Adverse childhood experiences, psychiatric morbidity and resilience in adulthood

Hilda Björk Daníelsdóttir

Thesis for the degree of Philosophiae Doctor

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School of Health Sciences

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Ágrip

Niðurstöður rannsókna benda til þess að fólk sem hefur upplifað ýmiss konar áföll í æsku, þar á meðal andlegt eða líkamlegt ofbeldi eða vanrækslu, sé í aukinni áhættu á að þróa með sér geðraskanir á fullorðinsárum. Hins vegar fá ekki allir með slíka áfallasögu í æsku, einkenni geðraskana á fullorðinsárum, heldur sýna seiglu eða hæfni til að halda heilsu þrátt fyrir áföll eða þungbærar aðstæður. Með því að nota gögn úr Áfallasögu kvenna á Íslandi og sænska tvíburagagnagrunninum, var markmið doktorsverkefnisins að rannsaka erfða- og umhverfisþætti í seiglu sem og geðheilsuvanda á fullorðinsárum í kjölfar áfalla í æsku.

Markmið **rannsóknar I** var að skoða hvort tengsl á milli áfalla í æsku og þróunar geðraskana á fullorðinsárum sé óháð fjölskyldutengdum þáttum, eins og erfðum og sameiginlegum umverfisþáttum í uppvexti. Þátttakendur voru 25,252 einstaklingar (18-47 ára) úr sænska tvíburagagnagrunninum sem svöruðu spurningalista um áföll í æsku. Upplýsingar um greiningu á geðröskunum á fullorðinsárum voru fengnar með samtengingu gagna við sænsku sjúkraskránna. Niðurstöður sýndu sterk tengsl á milli fjölda áfalla í æsku og aukinnar áhættu á þunglyndi, kvíða, áfallastreituröskun og áfengis- og vímuefnavanda á fullorðinsárum. Með því að bera saman tvíburapör þar sem annar tvíburinn hafði orðið fyrir áfalli í æsku en ekki hinn, kom í ljós að áhrif áfalla í æsku á þróun geðraskana á fullorðinsárum má að hluta til skýra með fjölskyldutengdum þáttum, eins og erfðum og æskuumhverfi. En þegar stjórnað er fyrir þessum þáttum, sýndu niðurstöður ennfremur að sterk áfallasaga í æsku, t.d. kynferðisofbeldi eða það að hafa orðið fyrir þremur eða fleiri tegundum áfalla í æsku, hefur sterk tengsl við þróun geðsjúkdóma á fullorðinsárum, óháð fjölskyldutengdum þáttum.

Markmið **rannsóknar II** var að skoða tengsl á milli áfalla í æsku og seiglu á fullorðinsárum. Seigla var aðgerðarbundin annarsvegar sem sjálfsmat á bjargráði eða hæfni til að takast á við áskoranir daglegs lífs og hinsvegar sem lág einkennabyrði geðraskana þrátt fyrir áfallasögu. Þáttakendur voru 26,198 konur (18-69 ára) sem tóku þátt í Áfallasögu kvenna á Íslandi og svöruðu ítarlegum spurningalista, meðal annars um áföll á lífsleiðinni ásamt spurningum um bjargráð og geðræn einkenni á fullorðinsárum. Niðurstöður sýndu sterk skammtaháð tengsl á milli fjölda áfalla í æsku og skertrar seiglu á fullorðinsárum, þar með talið skertrar getu til þess að takast á við áskoranir daglegs lífs og lægri einkennabyrði geðraskana. Þau áföll í æsku sem höfðu hvað sterkust tengsl við skerta seiglu á fullorðinsárum voru tilfinningaleg vanræksla, kynferðislegt ofbeldi, einelti og geðrænn vandi á heimili.

Markmið **rannsóknar III** var að skoða hlutfallslegan þátt erfða og umhverfis í seiglu á fullorðinsárum í kjölfar áfalla í æsku. Seigla var aðgerðarbundin sem lág einkennabyrði geðraskana þrátt fyrir áföll í æsku. Þátttakendur voru 8,606 einstaklingar (21-47 ára) úr sænska tvíburagagnagrunninum sem höfðu upplifað að minnsta kosti eitt áfall í æsku. Eins og í rannsókn I svöruðu þáttakendur spurningalista um áföll í æsku og upplýsingar um geðraskanir á fullorðinsárum voru fengnar með samtengingu gagna við sænsku sjúkraskránna sem og með samtengingu gagna við sænska lyfjagagnagrunninn. Niðurstöður sýndu að erfðir skýrðu 40% í breytileika seiglu á fullorðinsárum á meðan einstaklingsbundnir umhverfisþættir skýrðu restina eða 60% af einstaklingsmun í seiglu. Niðurstöður sýndu einnig að fjölgena áhættuskor fyrir geðrænar svipgerðir (t.d. fyrir áfallastreituröskun og þunglyndi) spáðu fyrir um seiglu á fullorðinsárum, sem gefur til kynna að erfðabreytileikar sem tengjast þessum svipgerðum hafa einnig áhrif á seiglu.

Lykilorð:

Áföll í æsku, geðræn einkenni, geðraskanir, seigla, aðlögunarhæfni, tvíburar

Abstract

Exposure to adverse childhood experiences (ACEs), including abuse, neglect and growing up in dysfunctional home environments, has consistently been associated with an elevated risk of multiple negative mental health outcomes extending into adulthood. Yet, not all individuals exposed to ACEs suffer from poor mental health in adulthood, and a substantial proportion of people remain resilient. Leveraging unique data sources from Sweden and Iceland, the overarching objective of this thesis was to examine the environmental and genetic contributions to the psychiatric morbidity-resilience dimension in the context of ACEs, with psychiatric disorders at one end of the spectrum and resilience at the other.

The aim of **study I** was to examine whether associations between ACEs and adult psychiatric disorders remained after adjustment for familial confounding due to shared genetic and environmental factors. Participants comprised 25,252 individuals (18-47 years) from the Swedish Twin Registry, which retrospectively reported exposure to ACEs via a web-based survey. Information about adult psychiatric disorders was obtained via linkage to the Swedish National Patient Register. We found that a greater number of ACEs was associated with increased odds of depression, anxiety, substance abuse and stress-related disorders in adulthood. In co-twin control analyses based on twins discordant on ACE exposure, we found that associations between ACEs and adult psychiatric disorders were somewhat attenuated, i.e., indicating a partial role of genetic predisposition and early environmental factors. Nonetheless, when accounting for these factors in monozygotic twin comparisons, we found that exposure to multiple types of ACEs and, specifically, exposure to sexual abuse in childhood, was robustly associated with increased odds of adult psychiatric disorders.

The aim of **study II** was to examine associations between a broad set of ACEs and two distinct measures of adult resilience. Resilience was conceptualized both as perceived coping ability and as psychiatric resilience defined as the absence of (or low) psychiatric morbidity after exposure to trauma. Participants comprised 26,198 women (18-69 years) from the Icelandic Stress-And-Gene-Analysis cohort that responded to a comprehensive online questionnaire covering a wide range of mental health assessments as well as information on ACEs. We found that a greater number of ACEs was negatively associated with perceived coping ability and psychiatric resilience in adulthood, in a dose-response fashion. Specifically, women reporting five or more ACEs had 36% lower prevalence of high coping ability and 58% lower prevalence of high psychiatric resilience, compared to women reporting no ACEs. Furthermore, of 13 measured ACEs, we found that emotional neglect, being bullied, sexual abuse and

growing up with a mentally ill household member were most robustly associated with reduced adult resilience.

The aim of **study III** was to investigate the relative contribution of genetic and environmental factors to individual variation in adult psychiatric resilience after exposure to ACEs. Psychiatric resilience was conceptualized as the absence of any adult diagnosis of common psychiatric disorder after exposure to ACEs. Participants comprised 8,606 individuals (21-47 years) from the Swedish Twin Registry that had experienced at least one ACE. As in study I, participants reported exposure to ACEs via a web-based survey and information about adult psychiatric disorders was obtained via linkage to the Swedish National Patient Register and the Swedish Prescribed Drug Register. We found that 40% of the variation in adult psychiatric resilience after ACEs was due to genetic factors, while the remaining 60% was due to individual-specific environmental factors. We further found that measured genetic risk for other psychiatric traits and disorders (e.g., PTSD and depression), was associated with lower odds of resilience to ACEs, indicating some shared genetic overlap.

Keywords:

Adverse childhood experiences, psychiatric morbidity, resilience, coping ability, twins

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List of Abbreviations

A	Additive genetic factors
ACE	Adverse childhood experience
ACE-IQ	Adverse Childhood Experiences International
ADHD	Attention deficit hyperactivity disorder
AIC	Akaikes Information Criterion
ATC	Anatomical Therapeutic Chemical Codes
AUDIT-C	The Alcohol Use Disorders Identification Test
C	Common/shared environmental factors
CATSS	The Child and Adolescent Twin Study in Sweden
CD-RISC	Connor-Davidson Resilience Scale
D	Dominance genetic factors
DZ	Dizygotic
E	Unique environmental factors
GAD	Generalized anxiety disorder
GAD-7	The Generalized Anxiety Disorder Scale
GWAS	Genome-wide association study
ICD	The International Classification of Diseases codes
LEC-5	Life Events Checklist for DSM-5
LSC-R	The Life Stressor Checklist-revised
MDD	Major depressive disorder
MI	Multiple imputation
MZ	Monozygotic
NPR	National Patient Register
PCL-5	The PTSD checklist for DSM-5
PDR	Prescribed Drug Register
PHQ-9	The Patient Health Questionnaire
PRS	Polygenic risk score
PSQI-A	The Pittsburgh Sleep Quality Index Addendum for PTSD
PTSD	Post traumatic stress disorder
rGE	Gene-environment correlation
SAGA	The Stress-And-Gene-Analysis cohort
SD	Standard deviation

SEM	Structural equation models
SNP	Single nucleotide polymorphism
STAGE	The Study of Twin Adults: Genes and Environment
STR	The Swedish Twin Registry
YATSS	The Young Adult Twins in Sweden Study

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List of Original Papers

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals (I, II, III):

I. Daníelsdóttir HB, Aspelund T, Shen Q, Halldorsdottir T, Jakobsdóttir J, Song H, Lu D, Kuja-Halkola R, Larsson H, Fall K, Magnusson PKE, Fang F, Bergstedt J, Valdimarsdóttir UA. Adverse childhood experiences and adult mental health outcomes. *JAMA Psychiatry*. 2024;6:e240039.
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III. Daníelsdóttir HB, Kuja-Halkola R, Aspelund T, Magnusson PKE, Halldorsdottir T, Jakobsdóttir J, Fall K, Fang F, Valdimarsdóttir UA, & Bergstedt J. Genetic and environmental contributions to variation in psychiatric resilience after childhood trauma: A Swedish twin study. *Manuscript*.

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Declaration of Contribution

I, Hilda Björk Daníelsdóttir, planned the research for studies I-III in close collaboration with my supervisor, Unnur Anna Valdimarsdóttir. I took a principal role in applying for the data from the Swedish Twin Registry. I performed the statistical analyses for each study under the sound guidance of my supervisor and doctoral committee, with particular guidance of an external advisor in Study III. I drafted the manuscripts for the three studies, prepared the final versions of the manuscripts for submission and responded to reviewers comments in collaboration with my supervisor and co-authors.

1 Introduction

1.1 Trauma and mental health

Exposure to traumatic events or significant life stressors (e.g., death of a loved one, exposure to violence) is common worldwide. Epidemiological studies indicate that most people will experience at least one and often several traumatic events during their lifetime.[1-4] The unexpected death of a loved one, being involved in a severe traffic accident or experiencing a life-threatening illness or injury are among the most common types of trauma in the general population.[1] People exposed to such events are at elevated risk of multiple forms of psychopathology, including but not limited to post-traumatic stress disorder (PTSD).[5] The risk of psychopathology differs across trauma types as well as according to the developmental timing of the exposure. For example, traumas involving interpersonal violence carry the highest risk for developing PTSD.[3] Importantly, children might be particularly vulnerable to the effects of trauma because of their ongoing neurobiological, emotional, and social development.[6]

1.1.1 Adverse childhood experiences

Severe experiences or traumatic events that occur in childhood or adolescence are referred to as adverse childhood experiences (ACEs). These include abuse (emotional, physical, sexual), neglect (emotional, physical), and growing up in dysfunctional home environments (e.g., parental substance abuse or witnessing domestic violence).[7] The prevalence of ACE exposure is high globally.[8,9] A cross-sectional survey from the US found that among 214,157 participants across 23 states, 62% had experienced at least one ACE.[10] The European Region, including the Nordic countries, is no exception.[11,12] A recent systematic review and meta-analyses including data from 10 European studies, with the majority of studies from northern Europe, estimated a pooled prevalence rate of 43% for exposure to at least one ACE.[13] However, it should be noted that the comparison of ACE prevalence between populations is complicated, meaning the reported figures on the prevalence of ACEs vary widely.[9] In addition to cultural and population variations, the differences in prevalence rates are also dependent on the number and type of ACEs measured in each study, the time period when the prevalence was measured, as well as other sample characteristics.

1.1.2 ACEs and adult health outcomes

Exposure to ACEs has consistently been associated with an elevated risk of a wide range of adverse mental and physical health outcomes across the life course.[14-18] ACEs

frequently co-occur,[19] with abuse, neglect, and parental mental illness or parental substance abuse often affecting the same children. There is growing evidence showing that risk of negative health outcomes after ACE exposure is substantially increased among those experiencing multiple types of ACEs.[16,17] In a large systematic review and meta-analyses consisting of 37 studies (n = 253,719), Hughes and colleagues found that experiencing ≥4 ACEs was associated with increased risk of all 23 adult health outcomes under study, including mental illness, some forms of cancer and heart disease.[16] The adult health outcomes most clearly associated with ACEs were further exposure to violence, heavy alcohol use, problematic drug use and other mental illness.[16] Similarly, in another recent systematic review and meta-analyses, Petruccelli and colleagues found that cumulative exposure to ACEs was more strongly associated with behavioral and mental health outcomes than physical health outcomes.[17] Moreover, the results showed a clear dose-response relationship between each additional type of ACE and the increased risk of most outcomes, including psychiatric disorders.[17]

1.1.3 The relationship between ACEs and adult psychiatric disorders

Although studies have consistently reported associations between ACEs and elevated risks of psychiatric disorders in adulthood, such as depression,[20-22] anxiety,[23] PTSD,[24,25] and substance abuse,[26] few studies have examined the extent to which these associations reflect familial (genetic and environmental) confounding. This is an important limitation, since associations between ACEs and psychiatric disorders could be attributable to confounders shared by family members (i.e., environmental and genetic factors). Indeed, twin studies show that genetic factors are important for the etiology of psychiatric disorders, with heritability estimates ranging from 40% to 60% depending on the disorder in question.[27] Furthermore, exposures that are considered to be environmental, such as ACEs, can be influenced by genetic factors; this is typically referred to as gene-environment correlation (rGE). There are three mechanisms of rGE: passive, evocative, and active. Passive rGE arises when parental genetic factors influence their family environments (e.g., child rearing practices) and are also inherited by their offspring. Evocative rGE arises when an individual's genetically influenced behaviour elicit different responses from others. Active rGE arises when an individual's genetically influenced characteristics affect the environments that they select.[28-30] Indeed, recent research indicates that liability to ACEs is influenced by genetic factors (through gene-environment correlations),[31-34] some of which could be the same genetic factors as those predisposing individuals to psychiatric disorders. Additionally, early environmental conditions, such as parenting practices and socio-economic disadvantage when growing up,[35,36] may similarly confound the association between ACEs and adult psychiatric disorders. Therefore, previously observed associations between ACEs and adult psychiatric disorders could potentially be confounded by unmeasured genetic and environmental factors.

1.1.4 Strengthening causal inference using twin data

In situations where randomized controlled trials are not feasible, quasi-experimental designs can be used to strengthen causal inference, and could help disentangle the causal effects of ACEs on adult psychiatric disorders. That is, these designs use methodological features to rule out alternative explanations for an association (i.e., unmeasured confounding) by generally using comparison groups that share common causes.[28,37] Family-based designs are an example of quasi-experiments, since they capitalize on varying genetic and environmental relationships between family members to account for familial (genetic and environmental) confounding. The co-twin control design (also referred to as the discordant twin-pair design), is a particularly stringent method to account for unmeasured genetic and environmental confounders, since twins share both their early environment and genes.[38,39] Monozygotic (MZ) twins are genetically identical and dizygotic (DZ) twins share on average 50% of their segregating genes, whereas both MZ and DZ twins share their family environment. The co-twin control design tests whether twins that are discordant on an exposure (e.g. exposure to ACEs) differ in an outcome (e.g., mental health problems).

Studies employing the co-twin control design to investigate environmental exposures in childhood and psychopathology in adulthood are rare, as few twin data sources have information on both ACEs and adult mental health. Nonetheless, a set of studies using this methodology have examined specific forms of ACEs, i.e. child sexual abuse,[40] and exposure to bullying,[41] finding evidence supporting causal effects of these exposures on depression, anxiety and substance abuse, after adjusting for familial confounders. Other studies, including broader assessments of ACEs (but confined to selected mental health outcomes), have found that associations with psychotic experiences,[42] adult attention-deficit/hyperactivity disorder (ADHD) symptoms,[43] and alcohol dependence,[44,45] are partly causal and partly due to familial confounding. Existing evidence is additionally limited by relatively small samples, cross-sectional designs and/or the use of self-reported mental health assessments. Therefore, more research is needed to examine the relationship between a broader range of ACEs and psychiatric symptoms and disorders in nationwide studies of twins. To our knowledge, no study to date has examined whether ACEs are associated with increased odds of clinically confirmed psychiatric disorders, while carefully adjusting for familial confounding using the co-twin control design.

1.2 Resilience in the context of trauma

Although ACEs have consistently been associated with a wide range of psychiatric symptoms and disorders extending into adulthood,[16,17,23,24] there is substantial heterogeneity in long-term outcomes after exposure to ACEs.[46] That is, a considerable proportion of children exposed to ACEs do not develop psychiatric disorders,[47,48] but

instead maintain psychological health through adulthood despite significant adversity, and therefore demonstrate resilience.[49,50]

1.2.1 Operational approaches of resilience

Resilience is generally defined as positive psychological functioning or maintained mental health despite significant exposure to trauma or adversity.[50-53] The scientific investigation of resilience can be traced back to the 1970s, when the resilience concept first appeared in the developmental literature, as researchers noted unexpectedly positive adjustment among some children that had experienced significant trauma (for a review see[49]). In the early 2000s the concept of resilience started to emerge in research on adults.[54] Since then, resilience has been conceptualized in various ways in the literature,[55] and a distinction has for example been made between resilience as a perceived coping ability (also referred to as trait resilience) and psychiatric resilience (also referred to as outcome-based resilience). Perceived coping ability reflects one's perceived ability to overcome stress and/or adversity and is typically measured via self-report.[56,57] Psychiatric resilience has been operationalized in a few different ways. Conceptually psychiatric resilience reflects the outcome of a dynamic process of resilience that unfolds during or after adversity.[51,52] This outcome-oriented definition of resilience is two-dimensional and entails trauma exposure as well as the achievement of positive adaptation, despite major disruptions to the developmental process.[51,58-60] In fact, one way to operationalize psychiatric resilience is as the absence of PTSD or other psychiatric disorders among individuals exposed to adversity or trauma.[61,62] Another way is to regress psychiatric symptom scores on adversity/trauma exposure and use the residual between actual and predicted symptom scores to define resilience (also referred to as residual-based resilience or discrepancy based resilience in the literature).[63]

Prevalence rates of resilience across different study populations vary, making it difficult to obtain an accurate global estimate. The variability in prevalence rates between studies (ranging from a prevalence of 23% to 87%)[61,62,64-68] are likely to be due to differing definitions of resilience, as well as differences between the study samples and confined to specific types of adversity (e.g., combat trauma).[61] However, as previously noted by various researchers in the field, when operationalizing psychiatric resilience, it is crucial to clarify the nature of the adversity or trauma and measure resilience by a defined criterion of positive adaptation.[51,69]

Given that resilience as a perceived coping ability is generally self-reported and measured on a continuous scale, it should be noted that prevalence estimates of this phenotype are rarely reported. Interestingly, Nishimi and colleagues[62] compared four different measures of resilience (including perceived coping ability) in a community sample, finding only moderate correlations between definitions, e.g., r = 0.35 between perceived coping ability and psychiatric resilience. Together with previous literature,

these findings suggest that the different definitions of resilience are not mutually exclusive, but rather complimentary and may capture different patterns of adaptive functioning following adversity.[61,70,71]

1.2.2 Environmental predictors of resilience

An individual's level of resilience is likely determined by multiple influences, ranging from individual factors (e.g., psychological factors such as self-efficacy and problem-solving skills) to broader environmental factors (e.g., availability of social support and community resources).[60] Indeed, research suggests that socio-demographic,[56,62,72] genetic,[63,73] psychological,[74,75] and environmental factors[76] are all likely involved in the etiology of resilience. At the individual-level, resilience-enhancing factors include self-efficacy, having a sense of meaning in life, and personality traits such as positive emotionality and high levels of dispositional optimism.[75,77] Furthermore, socio-demographic factors, such as older age, male sex, and higher educational level, have been associated with higher levels of resilience.[56,62,72] In addition, studies suggest that broader environmental factors, such as community resources and the availability of social support can protect against the detrimental effects of trauma or adversity and have been associated with resilient outcomes following stress and adversity.[60,76]

Importantly, previous research has suggested that ACEs may be an environmental risk factor for lower resilience in adulthood. That is, a few studies have found childhood maltreatment, variously defined, to be associated with reduced psychiatric resilience in adults[78-81] as well as lower self-reported coping ability in adulthood.[56,82] However, most studies to date have focused on childhood maltreatment generally (i.e., creating a binary score based on various indicators of maltreatment) or included only a small number of ACEs, without considering that the association between ACEs and resilience may vary depending on the ACE subtype. That is, to our knowledge, no study has to date comprehensively assessed the cumulative number and types of ACEs and their association to adult resilience.

1.2.3 Twin studies of resilience

Accumulating evidence point towards a genetic contribution to individual variation in resilience. The classical twin design offers a valuable framework for estimating the relative contribution of genetic (i.e. heritability) and environmental factors to the observed variance of a phenotype.[83,84] Similar to the co-twin control design, the classical twin design takes advantage of the fact that MZ twins are genetically identical while DZ twins share on average 50% of their segregating genes, while both MZ and DZ twins share their family environment.

A few previous twin studies have assessed the heritability of resilience. Results from previous studies show moderate heritability of resilience, with heritability estimates ranging from 25% to 50% depending on the trauma context and how resilience is

defined.[63,75,85-87] For example, a study by Wolf et al., of 3,318 male twins from the Vietnam Era Twin Registry, measured perceived coping ability using the self-reported Connor-Davidson Resilience Scale (CD-RISC), and found that perceived coping ability was moderately heritable at 25%.[87] Another study, by Amstadter et al., of 7,500 twins from the Virginia Twin Registry, operationalized psychiatric resilience as the residuals of a regression model where internalizing symptoms were predicted from number of stressful life events, finding that psychiatric resilience was moderately heritable at 30%. Furthermore, after taking into account measurement error and occasion-specific environmental influences, the heritability of the phenotype was estimated to be 50%.[63] However, to the best of our knowledge, no previous studies have examined the genetic and environmental contributions to variation in psychiatric resilience in the context of ACEs.

Using twin studies, it is also possible to explore genetic overlap between two or more phenotypes. In fact, at least three twin studies have investigated possible genetic overlap between resilience and other psychiatric phenotypes (i.e., neuroticism, internalizing and externalizing disorders). For example, a study by Amstadter et al.,[88] based on data from the Virginia Twin Registry described above, found that genetic factors contributing to residual-based resilience (definition described above) accounted for 42% of the heritability of depression and 61% of the heritability of anxiety. Moreover, they found that the genetic overlap between resilience and externalizing disorders was lower, e.g., 20% of the heritability of alcohol abuse or dependence could be accounted for by genetic factors that influence resilience.[88] Similarly, in another study based on the Virginia Twin Registry, Amstadter et al.,[89] found modest genetic overlap between resilience and neuroticism as well as other cognitive/psychological traits (e.g., optimism and self-esteem). Finally, Wolf et al.,[87] also found evidence for genetic overlap between resilience (perceived coping ability) and PTSD. They estimated that a single (latent) genetic factor explained 59% of the negative phenotypic correlation between resilience and PTSD, concluding that genetic factors may contribute to a dimension of traumatic stress responses, with resilience at one end of the dimension and high psychiatric morbidity at the other end.[87] Together these studies suggest genetic overlap between resilience and common psychiatric disorders, but they also highlight that a part of the genetic contribution to resilience is independent, i.e., not shared with common psychiatric disorders. Further research is needed to understand the genetic underpinnings of resilience, both in terms of independent and shared genetic factors.

1.2.4 Molecular genetic studies of resilience

There is currently a scarcity of molecular genetic studies seeking to validate the heritable component of resilience. To date, most genetic studies on resilience have been based on the candidate gene approach, with inconclusive findings.[90-97] Indeed, candidate gene studies have been broadly criticized for poor replicability,[98] and

therefore their results should be interpreted with caution. Also, like other psychiatric phenotypes, resilience reasonably has a highly polygenic nature, meaning that many genetic variants or single nucleotide polymorphisms (SNPs) contribute to the variation in resilience. As such, during the last two decades, genomic methods have been developed such as genome-wide association studies (GWAS) which are better suited to identify genetic variants associated with resilience.

To our knowledge only two GWAS on resilience have previously been published, reporting conflicting results.[73,99] Stein et al., conducted a GWAS of perceived coping ability, measured with five items assessing an individual's ability to handle stress, among 11,492 US Army soldiers, finding one genome-wide significant SNP.[73] The authors also conducted an exploratory GWAS on psychiatric resilience, defined as the absence of new-onset stress-related psychiatric disorders: PTSD, major depressive disorder (MDD), generalized anxiety disorder (GAD) and panic disorder, and found a genome-wide significant SNP when the analyses were restricted to soldiers exposed to high levels of deployment-related trauma (n = 521).[73] In contrast, a GWAS of residual-based resilience (defined as internalizing symptoms after lifetime trauma had been regressed out) conducted by Cusack et al., found no genome-wide significant SNPs among 6,634 US college students.[99] Importantly, neither of the genome-wide significant SNPs identified by Stein et al.,[73] were replicated by Cusack et al.,[99] likely due to limited sample size and different sample characteristics.

Although the primary aim of GWAS is to identify common genetic variants (i.e., SNPs) that are associated with a certain phenotype[100] the utility of GWAS in epidemiology extends beyond this. The polygenic risk score (PRS) approach, for example, uses results from large GWAS meta-analysis to create an individual genetic risk score by summing up all genetic effects detected by GWAS.[101] PRSs may then be used to explore genetic overlap between phenotypes (similar to twin studies described above). Using PRS analyses, Cusack et al., found some indication for genetic overlap between resilience and PTSD. However, genetic risk indicated in PRS (i.e., the PTSD PRS) was positively associated with resilience, which contradicts what would be expected based on previous literature (i.e., non-genomic studies).[87,101,102]

Clearly, larger sample sizes are needed in future GWAS of resilience. In the meantime, since twin studies indicate negative genetic correlations between resilience and other psychiatric phenotypes, well-powered polygenic risk prediction could examine whether common genetic risk variants associated with other psychiatric traits and disorders are also associated with resilience. Indeed, examining genetic overlap with other psychiatric phenotypes could help us gain insights into the etiology of resilience.

2 Aims

The overarching objective of this thesis was to examine environmental and genetic contributions to the psychiatric morbidity-resilience dimension, as defined as a) clinically confirmed psychiatric disorders (Study I); b) perceived coping ability reflecting individual's perceptions of their ability to cope effectively with stress and adversity (Study II); and c) psychiatric resilience defined as the absence of (or low) psychiatric morbidity after exposure to lifetime trauma (Study II) or exposure to ACEs (Study III).

2.1 Study I

The aim of Study I was to assess whether associations between ACEs and common adult psychiatric disorders remained after adjustment for familial confounding due to shared genetic and environmental factors.

2.2 Study II

The aim of Study II was to examine the association between ACEs and two distinct measures of adult resilience, i.e., perceived coping ability and psychiatric resilience in the context of lifetime trauma.

2.3 Study III

The aim of Study III was to investigate the relative contribution of genetic and environmental factors to the variation in psychiatric resilience in the context of ACEs, as well as to assess whether genetic liability for psychiatric traits was associated with psychiatric resilience to ACEs.

3 Materials and Methods

3.1 Data sources

The studies included in this thesis used data from several resources: the Icelandic Stress-And-Gene-Analysis (SAGA) cohort, and three birth cohorts from the Swedish Twin Registry (STR); The Study of Twin Adults: Genes and Environment (STAGE), The Young Adult Twins in Sweden Study (YATTS), and The Child and Adolescent Twin Study in Sweden (CATSS), which have been linked to the Swedish National Patient Register (NPR) and the Swedish Prescribed Drug Register (PDR). A summary of the materials and methods for the three studies comprising this thesis are described in Table 1.

Table 1. Summary of the materials and methods used in each study

Study	Data sources	Study design	Exposures	Outcomes	Covariates	Statistical methods
I	▪ STAGE ▪ YATSS ▪ CATSS ▪ NPR ▪ PDR	▪ Co-twin control study	▪ 7 ACEs	▪ Clinical diagnosis of psychiatric disorders	▪ Age and sex	▪ Generalized estimating equations ▪ Conditional generalized estimating equations
II	▪ SAGA	▪ Cross-sectional study	▪ 13 ACEs	▪ Perceived coping ability ▪ Psychiatric resilience	▪ Age, childhood deprivation, education level, civil status, employment status and income	▪ Linear regression ▪ Generalized estimating equations
III	▪ STAGE ▪ YATSS ▪ NPR ▪ PDR	▪ Classical twin study	▪ NA ▪ PRS for psychiatri c traits	▪ Psychiatric resilience	▪ Year of birth and sex	▪ Twin structural equation models ▪ Generalized estimating equations

ACE = adverse childhood experience; CATSS = the Child and Adolescent Twin Study in Sweden; NPR = the National Patient Register; PDR = the Prescribed Drug Register; PRS = polygenic risk scores; STAGE = the Study of Twin Adults: Genes and Environment; YATSS = the Young Adult Twins in Sweden Study.

3.1.1 The Icelandic Stress-And-Gene-Analysis cohort

The SAGA cohort is a nationwide Icelandic study of the impact of trauma on women's health. All Icelandic-speaking women, aged between 18 to 69 years, residing in Iceland with an identifiable address or telephone number (target population n ≈ 104,197) were invited to participate in the study between March 2018 and July 2019. In total, 30,403 women (approximately 30% of the eligible women) consented to participate and were enrolled in the study. Participation involved answering an extensive web-based questionnaire including assessments on the history of trauma (in childhood and adulthood), physical and mental health, and demographic factors. The SAGA cohort participants are representative of the general Icelandic female population in terms of demographic characteristics, including age, level of education, monthly income and region of residence.[103]

3.1.2 The Swedish Twin Registry

The STR was established in 1959 and includes information on nearly 200,000 twins born in Sweden since 1886.[104-107] Karolinska Institutet manages the STR, and currently, parents of twins are contacted in connection to their children's 9th birthday and the twins are invited to be part of the registry. In addition to information about zygosity, data from several questionnaire data collections as well as biological sample collections are available for different birth cohorts within the STR. The STR has additionally been linked to nationwide health registers. Data from three birth cohorts from the STR were used in Study I and Study III of this thesis, described in detail below.

3.1.2.1 The Study of Twin Adults: Genes and Environment

The STAGE study population includes Swedish twins born between 1959 and 1985 (target population n ≈ 42,000 individuals), who participated in a web-based data collection between 2005 and 2006.[105,108] Participation involved completing an extensive survey containing questions on common health problems and exposures, including assessments of stressful/traumatic life events. To ensure that individuals who did not have access to the internet could also participate, non-responders were offered a telephone interview, supplemented with a mailed paper questionnaire for sensitive topics (i.e. trauma history assessment). In total, 25,313 twin individuals (approximately 60% of eligible individuals) answered either the web-based or telephone/paper questionnaire.

3.1.2.2 The Young Adult Twins in Sweden Study

The YATSS study population includes Swedish twins born between May 1985 and June 1992 (target population n ≈ 16,000), who participated in a web-based data collection between 2013 and 2014.[107] Participants completed a questionnaire including questions evaluating various somatic and psychiatric symptoms/disorders, as well as a few

questions on interpersonal trauma. Similar to the procedure in STAGE, the option of participating via telephone/paper survey was also offered in order to include twins who did not have access to the internet. In total, 6,870 twin individuals (approximately 42% of the eligible individuals) answered the questionnaire.[107]

3.1.2.3 The Child and Adolescent Twin Study in Sweden

CATSS is an ongoing, longitudinal study of all twins born in Sweden since July 1992.[109] The data collection began in 2004, where parents of twins were contacted after their twins turned 9 or 12 years old. Since then, interviews have been conducted annually with parents of twins born in Sweden in relation to the twins' 9th birthdays. By May 2019, with a target population of 32,952 twins, a total of 16,476 parental interviews had been completed (approximately 69% of the eligible individuals).[107] Independently of their participation in the initial interview, the twins and their parents were invited to complete questionnaires when the twins were 15, 18, and 24 years old. In Study I, we included all twins from CATSS who were born between 1992 and 1998 and had completed a web-based questionnaire (including assessments on stressful/traumatic life events and mental health screening instruments) in connection to their 18th birthday.[109]

In all three cohorts, zygosity was determined either based on DNA, or using questions on intra-pair similarities during childhood. The latter method was shown to have over 95% accuracy when validated against DNA testing.[104]

3.1.2.4 Record linkage to the Swedish Registers

The three birth cohorts from the STR were additionally linked to nationwide Swedish registers, using Swedish personal identification numbers. In Studies I and III we used linked data from the NPR and the PDR.

The NPR was established in 1964 by the National Board of Health and Welfare with nationwide coverage for inpatient care since 1987 and outpatient specialized care since 2001.[110] Diagnoses are reported to the NPR using the Swedish revisions of the International Classification of Diseases (ICD) codes, from the eight revision (ICD-8, 1973-1986), ninth revision (ICD-9, 1987-1996), and tenth revision (ICD-10, since 1997). For the studies in this thesis, data from the NPR were available until the end of 2016.

ational Board of Health and Welfare is also responsible for the PDR, which contains information on drug prescriptions dispensed at pharmacies in Sweden since 2005. Drug prescriptions are reported to the PDR using Anatomical Therapeutic Chemical (ATC) codes.[111] For the studies in this thesis, data from the PDR were available until the end of 2016.

3.2 Measures by cohort

3.2.1 Measures in the Stress-And-Gene-Analysis cohort (Study II)

3.2.1.1 Adverse childhood experiences

ACEs were measured with a modified Icelandic version of the Adverse Childhood Experiences International Questionnaire (ACE-IQ), originally developed by the World Health Organization.[112] This widely used questionnaire consists of 39 items assessing how often individuals were exposed to 13 different types of ACEs during the first 18 years of their life. The 13 types of ACEs can be grouped into four categories including *abuse* (emotional, physical, and sexual abuse), *neglect* (emotional and physical neglect), *household dysfunction* (domestic violence, substance abuse of a household member, incarceration of a household member, mental illness of a household member, and parental death, separation or divorce) and *other violence* (bullying, community violence, and collective violence/exposure to exposure to war). The ACE-IQ has been qualitatively tested in six culturally diverse settings.[48] Given that exposure to war or collective violence is rare in Iceland, the Icelandic ACE-IQ was modified by adding a screening question on collective violence (i.e., "During the first 18 years of your life, were you exposed to war/collective violence (e.g., from gangs or police)?").

Response options varied between items, using either a 5-point scale ranging from 0 (never) to 4 (always), on a 4-point scale ranging from 0 (never) to 3 (many times) or dichotomous response options 0 (no) and 1 (yes). We followed the WHO recommended frequency scoring system, which takes into account the level of exposure to each ACE.[112] We then derived three types of exposure variables:

1) ACE-IQ total score ranging from 0 to 13;

2) Categorized total score (0, 1, 2, 3-4 and ≥5 ACEs);

3) Binary variables for each ACE subtype.

