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Gene-environment influences on psychopathology

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Summary

Abstract

The negative effects of childhood maltreatment (CM) and poverty on mental health have been known for decades. However, examining the underlying mechanisms and disentangling causal relationships remain challenging with traditional observational designs. The conceptual challenges in defining and measuring CM and poverty further contribute to mixed findings. Overcoming these layers of complexity and identify potentially modifiable risk factors can have important implications for the development of preventive strategies to reduce the incidence of mental disorders.

This dissertation reports three studies employing contemporary psychiatric genetic epidemiology methods to investigate gene-environment influences on psychopathology.

The first study tested the hypothesis that genetic risk to schizophrenia (SZ) also increases the risk of CM and thus impacts psychosis risk. Structural equation modeling was used to test a mediation model from schizophrenia polygenic risk score (SZ-PRS) to psychotic-like experience (PLE), through CM, in two independent samples of young adults from the general population. The discovery sample was the Utrecht Cannabis Cohort (UCC, N=1262), and the replication sample was the IMAGEN cohort (N=1740). Results showed that around 30% of the effect of SZ-PRS to PLE was mediated by CM, adding a new perspective on the mechanisms linking genetic and environmental risks for psychosis.

The second study explored the impact of different types of CM - abuse, neglect, and combined abuse and neglect - on the risk of SZ, major depressive disorder (MDD), and bipolar disorder (BD) in three large longitudinal cohorts (total N=4037). Logistic regression models identified abuse as the strongest risk factor for SZ and neglect for BD. At the symptom level, abuse was associated with hallucinations and suicide attempts, whereas neglect was associated with agitation and reduced need for sleep. Mendelian randomization (MR) analyses supported a bidirectional causal relationship between abuse and SZ.

The third study employed genomic structural equation modeling to estimate a genome-wide association study (GWAS) of a general poverty factor (PF) derived from household income (HI), occupational income (OI), and social deprivation (SD) in the UK Biobank. Then, the causal effects of PF on nine mental disorders in the Psychiatric Genomic Consortium (PGC) - attention deficit and hyperactivity disorder (ADHD), anorexia nervosa (AN), anxiety disorder, autism spectrum disorder, BD, MDD, obsessive-compulsive disorder, post-traumatic stress disorder, and SZ - were investigated using MR. Findings suggested that SZ and ADHD causally contribute to poverty, while poverty contributes to MDD and SZ but decreases the risk of AN. Poverty may also contribute to ADHD, albeit with

uncertainty due to unbalanced pleiotropy. Adjusting for cognitive ability reduced the effects of poverty by approximately 30%. The findings suggest that interventions targeting poverty and cognitive ability, such as reducing income inequalities or facilitating educational opportunities, hold the potential to improve public mental health.

Overall, this dissertation shows that building on genetic data generated from large collaborative studies provides a novel way to revisit the role of the environment and illuminates the role of CM and poverty as important modifiable causal factors in mental health.

Keywords: mental disorders, childhood trauma, poverty, epidemiology, prevention.

1. Introduction

Psychopathology is the manifestation of mental health disorders. These conditions are influenced by a complex interplay of genetic, environmental, and psychosocial factors, each representing a critical focus for research into targeted interventions.

1.1. Mental health and mental disorders

The World Health Organization (WHO) defines mental health as "a state of mental well-being that enables people to cope with the stresses of life, realize their abilities, learn well and work well, and contribute to their community" [1]. Therefore, mental health is not an "all or nothing" condition; rather, it can be most effectively understood as a dynamic spectrum. On this continuum, experiences of mental health can vary both between individuals and across an individual's lifespan.

A mental disorder is characterized by a clinically significant disturbance in an individual's cognition, emotional regulation, or behavior, usually associated with distress or impairment in important areas of functioning [2] . As with mental health, experiences of mental disorders can vary significantly between individuals and throughout the disorder's course, where symptoms may fluctuate in severity and impact. This underscores the importance of recognizing mental health and mental disorders not as binary opposites but as interconnected points on a shared spectrum [3].

Psychopathology aims to classify mental disorders based on clinical signs and symptoms. The most widely used classification systems are the International Classification of Diseases (ICD), published by the WHO [4], and the Diagnostic and Statistical Manual of Mental Disorders (DSM), curated by the American Psychiatric Association (APA) [5].

Mental disorders can be classified into several categories:

- Anxiety disorders (ANX), characterized by excessive fear and worry and related behavioral disturbances. Types of anxiety disorders include generalized anxiety disorder, panic disorder, social anxiety disorder, and obsessive-compulsive disorder (OCD).
- Depressive disorders, marked by a persistent depressed mood - feeling sad, irritable, or empty - or a loss of pleasure or interest in activities, lasting for most of the day, nearly every day, for at least two weeks. Additional symptoms may include poor concentration, excessive guilt, low self-worth, hopelessness, thoughts of dying or suicide, disrupted sleep, changes in appetite or weight, and low energy levels. The most common type is major depressive disorder (MDD).

- Bipolar disorder (BD), characterized by alternating depressive episodes and periods of manic symptoms. During depressive episodes, individuals experience symptoms like those of MDD. Manic symptoms may include euphoria, irritability, increased activity or energy, talkativeness, racing thoughts, inflated self-esteem, decreased need for sleep, distractibility, and impulsive behavior.
- Post-traumatic stress disorder (PTSD), develops following exposure to extremely threatening or horrific events. It is characterized by intrusive re-experiencing of the traumatic events (e.g., flashbacks, nightmares), avoidance of reminders, and persistent feelings of heightened threat.
- Schizophrenia (SZ) and other psychotic disorders, characterized by reality distortion, cognitive disturbance, and negative symptoms. Common symptoms include delusions, hallucinations, disorganized thinking, highly disorganized behavior, and avolition. SZ is the fraction associated with the poorer long-term outcomes and increased disability.
- Eating disorders, such as anorexia nervosa (AN) and bulimia nervosa, involve abnormal eating and preoccupation with food as well as prominent body weight and shape concerns. AN often begins in adolescence or early adulthood and carries a high risk of premature death due to medical complications or suicide. Individuals with bulimia nervosa face increased risks for substance use, suicidality, and other health complications.
- Neurodevelopmental disorders arise during the developmental period and involve significant difficulties in intellectual, motor, language, or social functions. Examples include autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD). ADHD is characterized by a persistent inattention and/or hyperactivity-impulsivity that has a direct negative impact on academic, occupational, or social functioning. ASD is characterized by difficulties in social communication, reciprocal social interaction, and restricted, repetitive behaviors, interests, or activities.
- Personality disorders, characterized by enduring patterns of emotional dysregulation, impaired empathy, low stress tolerance, and maladaptive and unhealthy coping strategies.

According to the latest estimates, approximately one in eight people worldwide - or 970 million individuals - live with a mental disorder, with anxiety and depressive disorders the most common [6,7].

1.2. Pathogenesis of mental disorders

The pathogenesis of mental disorders is immensely complex, involving the interplay of genetic, environmental, and social factors. Current research conceptualizes mental disorders as polygenic and

multifactorial in nature, meaning that their heritability arises from the cumulative contributions of numerous genes, each exerting small effects [8,9]. Importantly, while genetic factors shape an individual's underlying vulnerability to mental disorders, there is little evidence of direct, deterministic genetic effects. Instead, these genetic predispositions intertwine dynamically with a range of environmental and social influences, which often serve as precipitating factors for the onset of mental disorders [8,9]. Environmental risk factors vary across different mental disorders, with their contributions supported by evidence of varying quality and effect size estimates [10,11]. These factors are continually updated as research advances, and they can be broadly categorized into the following domains [12–17]. Stressful life events, particularly exposure to extreme or chronic stress, play a significant role. Specific examples include traumatic experiences such as sexual, physical, or emotional abuse and neglect during childhood (collectively referred to as childhood maltreatment, or CM). Early-life adversity profoundly influences the developing brain, contributing to lifelong susceptibility to mental health issues. Other significant risk factors include obstetric complications, peer bullying, and markers of social exclusion, such as minority status, migration, and sensory impairments. Moreover, individuals in urban environments may face increased risks due to factors like social isolation, pollution, and reduced access to green spaces. Environmental toxins, such as infections (e.g., Toxoplasma Gondii, Cytomegalovirus, Herpes Simplex Virus, or Rubella) and substances of abuse, further compound the risk.

The interplay between genetic and environmental influences is shaped by two primary mechanisms: gene-environment interaction (G×E) and gene-environment correlation (rGE). G×E refers to the process by which an individual's genetic makeup modifies their sensitivity to environmental exposures [18]. For instance, certain genetic variants may amplify an individual's vulnerability to the effects of childhood trauma or substance use [19]. In contrast, rGE reflects how genetic predispositions can influence the likelihood of exposure to particular environments [20]. For example, an individual with a genetic propensity for impulsivity may be more likely to engage in risky behaviors, increasing their exposure to adverse life events [21]. Together, these mechanisms underscore the intricate bidirectional influences between genes and environment in shaping mental health outcomes.

Recognizing the pathogenesis of mental disorders as a multifactorial process underscores the importance of adopting integrative bio-psycho-social approaches to prevention and treatment. Effective interventions must comprehensively target biological and psychological vulnerabilities while simultaneously addressing the social and environmental determinants of mental health.

1.3. Mental health promotion and mental disorder prevention

Strategies for illness prevention are typically categorized into three phases: primary, secondary, and tertiary. According to Caplan (1964) [22], primary prevention aims to prevent the occurrence of illness and to promote health, when successful it reduces the incidence of an illness in the population. Secondary prevention focuses on the early detection of illness and timely intervention to decrease its duration, thereby reducing its prevalence. Finally, tertiary prevention aims to minimize the complications and long-term disability associated with an illness by ensuring appropriate treatment and rehabilitation.

In the context of mental disorders, these phases translate into distinct strategies. Instances of primary prevention are campaigns and initiatives designed to reduce exposure to risk factors, thereby lowering the occurrence of new cases. Secondary prevention involves early intervention services targeted at individuals identified as being at risk, aiming to delay or prevent the development of a full syndrome, ultimately reducing the number of existing cases. Tertiary prevention focuses on providing timely treatment to individuals experiencing the full syndrome, with the goal of mitigating its impact and preventing further complications. Despite their potential, these prevention strategies face notable limitations. Evidence supporting secondary prevention efforts for severe mental disorders, particularly psychosis, remains inconclusive [23]. Additionally, the high risk of chronic progression in mental disorders often constrains the effectiveness of tertiary prevention strategies, which are typically limited in scope and impact [24]. These challenges emphasize the need to prioritize primary prevention, where interventions targeting modifiable risk factors before illness onset hold the greatest potential for achieving public health benefits and reducing the burden of mental disorders [25].

Primary prevention requires identifying and addressing environmental, psychosocial, and potentially modifiable risk factors for mental disorders. Traditionally, this has been achieved through epidemiological observational studies, such as cohort and case-control designs. These studies have been instrumental in identifying critical risk factors, including childhood adversity, urban living, and exposure to environmental toxins [8,16,26]. However, the confidence in the findings from observational studies is often limited by methodological pitfalls, particularly reverse causation and residual confounding, which challenge causal inferences [27]. Moreover, implementing population-wide primary prevention interventions poses practical challenges. Such interventions may be costly and difficult to scale effectively, particularly in resource-limited settings. A more sustainable approach involves targeting interventions toward individuals with inherent vulnerabilities to mental disorders, thereby optimizing resource allocation and intervention effectiveness [28,29].

Psychiatric genetic epidemiology offers promising tools to address these limitations. By accounting for gene-environment influences, genetic epidemiological methods can address key issues such as reverse causation and residual confounding. Furthermore, the use of genetic measures can provide insights for designing precision interventions. Integrating genetic methodologies into observational studies has the potential to enhance the understanding of mental disorders pathogenesis and to inform the development of effective primary prevention strategies.

1.4. Genetic studies

Psychiatric genetics has a history spanning more than two centuries [30]. From its inception, the field recognized heredity as one of the strongest risk factors for mental disorders, even before the advent of modern statistical methods and biological understandings [31–33]. Early writings described the familial transmission of mental disorders, not as the direct inheritance of the disorder but rather as a predisposition or vulnerability to it [34–37]. This probabilistic nature of inheritance was evident in cases where mental disorders skipped generations or affected only a subset of siblings within the same family, suggesting the lack of mendelian inheritance [38,39]. Accordingly, the relatives of individuals with mental disorders were often found to exhibit a diverse range of psychiatric or even neurological conditions rather than the same specific disorder [37,39]. Homogeneous transmission - where the exact disorder was mirrored in relatives - was noted but considered rare [39,40]. Early clinicians also remarked on the presence of eccentric personality traits, such as peculiar or unconventional behaviors, which were often observed among the relatives of individuals with mental disorders [31–33,41].

Interestingly, these early reports also noted the impact of environmental factors on the transmission of mental disorders. Psychological stress, parental experiences, and intrauterine conditions were thought to contribute to the transmission of psychiatric vulnerability [42], representing early understanding of the interplay between genetics and environment.

While these observations lacked the rigor of modern methodologies, many of these have since been validated through contemporary research [43].

Current evidence of psychiatric genetics are derived from family studies, particularly those involving twins and adopted children, and genome-wide association studies (GWAS).

1.4.1. Family studies

Family studies are typically observational studies with cohort or case-control designs, that investigate the intergenerational transmission of mental disorders within families. However, family members share both genetic and environmental influences, making it challenging to disentangle the contributions of each. For example, children of parents with alcohol or substance dependence may inherit genetic predispositions while also being exposed to environmental adversities such as maltreatment or neglect during childhood.

To mitigate this limitation, twin and adoption studies have been conducted. The basic premise is that if a disorder is primarily influenced by genetic factors, individuals with greater genetic similarity should exhibit higher concordance rates for the disorder [44,45].

Twin studies compare the concordance rates of mental disorders between monozygotic (MZ) twins, who share 100% of their genetic material, and dizygotic (DZ) twins, who share approximately 50% of their genetic material. If a disorder has a strong genetic basis, concordance rates are expected to be significantly higher among MZ twins than DZ twins. These studies have consistently shown that MZ twins have a higher concordance for mental disorders, reinforcing the role of genetic influences [45].

Adoption studies examine individuals raised in environments different from their biological relatives. These studies compare the risk of mental disorders in adopted individuals to that in their biological and adoptive relatives. For example, research has shown that the risk of mental disorders increases for adopted children with biological parents who have mental disorders, and that this risk grows with the duration of time spent with those parents before adoption [46].

These studies have been instrumental in confirming that mental disorders cluster within families, suggesting a significant role for hereditary factors [47].

The heritability estimates from family studies varied across mental disorders and the cohort considered, ranging from 30-50% for depression [48], anxiety [49], and eating disorders [50], up to 60-80% for schizophrenia spectrum [51,52], autism spectrum [53], ADHD [54,55], and bipolar disorders [56].

Despite their significant contributions to understanding the familial aggregation of mental disorders, family studies are inherently limited in their capacity to disentangle genetic influences from shared environmental factors, leaving a considerable proportion of the heritability unexplained. This "heritability gap" has become a central focus in psychiatric genetics [57]. Bridging this gap requires approaches that can directly assess genetic contributions at the molecular level.

1.4.2. Genome wide association studies

The human genome is the complete set of deoxyribonucleic acid (DNA) instructions within a cell, organized into 23 pairs of chromosomes [58]. The genotype refers to the specific nucleotide sequence at a given location in the genome, which can vary among individuals. If the allele carrying a nucleotide variant occurs in more than 1% of the population, it is termed a single nucleotide polymorphism (SNP); if its prevalence is below 1%, it is classified as a single nucleotide variant (SNV) [58].

