involvement. We used multi-level growth curve models and maximum likelihood estimation to obtain estimates of AU trajectories of interest (Curran et al., 2010; Singer & Willett, 2003; Willett et al., 1998). These individual AU trajectories are characterized by their initial estimated status (intercept) and their changes over time (linear and non-linear slopes), which can be modeled independently.

Prior to model specification, we fit an unconditional means model (Model 0) estimating the annual linear and quadratic rates of change in AU (i.e., in AUDIT-C scores). The results revealed significant increases in AU over time (linear rate *estimate* = 0.65, 95% CI [0.57–0.74] and quadratic rate *estimate* = 0.11, 95% CI [0.09–0.12]) and more importantly, significant variation around these average AU trajectories (linear = 0.58, 95% CI [0.53–0.65]; quadratic = 0.006, 95% CI [0.003–0.012]), thus warranting further investigation. Accordingly, Model 1 estimated the initial levels and linear and quadratic annual rates of change in AU as a function of NLE (i.e., interaction of NLE with time and time^2), while Model 2 estimated the initial levels as well as the linear and quadratic annual rates of change in AU as a function of SP (i.e., interaction of SP with time and time^2). These preliminary models were partially adjusted for basic demographics only (i.e., gender and grade cohort at baseline).

Models 3 and 4 addressed our substantive questions and tested the moderating role of SP on the association between NLE and AU over time, and therefore included the NLExSP interaction term in the estimates of both the initial AU status (NLExSP) and its linear (NLExSPxTime; Model 3) and quadratic (NLExSPxTime^2; Model 4) rates of change over time. Significant NLExSPxTime and/or NLExSPxTime^2 terms would describe AU trajectories for adolescents with all combinations of high/low NLE and high/low SP, and test for putative protective effects of high SP against the high-NLE risk. Models 3 and 4 were fully adjusted for time-invariant characteristics (i.e., *gender*, *grade/cohort*, *immigrant background*, and *lifetime NLE history*), and for

time-varying characteristics assessed repeatedly (i.e., *moving out of home*, *sensation seeking*, *depressive symptoms*, *conduct problems*, *involvement in unstructured leisure activities*, *positive alcohol expectancies*, *number of close friends*, and *COVID-19 worries*).

Annual assessment (i.e., calendar year) was used as the indicator of time in all estimations. Given the co-occurrence of the COVID-19 conditions with our final two assessments, we selected this conservative time metric to preserve delineation of the pandemic period. The time variable was modeled as a continuous indicator and was centered such that time = 0 reflected the study baseline (Preacher et al., 2006; Willett et al., 1998). While centering of other predictors does not affect estimation but can improve interpretability of intercept estimates, we selected not to grand-mean center given the preponderance of categorical covariates, absence of meaningless zeroes in predictor variables, and our substantive interest in AU changes not as deviations from the sample averages but across the specific NLE risk and SP protective categories.

All growth models were estimated using Stata 17 −*mixed* command (StataCorp, 2021) with independent covariance structure and maximum likelihood (*ml*). Reported were non-standardized estimates with 95% CI to aid interpretation of the clinically-meaningful AUDIT-C scores, as well as the Bayesian and Akaike Information Criteria (BIC and AIC) to evaluate model fit (Singer & Willett, 2003). Model selection was based on the likelihood-ratio test (−*lrtest*) of the two substantive nested models (i.e., fully adjusted Model 3 vs. Model 4). Stata −*margins* and −*marginsplot* commands with *atmeans* option were used to probe and visualize the interaction results from the selected best-fitting model, including the graphic representation of AU trajectories at specific levels of NLE and SP and average levels of remaining predictors.

2.3.4 Results

Summaries of all study variables at baseline and their regression-based univariate associations with AUDIT-C scores at baseline are shown in **Table 3**.

Table 4 summarizes AUDIT-C scores, the number of reported family-specific NLE, and the number of past month SP days over the five annual study assessments. By the time all adolescents from our sample transitioned into high school (i.e., T4/T5), the average AUDIT-C scores exceeded thresholds (≥3) for hazardous AU.

Table 5 presents the results of the growth curve models examining non-linear trajectories of AU (AUDIT-C scores) across adolescent years as a function of family-specific NLE (Model 1), of SP (Model 2), and of their interactions (NLExSP; Models 3–4).

The results from our age- and gender-adjusted *Model 1* indicated a negative risk effect of family-specific NLE on the initial levels of AU, such that each additional NLE was associated with greater initial AUDIT-C scores (*estimate* = 0.14, 95% CI [0.06, 0.22]). Further, NLE were significantly associated with linear and non-linear rates of change in AU over time (NLExTime *estimate* = 0.23, 95% CI [0.11, 0.35]; NLExTime^2 *estimate* = -0.06, 95% CI [-0.08, −0.03]), such that youth with greater NLE had steeper linear increase but slower acceleration in AU over time.

The results from our age- and gender-adjusted *Model 2* indicated no significant effect of SP on the initial levels of AU. However, SP was significantly associated with linear and non-linear rates of change in AU over time (SPxTime *estimate* = -0.02, 95% CI [-0.03, −0.009]; SPxTime^2 *estimate* = 0.004, 95% CI [0.002, 0.007]), such that youth with greater SP had slower linear increase but steeper acceleration in AU over time.

In our fully adjusted *Model 3* and *4*, we explored whether SP moderated the risk association between NLE and AU over time. The results from Model 3 revealed a significant NLExSP effect on the initial levels of AU, such that the initial AUDIT-C scores were lower for adolescents with greater NLE if they had greater SP (*estimate* = -0.013, 95 %CI [-0.02, −0.006]). There was also a marginally significant NLExSP interaction with time, such that that adolescents with greater NLE had greater linear increases in AU over time at greater SP levels (NLExSPxTime *estimate* = 0.034, 95 %CI [-0.0002, 0.007]). The results from Model 4 show a marginally significant NLExSP effect on the initial levels of AU, and no significant NLExSP interactions with Time or Time^2. The likelihood ratio test revealed a significantly better fit of Model 3 over Model 4; LR(X^2), Δdf = 3, p = 0.003.

Figure 8 displays a graphic representation of the selected, best-fitting Model 3 results, and of NLExSP interactions of interest. Shown are prototypical trajectories of AU with 95 % Regions of Significance for 5 % top/bottom values of NLE (0 vs. 3) and SP (0 vs. 24 days past month) at average values of the remaining covariates.

Table 3. Study variables and their unadjusted associations with Alcohol Use (AU/AUDIT-C scores) at T1 baseline, n = 2,920.

Study variables at baseline T1	***n (%)* or *M* ± *SD***	**T1 AU (AUDIT-C) *estimate [95% CI]***
Substantive predictors		
Family-specific Negative Life Events (NLE) past year	0.44 ± 0.77	0.39 [0.34, 0.44]***
Sports Participation (SP) days past month	11.09 ± 8.18	-0.005 [-0.01, -.00001]*
Covariates		
Cohort:		
Grade 8	1,271 (37.1%)	Ref.
Grade 9	1,191 (34.8%)	0.14 [0.04, 0.24]**
Grade 10	960 (28.1%)	0.61 [0.50, 0.71]***
Gender:		
Girl	1,891 (55.3%)	Ref.
Boy	1,531 (44.7%)	0.005 [-0.08, 0.09]
Immigrant background:		
Yes	366 (10.7%)	Ref.
No	2,594 (75.8%)	0.04 [-0.08, 0.17]
Not reported	462 (13.5%)	-0.29 [-1.41, 0.83]
Lifetime history of family-specific NLE:		
None	812 (23.7%)	Ref.
1-2 events	1,454 (42.5%)	-0.02 [-0.12, 0.08]
3 or more events	684 (20.0%)	0.13 [0.02, 0.25]*
Not reported	472 (13.8%)	0.06 [-0.60, 0.71]
Depressive symptoms	5.99 (5.5)	0.04 [0.029, 0.05]***
Sensation seeking	2.93 (1.02)	0.20 [0.16, 0.24]***
Unstructured leisure time (days/past month)	2.95 ± 4.25	0.05 [0.04, 0.06]***
Alcohol expectancies (Social Facilitation)	1.72 (0.85)	0.45 [0.40, 0.50]***
Conduct problems past year	1.67 (3.10)	0.14 [0.13, 0.16]***
Number of close friends		
None	254 (8.6%)	Ref.
1-2	760 (25.7%)	0.006 [-0.15, 0.17]
3 or more	1,939 (65.7%)	0.014 [-0.13, 0.16]

Note: * $p < .05$; ** $p < .01$; *** $p < .001$; AU = Alcohol Use; AUDIT-C scores; NLE = number of family-specific Negative Life Events past year; SP = number of days in Sports Participation past month

Estimates represent coefficients and 95% CI obtained from univariate linear regression models with AUDIT-C at T1 as a dependent variable. Two additional time-varying covariates were not assessed at T1, but were included in T2-T5 (*moving out of parental home*) and in T4-T5 (*COVID-19 worries*) assessments.

Table 4. Alcohol Use (AU), family-specific Negative Life Events (NLE), and Sports Participation (SP) over five annual study assessments.

Variable	**T1 (2017)** *n* = 2,965 *n (%)* or *M* ± *SD*	**T2 (2018)** *n* = 2,854 *n (%)* or *M* ± *SD*	**T3 (2019)** *n* = 2,649 *n (%)* or *M* ± *SD*	**T4 (2020)** *n* = 2,327 *n (%)* or *M* ± *SD*	**T5 (2021)** *n* = 1,829 *n (%)* or *M* ± *SD*
AU (AUDIT-C)	.30 ± 1.15	.98 ± 2.09	2.00 ± 2.84	3.26 ± 3.32	4.31 ± 3.35
Family-specific Negative Life Events (NLE) past year:					
1. We have moved into a new home	210 (7.1%)	238 (8.3%)	252 (9.5%)	266 (11.4%)	328 (17.9%)
2. A close family member got seriously ill or died	464 (15.6%)	736 (25.8%)	613 (23.1%)	540 (23.2%)	406 (22.2%)
3. My parents separated	55 (1.9%)	102 (3.6%)	97 (3.7%)	95 (4.1%)	38 (2.1%)
4. My mother died	2 (.1%)	11 (.4%)	6 (.2%)	11 (.5%)	10 (.5%)
5. My father died	5 (.2%)	15 (.5%)	11 (.4%)	14 (.6%)	8 (.4%)
6. My mother got a new partner or remarried	65 (2.2%)	99 (3.5%)	102 (3.9%)	95 (4.1%)	41 (2.2%)
7. My father got a new partner or remarried	62 (2.1%)	114 (4.0%)	90 (3.4%)	82 (3.5%)	51 (2.8%)
8. The grown-ups at home argued a lot	230 (7.8%)	262 (9.2%)	255 (9.6%)	248 (10.7%)	153 (8.4%)
9. My father or mother lost their job	84 (2.8%)	116 (4.06%)	90 (3.4%)	92 (4.0%)	52 (2.8%)
10. My family had financial problems	127 (4.3%)	269 (9.4%)	258 (9.7%)	241 (10.4%)	188 (10.3%)
Family-specific NLE Sum	0.44 ± 0.77	0.69 ± 1.02	0.67 ± 1.01	0.72 ± 1.08	0.70 ± 0.97
Sports Participation (SP) days past month	11.09 ± 8.18	10.63 ± 8.26	10.28 ± 8.63	8.90 ± 8.75	7.95 ± 8.54

Note: Shown are the numbers of affirmative responses; proportions are based on the number of participants at each assessment. AU = Alcohol Use; AUDIT-C scores; NLE = number of family-specific Negative Life Events past year; SP = number of days in Sports Participation past month

Table 5. Adolescent Alcohol Use (AU) over time as a function of family-specific Negative Life Events (NLE) and Sports Participation (SP).

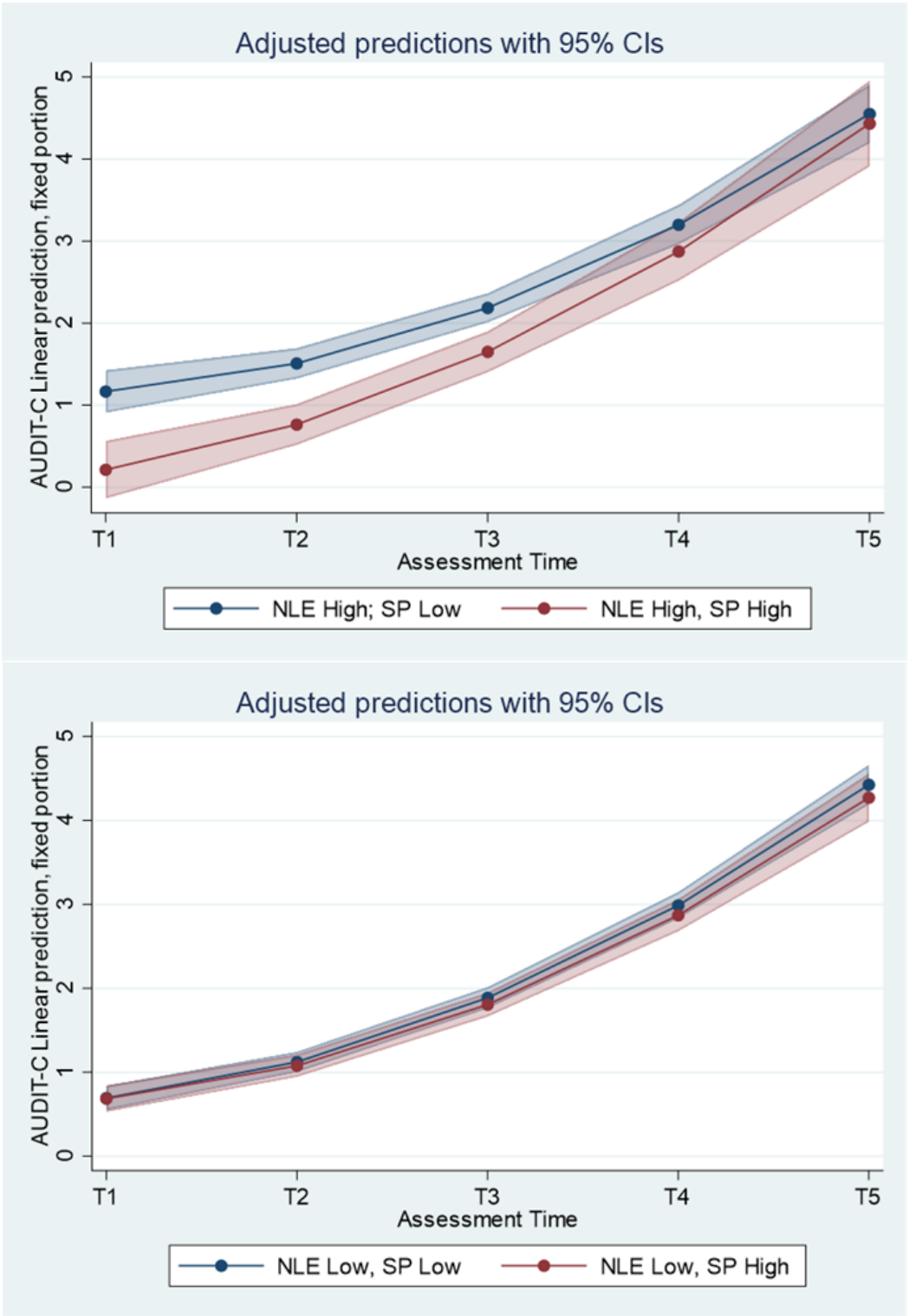
		Model 1 NLE Main effects	**Model 2 SP Main effects**	**Model 3 NLExSPxTime**	**Model 4 NLExSPxTime^2**
Fixed effects					
Initial status	Intercept	-0.23 (-0.38, -0.08)***	-0.12 [-0.29, 0.04]	-1.56 [-1.76, -1.35]***	-1.56 [-1.77, -1.34]***
	NLE	0.14 (0.06, 0.22)***	--	0.16 [0.07, 0.25]***	0.06 [-0.06, 0.17]
	SP	--	-0.003 [-0.01, 0.004]	-0.003 [-0.008, 0.007]	0.002 [-0.007, 0.01]
	NLE x SP	--	--	-0.013 [-0.02, -0.006]***	-0.008 [0.02, 0.0004] ^{f}
Linear Rate of change	Time	0.53 (0.43, 0.63)***	0.84 [0.71, 0.96]***	0.26 [0.16, 0.36]***	0.26 [0.11, 0.42]***
	NLE	0.23 (0.11, 0.35)***	--	-0.03 [-0.07, 0.01]	0.14 [0.008, 0.28]*
	SP	--	-0.02 [-0.03, -0.009]***	-0.002 [-0.005, 0.002]	-0.008 [0.02, 0.003]
	NLE x SP	--	--	0.034 [-0.0002, 0.007] ^{f}	-0.003 [-0.014, 0.008]
Quadratic Rate of change	Time^2	0.14 (0.12, 0.17)***	0.06 [0.02, 0.09]***	0.17 [0.14, 0.19]***	0.17 [0.12, 0.21]***
	NLE	-0.06 (-0.08, -0.03)***	--	--	-0.05 [-0.08, -0.011]**
	SP	--	0.004 [0.002, 0.007]***	--	0.002 [-0.0009, 0.005]
	NLE x SP	--	--	--	0.0016 [-0.001, 0.004]
No. of individual groups		3,418	3,419	3,367	3,367
Model fit	*-LLR*	-27,069.6	-27,099.87	-23,891.3	-23,975, 66
	df	13	13	30	33
	AIC	54,165.19	54,225.73	47,842.6	48,017.33
	BIC	54,261.72	54,322.26	48,062.65	48,259,39

Note: ^{f} $p \leq 0.10$; * $p \leq 0.05$; ** $p \leq 0.01$; ***$p \leq 0.001$; No. of individual groups = number of adolescents; AU = Alcohol Use; AUDIT-C scores; NLE = number of family-specific Negative Life Events past year; SP = number of days in Sports Participation past month.

Models 1-2 were partially adjusted for gender and grade/cohort only. Models 3-4 were fully adjusted for gender and grade/cohort, for all covariates shown in Table 3, as well as COVID-19 worries assessed at T4-T5 (2020-21) and whether the adolescent moved out of parental home (assessed T2-T5). All covariates save for the demographic ones (i.e., gender, cohort, and immigrant background) were modelled as time-varying including the substantive predictors of NLE and SP. All models accounted for school nesting. These fixed and random effects' estimates were not shown for brevity.

To aid interpretation, all estimates reflect non-standardized regression coefficients with 95% CI; i.e., each additional NLE was significantly associated with an increase of .14 points on the initial AUDIT-C scale scores in Model 1. Note that none of the predictor variables were mean-centered, informing interpretation of intercepts in all models. The likelihood ratio test revealed a significantly better fit of Model 3 vs. Model 4; LR(X2), Δdf = 3, p = 0.003.

Figure 8. Adolescent Alcohol Use (AU) over time as a function of family-specific Negative Life Events (NLE) and Sports Participation (SP).



Note. AU = Alcohol Use (AUDIT-C scores); NLE = number of family-specific Negative Life Events past year (Low NLE = 0, High NLE = 3); SP = number of days in Sports Participation past month (Low SP = 0 days, High SP = 24 days).

Shown are prototypical AU trajectories with 95% CI regions of significance based on the best-fitting Model 3 for adolescents scoring at the 5 % top/bottom values of NLE and SP, at average values of remaining predictors. That is, depicted are AU trajectories over five annual study assessments for adolescents characterized by a) low NLE (i.e., no family-specific negative events occurred during past year) at low and high SP (i.e., 0 vs. 24 days past month), and b) high NLE (i.e., 3 family-specific negative events occurred past year) at low and high SP (i.e., 0 vs. 24 days past month).

2.3.5 Discussion

We investigated trajectories of alcohol use (AU) across adolescent years as a function of family-specific negative life events (NLE; Model 1), of sports participation (SP; Model 2) and of their interaction (NLExSP; Models 3 and 4). Specifically, we were interested in the putative protective role of sports participation, and examined whether alcohol use trajectories would be less severe among high-NLE youth who engaged in sports more frequently. Our results revealed non-linear growth in alcohol use over time across all models, such that precipitous increases in AUDIT-C scores were observed after high school transition. The results from our fully adjusted moderator Model 3 revealed that while alcohol use was initially lower among high-NLE youth with more frequent sports participation, it also increased a bit more precipitously for this group and was indistinguishable from that of non-NLE youth by final assessment. Thus, sports participation was associated with a delayed onset and lowered levels of (hazardous) drinking among high-NLE adolescents primarily during the early adolescent years.

Our findings are consistent with previous research on the association between early alcohol-related risks and accumulated negative life events broadly defined (Cheney et al., 2018; Hoffmann & Jones, 2020; Lensch et al., 2020; Lloyd & Turner, 2008; Low et al., 2012). Also consistent with previous research (Cheney et al., 2018), we observed this association primarily during the period coinciding with final years in middle school. This pattern of results suggests that early adolescence may be a particularly vulnerable developmental period, but also that AU appears increasingly normative during later adolescence and is no longer necessarily a response to familial stress. This is likely the case in Norway, where the prevalence of alcohol intoxication sharply rises following high school entry at age 16 and where cultural norms entail less frequent but high quantity alcohol consumption even among youth (ESPAD Group,

2020; Pedersen & von Soest, 2013). This is consistent with our adolescent sample, where alcohol use developed over time along quadratic trajectories, and where the sample average AUDIT-C scores exceeded thresholds (≥3) for hazardous drinking by late adolescence. Another cultural aspect to be considered is the nature of sports involvement in Norway, characterized by a significant societal commitment and youth participation in organized sport activities (Skille, 2011). In that respect, our findings align with other Nordic evidence showing that participation in *organized sports* may reduce substance use among youth in general (Kristjansson et al., 2010), as well as among youth who may be more vulnerable for alcohol involvement due to various peer- and family-specific risks (Halldorsson et al., 2013).

To the best of our knowledge, this is the first longitudinal study to provide empirical support for the resilience processes (Fergus & Zimmerman, 2005) in relation to adolescent alcohol use while considering family-specific negative life events as a putative source of risk and sports participation as a putative source of protection. Although the protective nature of sports appeared to subside throughout adolescence, our results imply that sports participation may in fact delay the onset and extent of (hazardous) drinking among middle school youth experiencing multiple familial stressors. These findings are thus of direct relevance to prevention strategies.

However, the study has several limitations. Firstly, we did not consider sports types (e.g., skiing vs. soccer) or contexts (e.g., team vs. individual sports) despite their potentially different associations with early alcohol involvement (Wichstrøm & Wichstrøm, 2009; Williams et al., 2021). Secondly, the study's two final assessments coincided with the COVID-19 pandemic. For this reason, it may be difficult to separate changes in drinking reflecting normative developmental transitions (ESPAD Group, 2020) from those plausibly associated with the pandemic conditions (Burdzovic Andreas & Brunborg, 2022a). Indeed, earlier findings revealed increased drinking quantities (Burdzovic Andreas & Brunborg, 2022a) but also lowered sports participation (Burdzovic Andreas & Brunborg, 2021, 2022b) among youth from this sample during the initial pandemic year. We attempted to account for the unforeseen pandemic event by preserving the calendar metric and by controlling for a range of relevant covariates in our models − including the time-varying levels of COVID-19 worries. We know that these worries varied as a function of community-level infection rates and, indirectly, containment measures which included closures of sports venues and alcohol sales outlets (Burdzovic Andreas & Brunborg, 2021, 2022b). Thus, our

results should be considered in light of the possibility that the pandemic disrupted normative developments in both alcohol use and sports participation in yet to be fully understood ways. Nevertheless, we believe that our results remain highly relevant, as they underscore the protective role of sports participation during middle school years and well before the pandemic conditions. Thirdly, we did not explore mediating mechanisms through which either family-specific negative life events or sports participation may exert influence on adolescent drinking. In the case of negative life events, these may include parental distress and hostility, or decreased supportive and increased harsh parenting (Diggs & Neppl, 2018; Hardaway & Cornelius, 2014). In the case of sports participation, these may include drinking behaviors of the athletic peers and other social learning mechanisms (Vest & Simpkins, 2013), parental monitoring (Kristjansson et al., 2010), or general promotion of psychosocial health (Eime et al., 2013). Finally, the study relied on adolescent self-reports only, thus possibly suffering known yet unavoidable biases and measurement errors embedded in this methodology. Thus, the current findings should be interpreted in light of these limitations, while future research may seek to address them in greater detail.

2.3.6 Conclusions

Family-specific negative life events constitute a risk factor for greater alcohol use during early adolescence. Participation in sports may be a protective factor against alcohol use during the same developmental period for youth experiencing multiple negative events in their families. Thus, prevention efforts aiming to reduce alcohol use among middle school students may utilize organized sports as a potential resource early on.

2.4 Study IV: Can high-intensity interval training improve health outcomes among people with substance use disorders? A systematic review and preliminary meta-analysis[4]

2.4.1 Abstract

Background and aim: Substance use disorders (SUDs) are marked by high relapse rates and comorbid somatic and mental health issues. High-intensity interval training (HIIT), a time-efficient form of exercise, may offer potential benefits in addressing these issues. The aim of this systematic review and preliminary meta-analysis was to evaluate the health benefits, safety and adherence of HIIT interventions in individuals with SUDs.

Methods: Systematic searches were conducted in PubMed, Embase, Cochrane Library, Web of Science Core Collection, PsycINFO, ClinicalTrials.gov and the ICTRP for intervention studies published from inception until March 12, 2024. Study quality was assessed using the EPHPP tool. Preliminary meta-analyses were conducted if ≥ 3 studies reported data on the outcomes of interest. To compare the HIIT and control groups, mean differences (MDs) were calculated as effect sizes for outcomes measured on the same scale, while Hedges' g was used for outcomes measured on different scales.

Results: Six intervention studies (N = 327 at baseline; 99% men) were included, comprising one non-randomised and five randomised controlled trials. Preliminary meta-analyses indicated a moderate increase in VO2max after 2–4 months (3 studies; MD = 2.06 ml/kg/min, 95% CI = 1.02 to 3.09, $p < 0.001$) and a modest reduction in drug craving after 3 weeks to 6 months (3 studies; Hedges' g = -0.31, 95% CI = -0.59 to -0.03, $p < 0.05$) in the HIIT groups, compared to control groups. No evidence for heterogeneity among the included trials was found. Data on other outcomes were insufficient or inconsistent, limiting interpretability. The included trials were rated as being of low to moderate quality.

Conclusion: HIIT may improve cardiorespiratory fitness and reduce drug craving among individuals with SUDs, potentially improving treatment outcomes and lowering the risk of relapse. Further research is needed to assess its impact on other outcomes

[4] **Published as:** Türkmen, C., Martland, R., Grilli, M., Stubbs, B., Roessler, K. K., & Hallgren, M. (2024). Can high-intensity interval training improve health outcomes among people with substance use disorders? A systematic review and preliminary meta-analysis. Mental Health and Physical Activity, 27, 100622. https://doi.org/https://doi.org/10.1016/j.mhpa.2024.100622

(e.g., cognitive functioning and mental health), and to compare its effectiveness with other forms of exercise. Supported HIIT interventions are shown to be feasible and safe among inpatients, but studies involving outpatients and non-treatment seekers are also needed.

2.4.2 Background

Substance use disorders (SUDs) remain a prevalent public health issue, with approximately 283 million global cases of alcohol use disorders alone reported in 2018 (World Health Organization, 2018). SUDs are among the major mental disorders with the highest mortality risk, accounting for approximately 9–24 years of life lost (Chesney et al., 2014). In addition, substance use contributes substantially to the global burden of disease (GBD 2016 Alcohol and Drug Use Collaborators, 2018), and much of this burden is attributed to its effect on other health outcomes such as injury as well as cardiovascular and infectious diseases (Larney et al., 2017; Rehm et al., 2017). Given the substantial individual and societal costs, there is a need to further improve intervention and prevention programmes.

While psychosocial interventions (e.g., contingency management, cognitive behavioural therapy) can yield moderate treatment effects for SUDs (Dutra et al., 2008), relapse remains a key challenge in SUD treatment, affecting as many as 37–75% of patients following treatment (Alterman et al., 2000; Andersson et al., 2019; Gossop et al., 2002). Various risk factors for a heightened risk of relapse have been identified, such as younger age, polysubstance use, psychiatric comorbidities, treatment non-completion as well as drug craving (Andersson et al., 2019; Domino et al., 2005; Kabisa et al., 2021; Vafaie & Kober, 2022). In addition, individuals with SUDs frequently experience somatic health issues (e.g., liver disease, tuberculosis, ischemic stroke), reduced quality of life, and cognitive impairments, which are not directly addressed by psychosocial and psychopharmacological treatments (Bruijnen et al., 2019; Holst et al., 2017; Skarstein et al., 2023; Vederhus et al., 2016).