3.2.1.2 Perceived coping ability

Perceived coping ability was assessed using the 10-item version of the Connor-Davidson Resilience Scale (CD-RISC-10).[113] The CD-RISC-10 is a self-report questionnaire which measures individuals' perceptions of their ability to cope with stress and/or adversity. Items on the scale reflect, for example, the ability to adapt to change, the tendency to bounce back after illness or hardship, and the ability to achieve goals despite obstacles. The CD-RISC-10 has demonstrated good reliability and validity.[4] Participants rate all items on a 5-point scale ranging from 0 (not true at all) to 4 (true nearly all the time), which are then summed to create a total score ranging from 0 to 40, with a higher score indicating higher levels of perceived coping ability. Since there is no standardized cut-off for the CD-RISC-10, the total score was divided into

quintiles, and a binary variable was created where the highest quintile was used to define a high level of perceived coping ability (i.e. high resilience) and the four lowest quintiles were merged to define a lower level of perceived coping ability (i.e. low resilience).

3.2.1.3 Psychiatric resilience

In line with previous studies,[62,70,73] we operationalized psychiatric resilience as the absence of or low psychiatric morbidity among women that experienced a traumatic event at some point during their lifetime. Psychiatric morbidity was assessed using the following scales:

The PTSD checklist for DSM-5 (PCL-5) was used to assess symptoms of PTSD in the past month,[114] with a validated clinical cut-off score of 33 to indicate probable PTSD.[115] Before answering the PCL-5, women answered the Life Events Checklist for DSM-5 (LEC-5) to assess their lifetime exposure to traumatic events. The women were asked to indicate the worst traumatic event they had experienced and answer the PCL-5 according to the selected trauma. Trauma-related sleep disturbances were assessed using the Pittsburgh Sleep Quality Index Addendum for PTSD (PSQI-A), with a clinical cut-off score of ≥4.[116] Binge drinking was assessed using the following question from the Alcohol Use Disorders Identification Test (AUDIT-C): *"How often have you had 6 or more units of alcohol on a single occasion in the last year? (one unit corresponds to a single measure of spirits)"*.[117] Binge drinking was coded as 1 if participants responded monthly, weekly and daily or almost daily, and 0 if they answered never or less than monthly. The Patient Health Questionnaire (PHQ-9) was used to assess symptoms of depression (over the past two weeks), with a score of ≥10 indicating clinically relevant depression.[118] The Generalized Anxiety Disorder Scale (GAD-7) was used to assess symptoms of generalized anxiety (over the past two weeks), with a score of ≥10 representing a validated cut-off score for clinically relevant anxiety symptoms.[119,120]

To derive the psychiatric resilience phenotype, we started by calculating binary variables using the clinical cut-off scores described for each measure above. The binary variables were then summed to create a total score. The total score was reversed yielding a psychiatric resilience variable ranging from 0 to 5, with higher scores indicating higher resilience. We additionally derived a binary variable indicating high psychiatric resilience, categorizing individuals that were below the clinical thresholds on all measures above (absence of psychiatric morbidity) as highly resilient.

3.2.1.4 Covariates

Demographic covariates included age (at time of survey), education level (primary, secondary, BSc or equivalent, MSc or above), employment status (employed, retired/disability/sick leave), civil status (married/in a relationship, single/widowed), monthly income (low, low-medium, medium, medium-high, high), and childhood

deprivation. Childhood deprivation was assessed with the question *"Was your family's economic situation ever so bad that you suffered any deprivation as a consequence? For example, this could apply to deprivation of nutritious food and/or deprivation of warm clothes and appropriate footwear during the winter months"*. Response options ranged from 0 (never) to 4 (often). For a more detailed description of the covariate assessment, please refer to the attached paper II or corresponding article.[103]

3.2.2 Measures in the Swedish Twin Registry (Studies I & III)

3.2.2.1 Adverse childhood experiences

In Study I and III (using data from the STR), ACEs were measured using seven items adapted from the Life Stressor Checklist-revised (LSC-R).[121,122] The original LSC-R consists of 30 items assessing potentially traumatic life events according to DSM-IV criteria for PTSD as well as other traumatic events. For Study I and III, we used seven yes/no questions from the LSC-R to assess the following types of ACEs: emotional neglect/abuse, physical neglect, physical abuse, sexual abuse, rape, hate crime, and witnessing family violence. When an ACE item was endorsed, follow-up questions were asked to specify when the respective event first occurred, using the following age intervals: 0-6, 7-12, 13-15, 16-18, or >18 years. Participants were categorized as exposed to any ACE if they responded that they have experienced one of the seven ACEs when they were aged 18 years or younger.

In Study I, we generated three types of exposure variables:

1) ACE total score ranging from 0 to 7;
2) Categorized total score (0, 1, 2, and ≥3 ACEs);
3) Binary variables for each ACE subtype.

In Study III, the analytic sample was restricted to twins reporting an ACE (see description of psychiatric resilience after ACEs below).

3.2.2.2 Adult mental health outcomes

Using the NPR, we identified all individuals with any first inpatient or outpatient hospital visit that resulted in a diagnosis of depressive disorders, anxiety disorders, alcohol or drug misuse disorders and stress-related disorders, after their 19th birthday. The diagnoses were assigned in accordance with the International Classification of Diseases (see Table 2 for ICD codes).

Since the NPR includes only information related to inpatient or specialized outpatient hospital visits, we additionally used information about dispensed antidepressants or anxiolytics (see Table 2 for ATC codes) as an indication of milder psychiatric disorders not requiring specialized care.

Table 2. ICD codes, versions eight (ICD-8; 1969-1986), ninth (ICD-9; 1987-1996), and tenth (ICD-10; 1997-2016) used to identify psychiatric disorders, as well as ATC codes used to identify dispensed medications

Psychiatric diagnosis	ICD-8	ICD-9	ICD-10
Alcohol or drug misuse disorders	303, 304	291E, 292.0, 303, 304, 305	F10-F19
Depressive disorders	296.0, 300.4	296, 311	F32-F34, F38-F39
Anxiety disorders	300.0, 300.1	300A, 300C, 300D	F40, F41, F42, F44
Stress-related disorders	307	308, 309	F43
Dispensed medications	ATC		
Antidepressants	N06A		
Anxiolytics	N05B		

This Table is adapted from eTable 2 in Daníelsdóttir et al., JAMA Psychiatry. 2024.[123]

3.2.2.3 Psychiatric resilience after ACEs

Based on information from the NPR and PDR, in Study III, we derived a phenotype of psychiatric resilience. The resilience phenotype was operationalized as the absence of clinically diagnosed psychiatric disorders (i.e., depression, anxiety, substance abuse and stress-related disorders) as well as the absence of dispensed antidepressants and anxiolytics among individuals exposed to ACEs.

3.2.2.4 Genotype data

A part of the STR participants have provided saliva samples, which have subsequently been genotyped using the 650K Illumina Global Screening Array (GSA) BeadChip.[107] Detailed information about the processing of the genotype data can be found in the attached manuscript for Study III in this thesis. Genotype data was used to derive PRS scores for five psychiatric traits and disorders in Study III (described below in the analytical and statistical methods for Study III).

3.3 Analytical and statistical methods

3.3.1 Study I – a co-twin control study

3.3.1.1 Study design

In Study I, we used a co-twin control design to determine whether associations between ACEs and adult psychiatric disorders remained after adjusting for familial confounding (i.e., unmeasured genetic and environmental factors). The study population consisted of 25,252 twin individuals, aged 18-47 years, from the STAGE, YATSS and CATSS cohorts, with complete information on the ACE assessment. Of these individuals, n = 1,554 DZ twin-pairs, and n = 1,010 MZ twin-pairs were discordant on ACE exposure (see Figure 1). Participants were followed up in the NPR from their 19th birthday until the end of 2016, with follow-up time ranging from 0 years (in CATSS) to 39 years (in STAGE) (see Figure 1).

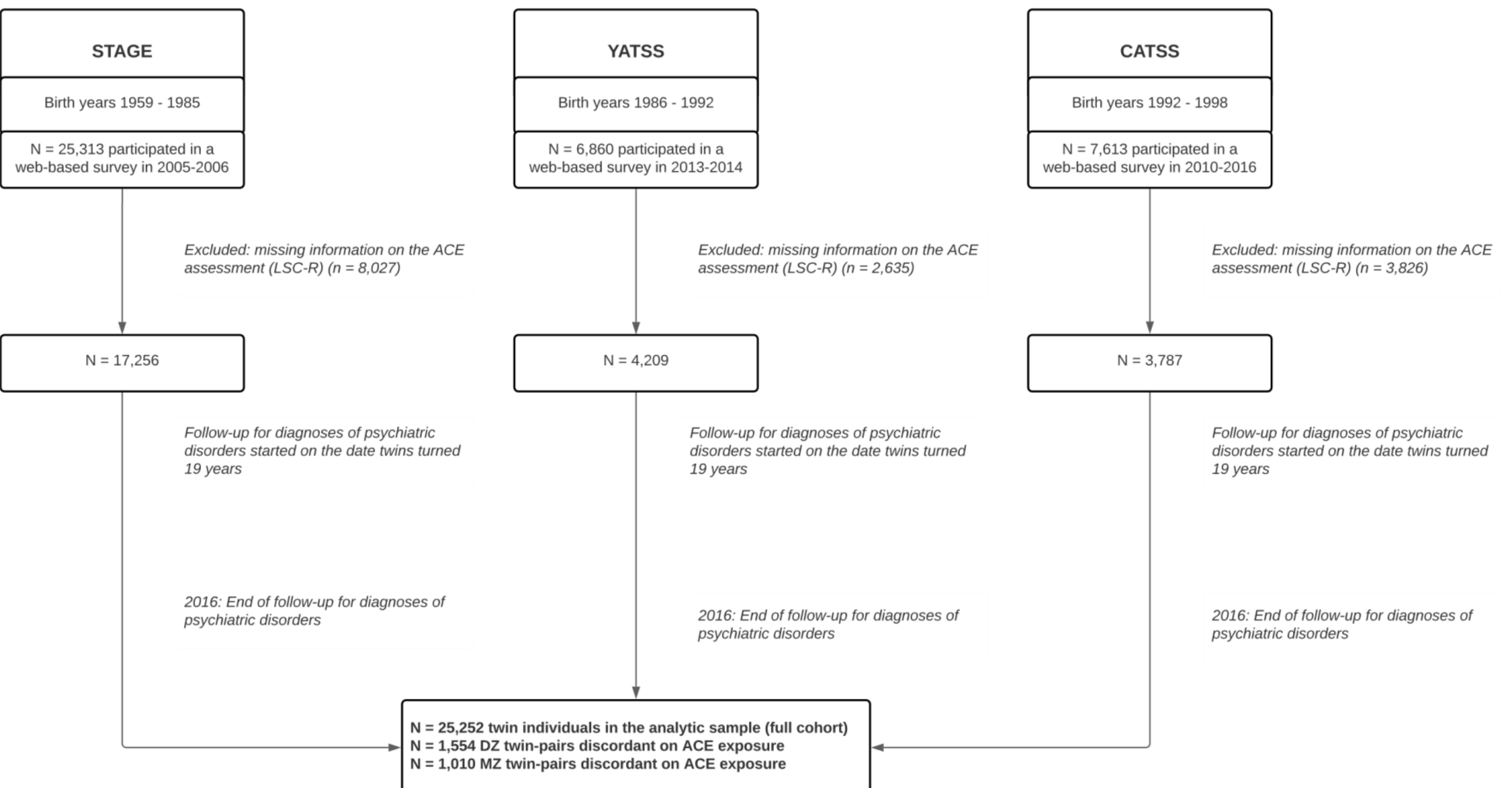

Figure 1. Flow-chart of the analytic sample for Study I

STAGE = the Study of Twin Adults: Genes and Environment; YATSS = the Young Adult Twins in Sweden Study; CATSS = the Child and Adolescent Twin Study in Sweden.

The co-twin control design takes advantage of the fact that MZ twins are genetically identical while DZ twins share on average 50% of their segregating genes, while both MZ and DZ twins share their family environment. This method provides an opportunity to adjust for unmeasured genetic and environmental confounders when evaluating the relationship between a putative risk factor and an outcome.[38,39] Using twin data it is possible to test whether twins that are discordant on an exposure (e.g., childhood adversity) differ in an outcome (e.g., a psychiatric disorder in adulthood). If the effect of ACEs on psychiatric disorders is beyond familial influences (consistent with a causal hypothesis), we would expect that the exposed twin is more likely to be diagnosed with a psychiatric disorder compared to the unexposed (for binary variables) or less exposed co-twin (for the cumulative number of ACEs). However, if the associations are better explained by shared underlying factors (e.g., genetic factors), the strength of the association would be attenuated within DZ twin-pairs and especially within MZ twin-pairs. Therefore, the associations within twin-pairs were also compared to the associations observed in the whole cohort.

3.3.1.2 *Statistical analysis*

Logistic regression models were used to examine associations between ACEs and any adult psychiatric disorder (i.e., any of the following: depressive disorders, anxiety disorders, alcohol or drug misuse disorders and stress-related disorders). First, we examined the associations in the full cohort (i.e., not within twin-pairs) adjusting the analysis for sex and age (at time of survey). To account for the lack of independence of twin data, the logistic regression models were fit using generalized estimating equations (GEE) (drgee package in R)[124] with cluster robust standard errors (i.e., using sandwich estimation on twin-pair ID). As previously described, ACEs were analyzed as a numerical variable (ACE total score with range 0-7), a binary variable (exposed to any ACE vs. not exposed), and a categorical variable (0, 1, 2, or ≥3 ACEs). Each ACE subtype was also analyzed separately.

Next, we used co-twin control analysis to adjust for familial (genetic and environmental) factors shared within twin-pairs. To do this, we selected MZ and DZ twin pairs discordant for ACEs (discordant on ACE total score, any ACE, or individual ACEs, depending on the analyses), and fit logistic regression models conditional on twin-pairs using GEE[124] separately in monozygotic (MZ) and dizygotic (DZ) twin-pairs. Confounding by age was intrinsically adjusted for by the co-twin control design. In addition, confounding by sex was intrinsically adjusted for by the co-twin control design for MZ twin-pairs, but for DZ twin-pairs we adjusted for sex by including it as a covariate in the models.

Sensitivity analyses were conducted additionally using dispensed antidepressants or anxiolytics as indication of milder psychiatric disorders not requiring specialized care. We also performed a sensitivity analyses where we restricted the follow-up time to after the completion of the ACE assessments (please refer to Study II, Supplement 1 – eFigure 2).[123]

3.3.2 Study II – a cross-sectional study

3.3.2.1 Study design

In Study II, we performed cross-sectional analyses to assess the association between a broad spectrum of ACEs and two distinct measures of adult resilience. The study population consisted of 26,198 women, aged 18 to 69 years, who participated in the baseline assessment of the ongoing SAGA cohort and had information on all key variables of interest (see Figure 2). Given that psychiatric resilience is a key outcome measure (and trauma exposure is conceptually a part of psychiatric resilience), the analytic sample was restricted to women who reported experiencing a worst traumatic event at some stage in their life (as outlined in the description of PCL-5 above). Furthermore, women with more than 25% missing values on each scale were excluded from the analytic sample, which resulted in a final study population of 26,198 women (see Figure 2).

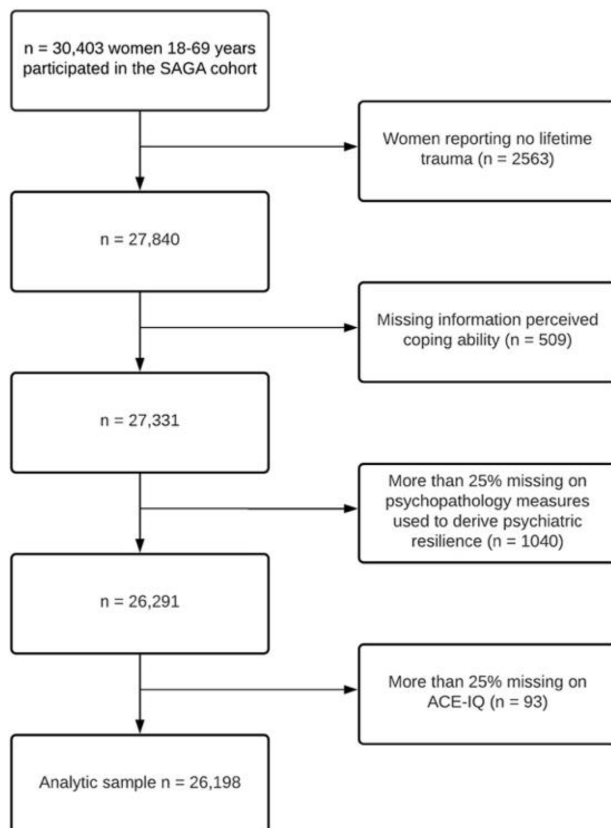

Figure 2. Flow-chart of the analytic sample for Study II

ACE-IQ = Adverse childhood experiences – International Quationnaire; SAGA = the Stress-And-Gene-Analysis cohort. This Figure was adapted from Appendix 1 - Figure 1 in Daníelsdóttir et al., elife. 2022.[103]

3.3.2.2 Statistical analysis

The ACE-IQ and the five scales used to derive psychiatric resilience, i.e., PHQ-9, GAD-7, PCL-5, PSQI-A and AUDIT-C, had missing values which resulted in a reduced sample size. While participants with more than 25% missing on each scale were excluded from the analytic sample, multiple imputation (MI) was used to replace missing data for participants with less than 25% missing with m = 20 rounds of imputations, using predictive mean matching.[125] All analyses (described below) were performed using the imputed dataset, but we also performed complete case analysis for comparison (please refer to the attached Study II or the corresponding article for those results).[103]

Linear regression and log-linear Poisson regression models with robust error variance[126] were used to examine the associations between ACEs and perceived coping ability and psychiatric resilience, where the outcome was modelled both as a numerical and a binary variable (high perceived coping ability/ high psychiatric resilience), respectively. The Poisson regression models were fitted using GEE (geepack package in R).[127] We estimated standardized regression coefficients from the linear regression models and prevalence ratios (PR) from the Poisson regression models.[126]

In all analyses, we started by fitting a simpler model, adjusting for age (at time of survey) and childhood deprivation, and then we additionally adjusted for adult education level, civil status, monthly income and employment status in an extended model. As previously described, ACEs were analyzed as a numerical variable (ACE-IQ total score with range 0-13) and a categorical variable (0, 1, 2, 3-4 and ≥5 ACEs). Each ACE subtype was also analyzed separately, and given the interrelatedness of ACEs[19] we ran a final model mutually adjusting for other ACE subtypes.

Additionally, to assess whether the association between the cumulative number of ACEs and resilience differed by levels of social support, we performed stratified analyses by low, moderate, and high levels of perceived social support.

3.3.3 Study III – a classical twin study

3.3.3.1 Study design

In Study III we used a classical twin design to estimate the relative contribution of genetic and environmental factors to the liability of resilience to ACEs. The study population consisted of 8,606 twin individuals, aged 25-47 years, from the STAGE and YATSS cohorts, which reported exposure to at least one ACE (Figure 3). That is, since trauma exposure is intrinsic to the conceptualization of psychiatric resilience and given that we aimed to investigate resilience to ACEs in the present study, the analytic sample was restricted to twins reporting an ACE. This resulted in a final analytic sample of 8,606 twin individuals, of which 3,408 were MZ twins (732 complete twin-pairs), 2,522 were DZ same-sex twins (394 complete twin-pairs) and 2,676 were DZ opposite sex

twins (323 complete twin-pairs) (see Figure 3). Twins with unknown zygosity were excluded (Figure 3), while single twins were retained as they contributed to information relating to the prevalence of resilience.

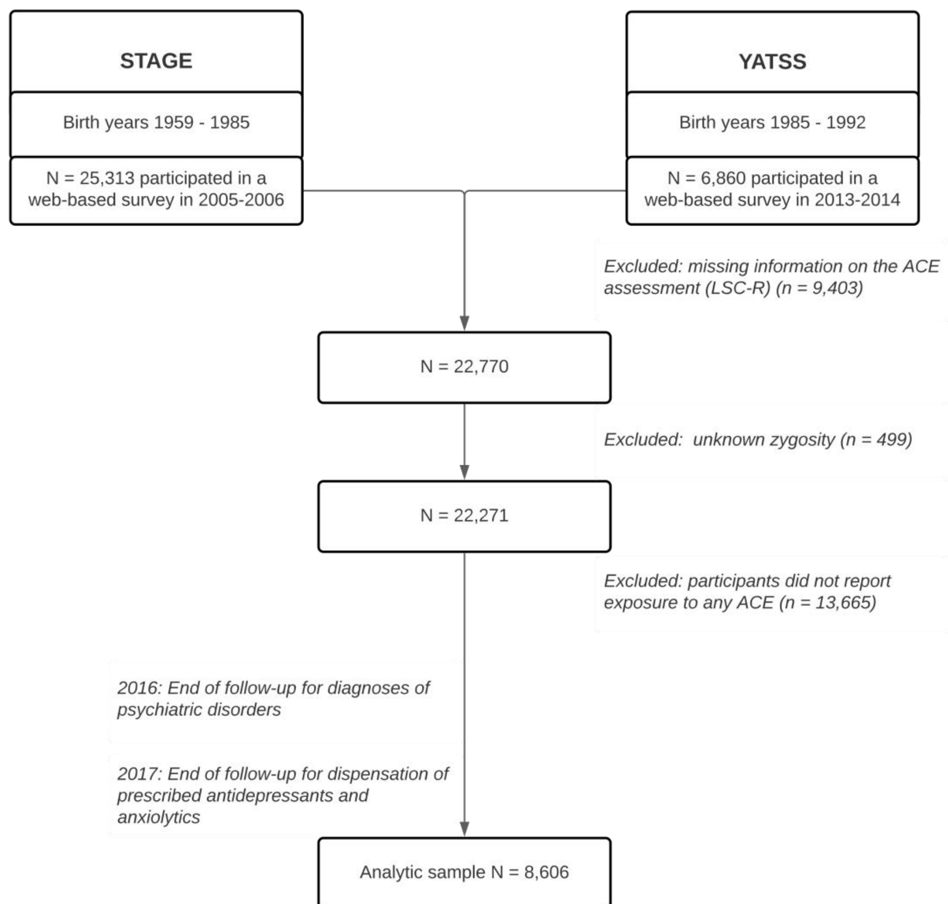

Figure 3. Flow-chart of the analytic sample for Study III

ACE = adverse childhood experience; STAGE = the Study of Twin Adults: Genes and Environment; YATSS = the Young Adult Twins in Sweden Study.

The aim of quantitative genetics is to study the relative contributions of genetic (i.e., heritability) and environmental factors to the variation of a phenotype in a population.[128] In the classical twin design, this can be accomplished by comparing the observed resemblance between MZ and DZ twins, and as in the co-twin control design, by capitalizing on the fact that MZ twins share all of their genes while DZ twins share on average 50% of their segregating genes.[129] Furthermore, as in the co-twin control design, it is assumed that co-twins within MZ and DZ twin pairs share their rearing environment to the same extent (referred to as the equal environments assumption).[33,128]

The observed resemblance between twins in a pair is expressed in correlations. Therefore, if a phenotype is heritable, e.g., psychiatric resilience, MZ twin pairs would have a larger within-twin pair correlation (also called intra-pair correlation; i.e., the correlation of resilience in twin 1 with resilience in twin 2) than DZ twin pairs.

By fitting twin-based structural equation models (SEM), it is possible to decompose the variance of a phenotype into the following genetic and environmental components: *additive genetic* (A), *dominance genetic* (D), *common/shared environmental* (C), and *unique environmental factors* (E). **A** reflects the sum of additive allelic effects at all loci that influence the phenotype; **D** reflects the sum of interactions between allelic effects at the same locus; **C** reflects environmental influences that are shared by family members e.g., co-twins share parenting practices and childhood socio-economic conditions; **E** reflects individual-specific environment, which contributes to differences between co-twins (E also includes measurement error).[128] Taken together, in the classical twin design, it is assumed that A and D have a perfect positive correlation (i.e., correlation of 1.00) in MZ twins, while A is assumed to correlate 0.50 in DZ twins, and D is assumed to correlate 0.25. The C component is assumed to correlate 1.00 in both MZ and DZ twins, whereas E is uncorrelated in both MZ and DZ twins.[128]

In addition, we used a PRS approach to test whether genetic liability for various psychiatric traits and disorders are associated with resilience. To calculate PRSs, two independent samples with genotype data are required. First, GWAS results for the phenotype of interest is needed from where the effect sizes for each SNP are derived (typically referred to as the discovery sample). In an independent sample (typically referred to as the target sample), an individual genetic risk score (PRS) is created by counting the number of risk alleles, multiplying with the effect size and summing the values across all investigated SNPs.[101,130]

In Study III, PRSs were calculated for a sub-sample of individuals with available genotype data in our sample (n = 4,013 with available genotype data and reporting at least one ACE), using GWAS summary statistics from the largest published studies available for PTSD,[131] major depressive disorder (MDD),[132] anxiety,[133] bipolar disorder,[134] and neuroticism.[135] The PRSs were estimated using Ldpred2-auto,[136] with recommended parameter settings.

3.3.3.2 Statistical analysis

In Study III, we estimated the relative contribution of genetic and environmental factors to the liability of resilience by fitting twin-based SEMs using the packages OpenMx (version 2.20.6)[137] and umx[138] using R statistical software, which use full information maximum likelihood. Since we conceptualized resilience as a binary trait, we used a so-called liability threshold approach, i.e. this approach is based on dichotomous data, but each individual is assumed to have an underlying normally distributed liability of resilience (the binary construct).

It should be noted that C and D cannot be estimated simultaneously in twin-based SEMs, which include only two pairs of relatives (it is possible when including more relatives). That is, information from MZ and DZ twins is not sufficient to estimate both C and D simultaneously, together with the A and E components. Therefore, we fit separate ACE and ADE models, and these two models were compared against the AE model to determine whether the C or D parameters could be excluded without a significant loss in model fit. Likelihood ratio tests were used to compare the goodness of fit between the saturated model and the ACE/ADE models. In addition, the ACE/ADE models were compared to nested submodels (AE). Akaike's Information Criterion (AIC; a lower value suggests a better model fit) was used for model comparison. All models were adjusted for sex and birth year.

Finally, to examine the association between genetic liability to the psychiatric traits (disorders and neuroticism) and resilience, we conducted PRS analyses. The associations between the PRSs and resilience were estimated with logistic regression using GEE with cluster robust standard errors (i.e., using sandwich estimation on twin-pair ID) to adjust for the lack of independence of twin data.[124] We included sex, birthyear, and 10 principal components of the genetic relatedness matrix (to account for population stratification) as covariates in the models.

All data management and statistical analyses of the three studies were performed using the R statistical software.

3.4 Ethical permits

In this thesis, already collected data was analyzed and the main ethical issue raised by the three studies within the PhD project was the protection of participants integrity and privacy while using their sensitive information. All participants gave informed consent before participation. The data was analyzed in "pseudonymized" form (e.g. personal identifiers were replaced by a code) and personal identification was therefore not possible. All sensitive information was treated confidentially and accessed only by authorized persons according to the Personal Data Act (1998). The study procedures have been carried out in accordance with the Helsinki Declaration regarding international ethical standards on human experimentation. All studies were approved by the following ethical review boards:

Studies I and III: The Regional Ethical Review Board in Stockholm, Sweden (2018/960-31/2).

Study II: The National Bioethics Committee of Iceland (17-238).

4 Results

4.1 Study I – ACEs and adult psychiatric disorders

The mean age of the analytic sample included in Study I (n = 25,252 twin individuals) was 30 years (standard deviation (SD) 9 years). Overall, 15,501 participants (61.4%) reported no ACEs and 9,751 participants (38.6%) reported being exposed to at least one ACE, of which 2,046 participants (8.1%) reported exposure to ≥3 ACEs. During the study period, 2,379 (9.4%) participants were diagnosed with a depressive disorder, anxiety disorder, alcohol or drug misuse disorder or a stress-related disorder during an inpatient or specialized outpatient hospital visit in Sweden. The proportion of participants that received a clinical diagnosis of any of the above-mentioned psychiatric disorders increased from 6.4% among individuals with 0 ACEs to 24.6% among individuals reporting exposure to three or more ACEs.

Table 3 shows the association between the cumulative number of ACEs and clinical diagnosis of any psychiatric disorder in adulthood. At the cohort level, exposure to ≥1 ACEs (compared to 0 ACEs) was associated with increased odds of receiving a clinical diagnosis of any psychiatric disorder (Table 3, Model 1). We found that the odds of any psychiatric disorder increased in a dose-response fashion, where each additional ACE was associated with 52% increased odds of receiving a clinical diagnosis of any psychiatric disorder (OR = 1.52; 95% CI, 1.48-1.57). The co-twin control analyses revealed a statistically significant but lower increase in the odds of any psychiatric disorder in relation to every additional ACE within DZ twin-pairs (OR = 1.29; 95% CI 1.14-1.47). The attenuation was even greater in MZ twin-pairs (OR = 1.20; 95% CI 1.02-1.40). Furthermore, exposure to ≥3 ACEs (compared to 0 ACEs) was associated with greater odds of any psychiatric disorder at the cohort level and within DZ and MZ twin-pairs (Table 3). The association was substantially lower within DZ twin-pairs compared with the association at the cohort level and even lower within MZ twin-pairs (Table 3).

In sensitivity analysis, the pattern of associations remained the same when dispensed psychotropic medications were included as an indication for milder psychiatric disorders (Table 4). Furthermore, the pattern of associations remained the same in the cohort level and DZ co-twin control analyses when follow-up of psychiatric diagnosis was restricted to after the ACE assessments, while point estimates had low precision and were diluted in the MZ co-twin control analyses (data not shown, please refer to Study I, Supplement 1 – Table 11).

Table 3. Associations between the number of ACEs and any adult psychiatric disorder in the full cohort and within exposure discordant twin-pairs

	Model 1 (Full cohort)			Model 2 (Within DZ twins)			Model 3 (Within MZ twins)		
	N total	cases[a]	OR (95% CI)	N[b]	cases	OR (95% CI)	N[b]	cases	OR (95% CI)
ACE total score[c]	25,252	2379	1.52 (1.48, 1.57)	4018	402	1.29 (1.14, 1.47)	2834	339	1.20 (1.02, 1.40)
Any ACE									
0 ACE	15,501	993	1.00 (ref.)	1554	100	1.00 (ref.)	1010	88	1.00 (ref.)
≥ 1 ACE	9751	1386	2.39 (2.19, 2.60)	1554	167	1.72 (1.31, 2.28)	1010	99	1.19 (0.84, 1.70)
Number of ACEs									
0 ACE	15,501	993	1.00 (ref.)	1554	100	1.00 (ref.)	1010	88	1.00 (ref.)
1 ACE	5531	562	1.65 (1.48, 1.84)	1077	95	1.46 (1.07, 1.98)	724	62	1.17 (0.80, 1.72)
2 ACE	2174	321	2.47 (2.16, 2.83)	301	40	2.37 (1.52, 3.70)	189	19	0.84 (0.50, 1.42)
≥ 3 ACEs	2046	503	4.57 (4.05, 5.15)	176	32	2.25 (1.41, 3.61)	97	17	2.11 (1.13, 3.94)

Models were adjusted for age and sex; 95% CIs are based on robust standard errors, calculated using generalized estimating equations; ACEs = Adverse childhood experiences; DZ = Dizygotic twins; MZ = Monozygotic twins; OR = Odds Ratio; CI = Confidence interval; [a]Any adult psychiatric disorder; [b]Exposure discordant twins, the number of individual twins from exposure discordant twin pairs in the analysis; [c]OR for every additional ACE. This Table was adapted from Table 2 in Daníelsdóttir et al., JAMA Psychiatry. 2024.[123]

Table 4. Associations between the number of ACEs and any adult psychiatric disorder, additionally including dispensed psychotropic medications as an indication for mild psychiatric disorders not attended by specialist care, in the full cohort and within exposure discordant twin-pairs

	Model 1 (Full cohort)			Model 2 (Within DZ twins)			Model 3 (Within MZ twins)		
	N total	cases[a]	OR (95% CI)	N[b]	cases	OR (95% CI)	N[b]	cases	OR (95% CI)
ACE total score[c]	25,252	6726	1.40 (1.37, 1.44)	4018	1102	1.26 (1.14, 1.38)	2834	882	1.16 (1.03, 1.31)
Any ACE									
0 ACE	15,501	3348	1.00 (ref.)	1554	330	1.00 (ref.)	1010	257	1.00 (ref.)
≥ 1 ACE	9751	3378	1.90 (1.80, 2.02)	1554	449	1.49 (1.24, 1.80)	1010	275	1.14 (0.90, 1.46)
Number of ACEs									
0 ACE	15,501	3348	1.00 (ref.)	1554	330	1.00 (ref.)	1010	257	1.00 (ref.)
1 ACE	5531	1594	1.48 (1.38, 1.59)	1077	278	1.34 (1.08, 1.65)	724	183	1.06 (0.82, 1.38)
2 ACE	2174	798	2.06 (1.86, 2.27)	301	104	1.66 (1.23, 2.24)	189	55	1.21 (0.82, 1.79)
≥ 3 ACEs	2046	986	3.20 (2.90, 3.53)	176	67	2.20 (1.53, 3.15)	97	37	1.62 (1.04, 2.53)

Models were adjusted for age and sex; 95% CIs are based on robust standard errors, calculated using generalized estimating equations; ACEs = Adverse childhood experiences; DZ = Dizygotic twins; MZ = Monozygotic twins; OR = Odds Ratio; CI = Confidence interval; [a]Any adult psychiatric disorder or dispensed psychotropic medication; [b]Exposure discordant twins, the number of individual twins from exposure discordant twin pairs in the analysis; [c]OR for every additional ACE. This Table was adapted from eTable 9 in Daníelsdóttir et al., JAMA Psychiatry. 2024.[123]

A greater number of ACEs was significantly associated with elevated odds of stress-related disorders, depressive disorders and anxiety disorders in the cohort level analyses as well as in the co-twin control analyses (Figure 4). However, while the cumulative number of ACEs were significantly associated with increased odds of substance use disorders at the cohort level and within MZ twin-pairs, the association was not significant within DZ twin-pairs (Figure 4).

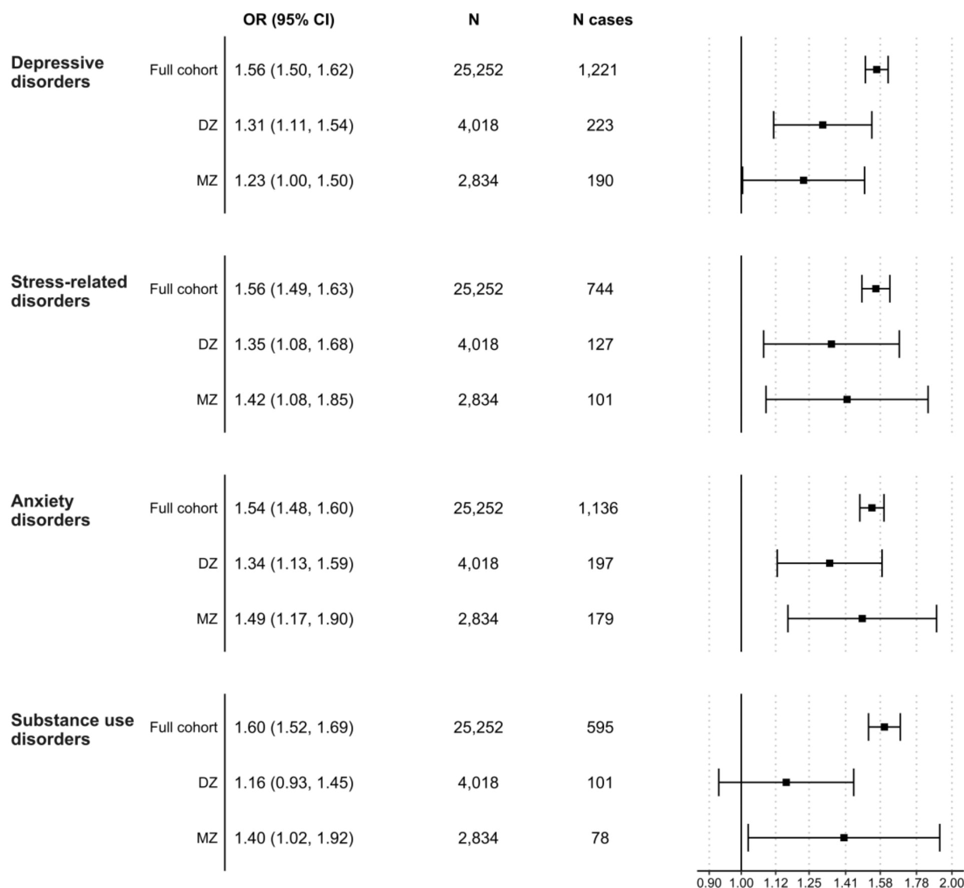

Figure 4. Associations between the number of ACEs and adult psychiatric disorder subtypes in the full cohort and within exposure discordant twin-pairs

Models were adjusted for age and sex; 95% CIs are based on robust standard errors, calculated using generalized estimating equations; DZ = Dizygotic twins; MZ = Monozygotic twins; OR = Odds Ratio; CI = Confidence Interval. This Figure was adapted from Figure 2 in Daníelsdóttir et al., JAMA Psychiatry. 2024.[123]

At the cohort level, all individual types of ACEs were associated with greater odds of any psychiatric disorder (Figure 5). In the co-twin control analyses, the point estimates were considerably attenuated, and became non-significant, for all ACE subtypes, except for sexual abuse, for which the association remained statistically significant within both DZ and MZ twin-pairs (Figure 5).