A genome-wide association study (GWAS) is a research approach that systematically screen the entire genome of a large number of individuals to identify genetic variants, such as SNPs, that are statistically associated with a particular phenotypic trait or disease [59]. Genetic material is typically obtained from biological samples, such as blood or saliva. Then, for each participant, phenotypic data are collected, encompassing a wide range of characteristics, including physical traits (e.g., height, weight), health-related information (e.g., presence of schizophrenia or depression), behavioral patterns (e.g., smoking habits), and even socio-environmental factors (e.g., income or exposure to childhood maltreatment).

The first GWAS was conducted in 2005 [60]. Since then, the field has advanced rapidly, driven by increasing sample sizes, refined phenotypic classifications, and higher-resolution genomic analyses. To date, GWAS have been applied to investigate more than 5,000 traits, yielding a wealth of genetic data [61]. One distinctive feature of GWAS is its stringent threshold for statistical significance. To account for the massive number of simultaneous comparisons across the genome, a p-value threshold of 5×10^{-8} is typically required to consider an association as statistically significant [58]. This threshold is much stricter than those used in classic observational studies, reflecting the need to minimize false-positive findings in such high-dimensional analyses.

GWAS has significantly advanced our understanding of genetic heritability, as well dispelling the misconception of genetic determinism for complex traits such as mental disorders [9]. The notion of identifying a singular “schizophrenia gene” or similar deterministic factors is now recognized as overly simplistic and fundamentally incorrect. Instead, GWAS findings reveal that heritability for complex traits is polygenic: many genetic variants, each with small individual effects, collectively contribute to the heritability of these traits [59,62,63]. For example, even the largest GWAS dataset for schizophrenia, comprising approximately 400,000 individuals, explains less than 10% of the trait's heritability based on identified genetic variants [64]. This figure is substantially lower than heritability estimates derived from family studies, underscoring the significant role of environmental contributions to the etiology of mental disorders [11,43].

Despite these limitations, GWAS has catalyzed major advancements in psychiatric genetic epidemiology. Results from GWAS are systematically compiled in publicly accessible repositories, such as the European Bioinformatics Institute GWAS Catalog (ebiGWAS; https://www.ebi.ac.uk/gwas/home) [65], allowing researchers worldwide to access and use this data. Two key methodologies derived from GWAS are polygenic risk score (PRS) and Mendelian randomization (MR).

1.4.3. Polygenic risk score

GWASs have identified a large number of genetic variants significantly associated with a wide range of complex traits [64,66,67]. However, these variants typically have a small effect and have limited predictive power [68–70]. It has been demonstrated that much of the heritability of a trait can be explained by evaluating the combined effects of all SNPs simultaneously [68,70]. This approach produces a polygenic score, or PRS, serving as an estimation of an individual's genetic liability to a trait or disease. PRS is calculated by summing the number of risk alleles carried by an individual, weighted by the effect sizes of these alleles as determined by GWAS [66].

The units of PRS reflect the GWAS effect sizes. For continuous traits, such as height, PRS is expressed in the same units as the trait (e.g., centimeters). For binary traits, such as disease status, the effect sizes are typically expressed as log odds ratios. Importantly, PRS does not provide an absolute measure of risk; instead, it represents a relative risk compared to a hypothetical baseline individual carrying no risk alleles.

PRS is non-invasive and require only a single measurement over an individual's lifetime, making them cost-effective and potentially scalable for research and precision medicine [71]. However, PRS accuracy and interpretability critically depend on the quality of the GWAS from which they are derived, including sample size, phenotypic definition, and diversity of the studied populations. Current PRS explains only a fraction of the phenotypic variance, often less than 10%, which is substantially lower than the heritability estimates from family studies [66].

The practical utility of PRS is to translate an individual's genetic information into a single score representing their genetic relative risk for a given trait or disease. However, the clinical utility in experimental settings remains limited by its current low predictive power of disease at the individual level [66]. Still, PRS holds the potential for broad applications across biomedical research, including studies of shared etiology between traits, assessments of genetic contributions to disease, and experimental designs that stratify individuals by genetic liability [66,71]. Nowadays, the integration of

PRS into traditional observational designs has advanced epidemiological research. In psychiatric epidemiology, the inclusion of PRS allowed investigation of rGE and G×E, improving the understanding of gene-environment influences in the pathogenesis of mental disorders [43,72].
As GWAS sample sizes increase and their quality improves, PRS is becoming more powerful and applicable across diverse contexts, allowing for a more precise investigations into biological mechanisms and treatment responses.

1.4.4. Mendelian randomization

A pre-requisite for a robust primary prevention intervention is a causal relationship between the modified risk factor and the risk of illness [73].
Traditional observational epidemiological studies often yield inconsistent results, particularly in mental health research, due to biases like reverse causation and residual confounding. For instance, the higher prevalence of cannabis use among individuals with psychosis may reflect a true causal effect of cannabis on psychosis risk, reverse causation (SZ increasing cannabis use behavior), or shared risk factors [74,75]. The gold standard for determining causality is the randomized controlled trial (RCT). However, RCTs are neither ethical nor practical for many risk factors.
MR has emerged as a valuable alternative, leveraging genetic data obtained from GWAS to address these challenges [76]. MR uses genetic variants as instrumental variables to test the causal effect of an exposure (e.g., cannabis use) on an outcome (e.g., psychosis) [77,78]. MR grounds on the Mendel's second law, postulating that during meiotic crossover, genetic variants are randomly assorted to gametes, thus passed on randomly from generation to generation. Additionally, the generic variants are fixed at conception, meaning they inherited independently of confounding lifestyle factors. Therefore, they can be used as proxies for levels of the exposure in an instrumental variable analysis. This is similar to a natural experiment, where the distribution of SNP associated with a postulated risk factor for a specific disease is analyzed among cases and controls [76].
MR relies on three core assumptions for valid causal inference (see also Figure 1) [79–81]:
(A) Relevance assumption: The genetic instrument must be strongly associated with the exposure. For example, only SNPs associated with the exposure at GWAS statistically significant threshold ($p<5*10^{-8}$) should be used as instrumental variable.
(B) Independence assumption: The genetic instrument must not be associated with confounders of the exposure-outcome relationship.

(C) Exclusion-Restriction assumption: The genetic instrument must influence the outcome only through the exposure, without alternative pathways (no pleiotropy rule). Pleiotropy describes the instance of a genetic variant influencing multiple traits. There are two types of pleiotropy: (1) vertical pleiotropy refers to the effect of the genetic variants on different phenotypes on the same causal pathway (e.g., SNP→protein→neurons→cognition→mental disorder), and it is less problematic in MR studies; (2) horizontal pleiotropy occurs when a genetic variant affects the outcome through pathways other than the exposure, it is problematic in MR studies as it bias estimates by reintroducing confounding.

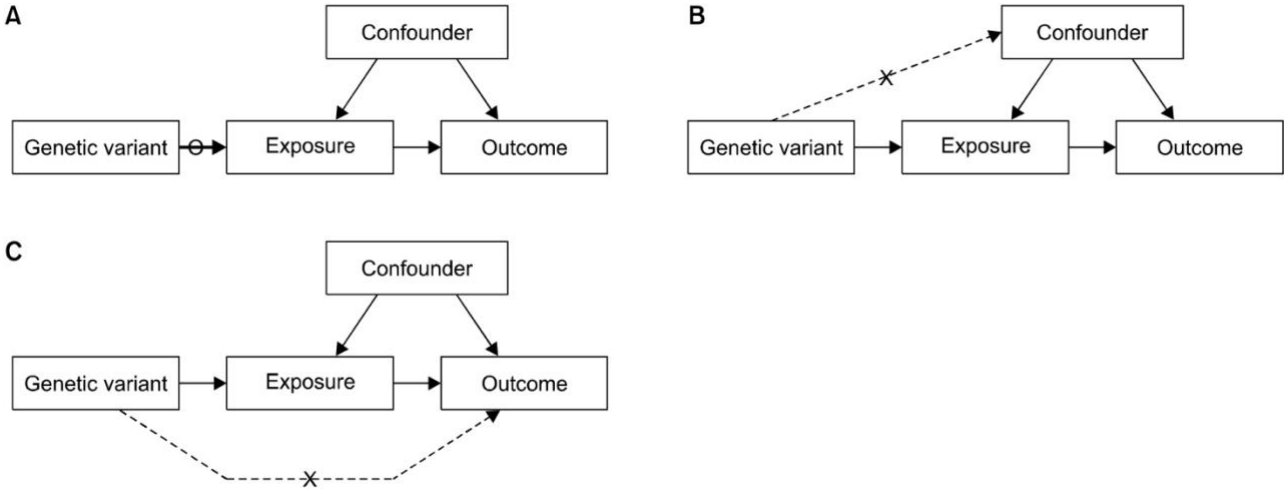


Figure 1: MR assumptions.
Adapted from: J Rheum Dis 2020;27:241 [82].

The effectiveness in using MR in psychiatry is largely related to the phenotypic complexity of mental disorders and related risk factors. The main challenges are related to pleiotropic effects; heterogeneity in psychiatric phenotypes, particularly in terms of severity and course; and bi-directional relationships, that may reflect true bidirectionality, shared genetic risks, or confounding due to linkage disequilibrium. To address these challenges, advanced MR methods have been developed, including MR-Egger regression [83], MR Pleiotropy Residual Sum and Outlier (MR-PRESSO) [84], Steiger filtering [85], and multivariable MR (MVMR) [81]. These methods improve robustness by accounting for pleiotropy and refining causal estimates.

MR offers several advantages. Since it uses GWAS summary statistics that are in large part already available, it is faster and less expensive than RCTs when suitable genetic and phenotypic data are available. It can identify causal risk factors worth prioritizing for further investigation in RCTs or

intervention trials. In psychiatric epidemiology, MR is going to be instrumental in disentangling the complex relationships between mental disorders and behavioral or environmental risk factors, particularly in contexts where RCTs are impractical or unethical [27].
As the quality and diversity of GWAS data improve, MR is going to play a crucial role in advancing our understanding of causal mechanisms, ultimately guiding the development of targeted primary prevention strategies.

1.4.5. Paradigm shift: genes associated with environmental exposures

Using genetic data to identify environmental risks may appear unconventional since environmental exposures are not traditionally viewed as a biological conditions or traits. However, with increasing GWAS sample sizes, there is growing power to detect SNPs associated with multifactorial phenotypes like mental disorders, or social conditions such as CM and poverty. Clearly, the more complex or multifactorial the phenotype is, the less likely is to observe a direct genetic effect. For example, in anorexia nervosa or ADHD, two multifactorial disorders, GWAS could identify genetic variants associated not only with the disorder itself but also facilitative of something else that is linked to individual's environment, such as educational attainment. In such cases, the genetic variants associated with upstream or downstream factors exhibit pleiotropic effects. This understanding challenges the traditional division between genetic and environmental risks, suggesting that genetic predispositions can influence an individual's environment, which in turn may influence health-related phenotypes. This gene-environment correlations have also been identified for CM and poverty, highlighting that genetic factors may contribute to the risk of exposure to adverse environments [86–91]. However, discovering genetic associations with such traits does not mean that other environmental and genetic factors do not influence them. As such, these are not proof of genetic determinism. To prevent discrimination and stigmatization, it is crucial to emphasize the importance of creating inclusive and supportive environments that foster equal opportunities and access to resources for all individuals, regardless of their genetic or environmental backgrounds. For instance, although intelligence and cognitive abilities have a genetic component, environmental factors such as access to quality education, supportive learning environments, and parental involvement play crucial roles in determining educational outcomes. Individuals with the same genetic make-up can achieve different educational levels based on their environment and opportunities. Notably, if environmental conditions were made uniform for all individuals, the relative contribution of genetics to inter-individual differences would rise to 100% [92].

By addressing the broader social determinants of mental health and socioeconomic disparities, society can work towards greater equity, promoting mental well-being and socioeconomic mobility for all.

1.5. The current research

In the current dissertation genetic psychiatric epidemiology methods, including PRS and MR, will be used to improve the understanding of gene-environment influences in the pathogenesis of mental disorders. Specifically, the focus is on two key environmental risk factors: CM and poverty.

1.5.1. Childhood maltreatment studies

CM is a major public health concern and one of the strongest environmental risk factors to mental disorders [43,93–95]. Across the world, approximately 35% of children have been exposed to emotional abuse, 23% to physical abuse, 18% to neglect (emotional and/or physical), and 13% to sexual abuse, based on self-report studies that suggest a much higher prevalence than informant-based prevalence rates of around 0.3% [96]. The impact of CM is not limited to a single health outcome but increases the risk for a diversity of mental disorders [97], worse treatment outcomes [98,99], decreased social function [100], frequent hospitalizations [101], and high risk for suicide [102,103]. Such a broad range of adverse consequences points to large individual differences in responses to CM exposure [104–107] and may suggest diversity in pathways of the negative impact of CM.

A likely contributor to the diversity of outcomes of CM exposure is the nature of CM. CM is defined as one or multiple negative life events occurring before the age of 18 years, but the nature of these events diverge largely, and it is not self-evident they all have the same impact [108]. Whereas there are many potential subdivisions of the experience of CM, a broad but relevant division is the distinction between abuse and neglect as they comprise fundamentally different psychological experiences [109]. Abuse is defined as any non-accidental act which causes or creates a substantial risk, physical or emotional injury and covers a highly threatening event. Abused children are more likely to perceive their harmful environment as dependent on their own behavior than neglected children [110]. Neglect is defined as the shortcoming, deliberately or through negligence or inability, to take those actions necessary to provide a child with minimally adequate food, clothing, shelter, medical care, supervision, emotional stability, and growth and deprives the child from basic care and stimulating experiences. As to be expected when growing up in a harmful environment, childhood abuse and neglect often co-occur [111]. Experiencing multiple types of CM is related to an accumulation of detrimental consequences later in life, suggesting

a dose-response relationship [112–114]. The experience of both abuse and neglect could therefore be seen as a third type.

Previous observational studies investigated either one specific CM type, such as sexual abuse, specific disorders, or did not differentiate between CM types [115,116]. In these studies, childhood abuse has been related to higher risks of SZ [117,118]. Childhood neglect, physical and emotional abuse were associated with risk for MDD [119–122]. In BD, the limited evidence pointed to a stronger association of childhood abuse with symptom severity than childhood neglect [123].

Recent GWAS have identified genetic risks to CM and proposed causal relations between CM and severe mental health conditions, especially SZ [108]. Furthermore, SZ risk genes contributed to poorer child mental health, through increased exposure to CM [88].

Taken together, these findings suggest the existence of direct genetic effects to CM and potential rGE involving CM in the pathogenesis of mental disorders.

In the current dissertation, two research investigating the relationship between CM and mental disorders are reported.

The first is the **TRAIL (childhood Trauma, polygenic Risk score Association In psychotic-Like experience) study**, exploring the relationship between genetic risk to SZ estimated through SZ-PRS, CM, and psychotic-like experiences (PLE) using mediation analysis. PLE are subclinical manifestations that do not necessarily cause significant distress or impairment to warrant a clinical diagnosis [10,124], and can be considered expression of psychosis on the continuum between clinical and non-clinical population. PLE are thought to reflect risk to psychosis and non-psychotic psychopathology, including mood disorders, ADHD, and suicidality [125–127].

The **REM (Risk of mental disorders and childhood Experiences of Maltreatment) study** investigated the differential impacts of CM types (abuse, neglect, and combined maltreatment) on MDD, BD, and SZ was investigated through linear regression and MR analyses.

1.5.2. Poverty study

The association between mental disorder and social class was first demonstrated in a 1958 study by Hollingshead and Redlich, who found that individuals from lower socioeconomic backgrounds had a higher incidence of severe and persistent mental disorder and received less adequate treatment [128].

More than sixty years later, the same social conditions persist, with numerous studies confirming an association between mental health and socio-economic status (SES) worldwide [129–135].