To address these shortcomings, alternative treatments are needed (Søgaard Nielsen et al., 2016). Physical exercise, a structured and planned subset of physical activity, has emerged as a promising adjunct treatment (Roessler, Bilberg, et al., 2017; Søgaard Nielsen et al., 2016). It can help reduce substance use, promote abstinence, ease withdrawal symptoms, improve cognitive functioning and quality of life, and

reduce anxiety and depression among individuals with SUDs (Giménez-Meseguer et al., 2020; Piché et al., 2023; Wang et al., 2014; Zheng et al., 2024). In addition, growing evidence indicates that moderate-intensity exercise can reduce craving for various drugs such as alcohol, cannabis and cigarettes (Brown et al., 2016; Buchowski et al., 2011; Haasova et al., 2013; Hallgren et al., 2021; Ussher et al., 2004). This makes it a promising candidate as a relapse prevention strategy due to the significant predictive value of drug craving for relapse (Vafaie & Kober, 2022). These findings align with recent qualitative data showing that physical activity is perceived by individuals with SUDs as protective against relapse by offering an alternative “high” and enhancing emotion regulation (Fagan et al., 2021; Piché et al., 2023). Recent evidence also suggests that reductions in anxiety may partly explain the beneficial effects of higher exercise intensity on craving (Pechtl et al., 2024).

Despite these benefits, physical activity levels tend to be low among individuals with SUDs, with a recent study indicating that 51% of 1293 patients in treatment for SUDs reported not meeting physical activity guidelines (Churchill et al., 2024). Another study has found that patients with alcohol use disorder tend to be less physically active and have lower physical fitness than matched healthy controls (Vancampfort et al., 2019). Importantly, low physical fitness as well as a lack of time, among other factors, have been identified as motivational barriers for engaging in physical activity among individuals SUDs (Horrell et al., 2020; Nock et al., 2023).

To overcome these barriers, high-intensity interval training (HIIT) has been proposed as a time-efficient form of exercise with comparable health benefits to less intensive exercise methods despite requiring less time commitment (Gillen & Gibala, 2014). Indeed, one notable advantage of HIIT compared to, for example, steady state aerobic exercise (e.g., long distance running) is that the same total work and frequency of HIIT has been shown to be significantly more effective in improving cardiorespiratory fitness (Helgerud et al., 2007). Importantly, the time efficiency and constantly changing stimulus of HIIT are perceived by some as more enjoyable than moderate-intensity continuous training (MICT), which may foster exercise adherence (Thum et al., 2017). Recent meta-analyses have also demonstrated that HIIT improves a range of health outcomes (e.g., cardioresipratory fitness, mental health) in the general population and among individuals with mental and physical illnesses (Martland et al., 2022; Martland et al., 2020). Yet, HIIT remains relatively understudied in the context of SUDs. Existing evidence suggests that HIIT is a feasible intervention for inpatients with SUDs

(Flemmen et al., 2014). Despite this initial work, there is a lack of clarity in the current body of evidence on the health benefits, safety, and adherence rates of HIIT within SUD populations. The current systematic review and preliminary meta-analysis aimed to address these research gaps.

2.4.3 Methods

This systematic review was pre-registered on PROSPERO (registration number CRD42024519702), and reported following the recommendations of the updated PRISMA guidelines for systematic reviews and meta-analyses (Page et al., 2021).

2.4.3.1 Definition of HIIT

HIIT was defined as involving several short bouts of high-intensity movements intended to reach ≥85% HR_{peak}/≥80% VO_{2peak}, alternated with brief active periods (≤5 min) of continued but less intensive movements (Weston et al., 2014). While this definition served as a guidance for determining whether HIIT was adequately implemented, the threshold for HR_{peak} and VO_{2peak} was flexible for purposes of inclusion. However, if substantial differences were observed across the studies, the findings were discussed in light of this heterogeneity.

2.4.3.2 Search strategy

The following databases and registers were systematically searched from inception until March 12, 2024: PubMed, Embase, Cochrane Library, Web of Science Core Collection, PsycINFO, ClinicalTrials.gov and the International Clinical Trials Registry Platform (ICTRP). No restrictions were applied. The search was complemented by screening the reference lists of included studies and of a relevant systematic review on HIIT in people with mental illnesses (Martland et al., 2020). Principal investigators of unpublished studies were contacted, with a two-week interval between each attempt, to obtain data. The full search strategy for each database and register is provided in **Supplement 1**.

2.4.3.3 Study selection and eligibility criteria

Two reviewers (C.T. and R.M.) independently screened the titles and abstracts of all studies. Full-text reports of potentially relevant studies were retrieved and checked for eligibility. We included intervention studies (randomised controlled trials, RCTs; non-

randomised controlled trials, NRCTs; pre-post-test single-arm trials) assessing HIIT in any setting or age range. The population of interest was individuals diagnosed with any type of SUD according to standardised diagnostic criteria such as Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (American Psychiatric Association, 2013) or International Classification of Diseases, 10th revision (World Health Organization, 2004). For studies that included a control group, the type of control group (e.g., usual care, psycho- or pharmacotherapy, other exercise intervention) did not impact study eligibility. HIIT could be delivered as monotherapy or in conjunction with other treatments (e.g., regular care, pharmacotherapy). Any form of HIIT exercise (e.g., treadmill activity, body-weight exercises), regardless of its duration (i.e., acute and long-term), was eligible. Discrepancies regarding study eligibility were resolved by consulting a third reviewer (M.H.).

2.4.3.4 Primary and secondary outcomes

The following primary outcomes were selected based on a previous systematic review and meta-analysis of HIIT in people with mental illnesses (Martland et al., 2020): 1) cardiorespiratory fitness, namely maximal oxygen uptake (VO_{2max}), 2) drug craving, 3) cardiometabolic risk factors (e.g., total cholesterol, body mass index, blood pressure), 4) inflammatory markers as biomarkers for cardiovascular health (e.g., high-sensitivity serum C-reactive protein (hs-CRP)), 5) strength and endurance, 6) psychological outcomes such as cognitive functioning (e.g., behavioural control, working memory) and emotion regulation, and 7) mental health outcomes such as depression, anxiety and insomnia.

Secondary outcomes included 1) safety (adverse events), 2) feasibility and acceptability, including enjoyment and adherence, 3) dropout rates, and 4) quality of life.

2.4.3.5 Data extraction

Three reviewers (C.T., B.S. and M.H.) extracted data from the included studies for the following variables: authors, publication year, country of origin, study design, sample size, percentage of men at baseline, participant demographics, intervention descriptions (including control interventions), information regarding primary and secondary outcome measures, results, adverse events, adherence rates, and conclusions of the studies. Data for relevant outcomes that were reported by at least three studies were extracted using a pre-defined extraction sheet for the meta-

analyses. If multiple measurement timepoints were reported, we selected the timepoint that most closely matched those from other studies. For example, if two studies reported data for an outcome at 2 and 3 months, and another study reported data at 4 and 8 months, we selected the 4-month data of the latter study to reduce substantial heterogeneity and improve interpretability. Relevant data which were not reported in the required format were requested from the study authors.

For each study, we also reported data regarding intervention description using the Template for Intervention Description and Replication (TIDieR) (Hoffmann et al., 2014) and the Consensus on Exercise Reporting Template (CERT) (Slade et al., 2016) to ensure complete reporting. The following details of the intervention were covered: materials used, details of the intervention provider, location, modes of delivery, individual modifications, rules for exercise progression, as well as details regarding the intensity, duration and frequency of the intervention. When an item appeared in both the TIDieR and CERT checklists, it was only reported once in the TIDieR checklist and thus not duplicated in the CERT checklist.

2.4.3.6 Methodological quality assessment of studies

Two reviewers (C.T. and R.M.) independently assessed the methodological quality of the included studies using the Effective Public Health Practice Project (EPHPP) quality assessment tool. The following domains were assessed: (A) selection bias, (B) study design, (C) confounders, (D) blinding, (E) data collection methods, and (F) withdrawals/dropouts. Each domain was rated as “weak”, “moderate” or “strong”. A global rating for each study was determined by assessing the number of weak ratings across the domains. A strong global rating was given if there were no weak ratings, a moderate global rating if there was one weak rating, and a weak global rating if there were two or more weak ratings. Discrepancies between the reviewers were resolved by consensus or through consultation of another reviewer.

2.4.3.7 Data synthesis

Meta-analyses were performed if at least three studies reported data on the outcomes of interest. Provided that an outcome was measured on the same scale, mean differences and 95% confidence intervals (95% CI) were calculated to indicate differences between the HIIT and control groups. Hedges’ g was used as a measure of effect size in case of different measurement scales. It was computed as the size of the difference between the mean scores of the HIIT group and control group at each

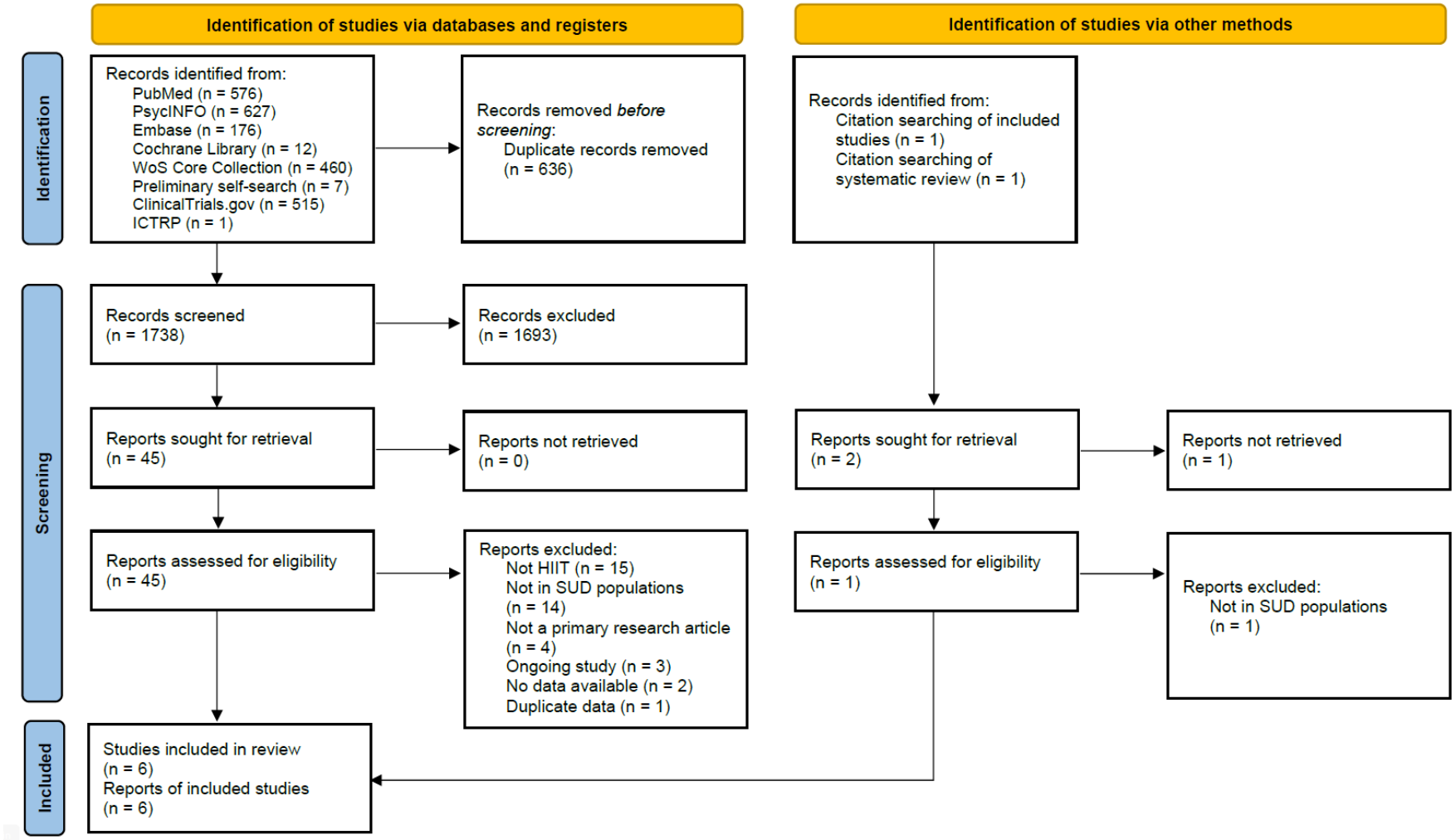
time point (i.e., post-treatment, first follow-up), divided by the pooled standard deviation. For the analyses, we used intention-to-treat data where available. We calculated effect sizes using the post-means only, instead of a change score between baseline- and post-means. Based on the assumption that there was a distribution of true effect sizes rather than a single true effect size, a random-effects model was used when pooling the primary studies, in line with the recommendation by Borenstein et al. (2010). The degree of heterogeneity between the studies was assessed using I^2, which describes the proportion of total variation in estimated effect sizes attributable to differences among the studies. An I^2 value of 50% or higher is commonly considered an indicator of substantial heterogeneity. An assessment of publication bias was not considered feasible due to the limited number of included trials ($n < 10$) (Sterne et al., 2011). All analyses were conducted using the meta package (Balduzzi et al., 2019) in the statistical software environment R, version 4.3.3 (R Core Team, Vienna, Austria).

2.4.4 Results

2.4.4.1 Search results

Figure 9 provides an overview of the study selection. The systematic search yielded 1738 records upon deduplication. Of these, 47 records (including two records from citation searching) were considered potentially relevant and reviewed at the full-text level. Overall, six intervention studies were included (N = 327 at baseline; 99% men), including four studies in individuals with stimulant use disorder (methamphetamine) (Li et al., 2024; J. Tan et al., 2023; Yan-Guang et al., 2021; Yin et al., 2022), one study in individuals with opioid use disorder (Dürmüs et al., 2020), and one study in individuals with various SUDs (Flemmen et al., 2014). A list of all studies excluded from the systematic review after full-text screening with reasons for exclusion is provided in **Supplementary Table 1**.

Figure 9. PRISMA flow diagram.



Note. *Note.* HIIT, high-intensity interval training; ICTRP, International Clinical Trials Registry Platform; SUD, substance use disorder; WoS Core Collection, Web of Science Core Collection.

2.4.4.2 Characteristics of included studies

Details of the sample and intervention characteristics, and main findings of each study are summarised in **Table 6**, **Table 7**, respectively. Five studies used an RCT-design (Flemmen et al., 2014; Li et al., 2024; J. Tan et al., 2023; Yan-Guang et al., 2021; Yin et al., 2022), while one study followed an NRCT design (Dürmüs et al., 2020). The duration of the HIIT intervention ranged from a single session (Yin et al., 2022) to 12 months (Yan-Guang et al., 2021). Two RCTs used other forms of exercise as active control groups, including MICT (Yan-Guang et al., 2021) and tai chi (Yin et al., 2022). One study did not provide details on the control group (Dürmüs et al., 2020). In the remaining studies, the participants in the control group participated in the regular treatment programme (Flemmen et al., 2014; J. Tan et al., 2023) or undertook quiet reading (Li et al., 2024). All HIIT sessions took place in a residential treatment or laboratory setting and were supervised in four long-term studies (Flemmen et al., 2014; Li et al., 2024; J. Tan et al., 2023; Yan-Guang et al., 2021). The exercise protocols included various modes of exercise such as bicycle-based sessions, treadmill workouts, aerobic calisthenics, and combined aerobic and resistance exercises, with session frequencies ranging from a single session to 3 to 5 times weekly, incorporating warm-ups, high-intensity intervals, and cool-downs. The duration of the HIIT training ranged from 17.5 to 60 min. Further details regarding the HIIT interventions are provided in **Supplementary Tables 2 and 3**.

2.4.4.3 Quality of included studies

The methodological quality was primarily limited by a weak rating in the selection bias domain due to a low participation agreement rate prior to randomisation. In addition, there was a lack of detail regarding the method of randomisation, which limited an assessment of how randomisation was implemented, warranting downrating in the study design domain. There was also a lack of blinding of outcome assessors (or a lack of description thereof) as well as a lack of descriptions regarding the extent to which participants were aware of the research question, which warranted downrating in the blinding domain. Two studies (Dürmüs et al., 2020; J. Tan et al., 2023) received a low overall quality rating, while four studies (Flemmen et al., 2014; Li et al., 2024; Yan-Guang et al., 2021; Yin et al., 2022) received a moderate overall quality rating. Further details on the individual domain quality ratings can be found in **Supplementary Table 4.**

Table 6. Study characteristics.

Study	Country	Study Design and Sample Included	Sample Size (Baseline)	Age, mean (SD)	% male	Sample Characteristics	Exercise Intervention	Control Group
Dürmüs et al. (2020)	Turkey	Two-armed controlled study. Male inpatients with opioid use disorder completed 5 sessions of HIIT or control	HIIT = 11; Control = 11	HIIT = 27 (7.3); Control = 27.1 (5.2)	100%	Male inpatients aged 18–45 years diagnosed with opioid use disorder according to DSM-5 criteria. BMI was 21.8 ± 2.2 in the HIIT group and 21.8 ± 2.1 in the control group	Five bicycle-based HIIT sessions over 21 days. Sessions included a 4-min warm-up, and three 30-second bursts of loading at high Intensity interspersed with 4 min of resting on the 30 W pedal.	No details provided.
Flemmen et al. (2014)	Norway	Two-armed RCT. Patients with SUD were randomly assigned to either HIIT or a conventional rehabilitation control group. Effects of exercise on physical and mental health parameters were measured.	HIIT = 12; Control = 12	HIIT = 33 (11); Control = 31 (8)	81.25% *	Health status: All participants had a diagnosis of SUD according to ICD-10. All participants were long-term residents in a substance abuse treatment clinic, due to abuse of illegal drugs including heroin, benzodiazepines, amphetamines and cannabis.	Duration: 8 weeks Frequency: exercise performed 3 times weekly Mode of exercise: treadmill exercise Supervised: yes Intervention provider: not reported Exercise protocol: 4 X 4-min of high aerobic intensity exercise conducted at 90–95% of HRmax, interspersed by 3-min recovery periods conducted at 70% HRmax. Session length: 25 min	The control group participated in ballgames, yoga, stretching, outdoor walking, low resistance strength training, ceramics, TV games, and card games as did the HIIT group. Additionally, within the same time period as the HIIT group performed HIIT sessions, the patients allocated to the control group participated in a self-elected activity

Study	Country	Study Design and Sample Included	Sample Size (Baseline)	Age, mean (SD)	% male	Sample Characteristics	Exercise Intervention	Control Group
							excluding warm-up and cool-down. Additional clinic treatment program: All participants also participated in ballgames, yoga, stretching, outdoor walking, low resistance strength training, ceramics, TV games, and card games	among the offered sports or games in the clinical treatment program. These activities reached an estimated intensity level of <70% of HRmax.
Li et al. (2024)	China	Two-group parallel RCT: aerobic HIIT versus control. Participants were those with substance dependence (methamphetamine).	HIIT = 30; Control = 24	HIIT = 29 (4); Control = 28 (5)	100%	Sixty adults with clinician-diagnosed substance use disorder (methamphetamine) were recruited from a compulsory detoxification education and correction centre in Chongqing, China. The following criteria were applied: (1) age 18-45 years; (2) elementary school education or above; (3) SUD assessed by structured diagnostic interview (DSM-5); (4) currently imprisoned and > three months of forced rehabilitation; (5) no congenital heart or	The aerobic exercise group received high-Intensity intermittent aerobic calisthenics intervention (75%–85% HRmax) 40 min/time, three times a week. HIIT sessions included a 5-min warm-up, 30 min of aerobic calisthenics using bodyweight (3 different exercises, e.g., sit ups, leg lifts, jumps) with 1-min rest between each exercise, and a 5-min recovery.	The control group did not participate in the exercise intervention or other forms of physical activity, and instead undertook quiet reading (40 min) in a separate room.

Study	Country	Study Design and Sample Included	Sample Size (Baseline)	Age, mean (SD)	% male	Sample Characteristics	Exercise Intervention	Control Group
						cardiovascular disease; (6) no medical contraindications against exercise		
Tan et al. (2023)	China	Two-group parallel RCT: HIIT versus control. Participants were those with substance dependence (methamphetamine).	HIIT = 30; Control = 30	HIIT = 32 (6); Control = 31 (5)	100%	All participants were in compulsory isolation, and detoxification in the Hunan Province, China. Criteria: (1) methamphetamine dependence based on diagnostic interview (DSM-5); (2) not on other drugs; (3) no history of mental illness; (4) no history of musculoskeletal, cardiovascular, cerebrovascular, or immune disease; (5) no history of major trauma and surgery; (6) non-regular exerciser (<30 min/day).	HIIT was done 4 x weekly (60-min sessions) for 8 months. Ten-min warm-up, 40 min of combined aerobic and resistance exercise, and 10 min of stretching and relaxation exercises. Intensity = 76–96% of HRmax (average HR was 150–170 bpm while training and 120–140 during recovery).	Routine rehabilitation therapy.
Yan-Guang et al. (2021)	China	Two-group parallel RCT: HIIT versus moderate-intensity	HIIT = 60; Control = 60	HIIT = 33 (4); Control = 32 (5)	100%	Male amphetamine-type stimulant (ATS) dependent individuals. Criteria: (1) age 18–40 years; (2) Methamphetamine	HIIT was done 3 x weekly (60-min sessions) for 12 months. Ten-min warm-up, 40 min of combined aerobic	The MICT group was trained with Tai Chi, mind-body exercise and recreational activity. The

Study	Country	Study Design and Sample Included	Sample Size (Baseline)	Age, mean (SD)	% male	Sample Characteristics	Exercise Intervention	Control Group
		continuous training.				dependence using DSM-IV-based interview; (3) prior treatment >1 year; (4) no serious medical or mental illness; and (5) educational attainment ≥ primary school.	and resistance exercise, and 10 min of stretching and relaxation exercises. Intensity = 80–85% of HRmax (average HR was 150–160 bpm while training and 130–140 during recovery).	average HR during exercise was maintained at 105–125 beats per minute (55–65% of HRmax).
Yin et al. (2022)	China	Two-group parallel, randomized acute exercise trial: HIIT versus Tai Chi	HIIT = 23; Control = 24	HIIT = 32 (4); Control = 31 (5)	100%	Methamphetamine dependent adult males receiving treatment in a compulsory drug rehabilitation program. Criteria: (1) age 18–40 years, (2) met the DSM-IV criteria for SUD; (3) treatment duration >1 year, (4) no serious mental illness, and (5) completed primary school or a higher level of education.	HIIT: 5-min warm-up, 20 min of HIIT (55–75% HRmax) and a 5 min cool-down. Five cycles of 2 min of running at 85–95% HRmax (estimated as 220 - age) separated by 2 min of self-paced walking	Traditional Tai Chi for 30 min.

Note. HIIT, high-intensity interval training; HRmax, maximum heart rate; MICT, moderate-intensity continuous training; SUD, substance use disorder;

*based on study completers (not on baseline sample)

Table 7. Primary and secondary outcomes, adverse events, adherence and conclusions of studies.

Study	Primary Outcome Measures	Secondary Outcome Measures	Primary Outcomes	Secondary Outcomes	Adverse Events	Adherence	Conclusions
Dürmüs et al., (2020)	Depression severity (Hamilton Depression Rating Scale), anxiety severity (Hamilton Anxiety Rating Scale), drug craving (Substance Craving Scale), serum cortisol, and cytokines	N/A	Comparison of the pre- and post-treatment scores of the two groups indicated a significant reduction in the HIIT group for depression severity ($p < 0.001$), anxiety severity ($p = 0.021$) and craving ($p = 0.001$). A significant increase was observed in the post-treatment IGF-1 level of the HIIT group, compared to the control group ($p = 0.003$). No differences were observed between the cortisol, IFN-γ and IL-17 levels of the HIIT and control groups.	N/A	One participant incurred muscle injury outside the treatment program; treatment-related adverse events were not reported.	Five of the 11 HIIT participants completed the full program; others dropped out due to personal reasons, beta agonist therapy, and non-exercise related muscle injury.	HIIT may be a beneficial adjunctive treatment in inpatients with opioid use disorder.
Flemmen et al., (2014)	VO2max, velocity and inclination at VO2max, work economy, HR at work economy, depression and anxiety severity (Hospital Anxiety and Depression questionnaire), and insomnia severity (Insomnia Severity Index).	N/A	Physical health: VO2max (ml · min 1 ·kg 1) increased significantly by 15 ± 7 % following HIIT (pre 42.3 ± 7.2, post 48.7 ± 9.2, $p < 0.01$). This improvement was significantly ($p < 0.01$) greater than that seen in the control group where no improvement was observed (pre 41.8 ± 12.3, post 42.6 ± 12.1). There was an increase in velocity and inclination at VO2max from 9.2 ± 2.3 km · h 1 and 5.6 ± 1.1% at pre-test to 9.3 ± 2.2 km · h 1 and 8.3 ± 2.4% at post-test in the HIIT group and no change in the control group. There were no significant changes in work economy in either	N/A	None of the participants reported any problems or discomfort following training, other than "normal strain" following HIIT.	Of the 12 participants in the HIIT group, 3 dropped out: 2 withdrew due to personal reasons and one for unknown reasons. Of the 12 participants in the control group, 5 dropped out, all due to unknown reasons. The SUD patients that completed the training period carried out 22 ± 1 (out of 24) of the training sessions.	HIIT improves aerobic power in patients with SUDs.

Study	Primary Outcome Measures	Secondary Outcome Measures	Primary Outcomes	Secondary Outcomes	Adverse Events	Adherence	Conclusions
			HIIT or control groups, however, the HR at work economy workload decreased significantly ($p < 0.05$) by 9 ± 12% in the HIIT group (pre 116 ± 17, post 105 ± 18), although no significant between-group difference was observed ($p = 0.158$). Mental health: There was a significant decrease in depression severity following HIIT (pre 8.5 ± 4.8, post 5.3 ± 3.9, $p < 0.05$), whereas there was a significant decrease in anxiety severity in the control group, (pre 9.1 ± 5.3, post 6.3 ± 3.4, $p < 0.05$), although no significant between-group differences were observed. No significant differences in insomnia severity were observed.				
Li et al., (2023)	Blood pressure (BP) including systolic (SBP) and diastolic (DBP), heart rate variability (HRV), respiratory function including VO2max, AT, VO2/HRpeak, and MVV.	N/A	BP: Throughout the intervention, there were no significant differences in SBP or DBP between the HIIT and control groups. HRV: Compared to the control group, the HIIT group had significant increases in SDNN in week 8 and 12 ($p = 0.000$), RMSSD in week 8 and 12 ($p = 0.005$) and HFn in week 12 ($p = 0.009$), and a significant reduction in LFn in week 12 ($p = 0.009$). Respiratory function: After the intervention, there was a significant increase in VO2max ($p = 0.001$), VO2/HRpeak ($p = 0.018$) and AT	N/A	Not reported	Not reported	HITT improves HRV and cardiorespiratory fitness, but does not significantly impact blood pressure, compared to control.

Study	Primary Outcome Measures	Secondary Outcome Measures	Primary Outcomes	Secondary Outcomes	Adverse Events	Adherence	Conclusions
			(p = 0.004), but not in MVV, in the HIIT group, compared to the control group				
Tan et al., (2023)	BMI, heart rate and blood pressure, muscle strength (gripping device + push-ups), Explosive power (quadrant jump), VO2max, balance (one-legged test), flexibility (sitting bend), reaction time (button press test), health-related quality of life (36-Item Short Form Survey) aggregated into physical and mental	Drug craving (Visual Analogue Scale)	Compared to the control group, significant reductions were found in the HITT group at 8 months on: body weight ($p < 0.001$), waist circumference ($p < 0.001$), body fat % ($p < 0.001$), heart rate ($p < 0.05$), DBP ($p < 0.01$), reaction time ($p < 0.001$), sleep quality ($p < 0.001$), total cholesterol ($p < 0.001$), triglycerides ($p < 0.001$), blood sugar ($p < 0.001$). VO2max ($p < 0.05$), grip strength ($p < 0.05$), balance ($p < 0.001$), flexibility ($p < 0.001$), explosive strength ($p < 0.001$), push-ups ($p < 0.001$), physical composition summary ($p < 0.001$), and mental composition summary ($p < 0.001$) significantly increased (improved) at 8 months.	Compared to the control group, drug craving significantly decreased after 8 months in the HIIT group ($p < 0.001$).	Two patients (6.7%) withdrew due to injuries.	Not reported	Eight months of HIIT can improve physical health and health-related quality of life of men with substance use disorders, and reduce the desire for drugs.