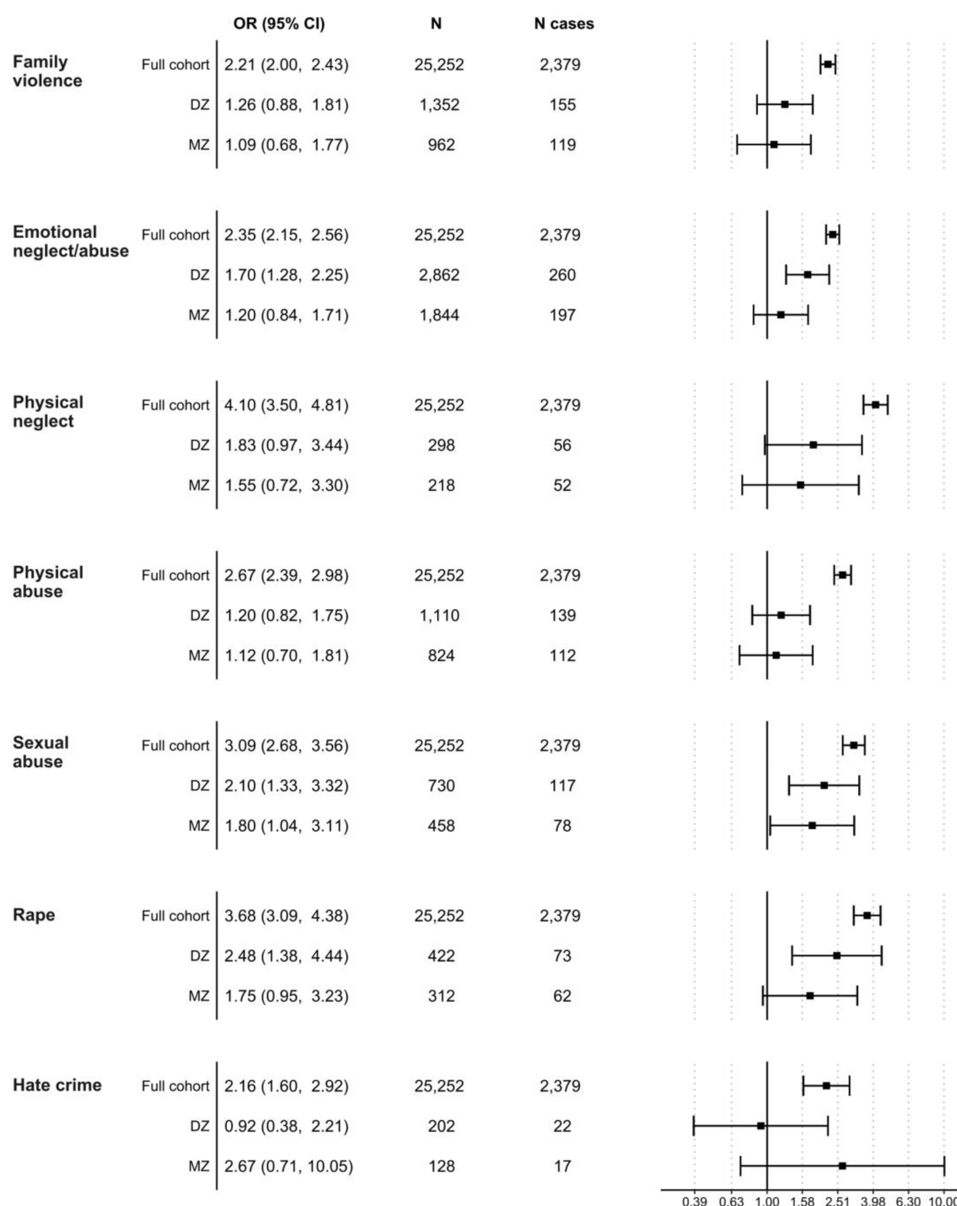

Figure 5. Associations between ACE subtypes and any adult psychiatric disorder in the full cohort and within exposure discordant twin-pairs

Models were adjusted for age and sex; 95% CIs are based on robust standard errors, calculated using generalized estimating equations; DZ = Dizygotic twins; MZ = Monozygotic twins; OR = Odds Ratio; CI = Confidence Interval. This Figure was adapted from Figure 3 in Daníelsdóttir et al., JAMA Psychiatry. 2024.[123]

4.2 Study II – ACEs and adult resilience

The mean age of the analytic sample included in Study II (n = 26,198 women) was 44 years (SD 13 years). In total, 5,149 women (19.7%) reported no ACEs and 5,351 women (20.4%) reported exposure to ≥5 ACEs. The two resilience measures, i.e., perceived coping ability and psychiatric resilience, were moderately correlated (r_s = 0.47). More detailed sample characteristics are reported in the corresponding article.[103]

The prevalence of high resilience according to each measure was 4,959 (23.3%) and 10,518 (40.1%) for high perceived coping ability and high psychiatric resilience, respectively. The prevalence of high perceived coping ability decreased from 25.9% among women with 0 ACEs to 13.3% among those reporting ≥5 ACEs, and similarly the prevalence of high psychiatric resilience decreased from 60.0% among women without any ACEs to 19.5% among those with ≥5 ACEs.

A greater number of ACEs was associated with attenuated perceived coping ability and psychiatric resilience in a dose-dependent manner (Table 5). Hereby, every 1 SD unit increase in the ACE-IQ scores was associated with lower levels of perceived coping ability (β = -0.19; 95% CI -0.20, -0.17) and psychiatric resilience (β = -0.32; 95% CI -0.34, -0.31) after adjustment for age and childhood deprivation (Table 5, Model 1). The associations were somewhat attenuated, yet remained statistically significant, in the fully adjusted model (Table 5, Model 1).

Similarly, every additional ACE was associated with lower prevalence of high perceived coping ability (PR = 0.93, 95% CI 0.92, 0.94) and high psychiatric resilience (PR = 0.87, 95% CI 0.86, 0.87) in the fully adjusted model (Table 6, Model 2). Indeed, the prevalence ratios gradually decreased over categories of ACEs. Specifically, compared to women without any ACEs, women with ≥5 ACEs had 36% lower prevalence of high perceived coping ability (PR = 0.64, 95% CI 0.59, 0.70) and 58% lower prevalence of high psychiatric resilience (PR = 0.42, 95% CI 0.39, 0.45) (Table 6, Model 2).

The associations between ACEs and both resilience measures remained significant across levels of social support, although we observed slightly stronger associations among women with low perceived social support (data not shown, please refer to Study II, Appendix 1 – Table 4).[103]

Table 5. Associations betwen the number of ACEs and perceived coping ability and psychiatric resilience (β and 95% CI)*

		Perceived coping ability		Psychiatric resilience	
	N (%)	Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]
ACE-IQ total score **	26,198	-0.19 (-0.20, -0.17)	-0.14 (-0.15, -0.13)	-0.32 (-0.34, -0.31)	-0.28 (-0.29, -0.27)
Number of ACEs					
0 ACE	5,149 (19.7)	0 (ref.)	0 (ref.)	0 (ref.)	0 (ref.)
1 ACE	5,567 (21.3)	-0.07 (-0.08, -0.05)	-0.05 (-0.07, -0.04)	-0.09 (-0.10, -0.07)	-0.07 (-0.09, -0.06)
2 ACE	4,491 (17.1)	-0.10 (-0.11, -0.08)	-0.08 (-0.10, -0.07)	-0.13 (-0.15, -0.12)	-0.12 (-0.13, -0.10)
3-4 ACE	5,640 (21.5)	-0.16 (-0.17, -0.14)	-0.13 (-0.14, -0.11)	-0.22 (-0.23, -0.20)	-0.19 (-0.21, -0.18)
≥ 5 ACEs	5,351 (20.4)	-0.22 (-0.24, -0.20)	-0.16 (-0.18, -0.15)	-0.36 (-0.37, -0.34)	-0.31 (-0.33, -0.30)

*Coefficients are standardized; **per 1 SD unit increase in ACE-IQ scores; [a]adjusted for age and childhood deprivation; [b]additionally adjusted for education level, civil status, employment status and income. ACE-IQ = Adverse childhood experiences – International Questionnaire. This Table was adapted from Table 3 in Daníelsdóttir et al., elife. 2022.[103]

Table 6. Prevalence Ratios (with 95% CI) of high perceived coping ability and high psychiatric resilience (absence of psychiatric morbidity) in relation to the number of ACEs

		Perceived coping ability		Psychiatric resilience	
	N (%)	Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]
ACE-IQ total score	26,198	0.91 (0.90, 0.92)	0.93 (0.92, 0.94)	0.85 (0.84, 0.86)	0.87 (0.86, 0.87)
Number of ACEs					
0 ACE	5,149 (19.7)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
1 ACE	5,567 (21.3)	0.83 (0.77, 0.89)	0.87 (0.81, 0.93)	0.82 (0.79, 0.84)	0.84 (0.81, 0.87)
2 ACE	4,491 (17.1)	0.71 (0.66, 0.77)	0.75 (0.70, 0.81)	0.73 (0.70, 0.76)	0.75 (0.72, 0.78)
3-4 ACE	5,640 (21.5)	0.61 (0.56, 0.66)	0.66 (0.61, 0.71)	0.59 (0.56, 0.61)	0.62 (0.60, 0.65)
≥ 5 ACEs	5,351 (20.4)	0.56 (0.51, 0.61)	0.64 (0.59, 0.70)	0.38 (0.35, 0.40)	0.42 (0.39, 0.45)

[a]adjusted for age and childhood deprivation; [b]additionally adjusted for education level, civil status, employment status and income. ACE-IQ = Adverse childhood experiences – International Questionnaire. This Table was adapted from Table 4 in Daníelsdóttir et al., elife. 2022.[103]

All individual types of ACEs were associated with lower levels of perceived coping ability and psychiatric resilience (data not shown, please refer to Study II, Appendix 1–Figure 5).[103] Furthermore, all individual types of ACEs were associated with lower prevalence of high psychiatric resilience (Figure 6). Emotional neglect and abuse, sexual abuse, domestic violence, bullying, substance abuse in the household and growing up with a mentally ill household member were also associated with lower prevalence of high perceived coping ability (Figure 7).

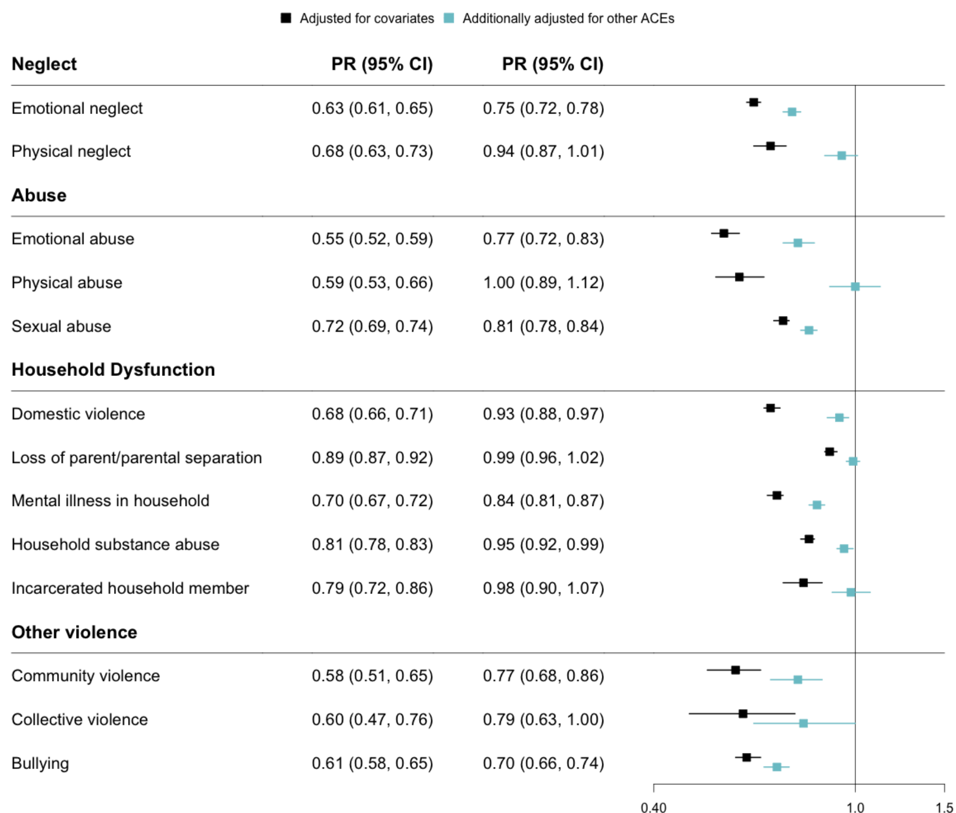

Figure 6. Associations between ACE subtypes and high psychiatric resilience

Models were corrected for age, childhood deprivation, educational level, civil status, employment status, income and additionally adjusted for other ACEs.

After mutual adjustment for all individual types of ACEs, emotional neglect, sexual abuse, bullying and mental illness of a household member, remained consistently associated with resilience, i.e., both with lower levels of resilience in linear regression models (data not shown, please refer to Study II, Figure 1),[103] and with a lower prevalence of resilience in Poisson regression models (Figure 6 and 7).

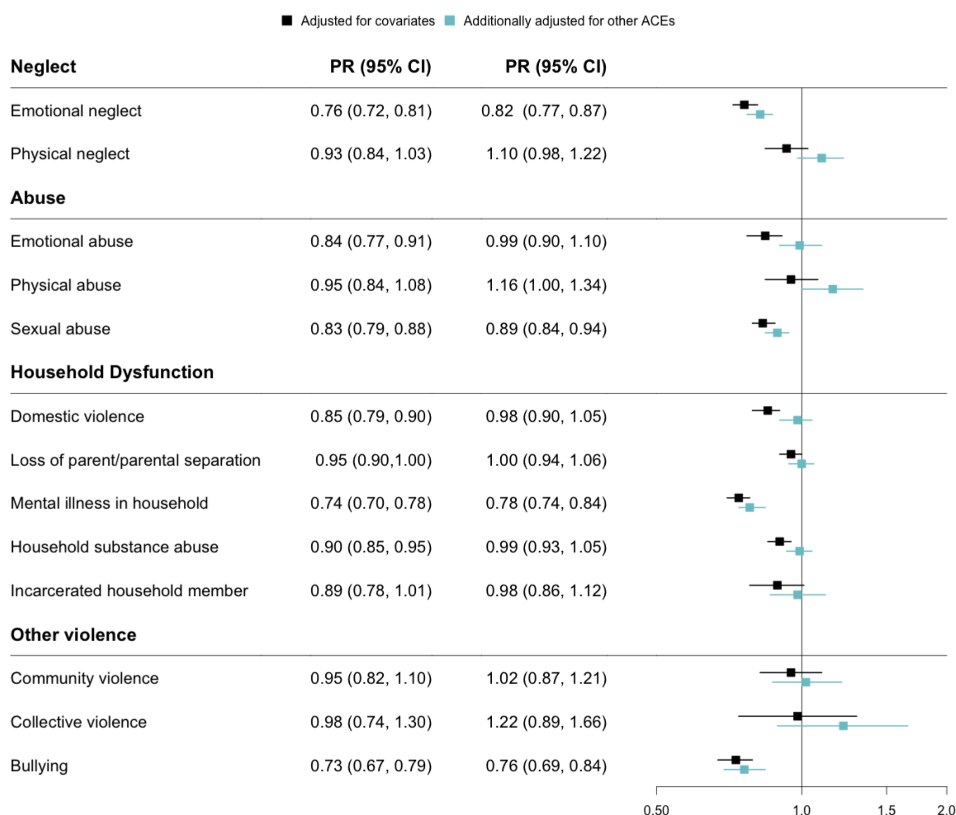

Figure 7. Associations between ACE subtypes and high perceived coping ability

Models were corrected for age, childhood deprivation, educational level, civil status, employment status, income and additionally adjusted for other ACEs.

4.3 Study III – Heritability of adult resilience to ACEs

The mean age of the analytic sample included in Study III (8,606 twin individuals) was 32 years (SD 8 years). Among the analytic sample, 5,240 (61%) twin individuals were categorized as resilient, i.e., had no record of the studied psychiatric disorders or psychotropic medication use.

To examine whether individual differences in resilience were influenced by genetic factors, we started by calculating the within twin-pair correlations, separately for each zygosity, adjusting for sex and birthyear. The within twin-pair correlation for MZ twins was greater than that for DZ twins (r_{MZ} = 0.47, 95% CI 0.37-0.57; r_{DZ} = 0.17, 95% CI 0.05-0.28), suggesting that the resilience phenotype is heritable. Since the DZ twin-pair correlations were less than half of the MZ twin-pair correlations, this suggests that dominance genetic factors (D) rather than shared environmental factors (C) play a role.

The model fit results for the twin models are presented in Table 7. According to the likelihood ratio tests, the ADE model did not fit the observed data significantly worse than the saturated model. Furthermore, the ADE model had extremely large 95% CIs for the A and D parameters (ranging from -0.51 to 0.96, see Table 8) suggesting that the model is underpowered. Correspondingly, the AE model did not fit the data significantly worse than the ADE model (Table 7). Taken together, with the lowest AIC, the AE model showed the best fit to the data. In this model, the heritability of the ACE resilience phenotype was 0.40 (95% CI 0.28-0.52), and the unique environment effect was 0.60 (95% CI 0.48-0.72).

Table 7. Model fitting results from the structural equation models estimating the relative genetic and environmental contribution to variation in psychiatric resilience

Base model	Comparison model	-2LL	df	AIC	Δ-2LL	Δdf	p
Saturated		11187.4	8597	11205.4			
ADE	Saturated	11188.3	8600	11202.3	0.91	3	0.82
AE	ADE	11189.5	8601	11201.5	1.15	1	0.28

Models were adjusted for sex and birthyear; -2LL = minus two log-likelihood;AIC = Akaike Information Criterion; df = degrees of freedom. A lower AIC represents a better model fit. A non significant p-value (p>0.05) indicates that the base model does not dit the data significantly worse than the comparison model.

Table 8. Parameter estimates from the structural equation models estimating the relative genetic and environmental contribution to variation in psychiatric resilience

	A	D	E
ADE	0.16 (-0.51, 0.82)	0.27 (-0.43, 0.96)	0.58 (0.45, 0.71)
AE	0.40 (0.28, 0.52)	NA	0.60 (0.48, 0.72)

Models were adjusted for sex and birthyear; A = Additive genetics; D = Dominance genetics; E = Unique environment & measurement error.

In the PRS analyses, the PRSs for PTSD, MDD, anxiety, bipolar disorder and neuroticism were associated with reduced odds of the psychiatric resilience phenotype (Figure 8). The MDD-PRS had the strongest association with resilience, i.e., 1 SD increase in MDD-PRS was associated with a 25% reduction in resilience (OR = 0.75 per SD increase in PRS; 95% CI 0.70-0.80).

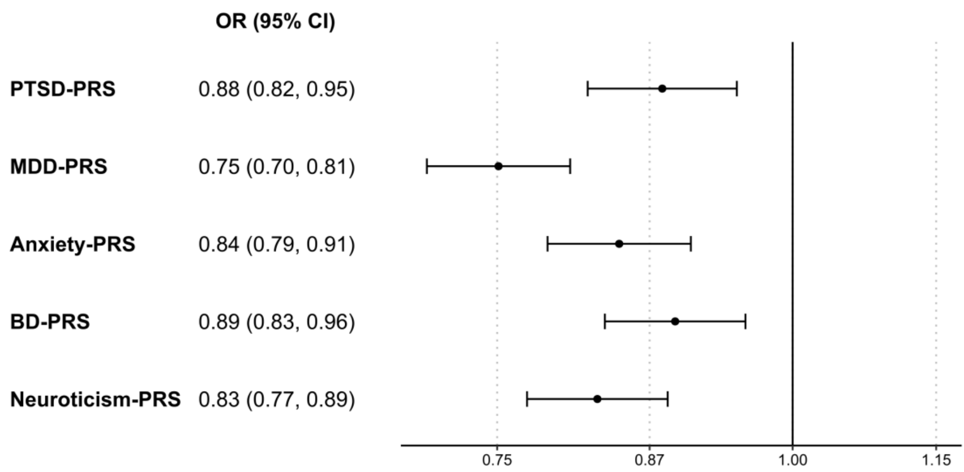

Figure 8. Associations between polygenic risk scores for psychiatric traits and resilience.

Models were adjusted for sex, birthyear, and 10 principal components. OR = Odds Ratio for every standard-deviation increase in PRS. BD = bipolar disorder. PRS = polygenic risk score. PTSD = posttraumatic stress disorder. MDD = major depressive disorder.

5 Discussion

5.1 Main findings

Overall, the studies compiled in this thesis show that adverse childhood experiences (ACEs) can significantly impact long-term mental health, i.e., compromised resilience in adulthood and adult psychiatric disorders, even when accounting for familial factors. At the same time, this work also provides evidence that family-wide risk factors, such as childhood environmental conditions and genetic predisposition, also contribute to adult mental health outcomes among individuals exposed to ACEs and that resilience to ACEs is partly heritable.

Specifically, in **Study I**, we provide robust evidence showing that exposure to ACEs is associated with clinically confirmed adult psychiatric disorders, over and above familial confounding factors. That is, even after adjusting for underlying genetic and shared environmental factors in stringent twin analyses including twin-pairs discordant on ACE exposure, the association between ACEs and psychiatric disorders in adulthood remained evident, particularly for exposure to multiple ACEs or exposure to sexual abuse. However, these associations were attenuated within DZ twin-pairs and even further in MZ twin-pairs, which lends support to considerable familial confounding in the ACE-mental health link.

Furthermore, in **Study II**, we found a negative dose-response association between the cumulative number of ACEs and two distinct measures of resilience in adulthood. Specifically, compared to women with no ACEs, women who reported exposure to multiple ACEs (≥5 ACEs) had 36% lower prevalence of high perceived coping ability and 58% lower prevalence of high psychiatric resilience. The association between ACEs and adult resilience remained robust across levels of the women's current social support. Moreover, of 13 studied ACEs, emotional neglect, sexual abuse, being bullied and growing up with someone mentally ill in the household were the ACEs most robustly associated with both lower perceived coping ability and lower psychiatric resilience in adulthood.

Finally, **in Study III**, we found that the variation in adult resilience after exposure to ACEs was attributable to a combination of genetic factors and individual specific environmental factors. That is, we estimated that the heritability of psychiatric resilience after ACEs was 40% while the remaining variation seems to be shaped by individual-specific environmental factors. In parallel, we found that genetic liability for psychiatric traits (i.e., neuroticism, PTSD, MDD, anxiety and bipolar disorder) predicted lower adult resilience to ACEs, indicating genetic overlap.

5.2 Comparison with findings from previous studies

5.2.1 ACEs and adult psychiatric disorders

Overall, the results of Study I are in line with a large body of literature,[13,16,17,139] i.e., in the cohort analyses we found that exposure to ACEs was associated with adult psychiatric disorders in a dose-dependent manner. Expanding on previous research, we found that exposure to ACEs was associated with elevated odds of clinically confirmed adult psychiatric disorders, after adjusting for familial confounding due to shared genetic and environmental factors using a co-twin control design. This finding is in line with a causal interpretation, indicating that exposure to ACEs directly contributes to adult mental health outcomes. However, the attenuation of the effect size in DZ twins, and even further in MZ twins, also suggests that part of the association between ACEs and adult psychiatric disorders is due to familial confounding (i.e., shared genetic and environmental factors).

This pattern of findings is broadly consistent with previous cross-sectional co-twin control studies, which found that associations between ACEs and self-reported alcohol dependence, personality disorders, and ADHD symptoms in adulthood, are, at least partly, driven by familial confounding.[42-45] Furthermore, our findings align with a recent meta-analysis of quasi-experimental studies, that found a modest causal contribution of ACEs to mental health problems (primarily measured in adolescence and early adulthood).[140] Study I complements this literature by using prospectively ascertained data on clinically confirmed common adult psychiatric disorders, yielding results that support a causal role of ACEs, notwithstanding considerable familial confounding in these associations.

Although the associations between individual types of ACEs and adult psychiatric disorders were substantially attenuated in the most stringent MZ analyses, the point estimate for sexual abuse remained statistically significant. These results suggest that the effect of sexual assaults on adult mental health is to a lesser extent confounding by familial factors, which is in line with previous co-twin control research consistently indicating independent effects of child sexual abuse on self-assessed depression, anxiety and substance abuse.[20,40,141,142]

We also observed that MZ twins exposed to multiple ACEs (≥3 ACEs) remained more likely than their non-exposed co-twins to be diagnosed with a psychiatric disorder in adulthood. Indicating that, in addition to sexual violence, exposure to multiple ACEs has a specifically deleterious and lasting impact on adult mental health, consistent with the growing phenotypic literature showing that risk of poor health outcomes (physical and mental) is substantially increased among those that experienced multiple types of ACEs.[16,17,143] Study I therefore complements previous work by suggesting a causal link when considering exposure to multiple ACEs and independently ascertained clinically diagnosed psychiatric disorders.

5.2.2 ACEs and adult resilience

Overall, the results of Study II on the cumulative number of ACEs and attenuated resilience in adulthood are in line with previous studies on a single or fewer types of ACEs.[56,78,79,81,82] One previous study measuring four types of ACEs (emotional abuse, physical abuse, sexual abuse and domestic violence) also indicated a dose-response relationship with perceived coping ability (measured using CD-RISC). Study II extended these findings to psychiatric resilience as an outcome, and further demonstrated that a broad set of ACEs are negatively associated with perceived coping ability and psychiatric resilience in adulthood in a graded fashion; with every additional type of ACE associated with lower resilience. These associations where independent of age (at survey) and childhood deprivation. Importantly, we found that the associations between ACEs and adult resilience were only slightly attenuated when we additionally adjusted for adult socio-demographic characteristics and were to a limited extent modified by current social support. This suggests that adult characteristics such as education, social support and employment status do not compensate for the deleterious impact of ACEs on adult resilience.

To our knowledge no previous study has covered 13 ACE subtypes in one sample and analyzed associations of each of them with resilience. Specifically, ACEs included in the seminal CDC-Kaiser ACE study,[14,18] such as being bullied and parental loss or parental separation/divorce, have received less attention in research, despite being prevalent experiences in childhood.[144] The results of Study II suggest that all 13 ACE subtypes were associated with perceived coping ability and psychiatric resilience in adulthood. However, of the 13 ACEs, sexual abuse, experiencing bullying, emotional neglect, and growing up with someone mentally ill in the household, were the specific experiences with the most robust independent associations with both resilience measures (i.e., after mutual adjustment for other ACEs).

In line with our findings, a recent study found that childhood emotional neglect was particularly strongly associated with adult psychiatric disorders (depression, anxiety and substance abuse).[145] Similarly, multiple previous studies have found that childhood sexual abuse is robustly associated with an increased risk of depressive disorders,[146] aligning with the findings from Study I of this thesis,[123] and previous cross-sectional co-twin control studies indicating that childhood sexual abuse is robustly associated with depression, anxiety and substance abuse.[20,40,141,142] Extending on these findings, we found that specific ACEs, such as emotional neglect and sexual abuse, may have a particularly negative influence on resilience in adulthood. While emotional dysregulation and impaired emotional clarity have been suggested as possible mechanisms linking sexual abuse and poor mental health outcomes[147] as well as emotional neglect and depression,[148] further research is needed to understand why these ACEs are so strongly associated with reduced adult resilience.

Additionally, we found that being bullied in childhood and growing up with a mentally ill household member uniquely predicted reduced adult resilience. These ACEs have, to our knowledge, not been considered in previous resilience research. Since being bullied represents a frequently occurring childhood experience,[144] it may be a highly relevant target for preventive approaches that could in turn enhance adult resilience. Similarly, although shared genetic factors may play a role in the observed association between growing up with a mentally ill household member and resilience, this finding highlights the importance of supporting children of individuals with psychiatric disorders with the aim of promoting resilience and preventing the development of psychiatric disorders. However, future genetically informative studies are warranted to investigate familial confounding in the associations between ACEs and adult resilience, and particularly in the association between resilience and growing up with someone mentally ill in the household.

5.2.3 Heritability of adult resilience to ACEs

The finding of Study III that 40% of the variation in adult resilience to ACEs is due to genetic factors, is in line with existing studies on resilience to past-year stressors, which reported heritability's in the range of between 38% and 52%.[63,85] The heritability to lifetime stressors seems to be slightly lower, or between 24% and 30%,[75] along with the heritability of perceived coping ability which has been estimated at 25%.[87] Importantly, the results of Study III complement previous research by estimating the heritability of resilience among individuals exposed to significant childhood adversity, and also by conceptualizing resilience based on independent assessments of ACEs and psychiatric disorders.

Indeed, although a handful of previous twin studies have examined the etiology of psychiatric resilience, studies to date have conceptualized resilience based on residuals utilizing different measures, i.e., as residuals of positive affect after lifetime stressors had been regressed out;[85] as residuals of internalizing symptoms after adjusting for stressful life events in the past year;[63] or as residuals of symptoms of anxiety/depression after adjusting for lifetime adversity.[75] However, an important limitation of this approach is that vulnerability in the absence of adversity is included in the operationalization together with resilience following adversity. Relatedly, the residuals usually remain highly correlated with the outcome itself, and even more problematic is the fact that error in the measurement of an outcome could be considered resilience.

While our approach of conceptualizing resilience as the absence of psychopathology (as indicated by either clinical diagnosis of a psychiatric disorder or dispensation of psychotropic medications) among individuals exposed to ACEs is far from perfect (see discussion about information bias below), it aligns well with the conceptual definition of resilience. That is, the conceptual definition of resilience entails two essential components: i) experiencing significant trauma or adversity, and ii) an achievement of

positive adaptation[51,58,59] and we therefore indirectly ascertained resilience based on evidence of these two components. Similar to the exploratory GWAS of psychiatric resilience among highly traumatized soldiers by Stein et al.,[73] examining the absence of psychiatric disorders among individuals exposed to significant levels of adversity may allow us to determine the heritability of resilience, rather than the heritability of the psychiatric disorder or the adversity exposure that would in contrast likely be caught by the residual approach which also includes individuals with psychiatric disorders in the absence of adversity.

Furthermore, the results of Study III indicate that environmental factors that are unique to individuals may play a pivotal role in the development of adult resilience to ACEs. As such, we found that a substantial proportion of the variation of adult resilience to ACEs is shaped by individual-specific environmental factors. This may reflect the multidimensional nature of resilience, in which diverse social, cognitive and psychological factors have previously been associated with resilience.[60] This also emphasizes the potential for intervention efforts to facilitate adult resilience among individuals exposed to ACEs. Although a handful of potentially modifiable environmental factors have been identified in previous research, e.g., self-efficacy and having a sense of meaning in life,[75,77] future research is needed to identify resilience-promoting factors that may aid in preventing poor health outcomes among individuals exposed to ACEs.

Lastly, PRS analyses indicated that genetic factors influencing psychiatric traits and disorders (i.e., neuroticism, PTSD, MDD, anxiety and bipolar disorder) also predicted reduced odds of adult resilience to ACEs. These results support evidence that resilience and other psychiatric traits are partly influenced by overlapping genetic factors. While these results are in contrast to the only previous study to date that has examined PRS for PTSD and resilience (indicating a positive association between PTSD PRS and residual-based resilience),[99] our findings are consistent with previous observational studies[102] and twin studies,[87-89] and add novel insights on the underlying genetics of resilience.

5.3 Methodological considerations

5.3.1 Assumptions and limitations of twin studies

Study I and III are based on twin data using two different methodologies (i.e., the co-twin control design and the classical twin design) that take advantage of the fact that MZ twins are genetically identical while DZ twins share, on average, half of their genes. In addition, it is assumed that MZ and DZ twin pairs share their rearing environment to the same extent, referred to as the equal environment assumption.[33,128] The validity of the equal environment assumption has been previously evaluated and confirmed, including studies on numerous psychological traits and psychiatric disorders.[149,150]

Study III employed the classical twin design which also relies on two other main assumptions, i.e., random mating (no assortment) in a population and minimal gene-environment interactions for the phenotype.[128] Assortative mating has been reported for several phenotypes, including psychiatric disorders.[151,152] Violation of the random mating assumption in twin research may lead to an overestimation of the shared environmental estimate, since greater similarity between parents would lead to increased average genetic relatedness between DZ twins.[128] Given that Study III found no indication of a shared environmental component in adult resilience to ACEs, it is unlikely that a violation of this assumption biased our results. Finally, the classical twin design assumes minimal interaction between the A, D, C, and E variance components.[128] Study III is limited by the fact that we did not evaluate this assumption (although we suspect there may be gene-environment interactions at play in adult resilience). Further research is needed to assess gene-environment interplay, to gain further insight into the etiology of adult resilience.

Study I employed a co-twin control design to adjust for confounders shared within twin-pairs. When using this approach only twin-pairs that are discordant on the covariates included in the model are informative for the analysis. The main limitations of the co-twin control design are therefore decreased statistical power and limited generalizability of the results beyond the discordant twin-pairs. Although we tried to be explicit about the varied statistical power by presenting the number of observations behind each analysis in Study I, it still remains unclear whether twin-pairs discordant on ACEs are representative of the source population.

A similar issue to be considered in relation to twin studies (Studies I and III of this thesis) is whether results from twin samples generalize to the general population. Despite the fact that twins grow up with a sibling of the same age and are also typically born earlier than singletons, a bulk of research shows that twins and non-twins are similar in many aspects, including rates of psychopathology.[84,153-157] We therefore believe that the results of Study I and III can be generalized to non-twin populations.

5.3.2 Selection bias

Selection bias can arise when participants in a study do not represent the target population.[158] The potential for selection bias is a concern in most epidemiological studies, since participants need to agree to participate (and provide informed consent), and there is always a possibility that these participants differ from those who decline to participate.[158]

In Study II, the target population of the SAGA cohort included all Icelandic speaking women residing in Iceland (aged 18-69 years old, with an identifiable address or telephone number), with approximately 30% of the entire source population agreeing to participate. If the participants of the SAGA cohort differ from the general female population of Iceland, the results of Study II could be susceptible to selection bias.

Potential selection into the study was examined by comparing demographic characteristics of SAGA cohort participants to those of the source population (data on the general female population was obtained from Statistics Iceland). We found that the participants of the SAGA cohort represent the general Icelandic female population well in terms of demographic characteristics, including age, education, income and geographic residence.[103] However, we cannot exclude the possibility that women with a history of traumatic experiences were more or less likely to participate in the SAGA cohort. Yet, the prevalence of lifetime exposure to violence in the SAGA cohort was similar to that reported in earlier studies conducted in Iceland,[159] and other Nordic countries.[160-162]

Similarly, Studies I and III may be susceptible to selection bias if the participants of the Swedish Twin Registry differ from Swedish twins in general. The response rates of the web-based surveys, including the ACE assessments, were relatively low (60%, 42% and 69% for the STAGE, YATSS and CATSS cohorts respectively).[107] Although previous studies based on data from the STR have found only minor differences between responders and non-responders,[109,163] we were not able to examine whether individuals exposed to ACEs were more or less likely to participate in the data collections.