Although the association between poverty and mental disorders is strong across these studies, several factors, such as reverse causation and residual confounding, make it difficult to determine causal inference. To date, uncertainty remains with respect to the direction of the association between poverty and mental disorder, and two explanatory hypotheses compete: social causation and social selection [136]. According to the social causation theory, the socio-economic adversity faced by lower socio-economic groups precipitates mental disorder in vulnerable individuals possibly mediated by factors such as housing insecurity, substance use, and stress. Conversely, the social selection theory suggests that the overrepresentation of lower socio-economic status among people with mental disorder is mainly attributable to downward social mobility as a consequence of the impairment associated with poor mental health [137].

Studies on poverty come with the challenge of defining poverty. Most of them often make use of a single measure, usually based on income recorded at the household level or as individual income or operationalized employment status of an individual, by occupational income [133,137]. However, no single indicator can capture the multiple dimensions of poverty, such as lack of material goods, limited access to education and healthcare services, inadequate living standards, disempowerment, poor quality of work, the threat of violence, and living in areas that are environmentally hazardous, among others [138–141]. For that reason, the UK health authorities commonly use a composite measure known as the Townsend Deprivation Index to assess material deprivation within a population [142].

In the **MONEY (Mendelian randomization of meNtal hEalth and povertY) research**, to maximize the power required to examine the common effects of poverty across its multidimensional aspects, a poverty factor (PF) GWAS was estimated from household income (HI), occupational income (OI), and social deprivation (SD). These three measures capture poverty at the level of the individual, the household, and of the area in which one lives and so facilitate a more informed understanding of which aspects of poverty are those that present the greatest risk to individual mental health. Then, the SNPs associated with this PF were used as instrumental variable in MR analyses to investigate causal relationships between poverty and nine mental disorders.

2. Aim

The main aim of the current dissertation was to present three psychiatric genetic epidemiology studies, demonstrating the effective integration of traditional observational designs - such as, observational cohort and registry-based analyses - with modern genetic methods, to improve understanding of pathogenetic mechanisms to mental disorders. This integrative approach aimed to account for individual liability to environmental risk exposure and mental disorders, and to circumvent bias related to residual confounding and reverse causation in examining causal inference.

Specifically, the aims of the three studies can be summarized as follows:

1) TRAIL:

   To investigate the relationship between SZ-PRS, CM, and PLE in a cohort of young adults of European ancestry and test replication in an independent cohort.

   To account for other active rGE mechanisms, whereby genetic risk might lead to behaviors relevant for high-risk exposures (such as thrill-seeking), the analyses were adjusted for cannabis use and tobacco smoking. To gain further insight into whether any of the identified associations are specific for CM subtypes and PLE dimensions, supplementary models included the subscores of our CM and PLE assessments (emotional, physical abuse and neglect, and sexual abuse; and positive, negative, and depressive PLE, respectively), and, to alleviate concerns about the self-reporting of CM the measure of neuroticism.

2) REM:

   To investigate the relative impact of childhood abuse, neglect, and combined abuse and neglect, on MDD, BD, and SZ, both at the disorder level and trans-diagnostically at the symptom level. Furthermore, to explore causal relationships using MR.

3) MONEY:

   To use MR to investigate the causal effects of poverty on nine mental disorders, including ADHD, AN, ANX, ASD, BD, MDD, OCD, PTSD, and SZ.

   To do so, a new PF GWAS was estimated from HI, OI, and SD using Genomic structural equation modeling (GSEM) [143].

   To account for potential confounding effects, MVMR was also performed to control for the effect of cognitive ability (CA).

3. Methods

3.1. TRAIL study

3.1.1. Study design and participants - Discovery sample

The Utrecht Cannabis cohort (UCC) consists of 1262 Dutch young adults aged from 18 to 25 years, recruited using a project website launched in 2006 [144]. A selective sampling strategy aimed at increasing the power for GxE detection was implemented, as reflected by higher cannabis use and PLE levels in UCC [18]. Data on genetics, PLE, socio-demographics, and cannabis use were fully complete. The exposure to CM was assessed through the self-reported Childhood Trauma Questionnaire (CTQ - available in the Appendix) [109]. For 341 subjects there were response items missing (less than 10% of the total number of items in the questionnaire) that were imputed using case-wise maximum likelihood estimation [145]. Participants gave written informed consent, and the study was approved by the University Medical Centre Utrecht medical ethical committee.

3.1.2. Study design and participants - Replication sample

The IMAGEN cohort is a longitudinal imaging genetics study of over 2000 non-clinical adolescents, mostly of European descent. Detailed descriptions of this study, genotyping procedures, and data collection have previously been published [146]. The current study uses data from 1740 participants who contributed their genetic data and completed the PLE measure. Of these 1740 subjects, 234 had missing data about cannabis use status, and for 396 there were missing response items to CTQ, both of this missing information were imputed using case-wise maximum likelihood estimation. The multicentric IMAGEN project had obtained ethical approval by the local ethics committees (at their respective sites) and written informed consent from all participants and their legal guardians.

3.1.3. Genetic data and PRS

SZ-PRS were calculated for each of the UCC and IMAGEN individuals, who passed genetic quality control (QC). Only autosomes were included in the calculation of PRS [66]. SZ-PRS were build using data from the most recent schizophrenia GWAS based on 40,675 cases and 64,643 controls as a training set [147]. PRS were calculated using PRSice2 [148]. For each individual, SZ-PRS was calculated using 13 different p-value thresholds (pt): 5×10^{-8}, 5×10^{-7}, 5×10^{-6}, 5×10^{-5}, 5×10^{-4}, 5×10^{-3}, 5×10^{-2}, 0.5, 0.4, 0.3, 0.2, 0.1, 1. From these thresholds one optimal threshold was selected. First, a LASSO regression was

fitted to identify which SZ-PRS pt constituted the best predictor of PLE within the sample, while adjusting for age, gender, and the first three principal components. This approach has been shown to be the best way to select the right predictor from a set of variables [149]. In case of multiple PRS-pt identified by the LASSO, the linear regression model's variance explained (i.e., the R^2) was used to select the SZ-PRS pt with the highest explained variance.

3.1.4. Assessments

In both the discovery and replication samples, CM was assessed using the 25-item version of the Childhood Trauma Questionnaire [109]. The CTQ assesses self-reported CM consisting of emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect. Each item was answered on a Likert scale ranging from (1) "never", (2) "rarely", (3) "sometimes", (4) "often", (5) "very often". The validity of the CTQ has been demonstrated in clinical and community samples [150,151]. The CTQ continuous sum score was used as measure of CM.

Neuroticism was assessed both in the discovery and the replication sample using the neuroticism scale of the NEO Personality Inventory [152], a validated 240-items self-reported questionnaire examining a person's big five personality traits [153].

In the discovery sample the self-reported lifetime cannabis exposure was measured on a scale ranging from never, 1, 2, 5-9, ≥10 times. The possible concomitant use of recreational drugs and tobacco was assessed with the substance-abuse module of the Composite International Diagnostic Interview (CIDI) [154]. In the replication sample, participants were repeatedly assessed for cannabis use using the European School Survey of Alcohol and other Drugs (ESPAD) questionnaire at 14, 16, 18 and 21 years of age. The ESPAD is a self-report questionnaire that measures use of various drugs, including cannabis and tobacco [155]. Cannabis use data were drawn from the 18-year-old follow-ups and categorized based on the lifetime frequency of reported exposure (as never, "1–2", "3–5", "6–9", "10-19", "≥20" times). To allow for direct comparison between the two cohorts, cannabis use data was dichotomized into "case/control" status, where ≥10 lifetime uses are considered cases.

The Community Assessment of Psychic Experiences (CAPE) was used to assess psychotic experiences in both cohorts. This validated 42-items self-report questionnaire measures the prevalence of psychotic experiences on a frequency scale ranging from "never" (1), "sometimes" (2), "often" (3), to "nearly always" (4). Conceptually, the questionnaire may be thought as structured in a 3-factor model consisting of "positive" (corresponding to involvement in bizarre experiences, delusional ideations, and

perceptual anomalies), "negative" (consisting of social withdrawal, affective flattening, and avolition), and "depressive" psychotic-like experience [156]. The CAPE displays discriminative validity in assessing psychotic experiences in the general population [157]. The continuous total score of the scale was used as measure of PLE.

3.1.5. Statistical analyses

First, multivariate linear regression was used to examine the relationship between PLE, as the outcome, and CM and SZ-PRS, as main determinants, alongside age and gender as covariates.
For mediation analysis, we obtained the variance/covariance matrix (see Data availability section), calculating the correlation among each variable. Then we performed parallel multiple mediation analysis using maximum likelihood estimation (MLE) path analysis to assess the effect of SZ-PRS on PLE directly and through the postulated mediators. The bias-corrected bootstrap 95% confidence interval (95% CI) for the indirect effect was tested to be entirely above zero based on 5,000 bootstrap samples applying the adjusted bootstrap percentile method (BCa). Statistical analyses were performed with R [158], using the packages *glmnet* [159] for the LASSO, *lavaan* [160], and *tidySEM* [161] for the mediation analysis.

3.2. REM study

3.2.1. Study participants

Data from three large longitudinal Dutch cohort studies were used for this study (total N=4037): the Genetic Risk and Outcome in Psychosis study, focusing on schizophrenia spectrum disorders (GROUP, subsample total N=981; cases SZ=577, MDD=74; controls=330) [162], the Dutch Bipolar Cohort focusing on bipolar disorder (DBC, total N=1453; cases BD=1255; controls=198) [163], and the Netherlands Study of Depression and Anxiety (NESDA, total N=1603; cases MDD=1166, BD=84; controls=353) [164,165], focusing on depressive disorders and anxiety. The distribution of diagnosis categories (MDD, BD, SZ) and controls in the total dataset, and for each cohort study, are displayed in Supplementary Figure 1. For the MR analyses, genetic data of 143,473 individuals with self-reported white European ancestry were retrieved from the UK Biobank, a large nation-wide cohort study from the United Kingdom [108], and from the Psychiatric Genomic Consortium (PGC) [64,166,167]. All procedures

contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

3.2.2. Assessments

Baseline assessments in the three cohort studies included history of current psychiatric disorders, standardized interview for DSM diagnosis or control status. In GROUP, the Comprehensive Assessment of Symptoms and History (CASH) [168] and Schedules for Clinical Assessment in Neuropsychiatry (SCAN) [169] were administered. DBC used the Structural Clinical Interview for DSM-IV (SCID-I) [170] and Mini-International Neuropsychiatric Interview-plus (MINI-plus) [171]. NESDA used the CIDI [154]. Inclusion criteria for the combined analysis were a diagnosis of a major psychiatric disorder at baseline with available data on symptom level, and on CM. Participants diagnosed with solitary anxiety disorder at baseline were excluded due to lack of data on the symptom level in this group. In NESDA, data from multiple waves were collapsed, and MDD was defined as a lifetime diagnosis of MDD. Participants without a history of mental disorder assessed by either the SCID-I, CIDI, CASH, MINI-plus or SCAN were included as controls. For assessment of CM under the age of 18 years, all three cohorts administered the CTQ [109,151]. Total CTQ-scores, subscale scores (physical abuse, emotional neglect, emotional abuse, physical neglect, and sexual abuse) and item-scores were reported in all cohorts. Incomplete CTQ scores (0.13% of items missing at random) were imputed at item-level using the multiple imputation algorithm for maximum likelihood (ML) estimation. Outcome ranges of pooled outcomes are presented in the result section. Based on the source publication of the CTQ [109,150,151], abuse was defined as moderate or above scores on only CTQ dimensions emotional abuse (score≥13), physical abuse (score≥10) or sexual abuse (score≥8). Neglect was defined as moderate or above scores for only emotional neglect (score≥15) or physical neglect (score≥10). Subjects scoring moderate or above on both neglect and abuse subscales were classified as combined CM. Lastly, subjects with CTQ subscale scores below cutoff for both abuse and neglect were classified as “no CM”. Comorbid psychiatric and somatic disorders were either unavailable or inconsistently reported across studies and were therefore not taken into account in the analysis.

3.2.3. Dataset harmonization on symptom level

The lifetime presence or absence of symptoms of SZ, BD, and MDD was reported for all participants of GROUP and DBC. In NESDA, SZ cases were not included since they fell outside the scope of the

study. Therefore, only the presence or absence of bipolar and depressive disorder symptoms was reported for NESDA participants. Patients with completely lacking symptom data were excluded. For the control group and for GROUP participants assessed with the SCAN, symptom data was not available. To harmonize the available data from the SCID-I, CIDI, and CASH, all symptoms were scored dichotomously, with 0= symptom not present, and 1= symptom is present. In the DBC study, symptoms coded as 2= "possibly present" (in <1% of cases) were recoded into 0=symptom not present. The SZ symptoms that were scored on a 5-point Likert scale were recoded into dichotomous variables. Symptoms with an original score of 0-2 were reclassified as 0: not/not fully present, not/moderately severe, or not/moderately bizarre. Symptoms with a score of 3-5 were reclassified as 1: present, severe, or bizarre. All symptoms were kept as detailed as possible, for instance hypersomnia and insomnia were both used instead of being merged into a broader term such as sleep disturbances. Some symptoms, however, needed to be combined due to differences in structure of the SCID-I, CIDI and CASH. Symptoms combined were, for MDD: weight loss + decreased appetite, weight gain + increased appetite, and for BD: expansive mood + irritable mood, increased activity + agitation. For SZ, all types of delusions were merged into presence or absence of delusions. The same was applied for hallucinations, merging all types into one variable indicating presence or absence of hallucinations.

3.2.4. Statistical analyses

The data was analyzed using Statistical Package for the Social Sciences (SPSS, v26; SPSS Inc., Chicago, Illinois, USA). Chi-square tests were performed for analyzing differences in the distribution between groups. In a multivariate logistic regression model, the contribution of CM types of abuse, neglect, and combined CM was modelled as three dichotomous indicators (with no CM as reference) with presence/absence of each diagnosis as the outcome. A significant Wald-test statistic for one of the CM types indicated that the experience of this CM type increased the likelihood of a certain diagnosis, as compared to the reference group of no CM. Subsequently, differences between abuse, neglect, and combined CM were analyzed in turn by adapting the reference categories. Similarly, the contribution of CTQ subtypes emotional abuse (EA), physical abuse (PA), sexual abuse (SA), emotional neglect (EN), and physical neglect (PN) for each diagnosis was estimated in a multivariate logistic regression model. At the symptom level, the contribution of abuse, neglect, and combined CM was estimated in a multivariate logistic regression model (with no CM as reference) for the presence or absence of each symptom as a dichotomous outcome. For all these analyses the assumptions were verified and met.

Logistic regression results are presented as odds ratios (OR) with 95% confidence intervals (95%CIs). Confounder analysis was performed by examining the relation of age, gender, and level of education (none, basic, low, intermediate, and high) as determinants, with CM types and diagnosis as the outcome. For education, educational level was coded by using four dummy variables signifying the difference compared to no education. Variables with a significant association with both diagnosis and CM were added as covariates to the multivariate models. Significance of the differences between the OR of a particular CM type between disorders was estimated with the same multivariate logistic regression models but alternating diagnosis categories as reference category in order to obtain head-to-head comparisons (for instance for the contribution of abuse to MDD as compared to SZ).
The Relative Excess Risk due to Interaction (RERI) [172,173] was calculated to measure the deviation from additivity of the exposure effect on an odds ratio scale [174]. A RERI<1 indicates a negative interaction and a RERI=0 means no interaction or exact additivity. If RERI>0, an interaction on an additive scale is indicated, meaning that the combined effect of two exposures is larger than the sum of the individual effects of the two exposures.