Study	Primary Outcome Measures	Secondary Outcome Measures	Primary Outcomes	Secondary Outcomes	Adverse Events	Adherence	Conclusions
	composition summaries, sleep quality (Pittsburgh Sleep Quality Index), total cholesterol, triglycerides, and blood sugar.						
Yan-Guang et al., (2021)	Blood pressure and physical fitness (push-up, flexibility, balance, BMI, grip strength, reaction time).	Drug craving (Visual Analogue Scale)	Compared to continuous aerobic exercise, no significant group differences were seen at follow-up.	Compared to continuous aerobic exercise, no significant group differences were seen at follow-up.	Not reported	Not reported	No group differences, but positive within-group changes in blood pressure, physical fitness, and craving.

Study	Primary Outcome Measures	Secondary Outcome Measures	Primary Outcomes	Secondary Outcomes	Adverse Events	Adherence	Conclusions
Yin et al., (2022)	Cognitive functioning (Go-no go task, Stroop).	N/A	Larger pre-post exercise improvements in accuracy (Go, no-go test) in the HITT group compared to Tai Chi ($p < 0.05$).	N/A	None	N/A (single session)	Both Tai Chi and HIIT can promote inhibitory control in individuals with SUD. Compared with Tai Chi, the HIIT group showed greater improvements in response accuracy.

Note. AT, anaerobic threshold; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; HFn, high-frequency power in normalised units; HIIT, high-intensity interval training; HRV, heart rate variability; IFN-γ, interferon-gamma; IGF-1, insulin-like growth factor 1; IL-17, interleukin-17; LFn, low-frequency power in normalised units; MVV, maximal voluntary ventilation; RMSSD, root mean square of successive differences; SBP, systolic blood pressure; SDNN, standard deviation of normal-to-normal intervals; SUD, substance use disorder; VO_2/HR_{peak}, peak oxygen pulse; VO_{2max}, maximal oxygen uptake.

[a]Reported as secondary outcomes in the respective study, and not according to the list of secondary outcomes in the present review.

2.4.4.4 Outcome results

A summary of the primary and secondary outcome measures can be found in **Table 7**. For conciseness, only outcomes that were reported at least twice are narratively summarised below.

Primary outcomes

Cardiorespiratory fitness

VO_{2max} (ml/kg/min) was used as a measure of cardiorespiratory fitness, for which three RCTs reported data (Flemmen et al., 2014; Li et al., 2024; J. Tan et al., 2023). A preliminary meta-analysis using mean differences was performed (see **Figure 10a**), which indicated a greater effect of HIIT on VO_{2max} by 2.06 ml/kg/min after 2–4 months, compared to the control groups (MD = 2.06, 95% CI = 1.02–3.09, $p < 0.001$). There was no evidence of heterogeneity ($I^2 = 0\%$; $\chi^2 = 0.60$, $p = 0.74$).

Drug craving

Two RCTs (J. Tan et al., 2023; Yan-Guang et al., 2021) and one NRCT (Dürmüs et al., 2020) reported data on drug craving using different scales. A preliminary meta-analysis was performed using Hedges' g as a measure of effect size (see **Figure 10b**), which indicated lower drug craving in the HIIT groups, compared to the control groups, after 3 weeks to 6 months (Hedges' g = −0.31, 95% CI = −0.59 to −0.03, $p < 0.05$). Of note, the effect size was smaller in the RCT by Yan-Guang et al. (2021), in which the control group was exposed to an exercise intervention of moderate intensity (MICT). No evidence of heterogeneity was found ($I^2 = 0\%$; $\chi^2 = 0.90$, $p = 0.64$).

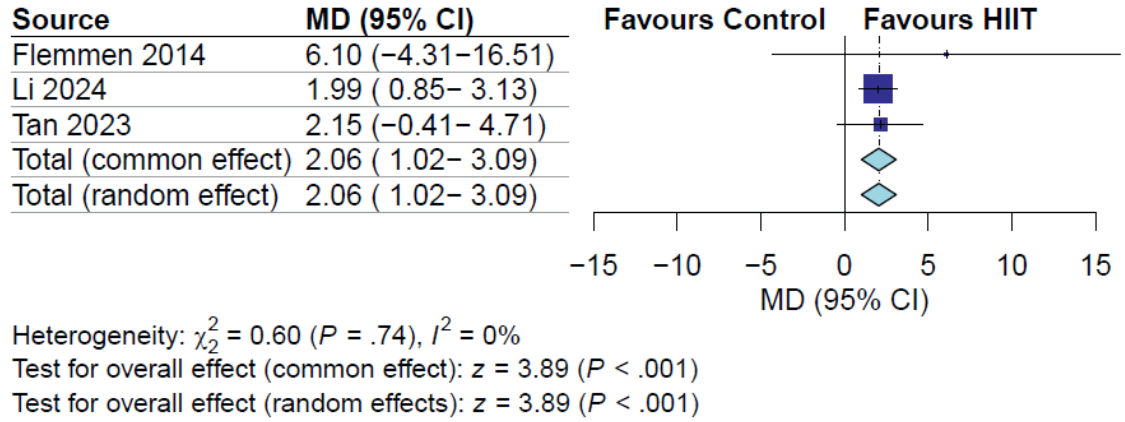
Blood pressure

Three RCTs (Li et al., 2024; J. Tan et al., 2023; Yan-Guang et al., 2021) reported both systolic blood pressure (SBP) and diastolic blood pressure (DBP). Whereas J. Tan et al. (2023) found a significant group difference in DBP between the HIIT group (baseline = 75.50 ± 7.23 mmHg; 8 months = 73.04 ± 6.24 mmHg) and control group (baseline = 73.82 ± 7.29 mmHg; 8 months = 74.82 ± 8.91 mmHg) after eight months, Li et al. (2024) and Yan-Guang et al. (2021) did not find significant group differences after three and twelve months, respectively. As one RCT (Li et al., 2024) did not report

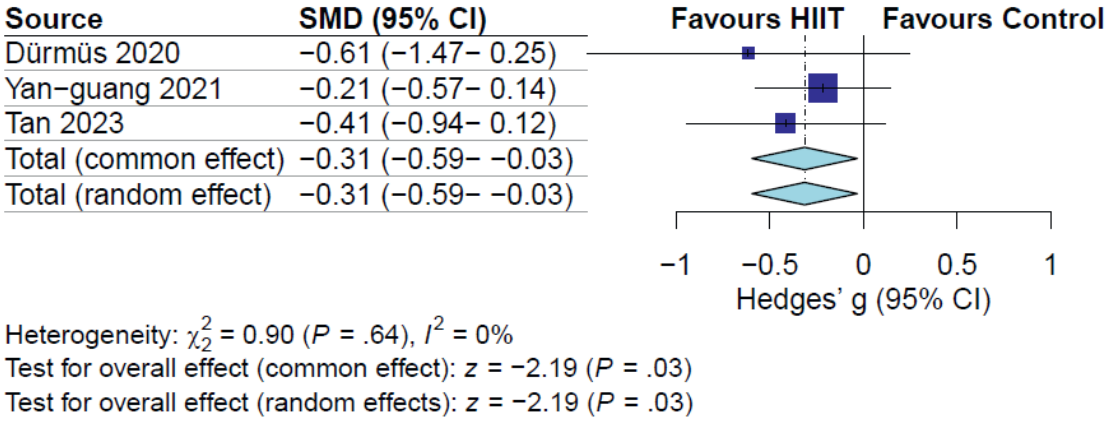
means and standard deviations for post-treatment, a meta-analysis was not undertaken.

Figure 10. Forest plots of outcomes with data from at least three studies.

a)



b)



Note. a = VO_{2max} (ml/kg/min); b = drug craving; MD, mean difference; SMD, standardised mean difference.

Strength and endurance

Two RCTs (J. Tan et al., 2023; Yan-Guang et al., 2021) reported data on muscle strength (grip strength, push-ups). While both trials reported improvements in grip strength and push-ups from baseline to 8–12 months in the HIIT group, only J. Tan et

al. (2023) found significant group differences favouring HIIT, compared to a regular care control group, for both outcomes. It should be noted that Yan-Guang et al. (2021) utilised a moderate-intensity exercise intervention as a control group.

Depression and anxiety

One RCT (Flemmen et al., 2014) and one NRCT (Dürmüs et al., 2020) assessed changes in depression and anxiety. Flemmen et al. (2014) reported a significant decrease in depression following the eight-week HIIT intervention, whereas there was a significant decrease in anxiety in the control group post-treatment. No significant between-group differences were observed. Dürmüs et al. (2020) found a significant reduction in both depression and anxiety in the HIIT group, relative to the control group, at post-treatment (three weeks).

Sleep

One RCT (Flemmen et al., 2014) assessed changes in insomnia severity, and found no significant pre-post changes or group difference between the HIIT group and control group after 8 weeks. Another RCT (J. Tan et al., 2023) reported data on sleep quality and found that at post-treatment (8 months), participants in the HIIT group had significantly improved sleep quality compared to the control group ($p < 0.001$).

Secondary outcome results

Adverse events

In one study (Flemmen et al., 2014), patients in the HIIT group did not report any problems or discomfort other than “normal strain”. In another study (J. Tan et al., 2023), two patients (6.7%) in the HIIT group withdrew from the study due to injuries. Dürmüs et al. (2020) and (Yin et al., 2022) did not find any treatment-related adverse events. In the remaining two studies (Li et al., 2024; Yan-Guang et al., 2021), adverse events were not reported.

Adherence and enjoyment

Adherence was documented in two of the six studies. In the NRCT by Dürmüs et al. (2020), five out of eleven participants (45%) in the HIIT group completed the full

programme, while in the RCT by Flemmen et al. (2014), nine out of 12 participants (75%) completed the HIIT programme with a completion of, on average, 22 out of 24 (92%) HIIT sessions. Adherence was not applicable to the RCT by Yin et al. (2022), as only a single session of HIIT was assessed. The remaining trials did not report information on adherence rates. Quantitative or qualitative data on the enjoyment of the HIIT interventions were not reported.

Dropout

Across the long-term studies, the pooled dropout rate was 23.08%. The studies conducted in compulsory detoxification/rehabilitation centres had a lower dropout rate (20%) compared to those conducted in non-compulsory residential treatment settings (39%).

2.4.5 Discussion

The present study aimed to narratively and quantitatively synthesise the health benefits, safety, and adherence rates of HIIT within SUD populations. The present study provides preliminary meta-analytic evidence that HIIT improves cardiorespiratory fitness and reduces drug craving among individuals with SUDs. However, for other outcomes that were narratively synthesised, a paucity of data or inconsistencies regarding the effects of HIIT on these outcomes limit the interpretability.

The findings regarding the benefits of HIIT on cardiorespiratory fitness are consistent with previous meta-analyses on HIIT in healthy adults (Milanović et al., 2015) and in people with mental illnesses (Martland et al., 2020). Most of the evidence in the present meta-analysis stems from individuals with stimulant use disorders whose cardiorespiratory fitness levels have been found to be below average (Stoutenberg et al., 2017). Thus, HIIT may represent a useful adjunct treatment for improving cardiorespiratory fitness in this population. Studies involving moderately to well-trained men suggest that HIIT is superior to other exercise protocols, such as long-distance running and sprint interval training, in improving cardiorespiratory fitness (Helgerud et al., 2007; Hov et al., 2023). Yet, it remains to be established whether these findings apply to clinical populations who may have lower physical fitness. This

is clinically relevant, as cardiorespiratory fitness can reduce cardiovascular and all-cause mortality, and mitigate various somatic health issues (Al-Mallah et al., 2018). Recent evidence also suggests that it predicts greater vagal autonomic activity under stress among people with SUDs (Cabral et al., 2019).

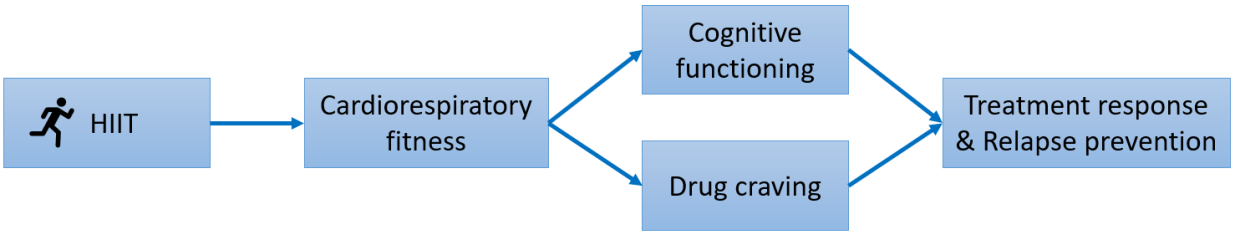
Moreover, the present finding that HIIT has a beneficial effect on drug craving extends previous research demonstrating that moderate-intensity exercise can reduce drug craving (Brown et al., 2016; Buchowski et al., 2011; Haasova et al., 2013; Hallgren et al., 2021; Ussher et al., 2004). Yet, the mechanisms driving reductions in drug craving remain unclear. One potential mechanism may lie in improved cardiorespiratory fitness, which has been associated with lower drug craving in one of the RCTs included in the current review (J. Tan et al., 2023). Another possible mechanism could be the possible mediating role of exercise-induced improvements in mood and anxiety symptoms (Pechtl et al., 2024). Indeed, exercise and drugs have been suggested to activate similar reward circuits in the brain (Lynch et al., 2013). It is possible that exercise could alter reward circuits and reduce craving via a hedonic substitution mechanism that replicates euphoric feelings by activating the mesolimbic dopaminergic reward pathway in a manner similar to drugs (Booher et al., 2020). However, it is unclear whether HIIT represents a more potent hedonic substitution, whereby more pronounced reductions in drug craving can be achieved. Dose-dependent effects of exercise intensity on craving have been explored in Haasova et al.'s (2013) meta-analysis, which found larger effects on cigarette craving when analyses were limited to studies with moderate-intensity exercise. In the present meta-analysis, only one RCT compared the effects of HIIT to moderate-intensity exercise on drug craving, and the added benefit of HIIT was minimal. Overall, these findings suggest that exercise may be a useful relapse prevention strategy in individuals with SUDs, although the underlying mechanisms driving reductions in drug craving as well as the role of exercise intensity warrant further investigation.

While the beneficial effects on cardiorespiratory fitness and drug craving are promising, ongoing studies have taken a particular interest in the effects of HIIT on cognitive functioning (Andreassen et al., 2019; Haberstroh et al., 2022; Menglu et al., 2021). To date, one RCT has demonstrated that a single session of HIIT can improve inhibitory control and response accuracy among individuals with SUD (Yin et al., 2022). Interestingly, evidence from a recent cross-sectional study suggests that

improved cardiorespiratory fitness predicts higher inhibitory control in patients with SUDs (Tavares et al., 2021). Given the potential interplay between cardiorespiratory fitness and cognitive functioning as well as drug craving, a conceptual framework is presented in **Figure 11** to guide ongoing and future research. In brief, it is hypothesised that improved cardiorespiratory fitness mediates improvements in cognitive functioning and reductions in drug craving which, in turn, improve treatment response (most treatments involve cognitive effort) and reduce the risk of relapse. It is important to note that the framework in its present form is limited to the current evidence base. Changes in brain-derived neurotrophic factor (BDNF), a key molecule involved in cognitive functioning (Miranda et al., 2019), should also be probed as a potential mediation pathway, given recent evidence suggesting that HIIT is the best exercise modality for increasing peripheral BDNF levels in adults (Rodríguez-Gutiérrez et al., 2024). Yet, it remains unclear whether this is also applicable to SUD populations. With more available evidence, it will be an important next step to build upon and extend this framework.

Collectively, these preliminary findings suggest that HIIT could serve as a valuable adjunct treatment by potentially exerting protective effects on somatic health, which are largely refractory to psychosocial or pharmacological treatments. HIIT also shows promise as a relapse prevention strategy by reducing drug craving although there is currently no evidence that HIIT is more effective than other forms of exercise in this respect. In addition, there is insufficient evidence that HIIT promotes greater long-term exercise adherence or superior health benefits compared to MICT (Ekkekakis & Biddle, 2023; Ekkekakis et al., 2023), particularly among SUD populations. While a notable advantage of HIIT lies in its time efficiency (Gillen & Gibala, 2014), further high-quality RCTs are necessary, in particular those including alternative forms of exercise as control groups, to determine if and to what extent HIIT may be superior in promoting exercise adherence and improving health outcomes before widespread adoption of HIIT in clinical settings can be recommended.

Figure 11. Conceptual framework: how HIIT may improve treatment response and relapse prevention in individuals with SUDs.



Note. The model proposes serial mediation pathways through which HIIT may reduce the risk of relapse and enhance treatment outcomes. Preliminary meta-analytic evidence from the current study indicates that HIIT improves cardiorespiratory fitness (VO_{2max}) and reduces drug craving in individuals with SUDs. In addition, one study has found that a single session of HIIT results in improved inhibitory control, with greater response accuracy compared to Tai Chi, among individuals with SUD (Yin et al., 2022). In individual studies, improved cardiorespiratory fitness has been associated with higher inhibitory control (Tavares et al., 2021) and lower drug craving (J. Tan et al., 2023) among individuals with SUDs. Therefore, it is hypothesised that improved cardiorespiratory fitness mediates improvements in cognitive functioning and reductions in drug craving which, in turn, improve treatment response and reduce the risk of relapse. Importantly, HIIT may have a differential impact on these outcomes, as existing evidence suggests that HIIT is superior to other exercise protocols in improving cardiorespiratory fitness (Helgerud et al., 2007; Hov et al., 2023). Yet, this remains to be established in individuals with SUDs to elucidate if and to what extent HIIT may serve as a more superior add-on or stand-alone intervention.

2.4.6 Limitations and future directions

Although the present preliminary findings are encouraging, it is important to acknowledge that the evidence base is still in its infancy. The current results must also be considered in light of some limitations.

First, the evidence is limited almost exclusively to men, with only one study (Flemmen et al., 2014) including a small number of women. The current evidence is also limited mostly to patients with stimulant use disorder (methamphetamine), warranting further research on HIIT in other SUDs such as alcohol or cannabis use

disorders, which are among the most prevalent SUDs worldwide (GBD 2016 Alcohol and Drug Use Collaborators, 2018). In addition, most participants were, on average, aged between 27 and 33. Thus, it remains unclear if HIIT is feasible and safe within elderly SUD populations. To improve the generalisability of the current results, future research should strive to include more female participants and assess the feasibility and acceptability of HIIT among older patients with SUDs. More research on prevalent SUDs is encouraged.

Second, information on adherence has been scarcely reported despite its importance for interpreting the results. Such information is also important for the implementation of HIIT in clinical practice, as health benefits are likely to be more notable if patients consistently adhere to HIIT protocols. In addition, further research is warranted to elucidate personal and clinical factors associated with exercise adherence. One study found that higher SUD severity, higher body mass index, psychiatric comorbidity, and lower education can negatively impact adherence among those with alcohol use disorder (Paul Welford et al., 2023). This suggests that additional support or motivational strategies may be necessary for patients with such characteristics. As none of the included studies reported the use of motivational strategies, it remains unclear which motivational aspects may be most effective among patients with SUDs. It may also be useful to identify if and to what extent SUD patients experience HIIT as motivating, especially considering the high intensity that may be perceived as demanding by some people.

Third, the HIIT sessions were limited to residential and laboratory settings, and small sample sizes in two studies. It remains to be established whether HIIT is also a feasible intervention for outpatients with SUDs or non-treatment seekers. As the HIIT sessions were described as supervised in most of the included trials, it is also important to establish whether unsupervised HIIT sessions (e.g., outside the clinic, home-based) are feasible in this population.

Fourth, it is important to note that there was heterogeneity in training regimens and durations across the included studies, making it difficult to reach clear conclusions regarding the optimal HIIT protocol for patients with SUDs. Intervention periods lasting eight weeks are commonly considered an appropriate duration for HIIT (Chapman et al., 2017; Flemmen et al., 2014), which may be used as a guidance. In addition, it has been proposed to administer exercise interventions shortly after treatment initiation

and to provide additional psychosocial support during the early phase (Sari et al., 2017). Future studies are also encouraged to utilise evidence-based HIIT protocols such as the widely used 4 x 4 regimen (for details, see Helgerud et al., 2007).

Lastly, there were some concerns in the methodological quality of the included trials as a result of insufficient reporting. This was particularly evident in areas such as the masking of outcome assessors or participants and the method of randomisation. In addition, attrition presents a challenge that warrants attention in future studies. Across the included long-term studies, the pooled dropout rate was 23.08%. Notably, studies conducted outside of China reported a substantially higher dropout rate of around 39%, compared to approximately 20% within the Chinese studies. The dropout rates from the non-Chinese studies align with a previous meta-analysis indicating that the pooled dropout rate for exercise interventions in alcohol use disorder is approximately 40% (Hallgren, Vancampfort, Giesen, et al., 2017). The regional disparity in dropout rates may be explained by cultural aspects and treatment settings, as all HIIT interventions were carried out in compulsory rehabilitation centres in the Chinese studies. Future studies should carefully document the reasons for dropouts (particularly those that are HIIT-related), and describe the results on an intention-to-treat basis. In addition, these studies should strive to blind outcome assessors to treatment allocation, which presented a potential source of bias in some of the included trials.

2.4.7 Conclusions

Preliminary meta-analytic evidence suggests that HIIT improves cardiorespiratory fitness and reduces drug craving among individuals with substance use disorders, potentially improving treatment outcomes and lowering the risk of relapse. The impact of HIIT on other outcomes such as mental and physical health and cognitive functioning warrants further assessment. Further trials are needed to determine if HIIT offers advantages over other forms of exercise in improving health outcomes, and to identify which patient groups are likely to benefit most from HIIT. While supported HIIT interventions appear to be safe and feasible for inpatients, adherence rates of HIIT have not been well-documented although these are clinically relevant.

3 DISCUSSION

ACE represent an important and costly risk factor associated with short- and long-term physical and mental health consequences, reduced quality of life, and increased rates of drug and alcohol misuse (Gilbert et al., 2009; Madigan et al., 2023; Witt et al., 2019). A notable gap in the literature is the paucity of research on potential protective factors (moderators), the role of the type and timing of ACE, and the pathways through which ACE may contribute to the development and maintenance of ACE-related disorders, particularly AUD (Herzog & Schmahl, 2018).

To address these gaps, the studies included in this dissertation utilized datasets from various populations, including heavy-drinking individuals, patients with AUD (and other SUD), and adolescents. One particular strength is the range of different methodologies that were employed across the studies, encompassing cross-sectional (f)MRI research, longitudinal research, as well as qualitative and quantitative synthesis methods (systematic review and meta-analysis). This diverse approach provides various lines of evidence to extend the existing literature on risk and protective factors underlying the association between ACE and AUD, which are discussed below.

3.1 Integration of current results into existing findings

3.1.1 Inhibitory control: a target for longitudinal research?

Inhibitory control is a key cognitive function that has a bidirectional relationship with excessive alcohol use such that deficits in inhibitory control can both contribute to and result from excessive alcohol use (López-Caneda et al., 2013). ACE can further attenuate such deficits (Hawkins et al., 2021; Lund et al., 2020; Ramey & Regier, 2019; Su et al., 2019), and it is possible that inhibitory control deficits may, at least partially, mediate the relationship between ACE and the development of AUD according to Edalati and Krank's (2016) model of cognitive pathways. Studies I and II build upon this cognitive framework of vulnerability, presenting cross-sectional findings from functional and structural MRI perspectives as well as from a behavioral perspective.

At a structural level, most previous studies have found that ACE-exposed individuals and those with AUD exhibit lower gray matter volume and cortical thickness

in the IFG (Momenan et al., 2012; Pollok et al., 2022; Wiers et al., 2015; Yang et al., 2023). For example, Wiers et al. (2015) have found reduced cortical thickness in the right IFG in those with AUD. The findings from Study I add to these findings by observing similar reductions in the left (rather than right) IFG. However, changes in GMV were not detected in whole-brain analyses or ROI analyses of the amygdala and hippocampus, thus partially supporting the first hypothesis. The results from Study I further showed that greater ACE severity was associated with reduced cortical thickness in the left IFG, but not with alterations in grey matter volume, partially confirming the second hypothesis. The third hypothesis, which predicted an interaction between ACE and AUD on gray matter volume and cortical thickness, was not confirmed. Study I also explored sensitive developmental periods using a machine learning approach. The results suggested that early adolescence may be a sensitive developmental period for the deleterious effects of ACE on the left IFG among individuals with AUD. Specifically, abuse – but not neglect – was associated with reduced cortical thickness in the left IFG, suggesting that the type of ACE may play an important role.

Study II examined the behavioral dimension of inhibitory control in heavy-drinking adults. The findings indicated that higher ACE severity was associated with better inhibitory control, confirming the fifth hypothesis although we did not put forward a specific hypothesis on the direction of the association. This finding appears to be unexpected, as it contrasts with the existing body of literature on maltreated adolescents who have been found to have worse inhibitory control (Kim & Bruce, 2022; van der Bij et al., 2020). However, it aligns with evidence suggesting that inhibitory control issues seem to diminish by late adolescence among trauma-exposed adolescents and those at-risk for substance use (Quach et al., 2020; van der Bij et al., 2020). These findings suggest a complex, possibly developmental stage-dependent, relationship between ACE and inhibitory control. Impaired inhibitory control may be a potent vulnerability factor for ACE-related increases in alcohol use during sensitive developmental periods such as early adolescence in those with early life adversities (Kim & Bruce, 2022). However, by late adolescence and emerging adulthood, increased alcohol use may no longer be a response to early life stress, as indicated by the findings from Study III. Similarly, inhibitory control deficits may subside by this

developmental stage, possibly due to compensatory mechanisms developed throughout adolescence (Quach et al., 2020; van der Bij et al., 2020).

Potential compensatory mechanisms may persist into adulthood, as shown by a recent study which found ACE to be associated with increased activation in inhibition-related brain areas, including the bilateral IFG, among adults, suggesting that ACE may have lasting effects on the neural circuitry underlying inhibitory control (Sacu et al., 2024). However, it is difficult to interpret whether these findings indicated an adaptive effect, as the authors did not find a behavioral correlate, such as higher performance on the task. The results of Study II showed differential activation patterns dependent upon the type of ACE. Specifically, emotional abuse was associated with higher activation in the left IFG during successful inhibition, while emotional neglect was associated with lower activation in the same region, in line with the fourth hypothesis which predicted functional alterations in prefrontal regions. The significance and implications of these activation patterns are not entirely clear; previous studies have found greater activation in the IFG in healthy preadolescents/adolescents during typical development (Chaarani et al., 2021; Rooij et al., 2015; Whelan et al., 2012), suggesting that reduced activation may not be advantageous at a developmental level. Consistent with this, Stinson et al. (2024) found that higher activation in this brain region was associated with reduced impulsivity. In the present heavy-drinking adult sample, the interpretation of the directionality of brain activation remains uncertain. Although the results from the exploratory analyses suggested that greater emotional neglect was associated with both better inhibitory control and lower activation in the left IFG during successful inhibition, it remains uncertain whether neural efficiency underlies this observation.

Taken together, longitudinal research is needed to further elucidate sensitive developmental periods, ACE type-specific effects, and how neural changes underlying inhibitory control issues may contribute to the development of AUD. While the present results emphasize the importance of inhibitory control, other cognitive functions such as attention and working memory should also be probed. Lastly, automatic non-conscious processes (habits) should be carefully considered, given the clinical importance of habit formation in addiction (Everitt & Robbins, 2005).

3.1.2 Early adolescence: a window of opportunity?

As demonstrated by the findings from Study III, early adolescence was the only period in which accumulated family-specific negative life events were associated with increased adolescent alcohol use. During this time, greater participation in organized sports mitigated the impact of these events on alcohol use. Both findings are contrary to Hypotheses 6 and 7 which predicted that these associations would persist over time (over the five-year period). Similarly, the type and timing analyses from Study I, which addressed the exploratory research question, showed that ACE were associated with reduced cortical thickness in an inhibition-related brain region during the same developmental period. Taken together, these findings suggest that early adolescence may be a sensitive developmental period for both the neural and behavioral effects of early life stress, while also being a critical period for the positive influence of sports participation.

Many studies to date have focused on identifying risks in relation to sensitive developmental periods. A recent systematic review of human observational studies has found that, although timing effects of childhood maltreatment on mental health were frequently reported, no consistent sensitive periods of increased vulnerability were identified (Schaefer et al., 2022). Similarly, a recent study by Grauduszus et al. (2024) was unable to replicate earlier findings regarding the effects of maltreatment type and timing on amygdala and hippocampal volumes, further underscoring the inconsistency across studies. Recent evidence also suggests that the effects of negative life events on mental health symptoms, including anxiety and depressive symptoms, are largely consistent across developmental periods (preschool, childhood, adolescence, late adolescence and young adulthood) (Copeland et al., 2024). These recent findings highlight the need for additional research to resolve these discrepancies and refine our understanding of sensitive developmental periods (Barzilay, 2024), with careful consideration of both allostatic load (Hoffman et al., 2024) and resilience mechanisms (Masten et al., 2021).