In longitudinal studies, selection bias can also arise when participants that are lost to follow-up differ from those who are not (e.g., when selection out of a study is related to development of a psychiatric disorder).[158] However, since psychiatric disorders were ascertained from Swedish nationwide health registers,[110] we have no reason to believe this type of selection bias affected our results.

5.3.3 Measurement error and information bias

All measurements are subject to measurement error; the influence of measurement error on either the exposure and/or outcome is referred to as information bias.[158] Measurement errors could be introduced for instance when crude measures of exposures and outcomes are used.

In Study II, based on data from the SAGA cohort, validated measurements of both the exposure (ACE-IQ) and outcomes (CD-RISC, and the psychopathology scales used to derive psychiatric resilience PHQ-9, GAD-7, PSQI-A, AUDIT-C, PCL-5) were used. Nonetheless, relying on self-reported symptoms, instead of clinical diagnosis, may lead to deviations in true symptom prevalence. We also relied on self-reports of ACEs that come with the potential risk of recall bias. However, considering that only a minority of ACE instances pass through the child welfare authorities, self-reported data may provide a more accurate way to assess a broad spectrum of ACEs. Although this is a widely used approach for assessing exposure to ACEs, we cannot exclude the possibility that current mental health symptoms affected the reporting of ACEs.[164,165] Indeed, there is a risk of misclassification of exposure, which may be differential between women with low and high resilience levels. Women with low resilience might

be more likely to report certain ACEs, which would in turn inflate estimates of association between ACEs and resilience.

In Study I and III, selected items from the LSC-R were used to capture exposure to ACE domains deemed important for the Swedish context. It should be noted that the STR has for decades implemented large scale and repeated data collections from participating twins including bio sample collections and extensive questionnaires covering multiple aspects of lifestyle, mental health and other health-related factors, with ACEs only being one among several hundred phenotypes assessed.[104-106] Therefore, measures are frequently shortened to avoid too much strain on participants, as was done when assessing ACEs. This, however, meant that several important ACEs were not captured, for example exposure to bullying. As such, a more thorough ACE assessment is warranted for future co-twin control studies.

Regarding information bias, in Study I, a proportion of the study population may have already experienced the outcome (clinical diagnosis of a psychiatric disorder) at the time of the evaluation of the exposure (ACE assessment), raising concerns of recall bias. However, in a sensitivity analyses where we restricted follow-up of psychiatric diagnosis after the survey of ACEs, point estimates decreased only slightly in the cohort level and DZ co-twin control analyses, although estimates had low precision and were diluted in the MZ co-twin control analyses.

In Study I and III, psychiatric disorders were ascertained through inpatient or specialized outpatient hospital visits which may have led to misclassification of the outcome. That is, using this data source we were likely to capture the most severe cases of psychiatric disorders and for example miss individuals that seek primary care only. Yet, concerns of information bias were to some extent alleviated since we observed similar results in Study I where we performed a sensitivity analyses additionally considering dispensed antidepressants and anxiolytics as an indication of psychiatric disorders covered in primary care.

In Study II and III, resilience was operationalized as an empirically derived outcome based on evidence from two separate components: trauma exposure (lifetime in Study II and ACEs in Study III) and psychopathology (self-reported symptom scales in Study II and clinically diagnosed psychiatric disorders in Study III). Therefore, there are two potential sources of measurement error: error in the assessment of trauma and error in the psychopathology assessment (discussed above), which may further lead to misclassification of resilience.

5.4 Directions for future studies

Research on ACEs has expanded considerably during the past two decades,[166] with growing evidence indicating that ACEs can negatively affect people's health throughout the life-course.[16,17] Contributing to the literature, this thesis provides new knowledge

regarding both environmental and genetic contributions to psychiatric morbidity and resilience after exposure to ACEs. However, research into ACEs and associated health consequences is far from complete.

Moving forward, it is crucial for future research to examine gene-environment interactions in the psychiatric morbidity – resilience dimension in the context of ACEs. Gene-environment interactions could help us to understand why some people develop psychiatric disorders following ACE exposure while others remain resilient.[167] Indeed, the diathesis-stress model states that the development of psychiatric disorders is a consequence of genetic vulnerability, or diathesis, that is activated by stressors (i.e. gene-environment interaction).[168,169] Since individuals differ in their genetic vulnerability to psychiatric disorders, some people may require greater levels of environmental exposure to activate the genetic vulnerability, which could potentially determine people's psychological response to ACEs on the psychiatric morbidity – resilience spectrum. For example, some people may be resilient to the experience of one ACE but not towards the co-occurrence of many different types of ACEs, while others are less resilient to any ACE experiences.

Furthermore, considering that studies have found low agreement between retrospective and prospective measures of ACEs,[170] it would be of value to examine the psychiatric-morbidity resilience dimension in the context of ACEs obtained through official records such as child protection services. Compared with objective ACE indicators, self-reported ACEs have been associated more strongly with mental health problems.[165,171] Although a recent meta-analyses found no differences in associations between retrospective and prospective ACE measures and mental health problems,[140] there is growing evidence suggesting that an individual's subjective interpretation of an event as traumatic, captured via self-report, is important for the prediction of later psychopathology.[165,172] For example, Danese & Widom[165] found that among children with documented court records of maltreatment, associations with psychopathology were negligible when the child maltreatment was not also self-reported. On the other hand, the child maltreatment – psychopathology association remained strong irrespective of a corresponding court record. However, objective ACE indicators obtained through official records come with their own set of limitations and are particularly vulnerable to misclassification since only a minority of cases pass through the child welfare authorities (i.e., only the most severe cases). To triangulate evidence, future twin studies are warranted comparing objective vs. subjective ACE indicators.

Studies II and III in this thesis employed three different operationalization's of resilience, and although we were able to examine two distinct conceptualizations of resilience in the same sample in Study II, we were limited by the available data in the Swedish Twin Registry in Study III. Given the challenges of assessing psychiatric resilience due to the different potential sources of error (e.g., the assessment of adversity and psychopathology), future twin research would benefit from using a multi-

modal approach to measuring resilience (i.e. studying self-assessed coping ability and psychiatric resilience in the same study). Moreover, future research would benefit from a longitudinal design including repeated measurements of trauma and psychopathology to better capture the dynamic process of resilience as adaptive functioning following adversity.

Finally, the results from Study III indicate that a substantial proportion of the individual variation in adult resilience to ACEs is due to environmental influences, which highlights the potential of intervention- and health promotion programs and policies to foster resilience among ACE exposed individuals. That is, even though individuals vary genetically in their sensitivity to adversity, strengthening family- and community situations could theoretically enhance resilient outcomes among individuals exposed to ACEs. Since previous research has only identified a handful of modifiable protective factors,[75,77] future studies leveraging large cohort datasets could potentially identify other important factors that may aid in preventing poor mental health outcomes among individuals who experienced ACEs.

6 Conclusions

The findings presented in this thesis contribute valuable information to the growing literature on the impact of ACEs on people's long-term mental health and resilience to trauma/adversities.

First, the findings of **Study I** suggest that the link between ACEs and adult psychiatric disorders involves both a direct causal effect of ACEs and the influence of familial confounding (i.e., genetic predisposition and early environmental factors). The former suggests that interventions directly targeting ACEs, both primary prevention as well as improved access to evidence-based trauma therapies for those exposed, could reduce the risk of future psychiatric disorders. At the same time, the considerable familial contribution in the ACE-mental health link highlights the need to address risk factors within the whole family (and society at large), and the importance of ensuring a stable and nurturing environment for all children.

Second, the findings from **Study II** suggest that ACEs are negatively associated with adult resilience in a dose-response manner, with emotional neglect, bullying, sexual abuse and growing up with a mentally ill household member presenting the most robust associations. These findings, if confirmed through prospective and co-twin control designs, call for targeted intervention strategies aimed at enhancing resilience among individuals exposed to ACEs. Future studies should address how ACE exposed individuals can be supported to enhance adult resilience.

Finally, the findings from **Study III** suggest that individual differences in adult resilience after exposure to ACEs are attributable to both genetic and individual-specific environmental factors. We further found using PRS analyses that genetic liability for several psychiatric traits was associated with lower odds of adult resilience to ACEs, providing supportive evidence that psychiatric traits and resilience are influenced by overlapping genetic factors. Taken together, the observed genetic contribution in adult resilience motivates further studies to identify genetic loci and biological factors underlying resilience, while the large contribution of individual-specific environmental factors once again highlights the need for the development of interventions to enhance resilience among individuals exposed to ACEs.

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Original Publications

Paper I

Paper I

JAMA Psychiatry | Original Investigation

Adverse Childhood Experiences and Adult Mental Health Outcomes

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Supplemental content

IMPORTANCE Exposure to adverse childhood experiences (ACEs) has consistently been associated with multiple negative mental health outcomes extending into adulthood. However, given that ACEs and psychiatric disorders cluster within families, it remains to be comprehensively assessed to what extent familial confounding contributes to associations between ACEs and clinically confirmed adult psychiatric disorders.

OBJECTIVE To investigate whether associations between ACEs and adult mental health outcomes remain after adjusting for familial (genetic and environmental) confounding.

DESIGN, SETTING, AND PARTICIPANTS This Swedish twin cohort study used a discordant twin pair design based on monozygotic (MZ) and dizygotic (DZ) twins. A total of 25 252 adult twins (aged 18-47 years) from the Swedish Twin Registry born between 1959 and 1998 were followed up from age 19 years until 2016, with a maximum follow-up time of 39 years. Data were analyzed from April 2022 to November 2023.

EXPOSURES A total of 7 ACEs, including family violence, emotional abuse or neglect, physical neglect, physical abuse, sexual abuse, rape, and hate crime, were assessed with items from the Life Stressor Checklist-Revised in a web-based survey.

MAIN OUTCOMES AND MEASURES Adult (ages >18 years) clinical diagnosis of psychiatric disorders (ie, depressive, anxiety, alcohol or drug misuse, or stress-related disorders) were obtained from the Swedish National Patient Register.

RESULTS Of 25 252 twins included in the study (15 038 female [59.6%]; mean [SD] age at ACE assessment, 29.9 [8.7] years), 9751 individuals (38.6%) reported exposure to at least 1 ACE. A greater number of ACEs was associated with increased odds of any psychiatric disorder in the full cohort (odds ratio [OR] per additional ACE, 1.52; 95% CI, 1.48-1.57). The association remained but ORs per additional ACE were attenuated in DZ (1.29; 95% CI, 1.14-1.47) and MZ (1.20; 95% CI, 1.02-1.40) twin pairs. Individuals who were exposed to sexual abuse compared with those who were not exposed had increased odds of any clinically confirmed psychiatric disorder in all comparisons: full cohort (OR, 3.09; 95% CI, 2.68-3.56), DZ twin pairs (OR, 2.10; 95% CI, 1.33-3.32), and MZ twin pairs (1.80; 95% CI, 1.04-3.11).

CONCLUSIONS AND RELEVANCE This study found that associations between ACEs and adult mental health outcomes remained after controlling for shared genetic and environmental factors, which was particularly evident after multiple ACEs or sexual abuse. These findings suggest that targeted interventions may be associated with reduced risks of future psychopathology.

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Adverse childhood experiences (ACEs) are common, affecting the lives of millions of children and adolescents across the world.[1-5] ACEs represent exposures to severe stressors, such as emotional, physical, and sexual abuse, as well as growing up in dysfunctional home environments.[6] A large body of evidence has shown that children exposed to ACEs have increased risks of an array of adverse mental and physical health outcomes throughout life.[7-10]

Studies have consistently reported associations between ACEs and an increased risk of psychiatric disorders in adulthood, such as posttraumatic stress disorder (PTSD),[11,12] depression,[13-15] anxiety,[16] and substance abuse.[17,18] However, given that ACEs and psychiatric disorders cluster within families,[19-21] few studies examining associations of ACE exposure with subsequent psychiatric disorders have been equipped to disentangle these associations from potential genetic confounding and other risk factors shared by family members. Indeed, twin studies show that psychiatric disorders are moderately heritable, with 40% to 60% of individual differences in, for example, depression, anxiety, and PTSD attributable to genetic factors.[22] In addition, twin and family studies suggest that liability for ACEs is also partly attributable to genetic factors,[23-25] some of which may overlap with genetic factors that predispose individuals to adverse mental health outcomes.[26] Previously reported associations between ACEs and psychiatric disorders may therefore, at least partly, reflect genetic confounding. Moreover, adjusting for environmental risk factors that contribute to familial confounding is equally important given that aspects of the family environment, such as parenting style[27] and socioeconomic disadvantage,[21] may similarly confound the association between ACEs and psychiatric disorders.

The discordant twin pair design provides a unique opportunity to adjust for unmeasured genetic and early environmental confounders.[28,29] A handful of previous studies have used this methodology to examine the ACE and mental health association, but these are limited by addressing only specific types of ACEs or selected mental health outcomes, including alcohol dependence, personality disorders, and attention-deficit/hyperactivity disorder (ADHD).[30-36] In addition, these studies were based on small samples, cross-sectional designs, or the use of self-reported measures of mental health. To our knowledge, evidence on how ACEs are associated with clinically confirmed psychiatric disorders with adjustment for familial confounding is completely lacking. Therefore, leveraging a nationwide sample of Swedish twins, we aimed to assess associations between ACEs and prospectively ascertained clinical diagnoses of common adult psychiatric disorders while adjusting for familial confounding. To capture a broader range of psychiatric morbidities, we also examined associations between ACEs and self-reported depressive symptoms.

Methods

An ethical permit was granted for this cohort study using twin data by the regional ethical review board in Stockholm, Sweden, and all participants gave written informed consent for participation. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Key Points

Question Are adverse childhood experiences (ACEs) associated with poor mental health in adulthood after adjustment for familial confounding due to shared genetic and environmental factors?

Findings In this cohort study using twin data, there were associations between ACEs and adult mental health outcomes in dizygotic and monozygotic twin pairs, while odds ratios were attenuated compared with the full cohort. Twins who were exposed to ACEs compared with co-twins who were not exposed had increased odds of clinically confirmed adult psychiatric disorders, particularly after sexual abuse or multiple ACEs.

Meaning These findings support an association between ACEs and poor mental health in adulthood, notwithstanding evidence for familial confounding from shared genetic and environmental factors.

Participants

We used data from 3 birth cohorts from the nationwide Swedish Twin Registry. Namely, we used the Study of Twin Adults: Genes and Environment (STAGE) comprising 25 313 twins (born 1959-1985) surveyed 2005 to 2006,[37,38] the Young Adult Twins in Sweden Study (YATSS) comprising 6860 twins (born 1986-1992) surveyed 2013 to 2014,[39] and the ongoing Child and Adolescent Twin Study in Sweden (CATSS) comprising 7613 twins (born 1992-1998)[40] surveyed in relation to their 18th birthday between 2010 and 2016.[40] All twins responded to web-based surveys, including assessments of ACEs and depressive symptoms, with response rates of 60.0%, 42.0%, and 69.0%, respectively, in the 3 cohorts.[39] Cohorts were additionally linked to nationwide health registers. In this study, we had access to data on ACEs from 25 252 twins (**Figure 1**).

Measures

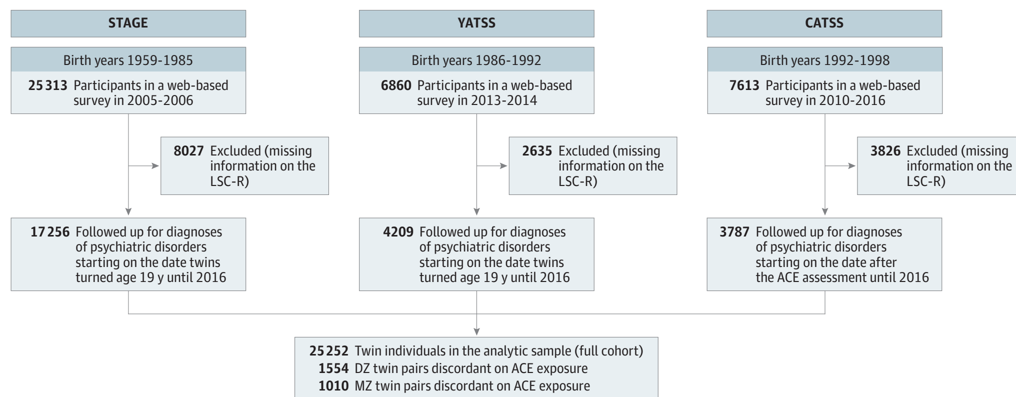
Adverse Childhood Experiences

ACEs were measured with items adapted from the Life Stressor Checklist-Revised (LSC-R).[41,42] For this study, 7 yes or no questions were used to assess exposure to the following ACEs: emotional neglect or abuse, physical neglect, physical abuse, sexual abuse, rape, hate crime, and witnessing family violence (eTable 1 in Supplement 1). The overall LSC-R has demonstrated good reliability (interrater reliability and test-retest reliability) and validity (content validity and construct validity) to measure trauma exposure and other negative life experiences.[41,42] Specific items used in this study have acceptable test-retest reliability (κ range, 0.56-0.66).[42] Follow-up questions were used to assess whether the 7 LSC-R items were endorsed before age 19 years. We examined exposure to the 7 types of ACEs individually (yes or no) and calculated an ACE total score ranging from 0 to 7, which we also categorized into 0, 1, 2, or 3 or more ACEs.

Clinical Diagnosis of Psychiatric Disorders

Using Swedish personal identification numbers, the Swedish Twin Registry was linked to the Swedish National Patient Reg-

Figure 1. Flowchart of Sample Selection



ACE indicates adverse childhood experience; CATSS, Child and Adolescent Twin Study in Sweden; LSC-R, Life Stressor Checklist-Revised; STAGE, Study of Twin Adults: Genes and Environment; YATSS, Young Adult Twins in Sweden Study.

ister, established in 1964 with nationwide coverage for inpatient care since 1987 and outpatient specialized care since 2001.[43] Through this resource, we identified all individuals with any inpatient or outpatient hospital visit that resulted in a diagnosis of a depressive disorder, anxiety disorder, alcohol or drug misuse disorder, or stress-related disorder after their 19th birthday (Figure 1). Participants were followed up in the National Patient Register from age 19 years until the end of 2016, resulting in a follow-up range of 13 to 39 years in STAGE, 6 to 13 years in YATSS, and 0 to 5 years in CATSS. Diagnoses were ascertained in accordance with the Swedish revisions of the *International Classification of Diseases, Eighth Revision* (*ICD-8*), *International Classification of Diseases, Ninth Revision* (*ICD-9*), or *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) (eTable 2 in Supplement 1).

Symptoms of Depression

Symptoms of depression during the past week were measured with the 11-item shortened version of the Center for Epidemiologic Studies Depression Scale (CES-D).[44] All items were answered on a 4-point scale and then summed to create a total score ranging from 0 to 33, with a higher score indicating higher levels of depressive symptoms.

Statistical Analysis

Descriptive statistics (means and frequencies) of age at survey, sex, zygosity, and mental health outcomes were summarized for the full analytic sample and by number of ACEs. We calculated the heritability (h^2) of the ACE total score (ie, the proportion of variance attributed to additive genetic factors) with a univariate twin model using the OpenMx package in R statistical software version 4.3.1 (R Project for Statistical Computing).[45]

We used generalized estimating equation analyses with cluster-robust standard errors (drgee package in R)[46] to examine the association between ACEs and any adult psychiatric disorder and subcategories of these disorders. First, we examined whether ACEs were associated with adult psychiatric disorders in the full cohort (ie, not in twin pairs). Given that outcomes were binary, we estimated odds ratios (ORs) and adjusted the analysis for sex and age (continuous) at the time of the survey. To account for the lack of independence of twin data, we used generalized estimating equation analyses with cluster robust standard errors (ie, using sandwich estimation on twin pair identification number).[46] We ran all models with the ACE score as a continuous variable (range, 0-7), binary variable (exposed to any ACE vs not exposed), and categorical variable (categories of 0, 1, 2, or ≥3 ACEs). We also carried out stratified analyses of these associations by sex. In addition, we ran separate models for each of the 7 types of ACEs.

Second, discordant twin pair analysis was used to estimate the association between ACEs and psychiatric disorders while controlling for familial (ie, genetic and environmental) factors shared in the twin pair. To do this, we fitted models conditional on twin pairs using generalized estimating equation analyses[46] separately in monozygotic (MZ) and dizygotic (DZ) twin pairs. These models tested whether a twin exposed to greater levels of ACEs had greater odds of psychiatric disorders compared with their co-twin who had fewer reported ACEs or was not exposed.[29] Confounding by sex and age was intrinsically adjusted for by the twin design, but given that same- and opposite-sex DZ twin pairs were included, we adjusted for sex in discordant DZ twin pair analyses.

We repeated all cohort-level and discordant twin pair models on self-reported depressive symptoms using generalized estimating equation analyses with identity link. The total score of depressive symptoms was log transformed (log1p function in R), and we obtained estimates as the percentage increase in depressive symptoms for every 1-unit increase in number of ACEs.

Table 1. Descriptive Characteristics of Study Cohort

Characteristic	Participants, No. (%)				
	Overall (N = 25 252)	0 ACEs (n = 15 501)	1 ACE (n = 5531)	2 ACEs (n = 2174)	≥3 ACEs (n = 2046)
Age at survey, mean (SD), y	29.9 (8.65)	29.9 (8.58)	29.6 (8.71)	30.2 (8.93)	30.6 (8.69)
Sex					
Female	15 038 (59.6)	8914 (57.5)	3319 (60.0)	1385 (63.7)	1420 (69.4)
Male	10 214 (40.4)	6587 (42.5)	2212 (40.0)	789 (36.3)	626 (30.6)
Zygosity					
MZ	9586 (38.0)	6016 (38.8)	2023 (36.6)	806 (37.1)	741 (36.2)
DZ same sex	7337 (29.1)	4504 (29.1)	1639 (29.6)	630 (29.0)	564 (27.6)
DZ opposite sex	7679 (30.4)	4617 (29.8)	1713 (31.0)	675 (31.0)	674 (32.9)
Unknown	650 (2.6)	364 (2.3)	156 (2.8)	63 (2.9)	67 (3.3)
Any psychiatric disorder	2379 (9.4)	993 (6.4)	562 (10.2)	321 (14.8)	503 (24.6)
Alcohol or drug misuse disorder	595 (2.4)	234 (1.5)	120 (2.2)	87 (4.0)	154 (7.5)
Depressive disorder	1221 (4.8)	444 (2.9)	309 (5.6)	184 (8.5)	284 (13.9)
Anxiety disorder	1136 (4.5)	443 (2.9)	268 (4.8)	149 (6.9)	276 (13.5)
Stress-related disorder	744 (2.9)	275 (1.8)	169 (3.1)	106 (4.9)	194 (9.5)
Depressive symptoms, mean (SD)[a]	7.05 (5.64)	5.78 (4.82)	8.16 (5.72)	9.25 (6.17)	11.1 (7.03)

Abbreviations: ACE, adverse childhood experience; DZ, dizygotic; MZ, monozygotic.

[a] Depressive symptoms were measured with the Center for Epidemiologic Studies Depression Scale. All items were answered on a 4-point scale and then summed to create a total score ranging from 0 to 33, with higher scores indicating greater levels of depressive symptoms.

Sensitivity Analysis

First, to examine whether associations varied by birth cohort, we conducted analyses excluding CATSS given that it is the youngest birth cohort with the shortest follow-up time. We also ran analyses in the youngest 2 birth cohorts (YATSS and CATSS) and the oldest cohort (STAGE) separately, to assess potential modification by birth cohort. Second, because the National Patient Register includes only information related to inpatient or specialized outpatient care, we ran a sensitivity analysis using information from the Swedish Prescribed Drug Register,[47] using dispensed antidepressants or anxiolytics (Anatomical Therapeutic Chemical codes N06A and N05B, respectively) as an indication of milder psychiatric disorders not requiring specialized care. Third, to inform risks of reverse causation, we carried out sensitivity analyses in which we excluded twins with any diagnosis of psychiatric disorders before age 19 years (eFigure 1 in Supplement 1). Fourth, to perform analyses in which psychiatric disorders were prospectively ascertained after administration of the ACE questionnaire, we restricted the follow-up time of all 3 cohorts to the date after the survey of ACEs and excluded twins who received a diagnosis of any psychiatric disorder before answering the survey (eFigure 2 in Supplement 1).

Results

Among 25 252 twins (15 038 female [59.6%]; mean[SD] age at ACE assessment, 29.9 [8.7] years), 9751 participants (38.6%) reported exposure to at least 1 ACE. A total of 2046 individuals (8.1%) reported 3 or more ACEs, while 15 501 individuals (61.4%) reported 0 ACEs (**Table 1**). A univariate twin model showed that variation in exposure to number of ACEs was accounted for by additive genetic factors (34.6%; 95% CI, 25.2%-44.0%), shared environmental factors (22.1%; 95% CI, 14.3%-29.9%), and nonshared environmental factors (43.3%; 95% CI, 40.1%-46.5%).

A total of 2379 twins (9.4%) received a clinical diagnosis of any psychiatric disorder during the study period (Table 1). The incidence of any psychiatric disorder increased from 993 individuals (6.4%) among participants without any ACEs to 503 individuals (24.6%) among those reporting 3 or more ACEs (Table 1); the pattern was also present for each subcategory and for depressive symptoms.

At the cohort level, a greater number of ACEs was associated with increased odds of any psychiatric disorder in a dose-dependent manner (**Table 2**). Every additional ACE was associated with 52% greater odds of any psychiatric disorder (OR, 1.52; 95% CI, 1.48-1.57). The same pattern was noted among males and females (eTable 3 in Supplement 1). Discordant twin pair analyses revealed statistically significant but lower increases in odds of any psychiatric disorder associated with every additional ACE (DZ twin pairs: OR, 1.29; 95% CI, 1.14-1.47; MZ twin pairs: OR, 1.20; 95% CI, 1.02-1.40), corresponding to 39.1% and 57.5% attenuated ORs in DZ and MZ twins, respectively. Moreover, compared with 0 ACEs, exposure to 3 or more ACEs was associated with greater odds of any psychiatric disorder at the cohort level and in DZ and MZ twin pairs (Table 2). However, ORs in DZ and MZ twins were approximately half of the cohort-level OR (full cohort: 4.57; 95% CI, 4.05-5.15; DZ twin pairs: 2.25; 95% CI 1.41-3.61; MZ twin pairs: 2.11; 95% CI, 1.13-3.94). Similar results were observed for depressive symptoms (eTable 4 in Supplement 1) but with lower attenuation in estimates in discordant twin pair models.

We observed associations between a greater number of ACEs and increased odds of depressive disorders, anxiety disorders, and stress-related disorders at the cohort level and in discordant twin pair models (**Figure 2**). However, there was an association with substance use disorder in MZ twin pairs but not in DZ twin pairs (Figure 2).

Table 2. Associations Between No. of ACEs and Any Adult Psychiatric Disorder

Outcome	Model 1 (full cohort)[a]			Model 2 (in DZ twins)[a]			Model 3 (in MZ twins)[a]		
	Participants, No.			Participants, No.			Participants, No.		
	Total	With disorder[b]	OR (95% CI)	Total[c]	With disorder[b]	OR (95% CI)	Total[c]	With disorder[b]	OR (95% CI)
ACE total score[d]	25 252	2379	1.52 (1.48-1.57)	4018	402	1.29 (1.14-1.47)	2834	339	1.20 (1.02-1.40)
Any ACE, No.									
0	15 501	993	1 [Reference]	1554	100	1 [Reference]	1010	88	1 [Reference]
≥1	9751	1386	2.39 (2.19-2.60)	1554	167	1.72 (1.31-2.28)	1010	99	1.19 (0.84-1.70)
No. of ACEs									
0	15 501	993	1 [Reference]	1554	100	1 [Reference]	1010	88	1 [Reference]
1	5531	562	1.65 (1.48-1.84)	1077	95	1.46 (1.07-1.98)	724	62	1.17 (0.80-1.72)
2	2174	321	2.47 (2.16-2.83)	301	40	2.37 (1.52-3.70)	189	19	0.84 (0.50-1.42)
≥3	2046	503	4.57 (4.05-5.15)	176	32	2.25 (1.41-3.61)	97	17	2.11 (1.13-3.94)

Abbreviations: ACE, adverse childhood experience; DZ, dizygotic; MZ, monozygotic; OR, odds ratio.

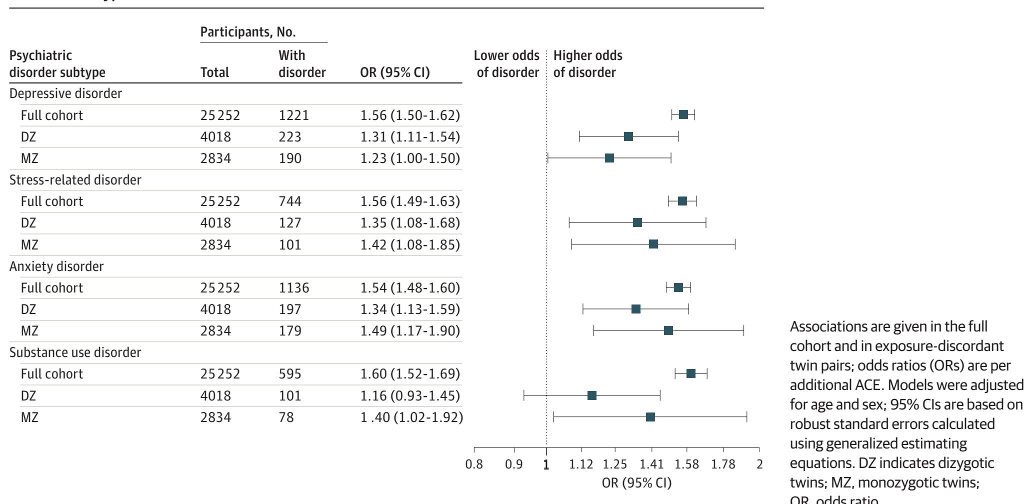
[a] Models were adjusted for age and sex; 95% CIs are based on robust SEs, calculated using generalized estimating equation analyses.

[b] Any adult psychiatric disorder.

[c] Total equals the number of individual twins from exposure-discordant twin pairs in the analysis.

[d] ORs are for every additional ACE.

Figure 2. Associations Between Number of Adverse Childhood Experiences and Adult Psychiatric Disorder Subtypes

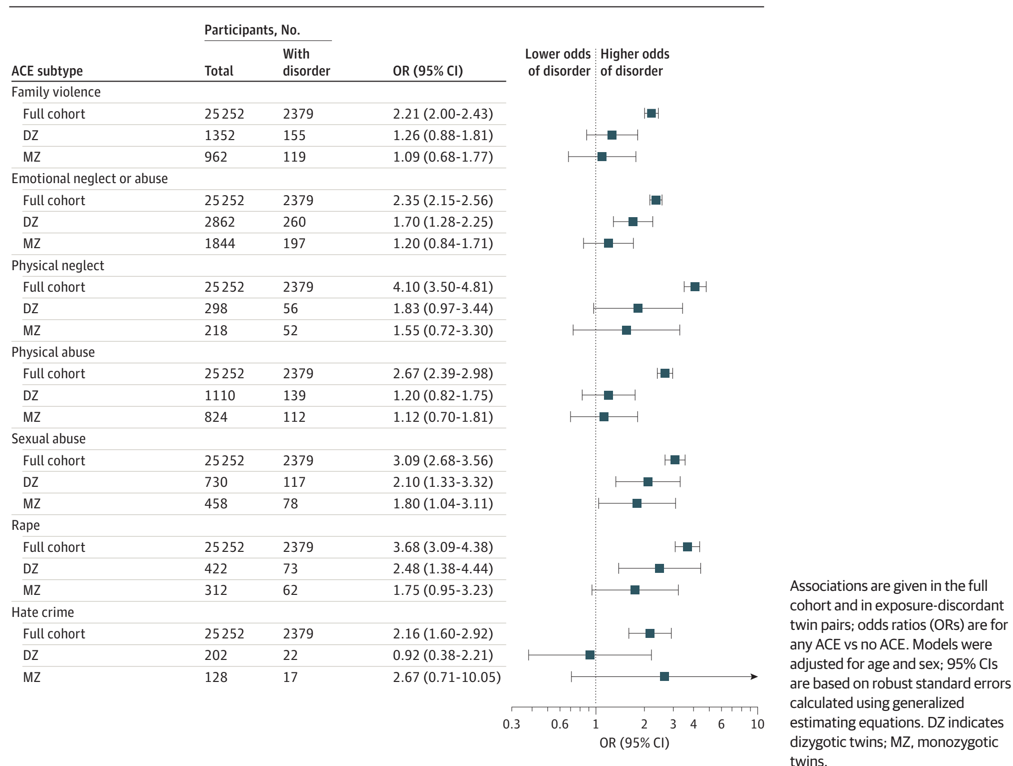


Associations are given in the full cohort and in exposure-discordant twin pairs; odds ratios (ORs) are per additional ACE. Models were adjusted for age and sex; 95% CIs are based on robust standard errors calculated using generalized estimating equations. DZ indicates dizygotic twins; MZ, monozygotic twins; OR, odds ratio.

All ACE subtypes were associated with increased odds of any psychiatric disorder in cohort-level analyses (**Figure 3**). Proportions of twin pair ACE discordance varied from 676 of 1080 twins with exposure (62.6%) on family violence to 211 of 227 twins with exposure (93.0%) on rape for DZ twin pairs and from 481 of 1045 twins with exposure (46.0%) on family violence to 156 of 180 twins with exposure (86.7%) on rape for MZ twin pairs (eTable 5 in Supplement 1). In discordant twin pair analyses, point estimates were considerably attenuated for all ACE subtypes except sexual abuse, for which there remained an association in all comparisons; ORs for individuals who were exposed to childhood sexual abuse compared with those who were not exposed were 3.09 (95% CI, 2.68-3.56) in the full cohort, 2.10 (95% CI, 1.33-3.32) in DZ twin pairs, and 1.80 (95% CI, 1.04-3.11) in MZ twin pairs (Figure 3). In contrast, the association between ACE subtypes and depressive symptoms remained in all discordant twin pair models except for physical abuse in MZ twin pairs (eFigure 3 in Supplement 1).

In sensitivity analyses, the pattern of associations remained the same when the youngest cohort (CATSS) was excluded from analyses (eTable 6 in Supplement 1), while estimates remained larger in the 2 youngest cohorts (YATSS and CATSS) (eTable 7 in Supplement 1) than in the oldest cohort (STAGE) (eTable 8 in Supplement 1). A similar pattern of associations was found when dispensed psychotropic medications were included as an indication for milder psychiatric disorders (eTable 9 in Supplement 1). Excluding participants with any psychiatric disorder prior to age 19 years revealed largely

Figure 3. Associations Between Adverse Childhood Experience (ACE) Subtypes and Any Adult Psychiatric Disorder



ACE subtype	Participants, No. Total	With disorder	OR (95% CI)
Family violence			
Full cohort	25 252	2379	2.21 (2.00-2.43)
DZ	1352	155	1.26 (0.88-1.81)
MZ	962	119	1.09 (0.68-1.77)
Emotional neglect or abuse			
Full cohort	25 252	2379	2.35 (2.15-2.56)
DZ	2862	260	1.70 (1.28-2.25)
MZ	1844	197	1.20 (0.84-1.71)
Physical neglect			
Full cohort	25 252	2379	4.10 (3.50-4.81)
DZ	298	56	1.83 (0.97-3.44)
MZ	218	52	1.55 (0.72-3.30)
Physical abuse			
Full cohort	25 252	2379	2.67 (2.39-2.98)
DZ	1110	139	1.20 (0.82-1.75)
MZ	824	112	1.12 (0.70-1.81)
Sexual abuse			
Full cohort	25 252	2379	3.09 (2.68-3.56)
DZ	730	117	2.10 (1.33-3.32)
MZ	458	78	1.80 (1.04-3.11)
Rape			
Full cohort	25 252	2379	3.68 (3.09-4.38)
DZ	422	73	2.48 (1.38-4.44)
MZ	312	62	1.75 (0.95-3.23)
Hate crime			
Full cohort	25 252	2379	2.16 (1.60-2.92)
DZ	202	22	0.92 (0.38-2.21)
MZ	128	17	2.67 (0.71-10.05)

Associations are given in the full cohort and in exposure-discordant twin pairs; odds ratios (ORs) are for any ACE vs no ACE. Models were adjusted for age and sex; 95% CIs are based on robust standard errors calculated using generalized estimating equations. DZ indicates dizygotic twins; MZ, monozygotic twins.

similar estimates, although with lower precision (eTable 10 in Supplement 1). Moreover, restricting follow-up of psychiatric disorder diagnosis to the date after the ACE assessment yielded a similar pattern of associations at the cohort level and in discordant DZ twin pair analysis, while estimates had low precision and were substantially diluted in the MZ twin pair analysis (eTable 1 in Supplement 1).