3.2.5. Mendelian Randomization

For MR investigation, instrumental variable (IV) for CM types was derived from the previous GWAS study of CM in the UK Biobank [108]. The UK Biobank participants completed the Childhood Trauma Screener (CTS), a retrospectively reported five-item questionnaire that consists of one question per childhood maltreatment subtype, with answers ranging from 0: never true, to 4: very often true [175]. Abuse was defined when one or more CTS abuse items were scored >0, neglect when one or more neglect items were scored >0 and combined CM when abuse and neglect were both present. To perform bidirectional, two-sample MR, all available genetic data of UK Biobank participants with self-reported white European ancestry were included for GWAS of traits abuse, neglect and combined childhood maltreatment. Therefore, three new GWAS were generated. All genotyped and imputed SNPs with a minor allele frequency >0.1%, that did not deviate from Hardy-Weinberg equilibrium ($p>1\times10^{-6}$), had a genotyping rate of 95%, or, for imputed SNPs, had an imputation R^2 >0.4, were used. Participants who had excessive genetic heterozygosity (i.e., who were >5 SD from the means of the first two genetic principal components), whose genetic sex did not match their reported sex or who had a genotyping rate <95%, were excluded. GWAS were conducted for over 15 million SNPs using FastGWA-GLMM

(software GCTA, version 1.93.2) [176]. Sex, year of birth, genotyping batch, and the first 10 genetic principal components (PCs) were included as covariates.

Two-sample MR [177,178] was performed to assess causal effects of abuse, neglect, and combined CM on SZ [64], BD [167], and MDD [166]. Putative causal links between CM type and diagnosis were investigated bidirectionally, i.e., whether a genetic predictor of CM type enhances the risk of SZ, BD, and MDD (forward direction) or whether CM type liability is altered because of liability to SZ, BD, or MDD (backward direction). To avoid bias in MR due to sample overlap [179], genetic data for the three mental health phenotypes of interest were sourced in the PGC, excluding UK Biobank participants. In the first attempt to extract instruments using independent GWAS loci, the standard p-value threshold of $p<5\times10^{-8}$ was used. This p-value threshold is applied in the MR backward analyses. In the MR forward analyses, no SNPs were selected at a p-value threshold of $p<5\times10^{-8}$, therefore the p-value threshold was stepwise increased until at least 2 SNPs were selected. This led to a threshold of $p<1\times10^{-6}$. As a follow-up analysis, designed to interrogate the influence of threshold variation and in order to gauge potential pleiotropy, the p-value threshold was further increased until the highest number of SNPs was included without significant evidence of horizontal pleiotropy as measured by the Egger's test (corresponding to the threshold $p<3\times10^{-6}$). Then, to ensure independence between IVs, a strict clumping procedure was applied (LD $r2< 0.001$ within 10 Mb, using the 1000G EUR as the reference panel). Following that, SNP alleles were harmonized between exposure GWAS and outcome GWAS before running the MR analyses. Each MR analysis was conducted using the following methods: inverse variance-weighted (IVW) MR, which assumes that all SNPs are valid instruments; weighted median (WM) MR, which provides valid estimates even if up to 50% of the instruments are invalid [180]; Q statistic, as an assessment of heterogeneity and first indicator of whether there might be pleiotropy; MR-Egger, which accounts for pleiotropy by including an intercept term in the IVW model [83]; and MR-PRESSO, which accounts for pleiotropy by detecting and removing outliers [84]. The mean F statistic was used to quantify instrument strength within the univariable IVW analyses, considering a mean $F<20$ as indicative of weak instruments. The Steiger test was used to assess the validity of IVs and confirm the direction of causality [85]. All analyses were performed in R [158], using the package *TwoSampleMR* [181].

3.3. MONEY study

3.3.1. Study design and data sources

We conducted a two-sample MR study using summary-level GWAS data that for the most part was publicly available. Specifically, for this study new GWAS on HI and SD were performed using UK Biobank data under application number 10279 (see Data availability section for the link to these data); OI data are publicly available and can be downloaded from https://osf.io/rg8sh/; CA data were obtained from the author of the relevant publication [89]); finally, the summary statistics files for the mental disorder phenotypes are publicly available for download from the PGC website https://pgc.unc.edu/for-researchers/download-results/. Ethical approval was obtained in all original studies.

The schematic overview of the study is represented in Figure 2.

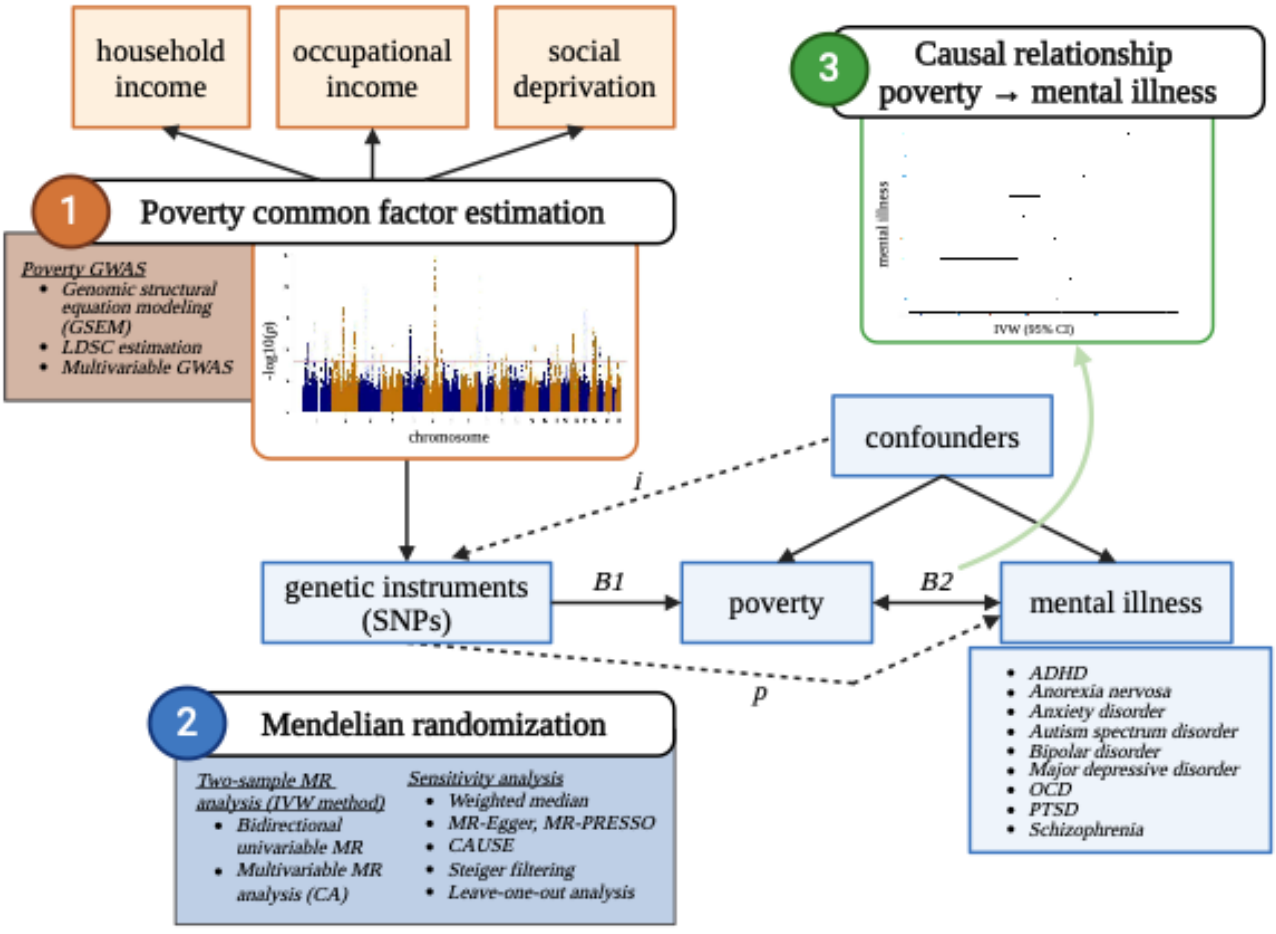


Figure 2: Research design.

Legend: $\beta 1$ is the association between the genetic variants and the exposure of interest (MR relevance assumption), i is the potential violation of the MR independence assumption, p is the potential

pleiotropic effect of the genetic variants on the outcome (that is, violation of the MR exclusion restriction assumption) and *β2* is the causal association of interest.
Created with BioRender.com.

3.3.2. Poverty and cognitive ability instruments

For this research, seven new GWAS were performed: five on HI, one on SD, and one on common factor of poverty. The GWAS on CA and OI were publicly available. A total of 379,598 participants of European ancestry provided genotype data and data on their level of yearly HI before tax. HI was primarily analyzed as a continuous variable. To investigate whether the relation between HI and mental disorder is particularly strong at any specific level of income, we further categorized HI as a dichotomous variable, defining the cases in the following way: (1) low HI: being less than £18,000; (2) low-mid HI: being less than £29,999; (3) mid-high HI: being more than £52,000; (4) high HI: being more than £100,000. One GWAS for each HI category versus all the other categories was performed. A total of 440,350 individuals of European ancestry had genotype data and data on their level of SD, measured with Townsend Deprivation index, and it was analyzed as a continuous variable. GWAS of HI and SD were performed in REGENIE [182]. REGENIE v3.1.3 is a two-step GWAS software that accounts for sample relatedness and population structure. In the first step, a whole genome regression model was fit to each trait using 581,097 post-QC genotype variants. In the second step, association test was performed for each of the 25,590,374 post-QC imputed variant using a leave-one-chromosome out (LOCO) scheme. The per-chromosome LOCO genomic predictions produced in the first step were fitted in the second step to account for sample relatedness and population structure. In addition, sex, age at assessment, assessment centers, genotyping array, genotyping bathes, and the first 40 PCs were fitted as covariates in both steps. For binary phenotypes, firth logistic regression test was performed in the second step to account for unbalanced case-control ratio. Afterwards, variants with MAF < 0.0005 and INFO < 0.3 in each subset were removed, resulting in 20,408,331 final variants for HI related phenotypes and 20,413,590 for SD.
Previously published GWAS summary data on cognitive ability of 248,482 individuals was included [89]. The CA measure was meta-analyzed from an already existing dataset of multiple cohorts that each had administered a battery of cognitive tests to their participants [89]. Correlations between tests of CA are high with estimates between r = 0.8 and r = 1.0 being reported [183,184]. There are two principal stages to this meta-analysis. First, publicly available GWAS summary statistics from Sniekers et al. [185] were

meta-analyzed with 120,934 participants from UK Biobank who took the test of verbal numerical reasoning using a sample size weighted meta-analysis [186]. This resulted in a sample size of 199,242. Second, data from these 199,242 participants was meta-analyzed with the publicly available GWAS summary statistics on educational attainment from Okbay et al. [187] using multi trait analysis of genome-wide association studies (MTAG) [188]. MTAG allows for the meta-analysis of genetically correlated traits in order to increase the statistical power in any one of those traits. In this study, CA was analyzed as a continuous variable.

Results from a meta-analysis of two OI GWAS [90], including UK Biobank and the Health and Retirement Study (the latter involving participants from White American ancestry), were used to generate the instruments for OI which were analyzed as continuous variable.

We estimated a latent factor GWAS of poverty (PF) by jointly modelling cross-trait liability of continuous HI, OI, and SD, using common factor model in GSEM [143]. Before running the multivariable GWAS, the alleles across HI, SD, and OI traits were aligned using the HAPMAP3 reference panel, and summary statistics passed quality control by selecting SNPs with minor allele frequency (MAF) >0.01 and INFO >0.9. Then, we estimated the Multivariable Linkage Disequilibrium Score Regression (LDSC) [189] across HI, OI, and SD using 1000G European reference panel. Finally, we combined the LDSC output with the HI, OI, and SD summary statistics to run the multivariable common factor GWAS. This common PF GWAS was built using as unit of identification HI, and the effective sample size was 453,689. To allow estimation of poverty - instead of income – in the MR analyses on mental disorder, the regression coefficients have been reversed.

3.3.3. Mental disorder instruments

Results from the most updated GWAS of ADHD [190], AN [191], ANX [192], ASD [193], BD [167], MDD [166], OCD [194], PTSD [195], and SZ [64] were obtained. Two-sample MR method requires minimal sample overlap between exposure and outcome GWAS [179]; therefore, mental disorder summary-level data were obtained mainly from the PGC excluding UK Biobank participants. The GWAS of the mental disorder traits considered were provided and analyzed as case/control. The effective sample size across the cohorts contributing to the GWAS meta-analysis was calculated for each trait and ranged from 320k (for SZ) to 10k (for OCD). Table 1 summarizes the GWAS information.

Table 1: GWAS information for each phenotype.

Trait	N	N cases	Consortium	First author, Year
Attention Deficit Hyperactivity Disorder	225,534	38,691	PGC	Demontis et al., 2023 [190]
Anorexia Nervosa	72,517	16,992	PGC	Watson et al., 2019 [191]
Anxiety Disorder	21,761	7,016	PGC	Otowa et al., 2016 [188]
Autism Spectrum Disorders	46,350	18,381	PGC	Grove et al., 2019 [193]
Bipolar Disorder	413,466	41,917	PGC	Mullins et al., 2021 [167]
Cognitive Ability	248,482	NA	UKB	Hill et al., 2018 [89]
Household Income	379,598	NA	UKB	NA
Major Depressive Disorder	138,884	43,204	PGC	Howard et al., 2019 [166]
Obsessive-Compulsive Disorder	9,725	2,688	PGC	Arnold et al., 2018 [194]
Occupational Income	282,963	NA	NA	Kweon et al., 2020 [90]
Post-Traumatic Stress Disorder	206,655	32,428	PGC	Nievergelt et al., 2019 [195]
Social Deprivation	440,350	NA	UKB	NA
Schizophrenia	320,404	76,755	PGC	Trubetskoy et al., 2022 [64]

Legend: Traits are presented in alphabetical order.

Abbreviations: N: number (e.g., sample size); PGC: Psychiatric Genomics Consortium; NA: not applicable; UKB: UK Biobank.

3.3.4. Mendelian Randomization

The full set of GWAS summary statistics for each exposure was first restricted to the variants reaching the genome-wide significance threshold (i.e., p-value$<5\times10^{-8}$). Then, to ensure independence between instruments, we applied a strict clumping procedure (LD r2$<$ 0.001 within 10 Mb, using the 1000G EUR as the reference panel). Following that, SNP alleles were harmonized between exposure GWAS and outcome GWAS, using action=2 (which try to infer positive strand alleles, using allele frequencies for palindromes), before running MR.

We conducted bidirectional univariable MR between each poverty measure and mental disorder. The IVW method was used to estimate effects in the primary analyses [196] and the results were presented using forest plots. The WM [180], MR-Egger [83], and MR-PRESSO [84] methods were used as sensitivity analyses, because each method makes different assumptions regarding instrument validity. Specifically, MR-Egger and MR-PRESSO are better than IVW in case of horizontal pleiotropy (i.e., violation of the exclusion restriction assumption). MR-PRESSO test identifies possible bias from horizontal pleiotropy. The test consists of three parts. (1) the MR-PRESSO global test which detects horizontal pleiotropy. (2) the outlier corrected causal estimate which corrects for the detected horizontal pleiotropy and (3) the

MR-PRESSO distortion test which estimates if the causal estimate is significantly different (at $p<0.05$) after adjustment for outliers. We conduct all three stages (with the argument NbDistribution=1000. namely using 1000 simulation form the null distribution to compute empirical p-values) and present the outlier adjusted causal estimates (OACE) when both global and distortion tests are significant.

In addition, we used the Causal Analysis Using Summary Effect Estimates (CAUSE) [197] to account for the presence of correlated or uncorrelated pleiotropy (i.e., violation of the independence and exclusion restriction assumptions). CAUSE grounds on estimating two models. One under the assumption that the relation between the instrument and the outcome is due to a pleiotropic effect (i.e., the shared model). and the second assuming that the relation is due to causal effect (i.e., the causal model). CAUSE also provides a test that the posteriors estimated under the causal model fit the data significantly better than posteriors estimated under the sharing model. If this is the case, it is possible to conclude that the data are consistent with a causal effect. CAUSE consists in 4 steps: (1) format the data for use with CAUSE; (2) calculate nuisance parameters; (3) LD pruning; (4) fit CAUSE. We estimated nuisance parameters setting a random subset of 1,000,000 variants and performed LD pruning setting R2 threshold to 0.01 and p-value threshold to 0.001.