Future research should shift from focusing predominantly on negative outcomes, a tendency we are inclined toward as humans (Baumeister et al., 2001), to exploring “windows of opportunity”. While much research has centered on identifying “windows of vulnerability” across childhood and adolescence during which brain development and mental health are differentially susceptible to the adverse effects of

ACE, it may be equally fruitful to explore periods where modifiable protective factors can differentially promote resilience processes (e.g., neuroplasticity or increases in BDNF). Shifting the focus towards protective factors could help to reshape how we approach sensitive periods and may be directly translated into prevention strategies. Within the range of modifiable protective factors, sports and exercise have emerged as promising protective factors for alcohol use (disorder) (Halldorsson et al., 2013; Hallgren, Vancampfort, Schuch, et al., 2017).

3.1.3 Physical exercise: potential mechanisms underlying its protective effects

While Study III emphasizes the protective role of sports participation in delaying the onset of hazardous alcohol use related to familiar stressors, it is important to establish a better understanding of the mechanisms to tailor and further improve this resource. Similarly, Study IV highlights the value of HIIT in the treatment of SUD, though understanding the mechanisms behind its beneficial effects is equally important. This chapter will discuss neuropsychological and neurobiological mechanisms through which exercise / sports may exert positive effects on alcohol use, and explore the role of exercise intensity. Social factors, which may interact with these mechanisms, will be explored in the context of prevention in **Chapter 3.4.1**.

3.1.3.1 Neuropsychological and neurobiological mechanisms: the role of exercise intensity

Alcohol craving and mood states

Depressive and anxiety symptoms, which commonly co-occur in patients with AUD, frequently trigger alcohol craving (Davidson & Ritson, 1993; McCaul et al., 2017), a key predictor for relapse in people with AUD (Schneekloth et al., 2012; Sliedrecht et al., 2019). Existing studies show that moderately intense aerobic exercise can reduce alcohol craving among individuals with AUD, with higher pre-exercise craving and lower fitness predicting clinically meaningful reductions in alcohol craving (Brown et al., 2016; Hallgren et al., 2021; Ussher et al., 2004). This evidence extends to higher-intensity exercise, as supported by the meta-analytic results from Study IV, which may

be partly explained by the beneficial effects of higher-intensity exercise on anxiety (Pechtl et al., 2024). Overall, the present body of evidence indicates that aerobic exercise, both of moderate and high intensity, may be a useful relapse prevention strategy.

Evidence from an fMRI study suggests that craving is associated with neural cue reactivity, which can be provoked by alcohol-related cues such as images of alcoholic beverages (Vollstädt-Klein et al., 2012). This reactivity has been observed primarily in the mesocorticolimbic reward system (Vollstädt-Klein et al., 2012). Exercise and alcohol have been suggested to activate similar reward circuits in the brain (Lynch et al., 2013). It is possible that exercise could alter reward circuits and reduce craving via a hedonic substitution mechanism that replicates euphoric feelings by activating the mesolimbic dopaminergic reward pathway in a manner similar to alcohol (Booher et al., 2020). At a neurotrophic level, high-intensity exercise, compared to low- and moderate exercise, has been associated with higher levels of cerebral dopamine neurotrophic factor, a protein with neurotrophic, neuroregenerative and neuroprotective properties (Lotharius et al., 1999; Shirvani et al., 2019).

While positive effects of HIIT on mood and anxiety have been reported in human samples (Borrega-Mouquinho et al., 2021; Brown et al., 2016), it remains unknown whether HIIT may represent a more potent hedonic substitution, by which more pronounced reductions in alcohol craving can be achieved. Further trials assessing the role of the type and intensity of exercise, complemented by alcohol cue reactivity-based neuroimaging paradigms, are needed to better understand the neurobiological mechanisms.

Cognitive functioning

Cognitive impairments are common in individuals with AUD and are associated with relapse (Domínguez-Salas et al., 2016; Stavro et al., 2013). Studies have shown positive effects of acute and chronic HIIT interventions on cognitive functioning among healthy adults (Ai et al., 2021; Mekari et al., 2020). In the context of SUD, a recent RCT has shown that a single session of HIIT can improve inhibitory control and response accuracy in a response inhibition task among men with methamphetamine dependence (Yin et al., 2022). A recent meta-analysis of fMRI studies suggests that exercise-induced changes in brain activation in parietal regions (e.g., cingulate gyrus,

precuneus) and related networks (e.g., dorsal attention network, frontoparietal network) may underlie exercise-induced cognitive improvements (Yu et al., 2021). Yet, similar to alcohol craving and mood states, the role of exercise type and intensity remains unclear (Yu et al., 2021).

Moreover, accumulating evidence demonstrates the importance of the brain-derived neurotrophic factor (BDNF), a key molecule involved in cognitive functioning (Miranda et al., 2019), in relation to exercise (Sleiman et al., 2016). While exercise has been found to promote the expression of BDNF (Sleiman et al., 2016), recent evidence suggests that high-intensity exercise, relative to no exercise or light-intensity exercise, is associated with larger magnitude increases in BDNF serum levels (Fernández-Rodríguez et al., 2022). This finding has received empirical support from a recent network meta-analysis indicating that HIIT may be the most effective exercise modality for improving peripheral BDNF levels (Rodríguez-Gutiérrez et al., 2024). However, it is important to acknowledge that many studies to date are limited by small sample sizes, and the “deeper“ mechanisms underlying changes in BDNF expression remain unclear (Fernández-Rodríguez et al., 2022). Larger-scale studies are needed to elucidate possible BDNF-modulating factors such as lactate (Ferris et al., 2007) and cortisol (Smith et al., 1995). In addition, future studies need to address potential sex differences (Fernández-Rodríguez et al., 2022), and extend current findings to individuals with AUD.

Stress reactivity and emotion processing

Different forms of stress (e.g., psychosocial stress) can contribute to the development and maintenance of AUD (Keyes et al., 2012). Chronic alcohol use leads to neural adaptations in the HPA axis, whereby alcohol-induced HPA axis dysregulation contributes to sensitized dopaminergic pathways, which may impact craving (Blaine et al., 2016; Sinha, 2012). Neural adaptations are marked by cortisol response dysregulation (Kreek & Koob, 1998) and deficits in emotion regulation (Sinha, 2001).

Regarding cortisol, a systematic review has indicated that higher physical activity and cardiorespiratory fitness levels among healthy people may attenuate cortisol reactivity to psychosocial stress (Mücke et al., 2018). This aligns with an fMRI study suggesting that the buffering effects of exercise to psychosocial stress may be attributed to feedback inhibition of the HPA axis and elevated positive affect (Zschucke

et al., 2015). Notably, there is some evidence suggesting that stress reactivity is more favorable among healthy individuals engaging in higher-intensity exercises, pointing to a potential dose-response relationship between exercise and stress reactivity (Mücke et al., 2018). While these findings are encouraging, future studies need to establish whether this observation translates to individuals with AUD.

Regarding emotion regulation, inefficient regulation strategies have been associated with alcohol craving and the maintenance of alcohol use (Petit et al., 2015). While exercise may serve as a buffer against negative emotions (Bernstein & McNally, 2018), future studies need to establish whether higher-intensity exercise is associated with a greater shift toward adaptive emotion regulation patterns. Such studies should be complemented by task-based neuroimaging paradigms. A recent fMRI study by Schmitt et al. (2019) employing an emotional face processing paradigm supports this research direction. Although positive affect was increased independent of exercise intensity, they found that both low- and high-intensity exercises were associated with reduced activation in distinct brain regions during the processing of fearful facial stimuli (Schmitt et al., 2019). Specifically, for the contrast of fearful facial stimuli versus neutral forms, low-intensity exercise was associated with decreased activity in the posterior cingulate cortex and precuneus, while high-intensity exercise was associated with decreased fear-related activity in ventral basal ganglia structures (Schmitt et al., 2019).

Collectively, these findings suggest that exercise can exert positive effects through several neuropsychological and neurobiological mechanisms. These findings also highlight the need for future research to elucidate the role of potential dose-dependent effects of exercise (e.g., light vs vigorous). In addition, other factors such as the type (e.g., endurance vs. strength), frequency (number of days per month) and duration (minutes per session) will be important to address. Identifying the optimal combination of these variables may help to maximize health benefits.

3.2 Synthesis of the current findings

Figure 12 presents an integrated framework that synthesizes the relationships between the key variables assessed across the studies included in this dissertation. This framework combines the model of cognitive pathways (Edalati & Krank, 2016) with the risk-protective model (Fergus & Zimmerman, 2005; Rutter, 1985) to delineate how specific variables may interact to influence potential pathways and outcomes. While not explicitly depicted, the proposed framework also incorporates elements from the conceptual model of “Health through Sport”, which was initially developed to address psychosocial health benefits in children and adolescents (Eime et al., 2013), and later extended to adults (Eather et al., 2023), emphasizing the importance of sports as a resource for improving psychosocial health across the lifespan.

The proposed framework adopts a developmental perspective, with a key focus on counteracting the effects of early life adversities (risk) to reduce or prevent alcohol use (outcome) through sports / exercise as a protective resource (moderator). Extant evidence suggests that alcohol use before the age of 15 is associated with a higher likelihood of developing AUD later in life (Dawson et al., 2008; Hingson et al., 2006). Notably, ACE may contribute to initiating alcohol use before age 15 (Dube et al., 2006), which aligns with the findings from Study III that underscore the ages of 13-15 as a sensitive period for early life adversity-related alcohol use. Thus, this developmental period represents a critical window for targeted prevention efforts.

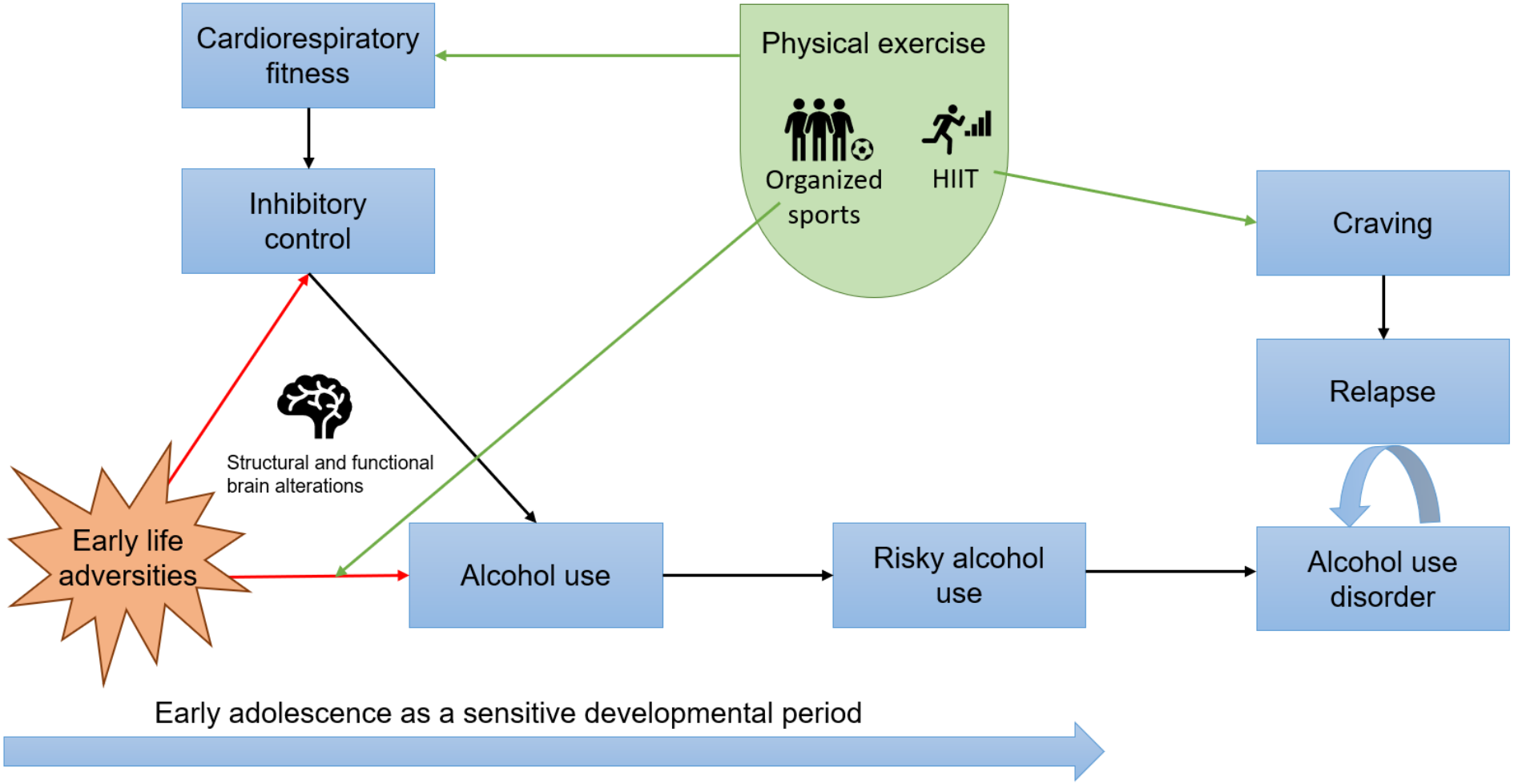
Building on the model of cognitive pathways, inhibitory control is proposed as a central mechanism, particularly during early adolescence, when it is particularly vulnerable to the negative effects of early life adversities (van der Bij et al., 2020). Recent evidence suggests that ACE-related deficits in inhibitory control may contribute to increased alcohol use during early-to-mid-adolescence (Kim & Bruce, 2022). By late adolescence and emerging adulthood, these deficits may become less apparent due to neural compensatory mechanisms (Quach et al., 2020; van der Bij et al., 2020). Building on existing research, future studies should explore the potential of vigorous exercise to enhance inhibitory control in adolescents (Browne et al., 2016; Li et al., 2022; Peruyero et al., 2017) and investigate whether this can help to mitigate the effects of ACE-related inhibitory control deficits on alcohol use, especially during the vulnerable period of early adolescence. The framework further integrates the Health through Sport model (Eather et al., 2023), proposing that sports-related improved

psychological and social health outcomes, along with neurobiological processes related to physical activity (see **Chapter 3.1.3.1**), may act synergistically to reduce the risk of alcohol use.

It is important to note that prevention strategies targeting adolescent alcohol use may not always be effective, potentially leading to the progression toward AUD. Based on the findings from Study IV, exercise may fulfill the function of an AUD relapse prevention strategy and add-on treatment for AUD by improving cardiorespiratory fitness and craving. To advance this line of research, future studies should further evaluate both factors (VO_{2max} for cardiorespiratory fitness and validated self-report measures for craving) in relation to treatment outcomes. High-quality RCTs are needed to investigate whether higher-intensity exercise (e.g., HIIT) can indirectly reduce alcohol craving by improving cardiorespiratory fitness and alleviating anxiety, as suggested by recent research (Pechtl et al., 2024; J. Tan et al., 2023). Adherence to exercise regimens will be an important consideration, as the effectiveness of exercise interventions may depend on the consistency with which individuals engage in prescribed activities.

Taken together, the present findings highlight the potential of sports / exercise as prevention and intervention strategies for addressing alcohol use and AUD. They also highlight the importance of identifying mechanisms and vulnerable developmental periods underlying the association between early life adversities and alcohol use, as well as understanding factors that moderate the transition to AUD. Future studies should validate and expand upon this framework by testing multiple plausible mechanisms outlined in **Chapter 3.1.3** and in the “Health through Sport” conceptual model (for an overview, see Eather et al., 2023). A longitudinal approach will be essential for untangling the complex interplay between the variables. Additionally, key facets of sports and exercise – such as intensity and type (team vs. individual sports) – should be explored as potential moderators. **Figure 13**, inspired by Eather et al. (2023), provides an overview of these moderators. The implications for prevention and intervention strategies will be discussed in **Chapters 3.4.1** and **3.4.2**, respectively.

Figure 12. Connections between key variables in the dissertation.



Note. HIIT = high-intensity interval training.

Green arrow = positive effects; red arrow = negative effects; black arrows = general pathways.

3.3 Limitations and future directions

Although many limitations have already been identified and discussed in the individual studies, there are noteworthy limitations across the studies which should be addressed in future studies.

First, in contrast to Study III which utilized a prospective design, Studies I and II were cross-sectional, which limits the ability to draw inferences regarding the causality of the findings. Notably, the finding that early adolescence is a vulnerable period for the effects of ACE on cortical thickness in regions related to inhibitory control needs to be further corroborated by longitudinal data.

Second, the concept of sensitive developmental periods is inherently complex, as the severity of ACE can fluctuate across childhood and adolescence, as shown in **Figure S1** in the supplementary materials of Study I. Likewise, the measurement of ACE can fluctuate across childhood and adolescence (e.g., relying on parent reports in the early childhood years and transitioning to self-reports in adolescent years). This variability can affect the reliability of the results. Similarly, if the probability of experiencing ACE varies across developmental stages, effect sizes can also be affected. For example, if the probability of ACE exposure is considerably higher in early adolescence than in childhood, the identified sensitive periods may not necessarily be of biological nature.

Third, all studies utilized self-report measures, which introduce biases inherent to this methodology. Study I and II relied on retrospective measures of ACE which may introduce recall biases (e.g., mood-congruent memory effects, psychological distress at the time of recall) inherent to this methodology (Colman et al., 2016; Gaddy & Ingram, 2014). In addition, it is important to note that a recent meta-analysis has indicated low agreement between prospective and retrospective measures of ACE, raising concerns about whether these two measurement approaches capture different groups of individuals (Baldwin et al., 2019). Indeed, studies with prospective designs often rely on official records and may predominantly include individuals with more severe ACE.

Fourth, Studies I and II included many individuals with minimal ACE severity, which may have diminished the observed correlations. This range restriction also undermined the ability to meaningfully compare differences between individuals with

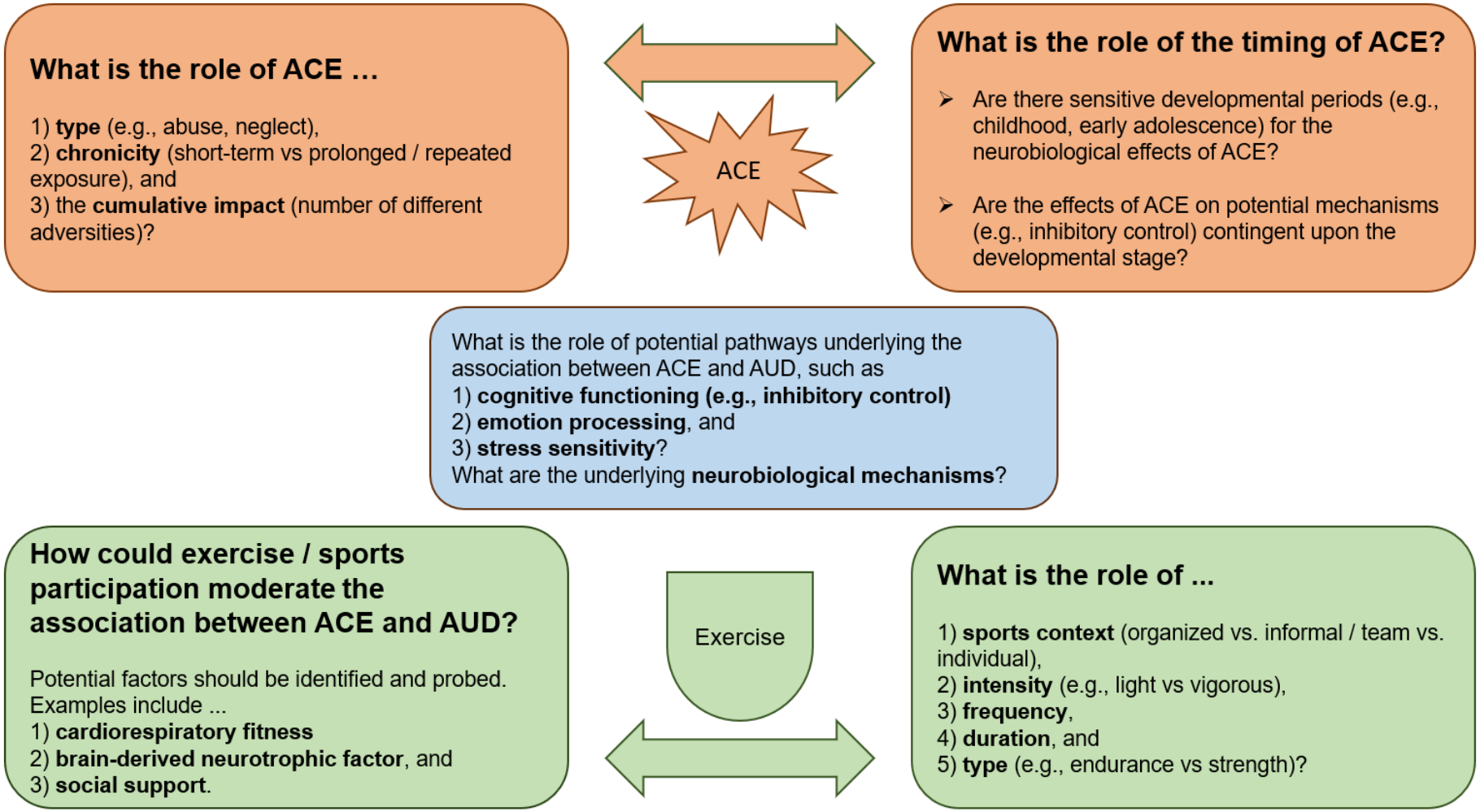
no to low ACE severity and those with moderate to high ACE severity, as initially planned in Study II (Türkmen et al., 2022). The high number of minimally traumatized participants in both studies is likely due to employing strict exclusion criteria related to psychiatric comorbidities. While these criteria increase confidence that the results were not significantly confounded by comorbidities, they also partially limit the generalizability of the findings to AUD populations, which often exhibit high rates of psychiatric comorbidities (Castillo-Carniglia et al., 2019). For example, individuals with comorbidities such as attention deficit hyperactivity disorder (ADHD), which appear to be common in those with AUD (Ohlmeier et al., 2008), were excluded from Studies I and II. This was carefully chosen, as research has shown that ADHD further worsens inhibitory control in adults with AUD (Vollstädt-Klein et al., 2020).

Fifth, while the large sample size (N = 3,422 adolescents) of Study III allowed for more robust statistical analyses, Studies I and II were limited by relatively modest sample sizes. This limitation reduced the statistical power and thus the robustness of the results. The limited number of studies included in the meta-analysis of Study IV presented the same issue. Thus, the findings should be interpreted with caution, as they are more preliminary.

Relatedly, given the modest small sample sizes, it was not feasible to assess the impact of sex/gender and the cultural/ethnic background, although these comprise important factors. For example, women with ACE are around six times more likely to develop an AUD compared to men (Broekhof et al., 2023). In addition, in the US for example, there is evidence to suggest that White and Native American individuals are at a higher risk for AUD compared to other ethnic groups (Chartier & Caetano, 2010).

Collectively, these limitations underscore the need for future studies to incorporate larger samples, covering a wider spectrum of ACE and AUD severity, and to assess the impact of sociodemographic factors. Lastly, while the present findings provide insights into both risk factors (e.g., ACE type, inhibitory control) and protective factors (e.g., organized sports), further research is needed to explore several key facets of these factors, which are summarized **Figure 13**.

Figure 13. Key research areas for advancing the understanding of risk and protective factors in the ACE-AUD relationship.



Note. ACE = adverse childhood experiences; AUD = alcohol use disorder.

3.4 Implications for prevention and intervention programs

AUD represents a widespread and persistent public health concern, with an estimated 283 million cases worldwide (World Health Organization, 2018), warranting the need for effective prevention and treatment programs to alleviate the burden of this debilitating disorder. Similarly, childhood maltreatment, a particularly common ACE, affects approximately 300 million children globally (World Health Organization, 2022). Importantly, ACE are associated with an increased risk of developing AUD (Broekhof et al., 2023; Felitti et al., 1998), making it an important target for both prevention and intervention strategies. The studies included in this dissertation provide valuable insights which could benefit stakeholders, policymakers and clinicians in further improving the design, implementation and effectiveness of these strategies.

3.4.1 Prevention

When considering the ACE-AUD association, there are two substantive approaches that can be employed to prevent AUD, namely (1) a direct approach that aims to prevent the occurrence of ACE altogether, thereby eliminating the ACE-AUD association, and (2) an indirect approach that aims to mitigate the effects of ACE by targeting pathways through which ACE may contribute to the development of AUD, thereby reducing the risk of developing AUD.

Although the direct approach seems straightforward, translating this into practice is challenging and falls outside the scope of this dissertation. Nevertheless, it is important to note that this area of research has gained increasing interest in recent years. For example, the Centers for Disease Control and Prevention (CDC) has invested in research initiatives focused on understanding the causes of ACE, strategies aimed at reducing and preventing them, and determining how effective strategies could be adapted and scaled at a public health level (Matjasko et al., 2022). Examples for potential strategies include parenting skill training programs designed to improve child-parent relationships as well as policies that could help parents in balancing work and family responsibilities (Centers for Disease Control and Prevention, 2024b). The findings from ongoing research initiatives will provide valuable insights into this level of prevention. Sociodemographic aspects such as socioeconomic status and ethnic/racial aspects are crucial to consider, as a higher

number of ACE (≥ 4) has been found to be especially prevalent in low-income households and minoritized racial/ethnic groups, such as Native Americans in the US (Madigan et al., 2023).

To maximize the beneficial effects of the direct approach, it is essential to also integrate the indirect approach. The foundation for the latter approach laid within this dissertation is to prevent an early onset of alcohol use, reduce adolescent alcohol use and mitigate the progression to adolescent hazardous drinking (e.g., binge drinking), all of which are associated with the development of AUD (Addolorato et al., 2018; Dawson et al., 2008). Although culturally- and gender-sensitive trauma-informed prevention strategies represent a fruitful approach for targeting ACE-related alcohol use among young adults (Rogers et al., 2022), the indirect approach may further benefit from identifying and elucidating modifiable protective resources for those at-risk of harmful alcohol use.

Study III identified sports participation as a promising protective resource for adolescent alcohol use related to familial stressors during early adolescence. However, the social context of sports involvement is crucial to consider. While the nature of sports involvement was not directly captured in Study III, it should be noted that the research was conducted in Norway, where participation in formally organized sports activities is common among adolescents (Skille, 2011). Although predominantly US-based studies have found sports participation to be associated with increased adolescent alcohol use (Kwan et al., 2014; Walczak et al., 2023), there is evidence from Nordic studies suggesting that participation in formally organized sports, compared to informal sports, may act as a protective factor against adolescent alcohol use (Halldorsson et al., 2013; Kristjansson et al., 2010). Importantly, the influence of potential risk factors, including low parental monitoring and broken family structure, on adolescent alcohol use has been found to become considerably weaker with greater involvement in formal sports (Halldorsson et al., 2013).

Moreover, sports participation provides multiple pathways for social learning, which may differentially affect alcohol use (Vest & Simpkins, 2013). Extant evidence suggests that peer influences, particularly the drinking behaviors of close friends, present a potential risk that can encourage alcohol use (or initiation thereof) among adolescents (Bot et al., 2005; Kaner et al., 2022; Urberg et al., 1997). This also translates to sports participation which appears to be protective against alcohol use if peers have low alcohol use but not if alcohol use is high (Vest & Simpkins, 2013). Thus,

peer influences can act as a double-edged sword and should be carefully considered in prevention strategies. Another aspect that is important to consider is the role of different types of sports (e.g., football vs swimming; endurance vs strength). For example, Wichstrøm and Wichstrøm (2009) have found that practicing endurance sports, compared to technical or strength sports, predicted reduced growth in alcohol intoxication. Collectively, factors such as the sports type and context, the broader social and cultural context, and the influence of close friends' drinking behaviors, among others, should be considered in the design and implementation of prevention strategies.

Studies I and III have emphasized the importance of sensitive developmental periods, during which early life stressors may exert disproportionately higher negative effects on alcohol use and brain development. These studies have shown that the ages 13 to 15 are particularly vulnerable to the effects of early life adversities. Notably, while Study I identified abuse as an important type of maltreatment, Study III indicated a cumulative impact of early life stressors, such that adolescent alcohol use increased as the number of familial stressors increased. Thus, prevention strategies should consider investing resources particularly during early adolescence, and pay close attention to adolescents with a history of abuse and a high early life stress load.

Lastly, Studies I and II highlight the neurobiological significance of targeting inhibitory control in prevention strategies. Evidence suggests that inhibitory control deficits in trauma-exposed youth and those at risk of substance use are more pronounced during early adolescence (Quach et al., 2020; van der Bij et al., 2020). Additionally, recent evidence suggests that the relationship between ACE and increased alcohol use in mid-adolescence may be mediated by inhibitory control deficits during early adolescence (Kim & Bruce, 2022), corroborating early adolescence as a vulnerable period. Addressing inhibitory control deficits early on may help to reduce ACE-related adolescent alcohol use. Evidence shows that physical exercise can enhance inhibitory control in adolescents (Browne et al., 2016), with vigorous exercise proving more effective than light-intensity exercise (Li et al., 2022; Peruyero et al., 2017).