Discussion

In this Swedish cohort study using twin data, we found that ACEs were associated with adult mental health outcomes after adjustment for familial confounding. That is, after adjusting for shared genetic and environmental factors in stringent twin analyses, the association between ACEs and clinically confirmed adult psychiatric disorders remained evident, with particularly large increases in odds after multiple ACEs or sexual abuse. However, attenuated estimates in DZ and MZ twin pairs suggest that familial confounding also contributed to the ACE-mental health association.

In line with a large body of research,[9,10,17,48] we found that exposure to ACEs was phenotypically associated with adult mental health outcomes in a dose-dependent manner. Complementing previous work, we observed that exposure to ACEs was associated with increased odds of clinically confirmed adult psychiatric disorders and increased levels of self-reported depressive symptoms after adjusting for familial confounding due to shared genetic and environmental factors. However, the attenuation of effect sizes from the full cohort to DZ twins (39.1%) and MZ twins (57.5%) also suggests that familial confounding contributed to the association between ACEs and adult mental health outcomes. In other words, our results indicate that childhood environmental conditions (eg, parental education level and other socioeconomic conditions) and genetic predisposition may have contributed to the association between ACEs and adult mental health outcomes. However, further research is needed to determine which factors (genetic factors, early environmental factors, or both) are associated with increases in the risk of adult psychiatric disorders among individuals who experienced ACEs.

Our findings are broadly consistent with previous cross-sectional discordant twin pair studies, which reported that familial confounding contributed at least partly to associations between ACEs and self-reported alcohol dependence, personality disorders, and ADHD symptoms in adulthood.[30-33,36] In addition, our results are in line with those of a 2023 meta-analysis[49] reporting associations between ACEs and

modest increases in risks of mental health problems (ie, assessed mostly in adolescence and young adulthood) after quasi-experimental adjustment for unmeasured confounders. Our study complements this literature with prospectively ascertained data on clinically confirmed adult psychiatric disorders, also yielding findings that associations between ACEs and psychiatric conditions in adulthood remained after adjustment for underlying shared confounders.

Although few estimates were significant between distinct types of ACEs and adult psychiatric disorders in the most stringent MZ analyses, our results demonstrated that familial factors contributed to a lesser extent to the association between sexual abuse and adult psychiatric disorders. This is in line with previous discordant twin pair research consistently indicating independent associations of child sexual abuse with self-assessed depression, anxiety, and substance abuse.[34,35,50,51] Furthermore, we observed that MZ twins exposed to multiple (≥3) ACEs remained more likely compared with their co-twins who were not exposed to be diagnosed with a psychiatric disorder in adulthood. These results are consistent with increasing evidence on the accumulation model of ACEs.[9,52]

Strengths and Limitations

The main strengths of this study include the large, nationwide twin sample and use of prospectively collected data on clinically confirmed psychiatric disorders, ascertained independently from ACE assessments. However, results of the study should be considered in the context of several limitations. First, although the discordant twin pair design inherently adjusts for shared environmental conditions, it is possible that some unmeasured factors that differed between twins, such as the rare occurrence of birth complications of 1 twin, contributed to observed estimates. Another important limitation is that ACEs were retrospectively reported and may thus be subject to recall bias.[53] This is a common approach for assessing ACEs, but we cannot exclude the possibility that current mental health status influenced the reporting of ACEs.[54,55] Although the agreement between retrospective and prospective measures of ACEs has been reported to be low,[56] both have been associated with adverse adult health outcomes.[54] Indeed, a 2023 meta-analysis[49] found no differences in associations between retrospective and prospective ACE measures and mental health problems. In our study, estimates observed for associations between ACEs and current depressive symptoms may certainly have been affected by recall bias; however, estimates of clinically confirmed psychiatric disorders may be less vulnerable to such bias.[54] This approach (ie, combining retrospectively reported ACEs and independently ascertained, clinically confirmed psychiatric disorders), as conducted in this study, has been recommended in previous literature.[54]

Similarly, given that our assessment of ACEs was based on selected items from the LSC-R deemed most relevant for the Swedish context, our findings are not directly comparable to findings of other studies from other countries and cultures with different sets of ACE items. Comparisons of ACE prevalence across cultures and populations is already complicated for several other reasons; for example, Sweden was the first country to legally ban physical punishment of children, in 1979.[57] Furthermore, twin pair discordance on specific ACEs varied considerably, from 46.0% for family violence in MZ twins to 93.0% for rape in DZ twins; this may reflect the varying familial nature of these exposures. Although family violence had the lowest twin discordance of all ACEs, it may still seem counterintuitive that 46.0% of MZ twins were discordant on family violence given that this exposure unquestionably takes place in the family environment. It should be noted, however, that the question on family violence refers to an incident (until age 18 years) in which the respondent witnessed violence between family members. Although twin pairs are likely to have witnessed a chronic pattern of family violence (ie, repeated events), sporadic incidences of family violence may be witnessed by 1 but not the other twin.

In addition, given that we identified psychiatric disorders through inpatient or specialized outpatient hospital visits, we captured a small proportion of all psychiatric disorders (ie, only the most severe cases). This may have further led us to underestimate the proportion of twins with prevalent psychiatric disorders at age 19 years. Importantly, we were unable to include individuals seeking primary care only; however, this concern was to some extent alleviated given similar results of a sensitivity analyses in which we additionally considered the use of dispensed psychotropic medications as an indication of psychiatric disorders covered in primary care. Furthermore, it should be noted that while nonresponse may have led to some bias, previous attrition analyses of the Swedish Twin Registry cohorts indicated minor differences between responders and nonresponders.[40,58] Additionally, although our study included a large sample of Swedish twins, it remains unknown whether the results can be generalized outside of Nordic countries.

Conclusions

This cohort study using twin data found that the association between ACEs and adult mental health outcomes remained after adjusting for familial confounding due to shared genetic and environmental factors. This suggests that interventions targeting ACEs, including primary prevention and enhanced access to evidence-based trauma therapies to individuals who experienced ACEs, may be associated with reduced risk of future psychopathology. However, our findings additionally indicate that family-wide risk factors (eg, genetic predisposition and socioeconomic disadvantage in childhood) also contributed to adult mental health outcomes among individuals who experienced ACEs, suggesting that there may be added value in addressing risk factors within the whole family.

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Supplemental Online Content

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eTable 1. Items Applied From the Life Stressor Checklist-Revised to Assess Adverse Childhood Experiences in the Swedish Twin Registry

eTable 2. International Classification of Diseases (ICD) Codes Used to Identify Psychiatric Disorders

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eTable 10. Associations Between No. of Adverse Childhood Experiences and Any Diagnosed Psychiatric Disorder in Full Cohort and in Exposure-Discordant Twin Pairs Excluding Twins Diagnosed With Any Psychiatric Disorder Before Age 19 y

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eTable 11. Associations Between No. of Adverse Childhood Experiences (ACEs) and Any Diagnosed Psychiatric Disorder in Full Cohort and in Exposure-Discordant Twin Pairs Excluding Twins Diagnosed With Any Psychiatric Disorder Before Answering web-Based Survey With ACE Assessment

eFigure 1. Flowchart of Analytic Sample Excluding Twins Diagnosed With Any Psychiatric Disorder Before Age 19 y

eFigure 2. Flowchart of Analytic Sample Where Follow-Up for Psychiatric Disorders Starts After Web-Based Surveys With Adverse Childhood Experience Assessment Excluding Twins Who Received Diagnosis of Any Psychiatric Disorder Before Answering Survey

eFigure 3. Associations Between Adverse Childhood Experience Subtypes and Depression Symptoms in Full Cohort and Within Exposure-Discordant Twin Pairs

eTable 1. Items Applied From Life Stressor Checklist-Revised Plus Hate Crime to Assess Adverse Childhood Experiences in the Swedish Twin Registry

This supplemental material has been provided by the authors to give readers additional information about their work.

Type of ACE	Item
Family violence	When you were young, before age 18, did you ever see physical violence between family members? For example, hitting, kicking or punching?
Emotional neglect/abuse	Have you ever been emotionally abused or neglected – for example, being frequently shamed, embarrassed, ignored, or repeatedly told that you were “no good”?
Physical neglect	Have you ever been physically neglected – for example, not fed, not properly clothed, or left to take care of yourself when you felt you were too young or ill?
Physical abuse	Have you ever been physically abused – for example, hit, choked, burned, or beaten, or severely punished, for example, locked up in a closet, tied up, or chained – by someone you knew well such as a parent, sibling, boyfriend or girlfriend?
Sexual abuse	Were you ever touched or made to touch someone else in a sexual way, because you felt forced in some way or threatened by harm to yourself or someone else?
Rape	Did you ever have sex because you felt forced in some way or threatened by harm to yourself or someone else? With sex, we mean orally, anally, and/or genitally
Hate crime	Have you ever been victim of a hate crime? This could include being subject to violence because of your race, ethnicity, gender, sexual orientation or religion.

*Hate crime was not included in the original Life Stressor Checklist-revised.

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eTable 2. International Classification of Diseases (ICD) codes, eight (ICD-8; 1969-1986), ninth (ICD-9; 1987-1996), and tenth (ICD-10; 1997-2016) used to identify psychiatric disorders.

Psychiatric diagnosis	ICD-8	ICD-9	ICD-10
Alcohol or drug misuse disorders	303, 304	291E, 292.0, 303, 304, 305	F10-F19
Depressive disorders	296.0, 300.4	296, 311	F32-F34, F38-F39
Anxiety disorders	300.0, 300.1	300A, 300C, 300D	F40, F41, F42, F44
Stress-related disorders	307	308, 309	F43

Note. Based on the Swedish version of the ICD version 8, 9 and 10 codes for the identification of diagnosis.

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eTable 3. Associations between the number of ACEs and any psychiatric disorder in the full cohort, stratified by sex.

	Women			Men			*P* for interaction
	N	cases[a]	OR (95% CI)	N	cases	OR (95% CI)	
ACE total score[b]	15,038	1621	1.53 (1.48, 1.59)	10,214	758	1.49 (1.41, 1.59)	0.51
Any ACE							
0 ACE	8914	626	1.00 (ref.)	6587	367	1.00 (ref.)	0.39
≥ 1 ACE	6124	995	2.58 (2.32, 2.87)	3627	391	2.04 (1.76, 2.37)	
Number of ACEs							
0 ACE	8914	626	1.00 (ref.)	6587	365	1.00 (ref.)	0.37
1 ACE	3319	376	1.71 (1.49, 1.96)	2212	184	1.55 (1.29, 1.87)	
2 ACE	1385	240	2.79 (2.37, 3.28)	789	80	1.89 (1.46, 2.43)	
≥ 3 ACEs	1420	377	4.79 (4.14, 5.53)	626	126	4.14 (3.31, 5.18)	

ACEs = adverse childhood experiences; OR = Odds Ratio; CI = Confidence Interval.
Models were adjusted for age;
95% CIs are based on robust SEs, calculated using generalized estimating equations;
[a]Any adult psychiatric disorder
[b]OR for every additional ACE.

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eTable 4. Associations between the number of ACEs and symptoms of depression in the full cohort and within exposure discordant twin-pairs

	Model 1 (Full cohort)			Model 2 (Within DZ twins)			Model 3 (Within MZ twins)		
	N total	Mean	exp(β) (95% CI)	N[a]	Mean	exp(β) (95% CI)	N[a]	Mean	exp(β) (95% CI)
ACE total score[b]	28,941	7.05	1.21 (1.20, 1.22)	4980	8.13	1.18 (1.16, 1.21)	3184	7.87	1.12 (1.09, 1.15)
Any ACE									
0 ACE	17,569	5.78	1.00 (ref.)	1910	6.16	1.00 (ref.)	1123	6.35	1.00 (ref.)
≥ 1 ACE	11,372	9.02	1.52 (1.49, 1.55)	1910	8.80	1.39 (1.33, 1.45)	1123	7.82	1.22 (1.15, 1.28)
Number of ACEs									
0 ACE	17,569	5.78	1.00 (ref.)	1910	6.16	1.00 (ref.)	1123	6.35	1.00 (ref.)
1 ACE	6479	8.16	1.39 (1.36, 1.42)	1325	8.28	1.33 (1.27, 1.40)	804	7.38	1.18 (1.12, 1.25)
2 ACE	2520	9.25	1.57 (1.52, 1.62)	368	9.31	1.47 (1.36, 1.59)	212	8.25	1.27 (1.17, 1.39)
≥ 3 ACEs	2373	11.13	1.87 (1.81, 1.93)	217	11.14	1.65 (1.52, 1.80)	107	10.23	1.38 (1.25, 1.53)

ACEs = adverse childhood experiences; DZ = Dizygotic twins; MZ = Monozygotic twins; CI = Confidence Interval.
Models were adjusted for age and sex;
Estimates are given as the percentage increase in depression symptoms, for every one-unit increase in ACEs;
95% CIs are based on robust SEs, calculated using generalized estimating equations;
[a]Exposure discordant twins, the number of individual twins from exposure discordant twin pairs in the analysis;
[b]exp(β) for every additional ACE.

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eTable 5. Number of twin individuals in full twin-pairs, number of exposed twin individuals and number of exposure discordant twins.

	Family violence	Emotional neglect	Physical neglect	Physical abuse	Sexual abuse	Rape	Hate crime
N total MZ in full pairs	6876	6876	6876	6876	6876	6876	6876
N exposed MZ	1045	1822	183	624	303	180	82
N discordant MZ	481 (46%)	922 (51%)	109 (60%)	412 (66%)	229 (76%)	156 (87%)	64 (78%)
N total DZ in full pairs	8464	8464	8464	8464	8464	8464	8464
N exposed DZ	1080	2453	225	735	417	227	109
N discordant DZ	676 (63%)	1431 (58%)	149 (66%)	555 (75%)	365 (88%)	211 (93%)	101 (93%)

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eTable 6. Associations between the number of ACEs and any diagnosed psychiatric disorder in the full cohort and within exposure discordant twin-pairs in the STAGE and YATSS cohorts (excluding CATSS).

	Model 1 (Full cohort)			Model 2 (Within DZ twins)			Model 3 (Within MZ twins)		
	N total	cases[a]	OR (95% CI)	N[b]	cases	OR (95% CI)	N[b]	cases	OR (95% CI)
ACE total score[c]	21,465	2240	1.52 (1.47, 1.57)	3072	365	1.26 (1.10, 1.44)	2442	313	1.21 (1.02, 1.41)
Any ACE									
0 ACE	13,260	949	1.00 (ref.)	1181	96	1.00 (ref.)	861	83	1.00 (ref.)
≥ 1 ACE	8205	1291	2.39 (2.18, 2.61)	1181	153	1.65 (1.24, 2.20)	861	93	1.19 (0.83, 1.70)
Number of ACEs									
0 ACE	13,260	949	1.00 (ref.)	1181	96	1.00 (ref.)	861	83	1.00 (ref.)
1 ACE	4580	529	1.69 (1.51 1.87)	806	89	1.42 (1.03, 1.95)	617	60	1.14 (0.77, 1.69)
2 ACE	1833	298	2.47 (2.15, 2.85)	230	36	2.42 (1.51, 3.88)	159	18	0.88 (0.51, 1.51)
≥ 3 ACEs	1792	464	4.41 (3.90, 5.00)	145	28	1.90 (1.16, 3.11)	85	15	2.07 (1.10, 3.87)

ACEs = adverse childhood experiences; DZ = Dizygotic twins; MZ = Monozygotic twins; OR = Odds Ratio; CI = Confidence Interval.
Models were adjusted for age and sex;
95% CIs are based on robust SEs, calculated using generalized estimating equations;
[a]Any adult psychiatric disorder
[b]Exposure discordant twins, the number of individual twins from exposure discordant twin pairs in the analysis;
[c]OR for every additional ACE.

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eTable 7. Associations between the number of ACEs and any adult psychiatric disorder in the full cohort and within exposure discordant twin-pairs in the YATSS and CATSS cohorts (excluding STAGE).

	Model 1 (Full cohort)			Model 2 (Within DZ twins)			Model 3 (Within MZ twins)		
	N total	cases[a]	OR (95% CI)	N[b]	cases	OR (95% CI)	N[b]	cases	OR (95% CI)
ACE total score[c]	7996	540	1.62 (1.52, 1.72)	1436	106	1.48 (1.14, 1.93)	868	73	1.58 (0.99, 2.51)
Any ACE									
0 ACE	5125	220	1.00 (ref.)	573	22	1.00 (ref.)	321	13	1.00 (ref.)
≥ 1 ACE	2871	320	3.04 (2.52, 2.66)	573	47	2.30 (1.31, 4.03)	321	23	2.43 (1.01, 5.86)
Number of ACEs									
0 ACE	5125	220	1.00 (ref.)	573	22	1.00 (ref.)	321	13	1.00 (ref.)
1 ACE	1652	115	1.88 (1.47 2.40)	403	22	1.53 (0.81, 2.90)	219	13	2.44 (0.92, 6.46)
2 ACE	634	74	3.17 (2.39, 4.20)	110	13	3.85 (1.51, 9.84)	61	5	1.15 (0.32, 4.08)
≥ 3 ACEs	585	131	6.34 (4.96, 8.09)	60	12	4.42 (1.74, 11.24)	41	5	7.35 (1.04, 52.18)

ACEs = adverse childhood experiences; DZ = Dizygotic twins; MZ = Monozygotic twins; OR = Odds Ratio; CI = Confidence Interval.
Models were adjusted for age and sex;
95% CIs are based on robust SEs, calculated using generalized estimating equations;
[a]Any adult psychiatric disorder
[b]Exposure discordant twins, the number of individual twins from exposure discordant twin pairs in the analysis;
[c]OR for every additional ACE.

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eTable 8. Associations between the number of ACEs and any adult psychiatric disorder in the full cohort and within exposure discordant twin-pairs in the STAGE cohort.

	Model 1 (Full cohort)			Model 2 (Within DZ twins)			Model 3 (Within MZ twins)		
	N total	cases[a]	OR (95% CI)	N[b]	cases	OR (95% CI)	N[b]	cases	OR (95% CI)
ACE total score[c]	17,256	1839	1.50 (1.44, 1.55)	2582	296	1.22 (1.05, 1.42)	1966	266	1.12 (0.95, 1.34)
Any ACE									
0 ACE	10,376	773	1.00 (ref.)	981	78	1.00 (ref.)	689	75	1.00 (ref.)
≥ 1 ACE	6880	1066	2.25 (2.04, 2.48)	981	120	1.56 (1.13, 2.17)	689	76	1.02 (0.69, 1.51)
Number of ACEs									
0 ACE	10,376	773	1.00 (ref.)	981	78	1.00 (ref.)	689	75	1.00 (ref.)
1 ACE	3879	447	1.61 (1.42, 1.82)	674	73	1.43 (1.00, 2.03)	505	50	1.01 (0.67, 1.54)
2 ACE	1540	247	2.34 (2.01, 2.74)	191	27	2.03 (1.21, 3.42)	128	14	0.77 (0.43, 1.38)
≥ 3 ACEs	1461	372	4.13 (3.60, 4.74)	116	20	1.72 (0.98, 3.02)	56	12	1.60 (0.81, 3.17)

ACEs = Adverse childhood experiences; DZ = Dizygotic twins; MZ = Monozygotic twins; OR = Odds Ratio; CI = Confidence interval.
Models were adjusted for age and sex;
95% CIs are based on robust SEs, calculated using generalized estimating equations;
[a]Any adult psychiatric disorder;
[b]Exposure discordant twins, the number of individual twins from exposure discordant twin pairs in the analysis;
[c]OR for every additional ACE.

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eTable 9. Associations between the number of ACEs and any adult psychiatric disorder, additionally including dispensed psychotropic medications as an indication for mild psychiatric disorder not attended by specialist care, in the full cohort and within exposure discordant twin-pairs.

	Model 1 (Full cohort)			Model 2 (Within DZ twins)			Model 3 (Within MZ twins)		
	N total	cases[a]	OR (95% CI)	N[b]	cases	OR (95% CI)	N[b]	cases	OR (95% CI)
ACE total score[c]	25,252	6726	1.40 (1.37, 1.44)	4018	1102	1.26 (1.14, 1.38)	2834	882	1.16 (1.03, 1.31)
Any ACE									
0 ACE	15,501	3348	1.00 (ref.)	1554	330	1.00 (ref.)	1010	257	1.00 (ref.)
≥ 1 ACE	9751	3378	1.90 (1.80, 2.02)	1554	449	1.49 (1.24, 1.80)	1010	275	1.14 (0.90, 1.46)
Number of ACEs									
0 ACE	15,501	3348	1.00 (ref.)	1554	330	1.00 (ref.)	1010	257	1.00 (ref.)
1 ACE	5531	1594	1.48 (1.38, 1.59)	1077	278	1.34 (1.08, 1.65)	724	183	1.06 (0.82, 1.38)
2 ACE	2174	798	2.06 (1.86, 2.27)	301	104	1.66 (1.23, 2.24)	189	55	1.21 (0.82, 1.79)
≥ 3 ACEs	2046	986	3.20 (2.90, 3.53)	176	67	2.20 (1.53, 3.15)	97	37	1.62 (1.04, 2.53)

ACEs = Adverse childhood experiences; DZ = Dizygotic twins; MZ = Monozygotic twins; OR = Odds Ratio; CI = Confidence interval.
Models were adjusted for age and sex;
95% CIs are based on robust SEs, calculated using generalized estimating equations;
[a]Any adult psychiatric disorder;
[b]Exposure discordant twins, the number of individual twins from exposure discordant twin pairs in the analysis;
[c]OR for every additional ACE.

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eTable 10. Associations between the number of ACEs and any adult psychiatric disorder in the full cohort and within exposure discordant twin-pairs, excluding twins diagnosed with any psychiatric disorder before age 19 years.

	Model 1 (Full cohort)			Model 2 (Within DZ twins)			Model 3 (Within MZ twins)		
	N total	cases[a]	OR (95% CI)	N[b]	cases	OR (95% CI)	N[b]	cases	OR (95% CI)
ACE total score[c]	24,743	2201	1.50 (1.46, 1.55)	3824	371	1.24 (1.08, 1.41)	2704	284	1.15 (0.98, 1.36)
Any ACE									
0 ACE	15,309	939	1.00 (ref.)	1490	93	1.00 (ref.)	973	76	1.00 (ref.)
≥ 1 ACE	9434	1262	2.33 (2.13, 2.54)	1490	151	1.66 (1.24, 2.21)	973	86	1.19 (0.82, 1.71)
Number of ACEs									
0 ACE	15,309	943	1.00 (ref.)	1490	93	1.00 (ref.)	973	76	1.00 (ref.)
1 ACE	5419	541	1.67 (1.50, 1.87)	1036	87	1.43 (1.04, 1.97)	701	56	1.19 (0.80, 1.77)
2 ACE	2111	302	2.45 (2.13, 2.82)	290	38	2.44 (1.53, 3.91)	181	16	0.86 (0.50, 1.47)
≥ 3 ACEs	1904	441	4.25 (3.75, 4.83)	164	26	1.86 (1.13, 3.03)	91	14	1.90 (1.00, 3.63)

ACEs = adverse childhood experiences; DZ = Dizygotic twins; MZ = Monozygotic twins; OR = Odds Ratio; CI = Confidence Interval.
Models were adjusted for age and sex;
95% CIs are based on robust SEs, calculated using generalized estimating equations;
[a]Any adult psychiatric disorder
[b]Exposure discordant twins, the number of individual twins from exposure discordant twin pairs in the analysis;
[c]OR for every additional ACE.

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eTable 11. Associations between the number of ACEs and any diagnosed psychiatric disorder in the full cohort and within exposure discordant twin-pairs, excluding twins diagnosed with any psychiatric disorder before answering the web-based survey with the ACE assessment.

	Model 1 (Full cohort)			Model 2 (Within DZ twins)			Model 3 (Within MZ twins)		
	N total	cases[a]	OR (95% CI)	N[b]	cases	OR (95% CI)	N[b]	cases	OR (95% CI)
ACE total score[c]	24,067	1449	1.45 (1.40, 1.51)	3,616	233	1.26 (1.07, 1.48)	2,575	159	1.02 (0.83, 1.24)
Any ACE									
0 ACE	15,034	637	1.00 (ref.)	1420	62	1.00 (ref.)	930	50	1.00 (ref.)
≥ 1 ACE	9033	812	2.20 (1.97, 2.45)	1420	103	1.59 (1.12, 2.27)	930	49	0.98 (0.63, 1.52)
Number of ACEs									
0 ACE	15,034	637	1.00 (ref.)	1420	62	1.00 (ref.)	930	50	1.00 (ref.)
1 ACE	5263	360	1.66 (1.45, 1.89)	1001	65	1.42 (0.97, 2.07)	674	34	1.11 (0.68, 1.80)
2 ACE	2018	192	2.32 (1.96, 2.75)	273	23	2.20 (1.22, 3.97)	172	9	0.62 (0.32, 1.20)
≥ 3 ACEs	1752	260	3.76 (3.22, 4.38)	146	15	1.96 (1.05, 3.65)	83	6	1.08 (0.50, 2.32)

ACEs = adverse childhood experiences; DZ = Dizygotic twins; MZ = Monozygotic twins; OR = Odds Ratio; CI = Confidence Interval.
Models were adjusted for age and sex;
95% CIs are based on robust SEs, calculated using generalized estimating equations;
[a]Any adult psychiatric disorder
[b]Exposure discordant twins, the number of individual twins from exposure discordant twin pairs in the analysis;
[c]OR for every additional ACE.

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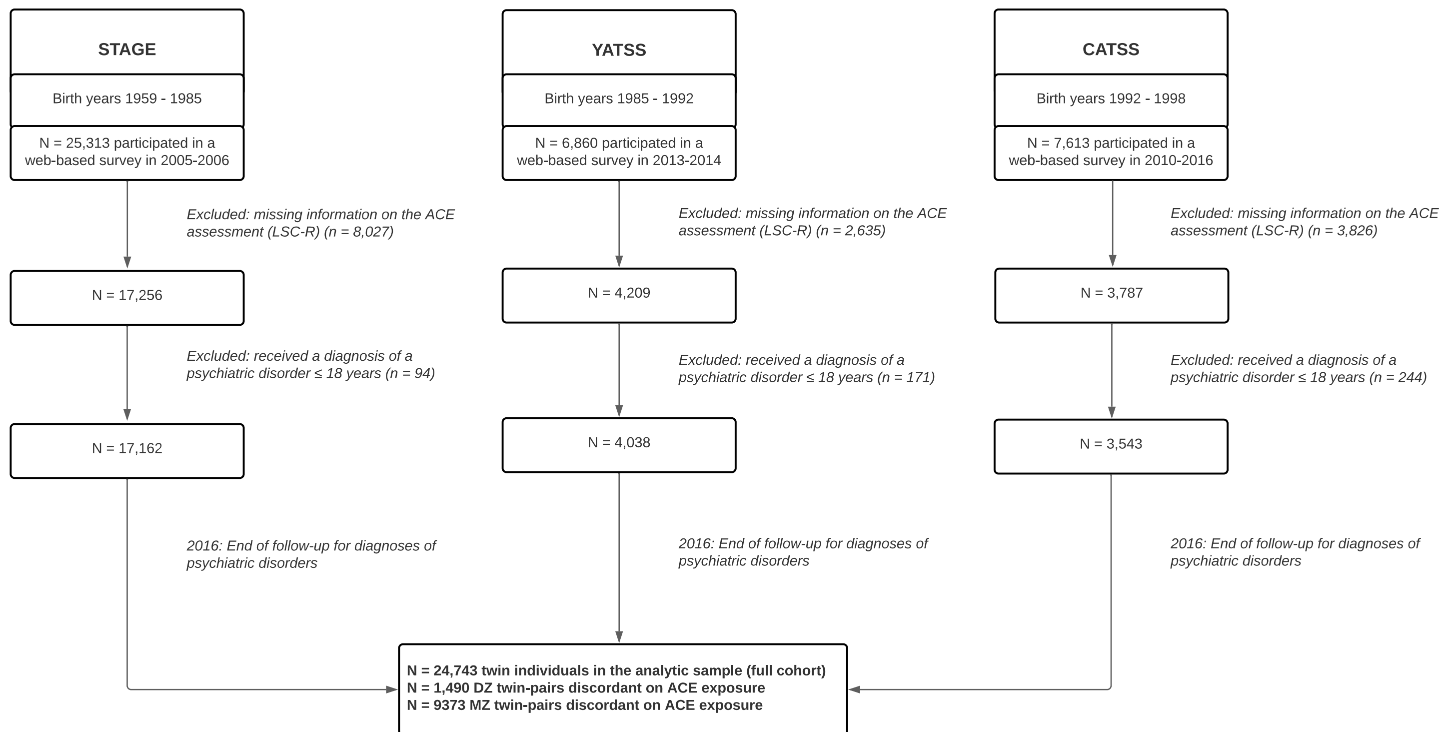

eFigure 1. Flow-chart of the analytic sample excluding twins diagnosed with any psychiatric disorder before age 19 years.

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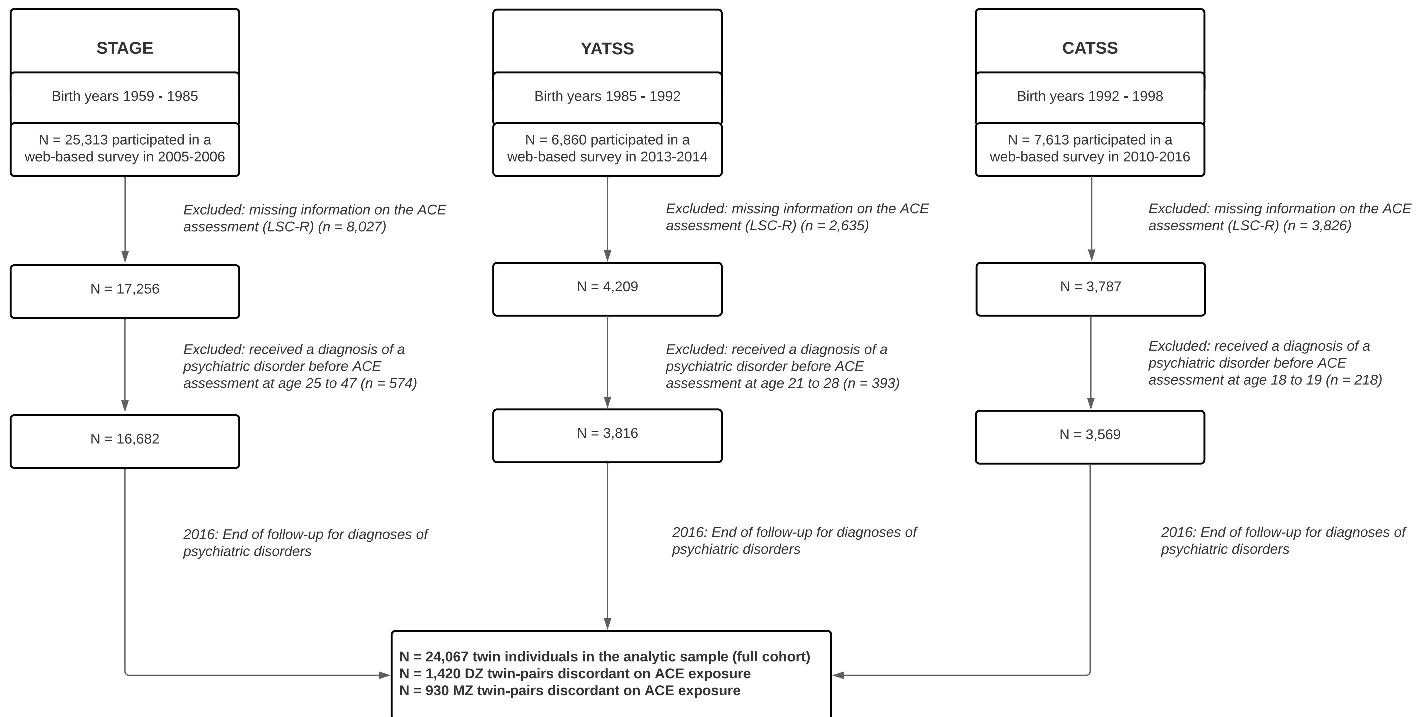

eFigure 2. Flow-chart of the analytic sample where follow-up for psychiatric disorders starts after the web-based surveys with the ACE assessment, excluding twins that received a diagnosis of any psychiatric disorder before answering the survey.

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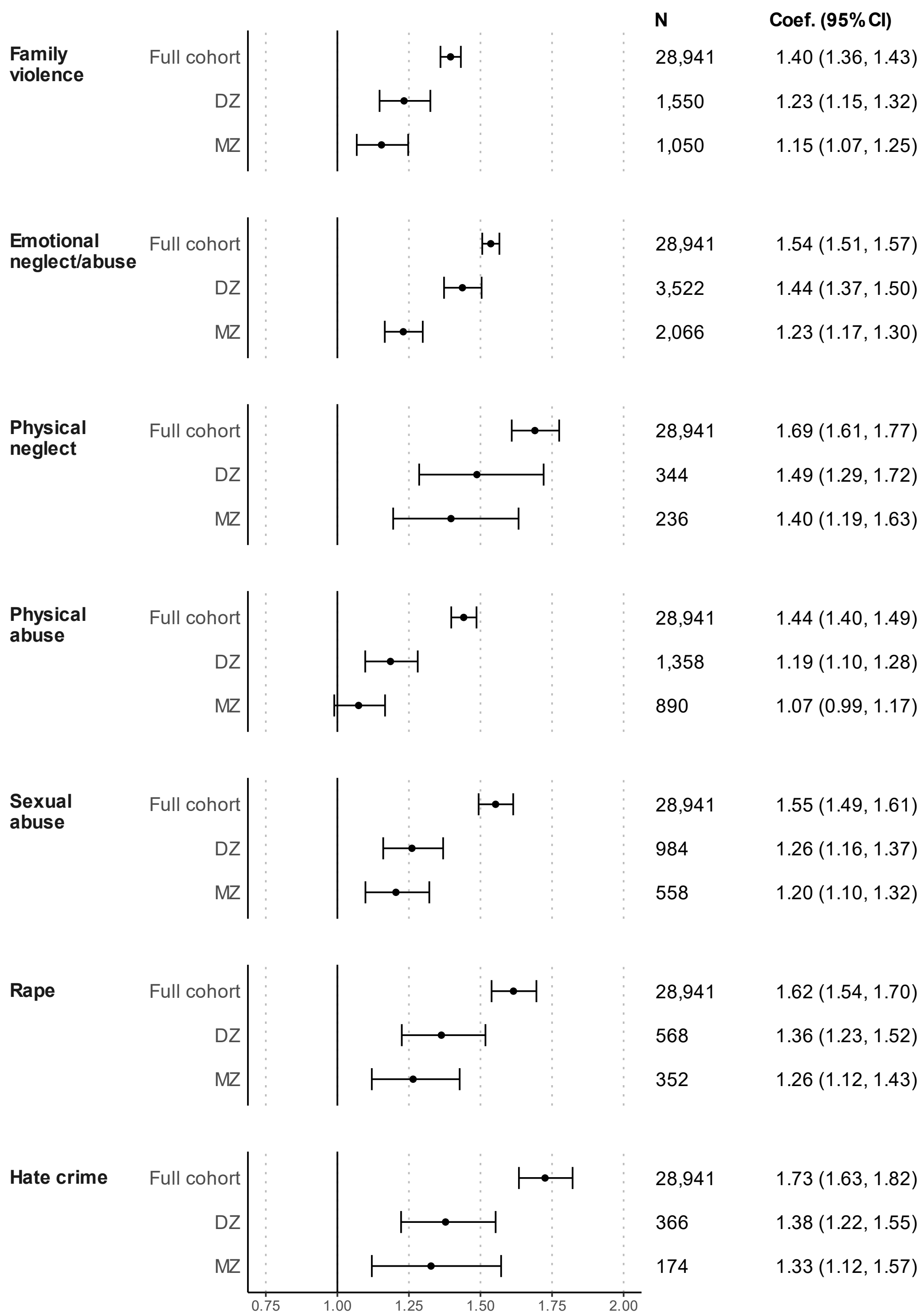

eFigure 3. Associations between ACE subtypes and depression symptoms in the full cohort and within exposure discordant twin-pairs.
Models were adjusted for age and sex; Estimates are given as the percentage increase in depression symptoms, comparing exposed vs. non-exposed twins; 95% CIs are based on

Paper II

Paper II

Adverse childhood experiences and resilience among adult women: A population-based study

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Abstract

Background: Adverse childhood experiences (ACEs) have consistently been associated with elevated risk of multiple adverse health outcomes, yet their contribution to coping ability and psychiatric resilience in adulthood is unclear.