We presented the results of MR analyses as Beta (B) corresponding to the log-odds for binary traits (e.g., mental disorder) or to the unstandardized linear regression coefficients for continuous traits (e.g., poverty measures) with their respective 95%CI. When the outcome of the analysis was binary (i.e., mental disorder and HI levels) we also provided a conversion to OR with corresponding 95%CI.

We also conducted leave-one-out analyses to investigate if the effects are driven by one or a subset of the SNPs and investigated whether the instruments represent the correct causal direction using Steiger analyses, including Steiger test and Steiger filtering [85]. Steiger filtering is particularly useful to avoid false positive findings due to reverse causation (i.e., violation of the exclusion restriction assumption). The *mr_wrapper()* function of the *TwosampleMR* package performs Steiger tests on each SNP, evaluating if the R^2 of the exposure was greater than the R^2 of the outcome, indicating the correct direction of the association. Subsequent Steiger filtering excluded SNPs with false results, allowing MR analyses to be performed on the subset of SNPs with verified associations.

Finally, we hypothesized that CA is likely involved in the poverty and mental disorder causal pathway, and our instruments for poverty are possibly related to CA. Therefore, we used MVMR [81] to estimate the direct effect of poverty on mental disorder, independent of CA. For this purpose, we clumped the full list of SNPs from each poverty indicator GWAS (to ensure only independent SNPs are included)

and restricted it to those SNPs found in the outcome GWAS and then ran the analyses on each instruments-mental disorder set.

Instrument strength was quantified using the mean F statistic within the univariable IVW analyses, considering a value of F <20 as indicative of weak instruments [198].

All the analyses were conducted in R [158], using the packages *TwosampleMR* [181], *CAUSE* [197], and *GenomicSEM* [143]. Statistical tests were two-tailed. The significance threshold was $p<0.05$. Since there is only one relationship that is tested - that between poverty and mental disorder - we did not apply a multiple testing p-value correction.

4. Results

4.1. TRAIL study

4.1.1. Description of the sample(s)

The main characteristics of both the discovery and replication samples are displayed in Table 2. There was no significant difference in the male/female ratio between the two cohorts ($p=0.986$). UCC participants were older ($p<0.001$), more exposed to cannabis ($p<0.001$) and reported more PLE ($p<0.001$) than those from IMAGEN which, however, reported higher exposure to CM ($p<0.001$). Missing data were imputed using case-wise maximum likelihood estimation for all the variable except for the outcome (i.e., CAPE). In the UCC there were no missing response items to the CAPE, therefore all missing data were imputed, and the imputed/missing ratio was 1; whereas in the IMAGEN that ranged from 0.03 (for gender) to 0.57 (for CTQ).

Table 2: Characteristics of the discovery sample and the replication sample

Variable	**Discovery sample UCC (N=1262)**	**Missing rates (%†)**	**Replication sample IMAGEN (N=2035)**	**Missing rates (%†)**
Male gender (%)	606 (48%)	0%	813 (47%)	305 (15%)
Age, mean (SD) in year	20.5 (2.5)	0%	19.4 (1.5)	529 (26%)
CTQ score, mean (SD)	31.9 (8.4)	341 (27%)	40.2 (6.5)	691 (34%)
Cannabis exposure ≥10 lifetime (%)	404 (32%)	0%	361 (24%)	529 (26%)
Tobacco daily consumption for at least 30 days in the last year (%)	227 (30%)	505 (40%)	594 (40%)	549 (27%)

CAPE-42 score, mean (SD)	67.3 (13.9)	0%	60.6 (11.4)	295 (14%)

Abbreviations: SD: standard deviation; CTQ: Childhood Trauma Questionnaire; CAPE: The Community Assessment of Psychic Experiences.

† The proportion of participants in which a response item was missing. The number of imputed data corresponds to the difference between the number of missing data for each variable and the number of missing data in the outcome (i.e., CAPE-42 score).

4.1.2. PRS p-threshold selection

In order to focus on PLE as the main outcome we selected optimal PRS-SZ p-value threshold by LASSO regression, which selected 3 out of 13 PRS-SZ pt as best predictors of PLE in the UCC. As can be seen in Supplementary Table 1, the highest explained variance for PLE was with SZ-PRS pt 0.5 (R^2=0.014), which was selected as the indicator of the genetic risk to schizophrenia in the subsequent analyses.

4.1.3. Linear regression

From the multivariate linear regression, both CM and SZ-PRS significantly increased the level of PLE in the UCC (unstandardized regression beta [B]=0.644, p<0.001; B=0.253, p=0.003, respectively), above and beyond the influence of age and gender.

4.1.4. Multiple mediation analysis in the discovery sample (UCC)

From the multiple mediation analysis conducted in the UCC, the genetic vulnerability to SZ influenced the level of PLE both directly and indirectly through its effect on CM. Furthermore, cannabis use was a significant mediator too.

Table 3 and Figure 3 (Panel A) show that subjects with higher load of SZ-PRS experienced more PLE (B=0.190), and subjects who were exposed to CM and cannabis reported more PLE (B=0.575, and B=2.71, respectively). The bootstrap 95% CIs for the indirect effect of both CM (B=0.098) and cannabis use (B=0.040) were entirely above zero (0.039 to 0.158, and 0.013 to 0.067, respectively), consistent with a significant contribution of SZ-PRS to PLE through cannabis and CM.

4.1.5. Multiple mediation analysis in the replication sample (IMAGEN cohort)

Table 3 and Figure 3 (Panel B) show the parallel multiple mediator model in the independent IMAGEN cohort. The indirect effect of SZ-PRS through CM (B=0.299) was confirmed (bootstrap 95% CI: 0.076 to 0.522). In contrast to the findings in the discovery set, neither the direct (B=0.489; p=0.131) nor the indirect effect through cannabis use (B=0.074 [bootstrap 95% CI: -0.001; 0.149]) were replicated, which imply a full mediation played by CM in the replication IMAGEN cohort.

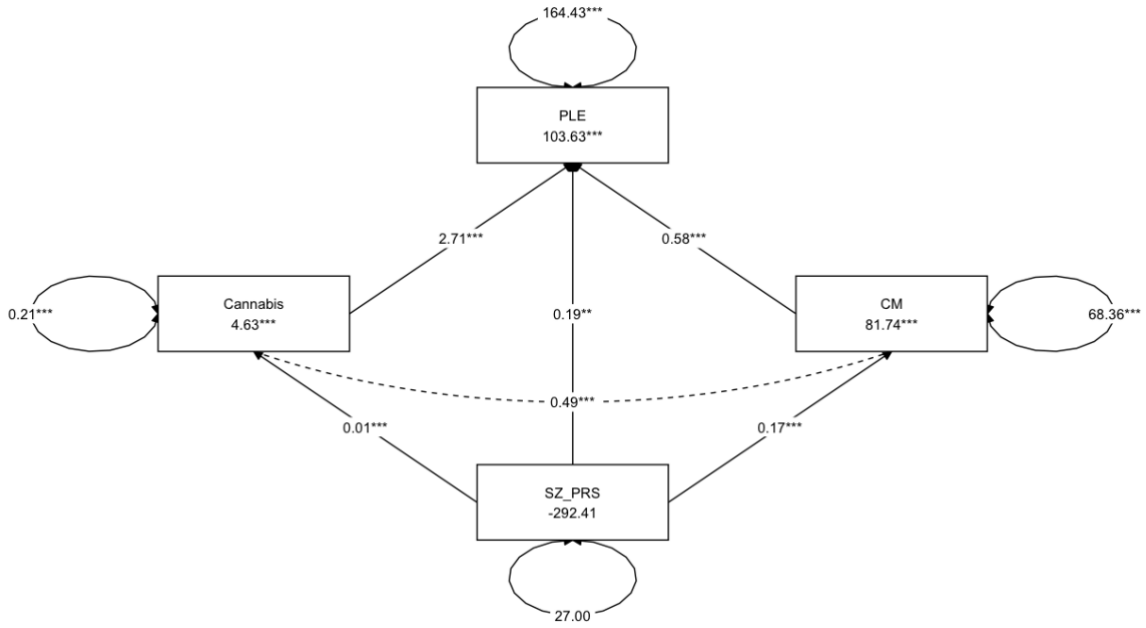
Table 3: Results of parallel multiple mediator model in the discovery sample (UCC - above) and in the replication sample (IMAGEN cohort - below)

Regressions	**Unstandardized estimate (95% CI)**	**Standardized estimate**	**p-value**
	UCC		
Direct effects			
Outcome model: PLE (R^2=0.148)			
SZ-PRS	0.190 (0.048; 0.331)	0.071	0.009
CM	0.575 (0.480; 0.671)	0.344	<0.001
Cannabis use	2.71 (1.12; 4.30)	0.091	0.001
Mediator model: CM (R^2=0.011)			
SZ-PRS	0.171 (0.072; 0.270)	0.107	0.001
Mediator model: Cannabis use (R^2=0.027)			
SZ-PRS	0.015 (0.010; 0.020)	0.164	<0.001
Covariances			
CM – Cannabis use	0.489 (0.248; 0.730)	0.129	<0.001
Indirect effects (proportion mediated)			
CM (29.9%)	0.098 (0.039; 0.158)	0.037	0.001
Cannabis (12.2%)	0.040 (0.013; 0.067)	0.015	0.004
Sum	0.138 (0.073; 0.204)	0.052	<0.001
Total effect	0.328 (0.181; 0.474)	0.123	<0.001
	IMAGEN cohort		
Direct effects			
Outcome model: PLE (R^2=0.114)			

SZ-PRS	0.489 (-0.145; 1.12)	0.042	0.131
CM	0.496 (0.402; 0.589)	0.316	<0.001
Cannabis use	1.79 (0.302; 3.27)	0.067	0.018
Mediator model: CM (R^2=0.007)			
SZ-PRS	0.603 (0.170; 1.04)	0.082	0.006
Mediator model: Cannabis use (R^2=0.009)			
SZ-PRS	0.041 (0.017; 0.065)	0.095	0.001
Covariances			
CM – Cannabis use	0.389 (0.191; 0.588)	0.123	<0.001
Indirect effects (proportion mediated)			
CM (34.7%)	0.299 (0.076; 0.522)	0.026	0.009
Cannabis (8.6%)	0.074 (-0.001; 0.149)	0.006	0.054
Sum	0.373 (0.135; 0.611)	0.032	0.002
Total effect	0.862 (0.200; 1.52)	0.075	0.011

Abbreviations: 95% CI: 95% bias-corrected bootstrap confidence interval; UCC: Utrecht cannabis cohort; PLE: psychotic-like experiences; CM: childhood maltreatment; SZ-PRS: schizophrenia polygenic risk score at p-value threshold 0.5.

Panel A: UCC



Panel B: IMAGEN

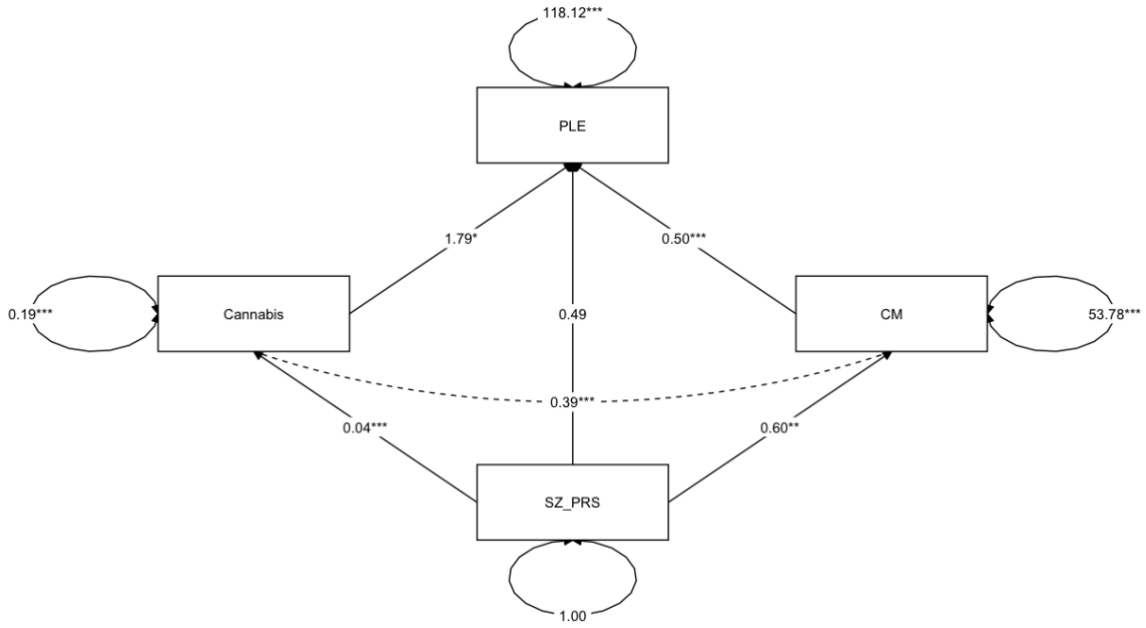


Figure 3: Path diagram of parallel multiple mediator model in the discovery sample (Panel A. UCC above) and in the replication sample (Panel B. IMAGEN cohort, below).

Legend: the estimates reported are the unstandardized regression coefficients. *p<0.05; **p<0.01; ***p<0.001.

Abbreviations: SZ-PRS: schizophrenia polygenic risk score at p-value threshold 0.5; CM: childhood maltreatment; PLE: psychotic-like experiences.

4.1.6. Sensitivity analysis for mediation and genetic threshold for mediation

Sensitivity analysis for the causal mediation effect of CM was conducted by calculating the correlation across the residual errors of the mediator and outcome models, defined as ρ (rho), which serves as the sensitivity parameter [199]. We derived the mediation effect as a function of ρ and interpreted ρ via the R^2 for understanding the influence of potential omitted variables in terms of its explanatory power (see Supplementary Figure 2 and Supplementary Figure 3 for graphical representations). In our model, the value of ρ at which the causal mediation effect of CM equals zero was 0.35, meaning that to nullify our conclusions a confounder would have to explain at least 12% (R^2=0.123) of the variance in CM thus supporting the robustness of our findings.

In order to test the robustness of our analytic procedure, and to alleviate any concerns with respect to the selection of PRS pt optimal for PLE rather than CM, we fitted the main model also for the PRS pt which best predicted CM (i.e., PRS-SZ pt 0.3). PRS-SZ pt 0.5 and pt 0.3 were highly correlated (r=0.99). The results were identical, and the proportion mediated only changed at the decimal place (proportion mediated=30.2%).

To understand at which level of genetic risk the mediation comes into play, we simulated a sample of ten times bigger size than the UCC with otherwise the same characteristics. Then, we repeated the multiple mediation analysis by stepwise removing the highest fifth percentile of genetic risk until the causal mediation effect became void (i.e., the bootstrap 95% CI included zero). This inductive approach allowed us to estimate that mediation by CM come into play for individuals at the 60th percentile of PRS-SZ.

4.1.7. Exploring other models and confounder analysis

To investigate the impact of potential confounders, some complementary models were assessed. Specifically, we aimed to account for neurotic traits of personality - since these may affect the self-reporting in questionnaires [200] - and tobacco smoking, given the strong correlation with cannabis use and previous studies showing its impact on PLE [201,202]. As shown in Table 4 and Figure 4, from the four-mediator path analysis, the SZ-PRS influenced the level of PLE both directly (B=0.187) and indirectly through CM and cannabis exposure (B=0.038 [bootstrap 95% CI: 0.003; 0.073] and B=0.035

[bootstrap 95% CI: 0.002; 0.068], respectively). Although SZ-PRS influenced nicotine exposure (B=0.012) and neurotic traits influenced the self-reporting of PLE (B=0.302), overall, there was no evidence for mediation by nicotine and neuroticism (B=0.029 [bootstrap 95% CI: -0.002; 0.059] and B=0.075 [bootstrap 95% CI: -0.036; 0.186], respectively). Also, the reported mediating role of CM was largely unchanged.