In conclusion, exercise, particularly participation in organized sports, seems to be a useful protective resource in the association between early life stress and the development of AUD. Vigorous exercise, in particular, appears to be effective in promoting inhibitory control, a key target for both the prevention and treatment of AUD

(Czapla et al., 2016). Indeed, in recent years, a growing body of evidence has recognized the potential benefits of exercise not only for prevention but also as an adjunct treatment for AUD (Hallgren, Vancampfort, Giesen, et al., 2017; Hallgren, Vancampfort, Schuch, et al., 2017; Lardier et al., 2021; Roessler, Bilberg, et al., 2017; Søgaard Nielsen et al., 2016)

3.4.2 Treatment

The treatment of AUD is highly complex and requires a multifaceted approach. Despite the moderate effectiveness of psychosocial interventions such as cognitive behavioral therapy and contingency management (Dutra et al., 2008), relapse remains a key challenge in AUD treatment, affecting up to two-thirds of patients after treatment completion (Alterman et al., 2000; Andersson et al., 2019; Gossop et al., 2002). Long-term remission is often complicated by multiple factors, such as craving, poor physical health, and psychiatric comorbidities (Sliedrecht et al., 2019). Cognitive impairments, particularly deficits in inhibitory control, are common in individuals with AUD and comprise an important risk factor for relapse in adults with AUD (Batschelet et al., 2021; Czapla et al., 2016; Domínguez-Salas et al., 2016).

Adjunct treatments, such as cognitive training and remediation interventions, have emerged as promising strategies for targeting such impairments in patients with SUD (Verdejo-Garcia et al., 2023). One particular strength of these add-on interventions lies in their flexibility. Treatment targets (e.g., inhibitory control, working memory), intervention approaches (e.g., cognitive remediation, cognitive bias modification), and active ingredients (e.g., guided practice, feedback, reward / incentive) can all be customized and tailored to the patient's needs. Moreover, different delivery modes (e.g., web-based vs. face-to-face) can accommodate patient preferences, and carry the potential to enhance the scalability of treatment (particularly with digital-based delivery modalities). This flexibility extends even to the intervention approaches themselves. For example, research efforts integrating leisure activities are underway to assess whether chess-based cognitive remediation training can serve as an effective adjunct treatment to improve treatment outcomes in patients with AUD and tobacco use disorder (Gerhardt, Lex, et al., 2022; Karl et al., 2023).

In addition to cognitive training and remediation interventions, Study IV offers preliminary evidence supporting HIIT as a time-efficient adjunct treatment for AUD by

potentially enhancing inhibitory control and reducing craving through improvements in cardiorespiratory fitness (J. Tan et al., 2023; Tavares et al., 2021). However, additional research is needed to support the potential of HIIT as a relapse prevention strategy and to evaluate its effectiveness compared to other forms of exercise. Exercise can be utilized to not only address cognitive impairments (Zheng et al., 2024), but also somatic health issues, which are frequently observed in patients with AUD (Holst et al., 2017), yet often go unaddressed by psychosocial or pharmacological approaches. These health issues can be exacerbated by poor physical fitness and low levels of physical activity commonly observed among patients with AUD (Vancampfort et al., 2019).

Given these challenges, promoting physical activity is of clinical relevance in this patient group, and particular attention should be paid to those with a history of ACE who may play display higher levels of physical inactivity (Al-shoaibi et al., 2024; Felitti et al., 1998). However, the success of encouraging physical activity may vary across population groups. For example, research suggests that women and nonsmokers are more likely to adhere to medical advice regarding physical activity (Tönges et al., 2006). AUD populations may be particularly difficult to encourage, as demonstrated by a meta-analysis which reported that dropout rates in exercise interventions for AUD are as high as 40% (Hallgren, Vancampfort, Giesen, et al., 2017). While Study IV reported a lower dropout rate for HIIT of 23%, studies conducted outside of China showed dropout rates similar to the 40% estimate, highlighting the need for strategies to improve retention.

There is evidence to suggest that, rather than a lack of motivation, there are various barriers to exercise participation among patients with AUD (Sari et al., 2017). These include structural barriers (e.g., type of exercise), social barriers (e.g., unsupportive relations), and emotional barriers (e.g., fear, shame) (Sari et al., 2017). Based on this, it has been proposed to administer exercise interventions shortly after treatment initiation and to provide additional psychosocial support during the early phase (Sari et al., 2017). Although integrating motivational aspects such as motivational interviewing may foster participation, it remains unclear which motivational aspect is most effective in patients with AUD (Roessler, Bramsen, et al., 2017).

As with any intervention, adherence is crucial for achieving meaningful benefits and maintaining treatment response in exercise-based treatments. Despite its importance, adherence to exercise interventions, especially in SUD populations, is often underreported. Among the HIIT trials reviewed in Study IV, only Flemmen et al.

(2014) provided detailed adherence data, reporting that nine out of 12 participants (75%) completed the HIIT program, with an average attendance of 22 out of 24 (92%) sessions. While these figures are encouraging, the overall lack of comprehensive adherence data is a cause for concern, as the effectiveness any exercise intervention depends on this aspect. If HIIT is effectively implemented, some evidence suggests that it may even outperform other exercise protocols in improving cardiorespiratory fitness (Helgerud et al., 2007; Hov et al., 2023). However, it remains unclear whether these findings apply to AUD populations. In addition, various factors such as higher AUD severity, higher body mass index, psychiatric comorbidity, and lower education need to be carefully considered as these can negatively impact adherence in this patient group (P. Welford et al., 2023). Special attention should be directed towards outpatients, women, and older adults with AUD, as there is a lack of evidence concerning these specific subgroups based on the findings from Study IV.

While Study IV suggests that HIIT Is a safe and feasible intervention, in addition to its time efficiency and constantly changing stimulus which may be perceived as more enjoyable than MICT (Thum et al., 2017), it is important to acknowledge the challenges involved in designing, implementing, and monitoring HIIT programs. HIIT interventions require a significant degree of coordination, and the relative intensity may be perceived as demanding by patients with AUD, particularly among those with lower levels of physical activity and fitness. In addition, clinicians often have busy schedules and may not possess the necessary knowledge and experience to administer HIIT, highlighting the importance of utilizing qualified personnel to oversee such programs. In Norway, for example, efforts have been made to implement HIIT as a mandatory treatment component at various inpatient clinics to enhance the physical health of patients with SUD. Intervention periods lasting around eight weeks have been found to be appropriate for HIIT programs (Chapman et al., 2017; Flemmen et al., 2014).

In conclusion, HIIT shows promise as a valuable adjunct treatment for improving physical fitness in those with SUD and as a relapse prevention strategy by reducing substance craving and potentially improving inhibitory control. However, further high-quality RCTs are needed to assess long-term adherence and the comparative effectiveness of HIIT to other forms of exercise before widespread implementation of HIIT is warranted.

4 SUMMARY

While existing studies have established an association between adverse childhood experiences (ACE) and the development of alcohol use disorder (AUD), there is a paucity of research on potential mechanisms underlying this association and on factors that might moderate it. The aim of this dissertation was to address these gaps, focusing on both risk and protective factors.

Study I assessed the association between ACE and changes in brain structure in adults with AUD, compared to a healthy control group (N = 63). The role of the type and timing of ACE was explored using a machine learning approach. Adults with AUD showed significantly reduced cortical thickness in brain regions linked to inhibitory control, notably in the left inferior frontal gyrus, compared to healthy controls. This reduction in cortical thickness was associated with higher ACE severity, specifically higher levels of abuse experienced during early adolescence, suggesting the potential relevance of inhibitory control in the association between ACE and AUD.

Study II extended Study I by examining the association between ACE and inhibitory control in heavy-drinking adults (N = 32) using a functional MRI-based behavioral inhibition paradigm (stop-signal task). Interestingly, greater ACE severity was associated with better inhibitory control in this population, which appeared to be driven primarily by emotional neglect. Lower activation in the left inferior frontal gyrus during successful behavioral inhibition, which was associated with higher levels of emotional neglect, may potentially reflect increased neural efficiency of inhibitory control after more severe emotional neglect, warranting further investigation in longitudinal studies.

Study III was a longitudinal study (N = 3422) that assessed adolescent alcohol use trajectories in relation to family-specific negative life events, sports participation, and their interaction. There was a negative effect of negative life events on initial alcohol use such that each additional event was associated with greater alcohol use in early adolescence. Alcohol use was initially lower for youth with a higher number of negative life events (three or more) who engaged in sports more frequently (24 days per month), but increased precipitously over time such that it was similar to those without negative life events by the final assessment. High sports participation delayed

the onset of risky alcohol use and reduced alcohol use in adolescents with a high negative life event load primarily during early adolescence.

Study IV was a systematic review and preliminary meta-analysis of six controlled intervention studies (N = 327) examining whether a time-efficient form of exercise, namely high-intensity interval training, can improve health outcomes in patients with substance use disorders. Preliminary results suggested that high-intensity interval training may improve cardiorespiratory fitness (VO_{2max}) and reduce substance craving in this population, potentially improving treatment outcomes and lowering the risk of relapse.

A key finding from Studies I and III is that early adolescence (years 13-15) appears to be a sensitive developmental period for both increased alcohol use and neural changes related to early life adversities. Study I additionally highlighted the importance of the type of adversity, as changes in brain structure were related specifically to abuse – but not neglect – during this developmental period. During the same period, increased sports participation emerged as a protective factor for mitigating the effects of negative life events on alcohol use. This protective effect, however, was dose-dependent such that benefits were observed only in adolescents who experienced multiple negative life events and engaged more frequently in sports. Studies I and II further emphasized the importance of inhibitory control in the relationship between early life adversities and alcohol use disorder. However, this relationship may be more complex in nature and potentially contingent on the ACE subtype and developmental stage. Study IV reviewed evidence suggesting that physical exercise may positively impact inhibitory control in individuals with substance use disorders through improved cardiorespiratory fitness, though the role of exercise intensity requires further investigation.

Collectively, these findings highlight 1) the potential of physical exercise and sports in prevention and intervention programs, 2) early adolescence as a potential “window of opportunity” for such programs, and 3) the need for further longitudinal research to explore the role of different types of ACE, cognitive functioning (in particular inhibitory control) and neurobiological changes over time using neuroimaging techniques.

5 ZUSAMMENFASSUNG

Während bisherige Studien einen Zusammenhang zwischen belastenden Kindheitserfahrungen und der Entwicklung einer Alkoholgebrauchsstörung nachgewiesen haben, gibt es nur wenige Untersuchungen zu den möglichen Mechanismen, die diesem Zusammenhang zugrunde liegen, sowie zu den Faktoren, die ihn möglicherweise moderieren könnten. Ziel dieser Dissertation war es, diese Lücken zu adressieren, wobei der Schwerpunkt sowohl auf Risiko- als auch auf Schutzfaktoren lag.

Studie I untersuchte den Zusammenhang zwischen belastenden Kindheitserfahrungen und Veränderungen der Gehirnstruktur bei Erwachsenen mit einer Alkoholgebrauchsstörung im Vergleich zu einer gesunden Kontrollgruppe (N = 63). Die Rolle der Art und des Zeitpunkts der belastenden Kindheitserfahrungen wurde mit Hilfe eines maschinellen Lernansatzes untersucht. Erwachsene mit einer Alkoholgebrauchsstörung wiesen im Vergleich zur gesunden Kontrollgruppe eine signifikant reduzierte kortikale Dicke in Hirnregionen auf, die mit der inhibitorischen Kontrolle in Verbindung stehen, insbesondere im linken Gyrus frontalis inferior. Diese Reduktion der kortikalen Dicke stand in Zusammenhang mit einem höheren Schweregrad belastender Kindheitserfahrungen, insbesondere mit einem höheren Ausmaß an Missbrauchserfahrungen in der frühen Adoleszenz, was auf die mögliche Bedeutung der inhibitorischen Kontrolle für den Zusammenhang zwischen belastenden Kindheitserfahrungen und Alkoholgebrauchsstörungen hinweisen könnte.

Studie II erweiterte Studie I, indem sie den Zusammenhang zwischen belastenden Kindheitserfahrungen und der inhibitorischen Kontrolle bei Erwachsenen mit riskantem Alkoholkonsum (N = 32) mit Hilfe eines funktionellen MRT-basierten Verhaltenshemmungsparadigmas (Stopp-Signal-Aufgabe, engl. Stop-Signal Task) untersuchte. Interessanterweise war ein höherer Schweregrad belastender Kindheitserfahrungen mit einer besseren inhibitorischen Kontrolle in dieser Population verbunden, die primär durch emotionale Vernachlässigung bedingt zu sein schien. Die geringere Aktivierung im linken Gyrus frontalis inferior während erfolgreicher Verhaltenshemmung, die mit einem höheren Grad an emotionaler Vernachlässigung verbunden war, könnte auf eine erhöhte neuronale Effizienz der Verhaltenshemmung nach schwerer emotionaler Vernachlässung hinweisen, was in Längsschnittstudien weiter untersucht werden sollte.

Bei Studie III handelte es sich um eine Längsschnittstudie (N = 3422), in der die Entwicklung des Alkoholkonsums von Jugendlichen in Zusammenhang mit familienspezifischen negativen Lebensereignissen, der Teilnahme am Sport und deren Interaktion untersucht wurde. Es zeigte sich ein negativer Effekt von negativen Lebensereignissen auf den anfänglichen Alkoholkonsum, so dass jedes zusätzliche Ereignis mit einem höheren Alkoholkonsum in der frühen Adoleszenz verbunden war. Bei Jugendlichen mit einer höheren Anzahl negativer Lebensereignisse (drei oder mehr), die häufiger Sport trieben (24 Tage pro Monat), war der Alkoholkonsum anfangs niedriger, stieg aber im Laufe der Zeit stärker an, so dass er beim letzten Untersuchungszeitpunkt ähnlich hoch war wie bei Jugendlichen ohne negative Lebensereignisse. Die hohe Teilnahme am Sport verzögerte den Beginn des riskanten Alkoholkonsums und reduzierte ihn bei Jugendlichen mit einer hohen Belastung durch negative Lebensereignisse vor allem in der frühen Adoleszenz.

Bei Studie IV handelte es sich um eine systematische Übersichtsarbeit und vorläufige Metaanalyse von sechs kontrollierten Interventionsstudien (N = 327), in denen untersucht wurde, ob eine zeiteffiziente Form der körperlichen Betätigung, nämlich hochintensives Intervalltraining, Gesundheitsergebnisse bei Patienten mit Substanzgebrauchsstörungen verbessern kann. Die vorläufigen Ergebnisse deuten darauf hin, dass hochintensives Intervalltraining die kardiorespiratorische Fitness (VO_{2max}) verbessern und das Substanzverlangen (Craving) in dieser Patientengruppe verringern kann, was zu besseren Behandlungsergebnissen und einem reduzierten Rückfallrisiko führen könnte.

Eine wichtige Erkenntnis aus den Studien I und III ist, dass die frühe Adoleszenz (13-15 Jahre) eine empfindliche Entwicklungsphase sowohl für einen erhöhten Alkoholkonsum als auch für neuronale Veränderungen im Zusammenhang mit frühen belastenden Lebensereignissen zu sein scheint. In Studie I wurde zudem die Bedeutung der Art der belastenden Kindheitserfahrungen hervorgehoben, da die Veränderungen der Gehirnstruktur in diesem Entwicklungszeitraum speziell mit Missbrauch – nicht aber mit Vernachlässigung – in Verbindung gebracht wurden. Während desselben Entwicklungsfensters erwies sich eine verstärkte Teilnahme am Sport als Schutzfaktor für die Abschwächung der Auswirkungen negativer Lebensereignisse auf den Alkoholkonsum. Dieser schützende Effekt war jedoch dosisabhängig, so dass nur bei Jugendlichen, die mehrere negative Lebensereignisse erlebten und häufiger Sport trieben, Vorteile beobachtet wurden. In den Studien I und

II wurde außerdem die Bedeutung der inhibitorischen Kontrolle für den Zusammenhang zwischen frühen negativen Lebensereignissen und Alkoholgebrauchsstörungen hervorgehoben. Dieser Zusammenhang könnte jedoch komplexer sein und möglicherweise von der Art der belastenden Kindheitserfahrungen und dem Entwicklungsstadium abhängen. In Studie IV wurden Belege geprüft, die darauf hindeuten, dass körperliche Betätigung bei Personen mit Substanzkonsumstörungen durch eine verbesserte kardiorespiratorische Fitness einen positiven Einfluss auf die inhibitorische Kontrolle haben kann, wobei die Rolle der Trainingsintensität noch weiter untersucht werden muss.

Zusammenfassend unterstreichen diese Ergebnisse 1) das Potenzial von körperlicher Betätigung und Sport in Präventions- und Interventionsprogrammen, 2) die frühe Adoleszenz als potenzielles „Zeitfenster“ für solche Programme und 3) den Bedarf an weiteren Längsschnittuntersuchungen, um die Rolle verschiedener Arten von belastenden Kindheitserfahrungen, kognitiver Funktionen (insbesondere der inhibitorischen Kontrolle) und neurobiologischer Veränderungen im Laufe der Zeit mithilfe von Neuroimaging-Techniken zu untersuchen.

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9 SUPPLEMENTARY INFORMATION

9.1 Study I Supplementary Materials: The association between adverse childhood experiences and alterations in brain volume and cortical thickness in adults with alcohol use disorder

Table S1

Exclusion criteria

- Withdrawal of the declaration of consent
- Exclusion criteria for an MRI scan (e.g., pregnancy, metal implants)
- Severe internal, neurological and psychiatric comorbidities (e.g., schizophrenia)
- Pharmacotherapy with psychoactive substances within the last 14 days (except treatment with SSRI/SNRIs for at least 28 days)
- Axis-I disorder according to ICD-10 and DSM 5 (except tobacco and alcohol use disorder, substance abuse with less than 2(11) criteria according to DSM-5, mild depressive episode, adaptation disorder and specific phobia within the last 12 months)
- positive urine drug screening (cannabis, amphetamine, opiates, benzodiazepines, cocaine)
- withdrawal symptoms (CIWA-AR > 7) (Sullivan et al., 1989)
- intoxication at time of investigation (breathalyzer > 0.3‰)
- suicidal tendency or potential danger for others
- Healthy participants reporting a risky amount of alcohol consumption (alcohol/day ≥ 12 g (female), 24 g (male) on up to 5 days/week) or more than minimal severity of ACE (cut-off score of 8 [2*1+3*2])

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Table S2. Descriptive statistics of KERF subscales.

Group	HC Mean (SD)	AUD Mean (SD)	Statistics
N	28	35	
KERF PEA	0.7 (1.6)	2.8 (2.8)	**T(54.7) = -3.71, p <**
KERF PEAS	0.0 (0.0)	0.6 (1.8)	T(34) = -1.89, p = .067
KERF PEER	1.2 (2.3)	4.1 (3.7)	**T(58.3) = -3.82, p <**
KERF WITS	0.6 (1.7)	2.2 (3.2)	**T(54.6) = -2.44, p =**
KERF PPA	0.9 (2.1)	3.4 (3.0)	**T(59.9) = -3.98, p <**
KERF EN	0.7 (1.5)	3.7 (3.7)	**T(47.2) = -4.41, p <**
KERF PN	0.3 (1.0)	0.7 (1.7)	T(57.9) = -1.30, p =
KERF WITP	0.4 (1.1)	1.2 (2.6)	T(48.4) = -1.76, p =
KERF SEXA_H	0.0 (0.0)	0.2 (1.0)	T(34) = -1.41, p = .169
KERF SEXA_O	0.3 (0.6)	0.4 (1.1)	T(61) = -.507, p = .614

Note. Significant group differences are highlighted in bold. AUD = Alcohol Use Disorder; g = grams; HC = healthy control; N = sample size; PEA = Parental Emotional Abuse; PEAS = Physical and Emotional Abuse by Siblings; PEER = Physical and Emotional Abuse by Peers; WITS = Witnessed Violence towards Siblings; PPA = Parental Physical Abuse; EN = Emotional Neglect; PN = Physical Neglect; WITP = Witnessed Violence towards Parents; SD = Standard Deviation; SEXA_H = Sexual Abuse by a Member of the Household; SEXA_O = Sexual Abuse by Others Not Living in the Same Household

Figure S1. Average severity of KERF40 sum, abuse and neglect scores for ages 3 to 17 in the AUD group.

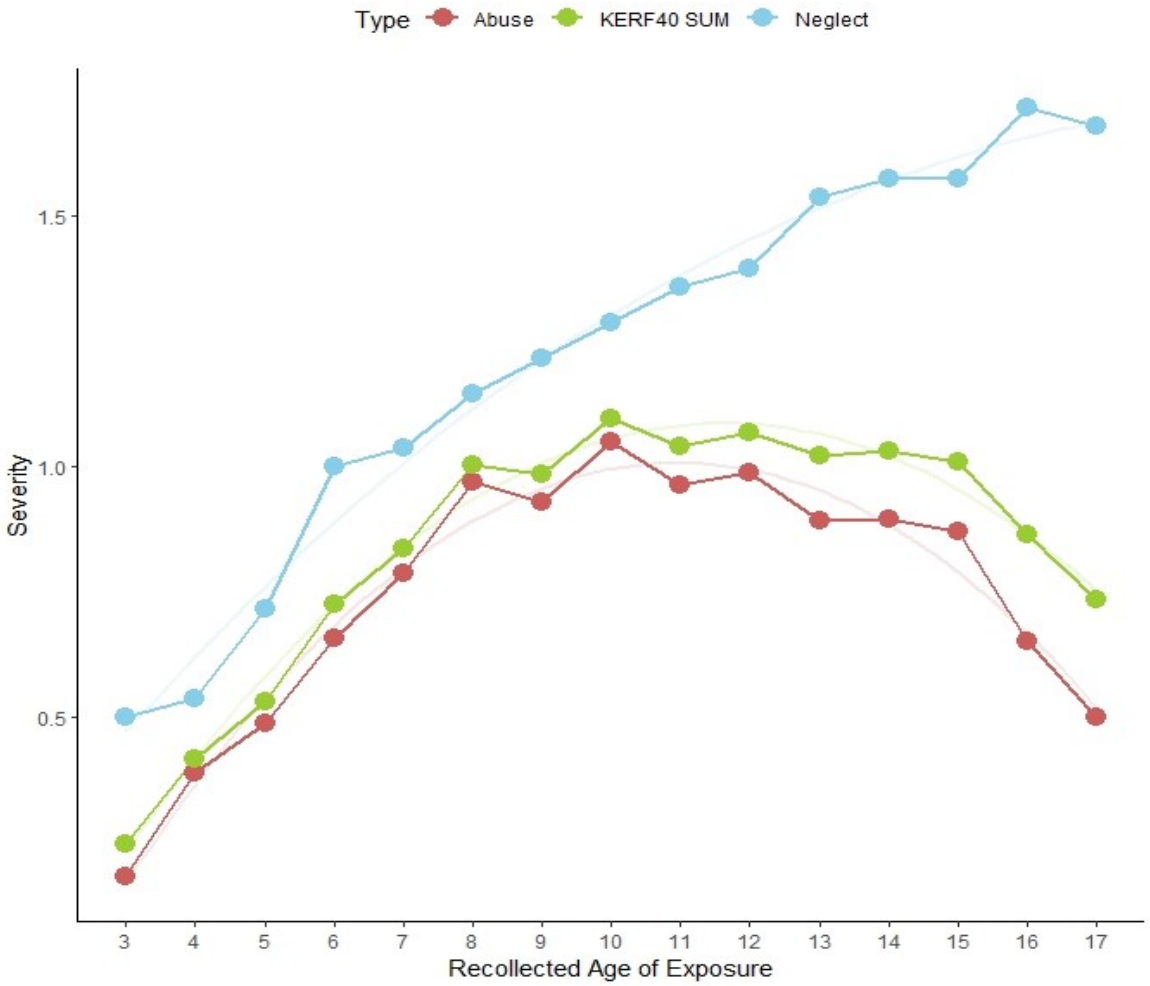
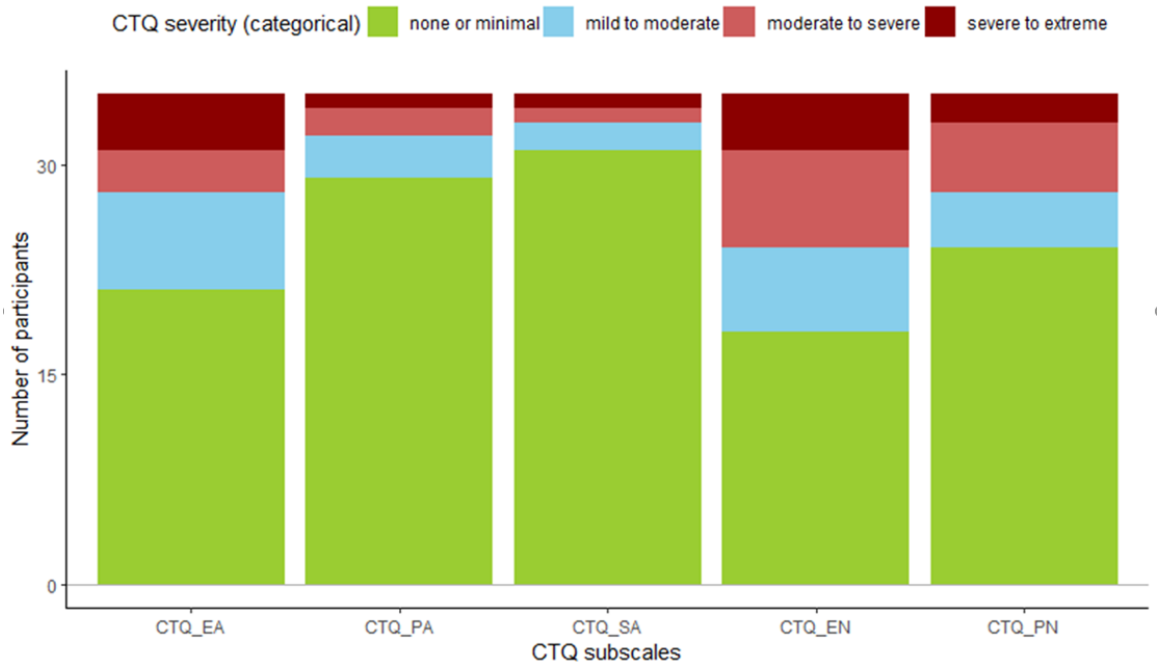
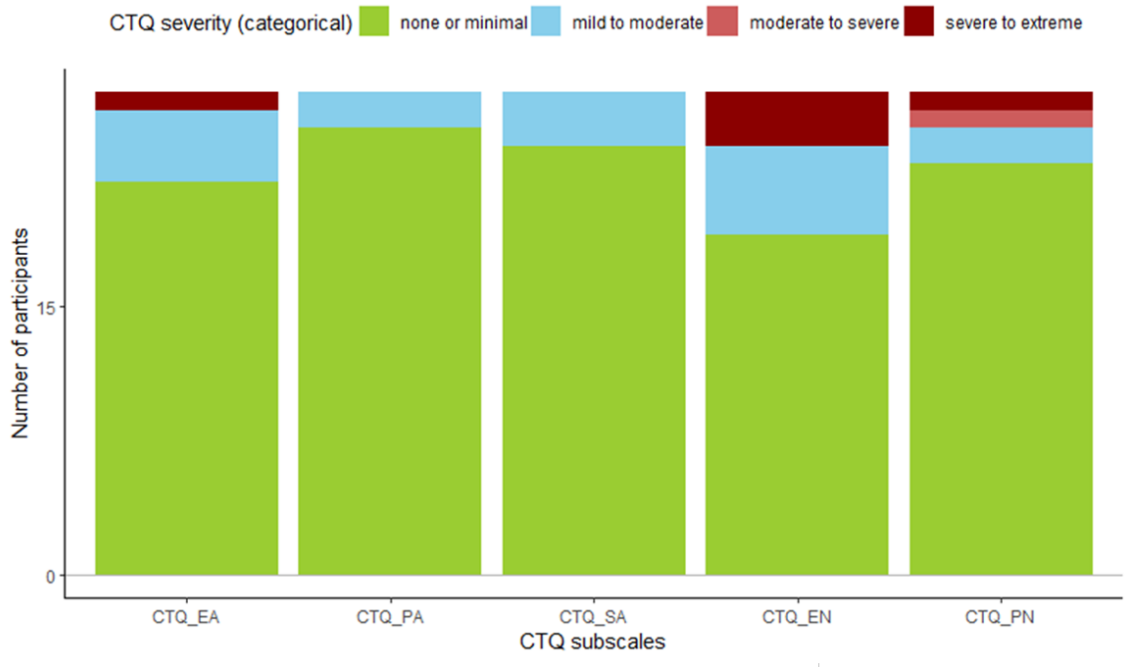


Figure S2. Categorical severity for each CTQ subtype in the AUD group.