Methods: Cross-sectional data were derived from the ongoing Stress-And-Gene-Analysis cohort, representing 30% of the Icelandic nationwide female population, 18–69 years. Participants in the current study were 26,198 women with data on 13 ACEs measured with the ACE-International Questionnaire. Self-reported coping ability was measured with the Connor-Davidson Resilience Scale and psychiatric resilience was operationalized as absence of psychiatric morbidity. Generalized linear regression assuming normal or Poisson distribution were used to assess the associations of ACEs with coping ability and psychiatric resilience controlling for multiple confounders.

Results: Number of ACEs was inversely associated with adult resilience in a dose-dependent manner; every 1SD unit increase in ACE scores was associated with both lower levels of coping ability ($\beta = -0.14$; 95% CI-0.15,–0.13) and lower psychiatric resilience ($\beta = -0.28$; 95% CI-0.29,–0.27) in adulthood. Compared to women with 0 ACEs, women with ≥5 ACEs had 36% lower prevalence of high coping ability (PR = 0.64, 95% CI 0.59,0.70) and 58% lower prevalence of high psychiatric resilience (PR = 0.42; 95% CI 0.39,0.45). Specific ACEs including emotional neglect, bullying, sexual abuse and mental illness of household member were consistently associated with reduced adult resilience. We observed only slightly attenuated associations after controlling for adult socioeconomic factors and social support in adulthood.

Conclusions: Cumulative ACE exposure is associated with lower adult resilience among women, independent of adult socioeconomic factors and social support, indicating that adult resilience may be largely determined in childhood.

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Editor's evaluation

This study aims to investigate the impact of adverse experiences during childhood on adult psychological and psychiatric resilience. Leveraging the excellent data from an ongoing cohort study on Icelandic women, the authors showed that in the face of accumulated adverse childhood events the prevalence of resilience declines, which supports earlier studies suggesting that resilience is not invincibility. The study makes an important contribution to raising awareness of the adverse childhood experiences and their impact on resiliency.

Introduction

Exposure to adverse childhood experiences (ACEs), including child abuse, neglect and growing up in dysfunctional households, is associated with elevated risk of a wide range of physical and mental health problems across the life course (***Anda et al., 2006***; ***Bellis et al., 2015***; ***Hughes et al., 2017***; ***Petruccelli et al., 2019***). The results from a recent meta-analysis (***Hughes et al., 2017***) suggest that the adult health outcomes most clearly associated with ACEs include problematic alcohol consumption and substance use, violence, and mental illness. However, there is great variation in long-term outcomes of children exposed to ACEs, and many children remain healthy despite excessive ACE exposure. Importantly, it has been documented that a substantial proportion of individuals exposed to ACEs do not develop mental illness in adulthood (***Green et al., 2010***; ***Kessler et al., 2010***), but instead exhibit resilience (***Holmes et al., 2015***; ***DuMont et al., 2007***).

Resilience is generally conceptualized as maintained mental health or positive adaptation despite trauma exposure (***Luthar et al., 2000***; ***Kalisch et al., 2017***; ***Choi et al., 2019***; ***Rutter, 2006***). And although the scientific investigation of resilience can be traced back to the 1970s (***Luthar et al., 2015***; ***Masten et al., 2008***; ***Garmezy, 1974***; ***Garmezy, 1990***; ***Werner, 1989***; ***Rutter, 1990***), the complexity of the concept has to date contributed to varying definitions and measurement approaches (***Southwick et al., 2014***). Two common contemporary approaches to operationalize the concept among adults, define resilience as *perceived coping ability* reflecting individuals' perceptions of their ability to cope effectively with stress and adversity (***Campbell-Sills and Stein, 2007***; ***Connor and Davidson, 2003***), and as *psychiatric resilience* reflecting an empirically derived outcome, such as the absence of PTSD or other psychiatric disorders among individuals exposed to traumatic events (***Nishimi et al., 2021***; ***Sheerin et al., 2018***). Indeed, it is important to note that psychiatric resilience is never directly measured as it consists of two separate components, trauma exposure and positive adaptation, and is therefore indirectly ascertained based on evidence of the two components (***Luthar, 2006***). The different resilience definitions (i.e. perceived coping ability and psychiatric resilience) are not mutually exclusive, but rather complementary and may capture different underlying dimensions of resilience (***Choi et al., 2019***; ***Sheerin et al., 2018***; ***Fisher and Law, 2020***).

Only a handful of previous studies have addressed the association between ACEs and adult resilience. Childhood maltreatment, variously defined, has been negatively associated with psychiatric resilience (***Mersky and Topitzes, 2010***; ***Topitzes et al., 2013***; ***McGloin and Widom, 2001***; ***Williams et al., 2006***) and perceived coping ability (***Campbell-Sills et al., 2009***; ***Nishimi et al., 2020***) in adulthood. However, most studies have focused solely on childhood maltreatment or included only a small number of ACEs. Therefore, to date, little is known about the association between cumulative ACE exposure and adult resilience, and whether specific ACE types are to a varying extent associated with resilience.

Leveraging a large nationwide study of Icelandic women, we aimed to investigate the association between the cumulative number of a broad spectrum of ACEs and two distinct measures of adult resilience, that is perceived coping ability and an outcome-based measure of low psychiatric morbidity.

Materials and methods

Study sample

In this study, we utilized data from the ongoing Stress-And-Gene-Analysis (SAGA) cohort, a population-based study in Iceland on the impact of trauma on women's health. All 18–69 year-old Icelandic speaking women residing in Iceland with an identifiable address or telephone number (n≈104,197), were invited to participate in the study from March 2018. Data collection continued until July 1st 2019, yielding a total of 30,403 participating women (30% of eligible women). The participants of the SAGA cohort represent the general Icelandic female population in terms of distribution of age, education level, geographical location, and monthly wages (***Appendix 1—figure 1***).

Since trauma exposure is intrinsic to psychiatric resilience, the analytic sample was restricted to women reporting a worst traumatic event at some point during their lifetime (see description of PCL-5 below). In addition, women who had more than 25% missing on perceived coping ability (n = 511), psychiatric resilience (n = 1040) and/or ACE-IQ (n = 93) were excluded, which resulted in a final study population of 26,198 women (***Appendix 1—figure 2***).

Measures

Adverse childhood experiences (ACEs)

ACEs were measured with a modified version of the Adverse Childhood Experiences International Questionnaire (ACE-IQ) developed by the WHO (***WHO, 2021***). The instrument consists of 39 items assessing how often individuals were exposed to the following 13 ACEs during the first 18 years of their life: emotional neglect, physical neglect, emotional abuse, physical abuse, sexual abuse, domestic violence, living with a household member who abuses drugs and/or alcohol, living with a household member who is mentally ill or suicidal, incarceration of a household member, parental death or separation/divorce, being bullied, witnessing community violence, and exposure to war/collective violence. Response options varied between items and items were either answered on a 5-point scale ranging from 0 (never) to 4 (always), on a 4-point scale ranging from 0 (never) to 3 (many times) or answered dichotomously 0 (no) and 1 (yes). For an overview of included items and their response options see ***Appendix 1—table 1***. The recommended frequency scoring system (***WHO, 2021***), which takes into account the level of exposure for each ACE, was used to generate three types of exposure variables: (1) a continuous ACE-IQ total score ranging from 0 to 13, reflecting the number of ACEs participants were exposed to; (2) the total score was categorized (0, 1, 2, 3–4 and ≥5 ACEs) based on the distribution of the sample; (3) binary variables for each individual ACE type (described above), coded as 0 (unexposed) and 1 (exposed).

Perceived coping ability

Perceived coping ability was assessed with the 10-item version of the Connor-Davidson Resilience Scale (CD-RISC-10) (***Campbell-Sills and Stein, 2007***). The scale, which measures individuals' perceptions of their ability to cope effectively with stress and adversity, such as the ability to adapt to change, achieving goals despite obstacles, and maintaining positivity in the face of stress, has demonstrated good reliability and validity (***Campbell-Sills and Stein, 2007***). All items were answered on a 5-point scale ranging from 0 (not true at all) to 4 (true nearly all the time). Items were summed to create a total score ranging from 0 to 40 with a higher score indicating higher levels of perceived coping ability. As there is no standardized cut-off for the CD-RISC, the total scores were divided into quintiles (for more details see the Appendix 1), and a binary variable was created where the highest quintile was used to define a high level of perceived coping ability (i.e. resilience, CD-RISC score ≥35).

Psychiatric resilience

Consistent with previous literature (***Choi et al., 2019***; ***Nishimi et al., 2021***; ***Stein et al., 2019***) psychiatric resilience was defined as absence of or low psychiatric morbidity among women exposed to lifetime trauma, that is total sum of the inverse number of above-threshold symptom levels on PTSD, trauma-related sleep disturbances, binge drinking, depression, and anxiety.

The PTSD Checklist for DSM-5 (PCL-5) is a 20-item valid instrument that assesses symptoms of PTSD in the past month according to the DSM-5 (***Weathers et al., 2013***; ***Blevins et al., 2015***; ***Wortmann et al., 2016***; ***Bovin et al., 2016***). Before answering the PCL-5, participants reported their

lifetime exposure to potentially traumatic events assessed with the Life Events Checklist for DSM-5 (LEC-5). Participants were asked to determine the worst traumatic event they had experienced and answer the PCL-5 according to the worst selected trauma. A clinical cut-off score of ≥33 was used to indicate probable PTSD (**Weathers et al., 2013**). The Pittsburgh Sleep Quality Index Addendum for PTSD (PSQI-A) is a seven-item valid questionnaire designed to assess the frequency of disruptive nocturnal behaviors common in individuals with PTSD (**Germain et al., 2005**). A clinical cut-off score of ≥4 was used to discriminate between participants with and without trauma-related sleep disturbances (**Germain et al., 2005**). Binge drinking was defined as having six or more units of alcohol on a single occasion (one unit corresponds to a single measure of spirits) at least once a month during the last year (**Bush et al., 1998**). The widely used Patient Health Questionnaire (PHQ-9) (**Kroenke et al., 2001**) and Generalized Anxiety Disorder Scale (GAD-7) (**Kroenke et al., 2010**; **Spitzer et al., 2006**; **Löwe et al., 2008**) were used to measure the presence of depression and anxiety symptoms, respectively, during the past 2 weeks. The standard cut-off score of ≥10 was used, indicating clinically relevant depression and anxiety (**Kroenke et al., 2001**; **Spitzer et al., 2006**).

Binary variables were created indicating whether an individual met the clinical cut-off for symptoms of each disorder above (0 = no, 1 = yes). The psychiatric resilience phenotype was derived by summing together the binary variables and reversing the score which resulted in a total score ranging from 0 to 5 where higher scores indicate greater psychiatric resilience in these trauma-exposed women. In addition, we created a binary variable where endorsement of 0 on all measures indicated high psychiatric resilience.

Covariates

We summarised variables with a conceptual rationale for being associated both with ACEs and perceived coping ability or psychiatric resilience in **Appendix 1—figure 3**. We considered as covariates, age (at responding) and childhood deprivation (potential confounders), as well as educational level, employment status, civil status and current monthly income at responding (potential mediators). Age was divided into five groups for descriptive purposes: 18–29 years, 30–39 years, 40–49 years, 50–59 years, and 60 years and older. The age covariate was used as a continuous variable in all models. Education was categorized as primary education, secondary education (high school or vocational education), tertiary education A (BSc or equivalent), and tertiary education B (MSc or above). Civil status was divided into married or in a relationship and single or widowed, and employment status was divided into employed (including being a student and being on parental leave) and retired or on disability or sick leave. Current monthly income was categorized into the following groups: low income (<$2527), low-medium income ($2528-$4212), medium income ($4213-$5897), medium-high income ($5898-$8424), and high income (>$8425; conversion rates according to Central Bank of Iceland, October 17, 2018). Childhood deprivation was assessed with the question: Was your family's economic situation ever so bad that you suffered any deprivation as a consequence? For example, this could apply to deprivation of nutritious food and/or deprivation of warm clothes and appropriate footwear during the winter months, with response options ranging from 0 (never) to 4 (often). In addition, current perceived social support, measured with the Multidimensional Scale of Perceived Social Support (MSPSS) (**Zimet et al., 1988**), and perceived happiness, measured with a 10-point visual digital scale, were included in additional analyses (for further details, see the Appendix 1).

Multiple imputation

The ACE-IQ scale and the five psychopathology scales (PHQ-9, GAD-7, PCL-5, PSQI-A and binge drinking) used to derive psychiatric resilience, had missing values which resulted in a reduced sample size (see **Appendix 1—figure 4**). We used multiple imputation (MI) to replace missing data with m = 20 rounds of imputations, using predictive mean matching (**van Buuren, 2019**). We imputed data for participants who responded to more than 75% of items on each scale and then calculated the total score for the scales. The subsequent analyses (described below) were conducted using the imputed dataset. For comparison, the main analyses were repeated in the original dataset with complete data.

Statistical analyses

Descriptive characteristics were compared using Chi-square tests for categorical data and ANOVAs for continuous data.

Rank order correlations were used to determine (i) the correlation between perceived coping ability and psychiatric resilience, (ii) correlations between perceived coping ability and different measures of psychopathology (PHQ-9, GAD-7, PCL-5, PSQI-A, binge drinking) used to derive psychiatric resilience, and (iii) correlations between different ACE subtypes.

We used linear regression models assuming normally distributed errors and log-linear Poisson regression models with robust error variance to determine the associations between ACEs and perceived coping ability and psychiatric resilience, as continuous and binary outcomes (high perceived coping ability/ high psychiatric resilience), respectively. In all analyses, we adjusted for age and childhood deprivation (model 1) and then additionally for adult educational level, civil status, employment level and income (model 2).

We ran all models with ACE-IQ as a continuous predictor and as a categorical predictor where we compared resilience levels of unexposed women (0 ACEs) to resilience levels of those who had been exposed to increasing number of ACEs (1, 2, 3–4, and ≥5 ACEs). In addition, we carried out stratified analyses to assess whether the association between ACEs and resilience differed by levels of perceived social support (linear models). Furthermore, because parental separation/divorce is a common childhood experience, we carried out a sensitivity analysis excluding this item from the ACE-IQ score and re-ran the linear models. Finally, to preclude whether a particular response style influenced the observed associations between ACEs and resilience, we excluded women who scored low or high on happiness (10% top/bottom scores) and re-ran the linear models.

To determine the independent associations of specific types of ACEs with resilience, we ran analyses on perceived coping ability and psychiatric resilience for each of the 13 ACEs. We first examined each ACE type separately while adjusting for covariates, and then re-ran the analyses with all ACE subtypes entered simultaneously into the model, as ACEs frequently co-occur (***Radford et al., 2013***).

Standardized regression coefficients were reported from all linear regression analyses and prevalence ratios (PR) were reported from the Poisson regression analyses. All statistical analyses were performed using R (version 3.6.1).

Results

Characteristics of the sample

Descriptive statistics of the study population are presented in ***Table 1***. Overall, 19.7% of participants reported no ACEs and 20.4% reported five or more ACEs. Middle aged women had on average higher scores on the ACE-IQ than younger or older women. Women with higher ACE scores were more often single or widowed, less educated, unemployed, had lower income and were more likely to report childhood deprivation and low perceived social support (***Table 1***).

Bivariate associations

Both perceived coping ability and psychiatric resilience were consistently associated with older age, higher educational level, being in a relationship or married, being employed, higher income, lower childhood deprivation and higher perceived social support (***Table 2***). The two resilience measures were moderately correlated (r_s = 0.47). Perceived coping ability was moderately negatively correlated with each of the measures used to derive the psychiatric resilience phenotype (i.e. symptoms of depression, anxiety, PTSD, and trauma-related sleep disturbances) but weakly correlated with binge drinking (***Appendix 1—table 2***). The 13 ACE subtypes were weakly to moderately correlated with each other (r_s ranging from 0.06 to 0.46), with emotional abuse showing the strongest correlation with other ACEs (***Appendix 1—table 3***).

Associations between ACEs and resilience

Linear models revealed that exposure to one or more ACEs (relative to 0 ACEs) was associated with lower perceived coping ability and psychiatric resilience in a dose-dependent manner (***Table 3***); every 1 SD unit increase in ACE-IQ scores was associated with lower levels of perceived coping ability (β = −0.14; 95% CI −0.15,–0.13) and psychiatric resilience (β = −0.28; 95% CI −0.29,–0.27) in the fully adjusted model. Associations between ACEs and perceived coping ability and psychiatric resilience were observed across levels of social support but were slightly stronger among women with low social support (***Appendix 1—table 4***). Sensitivity analyses showed that the associations remained evident

Table 1. Descriptive characteristics of the study population by number of adverse childhood experiences (ACE-IQ) (n = 26,198).

	Number of ACEs							ACE-IQ sum score	
	Total N (%)	0 ACE N (%)	1 ACE N (%)	2 ACEs N (%)	3–4 ACEs N (%)	≥ 5 ACEs N (%)	p-value global*	Mean (SD)	p-value global†
Total	26,198	5,149 (19.7)	5,567 (21.3)	4,491 (17.1)	5,640 (21.5)	5,351 (20.4)		2.6 (2.4)	
Age, mean (SD)	44.0 (13.6)	43.7 (13.9)	44.7 (13.9)	44.6 (13.6)	44.1 (13.4)	43.1 (12.8)	< 0.001		
Age groups									
18–29 years	4,881 (18.6)	1,043 (20.3)	993 (17.8)	805 (17.9)	1,045 (18.5)	995 (18.6)	< 0.001	2.6 (2.5)	< 0.001
30–39 years	5,309 (20.3)	1,074 (20.9)	1,128 (20.3)	864 (19.2)	1,107 (19.6)	1,136 (21.2)		2.7 (2.4)	
40–49 years	5,923 (22.6)	1,092 (21.2)	1,167 (21.0)	1,003 (22.3)	1,301 (23.1)	1,360 (25.4)		2.8 (2.5)	
50–59 years	6,055 (23.1)	1,091 (21.2)	1,281 (23.0)	1,088 (24.2)	1,356 (24.0)	1,239 (23.2)		2.7 (2.4)	
≥ 60 years	4,030 (15.4)	849 (16.5)	998 (17.9)	731 (16.3)	831 (14.7)	621 (11.6)		2.3 (2.2)	
Educational level									
Primary education	3,739 (14.3)	442 (8.6)	662 (11.9)	602 (13.4)	889 (15.8)	1,144 (21.4)	< 0.001	3.4 (2.61)	< 0.001
Secondary education	8,013 (30.6)	1,402 (27.2)	1,658 (29.8)	1,360 (30.3)	1,744 (30.9)	1,849 (34.6)		2.8 (2.32)	
Tertiary A (BSc or equivalent)	8,359 (31.9)	1,856 (36.0)	1,872 (33.6)	1,488 (33.1)	1,782 (31.6)	1,361 (25.4)		2.3 (2.09)	
Tertiary B (MSc or above)	5,990 (22.9)	1,437 (27.9)	1,360 (24.4)	1,022 (22.8)	1,210 (21.5)	961 (18.0)		2.3 (2.08)	
Unknown	97 (0.4)	12 (0.2)	15 (0.3)	19 (0.4)	15 (0.3)	36 (0.7)		3.7 (2.59)	
Civil status									
Married/in a relationship	19,750 (75.4)	4,061 (78.9)	4,309 (77.4)	3,442 (76.6)	4,173 (74.0)	3,765 (70.4)	< 0.001	2.5 (2.3)	< 0.001
Single/widowed	6,314 (24.1)	1,070 (20.8)	1,241 (22.3)	1,030 (22.9)	1,432 (25.4)	1,541 (28.8)		2.9 (2.5)	
Unknown	134 (0.5)	18 (0.3)	17 (0.3)	19 (0.4)	35 (0.6)	45 (0.8)		3.6 (2.8)	
Employment status									
Employed/studying	22,088 (84.3)	4,639 (90.1)	4,826 (86.7)	3,888 (86.6)	4,734 (83.9)	4,001 (74.8)	< 0.001	2.5 (2.3)	< 0.001
Retired/disability/sick leave	3,941 (15.0)	494 (9.6)	718 (12.9)	573 (12.8)	854 (15.1)	1,302 (24.3)		3.5 (2.8)	
Unknown	169 (0.6)	16 (0.3)	23 (0.4)	30 (0.7)	52 (0.9)	48 (0.9)		3.5 (2.6)	
Income									
Low income	7,723 (29.5)	1,206 (23.4)	1,532 (27.5)	1,216 (27.1)	1,750 (31.0)	2019 (37.7)	< 0.001	3.0 (2.6)	< 0.001
Low-medium income	7,862 (30.0)	1,478 (28.7)	1,663 (29.9)	1,406 (31.3)	1,717 (30.4)	1,598 (29.9)		2.6 (2.4)	
Medium income	6,050 (23.1)	1,352 (26.3)	1,363 (24.5)	1,081 (24.1)	1,236 (21.9)	1,018 (19.0)		2.3 (2.2)	
High-medium income	2,636 (10.1)	654 (12.7)	567 (10.2)	466 (10.4)	534 (9.5)	415 (7.8)		2.2 (2.2)	
High income	929 (3.5)	250 (4.9)	226 (4.1)	141 (3.1)	196 (3.5)	116 (2.2)		2.0 (2.0)	
Unknown	998 (3.8)	209 (4.1)	216 (3.9)	181 (4.0)	207 (3.7)	185 (3.5)		2.5 (2.4)	
Childhood deprivation									
Never	19,727 (75.3)	4,843 (94.1)	4,919 (88.4)	3,628 (80.8)	3,954 (70.1)	2,383 (44.5)	< 0.001	2.0 (2.0)	< 0.001
Rarely	2,929 (11.2)	218 (4.2)	430 (7.7)	516 (11.5)	833 (14.8)	932 (17.4)		3.5 (2.4)	
Sometimes	2,320 (8.9)	71 (1.4)	193 (3.5)	278 (6.2)	627 (11.1)	1,151 (21.5)		4.6 (2.5)	
Often	1,169 (4.5)	15 (0.3)	21 (0.4)	60 (1.3)	206 (3.7)	867 (16.2)		6.3 (2.6)	
Unknown	53 (0.2)	2 (0.0)	4 (0.1)	9 (0.2)	20 (0.4)	18 (0.3)		3.8 (2.0)	
Perceived social support									
Low	6,332 (24.2)	747 (14.5)	995 (17.9)	972 (21.6)	1,582 (28.0)	2036 (38.0)	< 0.001	3.5 (2.7)	< 0.001
Moderate	12,831 (40.0)	2,487 (48.3)	2,833 (50.9)	2,282 (50.8)	2,762 (49.0)	2,467 (46.1)		2.5 (2.3)	
High	6,151 (23.5)	1,790 (34.8)	1,579 (28.4)	1,102 (24.5)	1,075 (19.1)	605 (11.3)		1.8 (1.9)	
Unknown	884 (3.4)	125 (2.4)	160 (2.9)	135 (3.0)	221 (3.9)	243 (4.5)		3.2 (2.5)	

*p-values were obtained by χ^2 tests, except for mean age which was compared with an ANOVA.
†p-values were obtained by ANOVA.

Table 2. Distribution of perceived coping ability (CD-RISC) and psychiatric resilience scores by sociodemographic characteristics.

	Perceived coping ability		Psychiatric resilience	
	Mean (SD)	p-value global*	Mean (SD)	p-value global*
Total	28.0 (7.5)		3.6 (1.5)	
Age groups				
18–29 years	24.8 (7.9)	< 0.001	3.1 (1.6)	< 0.001
30–39 years	26.8 (7.5)		3.5 (1.6)	
40–49 years	27.8 (7.4)		3.7 (1.5)	
50–59 years	28.5 (7.2)		3.8 (1.4)	
≥ 60 years	28.8 (6.9)		4.0 (1.3)	
Educational level				
Primary education	24.2 (8.3)	< 0.001	3.1 (1.6)	< 0.001
Secondary education	26.3 (7.6)		3.4 (1.5)	
Tertiary A (BSc or equivalent)	28.0 (7.0)		3.8 (1.4)	
Tertiary B (MSc or above)	29.8 (6.5)		4.0 (1.3)	
Unknown	23.6 (8.1)		3.1 (1.7)	
Civil status				
Married/in a relationship	27.7 (7.4)	< 0.001	3.7 (1.4)	< 0.001
Single/widowed	26.3 (7.9)		3.3 (1.6)	
Unknown	24.7 (8.5)		2.7 (1.8)	
Employment status				
Employed/studying	28.0 (7.2)	< 0.001	3.7 (1.4)	< 0.001
Retired/disability/sick leave	23.9 (8.5)		3.0 (1.6)	
Unknown	23.3 (9.0)		2.8 (1.6)	
Income				
Low income	24.5 (8.0)	< 0.001	3.1 (1.6)	< 0.001
Low-medium income	27.0 (7.2)		3.6 (1.5)	
Medium income	29.3 (6.5)		4.0 (1.3)	
High-medium income	30.9 (6.1)		4.1 (1.2)	
High income	31.9 (6.1)		4.1 (1.2)	
Unknown	26.6 (7.9)		3.7 (1.5)	
Childhood deprivation				
Never	27.9 (7.3)	< 0.001	3.8 (1.4)	< 0.001
Rarely	26.4 (7.6)		3.3 (1.6)	
Sometimes	25.4 (7.9)		3.1 (1.6)	
Often	25.0 (8.4)		2.6 (1.6)	
Unknown	24.0 (8.9)		2.6 (1.6)	
Perceived social support				
Low	24.5 (8.0)	< 0.001	3.1 (1.6)	< 0.001
Moderate	27.2 (7.1)		3.7 (1.5)	
High	30.9 (6.4)		4.1 (1.2)	
Unknown	24.7 (8.0)		3.2 (1.6)	

*p-values were obtained by ANOVAs.

Table 3. Associations between the number of ACEs and perceived coping ability (CD-RISC) and psychiatric resilience (β and 95% CI)*.

	N (%)	Perceived coping ability		Psychiatric resilience	
		Model 1†	**Model 2** ‡	**Model 1**†	**Model 2** ‡
ACE-IQ total score **	26,198	–0.19 (-0.20,–0.17)	–0.14 (-0.15,–0.13)	–0.32 (-0.34,–0.31)	–0.28 (-0.29,–0.27)
Number of ACEs					
0 ACE	5,149 (19.7)	0 (ref.)	0 (ref.)	0 (ref.)	0 (ref.)
1 ACE	5,567 (21.3)	–0.07 (-0.08,–0.05)	–0.05 (-0.07,–0.04)	–0.09 (-0.10,–0.07)	–0.07 (-0.09,–0.06)
2 ACE	4,491 (17.1)	–0.10 (-0.11,–0.08)	–0.08 (-0.10,–0.07)	–0.13 (-0.15,–0.12)	–0.12 (-0.13,–0.10)
3–4 ACE	5,640 (21.5)	–0.16 (-0.17,–0.14)	–0.13 (-0.14,–0.11)	–0.22 (-0.23,–0.20)	–0.19 (-0.21,–0.18)
≥ 5 ACEs	5,351 (20.4)	–0.22 (-0.24,–0.20)	–0.16 (-0.18,–0.15)	–0.36 (-0.37,–0.34)	–0.31 (-0.33,–0.30)

*Coefficients are standardized; **per 1 SD unit increase in ACE-IQ scores.
†adjusted for age and childhood deprivation.
‡additionally adjusted for education level, civil status, employment status and income.

when excluding parental separation/divorce from the ACE-IQ score (***Appendix 1—table 5***), and when excluding women with top/bottom 10% happiness values (***Appendix 1—table 6***).

Poisson models revealed that compared to women with 0 ACEs, women with ≥5 ACEs had a lower prevalence of high perceived coping ability (PR = 0.64, 95% CI 0.59, 0.70), and high psychiatric resilience (PR = 0.42, 95% CI 0.39, 0.45) in the fully adjusted model (***Table 4***). Every unit increase in the ACE-IQ scores was associated with lower prevalence of high perceived coping ability (PR = 0.93, 95% CI 0.92, 0.94) and high psychiatric resilience (PR = 0.87, 95% CI 0.86, 0.87).

All ACE subtypes were associated with lower levels of perceived coping ability and psychiatric resilience (***Appendix 1—figure 5***) as well as lower prevalence of high psychiatric resilience and high perceived coping ability except for physical neglect- and abuse, parental death or separation/divorce, incarceration of a household member, and community- and collective violence (***Appendix 1—figure 6***). After mutual adjustment for all ACE subtypes, we found that emotional neglect, being bullied, sexual abuse, and growing up with a mentally ill household member had consistent associations with both resilience measures, both in linear models (***Figure 1***) and Poisson models (***Figure 2***). Associations were also suggested for emotional abuse, domestic- and community violence with psychiatric resilience in the full model while associations for other ACEs were substantially attenuated (***Figures 1 and 2***).

Table 4. Prevalence Ratios (with 95% CI) of high perceived coping ability (CD-RISC ≥35) and high psychiatric resilience (absence of psychiatric morbidity) in relation to the number of ACEs.

	N (%)	Perceived coping ability		Psychiatric resilience	
		Model 1†a	**Model 2** ‡	**Model 1**†	**Model 2** ‡
ACE-IQ total score*	26,198	0.91 (0.90, 0.92)	0.93 (0.92, 0.94)	0.85 (0.84, 0.86)	0.87 (0.86, 0.87)
Number of ACEs					
0 ACE	5,149 (19.7)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
1 ACE	5,567 (21.3)	0.83 (0.77, 0.89)	0.87 (0.81, 0.93)	0.82 (0.79, 0.84)	0.84 (0.81, 0.87)
2 ACE	4,491 (17.1)	0.71 (0.66, 0.77)	0.75 (0.70, 0.81)	0.73 (0.70, 0.76)	0.75 (0.72, 0.78)
3–4 ACE	5,640 (21.5)	0.61 (0.56, 0.66)	0.66 (0.61, 0.71)	0.59 (0.56, 0.61)	0.62 (0.60, 0.65)
≥ 5 ACEs	5,351 (20.4)	0.56 (0.51, 0.61)	0.64 (0.59, 0.70)	0.38 (0.35, 0.40)	0.42 (0.39, 0.45)

*per 1 SD unit increase in ACE-IQ scores.
†adjusted for age and childhood deprivation.
‡additionally adjusted for education level, civil status, employment status and income.

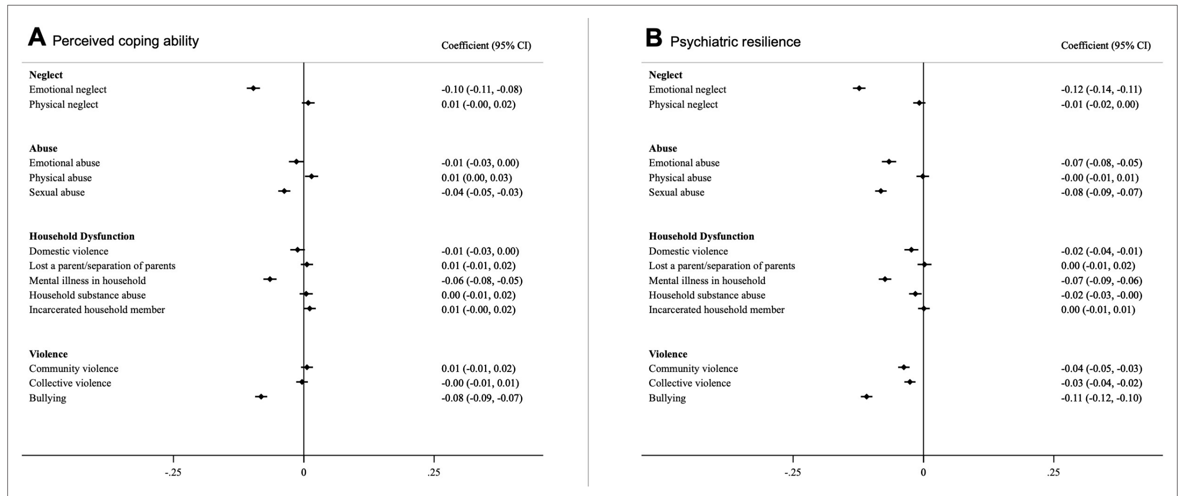

Figure 1. Associations between different types of ACEs and perceived coping ability (**A**) and psychiatric resilience (**B**) (β and 95% CI). Models were corrected for age, childhood deprivation, educational level, civil status, employment status, income and mutually adjusted for other ACEs. *Coefficients are standardized.

Overall, the results of the complete case analyses were similar to the results using multiple imputation (main analyses) in terms of both effect sizes and confidence intervals. See ***Appendix 1—tables 7 and 8*** (number of ACEs), and ***Appendix 1—figures 7 and 8*** (ACE subtypes) for the complete case analyses.

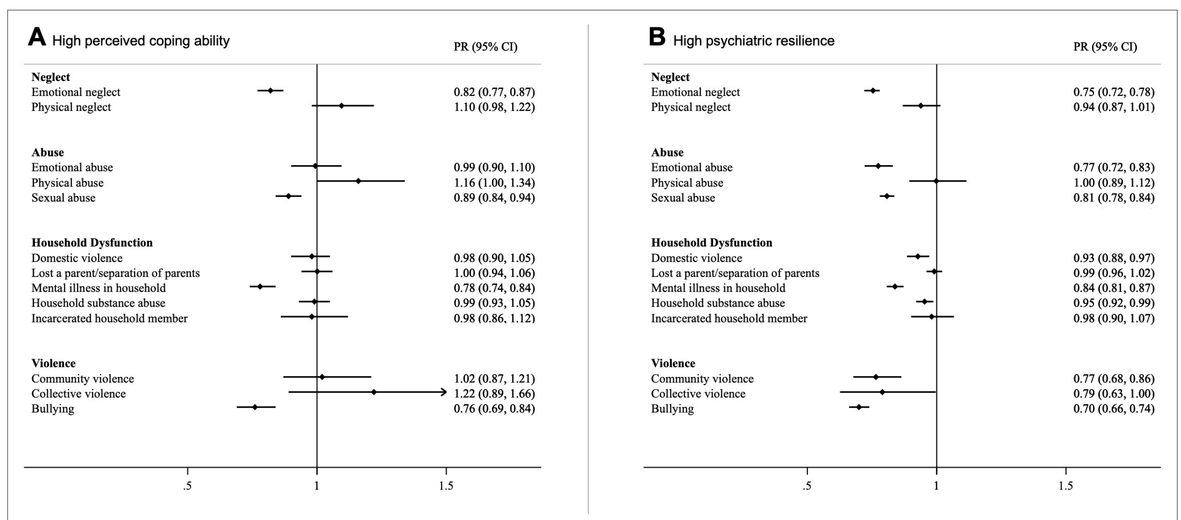

Figure 2. Prevalence Ratios (with 95% CI) of high perceived coping ability (**A**) and high psychiatric resilience (**B**) in relation to individual ACEs. Models were corrected for age, childhood deprivation, educational level, civil status, employment status, income and mutually adjusted for other ACEs.

Discussion

In a large nationwide study of Icelandic women, a comprehensive measure of 13 adverse childhood experiences (ACEs) was negatively associated with two distinct measures of resilience in adulthood in a dose-dependent manner. Indeed, women who endorsed five or more ACEs had 36% lower prevalence of high perceived coping ability and 58% lower prevalence of high psychiatric resilience compared to women who endorsed 0 ACEs. In addition, specific ACEs including emotional neglect, bullying, sexual abuse and growing up with a mentally ill household member were strongly associated with lower adult resilience.

To our knowledge, the present study is the first to consider a wide range of ACEs in relation to adult resilience, and to address their association with two distinct resilience measures. Overall, our results are in line with previous studies examining the association between childhood maltreatment and adult resilience (***Mersky and Topitzes, 2010***; ***Topitzes et al., 2013***; ***McGloin and Widom, 2001***; ***Williams et al., 2006***; ***Campbell-Sills et al., 2009***; ***Nishimi et al., 2020***). However, the existing evidence base is limited by relatively small sample sizes, consideration of only few ACEs (***McGloin and Widom, 2001***; ***Williams et al., 2006***; ***Campbell-Sills et al., 2009***; ***Nishimi et al., 2020***), and/or the use of composite measures of childhood adversity (***Mersky and Topitzes, 2010***; ***Topitzes et al., 2013***).