Table 4: Results of parallel four-mediator model in the discovery sample (UCC)

Regressions	**Unstandardized estimate (95% CI)**	**Standardized estimate**	**p-value**
Direct effects			
Outcome model: PLE (R^2=0.424)			
SZ-PRS	0.187 (0.035; 0.339)	0.072	0.016
CM	0.223 (0.117; 0.328)	0.143	<0.001
Cannabis use	2.78 (0.538; 5.02)	0.094	0.015
Neuroticism	0.302 (0.265; 0.338)	0.541	<0.001
Nicotine	2.57 (0.168; 4.61)	0.082	0.035
Mediator model: CM (R^2=0.011)			
SZ-PRS	0.172 (0.036; 0.307)	0.103	0.013
Mediator model: Cannabis use (R^2=0.021)			
SZ-PRS	0.013 (0.006; 0.019)	0.144	<0.001
Mediator model: Neuroticism (R^2=0.003)			
SZ-PRS	0.247 (-0.120; 0.614)	0.053	0.186
Mediator model: Nicotine (R^2=0.018)			
SZ-PRS	0.012 (0.006; 0.018)	0.136	<0.001
Covariances			
CM – Cannabis use	0.389 (0.065; 0.713)	0.101	0.018
CM – Neuroticism	80.89 (62.81; 98.97)	0.390	<0.001
CM – Nicotine	0.149 (-0.183; 0.481)	0.038	0.379
Cannabis – Nicotine	0.129 (0.112; 0.146)	0.628	<0.001
Cannabis – Neuroticism	0.080 (-0.791; 0.951)	0.007	0.858
Neuroticism – Nicotine	0.472 (-0.423; 1.37)	0.043	0.301
Indirect effects (proportion mediated)			
CM (10.5%)	0.038 (0.003; 0.073)	0.015	0.033

Cannabis (9.6%)	0.035 (0.002; 0.068)	0.013	0.038
Neuroticism (20.7%)	0.075 (-0.036; 0.186)	0.029	0.188
Nicotine (8.0%)	0.029 (-0.002; 0.059)	0.011	0.065
Sum	0.176 (0.045; 0.308)	0.068	0.009
Total effect	0.363 (0.181; 0.545)	0.140	<0.001

Abbreviations: 95% CI: 95% bias-corrected bootstrap confidence interval; PLE: psychotic-like experiences; CM: childhood maltreatment; SZ-PRS: schizophrenia polygenic risk score at p-value threshold 0.5.

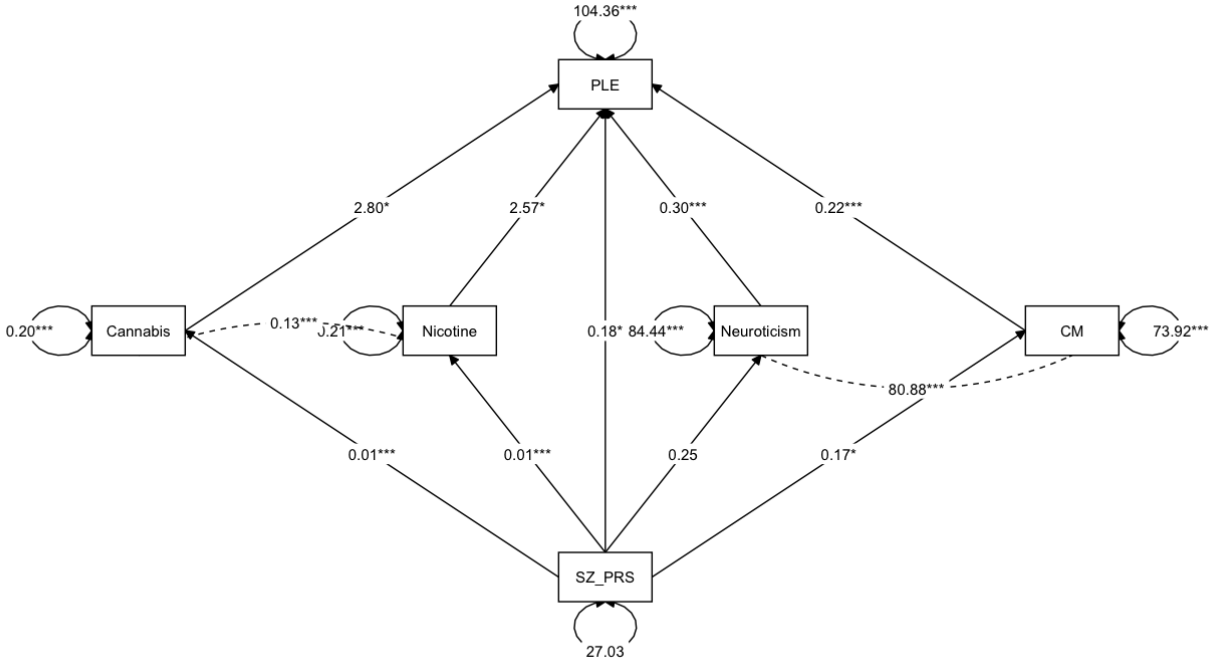


Figure 4: Path diagram of parallel four-mediator model in the discovery sample (UCC).
Legend: the estimates reported are the unstandardized regression coefficients. *p<0.05; **p<0.01; ***p<0.001.
Abbreviations: SZ-PRS: schizophrenia polygenic risk score at p-value threshold 0.5; CM: childhood maltreatment; PLE: psychotic-like experiences.

Finally, to investigate the influence of other potential confounders on the relationship between SZ-PRS and PLE, we examined the role of population stratification (using the first three PCs 1-3), age, and gender. We used a two-step procedure, whereby firstly we calculated the correlation between the

potential confounders and the outcome (i.e., PLE) and the main predictor (i.e., SZ-PRS). Those displaying a correlation coefficient higher than 0.7, or p-value<0.05, were subsequently included in a linear model to check whether the predictor's beta coefficient changed more than 10%, suggesting that the variable in question is likely a confounder, that needs to be controlled. The only variable that passed the first step was PC1, which resulted significantly associated with SZ-PRS (p<0.001), but affected the beta <10%, so it was not included in the models.

4.1.8. Exploring CM types and PLE subdomains

We explored which type of CM (based on subscores of the CTQ) was the strongest mediator of the relationship between SZ-PRS and the level of PLE. Results are displayed in Table 5 and Figure 5: emotional abuse had the largest effect size on PLE (B=1.49), and relevant association with SZ-PRS (B=0.038) but did not significantly mediate the effect of SZ-PRS on PLE (B=0.057 [bootstrap 95% CI: -0.002; 0.117]). Only emotional neglect was a significant mediator in the relationship between SZ-PRS and PLE (B=0.037 [bootstrap 95% CI: 0.007; 0.068]).

Table 5: Results of parallel multiple mediation analysis according to the trauma subtype in the discovery sample (UCC)

Regressions	**Unstandardized estimate (95% CI)**	**Standardized coefficient**	**p-value**
Direct effects			
Outcome model: PLE (R^2=0.168)			
SZ-PRS	0.242 (0.102; 0.382)	0.091	0.001
Sexual Abuse	0.287 (-0.137; 0.711)	0.044	0.184
Physical Abuse	-0.854 (-1.45; -0.257)	-0.099	0.005
Emotional Abuse	1.49 (1.19; 1.79)	0.354	<0.001
Physical Neglect	0.278 (-0.178; 0.735)	0.036	0.232
Emotional Neglect	0.481 (0.221; 0.742)	0.126	<0.001
Mediator model: Sexual abuse (R^2=0.002)			
SZ-PRS	-0.018 (-0.044; 0.008)	-0.044	0.176
Mediator model: Physical abuse (R^2=0.007)			
SZ-PRS	0.025 (0.006; 0.045)	0.082	0.010
Mediator model: Emotional abuse (R^2=0.004)			

SZ-PRS	0.038 (-0.001; 0.078)	0.061	0.006
Mediator model: Physical Neglect (R^2=0.003)			
SZ-PRS	0.019 (-0.003; 0.041)	0.055	0.090
Mediator model: Emotional neglect (R^2=0.012)			
SZ-PRS	0.077 (0.029; 0.126)	0.111	0.002
Indirect effects (proportion mediated)			
Sexual abuse (1.6%)	-0.005 (-0.016; 0.006)	-0.002	0.346
Physical abuse (7.0%)	-0.022 (-0.044; 0.001)	-0.008	0.060
Emotional abuse (18.1%)	0.057 (-0.002; 0.117)	0.021	0.060
Physical neglect (1.6%)	0.005 (-0.005; 0.016)	0.002	0.326
Emotional neglect (11.7%)	0.037 (0.007; 0.068)	0.014	0.017
Sum	0.073 (0.003; 0.134)	0.027	0.041
Total effect	0.315 (0.169; 0.461)	0.188	<0.001

Abbreviations: 95% CI: 95% bias-corrected bootstrap confidence interval; PLE: psychotic-like experiences; SZ-PRS: schizophrenia polygenic risk score at p-value threshold 0.5.

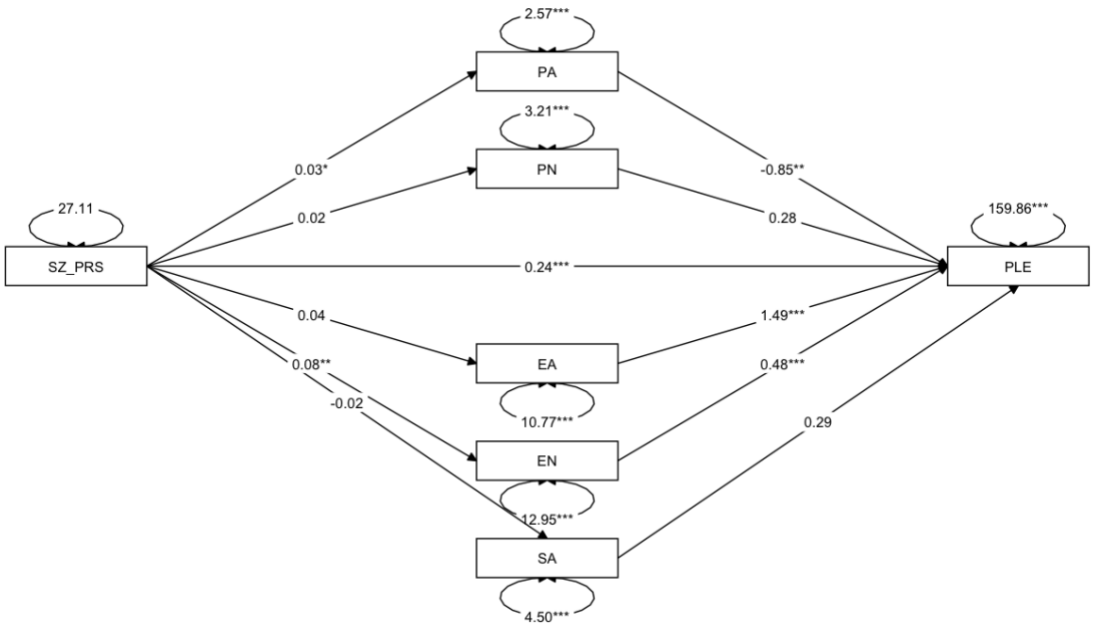


Figure 5: Path diagram of parallel multiple mediation analysis according to trauma subtype in the discovery sample (UCC).

Legend: the estimates reported are the unstandardized regression coefficients. *p<0.05; **p<0.01; ***p<0.001.
Abbreviations: SZ-PRS: schizophrenia polygenic risk score at p-value threshold 0.5; PLE: psychotic-like experiences; PS: physical abuse; PN: physical neglect; EA: emotional abuse; EN: emotional neglect; SA: sexual abuse.

The assessment of which PLE dimension (i.e., depression, negative, positive symptoms) is more affected by the set of predictors showed that the negative domain was influenced by SZ-PRS both directly (B=0.106) and indirectly through cannabis use and CM (B=0.023 [bootstrap 95% CI: 0.009; 0.037], and B=0.042 [bootstrap 95% CI: 0.017; 0.067]). PRS-SZ influenced the depressive dimension both directly (B=0.040) and indirectly only via CM (B=0.026 [bootstrap 95% CI: 0.011; 0.042]). Finally, the lack of correlation between PRS-SZ and the positive dimension, but significant indirect effect through CM (B=0.033 [bootstrap 95% CI: 0.012; 0.054]) and cannabis use (0.027 [bootstrap 95% CI: 0.012; 0.042]) is suggesting mediators to have a suppressor effect in that association. The results are displayed in Table 6 and Figure 6.

Table 6: Results of multiple outcome parallel mediation model in the discovery sample (UCC)

Regressions	**Unstandardized estimate (95% CI)**	**Standardized coefficient**	**p-value**
Direct effects			
Outcome model: PLE depression (R^2=0.131)			
SZ-PRS	0.040 (0.004; 0.077)	0.059	0.031
CM	0.150 (0.125; 0.175)	0.352	<0.001
Cannabis use	-0.083 (-0.493; 0.327)	-0.011	0.691
Outcome model: PLE negative (R^2=0.122)			
SZ-PRS	0.106 (0.036; 0.175)	0.082	0.003
CM	0.238 (0.191; 0.286)	0.295	<0.001
Cannabis use	1.56 (0.781; 2.33)	0.108	<0.001
Outcome model: PLE positive (R^2=0.075)			
SZ-PRS	0.037 (-0.037; 0.111)	0.028	0.322
CM	0.189 (0.141; 0.238)	0.223	<0.001
Cannabis use	1.81 (0.985; 2.64)	0.120	<0.001

Mediator model: CM (R^2=0.012)			
SZ-PRS	0.174 (0.075; 0.274)	0.109	0.001
Mediator model: Cannabis use (R^2=0.027)			
SZ-PRS	0.015 (0.010; 0.020)	0.164	<0.001
Covariances			
CM – Cannabis use	0.483 (0.242; 0.724)	0.127	<0.001
Indirect effects (proportion mediated)			
CM ~ PLE depression (7.8%)	0.026 (0.011; 0.042)	0.038	0.001
CM ~ PLE negative (12.7%)	0.042 (0.017; 0.067)	0.032	0.001
CM ~ PLE positive (9.9%)	0.033 (0.012; 0.054)	0.024	0.002
Cannabis ~ PLE depression (0.3%)	-0.001 (-0.007; 0.005)	-0.002	0.692
Cannabis ~ PLE negative (6.9%)	0.023(0.009; 0.037)	0.018	0.001
Cannabis ~ PLE positive (8.1%)	0.027 (0.012; 0.042)	0.020	0.001
Sum CM (30.4%)	0.101 (0.041; 0.161)	0.095	0.001
Sum Cannabis (14.5%)	0.048 (0.019; 0.078)	0.036	0.001
Total	0.149 (0.082; 0.217)	0.130	<0.001
Total effect	0.332 (0.177; 0.488)	0.298	<0.001

Abbreviations: 95% CI: 95% bias-corrected bootstrap confidence interval; PLE: psychotic-like experiences; CM: childhood maltreatment; SZ-PRS: schizophrenia polygenic risk score at p-value threshold 0.5.