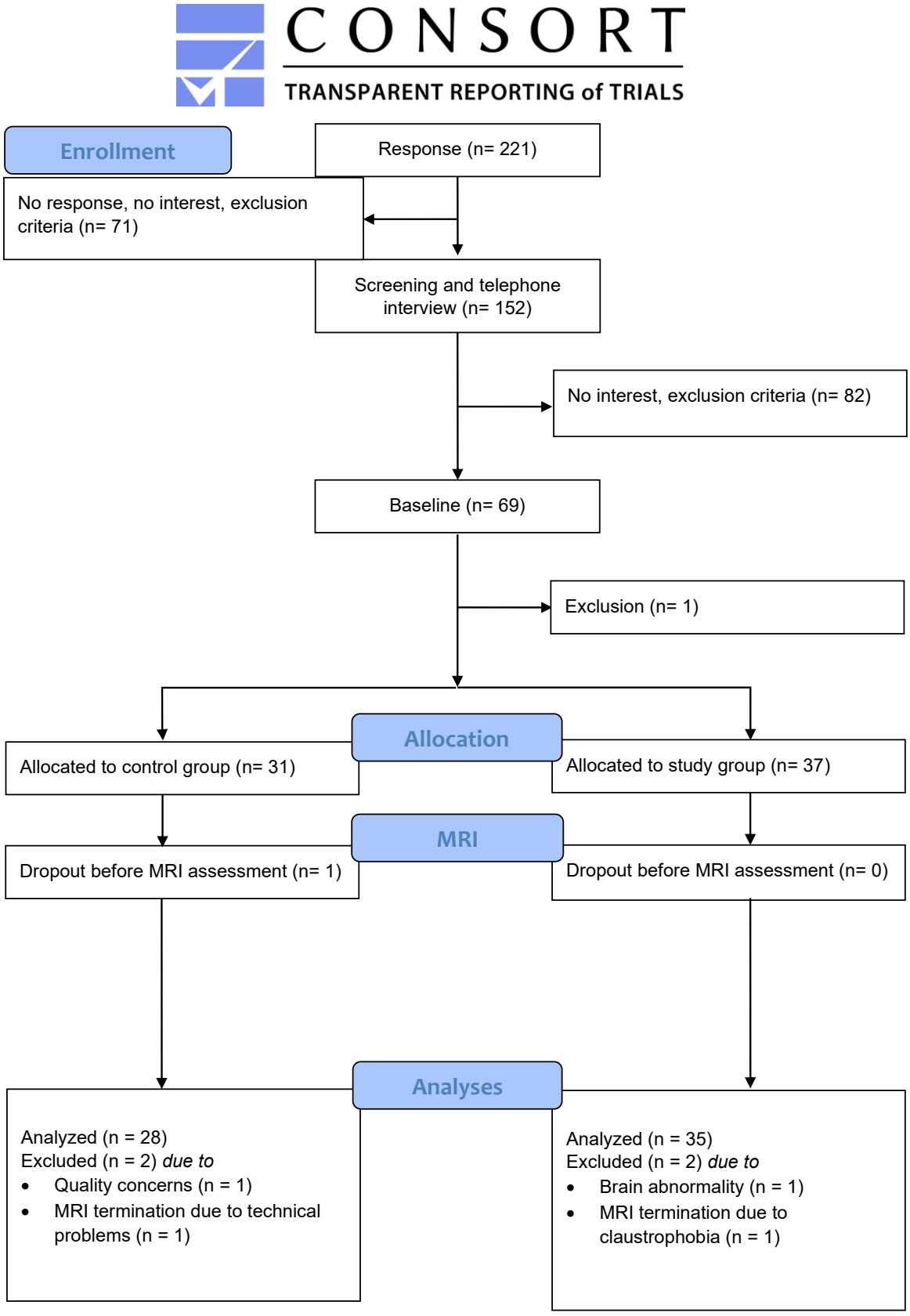
Note. EA = Emotional Abuse; PA = Physical Abuse; SA = Sexual Abuse; EN = Emotional Neglect; PN = Physical Neglect

Figure S3. Categorical severity for each CTQ subtype in the HC group.



Note. EA = Emotional Abuse; PA = Physical Abuse; SA = Sexual Abuse; EN = Emotional Neglect; PN = Physical Neglect

Figure S4. Flow diagram of study.



9.2 Study II Supplementary Materials: The association between adverse childhood experiences and inhibitory control in heavy-drinking adults: a functional MRI study

Supplement 1.

Practice session:

The practice session consisted of 30 trials (20% stop trials) lasting one minute, and was completed on a laptop outside of the MRI scanner using the left and right arrow keys of the keyboard.

The participants were given the following verbal instructions before the practice session:

"Please read through the following instructions carefully and let me know when you are done. Afterwards, you will begin with the practice trials."

Written instructions in Presentation®:

In the following, an arrow will be displayed on the screen. The arrow points either to the left or right.

<Depiction of arrows pointing left and right>

If the tip of the arrow points to the left, please press the left button with your left index finger; if it points to the right, please press the right button with your right index finger. It is important that you react as quickly and accurately as possible to the direction of the arrow in each trial. (Displayed in yellow for emphasis.)

Continue with ENTER!

In some trials, another arrow pointing upwards will appear shortly after the first arrow is presented.

<Depiction of an arrow pointing upward>

When this happens, your task is not to react. You should therefore not press a button, but try to stop your reaction.
It is perfectly normal that you will not always succeed.
It is important that you react as quickly and as accurately as possible to the direction of the first arrow in each trial. Do not wait for the second arrow to appear! (Displayed in yellow for emphasis.)
If anything is still unclear, please ask. Otherwise, continue with the exercise.

Continue with ENTER!

Main session:
Verbal instructions for the main task inside the MRI scanner:
"We will now start the main task. Please remember to respond as quickly and accurately as possible. It may happen that you won't always be able to stop your response when the second arrow pointing upwards appears. That is completely fine. Please remain still and avoid any movement during the task. The measurement will take approximately 10 minutes."

Written instructions in Presentation®:
Now the main task begins. This will take about 10 minutes.
Please remember to react as quickly and as accurately as possible to the direction of the first arrow in each trial. Do not wait for the second arrow to appear!
If anything is still unclear, please ask. Otherwise, we will start now. (Displayed in yellow for emphasis.)

Table S1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Men and women	Withdrawal of the declaration of consent
Aged between 18 and 65 years	Exclusion criteria for an MRI scan (pregnancy, metal implants, etc.)
Normal or correctable eyesight	Severe internal, neurological and psychiatric comorbidities
Sufficient ability to communicate with the investigators, and to answer questions in oral and written form	Axis-I disorder according to ICD-10 and DSM 5 (except tobacco use disorder, substance abuse with less than 2(11) criteria according to DSM-5, mild depressive episode, adaptation disorder and specific phobia within the last 12 months)
Written informed and fully informed consent	Pharmacotherapy with psychoactive substances within the last 14 days (except treatment with SSRI/SNRIs for at least 28 days)
Diagnosis of alcohol use disorder according to DSM-5 or 'heavy drinking' (alcohol intake > 40g/ more than 5 days (women) & 60g/ more than 5 days (men)) and varying levels of adverse childhood experiences	Positive urine drug screening (amphetamine, benzodiazepines, cocaine, methamphetamine, morphine/opiate, methadone, cannabinoids)
	Withdrawal symptoms (CIWA-Ar* > 7)
	Intoxication at time of investigation (breathalyzer > 0.3‰)
	Suicidal tendency or potential danger for others

Note. *CIWA-Ar, Revised Clinical Institute Withdrawal Assessment Scale for Alcohol; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th revision

Table S2. Results from the one sample t-tests assessing general inhibition-related brain activation.

		MNI coordinates			Cluster-level		Peak-level	
	Brain area	**x**	**y**	**z**	**FWE-corr.**	***k***	**FWE-corr.**	***t***
(A) Stop error > Stop success								
L	Precentral G.	-38	-18	50	0.001	600	0.230	5.21
L	Postcentral G.							
R	Cerebellum Ext.	12	-54	-20	0.012	388	0.245	5.18
R	Cerebellum Ext.	20	-52	-18			0.253	5.16
R	Lingual G.							
R	Fusiform G.							
(B) Stop error < Stop success								
R	Superior Frontal G.	18	8	50	0.026	322	0.591	4.65
R	Suppl. Motor Cortex							
R	Middle Frontal G.							
R	Accumbens Area	10	8	-12	0.071	242	0.004	7.10
R	Putamen	18	10	-14			0.010	6.66
(C) Conjunction of Stop error and Stop success								
R	Anterior insula	36	20	-8	0.000	18770	0.000	15.11
R	Posterior Orbital G.							
R	Orbital Part of IFG							
L	Anterior insula	-30	20	-10			0.000	11.85
L	Posterior Orbital G.							
L	Orbital Part of IFG							
L	Inferior Occipital G.	-44	-72	0	0.000	24430	0.000	11.07
L	Middle Temporal G.							
L	Inferior Temporal G.							
L	Supramarginal G.	-58	-44	26			0.000	10.90
R	Inferior Occipital G.	46	-70	-4			0.000	10.81
R	Middle Temporal G.							
R	Inferior Temporal G.							

	Brain Stem	10	-26	-20	0.000	2846	0.002	7.33
R	Ventral DC							
R	Parahippocampal G.	10	-28	-10			0.007	6.82
R	Thalamus Proper							
L	Thalamus Proper	0	-24	6			0.012	6.59
R	Thalamus Proper							
L	Middle Frontal G.	-28	48	32	0.001	593	0.359	5.00
L	Superior Frontal G.							
R	Middle Cingulate G.	4	-22	30	0.040	272	0.556	4.72
L	Middle Cingulate G.							
R	Posterior Cingulate G.							
L	Posterior Cingulate G.							

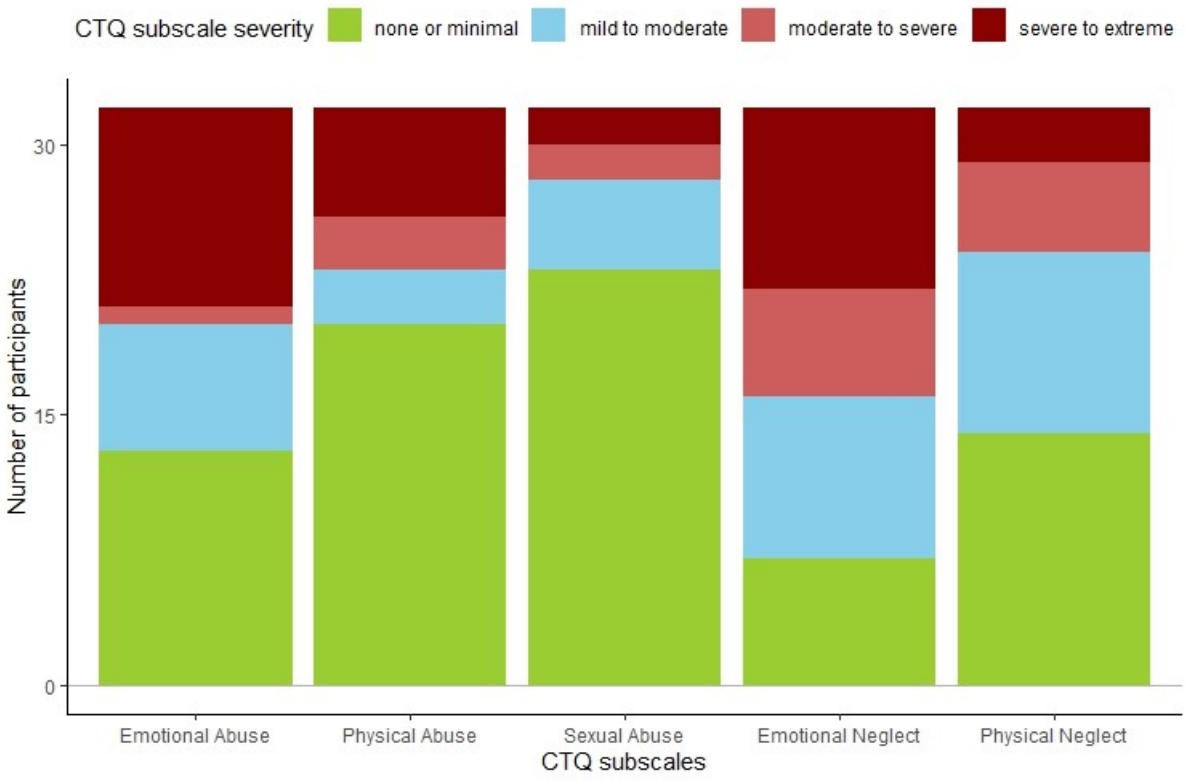
Note. DC = Diencephalon; Ext. = Exterior; FWE-corr. = family-wise error correction; G. = Gyrus; IFG = Inferior frontal gyrus; L = Left; R = Right; Suppl. = Supplementary. Voxel-wise significance threshold: $p < 0.001$, uncorrected.

Table S3. Descriptive statistics for stop-signal task

	Mean (SD)
SSRT (ms)	274.38 (92.72)
SSD (ms)	323.75 (160.76)
Mean Go RT (ms)	598.13 (103.05)
Probability of responding on a Stop trial (%)	52.81 (3.72)
Probability of Go omissions (%)	5.17 (6.45)
Probability of choice errors on Go trials (%)	1.16 (1.79)
RT of Go responses on unsuccessful trials	573.63 (130.15)

Note. ms, milliseconds; RT, reaction time; SSD, stop-signal delay; SSRT, stop-signal reaction time

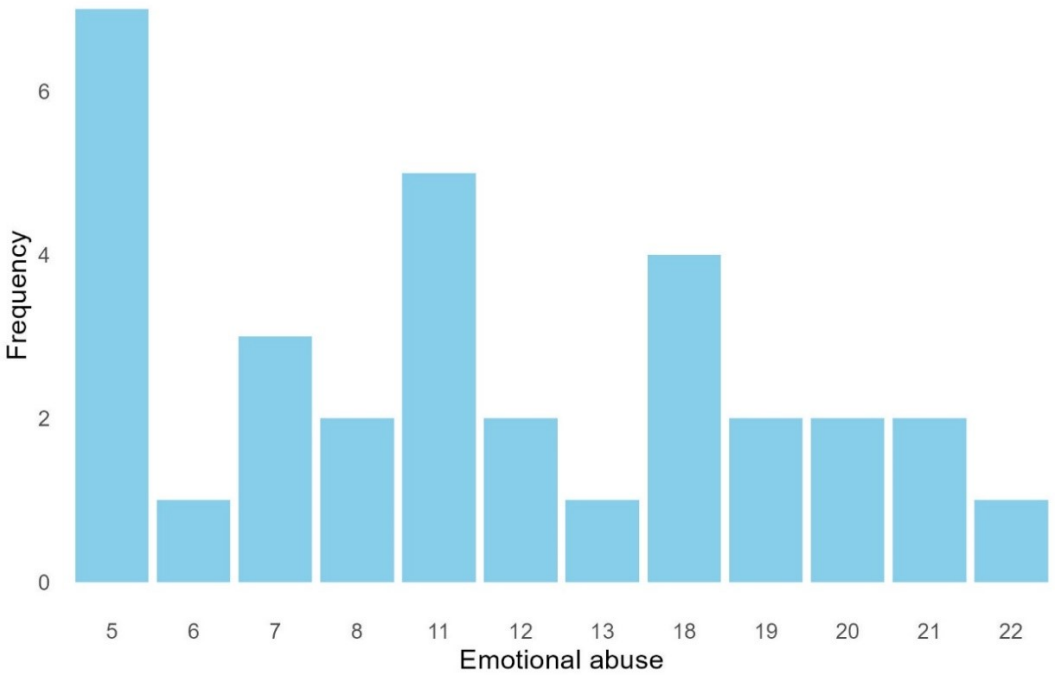
Figure S1. Categorical severity for each CTQ subtype.



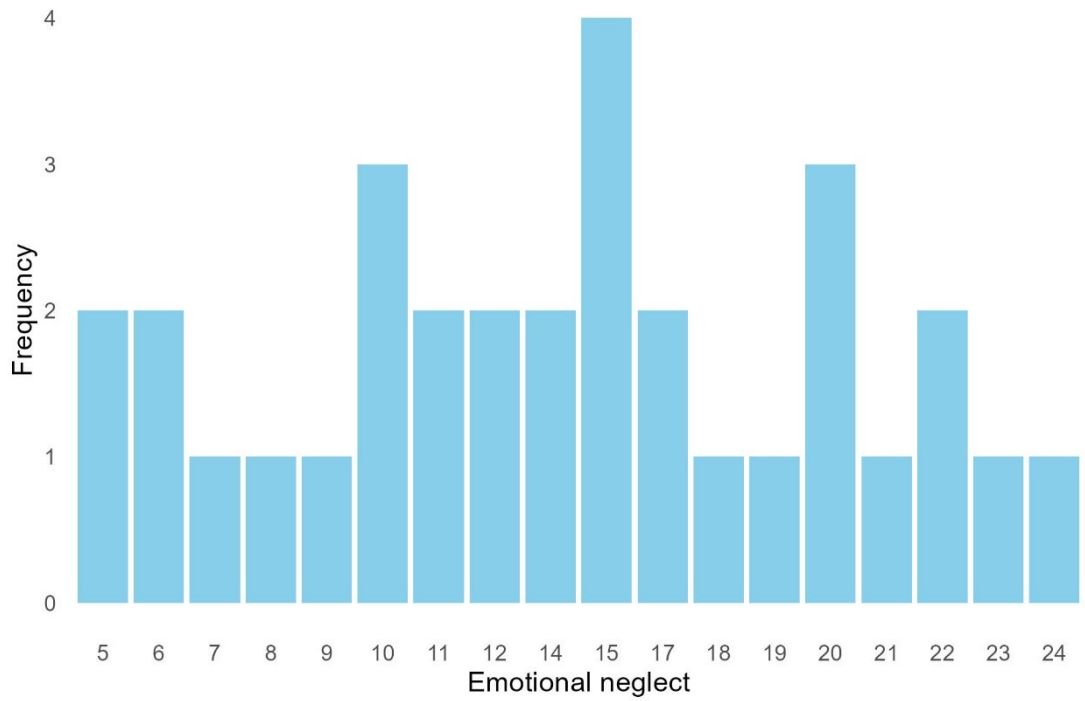
Note. CTQ, Childhood Trauma Questionnaire

Figure S2. Frequencies of CTQ subscale scores

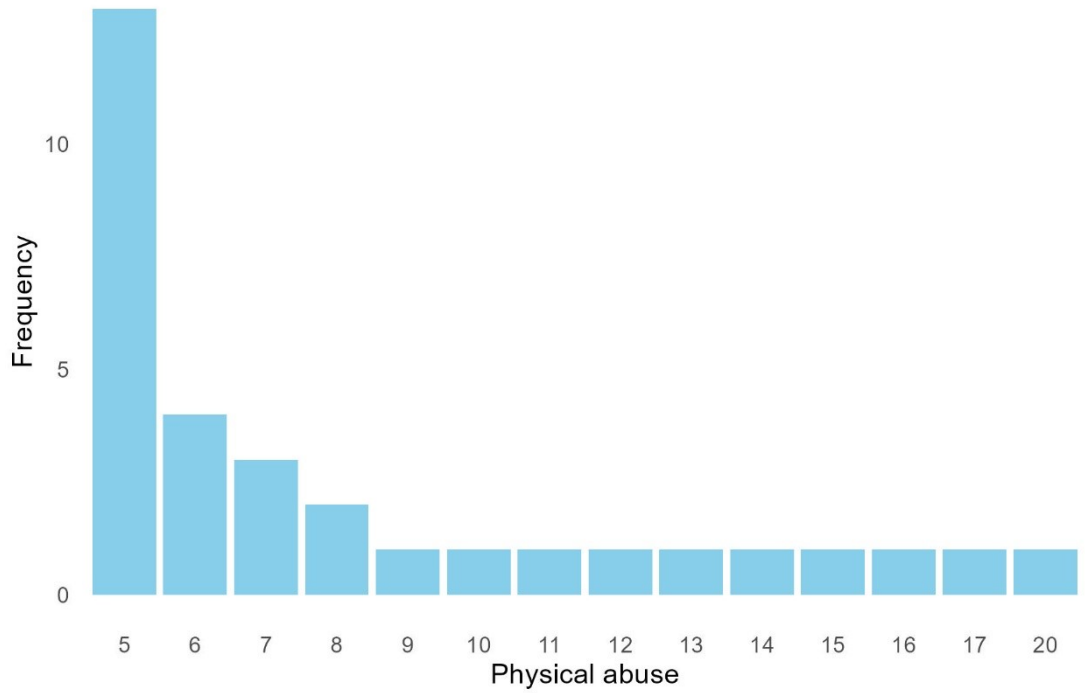
a)



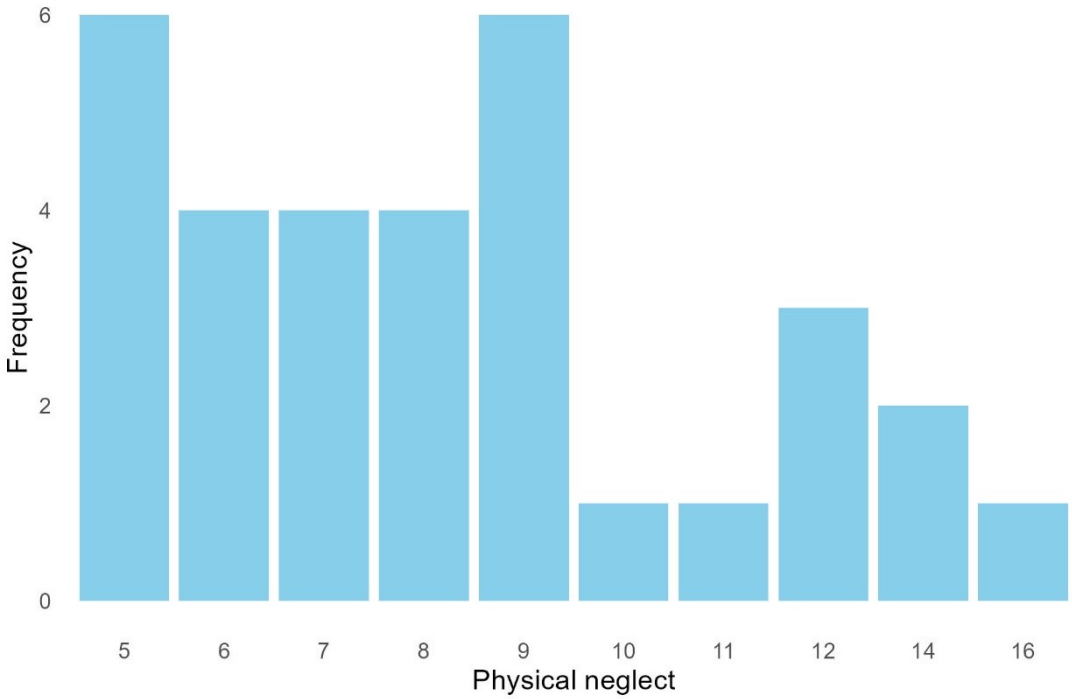
b)


Frequency
0
1
2
3
4
5 6 7 8 9 10 11 12 14 15 17 18 19 20 21 22 23 24
Emotional neglect

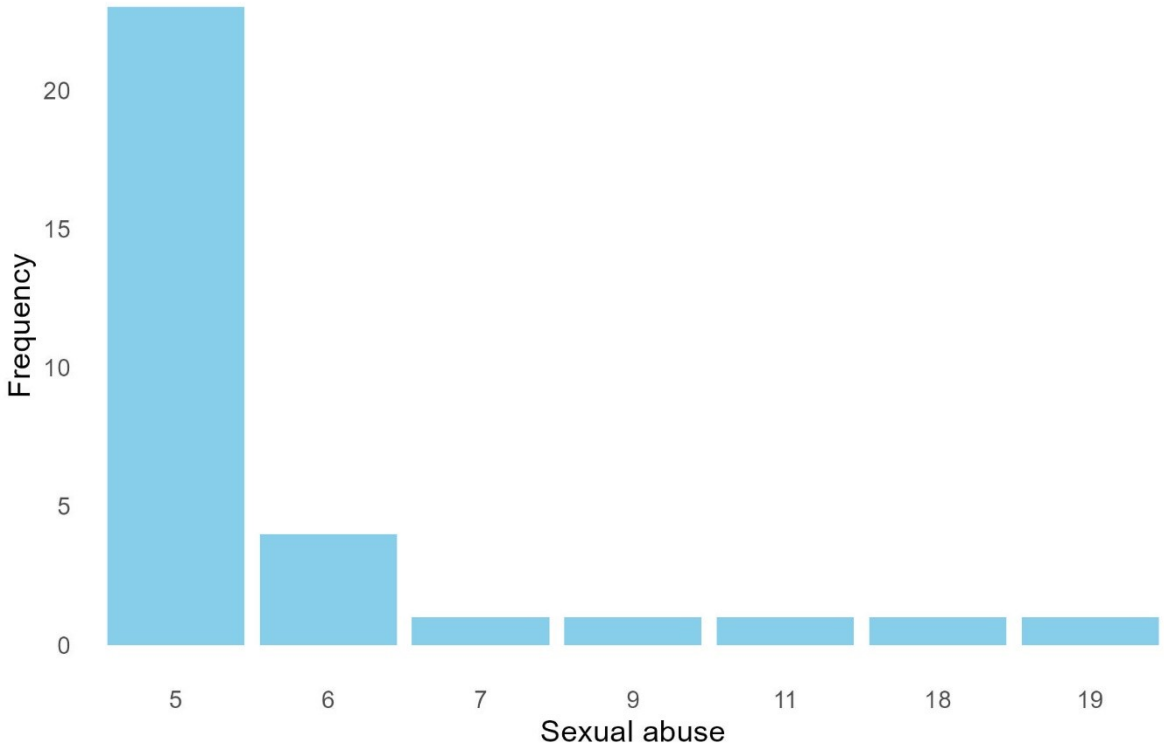
c)


Frequency
0
5
10
5 6 7 8 9 10 11 12 13 14 15 16 17 20
Physical abuse

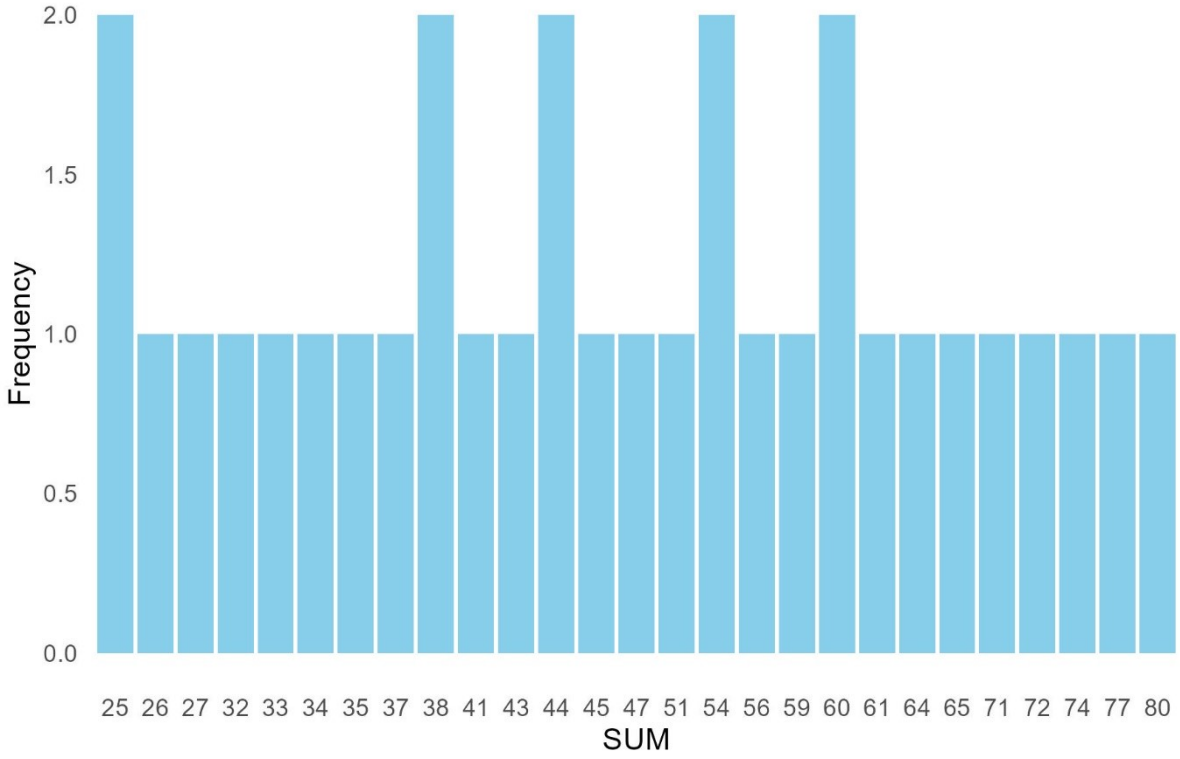
d)


6
4
2
0
Frequency
5
6
7
8
9
10
11
12
14
16
Physical neglect

e)


20
15
10
5
0
Frequency
5
6
7
9
11
18
19
Sexual abuse

f)


2.0
1.5
1.0
0.5
0.0
Frequency
25 26 27 32 33 34 35 37 38 41 43 44 45 47 51 54 56 59 60 61 64 65 71 72 74 77 80
SUM

9.3 Study III Supplementary Materials: Sports participation moderates the risk of family-specific negative life events on alcohol use among adolescents: Evidence from the longitudinal MyLife study

Supplement 1. Outcome measures for covariates.