Our results indicating a dose-response relationship between the cumulative number of ACEs and lower adult resilience is consistent with a recent cross-sectional study by ***Nishimi et al., 2020*** who observed a similar pattern between four ACEs (emotional abuse, physical abuse, sexual abuse, and witnessing domestic violence) and perceived coping ability, as measured with the CD-RISC. We have now extended these findings to psychiatric resilience as an outcome, and further demonstrated this pattern for a broad set of ACEs in a large nationwide study representing 30% of the Icelandic female population. Furthermore, our results suggest that all ACE subtypes are associated with perceived coping ability and psychiatric resilience. However, when mutually adjusting for other ACEs, only emotional neglect, sexual abuse, being bullied and growing up with a mentally ill household member were consistently associated with both resilience measures.

In line with previous literature (***Nishimi et al., 2021***; ***Sheerin et al., 2018***), we found that self-assessed coping ability and outcome-based psychiatric resilience were only moderately correlated with each other, indicating these may reflect different patterns of adaptive functioning following adversity. Collectively, our research adds to the growing literature on the nature of resilience as a construct. The associations between ACEs and adult resilience were independent of age, childhood deprivation and, importantly, other adult socio-demographic factors (i.e. educational level, civil status, employment level and income), suggesting that ACEs affect resilience over and above these potential mediating variables. Indeed, one possible mechanism through which ACEs could influence resilience, are functional outcomes in adulthood (e.g. social, financial and/or educational functioning). Previous research has found that ACEs are associated with greater risk of poor educational and financial outcomes, as well as poor social functioning (***Bellis et al., 2014***; ***Copeland et al., 2018***), both adult factors that have previously been associated with resilience (***Nishimi et al., 2021***; ***Campbell-Sills et al., 2009***; ***Southwick et al., 2016***). However, in the current study, effect sizes only diminished slightly when we additionally adjusted for adult socio-demographic factors, which indicates that adult characteristics such as education and employment level do not compensate for the deleterious impact of ACEs on adult resilience. This suggests that adult resilience may largely be determined in childhood and that situational factors in adulthood (e.g. high social support) only marginally buffer the association between ACEs and adult resilience.

The main strengths of the study include the population-based design and large sample size of the SAGA cohort, which represents the Icelandic adult female population in terms of distribution of age, residence, education and income. The wealth of measures in the SAGA cohort baseline assessments made it possible to derive two types of resilience measures and examine a wide range of ACEs. The wealth of relevant data also allowed us to adjust for childhood deprivation, an important confounder when examining ACEs and adult outcomes (***Copeland et al., 2018***; ***Arseneault et al., 2011***; ***Bellis et al., 2017***), which has not been taken into account in previous ACE-resilience studies. However, our study also has several limitations. First, the cross-sectional nature of our data does not allow us to make any inferences about the directionality of the studied associations. Second, we cannot rule out that the observed association between ACE growing up with a mentally ill household member and resilience, is due to a genetic predisposition for psychopathology rather than the experience

itself. Future genetically informative studies will need to examine the extent to which this association is confounded by genetic factors. Although we adjusted for an array of important confounding factors, we cannot exclude the possibility that unmeasured or residual confounding may contribute to our results. In addition, ACEs were retrospectively reported and thus may be subject to recall bias. However, previous studies have shown acceptable validity for retrospective assessments of ACEs (***Reuben et al., 2016***; ***Hardt and Rutter, 2004***; ***Widom and Shepard, 1996***; ***Widom and Morris, 1997***), although they may be influenced by current mental health status or response style (***Reuben et al., 2016***). Yet, the similar results obtained from our sensitivity analyses excluding individuals with extreme values on the happiness assessment, reduce concerns that our results are due to a particular response style. Finally, our results are based on an exclusively female sample, therefore, future studies should explore whether there are qualitative differences in how ACEs relate to adult resilience among men as well as among sexual and gender minorities.

In conclusion, in a large nationwide-representative female population, we observed a negative association between cumulative exposure of ACEs and two distinct measures of adult resilience. Specific ACEs, including exposure to emotional neglect and bullying, sexual abuse, and growing up with a mentally ill household member were consistently associated with lower adult resilience. If these findings are confirmed through prospective designs, there may be huge societal benefits of prevention strategies targeting the protection of children against traumatic occurrences and their consequences. Future research is needed to address how children exposed to ACEs can be supported to reduce risks of compromised adult resilience and health inequalities.

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Hilda Björk Daníelsdóttir, Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review and editing; Thor Aspelund, Data curation, Formal analysis, Methodology, Supervision, Writing – review and editing; Edda Bjork Thordardottir, Thorhildur Halldorsdottir, Arna Hauksdóttir, Methodology, Project administration, Resources, Writing – review and editing; Katja Fall, Fang Fang, Qian Yang, Karmel W Choi, Beatrice Kennedy, Writing – review and editing, Methodology; Gunnar Tómasson, Huan Song, Methodology, Project administration, Writing – review and editing; Harpa Rúnarsdóttir, Project administration, Writing – review and editing; Donghao Lu, Data curation, Methodology, Writing – review and editing; Jóhanna Jakobsdóttir, Data curation, Project administration, Writing – review and editing; Unnur Anna Valdimarsdóttir, Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Writing – original draft, Writing – review and editing

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Ethics

Human subjects: The study was approved by the National Bioethics Committee (NBC number: 17-238) and all participants gave informed consent before participation.

Decision letter and Author response

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Additional files

Supplementary files

- Transparent reporting form
- Reporting standard 1. Strobe Checklist.
- Source code 1. R scripts for the main analyses.

Data availability

The data used in this study are compiled in the Stress-And-Gene-Analysis (SAGA) cohort. We cannot make the data publicly available because of Icelandic laws regarding data protection and the approval for the current study granted by the National Bioethics Committee (NBC) of Iceland. The SAGA cohort contains extremely sensitive data and all use of data is restricted to scientific purposes only subjected to approval of the NBC (email: vsn@vsn.is). Interested researchers can obtain access to deidentified data by submitting a proposal to the SAGA cohort data management board (email: afallasaga@hi.is) which assists with submitting an amendment to the NBC. The corresponding author of the present study submitted a research proposal to the SAGA cohort data management board / the NBC and got access only to deidentified data, that cannot be shared in any way.

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Appendix 1

Perceived coping ability

The CD-RISC total scores were divided into quintiles which resulted in 21.50% of the sample in the lowest quintile (raw CD-RISC scores = 0–21), 20.95% in the lower middle quintile (raw CD-RISC scores = 22–26), 20.63% in the middle quintile (raw CD-RISC scores = 27–30), 17.99% in the higher middle quintile (raw CD-RISC scores = 31–34) and 18.93% in the highest quintile (raw CD-RISC scores = 35–40).

Covariate assessment

Social support was assessed with the Multidimensional Scale of Perceived Social Support (MSPSS) (***Zimet et al., 1988***). The instrument consists of 12 items answered on a 7-point scale ranging from 0 (very strongly disagree) to 6 (very strongly agree). Items were summed to create a total score ranging from 0 to 72, with higher scores indicating higher levels of perceived social support. In addition, the total scores were divided into quartiles which resulted in 25.09% of the sample in the lowest quartile (raw MSPSS scores = 0–49), 25.52% of the sample in the low-middle quartile (raw MSPSS scores = 50–61), 24.92% of the sample in the high-middle quartile (raw MSPSS scores = 62–69) and 24.47% of the sample in the highest quartile (raw MSPSS scores = 70–72). A categorical variable was then created where the highest tertile was used to define a high level of social support, the two middle quartiles were merged and used together to define a moderate level of social support and the lowest quartile was used to define a low level of social support. Happiness was assessed with the question "In general, how would you rate your happiness?", and participants rated their happiness with a slider ranging from 1 to 10.

Appendix 1—table 1. List of the 30 ACE-IQ items used to derive the 13 different ACEs and their response options.

ACE item	Scoring*
Neglect	
Emotional neglect	
Did your parents/guardians understand your problems and worries?	Always = 0, Most of the time = 1, Sometimes = 2, Rarely = 3, Never = 4
Did your parents/guardians really know what you were doing with your free time when you were not at school or work?	Always = 0, Most of the time = 1, Sometimes = 2, Rarely = 3, Never = 4
Physical neglect	
How often did your parents/guardians not give you enough food even when they could easily have done so?	Never = 0, Once = 1, A few times = 2, Many times = 3
Were your parents/guardians too drunk or intoxicated by drugs to take care of you?	Never = 0, Once = 1, A few times = 2, Many times = 3
How often did your parents/guardians not send you to school even when it was available?	Never = 0, Once = 1, A few times = 2, Many times = 3
Abuse	
Emotional abuse	
Did a parent, guardian or other household member yell, scream or swear at you, insult or humiliate you?	Never = 0, Once = 1, A few times = 2, Many times = 3
Did a parent, guardian or other household member threaten to, or actually, abandon you or throw you out of the house?	Never = 0, Once = 1, A few times = 2, Many times = 3
Physical abuse	
Did a parent, guardian or other household member spank, slap, kick, punch or beat you up?	Never = 0, Once = 1, A few times = 2, Many times = 3
Did a parent, guardian or other household member hit or cut you with an object, such as a stick (or cane), bottle, club, knife, whip etc?	Never = 0, Once = 1, A few times = 2, Many times = 3
Sexual abuse	

Appendix 1—table 1 Continued on next page

Appendix 1—table 1 Continued

ACE item	Scoring*
Did someone touch or fondle you in a sexual way when you did not want them to?	Never = 0, Once = 1, A few times = 2, Many times = 3
Did someone make you touch their body in a sexual way when you did not want them to?	Never = 0, Once = 1, A few times = 2, Many times = 3
Did someone attempt oral, anal, or vaginal intercourse with you when you did not want them to?	Never = 0, Once = 1, A few times = 2, Many times = 3
Did someone actually have oral, anal, or vaginal intercourse with you when you did not want them to?	Never = 0, Once = 1, A few times = 2, Many times = 3
Household dysfunction	
Domestic violence	
Did you see or hear a parent or household member in your home being yelled at, screamed at, sworn at, insulted or humiliated?	Never = 0, Once = 1, A few times = 2, Many times = 3
Did you see or hear a parent or household member in your home being slapped, kicked, punched or beaten up?	Never = 0, Once = 1, A few times = 2, Many times = 3
Did you see or hear a parent or household member in your home being hit or cut with an object, such as a stick (or cane), bottle, club, knife, whip etc.?	Never = 0, Once = 1, A few times = 2, Many times = 3
Lost a parent / separation of parents	
Were your parents ever separated or divorced?	No = 0, Yes = 1
Did your mother, father or guardian die?	No = 0, Yes = 1
Mental illness in household	
Did you live with a household member who was depressed, mentally ill or suicidal?	No = 0, Yes = 1
Household substance abuse	
Did you live with a household member who was a problem drinker or alcoholic, or misused street or prescription drugs?	No = 0, Yes = 1
Incarcerated household member	
Did you live with a household member who was ever sent to jail or prison?	No = 0, Yes = 1
Other violence	
Community violence	
Did you see or hear someone being beaten up in real life?	Never = 0, Once = 1, A few times = 2, Many times = 3
Did you see or hear someone being stabbed or shot in real life?	Never = 0, Once = 1, A few times = 2, Many times = 3
Did you see or hear someone being threatened with a knife or gun in real life?	Never = 0, Once = 1, A few times = 2, Many times = 3
Collective violence	
During the first 18 years of your life, were you exposed to war/ collective violence (e.g. from gangs or police)?†	No = 0, Yes = 1
Were you forced to go and live in another place due to any of these events?	Never = 0, Once = 1, A few times = 2, Many times = 3
Did you experience the deliberate destruction of your home due to any of these events?	Never = 0, Once = 1, A few times = 2, Many times = 3
Were you beaten up by soldiers, police, militia, or gangs?	Never = 0, Once = 1, A few times = 2, Many times = 3
Was a family member or friend killed or beaten up by soldiers, police, militia, or gangs?	Never = 0, Once = 1, A few times = 2, Many times = 3
Bullying	
How often were you bullied?	Never = 0, Once = 1, A few times = 2, Many times = 3

*all items also had the option „can't/don't want to answer".

†this is a screening question, only participants that responded yes got the following four questions.

Appendix 1—table 2. Rank order correlations for perceived coping (CD-RISC) and different measures of psychopathology used to derive the psychiatric resilience phenotype (n = 26,198).

	CD-RISC	PHQ-9	GAD-7	PCL-5	PSQI-A	Binge drinking
CD-RISC	1					
PHQ-9	–0.55	1				
GAD-7	–0.51	0.76	1			
PCL-5	–0.48	0.70	0.66	1		
PSQI-A	–0.41	0.62	0.62	0.63	1	
Binge drinking	–0.04	0.10	0.09	0.07	0.09	1

Appendix 1—table 3. Rank order correlations for ACE subtypes (n = 26,198).

	Emotional abuse	Physical abuse	Sexual abuse	Emotional neglect	Physical neglect	Domestic violence	Lost a parent/ separation	Mental illness in household	Household substance abuse	Incarcerated household member	Community violence	Collective violence	Bullying
Emotional abuse	1												
Physical abuse	0.46	1											
Sexual abuse	0.19	0.14	1										
Emotional neglect	0.36	0.23	0.22	1									
Physical neglect	0.29	0.18	0.14	0.27	1								
Domestic violence	0.51	0.31	0.18	0.34	0.30	1							
Lost a parent/ separation of parents	0.16	0.09	0.12	0.19	0.19	0.21	1						
Mental illness in household	0.33	0.18	0.14	0.26	0.23	0.37	0.19	1					
Household substance abuse	0.20	0.11	0.16	0.24	0.29	0.36	0.26	0.31	1				
Incarcerated household member	0.14	0.11	0.09	0.12	0.18	0.22	0.14	0.18	0.25	1			
Community violence	0.20	0.20	0.10	0.13	0.14	0.18	0.08	0.12	0.11	0.11	1		
Collective violence	0.09	0.08	0.06	0.07	0.08	0.09	0.06	0.07	0.06	0.10	0.11	1	
Bullying	0.21	0.16	0.13	0.15	0.11	0.15	0.06	0.16	0.08	0.06	0.12	0.08	1

Appendix 1—table 4. Associations between the number of ACEs and perceived coping ability (CD-RISC) and psychiatric resilience stratified by social support (n = 25,314) (β and 95% CI).

		Perceived coping ability			Psychiatric resilience		
	N (%)	Low support	Moderate support	High support	Low support	Moderate support	High support
Number of ACEs*							
0 ACE	5,024 (19.8)	0 (ref.)	0 (ref.)	0 (ref.)	0 (ref.)	0 (ref.)	0 (ref.)
1 ACE	5,407 (21.3)	–0.06 (–0.10,–0.02)	–0.05 (–0.06,–0.03)	–0.02 (–0.05,–0.00)	–0.10 (–0.14,–0.06)	–0.07 (–0.09,–0.05)	–0.05 (–0.07,–0.03)
2 ACE	4,356 (17.2)	–0.08 (–0.12,–0.05)	–0.06 (–0.08,–0.04)	–0.06 (–0.08,–0.03)	–0.13 (–0.16,–0.09)	–0.11 (–0.13,–0.09)	–0.09 (–0.11,–0.07)
3–4 ACE	5,419 (21.4)	–0.11 (–0.14,–0.07)	–0.09 (–0.11,–0.07)	–0.08 (–0.11,–0.06)	–0.22 (–0.25,–0.17)	–0.16 (–0.18,–0.14)	–0.13 (–0.16,–0.10)
≥ 5 ACEs	5,108 (20.2)	–0.14 (–0.17,–0.10)	–0.10 (–0.12,–0.08)	–0.08 (–0.11,–0.05)	–0.32 (–0.36,–0.28)	–0.27 (–0.29,–0.25)	–0.21 (–0.24,–0.1)

*Coefficients are standardized; adjusted for age, childhood deprivation, education level, civil status, employment status and income.

Appendix 1—table 5. Associations between the number of ACEs (excluding parental divorce/ separation) and perceived coping ability (CD-RISC) and psychiatric resilience (β and 95% CI)*.

		Perceived coping ability		Psychiatric resilience	
	N (%)	Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]
Number of ACEs*					
0 ACE	6,095 (23.3)	0 (ref.)	0 (ref.)	0 (ref.)	0 (ref.)
1 ACE	6,201 (23.7)	–0.08 (–0.09,–0.06)	–0.06 (–0.08,–0.05)	–0.10 (–0.11,–0.08)	–0.08 (–0.10,–0.07)
2 ACE	4,877 (18.6)	–0.12 (–0.13,–0.10)	–0.10 (–0.11,–0.08)	–0.16 (–0.17,–0.14)	–0.14 (–0.16,–0.13)
3–4 ACE	5,582 (21.3)	–0.18 (–0.19,–0.16)	–0.14 (–0.16,–0.13)	–0.25 (–0.27,–0.24)	–0.23 (–0.24,–0.21)
≥ 5 ACEs	3,443 (13.1)	–0.20 (–0.21,–0.19)	–0.15 (–0.15,–0.12)	–0.33 (–0.35,–0.32)	–0.29 (–0.30,–0.28)

*Coefficients are standardized; [a]adjusted for age and childhood deprivation; [b]additionally adjusted for education level, civil status, employment status and income.

Appendix 1—table 6. Associations between the number of ACEs and perceived coping ability (CD-RISC) and psychiatric resilience excluding participants with ≈10% lowest and highest happiness values (raw scores 1–5 and 10) (n = 15,449) (β and 95% CI)*.

		Perceived coping ability		Psychiatric resilience	
	N (%)	Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]
Number of ACEs*					
0 ACE	4,088 (20.38)	0 (ref.)	0 (ref.)	0 (ref.)	0 (ref.)
1 ACE	4,384 (21.86)	–0.05 (–0.07,–0.04)	–0.04 (–0.06,–0.02)	–0.09 (–0.10,–0.07)	–0.08 (–0.09,–0.06)
2 ACE	3,573 (17.82)	–0.08 (–0.09,–0.06)	–0.06 (–0.08,–0.05)	–0.12 (–0.14,–0.11)	–0.11 (–0.13,–0.10)
3–4 ACE	4,341 (21.65)	–0.12 (–0.14,–0.10)	–0.10 (–0.12,–0.08)	–0.19 (–0.20,–0.17)	–0.17 (–0.19,–0.16)
≥ 5 ACEs	3,669 (18.29)	–0.15 (–0.17,–0.13)	–0.12 (–0.13,–0.10)	–0.31 (–0.33,–0.29)	–0.28 (–0.30,–0.27)

*Coefficients are standardized; [a]adjusted for age and childhood deprivation; [b]additionally adjusted for education level, civil status, employment status and income.

Appendix 1—table 7. Associations between the number of ACEs and perceived coping ability (CD-RISC) and psychiatric resilience (β and 95% CI)*, complete case analyses.

		Perceived coping ability		Psychiatric resilience	
	N (%)	Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]
ACE-IQ total score*	19,637	–0.18 (-0.19,–0.16)	–0.13 (-0.15,–0.12)	–0.31 (-0.32,–0.30)	–0.28 (-0.29,–0.26)
Number of ACEs					
0 ACE	4,377 (22.3)	0 (ref.)	0 (ref.)	0 (ref.)	0 (ref.)
1 ACE	4,496 (22.9)	–0.07 (-0.09,–0.05)	–0.06 (-0.07,–0.04)	–0.08 (-0.10,–0.06)	–0.07 (-0.09,–0.05)
2 ACE	3,437 (17.5)	–0.10 (-0.11,–0.08)	–0.08 (-0.10,–0.06)	–0.13 (-0.14,–0.11)	–0.11 (-0.13,–0.10)
3–4 ACE	3,985 (20.3)	–0.14 (-0.16,–0.13)	–0.12 (-0.14,–0.10)	–0.20 (-0.21,–0.18)	–0.18 (-0.19,–0.16)
≥ 5 ACEs	3,342 (17.0)	–0.20 (-0.22,–0.18)	–0.15 (-0.17,–0.14)	–0.33 (-0.35,–0.31)	–0.29 (-0.31,–0.27)

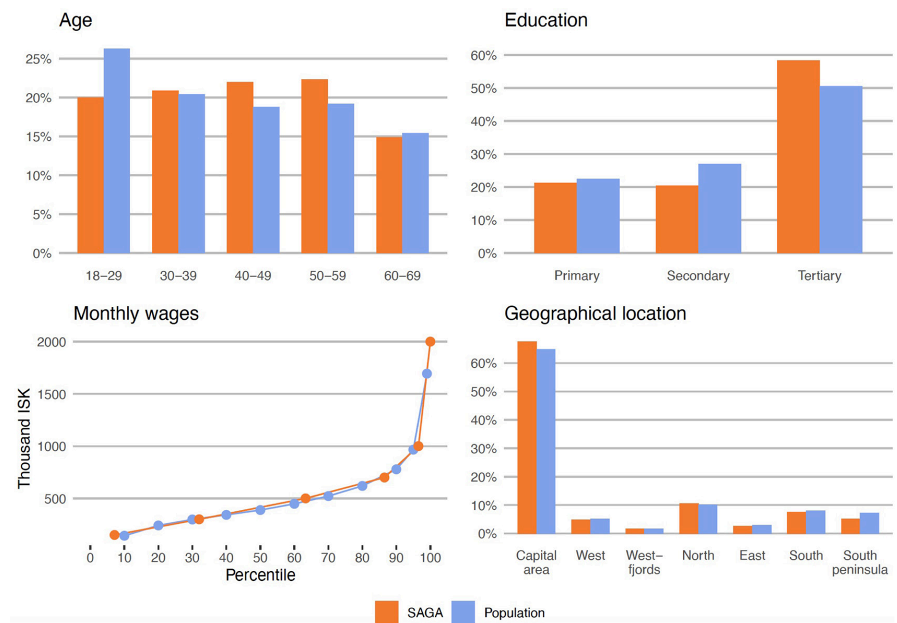
*Coefficients are standardized; **per 1 SD unit increase in ACE-IQ scores; [a]adjusted for age and childhood deprivation; [b]additionally adjusted for education level, civil status, employment status and income.

Appendix 1—table 8 Continued on next page

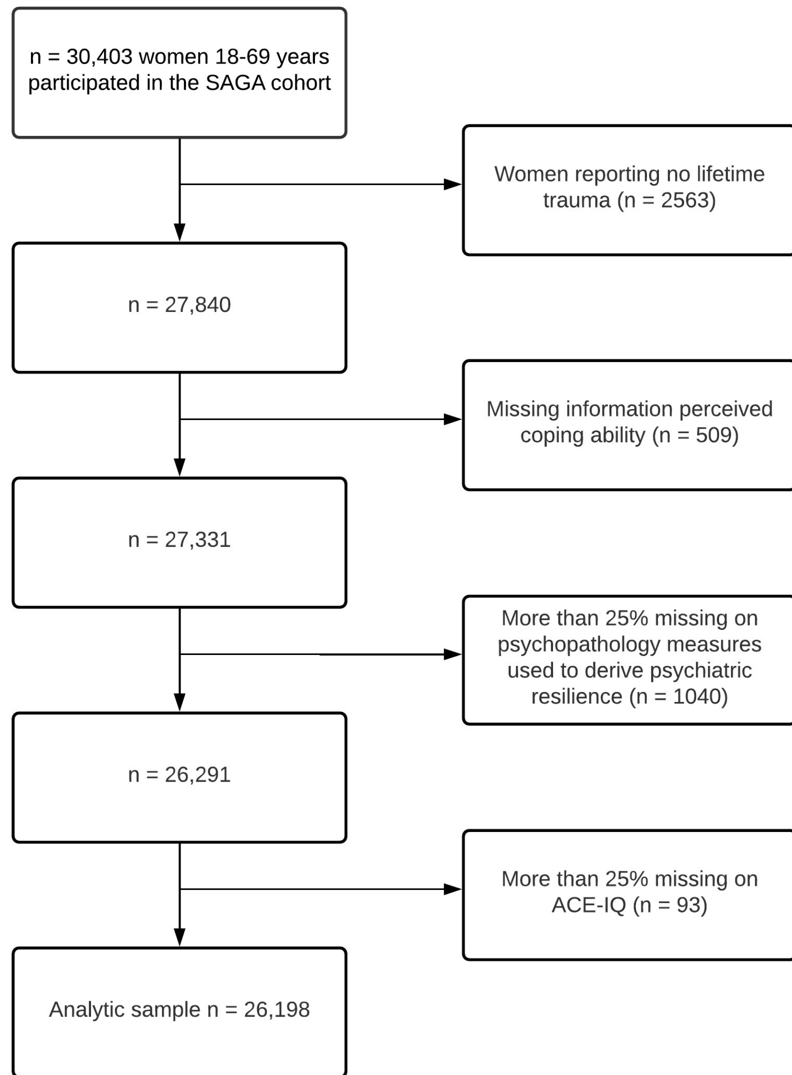
Appendix 1—table 8. Prevalence Ratios (with 95% CI) of high perceived coping ability (CD-RISC ≥35) and high psychiatric resilience (absence of psychiatric morbidity) in relation to the number of ACEs, complete case analyses.

		High perceived coping ability		High psychiatric resilience	
	N (%)	Model 1*	Model 2[b]	Model 1*	Model 2[b]
ACE-IQ total score*	19,637	0.92 (0.90, 0.93)	0.94 (0.92, 0.95)	0.86 (0.85, 0.87)	0.87 (0.87, 0.88)
Number of ACEs					
0 ACE	4,377 (22.3)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
1 ACE	4,496 (22.9)	0.83 (0.77, 0.89)	0.87 (0.81, 0.93)	0.84 (0.81, 0.87)	0.86 (0.83, 0.89)
2 ACE	3,437 (17.5)	0.73 (0.67, 0.79)	0.77 (0.71, 0.83)	0.74 (0.71, 0.78)	0.76 (0.73, 0.80)
3–4 ACE	3,985 (20.3)	0.66 (0.60, 0.71)	0.70 (0.65, 0.76)	0.62 (0.59, 0.65)	0.65 (0.62, 0.68)
≥ 5 ACEs	3,342 (17.0)	0.59 (0.53, 0.65)	0.67 (0.60, 0.74)	0.41 (0.38, 0.44)	0.44 (0.41, 0.48)

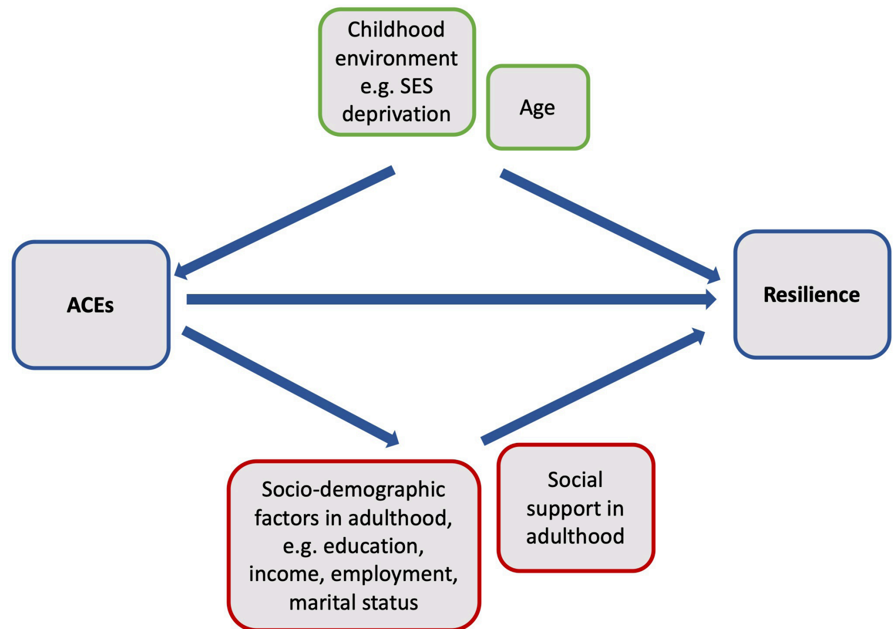
*adjusted for age and childhood deprivation; [b]additionally adjusted for education level, civil status, employment status and income.



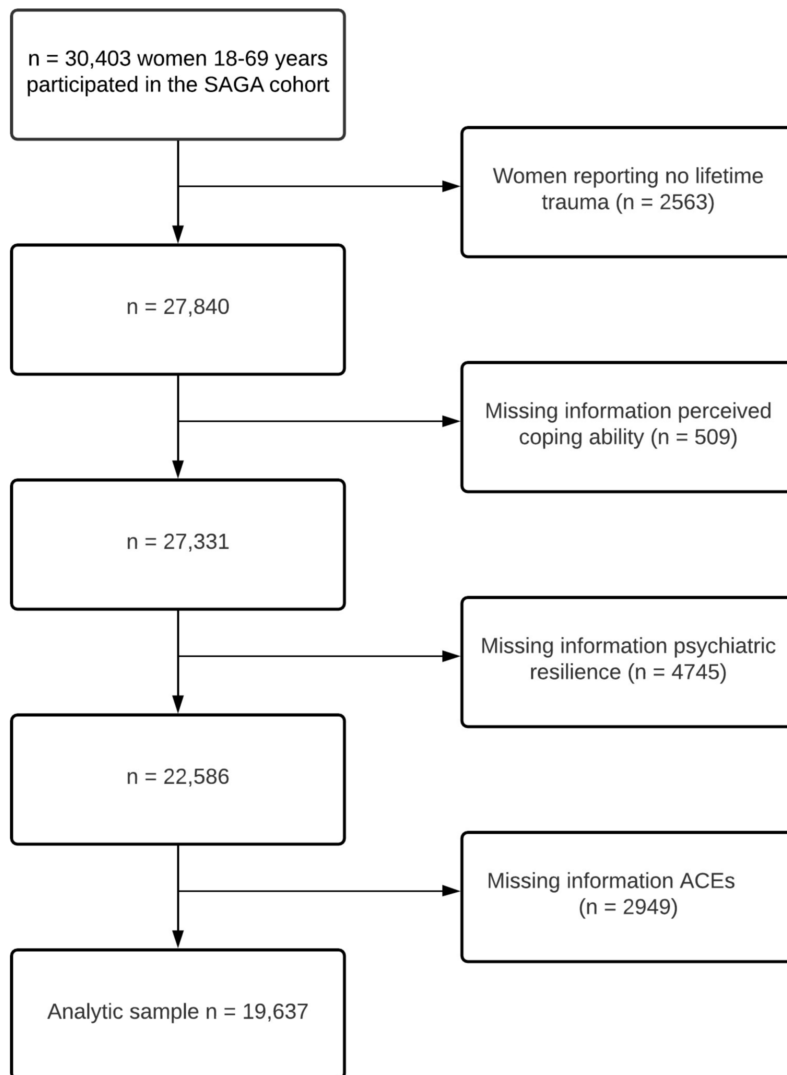
Appendix 1—figure 1. Sociodemographic characteristics of SAGA participants vs. the general female population of Iceland (see further: https://www.afallasaga.is/nidurstodur).



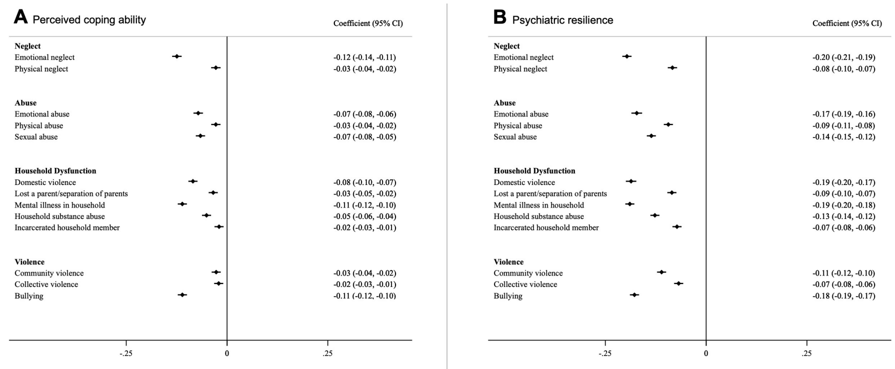
Appendix 1—figure 2. Flow-chart of the analytic sample.



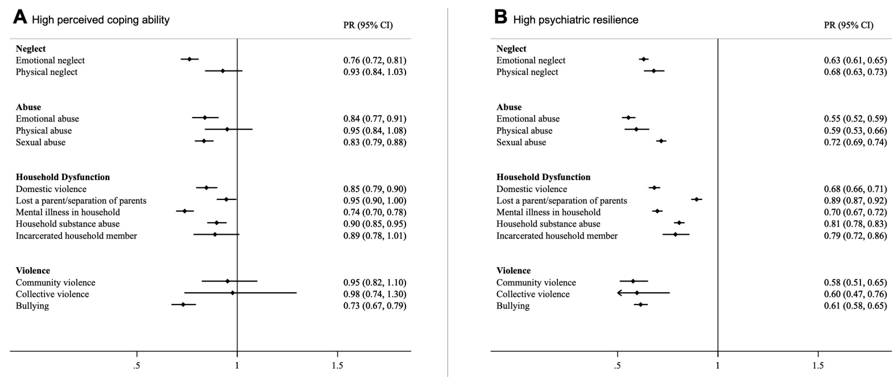
Appendix 1—figure 3. Proposed causal model with alternative pathways of how ACEs could influence resilience in adulthood.
Note: Boxes in green indicate potential confounders of the association between ACEs and adult resilience, whereas boxes in red indicate potential mediators of the association.



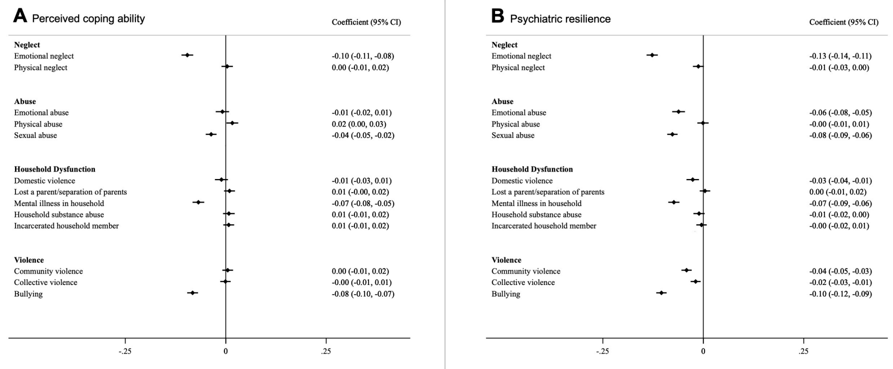
Appendix 1—figure 4. Flow-chart of the analytic sample (complete case analysis).



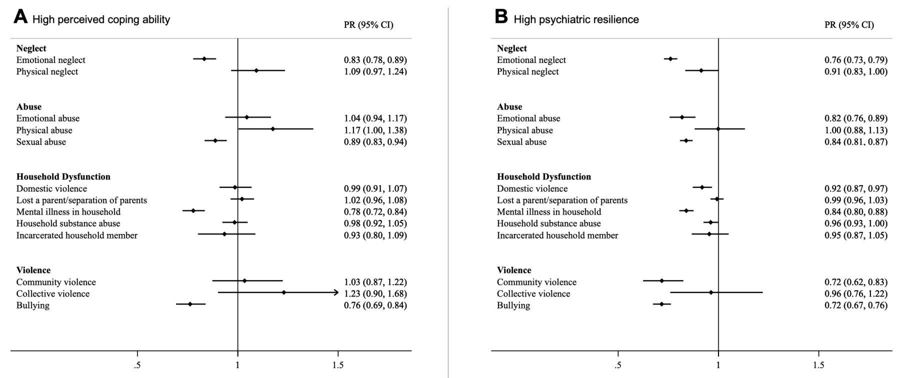
Appendix 1—figure 5. Associations between different types of ACEs and perceived coping ability (**A**) and psychiatric resilience (**B**) (β and 95% CI). Models were corrected for age, childhood deprivation, education level, civil status, employment status and income. *Coefficients are standardized.



Appendix 1—figure 6. Prevalence Ratios (with 95% CI) of high perceived coping ability (**A**) and high psychiatric resilience (**B**) in relation to individual ACEs. Models were corrected for age, childhood deprivation, education level, civil status, employment status and income.