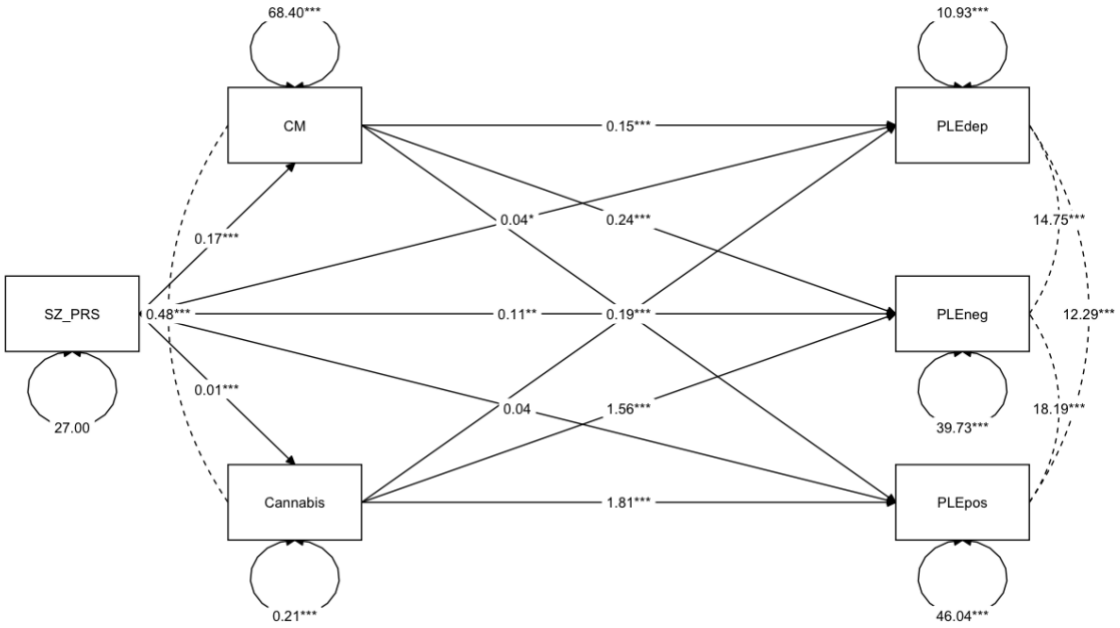


Figure 6: Path diagram of multiple outcome parallel mediation model in the discovery sample (UCC)
Legend: the estimates reported are the unstandardized regression coefficients. *p<0.05; **p<0.01; ***p<0.001.
Abbreviations: SZ-PRS: schizophrenia polygenic risk score at p-value threshold 0.5; CM: childhood maltreatment; PLE: psychotic-like experiences (pos: positive; neg: negative; dep: depression).

As can be seen in Supplementary Tables 2-4 and Supplementary Figures 4-6, the results from the secondary analyses performed in the replication sample were similar, with the exception of tobacco, which was negatively associated with PLE. However, accounting for the mediation played by tobacco resulted in an increased significance of the indirect effect of SZ-PRS on PLE through cannabis use (B=0.097 [bootstrap 95% CI: 0.017; 0.177]).

4.2. REM study

4.2.1. Description of the samples

The analyses comprised 3156 cases and 881 controls. Of total cases, 14.3% was diagnosed with SZ (N=577), 30.7% with MDD (N=1240), and 33.2% with BD (N=1339). Demographics of the total sample are listed in Table 7.

Table 7: Demographic characteristics of the total sample.

	Abuse	**Neglect**	**Combined CM**	**No CM**	**Total**
Diagnosis	*N (%)*	*N (%)*	*N (%)*	*N (%)*	*N (%)*
MDD	85 (6.9%)	255 (20.6%)	276 (22.3%)	624 (50.3%)	1240 (100%)
BD	101 (7.5%)	293 (21.9%)	278 (20.8%)	667 (49.8%)	1339 (100%)
SZ	77 (13.3%)	85 (14.7%)	97 (16.8%)	318 (55.1%)	577 (100%)
Control	51 (5.8%)	103 (11.7%)	60 (6.8%)	667 (75.7%)	881 (100%)
Gender	*N (%)*	*N (%)*	*N (%)*	*N (%)*	*N (%)*
Male	129 (7.3%)	342 (19.4%)	257 (14.5%)	1038 (58.7%)	1766 (100%)
Female	185 (8.1%)	393 (17.3%)	454 (20%)	1238 (54.5%)	2270 (100%)
Age	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*
Total	43.3 (14.0)	49.9 (13.4)	48.1 (13.2)	45.6 (13.89)	46.64 (13.8)
Education	*N (%)*	*N (%)*	*N (%)*	*N (%)*	*N (%)*
No education	2 (5.6%)	12 (33.3%)	7 (19.4%)	15 (41.7%)	36 (100%)
Basic	10 (7.9%)	44 (34.6%)	30 (23.6%)	43 (33.9%)	127 (100%)
Low	64 (8.5%)	160 (21.3%)	153 (20.3%)	375 (49.9%)	752 (100%)
Intermediate	107 (8.3%)	221 (17.2%)	217 (16.9%)	741 (57.6%)	1286 (100%)
High	131 (7.2%)	297 (16.2%)	301 (16.4%)	1102 (60.2%)	1831 (100%)

Abbreviations: BD: bipolar disorder; CM: childhood maltreatment; M: mean; MDD: major depressive disorder; N: number; SD: standard deviation; SZ: schizophrenia.

All types of CM were associated with the presence of MDD, BD, and SCZ in separate non-adjusted logistic regression models (Supplementary Table 5).

Independent t-tests for age showed significant differences between CM groups. Neglect and combined CM groups were significantly older ($t=7.44$, $p<0.001$ and $t=4.31$, $p<0.001$) and the abuse group was significantly younger ($t=2.77$, $p=0.01$) than individuals without CM. Compared to the control group, the MDD and BD diagnosis groups were significantly older ($t=8.25$, $p<0.001$ and $t=5.22$, $p<0.001$), whereas participants with SZ were significantly younger ($t=20.87$, $p<0.001$). Chi-square tests showed that CM groups significantly differed by gender ($p<0.001$), with more women in abuse and combined CM groups and relatively more men in the neglect and no CM groups. The CM groups also differed in level of education ($p<0.001$): participants in the no CM group had higher education in contrast to the neglect and combined group, which included more non- and basic educated individuals. To adjust for these potential confounders, age, gender, and education were added as covariates in all the analyses.

OR with respective 95%CI of the relation between CM type and major psychiatric disorder after adjusting the model for age, gender, and education are presented in Figure 7. Variance inflation factors (VIFs) were <1.5 for each predicting variable, indicating absence of multicollinearity.

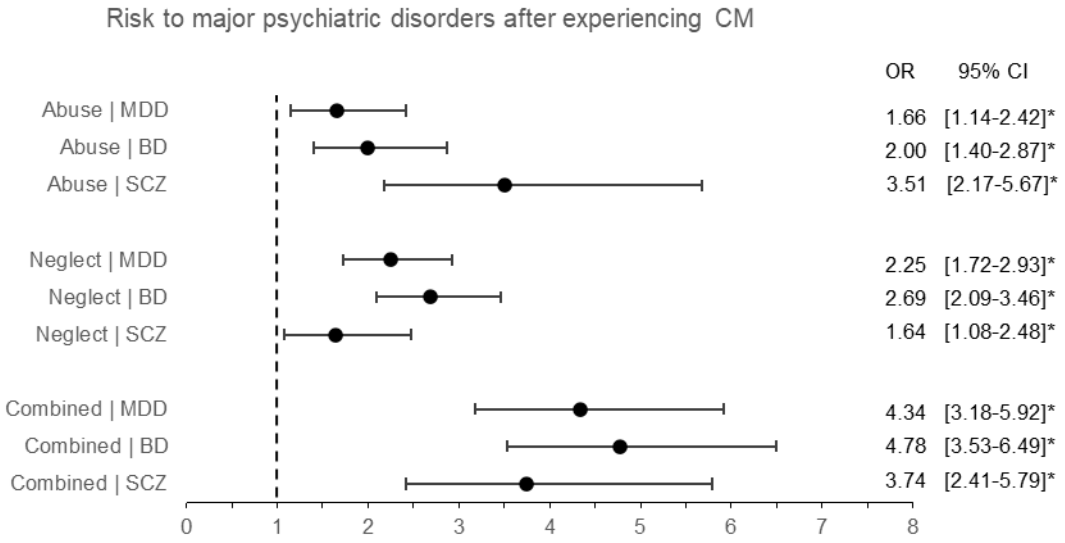


Figure 7: Forest plot of the adjusted multivariate logistic regression model of the relation between childhood maltreatment type (abuse, neglect, combined) and diagnosis (MDD, BD, SCZ) with age, gender, and education level added as covariates and healthy controls as the reference group. Dots represent odds ratios (OR), error bars represent 95% confidence intervals (CI).
Legend: *Significant with α=0.05.

Childhood abuse, neglect, and combined CM was related to higher odds of MDD, BD, and SZ compared to healthy controls. Comparing the relation between CM type and disorder, shows that the association of both childhood abuse and neglect with MDD and BD was similar, with largely overlapping confidence intervals. The association of childhood abuse with SZ, however, was significantly stronger than the association of childhood abuse with MDD and BD.
The RERI between CM types shows a significant additive interaction for combined CM in MDD (RERI=1.4) and BD (RERI=1.1) compared to the impact of abuse and neglect alone. This indicates that the combined effect of abuse and neglect is larger than the sum of their individual effects. Combined CM showed no additive interaction in SZ (RERI=0.6).
Comparing the impact of abuse, neglect, and their combination within diagnostic category (for instance, analysis whether the contribution of abuse was significantly larger that the contribution of

neglect to SZ risk) highlighted a significantly stronger effect of abuse than of neglect in risk for SCZ, and a disproportionately strong impact of combined CM as compared to abuse and neglect alone for MDD and BD, and compared to neglect for SCZ, as also indicated by the RERIs. The results of this analysis are reported in Table 8.

Table 8: Relation of CM type and mental disorder in an adjusted multivariate logistic regression model using each CM type as reference category.

	OR (95%CI) Abuse	**OR (95%CI) Neglect**	**OR (95%CI) Combined**	**OR (95%CI) No CM**
Reference: abuse				
MDD	.	1.35 [0.88-2.08]	**2.61 [1.65-4.13]***	**0.6 [0.41-0.87]***
BD	.	1.34 [0.89-2.02]	**2.39 [1.53-3.72]***	**0.5 [0.35-0.71]***
SZ	.	**0.47 [0.26-0.84]***	1.06 [0.58-1.94]	**0.28 [0.18-0.46]***
Reference: neglect				
MDD	0.74 [0.48-1.14]	.	**1.93 [1.33-2.8]***	**0.44 [0.34-0.58]***
BD	0.75 [0.49-1.12]	.	**1.78 [1.23-2.56]***	**0.37 [0.29-0.48]***
SZ	**2.15 [1.19-3.88]***	.	**2.28 [1.31-3.98]***	**0.61 [0.4-0.93]***
Reference: combined				
MDD	**0.38 [0.24-0.61]***	**0.52 [0.36-0.75]***	.	**0.23 [0.17-0.31]***
BD	**0.42 [0.27-0.65]***	**0.56 [0.39-0.81]***	.	**0.21 [0.15-0.28]***
SZ	0.94 [0.52-1.71]	**0.44 [0.25-0.76]***	.	**0.27 [0.17-0.41]***
Reference: no CM				
MDD	**1.66 [1.14-2.42]***	**2.25 [1.72-2.93]***	**4.34 [3.18-5.92]***	.
BD	**2.00 [1.40-2.87]***	**2.69 [2.09-3.46]***	**4.78 [3.53-6.49]***	.
SZ	**3.51 [2.17-5.67]***	**1.64 [1.08-2.48]***	**3.74 [2.41-5.79]***	.

Abbreviations: CM: childhood maltreatment; MDD: major depressive disorder; BD: bipolar disorder; SZ: schizophrenia; OR: odds ratio; 95%CI: 95% confidence interval.

Legend: *Significant with α=0.05. Analyses were adjusted for age, gender and education.

4.2.2. The relation of abuse and neglect with symptoms of depression, mania, and psychosis across diagnosis

Logistic regression analyses showed that the presence of symptoms of depression, mania, and psychosis differed between CM types, as presented in Table 9.

Table 9: Odds ratio with 95% confidence interval for presence of symptoms of depression (in MDD, BD and SCZ patients, n=3156), mania and psychosis (in BD and SCZ patients; n=1916) after experiencing abuse, neglect, or combined CM.

	OR (95%CI) Abuse	**OR (95%CI) Neglect**	**OR (95%CI) Combined**
Symptoms of depression			
Depressive mood	1.55 [0.94-2.56]	1.39 [0.98-1.97]	**1.59 [1.1-2.3]***
Loss of interest	1 [0.64-1.58]	1.24 [0.88-1.75]	1.16 [0.82-1.63]
Weight loss/decreased appetite	1.06 [0.8-1.41]	1.04 [0.86-1.27]	1.15 [0.95-1.4]
Weight gain/increased appetite	1.31 [0.98-1.75]	1.2 [0.98-1.48]	**1.43 [1.17-1.75]***
Insomnia	1.08 [0.81-1.46]	1.06 [0.86-1.31]	1.23 [0.99-1.52]
Hypersomnia	1.26 [0.95-1.66]	1.12 [0.92-1.36]	**1.3 [1.07-1.57]***
Agitation	1.08 [0.82-1.44]	**1.24 [1.02-1.51]***	**1.44 [1.19-1.75]***
Retardation	1.06 [0.8-1.41]	1.01 [0.83-1.23]	**1.31 [1.07-1.59]***
Loss of energy	0.96 [0.6-1.54]	0.95 [0.67-1.35]	1.18 [0.82-1.71]
Worthlessness/Guilt	**1.48 [1.02-2.14]***	1.04 [0.82-1.32]	**1.35 [1.05-1.73]***
Inefficient thinking	1.08 [0.64-1.81]	1.21 [0.82-1.79]	1.35 [0.89-2.04]
Returning thoughts of death	1.33 [0.98-1.82]	1.07 [0.87-1.32]	**1.52 [1.22-1.89]***
Suicide attempt	**2.16 [1.55-3.01]***	1.18 [0.89-1.55]	**1.48 [1.14-1.91]***
Symptoms of mania			
Expansive/irritable mood	1.3 [0.8-2.11]	1.2 [0.81-1.78]	1.2 [0.8-1.78]
Exaggerated confidence	0.87 [0.5-1.5]	1.45 [0.9-2.34]	**0.66 [0.45-0.97]***
Reduced need for sleep	1.27 [0.75-2.15]	**1.64 [1.08-2.48]***	**1.6 [1.05-2.44]***
Verbosity	0.88 [0.54-1.43]	0.94 [0.64-1.39]	1.29 [0.84-1.97]
Thought train	1.09 [0.66-1.82]	1.38 [0.94-2.04]	0.97 [0.67-1.39]
Reduced concentration	0.85 [0.55-1.32]	1.24 [0.88-1.75]	0.95 [0.68-1.32]
Increased activity	1.01 [0.56-1.82]	0.95 [0.61-1.49]	1.08 [0.68-1.71]
Reduced judgement	0.95 [0.65-1.4]	1.01 [0.76-1.34]	0.89 [0.67-1.18]
Symptoms of psychosis			
Delusions	**1.67 [1.08-2.58]***	**0.67 [0.47-0.96]***	0.94 [0.66-1.33]
Hallucinations	**1.56 [1.03-2.37]***	0.73 [0.52-1.04]	0.96 [0.68-1.36]

Abbreviations: BD: bipolar disorder; CM: childhood maltreatment; MDD: major depressive disorder; OR: odds ratio; SZ: schizophrenia; 95%CI: 95% confidence interval.

Legend: *Significant with α=0.05. Analyses were adjusted for age, gender and education.

Childhood abuse was the strongest risk factor for feelings of worthlessness/guilt, suicide attempt, delusions, and hallucinations. Childhood neglect showed no association with symptoms of psychosis, and even an opposite relation to the development of delusions. Combined CM was, consequently, not significantly associated with delusions or hallucinations. Both childhood neglect and combined CM stood out as a significant risk factor for reduced need for sleep. Combined CM increased the risks for the same symptoms as abuse and neglect alone, except for delusions. Furthermore, combined CM increased the odds of depressive mood, retardation and returning thoughts of death the most and showed many more statistically significant associations than abuse and neglect alone.