Immigrant background was measured at T1 based on the question “Which language do you speak at home?”. The original response options of “Both Norwegian and another language” or “Only another language” were recoded to reflect likely immigrant background vs. “Only Norwegian spoken at home”. Omitted responses were retained in all analyses as the “not reported” group.

Depressive symptoms during the past 2 weeks were measured using the 9-item Public Health Questionnaire (PHQ-9) modified for use with adolescents (Johnson et al., 2002). Participants responded to scale items (e.g., “I had sleep problems”) using the 4-point Likert scale responses ranging from 0 = “Not at all” to 3 = “Almost every day”, which were summed up to generate scale scores.

Sensation seeking was measured with the 4-item Brief Sensation Seeking Scale (BSSS) (Stephenson et al., 2003). Participants responded to scale items (e.g., “I like to do frightening things”) using the 5-point Likert scale responses ranging from 1 = “Completely disagree” to 5 = “Completely agree”, which were averaged to generate scale scores.

Unstructured leisure time was measured with the question “Think about the past 30 days, how often have you hung out in shopping malls, on the streets and the like just for fun?”. The response options ranging from “Not at all” to “5-7 days per week” were recoded as a continuous variable by selecting a mid-point value to reflect the actual number of days past month (i.e., 5-7 days per week = 6 days per week = 24 days past month).

Positive Alcohol Expectancies were measured using the 6-item Social Facilitation subscale of the Alcohol Outcome Expectancies Scale (AOES) (Leigh & Stacy, 1993). Participants responded to scale items assessing their expectations of alcohol use (e.g., “I become more social”) using the 5-point Likert scale responses ranging from 1 = “Definitely not” to 5 = “Definitely”, which were averaged to generate scale scores.

Conduct problems were measured using the nine items adopted from the Young in Norway Study (Frøyland et al., 2010) assessing the frequency of conduct problems

such as stealing and vandalism during the past 12 months. The response options ranging from “Never” to “Five times or more” were recoded as a continuous variable by selecting a mid-point value and then summed up to generate index of conduct problems frequency.

Friendships were assessed by asking participants how many close and trustworthy friends they have. The response options were “None”, “Not sure” (both coded as 0), “1”, “2” and “3 or more”.

Pandemic-associated anxiety (COVID-19) was measured using the three items based on the Pandemic Anxiety Scale (McElroy et al., 2020) that were added to the T4 (2020) and T5 (2021) assessments. Participants responded to scale items assessing their worries about SARS-CoV-2 infections and the remote schooling situation using the 3-point Likert scale responses ranging from 1 = “Not worried at all” to 3 = “Highly worried”, which were averaged to generate scale scores.

All covariates save for socio-demographic characteristics (gender, grade cohort, and immigrant background) and NLE life history were included as time-varying predictors in models to follow.

References

Frøyland, L. R., Strand, N. P., & von Soest, T. (2010). Young in Norway - cross-sectional: Documentation of design, variables and scales.

Johnson, J. G., Harris, E. S., Spitzer, R. L., & Williams, J. B. W. (2002). The patient health questionnaire for adolescents: validation of an instrument for the assessment of mental disorders among adolescent primary care patients. J Adolesc Health, 30(3), 196-204.

Leigh, B. C., & Stacy, A. W. (1993). Alcohol outcome expectancies: Scale construction and predictive utility in higher order confirmatory models. Psychological Assessment, 5(2), 216-229. https://doi.org/10.1037/1040-3590.5.2.216

McElroy, E., Patalay, P., Moltrecht, B., Shevlin, M., Shum, A., Creswell, C., & Waite, P. (2020). Demographic and health factors associated with pandemic anxiety in the context of COVID-19. Br J Health Psychol, 25(4), 934-944. https://doi.org/10.1111/bjhp.12470

Stephenson, M. T., Hoyle, R. H., Palmgreen, P., & Slater, M. D. (2003). Brief measures of sensation seeking for screening and large-scale surveys. Drug Alcohol Depend, 72(3), 279-286. https://doi.org/10.1016/j.drugalcdep.2003.08.003

Supplement 2. STATA Syntax for all tested models.

unconditional Model 0 quadratic time*
xtmixed auditc time0 c.time0##c.time|| schoolnumber: || id: time0, cov(ind) variance reml
estat ic
estat icc

**** Model 1, NLE main effect; quadratic time****
xtmixed auditc time0 c.time0##c.time i.boy i.level_1 nle c.nle##c.time0 c.nle##c.time0##c.time|| schoolnumber: || id: time0 , cov(ind) variance reml
estat ic
estat icc

**** Model 2, SP main effect; quadratic time****
xtmixed auditc time0 c.time0##c.time i.boy i.level_1 pm_daysports c.pm_daysports##c.time0 c.pm_daysports##c.time0##c.time|| schoolnumber: || id: time0 , cov(ind) variance reml
estat ic
estat icc

**** Model 3, NLExSPxTime; quadratic time****

xtmixed auditc time0 c.time0##c.time0 i.boy i.level_1 i.imm phq ss i.nle_fam1_sum_before_new i.movedout conduct alcexp_soci ib(2).cl_friends pm_daysmall covid_worry nle pm_daysports c.nle##c.time0 c.pm_daysports##c.time0 c.nle##c.pm_daysports##c.time0 || schoolnumber: || id: time0 , cov(ind) variance reml
estat ic
estat icc

**** Model 4, NLExSPxTimexTime; quadratic time****
xtmixed auditc time0 c.time0##c.time0 i.boy i.level_1 i.imm phq ss i.nle_fam1_sum_before_new i.movedout phq conduct alcexp_soci ib(2).cl_friends pm_daysmall covid_worry
nle c.nle##c.time0 c.nle##c.time0##c.time
pm_daysports c.pm_daysports##c.time0 c.pm_daysports##c.time0##c.time
c.nle##c.pm_daysports c.nle##c.pm_daysports##c.time0
c.nle##c.pm_daysports##c.time0##c.time0
|| schoolnumber: || id: time0 , cov(ind) variance reml
estat ic
estat icc

****plotting prototypical trajectories at conditional values of NLE and SP for selected Model 3****
margins, at(time0=(0(1)4) nle =(0) pm_daysport =(0 24)) atmeans
marginsplot, x(time0)

```
marginsplot, recastci(rarea) ciopt(color(%30))

margins, at(time0=(0(1)4) nle =(3) pm_daysport =(0 24)) atmeans
marginsplot, x(time0)
marginsplot, recastci(rarea) ciopt(color(%30))
```

9.4 Study IV Supplementary Materials: Can high-intensity interval training improve health outcomes among people with substance use disorders? A systematic review and preliminary meta-analysis

Supplement 1. Full Search Strategy

Main aspects

P

	Substance-related disorders	

I

	High intensity interval training	

No Limits

Search guide overview

1	P	
2	I	
3	1 AND 2	

Databases and platforms involved

- PubMed (via NCBI)
- Embase (via Elsevier)
- Cochrane Library (via Wiley)
- Web of Science (via Clarivate)
- Psycinfo (via Ebscohost)
- ClinicalTrials.Gov (via www.clinicaltrials.gov)
- ICTRP (via https://trialsearch.who.int/Default.aspx)

Results report

The results were saved and deduplicated in Endnote. For this, the settings DOI/ Author, Year, Title, Secondary Title/ Author, Year, Title, Pages/ Title/ Author, Year were applied. However, some items may appear more than once.

The hits are sorted by database in Endnote. The PubMed hits were the first to be exported to Endnote. These are therefore preferred for deduplication. This means that in the case of duplicates, entries from other databases are removed first.

The hit count for each database in this report relates to the status before deduplication in EndNote.

1.1 PubMed

Hits	Date
576	12.03.2024

P

1	**"Substance-Related Disorders"[Mesh] OR ((("Caffeine"[Mesh] OR "Hallucinogens"[Mesh] OR "Hypnotics and Sedatives"[Mesh] OR "Anti-Anxiety Agents"[Mesh] OR "Central Nervous System Stimulants"[Mesh] OR "Amphetamines"[Mesh] OR "Alcohol Drinking"[Mesh] OR** Amphetamine*[tiab] OR Caffeine[tiab] OR Hallucinogen*[tiab] OR Psychedelic*[tiab] OR Psychotomimetic*[tiab] OR Hypnotic*[tiab] OR Sedative*[tiab] OR Antianxiety[tiab] OR "Anti Anxiety"[tiab] OR Anxiolytic*[tiab] OR Stimulant*[tiab] OR Alcohol[tiab] OR Marijuana[tiab] OR Cannabis[tiab] OR Hashish[tiab] OR Inhalant*[tiab] OR Sniffing*[tiab] OR opioids[tiab] OR opiate[tiab] OR tobacco[tiab] OR Substance*[tiab] OR Drug*[tiab]) AND (disorder*[tiab] OR Abuse*[tiab] OR Depend*[tiab] OR Addiction*[tiab]))	804550

I

2	**"High-Intensity Interval Training"[Mesh] OR** ((intensive[tiab] OR "high intensity"[tiab] OR "high aerobic intensity"[tiab] OR sprint*[tiab])	41958

	AND (exercise*[tiab] OR training[tiab] OR "physical activit*"[tiab])) OR HIIT[tiab]	

Strings
1-2 as in the tables above

Field	String	Hits
3	#1 AND #2	576

1.2 Embase

Hits	Date
176	12.03.2024

P

1	**'drug dependence'/exp OR** **(('caffeine'/exp OR** **'psychedelic agent'/exp OR** **'hypnotic sedative agent'/exp OR** **'anxiolytic agent'/exp OR** **'central stimulant agent'/exp OR** **'amphetamine derivative'/exp OR** **'drinking behavior'/exp OR** Amphetamine*:ti,ab,kw OR Caffeine:ti,ab,kw OR Hallucinogen*:ti,ab,kw OR Psychedelic*:ti,ab,kw OR Psychotomimetic*:ti,ab,kw OR Hypnotic*:ti,ab,kw OR Sedative*:ti,ab,kw OR Antianxiety:ti,ab,kw OR "Anti Anxiety":ti,ab,kw OR Anxiolytic*:ti,ab,kw OR Stimulant*:ti,ab,kw OR Alcohol:ti,ab,kw OR Marijuana:ti,ab,kw OR Cannabis:ti,ab,kw OR Hashish:ti,ab,kw OR Inhalant*:ti,ab,kw OR Sniffing*:ti,ab,kw OR opioids:ti,ab,kw OR opiate:ti,ab,kw OR tobacco:ti,ab,kw OR Substance*:ti,ab,kw OR Drug*:ti,ab,kw) AND	

	(disorder*:ti,ab,kw OR Abuse*:ti,ab,kw OR Depend*:ti,ab,kw OR Addiction*:ti,ab,kw))	

I

2	**'high intensity interval training'/exp OR** ((intensive:ti,ab,kw OR "high intensity":ti,ab,kw OR "high aerobic intensity":ti,ab,kw OR sprint*:ti,ab,kw) AND (exercise*:ti,ab,kw OR training:ti,ab,kw OR "physical activit*":ti,ab,kw)) OR HIIT:ti,ab,kw	

Strings

Field	String	Hits
1	'drug dependence'/exp OR (('caffeine'/exp OR 'psychedelic agent'/exp OR 'hypnotic sedative agent'/exp OR 'anxiolytic agent'/exp OR 'central stimulant agent'/exp OR 'amphetamine derivative'/exp OR 'drinking behavior'/exp OR amphetamine*:ti,ab,kw OR caffeine:ti,ab,kw OR hallucinogen*:ti,ab,kw OR psychedelic*:ti,ab,kw OR psychotomimetic*:ti,ab,kw OR hypnotic*:ti,ab,kw OR sedative*:ti,ab,kw OR antianxiety:ti,ab,kw OR 'anti anxiety':ti,ab,kw OR anxiolytic*:ti,ab,kw OR stimulant*:ti,ab,kw OR alcohol:ti,ab,kw OR marijuana:ti,ab,kw OR cannabis:ti,ab,kw OR hashish:ti,ab,kw OR inhalant*:ti,ab,kw OR sniffing*:ti,ab,kw OR opioids:ti,ab,kw OR opiate:ti,ab,kw OR tobacco:ti,ab,kw OR substance*:ti,ab,kw OR drug*:ti,ab,kw) AND (disorder*:ti,ab,kw OR abuse*:ti,ab,kw OR depend*:ti,ab,kw OR addiction*:ti,ab,kw))	127351
2	'high intensity interval training'/exp OR ((intensive:ti,ab,kw OR 'high intensity':ti,ab,kw OR 'high aerobic intensity':ti,ab,kw OR sprint*:ti,ab,kw) AND (exercise*:ti,ab,kw OR training:ti,ab,kw OR 'physical activit*':ti,ab,kw)) OR hiit:ti,ab,kw	58036
3	#1 AND #2	1047

Embase filter to switch off PubMed

4	#3 NOT ([medline]/lim OR [pubmed-not-medline]/lim)	497

Embase filter to exclude document types not of interest

5	#4 NOT ('Conference Abstract'/it OR 'Note'/it OR 'chapter'/it)	176

1.3 Cochrane Library

Hits	Date

Reviews: 12 ~~Trials: 777~~ CENTRAL was not considered because there were too many irrelevant results included	12.03.2024

P

1	**[mh "Substance-Related Disorders"] OR** **(([mh "Caffeine"] OR** **[mh "Hallucinogens"] OR** **[mh "Hypnotics and Sedatives"] OR** **[mh "Anti-Anxiety Agents"] OR** **[mh "Central Nervous System Stimulants"] OR** **[mh "Amphetamines"] OR** **[mh "Alcohol Drinking"] OR** Amphetamine*:ti,ab,kw OR Caffeine:ti,ab,kw OR Hallucinogen*:ti,ab,kw OR Psychedelic*:ti,ab,kw OR Psychotomimetic*:ti,ab,kw OR Hypnotic*:ti,ab,kw OR Sedative*:ti,ab,kw OR Antianxiety:ti,ab,kw OR "Anti Anxiety":ti,ab,kw OR Anxiolytic*:ti,ab,kw OR Stimulant*:ti,ab,kw OR Alcohol:ti,ab,kw OR Marijuana:ti,ab,kw OR Cannabis:ti,ab,kw OR Hashish:ti,ab,kw OR Inhalant*:ti,ab,kw OR Sniffing*:ti,ab,kw OR opioids:ti,ab,kw OR opiate:ti,ab,kw OR tobacco:ti,ab,kw OR Substance*:ti,ab,kw OR Drug*:ti,ab,kw) AND (disorder*:ti,ab,kw OR Abuse*:ti,ab,kw OR Depend*:ti,ab,kw OR Addiction*:ti,ab,kw))	163987

I

2	**[mh "High-Intensity Interval Training"] OR** ((intensive:ti,ab,kw OR "high intensity":ti,ab,kw OR "high aerobic intensity":ti,ab,kw OR	18144

	sprint*:ti,ab,kw) AND (exercise*:ti,ab,kw OR training:ti,ab,kw OR physical NEAR/3 activit*:ti,ab,kw)) OR HIIT:ti,ab,kw	

Strings

1-2 as in the tables above

Field	String	Hits
3	#1 AND #2	789

1.4 Web of Science Core Collection

Hits	Date
460	12.03.2024

P

1	(Amphetamine* OR Caffeine OR Hallucinogen* OR Psychedelic* OR Psychotomimetic* OR Hypnotic* OR Sedative* OR Antianxiety OR "Anti Anxiety" OR Anxiolytic* OR Stimulant* OR Alcohol OR Marijuana OR Cannabis OR Hashish OR Inhalant* OR Sniffing* OR opioids OR opiate OR tobacco OR Substance* OR Drug*) AND (disorder* OR Abuse* OR Depend* OR Addiction*)	

I

2	((intensive OR "high intensity" OR	

	"high aerobic intensity" OR sprint*) AND (exercise* OR training OR "physical activit*")) OR HIIT	

Strings

1 (TI,AB,AK)	TI=((Amphetamine* OR Caffeine OR Hallucinogen* OR Psychedelic* OR Psychotomimetic* OR Hypnotic* OR Sedative* OR Antianxiety OR "Anti Anxiety" OR Anxiolytic* OR Stimulant* OR Alcohol OR Marijuana OR Cannabis OR Hashish OR Inhalant* OR Sniffing* OR opioids OR opiate OR tobacco OR Substance* OR Drug*) AND (disorder* OR Abuse* OR Depend* OR Addiction*)) OR AB=((Amphetamine* OR Caffeine OR Hallucinogen* OR Psychedelic* OR Psychotomimetic* OR Hypnotic* OR Sedative* OR Antianxiety OR "Anti Anxiety" OR Anxiolytic* OR Stimulant* OR Alcohol OR Marijuana OR Cannabis OR Hashish OR Inhalant* OR Sniffing* OR opioids OR opiate OR tobacco OR Substance* OR Drug*) AND (disorder* OR Abuse* OR Depend* OR Addiction*)) OR AK=((Amphetamine* OR Caffeine OR Hallucinogen* OR Psychedelic* OR Psychotomimetic* OR Hypnotic* OR Sedative* OR Antianxiety OR "Anti Anxiety" OR Anxiolytic* OR Stimulant* OR Alcohol OR Marijuana OR Cannabis OR Hashish OR Inhalant* OR Sniffing* OR opioids OR opiate OR tobacco OR Substance* OR Drug*) AND (disorder* OR Abuse* OR Depend* OR Addiction*))	539175
2 (TI,AB,AK)	TI=(((intensive OR "high intensity" OR "high aerobic intensity" OR sprint*) AND (exercise* OR training OR "physical activit*")) OR HIIT) OR AB=(((intensive OR "high intensity" OR "high aerobic intensity" OR sprint*) AND (exercise* OR training OR "physical activit*")) OR HIIT) OR AK=(((intensive OR "high intensity" OR "high aerobic intensity" OR sprint*) AND (exercise* OR training OR "physical activit*")) OR HIIT)	46015

3	1 AND 2	460

1.5 PsycInfo

Hits	Date
627	12.03.2024

P

1	DE "Toxic Disorders" OR DE "Acute Alcohol Intoxication" OR DE "Drug Induced Congenital Disorders" OR DE "Substance Induced Psychotic Disorders"	474590

	DE "Substance Use Disorder" OR DE "Drug Abuse Liability" DE "Caffeine" OR DE "Psychotropic Drugs" OR DE "Sedatives" OR DE "Amphetamines" OR DE "Alcohol Use" OR (TX (Amphetamine* OR Caffeine OR Hallucinogen* OR Psychedelic* OR Psychotomimetic* OR Hypnotic* OR Sedative* OR Antianxiety OR "Anti Anxiety" OR Anxiolytic* OR Stimulant* OR Alcohol OR Marijuana OR Cannabis OR Hashish OR Inhalant* OR Sniffing* OR opioids OR opiate OR tobacco OR Substance* OR Drug*) AND (disorder* OR Abuse* OR Depend* OR Addiction*))	

I

2	(TX ((intensive OR "high intensity" OR "high aerobic intensity" OR sprint*) AND (exercise* OR training OR "physical activit*"))) OR HIIT	10806

Strings

3	1 AND 2	627

1.6 ClinicalTrials.Gov

http://www.clinicaltrials.gov/

Hits	Date
515	12.03.2024

P

~~1~~	~~(Amphetamine OR Caffeine OR Hallucinogen OR Psychedelic OR Psychotomimetic OR Hypnotic OR Sedative OR Antianxiety OR "Anti Anxiety" OR Anxiolytic OR Stimulant OR Alcohol OR Marijuana OR Cannabis OR Hashish OR Inhalant OR Sniffing OR opioids OR opiate OR tobacco OR Substance OR Drug) AND (disorder OR Abuse OR Depend OR Addiction)~~	

P

1	"Drug Abuse" OR "drug depend"	The search terms were reduced because otherwise over 2400 mostly irrelevant results would be found.

I

2	((intensive OR "high intensity" OR "high aerobic intensity" OR sprint) AND (exercise OR training OR "physical activity")) OR HIIT	

Strings

Field	String	Hits
1	(EXPAND[Concept] ("Drug Abuse" OR "drug depend"))	3071
2	AND ((intensive OR EXPAND[Concept] "high intensity" OR EXPAND[Concept] "high aerobic intensity" OR sprint) AND (exercise OR training OR EXPAND[Concept] "physical activity")) OR HIIT	6681
3	1 AND 2	515

1.7 International Clinical Trials Registry Platform ICTRP (WHO Trials)

https://trialsearch.who.int/AdvSearch.aspx (advanced)

Hits	Date
advanced mode: 1	12.03.2024

P

1	Drug Abuse OR drug depend	The search terms were reduced due to the limited functionality of this search engine.

I

2	intensive exerciseOR high intensity exercise OR high aerobic intensity exercise OR sprint exercise OR intensive trainingOR high intensity training OR high aerobic intensity training OR sprint training	

Strings (in advanced mode)

Fields	String	Hits
1 (Title)	intensive exerciseOR high intensity exercise OR high aerobic intensity exercise OR sprint exercise OR intensive trainingOR high intensity training OR high aerobic intensity training OR sprint training	191
2 (Condition)	Drug Abuse OR drug depend	234
3 (Intervention)	intensive exerciseOR high intensity exercise OR high aerobic intensity exercise OR sprint exercise OR intensive trainingOR high intensity training OR high aerobic intensity training OR sprint training	381
4	1 AND 2	1
5	2 AND 3	0

Supplementary Table 1. Records excluded after full-text screening, with reasons

Record	Reason for exclusion
"Exercise as a Treatment for Substance Use Disorders Protocol" (2013)	Not HIIT
"Reinforcing Exercise in Substance Abusing Patients" (2015)	Not HIIT
"Exercise and Treatment-as-usual in Substance Use Treatment Outcomes" (2016)	Not HIIT
Abrantes et al. (2011)	Not HIIT
Ay and Pancar (2022)	Not HIIT
Brellenthin et al. (2021)	Not HIIT
Chen et al. (2021)	Not HIIT
Chen et al. (2020)	Not HIIT
Colledge et al. (2017)	Not HIIT
Gao et al. (2022)	Not HIIT
Pechtl et al. (2024)	Not HIIT
Wang et al. (2019)	Not HIIT
Zhang et al. (2020)	Not HIIT
Zhou et al. (2019)	Not HIIT
"High Intensity Interval Training With Strength/Power Exercises on VO2Max" (2016)	Not in SUD populations
"Aerobic Interval and Moderate Continuous Exercise Training on Ventricular Functions" (2017)	Not in SUD populations
"Affective Responses Following Aerobic Exercise With Different Intensities" (2017)	Not in SUD populations
"High Intensity Interval Training Versus Circuit Training" (2017)	Not in SUD populations
"Cardiovascular Effects of High-Intensity Interval Training (HIIT)" (2018)	Not in SUD populations
"High Intensity Interval Training vs Moderate Continuous Endurance Exercise Training on Program Adherence" (2018)	Not in SUD populations
"Home-based HIIT in a Primary-care Setting for at Risk Individuals: A Multidisciplinary Approach" (2019)	Not in SUD populations
"Effect of Ethnicity on Changes in VO2max and Cardiac Output in Response to Short-Term	Not in SUD populations

High Intensity Interval Training" (2019)	
"High Intensity Interval Training in Severe Mental Illness" (2021)	Not in SUD populations
"Effects of Hiit Associated With Emotional Regulation on Negative Emotions" (2022)	Not in SUD populations
"The Effect of Exercise Intensity on Adherence" (2022)	Not in SUD populations
"The HIIT Cognition Study" (2023)	Not in SUD populations
"HIIT vs. MICT Training Study" (2024)	Not in SUD populations
Chapman et al. (2017)	Not in SUD populations
Epstein et al. (2021)	Not in SUD populations
Haberstroh et al. (2022)	Not a primary research article
Loe et al. (2022)	Not a primary research article
Menglu et al. (2021)	Not a primary research article
Zhu et al. (2022)	Not a primary research article
Andreassen et al. (2019)	Not a primary research article
"Aerobic Exercise for Cognitive Functioning in Patients With Substance Use Disorder" (2024)	Ongoing study
"Structured Physical Exercise in Short-term Inpatient Treatment of Substance Use Disorder" (2024)	Ongoing study
"Increasing Smoking Cessation Success Through Sleep-amplified Memory Consolidation" (2026)	Ongoing study
"Brain Exercise and Addiction Trial" (2022)	No data available
Dürmüş et al. (2019)	Duplicate data

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Supplementary Table 2. TIDieR Checklist (Items 1-6)

Study	Item 1- Brief name of the intervention	Item 2- Why	Item 3- What- materials	Item 4- What- procedures	Item 5- Who provided	Item 6- How
Dürmüs et al., 2020	Intervention: HIIT Control group: CG – details lacking	High Intensity Interval Training is a type of exercise program consisting of short, intermittent and intense activity nearing the maximal effort of the individual to achieve 80-100% increase in the heart rate and interrupted by rest or low intensity exercise (Kong et al. 2018). HIIT has drawn attention as it is beneficial in a shorter term than aerobic exercising and increases the aerobic capacity (Baynaz et al. 2017). Our research has aimed at investigating in patients with OpUD the effects to HIIT on symptoms of depression, anxiety and substance craving and on the serum levels of cortisol, IGF-1, IFN-γ and IL-17.	The HIIT program was implemented by means of 3 consecutive Wingate anaerobic tests (Bar-Or 1987) on the Monark bicycle ergometer at the sports physiology laboratory. The procedure was carried out twice per week on nonconsecutive days similarly to that previously carried out for another study (Vardar et al. 2018).	At the start of the HIIT, the participants warmed up for 4 minutes on the 30W pedal. During the loading exercise the participants pedalled for 30 seconds as fast as they individually could while they were verbally motivated. Subsequently the participants worked on the 30W pedal for 4 minutes. This exercise session comprising 30 seconds of loading followed by 4minutes of resting on the 30W pedal was repeated 3 times. The participants rested 3 days between each of the 5 exercise sessions carried out during the 21-day HIIT treatment period when the detox treatment given in the hospital was also completed.	All sessions conducted in a psychiatric research facility. Unclear who supervised these.	Participants encouraged to follow the specific program. Assumed individual.

Study	Item 1- Brief name of the intervention	Item 2- Why	Item 3- What- materials	Item 4- What- procedures	Item 5- Who provided	Item 6- How
Flemmen et al., 2014	Intervention Group: HIIT Control group: Conventional rehabilitation control group (CG)	SUD is associated with an increased incidence of health and psychosocial problems including cardiovascular disease. HIIT has been shown to reduce the risk of cardiovascular disease in patients with CAD. Exercise also has an overall beneficial effect on mental health in patients with mental illness. The aim of this study was to evaluate whether HIIT was feasible for SUB patients, and whether it has beneficial health effects.	A treadmill was used for HIIT sessions. During exercise sessions, HR was monitored using a Polar F6 HR monitor (Polar Electro, Finland). MaxHR was assessed before exercise training using a test until exhaustion on the treadmill. Both HIIT and CG groups participated in clinical treatment activities throughout the program, these comprised ballgames (indoor-soccer and volleyball), yoga, stretching, outdoor walking, low resistance strength training, ceramics, TV games, and card games, thus a range of appropriate utensils were used for these tasks.	Intervention Group: 4 X 4 mins of high intensity exercise conducted at 90–95% of HRmax, interspersed by 3 min recovery periods conducted at ~70% of HRmax. Each session lasted 25 mins excluding warm-up and cool-down. Additional clinic treatment program: All participants also participated in clinical treatment activities throughout the program comprising sports and leisure activities. These activities reached an estimated intensity level of <70% of HRmax. Additionally, within the same time period as the HIIT sessions, the patients allocated to CG group participated in a self-elected activity among the offered sports or games in the clinical treatment program.	All exercise sessions were supervised, the qualifications of the supervisor were not reported.	Supervised exercise sessions were provided face-to-face. No mention of group or individual setting

Study	Item 1- Brief name of the intervention	Item 2- Why	Item 3- What- materials	Item 4- What- procedures	Item 5- Who provided	Item 6- How
Li et al., 2023	Intervention: aerobic HIIT calisthenics intervention (75% to 85% HRmax) 40 min/time three times a week. Control group: performed routine forced withdrawal life	Long-term HIIT can effectively improve the physical health of drug addicts, improve their physical fitness and functional status, enhance the body's antioxidant capacity, and promote benign changes in neurobiological functions. Based on this, this study used high-intensity intermittent aerobics as exercise intervention prescription, aiming to investigate the effects of 12-week high-intensity intermittent aerobic exercise on blood pressure, HRV, and respiratory function of people with MA use disorder, to provide a theoretical basis and practical reference for establishing a long-term mechanism of exercise detoxification.	A group exercise format was used for the HIIT. The exercise heart rate of the exercise group during exercise intervention was monitored by the training computer (Polar RCX3). The aerobic exercise session included a five min warmup, a 30 min aerobics calisthenics (the content of aerobic calisthenics was composed of three different aerobics, the one-minute interval between each set of exercises, and the action details include shoulder lift, cross step, front and back V-step, pony jump, et al., and the exercise load is gradually increasing during the exercise.), and a 5-minute recovery training (such as high leg lifts, sit-ups.	Intervention The aerobic exercise group received high-intensity intermittent aerobic calisthenics intervention (75% to 85% HRmax) 40 min/time three times a week. Control group - the control group did not participate in exercise intervention or other forms of physical activity, and only needed to complete the reading task of the same length in a separate room (such as reading books, reading newspapers, et al.).	Unclear.	Supervised sessions, face to face.