Appendix 1—figure 7. Associations between different types of ACEs and perceived coping ability (**A**) and psychiatric resilience (**B**) (β and 95% CI), complete case analyses (n = 19,637). Models were corrected for age, childhood deprivation, educational level, civil status, employment status, income and mutually adjusted for other ACEs. *Coefficients are standardized.



Appendix 1—figure 8. Prevalence Ratios (with 95% CI) of high perceived coping ability (**A**) and high psychiatric resilience (**B**) in relation to individual ACEs, complete case analyses (n = 19,637). Models were corrected for age, childhood deprivation, educational level, civil status, employment status, income and mutually adjusted for other ACEs.

Paper III

Paper III

Title: Genetic and environmental contributions to psychiatric resilience after childhood trauma: A Swedish twin study

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Background: Adverse childhood experiences (ACEs) are associated with an elevated risk of mental health problems, yet, not all individuals exposed to ACEs suffer mental health morbidities in adulthood, i.e. they remain resilient. However, what factors contribute to resilience after childhood adversity remains largely unknown.

Objective: We aimed to study the relative contribution of genetic and environmental factors to individual variation in adult resilience in the context of ACEs.

Method: We used data from the Swedish Twin Registry, comprising 8,606 twin individuals (n=3,408 monozygotic pairs, n=5,198 dizygotic pairs), aged 21 to 47 years, reporting at least one of the follwing ACEs: family violence, emotional abuse/neglect, physical neglect, physical abuse, sexual abuse, rape, and hate crime. We obtained information about first adult clinical diagnosis of a psychiatric disorder (i.e., anxiety, depression, substance abuse and stress-related disorders) from the Swedish National Patient Register and dispensed antidepressants and anxiolytics from the Swedish Prescribed Drug Register, defining the absence of such indications as resilience to ACEs. We used structural equation models to estimate the relative contribution of genetic and environmental factors to the variation in adult resilience in the context of ACEs. In addition, we used polygenic risk scores (PRS) for 6 psychiatric traits, to assess the association between genetic liability for these traits and resilience after ACEs.

Results: Genetic and non-shared environmental factors contributed to variation in the ACE resilience phenotype, 0.40 (95% CI 0.28-0.52) and 0.60 (95% CI 0.48-0.72) respectively, while we found no evidence of a shared environmental component. The PRS analyses revealed that genetic liability for all psychiatric traits was associated with reduced odds of ACE resilience (e.g., OR per standard-deviation increase in PRS for major depressive disorder = 0.75; 95% CI 0.70-0.80).

Discussion: These data suggest that variation in resilience after exposure to ACEs is influenced by both genetic and non-shared environmental factors. Further characterization of the specific contributing genetic and environmental factors is needed for targeted interventions aimed at enhancing resilience.

Background

Adverse childhood experiences (ACEs) are severe experiences, conditions or intensive stressors that occur in childhood or adolescence, including emotional and physical abuse or neglect and growing up in dysfunctional home environments (e.g., parental substance abuse or witnessing domestic violence) (Anda, Butchart, Felitti, & Brown, 2010). Although ACEs have consistently been associated with poor mental health outcomes extending into adulthood (Hughes et al., 2017; Li, D'Arcy, & Meng, 2016; Petruccelli, Davis, & Berman, 2019; Scott, Smith, & Ellis, 2010), there is considerable heterogeneity in long-term outcomes after exposure to ACEs (Kuzminskaite et al., 2021). That is, despite the robust link between ACEs and psychiatric symptoms and disorders, many individuals with a history of ACEs do not experience prolonged psychiatric symptoms extending into adulthood (Galatzer-Levy, Huang, & Bonanno, 2018). Indeed, previous research indicates that roughly 40% to 60% of ACE exposed children demonstrate resilient outcomes (S. Luthar, 2006; Masten, 2001).

Resilience is broadly defined as positive psychological functioning or maintained mental health in the context of significant exposure to trauma or adversity (Kalisch et al., 2017; S. S. Luthar, Cicchetti, & Becker, 2000; Rutter, 2006). The conceptual definition of resilience entails two essential components: a) experiencing significant trauma or adversity, and b) an achievement of positive adaptation (Garmezy, Masten, & Tellegen, 1984; S. S. Luthar et al., 2000; Masten, Lucke, Nelson, & Stallworthy, 2021). Indeed, one way to operationalize resilience is as the absence of PTSD or other psychiatric disorders among individuals exposed to traumatic events (Nishimi et al., 2021; Sheerin, Stratton, Amstadter, Education, & McDonald, 2018).

The determinants of resilience are multifactorial (Cicchetti, 2010), ranging from cognitive or psychological factors (e.g., self-efficacy and problem solving skills) to broader environmental factors (e.g., availability of social support and community resources).

Moreover, accumulating evidence point towards a considerable genetic contribution to variation in resilience. Twins offer a natural experiment to assess the relative contribution of genetic (i.e., heritability) and environmental factors to variability in a phenotype by comparing observed resemblance between MZ and DZ twins (Boomsma, Busjahn, & Peltonen, 2002; Hagenbeek et al., 2023). Results from twin studies indicate that between 25% and 50% of variance in resilience to lifetime or past-year stressors can be explained by genetic factors (Ananda B. Amstadter, Myers, & Kendler, 2014; Boardman, Blalock, & Button, 2008; Hofgaard, Nes, & Røysamb, 2021). These studies have conceptualized resilience based on residuals of positive affect (Boardman et al., 2008), or internalizing symptoms (Ananda B. Amstadter et al., 2014; Hofgaard et al., 2021) after lifetime stressors (Boardman et al., 2008; Hofgaard et al., 2021), or past year stressors (Ananda B. Amstadter et al., 2014) have been regressed out. To the best of our knowledge, no previous twin study has estimated the heritability of resilience among individuals exposed to significant childhood adversity.

Therefore, leveraging a large sample of Swedish twins, we aimed to examine the relative contribution of genetic and environmental factors to the variation in resilience, conceptualized as absence of psychiatric morbidity among adults reporting exposure to ACEs. In addition, we aimed to assess whether genetic liability for common psychiatric traits was associated with resilience among individuals exposed to ACEs.

Methods

Data sources / Study participants

Data from two birth cohorts of twins derived from the Swedish Twin Registry were used in the current study; The Study of Twin Adults: Genes and Environment (STAGE) and The Young Adult Twins in Sweden Study (YATSS). The STAGE study population includes Swedish twins born between 1959 and 1985 (N=25,313). A web-based data collection was carried out in 2005,

where participants answered an extensive questionnaire including sections on various traumatic experiences, and physical and mental health (Furberg et al., 2008; Lichtenstein et al., 2006). The YATSS study population includes Swedish twins born between 1986 and 1992 (N=6,860). During 2013 and 2014 participants answered an electronic questionnaire that consisted of questions evaluating various somatic and mental health symptoms, as well as questions about traumatic experiences in childhood (Zagai, Lichtenstein, Pedersen, & Magnusson, 2019). Furthermore, between 2017 and 2019, individuals from the STAGE and YATSS cohorts, who had previously donated saliva samples, were genotyped (Zagai et al., 2019). The STR cohorts were additionally linked to nationwide health registers (described below).

In both cohorts, zygosity was determined based on either DNA analysis or questions on intra-pair similarities during childhood, which had over 95% accuracy when validated against DNA testing (Lichtenstein et al., 2002). An ethical permit was granted by the regional ethical review board in Stockholm, Sweden (2018/960-31/2).

For the present analyses we excluded twins with unknown zygosity (2.19%). In addition, since trauma exposure is intrinsic to the conceptualisation of resilience, the analytic sample was restricted to twins reporting an ACE (see description of resilience below), which resulted in a final analytic sample of 8,606 twin individuals, of which 3,408 were MZ twins (732 complete twin-pairs), 2,522 were DZ same-sex twins (394 complete twin-pairs) and 2,676 were DZ opposite sex twins (323 complete twin-pairs) (see Table 1). Single twins were retained as they contribute to information relating to the prevalence of resilience.

Measures

Resilience

Resilience was defined as the absence of psychopathology among individuals exposed to ACEs. We therefore operationalized resilience by assessments in two domains: i) self-reported exposure to ACEs, and ii) independently assessed adult mental health outcomes.

ACEs were measured with seven items adapted from the Life Stressor Checklist-revised (LSC-R) (Wolfe & Kimerling, 1997). The instrument consists of 30 items assessing potentially traumatic life events according to DSM-IV criteria for PTSD as well as other traumatic events. For this study, seven yes/no questions from the LSC-R were used to assess exposure to the following ACEs: emotional neglect/abuse, physical neglect, physical abuse, sexual abuse, rape, hate crime, and witnessing family violence (see eTable 1 for a list of items). Follow-up questions were used to determine whether the seven LSC-R items were endorsed before 19 years. Since by definition resilience reflects „*relatively positive adaptation despite experiences of significant adversity or trauma*" (S. Luthar, 2006) one cannot be resilient without being exposed to adversity or trauma, and therefore in the current study, participants with no reported ACEs were excluded from the analytic sample.

Information about adult mental health outcomes was obtained from Swedish nationwide health registers. That is, using unique personal identification numbers, the STR was linked to the population-based Swedish National Patient Register (NPR) which has nationwide coverage for inpatient care since 1987 and outpatient specialized care since 2001 (Ludvigsson et al., 2011). Through these resources, we identified all individuals with any first inpatient or outpatient hospital visit that resulted in a diagnosis of depressive disorders, anxiety disorders, alcohol or drug misuse disorders and stress-related disorders, after their 19th birthday. The diagnoses were assigned in accordance with the International Classification of Diseases, eighth

revision (ICD-8), ninth revision (ICD-9), or tenth revision (ICD-10) (see eTable 2 for ICD codes). Data from the NPR were available until the end of 2016.

In addition, the STR was linked to the population-based Swedish Prescribed Drug Register (PDR), which includes all dispensations of prescribed drugs since 2005 (Wettermark et al., 2007). Since the NPR includes only information related to inpatient or specialised outpatient care, we additionally used information about dispensed antidepressants (ATC code N06A) or anxiolytics (ATC code N05B) as an indication of milder psychiatric disorders not requiring specialized care. Data from the PDR were available until the end of 2016.

Based on information from the NPR and PDR, we derived a primary and secondary phenotype of resilience. *Our main resilience phenotype* was operationalised as absence of clinically diagnosed psychiatric disorders (i.e., depression, anxiety, substance abuse and stress-related disorders) as well as absence of dispensed antidepressants and anxiolytics among individuals exposed to ACEs. To test the robustness of our results, we also conducted paralell analyses of resilience as absence of clinically diagnosed psychiatric disorders among individuals exposed to ACEs (disregarding information on medication use).

Polygenic risk scores

A total of 10,494 individuals from the STAGE and YATSS cohorts were genotyped using the 650K Illumina Global Screening Array (GSA) BeadChip (Zagai et al., 2019). To ensure quality of the genotype data, samples were processed using RICOPILI (Lam et al., 2020). Samples were filtered based on variant missingness, sex chromosome abnormalities, sex mismatch, unexpected relatedness patterns, per-sample call rate, and excessive heterozygosity. Variants were filtered based on per-SNP call rate, minor allele frequency (<0.01), and Hardy-Weinberg disequillibrium. For the STAGE and YATSS cohorts, 207,658 and 199,113 out of 700,078

measured variants, failed quality control. Imputation to the Haplotype Reference Consortium panel (HRC 1.1) was done using the Sanger imputation server (McCarthy et al., 2016).

Polygenic risk scores (PRS) were calculated for the sub-sample of individuals with available genotype data in our sample (n = 10,949), using GWAS summary statistics from the largest published studies available for PTSD (Nievergelt et al., 2019), major depressive disorder (MDD) (Als et al., 2023), anxiety (Purves et al., 2020), alcohol dependence (Walters et al., 2018), bipolar disorder (Mullins et al., 2021) and neuroticism (Nagel et al., 2018). The PRSs were estimated using Ldpred2-auto (Privé, Arbel, & Vilhjálmsson, 2020), with recommended parameter settings. The main hypothesis testing was done using a sample of n = 4013 with available genotype data and reporting at least one ACE.

Statistical analysis

The classical twin design allows partitioning of variance in a phenotype into genetic and environmental sources, capitalizing on the fact that MZ twins share all their genes while DZ twins share on average 50% of their segregating genes (Verweij, Mosing, Zietsch, & Medland, 2012). Sources of variance include *additive genetic* (*A*, sum of additive allelic effects across the genome), *dominance genetic* (*D*, interactions between alleles), *shared environmental* (*C*, environment shared by family members, e.g., prenatal environment or socio-economic conditions in childhood) and *unique environmental variance* (*E*, specific for individuals, contributes to differences between twins and also includes measurement error). In the classical twin design, it is assumed that A and D correlate 1.00 in MZ twins, while A is assumed to correlate 0.50 in DZ twins, and D is assumed to correlate 0.25. The C component is assumed to correlate 1.00 in both MZ and DZ twins, whereas E is uncorrelated in both MZ and DZ twins (Verweij et al., 2012).

Using these assumptions, we estimated the relative contribution of genetic and environmental factors to the liability of the resilience phenotype by fitting structural equation models using the packages OpenMx (version 2.20.6) (Neale et al., 2016) and umx (Bates, Maes, & Neale, 2019) in the R software. Since we conceptualized resilience as a binary trait, we used a liability threshold model where the observation of being resilient or not in each individual is assumed to reflect an underlying normally distributed liability. Before fitting twin models, we used saturated models to assess assumptions of equal thresholds across twin order and zygosity, and observed no violations (see eTable 3).

Next, we estimated cross-twin correlations (tetrachoric correlations since resilience is a binary trait), with a constrained saturated model where the thresholds were equated across twin order and across zygosity (correlations were adjusted for sex and birthyear). Cross-twin correlations indicate the degree to which each phenotype correlates within twin-pairs.

It should be noted that C and D cannot be estimated simultaneously, as they are confounded in the classical twin design. Therefore, we started by fitting separate ACE and ADE models. Next, we fitted AE models to determine whether the C or D parameters could be excluded from either the ACE or ADE models without a significant loss in model fit. Likelihood ratio tests were used to compare the goodness of fit between the saturated model and the ACE/ADE models. In addition, the ACE/ADE models were compared to nested submodels (AE). Akaikes Information Criterion (AIC; a lower value is better) was used for model comparison. All models were adjusted for sex and birth year. Birth year was adjusted for using a 2 degree-of-freedom polynomial.

Finally, to examine the association between genetic liability to the psychiatric traits (disorders and neuroticism) and resilience, we conducted PRS analyses. First, to validate the PRSs we assessed the association between each PRS and their respective trait/disorder (e.g., we tested the association between $PRS_{anxiety}$ and clinically diagnosed anxiety). Next, we

assessed associations between the PRSs and resilience. The associations between the PRSs and outcomes (i.e., each respective trait/disorder and the resilience phenotype) were estimated using generalized estimating equations (GEE) with cluster robust standard errors (i.e., using sandwich estimation on twin-pair ID) to adjust for the lack of independence of twin data. Since we operationalized resilience as a binary variable, we estimated odds ratios (OR), and included sex, birthyear, and 10 principal components of the genetic relatedness matrix as covariates in the models.

Results

Characteristics of the sample

Descriptive statistics of the sample are presented in Table 1. Among the 8,606 individual twins that reported at least one ACEs, 5,240 twin individuals were categorized as resilient (Table 1), whereas 7,199 twin individuals were categorized as resilient according to our secondary resilience phenotype (eTable 4).

Cross-twin correlations

The DZ twin correlations were less than half of the MZ twin correlations (MZ twins $r = 0.47$, 95% CI 0.37-0.57; DZ twins $r = 0.17$, 95% CI 0.05-0.28), suggesting that dominance genetic factors (D) rather than shared familial factors (C) play a role. Similar correlations were observed for an alternative definition of resilience (eTable 5).

The structural equation models

The model fitting results for the twin models are presented in Table 2. According to the likelihood ratio tests, the ACE/ADE models did not fit the observed data significantly worse than the saturated model. However, in the ACE model the C parameter was estimated at 0

(Table 3), and the AE model did not fit the data significantly worse than the ACE model (Table 2). Furthermore, the ADE model had large 95% CIs for the A and D parameters (ranging from -0.51 to 0.96, see Table 3) suggesting that these parameters are poorly identified in this model. Correspondingly the AE model did not fit the data significantly worse than the ADE model (Table 2). Taken together, with the lowest AIC, the AE model showed the best fit to the data (Table 2). In this model, the heritability of the primary ACE resilience phenotype was 0.40 (95% CI 0.28-0.52), and the unique environment effect was 0.60 (95% CI 0.48-0.72). These findings were confirmed using an alternative definition of resilience (disregarding information on prescription of antidepressants and anxiolytics) (eTable 6 and 7).

The PRS analyses

As expected, higher PRSs for PTSD, MDD, anxiety and bipolar disorder were associated with higher odds of receiving a diagnosis of the respective disorder (eFigure 1) while the PRS for alcohol dependence was not associated with a substance abuse diagnosis in this cohort of twins (and was therefore not used in the main hypothesis testing). Higher neuroticism-PRS was correspondingly associated with higher scores on the neuroticism scale from the Eysenck Personality Questionnaire-Revised in STAGE (β=0.64, 95% CI 0.55-0.73). The PRSs for PTSD, MDD, anxiety, bipolar disorder and neuroticism were associated with reduced odds of the ACE resilience phenotype (Figure 1). The MDD-PRS had the strongest association with resilience, i.e., one standard-deviation increase in MDD-PRS was associated with a 25% reduction in resilience (OR = 0.75 per standard-deviation increase in PRS; 95% CI 0.70-0.80). We found similar results using an alternative definition of resilience (i.e., disregarding information on prescription of antidepressants and anxiolytics; eFigure 2).

Discussion

Using a large sample of Swedish twins, we examined the etiology of resilience, conceptualised as the absence of clinically confirmed psychiatric disorders (i.e., depressive, anxiety, substance misuse, or stress-related disorders) as well as absence of dispensed antidepressants and anxiolytics among adult twins exposed to ACEs. We found that the variation in adult resilience after exposure to ACEs was attributed to both genetic and individual specific environmental influences. In parallel, we found that genetic liability for psychiatric traits (i.e., neuroticism, PTSD, MDD, anxiety and bipolar disorder) predicted reduced odds of adult resilience to ACEs.

Our finding that 40% of the variance in adult resilience to ACEs is due to genetic factors is in line with existing studies on resilience to past-year stressors, which reported a heritability of 38%-52% (Ananda B. Amstadter et al., 2014; Boardman et al., 2008). The heritability to life-time stressors seems to be slightly lower, or 24%-30% (Hofgaard et al., 2021). Perhaps somewhat surprisingly, we found that environmental factors shared by members within twin pairs had negligible influence on adult resilience to ACEs. This is, however, in accordance to previous twin studies on resilience among adults (in the context of lifetime or past-year stressors) (A. B. Amstadter et al., 2016; Ananda B. Amstadter et al., 2014; Boardman et al., 2008; Hofgaard et al., 2021), while in contrast to studies that have found that children's resilience to disadvantage is influenced by shared environmental factors (Kim-Cohen, Moffitt, Caspi, & Taylor, 2004; Vazquez et al., 2021).

Our results, however, indicate a major role of environmental effects in adult resilience to ACEs that are unique to individuals. That is, we found that a substantial proportion of the variation of adult resilience to ACEs is shaped by individual-specific environmental factors. This emphasises the potential for environmental efforts to facilitate adult resilience among individuals exposed to ACEs.

Furthermore, we found that genetic liability for psychiatric traits (i.e., neuroticism, PTSD, MDD, anxiety and bipolar disorder) significantly predicted reduced odds of adult resilience to ACEs. These results provide evidence that psychiatric traits and resilience are partly influenced by overlapping genetic factors,

The main strengths of the study include the large nationwide twin sample, which allowed us to confine the sample to twins reporting an ACE and evaluate the etiology of resilience in an exclusively high-risk twin sample. Furthermore, we believe another strength of our study was to operationalise resilience based on a combination of self-report (ACEs) and independently ascertained psychiatric morbidity obtained through linkages to national registers.

However, our study also has several limitations. First, resilience reflects a dynamic process that unfolds during or after adversity (S. S. Luthar et al., 2000; Rutter, 2006) and while we operationalize resilience as the outcome of this process we cannot fully capture the process of resilience that unfolds after ACEs. Future research would benefit from a longitudinal design including repeated measurements of trauma and psychopathology to better capture the dynamic process of resilience as adaptive functioning following adversity. Second, ACEs were retrospectively reported and may thus be subject to recall bias. Although this is a common approach for assessing ACEs, we cannot exclude the possibility that current mental health symptoms affected the reporting of ACEs (Danese & Widom, 2020; Reuben et al., 2016). To triangulate evidence, future research could investigate adult resilience in the context of objective ACE indicators, obtained through official records such as child protection services. Finally, given that our assessment of ACEs was based on selected items from the LSC-R, we may have missed several important ACE domains, such as exposure to bullying. Therefore, a more thorough ACE assessment is warranted in future studies examining the etiology of adult resilience to ACEs.

Conclusion

Taken together, our findings demonstrate that individual differences in adult resilience to ACEs are attributable to both genetic and individual-specific environmental factors. We further found in PRS analyses that genetic liability for several psychiatric traits was associated with lower odds of adult resilience to ACEs, providing supportive evidence that psychiatric traits and resilience are influenced by overlapping genetic factors. The contribution of individual-specific environmental factors highlights the need for continued development of interventions to enhance resilience among individuals exposed to ACEs. At the same time, the observed genetic contribution motivates further studies identifying genetic loci and biological factors underlying adult resilience.

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Main Tables and Figures

Table 1. Descriptive characteristics of the analytic sample

	Overall	Resilience	
		Resilient	Not resilient
Total, n	8606	5240	3366
Age at survey, mean (SD)	32.0 (7.91)	31.8 (7.91)	32.4 (7.91)
Birthyears, n (%)			
1959-1963	1418 (16.5)	812 (15.5)	606 (18.0)
1964-1968	1480 (17.2)	886 (16.9)	594 (17.6)
1969-1973	1291 (15.0)	786 (15.0)	505 (15.0)
1974-1978	1182 (13.7)	723 (13.8)	459 (13.6)
1979-1983	1380 (16.0)	866 (16.5)	514 (15.3)
1984-1988	1125 (13.1)	692 (13.2)	433 (12.9)
1989-1992	730 (8.5)	475 (9.1)	255 (7.6)
Sex, n (%)			
Male	3127 (36.3)	2235 (42.7)	892 (26.5)
Female	5479 (63.7)	3005 (57.3)	2474 (73.5)
Zygosity, n (%)			
MZ	3408 (39.6)	2091 (39.9)	1317 (39.1)
Twins from complete pairs	1464 (42.9)	586 (28.0)	392 (29.8)
DZ same sex	2522 (29.3)	1539 (29.4)	983 (29.2)
Twins from complete pairs	788 (31.2)	306 (19.9)	162 (16.5)
DZ opposite sex	2676 (31.1)	1610 (30.7)	1066 (31.7)
Twins from complete pairs	646 (24.1)	280 (17.4)	84 (7.9)

Note. Resilience is operationalized as absence of clinically diagnosed psychiatric disorders as well as absence of dispensed antidepressants and anxiolytics among ACE exposed individuals.

Table 2. Model fitting results from the structural equation models estimating the relative genetic and environmental contribution to variation in resilience.

	Base model	Comparison model	-2LL	df	AIC	Δ-2LL	Δdf	p
I	Saturated		11187.4	8597	11205.4			
II	ADE	I	11188.3	8600	11202.3	0.91	3	0.82
III	AE	II	11189.5	8601	11201.5	1.15	1	0.28
IV	ACE	I	11189.5	8600	11203.5	2.06	3	0.56
V	AE	IV	11189.5	8601	11201.5	0.00	1	1

All models are adjusted for sex and birthyear; -2LL = minus two log-likelihood;AIC = Akaike Information Criterion; df = degrees of freedom. A lower AIC represents a better model fit. A non significant p-value ($p>0.05$) indicates that the base model does not dit the data significantly worse than the comparison model.

Table 3. Parameter estimates from the structural equation models estimating the relative genetic and environmental contribution to variation in resilience.*

	A	D/C	E
ADE	0.16 (-0.51, 0.82)	0.27 (-0.43, 0.96)	0.58 (0.45, 0.71)
ACE	0.40 (0.28, 0.52)	0.00 (-0.00, 0.00)	0.60 (0.48, 0.72)
AE	0.40 (0.28, 0.52)	NA	0.60 (0.48, 0.72)

All models are adjusted for sex and birthyear; A = Additive genetics; D = Dominance genetics; C = Shared environment; E = Unique environment & measurement error.

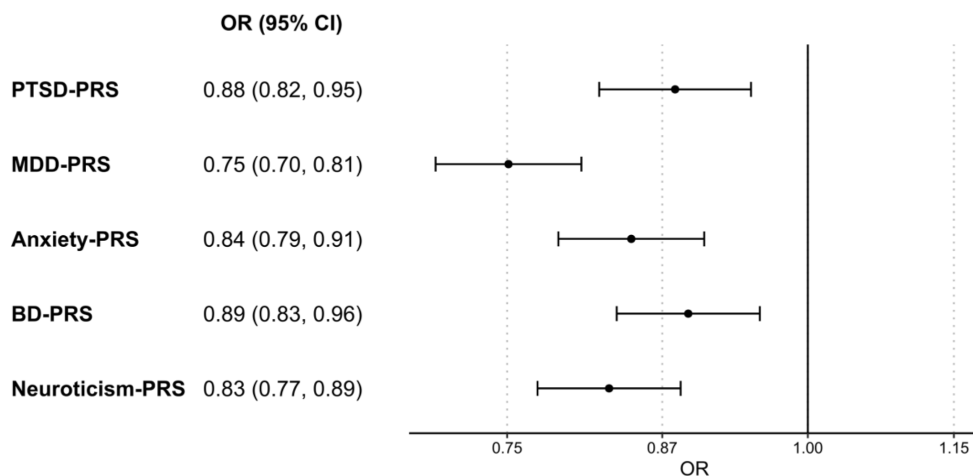


Figure 1. Associations between PRSs for psychiatric traits and resilience.
Models were adjusted for sex, birthyear, and 10 principal components. OR = Odds Ratio for every standard-deviation increase in PRS. BD = bipolar disorder. PTSD = posttraumatic stress disorder. MDD = major depressive disorder.

Supplementary Materials

eTable 1. Items applied from the Life Stressor Checklist-revised (plus hate crime)* to assess ACEs in the Swedish Twin Registry

Type of ACE	Item
Family violence	When you were young, before age 18, did you ever see physical violence between family members? For example, hitting, kicking or punching?
Emotional neglect/abuse	Have you ever been emotionally abused or neglected – for example, being frequently shamed, embarrassed, ignored, or repeatedly told that you were “no good”?
Physical neglect	Have you ever been physically neglected – for example, not fed, not properly clothed, or left to take care of yourself when you felt you were too young or ill?
Physical abuse	Have you ever been physically abused – for example, hit, choked, burned, or beaten, or severely punished, for example, locked up in a closet, tied up, or chained – by someone you knew well such as a parent, sibling, boyfriend or girlfriend?
Sexual abuse	Were you ever touched or made to touch someone else in a sexual way, because you felt forced in some way or threatened by harm to yourself or someone else?
Rape	Did you ever have sex because you felt forced in some way or threatened by harm to yourself or someone else? With sex, we mean orally, anally, and/or genitally
Hate crime	Have you ever been victim of a hate crime? This could include being subject to violence because of your race, ethnicity, gender, sexual orientation or religion.

*Hate crime was not included in the original Life Stressor Checklist-revised.

eTable 2. International Classification of Diseases (ICD) codes, eight (ICD-8; 1969-1986), ninth (ICD-9; 1987-1996), and tenth (ICD-10; 1997-2016) used to identify psychiatric disorders.

Psychiatric diagnosis	ICD-8	ICD-9	ICD-10
Alcohol or drug misuse disorders	303, 304	291E, 292.0, 303, 304, 305	F10-F19
Depressive disorders	296.0, 300.4	296, 311	F32-F34, F38-F39
Anxiety disorders	300.0, 300.1	300A, 300C, 300D	F40, F41, F42, F44
Stress-related disorders	307	308, 309	F43

Note. Based on the Swedish version of the ICD version 8, 9 and 10 codes for the identification of diagnosis.

eTable 3. Assumption testing for the twin structural equation models for the different resilience phenotypes (adjusted sex and birth year)

Model	-2LL	df	AIC	ΔLL	Δdf	p
Main resilience phenotype (based on ICD and ATC codes)						
Fully saturated model	11187.42	8597	11205.42	NA	NA	NA
Equal thresholds within same-sex twin-pairs	11187.60	8599	11201.60	0.19	2	0.91
Equal thresholds across zygosity for same-sex twin-pairs	11188.32	8600	11200.32	0.91	3	0.82
Secondary resilience phenotype (based on ICD codes)						
Fully saturated model	7574.617	8597	7592.617	NA	NA	NA
Equal thresholds within same-sex twin-pairs	7574.824	8599	7588.824	0.21	2	0.90
Equal thresholds across zygosity for same-sex twin-pairs	7575.320	8600	7587.320	0.70	3	0.87

eTable 4. Descriptive characteristics of the analytic sample by the secondary resilience phenotype.

	Overall	Resilience	
		Resilient	Not resilient
Total, n	8606	7199	1407
Age at survey, mean (SD)	32.0 (7.91)	31.8 (7.91)	32.1 (7.92)
Birthyears, n (%)			
1959-1963	1418 (16.5)	1185 (16.5)	233 (16.6)
1964-1968	1480 (17.2)	1254 (17.4)	226 (16.1)
1969-1973	1291 (15.0)	1094 (15.2)	197 (14.0)
1974-1978	1182 (13.7)	992 (13.8)	190 (13.5)
1979-1983	1380 (16.0)	1138 (15.8)	242 (17.2)
1984-1988	1125 (13.1)	923 (12.8)	202 (14.4)
1989-1992	730 (8.5)	613 (8.5)	117 (8.3)
Sex, n (%)			
Male	3127 (36.3)	2733 (38.0)	394 (28.0)
Female	5479 (63.7)	4466 (62.0)	1013 (72.0)
Zygosity, n (%)			
MZ	3408 (39.6)	2857 (39.7)	551 (39.2)
Twins from complete pairs	1464 (42.9)	1044 (36.5)	96 (17.4)
DZ same sex	2522 (29.3)	2115 (29.4)	407 (28.9)
Twins from complete pairs	788 (31.2)	550 (26.0)	32 (7.9)
DZ opposite sex	2676 (31.1)	2227 (30.9)	449 (31.9)
Twins from complete pairs	646 (24.1)	480 (21.6)	18 (4.0)

Note. Resilience is operationalised as absence of clinically diagnosed psychiatric disorders among ACE exposed individuals.

eTable 5. Cross-twin correlations for the secondary resilience phenotype.

	Resilience*
MZ	0.42 (0.29, 0.55)
DZ	0.15 (-0.02, 0.31)

The correlations are adjusted for sex and birthyear.
Note. Resilience is operationalised as absence of clinically diagnosed psychiatric disorders among ACE exposed individuals.

eTable 6. Model fitting results from the structural equation models estimating the relative genetic and environmental contribution to variation in the secondary resilience phenotype.

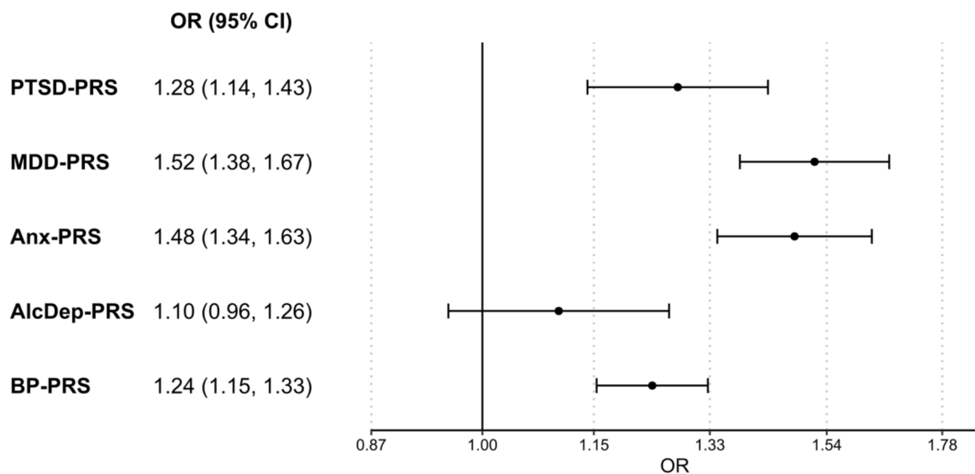
	Base model	Comparison model	-2LL	df	AIC	Δ-2LL	Δdf	p
I	Saturated		7574.6	8597	7592.6			
II	ADE	I	7575.3	8600	7598.3	0.70	3	0.872
III	AE	II	7575.9	8601	7587.9	0.56	1	0.45
IV	ACE	I	7575.9	8600	7589.9	1.27	3	0.737
V	AE	IV	7575.9	8601	7587.9	0.00	1	1

All models are adjusted for sex and birthyear;.-2LL = minus two log-likelihood;AIC = Akaike Information Criterion; df = degrees of freedom. A lower AIC represents a better model fit. A non significant p-value ($p>0.05$) indicates that the base model does not dit the data significantly worse than the comparison model.

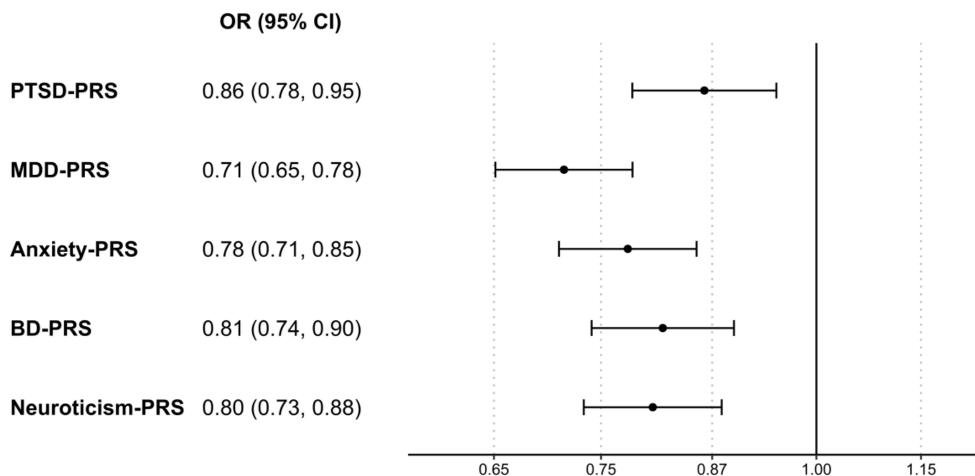
eTable 7. Parameter estimates from the structural equation models estimating the relative genetic and environmental contribution to variation in the secondary resilience phenotype.

	A	D/C	E
ADE	0.19 (-0.29, 0.67)	0.28 (-0.23, 0.79)	0.53 (0.43, 0.63)
ACE	0.45 (0.36, 0.54)	0.00 (-0.00, 0.00)	0.55 (0.46, 0.64)
AE	0.45 (0.36, 0.54)	NA	0.55 (0.46, 0.64)

All models are adjusted for sex and birthyear; A = Additive genetics; D = Dominance genetics; C = Shared environment; E = Unique environment & measurement error.
Note. Resilience is operationalised as absence of clinically diagnosed psychiatric disorders among ACE exposed individuals.



eFigure 1. Associations between PRSs for psychiatric traits and each respective disorder.
Models were adjusted for sex, birthyear, and 10 principal components. OR = Odds Ratio for every standard-deviation increase in PRS. BD = bipolar disorder. PTSD = posttraumatic stress disorder. MDD = major depressive disorder.



eFigure 2. Associations between PRSs for psychiatric traits and the secondary resilience phenotype.
Models were adjusted for sex, birthyear, and 10 principal components. OR = Odds Ratio for every standard-deviation increase in PRS. BD = bipolar disorder. PTSD = posttraumatic stress disorder. MDD = major depressive disorder. *Note*. Resilience is operationalised as absence of clinically diagnosed psychiatric disorders among ACE exposed individuals.