Study	Item 1- Brief name of the intervention	Item 2- Why	Item 3- What- materials	Item 4- What- procedures	Item 5- Who provided	Item 6- How
Tan et al., 2023	Intervention: 8-month HIIT. Control group: Routine rehabilitation.	In recent years, HIIT has emerged as an alternative or complementary form of training to aerobic exercise. In both long-term and short-term studies, HIIT is as valuable or even superior to aerobic exercise in terms of short-term fitness, cardiovascular function, quality of life, exercise efficiency, safety, tolerance, and exercise compliance. Therefore, the main purpose of this study was to investigate the effect of HIIT on improvements in physical fitness level and health-related quality of life of drug withdrawal patients and to observe the sleep quality, cue-induced craving, blood sugar and lipid levels, etc., of drug withdrawal patients as auxiliary indicators.	Participants completed an incremental load exercise test of the modified Bruce protocol (Table 2) on a treadmill (Cosmos Pulsar 4.0) and adjusted the speed and inclination level (increasing after level 7) according to the protocol until volitional fatigue. Subjective perception of effort (RPE) was measured at the last minute of each load level. The termination criteria of the incremental stress exercise test were: aberrant electrocardiogram, reaching personal maximum heart rate, abnormal blood pressure, RPE greater than 17, respiratory quotient greater than 1.15, etc. Group heart rate monitoring equipment (Polar Team Pro) was used to monitor heart rate intensity. Supervisors urged trainers to maintain the HR at 76–96% HRmax of the subjects (the maximum heart rate of each person was determined with the VO_{2max} test before the exercise session), allowing HR responses to fluctuate within the target HR range	HIIT - The exercise course lasted 60 min each session, 4 times a week, for a total of 8 months, including 10 min of warm-up exercise, 40 min of basic content exercises, and 10 min of stretching and relaxation exercises. Control group – received routine rehabilitation. No further information on this.	Doctoral and Master students in physical education.	Supervised, face to face.

Study	Item 1- Brief name of the intervention	Item 2- Why	Item 3- What- materials	Item 4- What- procedures	Item 5- Who provided	Item 6- How
Yan-Guang et al., 2021	Intervention: HIIT, 1 hour a week, 3 x a week for 12 months. Control group: MICT.	Considering the benefits and theoretical results of HIIT in the study of many chronic diseases, it is feasible to apply it in SUD. Therefore, this study proposes the following question: which exercise is better for SUD: HIIT or MICT?	The training contents in the HIIT group included nonconfrontational basketball training, resistance training (weight training and strength machines), rope skipping and running.	HIIT session for one hour, 3x a week for 12 months The duration of each training session was 60 min, including 10 min of warm-up, 40 min of HIIT session and 10 min of cool down. Control – tai chi or yoga for same period.	HIIT supervised by experienced instructors from Shanghai University of Sports. Control group – Experienced instructor from Shanghai University of Sports.	Supervised, face to face in group setting.

Study	Item 1- Brief name of the intervention	Item 2- Why	Item 3- What- materials	Item 4- What- procedures	Item 5- Who provided	Item 6- How
Yin et al., 2022	Intervention: One-off HIIT session for 30 min Control group: One-off session of Tai Chi for 30 minutes.	The theoretical basis of Tai Chi and HIIT beside the cognitive treatment of SUD has not been fully confirmed in the scientific literature.	HIIT group received one off HIIT session for 30 minutes. The HIIT protocol includes a 5 min warm-up, 20 min of interval exercise, and a 5 min cooldown. The exercise was running. Control group - One off 30-minute session. 5-minute warm up, 20 minutes of Tai chi and then 5-minute cool down.	All voluntary patients in a 6-month admission. As one-off session, measuring outcomes before and after, this is less relevant.	Both the HIIT and tai chi group sessions were overseen by local experts.	One-off supervised session in a laboratory for both groups.

Note. CAD = coronary artery disease, CG = control group, HIIT = high-intensity interval training, HR = heart rate, HRmax, maximum heart rate, HRV, heart rate variability, MA, methamphetamine, MICT = moderate-intensity continuous training, OpUD = opioid use disorder, RPE = Rating of Perceived Exertion, SUD = substance use disorder, VO_{2max} = maximal oxygen uptake

Supplementary Table 2. TIDieR Checklist continued (Items 7-12)

Study	Item 7- Where	Item 8- When and how much	Item 9- Tailoring	Item 10- Modifications	Item 11- How well- planned	Item 12- How well- actual
Dürmüs et al., 2020	A psychiatric substance use disorder facility (opioid).	HIIT conducted over 3 consecutive weeks, twice per week (6 total).	Due to non-active participants and smokers, the load was reduced by 0.050 kg body weight and the number of loading periods were limited to 3 repeats.	None reported.	At the start of the HIIT, the participants warmed up for 4 minutes on the 30W pedal. During the loading exercise the participants pedalled for 30 seconds as fast as they individually could while they were verbally motivated.	Unclear.

Study	Item 7- Where	Item 8- When and how much	Item 9- Tailoring	Item 10- Modifications	Item 11- How well-planned	Item 12- How well-actual
Flemmen et al., 2014	A residential long-term treatment clinic for SUDs.	Exercise training was carried out 3 times a week for 8 weeks, in total 24 training sessions were completed.	Training intensity in the HIIT group was prescribed in relation to individual estimated HRmax achieved during a treadmill-based exercise to exhaustion test at baseline. This test used the Cortex Metamax II portable metabolic test system (Cortex Biophysik GmbH, Leipzig, Germany) whereby participants walked at 4.5km.h-1 at 5% inclination on a treadmill until exhaustion. Participants in the control group could choose which activity to undergo in their sessions from those offered in the clinical treatment program.	No modifications reported.	Adherence: The subjects needed to have an adherence of at least 20 out of 24 training sessions in order to be included in the data analyses. Number of drop-outs, who did not complete a minimum of 20 sessions, was recorded and reasons for drop-out were sought.	Of the 12 participants enrolled in HIIT 3 dropped-out: 2 withdrew due to personal reasons and one for unknown reasons. Of the 12 participants in the control group 5 dropped-out. The SUD patients that completed the training period carried out 22±1 (out of 24) of the training sessions. No amendments to the intervention were reported.

Study	Item 7- Where	Item 8- When and how much	Item 9- Tailoring	Item 10- Modifications	Item 11- How well-planned	Item 12- How well-actual
Li et al., 2023	Compulsory detoxification education and correction centre in Chongqing, China.	Aerobic calisthenics intervention (75% to 85% HRmax) 40 min/time three times a week.	Adapted unclear.	Unclear.	Adherence unclear.	Unclear.

Study	Item 7- Where	Item 8- When and how much	Item 9- Tailoring	Item 10- Modifications	Item 11- How well-planned	Item 12- How well-actual
Tan et al., 2023	Compulsory detoxification unit, China.	The exercise course lasted 60 min each session, 4 times a week, for a total of 8 months, including 10 min of warm-up exercise, 40 min of basic content exercises, and 10 min of stretching and relaxation exercises.	Adapted according to baseline fitness.	Unclear.	Unclear.	Unclear.

Study	Item 7- Where	Item 8- When and how much	Item 9- Tailoring	Item 10- Modifications	Item 11- How well-planned	Item 12- How well-actual
Yan-guang et al., 2021	Participants were having treatment in a Shanghai Compulsory Rehabilitation Centre (SCRC).	HIIT sessions were an hour, 3x a week for 12 months. This included nonconfrontational basketball training, resistance training (weight training and strength machines), rope skipping and running. The duration of each training session was 60 min, including 10 min of warm-up, 40 min of HIIT session and 10 min of cool down.	Adapted based on fitness at baseline and response by HR in session.	Unclear.	Adherence to intervention unclear but 20 (from 60) dropped out from the HIIT group versus 14 (from 60) in the MICT group.	Unclear how well intervention adhered to.

Study	Item 7- Where	Item 8- When and how much	Item 9- Tailoring	Item 10- Modifications	Item 11- How well-planned	Item 12- How well-actual
Yin et al., 2022	Meth addicted people, voluntarily attending Shanghai Compulsory Rehabilitation Centre (SCRC).	One-off 30-minute HIIT session, 5-minute warm up, 20-minute running HIIT session and 5-minute cool down.	Unclear	Unclear	N/A	Unclear

Note. HIIT = high-intensity interval training, HR = heart rate, HRmax, maximum heart rate, MICT = moderate-intensity continuous training, SUD = substance use disorder

Supplementary Table 3. CERT Checklist

Study	Item 6- HOW: delivery- motivation strategies	Item 7a- HOW: delivery- decision rule(s) for exercise progression	Item 7b- HOW: delivery- how exercise was progressed	Item 9- HOW: delivery- home program component (s)	Item 10- HOW: delivery- non-exercise components	Item 15- TAILORING: what, how- decision rule for determining starting level
Dürmüs et al., 2020	Verbal motivation but not specified.	HIIT: decision rules for exercise progression not mentioned. Control group: unclear.	Not clear.	N/A	Took part in psychiatric/addiction facility. Further details on the treatment group or control group lacking.	Unclear.

Study	Item 6- HOW: delivery- motivation strategies	Item 7a- HOW: delivery- decision rule(s) for exercise progression	Item 7b- HOW: delivery- how exercise was progressed	Item 9- HOW: delivery- home program component (s)	Item 10- HOW: delivery- non-exercise components	Item 15- TAILORING: what, how- decision rule for determining starting level
Flemmen et al., 2014	No motivational strategies were reported.	HIIT Group: High intensity intervals were conducted at 90-95% of HRmax. As subjects improved, velocity and incline were increased to meet the target HR intensity. Control Group: The exercise did not progress in intensity or form throughout the duration of the trial.	If the target intensity was not achieved during the HIIT session the velocity and incline of the treadmill were gradually increased until the target HR was met.	N/A	Participants in both the HIIT and control group took part in a clinical treatment program comprising ballgames (indoor-soccer and volleyball), yoga, stretching, outdoor walking, low resistance strength training, ceramics, TV games, and card games. This program was a standard program offered at the residential long-term substance abuse treatment clinic designed to reduce illegal drug usage.	Exercise did not fall into different levels. Intensity did not progress throughout the trial. However, if the target intensity was not achieved at the beginning of the HIIT session the velocity and incline of the treadmill were gradually increased until the target HR was met.

Study	Item 6- HOW: delivery- motivation strategies	Item 7a- HOW: delivery- decision rule(s) for exercise progression	Item 7b- HOW: delivery- how exercise was progressed	Item 9- HOW: delivery- home program component (s)	Item 10- HOW: delivery- non-exercise components	Item 15- TAILORING: what, how- decision rule for determining starting level
Li et al., 2023	No motivation strategies were reported.	HIIT -- Participants exercised three times each week for 12 weeks as required, the Hrmax was defined by the formula “HRmax = 206.9 − 0.67 × age. Unclear how/when progressed over time Control group – no exercise	Not clear.	N/A	All participants took part in usual care for SUD. This did not include any exercise.	Unclear.

Study	Item 6- HOW: delivery- motivation strategies	Item 7a- HOW: delivery- decision rule(s) for exercise progression	Item 7b- HOW: delivery- how exercise was progressed	Item 9- HOW: delivery- home program component (s)	Item 10- HOW: delivery- non-exercise components	Item 15- TAILORING: what, how- decision rule for determining starting level
Tan et al., 2023	None reported.	HIIT group received 8 months of four 60-min sessions per week under supervision. Control Routine rehabilitation.	Group based by MSc PhD students. Unclear how progressed.	N/A	All people took part in routine rehabilitation.	Tailored based on fitness.
Yan-guang et al., 2021	Unclear, supervised and instructors oversaw, but motivation unclear.	HIIT group 1 hour, 3x a week for 12 months.	Group based by experienced trainers at university.	N/A	All people took part in compulsory rehabilitation activities.	Based on baseline fitness and estimate HR intensity zones.

Study	Item 6- HOW: delivery- motivation strategies	Item 7a- HOW: delivery- decision rule(s) for exercise progression	Item 7b- HOW: delivery- how exercise was progressed	Item 9- HOW: delivery- home program component (s)	Item 10- HOW: delivery- non-exercise components	Item 15- TAILORING: what, how- decision rule for determining starting level
Yin et al., 2022	Motivation strategies unclear.	HIIT one-off session for 30 minutes.	Individual in a lab by experienced trainer.	N/A	Voluntary admission for methamphetamine addiction. All people in both groups carried on with usual activities, unclear if this included exercise.	Unclear.

Note. HIIT = high-intensity interval training, HR = heart rate, HRmax, maximum heart rate, SUD = substance use disorder
Items 1 (What materials), 2 (Who provided), 3 (How: delivery- individually or group), 4 (How: delivery- supervised or unsupervised), 5 (How: delivery- adherence), Item 8 (How: delivery- descriptions to enable replication), Item 12 (location), Item 13 (dosage), Item 14a and 14b (Tailoring), Item 16a and 16b (How well) are provided on the TIDieR checklist, and thus not duplicated in this checklist. Moreover, Item 11 (Adverse Events) is provided in Table 8, and thus not duplicated in this checklist

Supplementary Table 4. Effective Public Health Practice Project (EPHPP) ratings

Components	Dürmüs et al. 2020	Flemmen et al. 2014	Li et al. 2024	Tan et al. 2023	Yan-guang et al. 2021	Yin et al. 2022
Selection Bias 1. Are the individuals selected to participate likely to be representative of the target populations?	Referred from clinic, 2 = Somewhat likely	Referred from clinic, 2 = Somewhat likely	Referred from detoxficiation education and correction centre, 2 = Somewhat likely	Referred from rehabilitation centre, 2 = Somewhat likely	Referred from rehabilitation centre, 2 = Somewhat likely	Referred from rehabilitation centre, 2 = Somewhat likely
Selection Bias 2. What percentage of the selected individuals agreed to participate?	2 = 60 - 79% agreement	1 = 80 - 100% agreement	Can't tell	3 = Less than 60% agreement	3 = Less than 60% agreement	3 = Less than 60% agreement
A. SELECTION BIAS RATING	MODERATE	MODERATE	WEAK	WEAK	WEAK	WEAK
Study design	Controlled clinical trial	Randomised controlled trial	Randomised controlled trial	Randomised controlled trial	Randomised controlled trial	Randomised controlled trial
Was the study described as randomized?	No	Yes	Yes	Yes	Yes	Yes
Was the method of randomization described?	Not applicable	No	Yes	No	Yes	No
Was the randomization process appropriate?	Not applicable	Not applicable	Yes	Not applicable	Yes	Not applicable
B. STUDY DESIGN RATING	WEAK	MODERATE	STRONG	MODERATE	STRONG	MODERATE
Were there important differences between groups prior to the intervention?	No	No	No	Yes, groups differed substantially on drug history (months); Exercise group = 69.43 ± 30.98; Control group = 53.25 ± 36.07.	No	No
What percentage of relevant confounders were controlled?	Not applicable	Not applicable	Not applicable	3 = Less than 60% (few or none); drug history was not controlled for in the analyses	Not applicable	Not applicable
C. CONFOUNDERS RATING	STRONG	STRONG	STRONG	WEAK	STRONG	STRONG
Were the outcome assessors aware of the intervention status of participants?	3 = Can't tell	3 = Can't tell	3 = Can't tell	3 = Can't tell	2 = No	2 = No
Were the participants aware of the research question?	3 = Can't tell	3 = Can't tell	2 = No	3 = Can't tell	1 = Yes	1 = Yes

D. BLINDING RATING	WEAK	WEAK	MODERATE	STRONG	MODERATE	MODERATE
Were data collection tools shown to be valid?	1 = Yes	1 = Yes	1 = Yes	1 = Yes	1 = Yes	1 = Yes
Were data collections tools shown to be reliable?	1 = Yes	1 = Yes	1 = Yes	1 = Yes	1 = Yes	1 = Yes
E. DATA COLLECTION METHOD RATING	STRONG	STRONG	STRONG	STRONG	STRONG	STRONG
Were withdrawals and drop-outs reported in terms of numbers/reasons per group?	1 = Yes	1 = Yes	2 = Yes	3 = Yes	4 = Yes	5 = Yes
Percentage of participants completing the study	3 = Less than 60%	2 = 60 - 79%	1 = 80 - 100%	1 = 80 - 100%	2 = 60 - 79%	1 = 80 - 100%
F. WITHDRAWALS AND DROPOUTS RATING	WEAK	MODERATE	STRONG	STRONG	MODERATE	STRONG
GLOBAL RATING	**WEAK**	**MODERATE**	**MODERATE**	**WEAK**	**MODERATE**	**MODERATE**
What percentage of participants received the allocated intervention?	4 = Can't tell	1 = 80 - 100%	4 = Can't tell	4 = Can't tell	4 = Can't tell	1 = 80 - 100%
Was the consistency of the intervention measured?	3 = Can't tell	1 = 80 - 100%	3 = Can't tell	3 = Can't tell	3 = Can't tell	1 = 80 - 100%
Is it likely that subjects received an unintended intervention (contamination or co-intervention) that may influence results?	5 = No	5 = No	5 = No	5 = No	5 = No	5 = No
Unit of allocation	Individual	Individual	Individual	Individual	Individual	Individual
Unit of analysis	Individual	Individual	Individual	Individual	Individual	Individual
Are the statistical methods appropriate for the study design?	1 = Yes	1 = Yes	1 = Yes	1 = Yes	1 = Yes	1 = Yes
Is the analysis performed by intervention allocation status (i.e. Intention to treat) rather than the actual intervention received?	2 = No	1 = Yes	1 = Yes	1 = Yes	2 = No	1 = Yes

10 CURRICULUM VITAE

Çağdaş Türkmen

Personal information

Date of birth: 04.04.1996
Place of birth: Oberhausen
Nationality: German

Education

July 2021 - current Mannheim, Germany

PhD Candidate

Heidelberg University, Medical Faculty Mannheim

Advisors:
apl. Prof. Sabine Vollstädt-Klein, Prof. Falk Kiefer

Sept. 2019 - Aug. 2020 Maastricht, Netherlands

MSc Neuropsychology

Maastricht University, Faculty of Psychology and Neuroscience

Advisors:
Prof. Rob Markus, Prof. Philip Cowen (University of Oxford)

Thesis title:
What are the effects of 5-HT_4 receptor agonism on human memory? A randomised, double-blind, placebo-controlled fMRI study of prucalopride in healthy volunteers.
Thesis grade: 9.00/10.00

Jan. 2020 - Jul. 2020 Oxford, UK

Visiting Student (Research)

University of Oxford, Department of Psychiatry

Sept. 2015 - Oct. 2018 Maastricht, Netherlands

BSc Psychology

Maastricht University, Faculty of Psychology and Neuroscience

Advisors:
Dr. Jens van Dalfsen, Dr. Wolfgang Viechtbauer

Thesis title:
Suicidality and insomnia in children and adolescents treated with newer generation antidepressants: a meta-analysis of randomized controlled trials.
Thesis grade: 9.00/10.00

Sept. 2017 - Dec. 2017 Norwich, UK

Exchange Student (Psychology)

University of East Anglia

Professional Experience

Apr. 2021 - current Mannheim, Germany

Doctoral Researcher in the Neuroimaging of Addictive Behaviour research group

Central Institute of Mental Health, Department of Addictive Behaviour and Addiction Medicine, Medical Faculty Mannheim, Heidelberg University

Supervisors:
apl. Prof. Sabine Vollstädt-Klein, Prof. Falk Kiefer

I am currently a doctoral researcher and member of the Graduiertenkolleg (GRK) 2350 (https://grk2350.de/), which is a Research Training Group that aims to investigate the impact of adverse childhood experiences on psychosocial and somatic conditions across the lifespan.

I have recently completed the curriculum and doctoral training in the GRK2350.

In addition I have gained the following experience and skills through my PhD project and employment at the Central Institute of Mental Health in Mannheim:

- I led a research project (sub-project "B5-Addiction" within the GR2350) on the neurobiological mechanisms underlying the relationship between chilhood maltreatment and alcohol use disorder (AUD) using functional MRI (fMRI).
- I recruited patients with AUD from an addiction ward and addiction day unit, and a non-clinical sample of individuals engaging in heavy drinking.
- I administered clinical interviews (e.g., SCID-5, Form 90) during a diagnostic (baseline) session, and carried out fMRI measurements with a medical technical assistant.
- I analysed behavioural data using SPSS and R as well as structural and functional MRI data using SPM12.

  For my thesis, I employed a machine learning approach to identify if specific ages of exposure to childhood maltreatment had an effect on brain volume, and examined data from fMRI paradigms (working memory and behavioural inhibition).
- I published manuscripts in peer-reviewed journals, and presented the findings at scientific conferences.
- I led the writing of a research grant proposal of my research group,which was submitted to the German Research Foundation.

Skills

Data analysis

- SPSS
- SPM
- R

Methods

- fMRI
- Randomised controlled trials
- Observational studies
- Meta-analysis
- Systematic reviews

Language

German	Native
Turkish	Native
English	Fluent
Norwegian	Intermediate
Dutch	Intermediate

Professional Experience cont.

Oct. 2023 - Nov. 2023 Cambridge, UK

Visiting researcher in the Addiction Research Group

University of Cambridge, Department of Psychiatry

Supervisor:
Prof. Karen Ersche

I completed a 6-week research visit in the Addiction Research Group (AddCam), where I learnt about the importance of habit formation and its potential as a therapeutic target in the treatment of substance use disorders. I assisted with recruitment for a project aiming to investigate how to break habits. In addition, I tested multiple newly developed behavioural tasks, translated task instructions, and created standard operating procedures.

Oct. 2022 - Dec. 2022 Oslo, Norway

Visiting researcher in the MyLife working group

Norwegian Institute of Public Health (NIPH), Department of Alcohol, Tobacco and Drugs

Supervisor:
Dr. Jasmina Burdzovic Andreas

I completed a 6-week research visit in the MittLiv-undersøkelsen research group (https://www.fhi.no/le/studier/mittliv/). I generated research questions and hypothesis based on the large MittLiv dataset, interpreted longitudinal data, and first-authored a manuscript, which was recently published in *Addictive Behaviors*.

Jan. 2020 - Jul. 2020 Oxford, UK

Research internship in the Psychopharmacology and Emotion Research Laboratory (PERL)

University of Oxford, Department of Psychiatry

Supervisors:
Prof. Philip Cowen, Dr. Angharad de Cates

I completed a 6-month research internship in PERL. I was involved in writing a research proposal and obtaining ethical approval for a double-blind, placebo-controlled sleep EEG study aiming to investigate the effects of the 5-HT_4 receptor agonist prucalopride on sleep architecture in healthy volunteers. I also prepared a Trial Master File and study materials. Due to the COVID-19 pandemic, I could not recruit participants during my internship. Thus I joined a completed project, in which I investigated the effects of prucalopride on episodic memory in healthy volunteers using fMRI data. I took a closer look at the hippocampus as a region of interest for my thesis.

PUBLICATION LIST

*shared first authorship

Bougelet, E., Deffaa, M., **Türkmen, C.**, Kiefer, F., Vollstädt-Klein, S., & Gerhardt, S. (2024). The Role of Perceived Stress in the Relation between Childhood Maltreatment and Severity of Alcohol Use Disorder: A Mediation Analysis. *Eur Addict Res*, 1-10. https://doi.org/10.1159/000539711

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Türkmen, C., Machunze, N., Lee, A., Bougelet, E., Ludin, N., de Cates, A., Vollstädt-Klein, S., Bach, P., Kiefer, F., Burdzovic Andreas, J., Kamphuis, J., Schoevers, R. A., Emslie, G. J., Hetrick, S., Viechtbauer, W., & van Dalfsen, J. H. Systematic Review and Meta-Analysis: The Association between Newer Generation Antidepressants and Insomnia in Children and Adolescents with Major Depressive Disorder. Accepted Pending Minor Revision.

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Türkmen, C., Schneider, C. L., Viechtbauer, W., Bolstad, I., Chakravorty, S., Miller, M. B., Kallestad, H., Angenete, G. W., Johann, A., Feige, B., Spiegelhalder, K., Riemann, D., Vedaa, Ø., Pallesen, S., & Hertenstein, E. Cognitive Behavioral Therapy for Insomnia across the Spectrum of Alcohol Use Disorder: A Systematic Review and Meta-Analysis. Under Review.

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11 ACKNOWLEDGEMENTS

First of all, I would like to thank Prof. (apl.) Dr. Sabine Vollstädt-Klein for her unwavering support throughout my PhD journey. Her excellent mentorship, openness to my scientific pursuits and availability around the clock were truly invaluable. I would also like to extend my gratitude to Prof. Dr. Falk Kiefer, director of the research department I work in, for our insightful discussions which enriched my professional development. Moreover, I am grateful to Prof. (apl.) Dr. Inga Niedtfeld and Dr. Anita Hansson for their support in helping me overcome hurdles that I encountered.

My deep gratitude also goes to all participants who invested their valuable time in the studies. Without their commitment, the work presented here would have not been possible. In this regard, I also want to thank Noah Machunze, Emilie Bougelet and Alycia Lee for supporting me in participant recruitment and data collection.

I would also like to thank Dr. Haoye Tan for being such a kind and patient colleague. His experience in neuroimaging and programming was incredibly helpful and made my work much easier to manage.

During my PhD journey, I had the privilege of being a member of the research training group GRK2350. I would like to thank our spokesperson, Prof. Dr. Christian Schmahl, and our study coordinators, Dr. Sylvia Steinmann and Dr. Julia Herzog, for their dedication to creating and maintaining such an outstanding research environment. It was a highly rewarding experience to participate in the structured programme of the GRK2350, which created an open space for exchanging ideas with an interdisciplinary group of doctoral students. I was also fortunate to complete two funded research internships – one at the Norwegian Institute of Public Health and another one at the University of Cambridge. For this, I would like to thank the German Research Foundation (DFG) not only for funding my PhD project, but also for providing opportunities for gaining international research experience and expanding my professional network.

At the Norwegian Institute of Public Health, I am especially thankful to Dr. Jasmina Burdzovic Andreas who made a great effort in helping me to write a collaborative manuscript, based on the complex longitudinal data from the MyLife project. I would also like to thank Dr. Geir Scott Brunborg, Dr. Ingunn Olea Lund, and the PsychGen research group for enriching my research stay and for bringing the Norwegian work culture closer to me.

At the University of Cambridge, I would like to thank Prof. Dr. Karen Ersche and Dr. Tsen Vei Lim for giving me the opportunity to learn about their cutting-edge research on habits and how to break them. Being part of their excellent research group was an incredibly rewarding experience.

Science knows no borders. I want to thank all my international collaborators for encouraging me to pursue my scientific ideas. I would especially like to thank Dr. Jens H. van Dalfsen, Dr. Wolfgang Viechtbauer, Dr. Mats Hallgren and PD Dr. Elisabeth Hertenstein for guiding me on international meta-analysis projects.

A big thank you goes to my friends who have been an incredible source of strength and support throughout my PhD journey. A special mention goes to Timo, my lifelong best friend, who has always stood by my side.

I am forever grateful to my loving parents and my brother. Your unwavering support has been the backbone of my journey – I could not have come this far without you.

Finally, thank you, Kristine, for all your love, patience, support and for all the peaceful moments we shared hiking and picking wild berries around your home in beautiful Nordmøre. You have always helped me find balance and perspective in life.