4.2.3. Impact of five CM subtypes across psychiatric disorders

The results of logistic regression of CTQ subscales on psychiatric diagnosis, while adjusting for age, gender, and education (no multicollinearity: VIFs <1.5) are shown in Table 10.

Table 10: Odds ratio with 95% confidence interval for MDD, BD or SCZ after experiencing a subtype of childhood maltreatment: emotional abuse or neglect, physical abuse or neglect or sexual abuse.

CM type	**OR (95%CI) MDD**	**OR (95%CI) BD**	**OR (95%CI) SZ**
Emotional abuse	1.69 [0.84-3.39]	1.92 [0.99-3.73]	**2.86 [1.19-6.83]***
Physical abuse	0.69 [0.19-2.43]	1.66 [0.64-4.33]	**3.93 [1.25-12.32]***
Sexual abuse	**1.86 [1.17-2.96]***	**2.13 [1.35-3.35]***	**3.76 [2.02-6.99]***
Emotional neglect	**3.38 [2.31-4.95]***	**3.75 [2.58-5.44]***	**1.95 [1.06-3.58]***
Physical neglect	**1.55 [1.10-2.19]***	**2.05 [1.49-2.82]***	1.45 [0.85-2.44]

Abbreviations: BD: bipolar disorder; CM: childhood maltreatment; MDD: major depressive disorder; OR: odds ratio; SZ: schizophrenia; 95%CI: 95% confidence interval.
Legend: *Significant with α=0.05. Analyses were adjusted for age, gender and education.

All abuse types were most strongly related to increased odds of SZ compared to the other diagnoses. Physical abuse stood out as a risk factor specifically for SZ. Neglect, and especially emotional neglect, was the strongest risk factor for MDD and BD.

4.2.4. Investigating evidence of causality between childhood maltreatment type and psychiatric disorders using MR

Forward MR analyses were consistent with a causal relationship of childhood abuse with SZ (IVW=0.125 [95%CI: 0.01; 0.24] p=0.032), based on 2 SNPs. Steiger test indicated a correct direction of causality between the exposure and outcome. Cochran's Q statistic was statistically significant for the analysis of abuse against SZ, indicating possible risk of pleiotropy. Such limited number of 2 selected SNPs was also insufficient to perform WM, MR-Egger, and MR-PRESSO analyses. The follow-up MR analysis, in which the SNP selection threshold was lowered by increasing the p-value to $p<3\times10^{-6}$, confirmed statistical significance with no evidence of horizontal pleiotropy (IVW=0.112 [95%CI: 0.05-0.18] p=0.001, Q p-value 0.186, based on 6 SNPs). This suggests that the more lenient threshold of 1e-06 is not the main explanation of the found relation, and that the suggestion of pleiotropy disappears with a higher number of SNPs selected. The relation between child abuse and SZ is the only consistent statistically significant relation in the MR analyses. The MR results for the association between neglect and combined CM and psychiatric disorders showed no consistent patterns of statistically significant causal effect. Backward MR supported a causal relationship of genetic variants linked to SZ on abuse, neglect, and combined CM. The results of MR analyses are presented in Supplementary Table 6.

4.3. MONEY study

4.3.1. Latent poverty-factor estimation

To analyze the joint genetic architecture of poverty we ran a multivariable GWAS for which a common factor defined by genetic indicators is regressed on a SNP. The multivariable GWAS of the latent poverty factor (PF) was modelled from three indicators: HI, SD, and OI. Supplementary Table 7 reports the factor loading of each indicator.

The heritability of the common factor GWAS was estimated with the h^2 and resulted around 8.4%. Mean chi^2, LDSC intercept, and h^2 for the common factor GWAS and GWAS of HI, SD, and OI are presented in Table 11.

Table 11: Summary statistics of the common poverty factor, household income, social deprivation, and occupational income

	Mean Chi^2	**LDSC intercept (SE)** **[N SNPs]**	**Heritability** **h^2 % (SE)**
HI	1.5669	1.0426 (0.0099) [1165506]	7.08% (0.0031) **$p=4.33\times10^{-113}$**
SD	1.3379	1.0423 (0.0081) [1165534]	3.01% (0.0015) **$p=2.15\times10^{-93}$**
OI	1.5145	1.0015 (0.0092) [1177612]	9.14% (0.004) **$p=4.59\times10^{-115}$**
PF	1.7301	0.9883 (0.0108) [1158117]	8.38% (0.0031) **$p=4.24\times10^{-164}$**

Abbreviations: LDSC: Linkage Disequilibrium Score Regression; SE: standard error; PF: poverty factor; HI: household income; SD: social deprivation; OI: occupational income.

Legend: Mean Chi^2 measures the overall strength of association between genetic variants and the phenotype of interest; a high Mean Chi^2 value indicates that there are many genetic variants that are strongly associated with the trait. The Linkage Disequilibrium Score Regression (LDSC) intercept captures the contribution of factors other than polygenicity (such as population stratification) to inflation in association test statistic. Narrow sense heritability (h^2) is a measure of the proportion of phenotypic variation that is attributable to genetic variation. The p-values are calculated from two-sided chi^2 test and are not adjusted for multiple testing, therefore p-value<0.05 was considered significant (and reported in bolded text).

The GWAS of the latent poverty factor identified 90 significantly associated independent loci at GWAS threshold (p-value$\leq5\times10^{-8}$), as displayed in Figure 8.

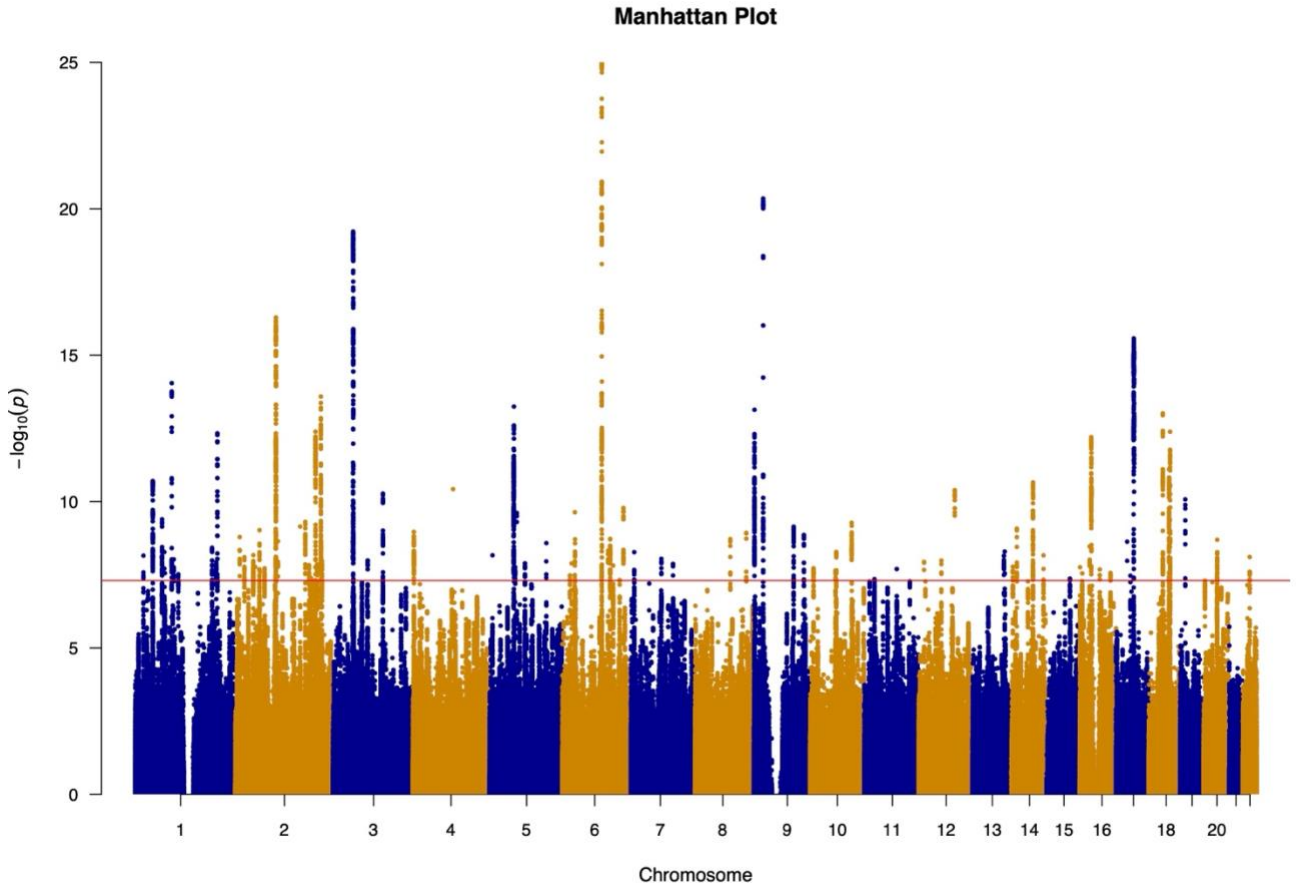


Figure 8: Manhattan plot of the latent poverty factor.

Legend: The x axis indicates the chromosomal position, and the y axis indicates the significance of the association (−log10(P)). The red line represents the genome-wide significance level (5×10^{-8}). SNP effects are estimated with a linear regression model. The p-values are two-sided and not adjusted for multiple testing.

The genetic correlation between PF and CA was strong (rg was 0.74 standard error [SE]: 0.029). Strong associations were found also between CA and the other poverty indicators, although the association was weaker with SD. These results are presented in Table 12.

Table 12: genetic correlation (rg) between the common factor poverty, household income, social deprivation, occupational income, and cognitive abilities

	PF		
PF	1.00	**HI**	
HI	0.9826	1.00	**SD**

	(0.0398)				
SD	-0.8007 (0.0344)	-0.7712 (0.0345)	1.00	**OI**	
OI	0.9509 (0.0372)	0.9067 (0.0391)	-0.6318 (0.0325)	1.00	**CA**
CA	0.7396 (0.0289)	0.7019 (0.0315)	-0.4092 (0.0276)	0.8147 (0.0334)	1.00

Abbreviations: PF: poverty factor; HI: household income; SD: social deprivation; OI: occupational income; CA: cognitive abilities.

Legend: genetic correlations are presented as rg(standard error)

Running bidirectional MR of CA against PF, we found stronger evidence supporting the causal effect of CA on PF (IVW $B_{CA \rightarrow PF}$=-0.390 [95%CI: -0.408; -0.372]) rather than vice versa (IVW $B_{PF \rightarrow CA}$=-0.274 [95%CI: -0.288; -0.261]), as suggested by the results of Steger's test ($p<0.001$; $p=0.423$, respectively).

4.3.2. Bidirectional univariable MR of common factor poverty against mental disorder

For the univariable analyses, the mean F statistic ranged from 31.5 to 45.6, indicating that the estimates were not likely subject to weak instrument bias. Forward IVW analysis of PF against the considered mental disorders showed significant causal effect of PF on ADHD (B=0.330 [95%CI: 0.287; 0.373]), ANX (B=0.229 [95%CI: 0.101; 0.357]), MDD (B=0.115 [95%CI: 0.074; 0.156]), PTSD (B=0.140 [95%CI: 0.073; 0.207]), SZ (B=0.110 [95%CI: 0.074; 0.145]), and with opposite direction on AN (B=-0.192 [95%CI:-0.254; -0.129]) and OCD (B=-0.202 [95%CI: -0.355; -0.049]). The estimate of the causal effect using WM method, was consistent in the magnitude for ADHD, AN, MDD, PTSD, and SZ, but not for ANX and OCD. We did not identify any significant causal effect of PF on BD and ASD. Backward IVW analysis of mental disorder against PF showed significant causal effect of ADHD (B=0.402 [95%CI: 0.348; 0.455]), BD (B=-0.091 [95%CI: -0.133; -0.049]), and SZ (B=0.082 [95%CI: 0.061; 0.102]) on PF. The estimate of the causal effect using WM method, was confirmed for both ADHD and SZ, but not for BD.

The results are displayed in Figure 9, and in the Table 13 (see also Supplementary Table 8 for conversion to OR).

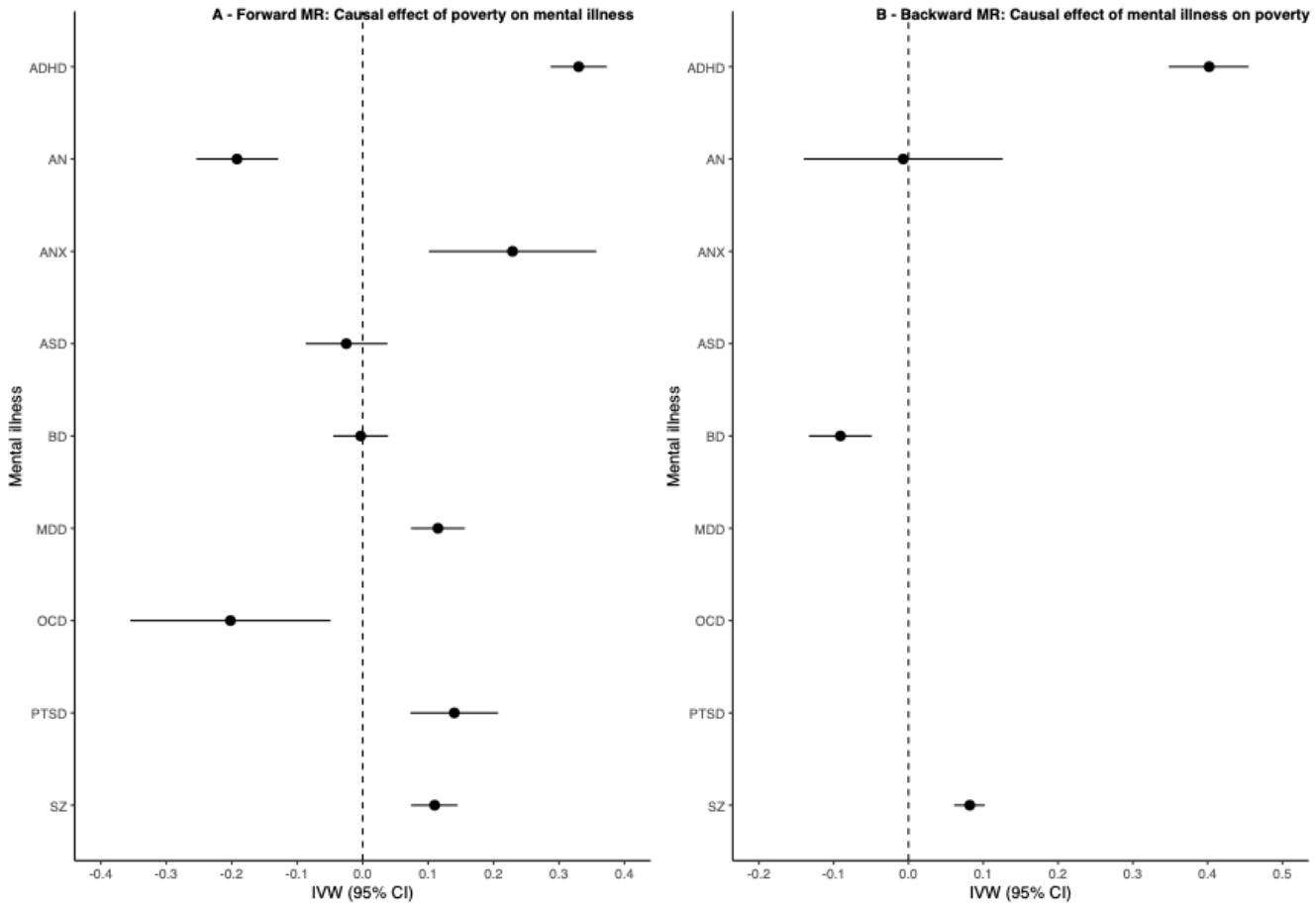


Figure 9: Results of univariable bidirectional MR analysis of poverty against mental disorder. a, Forward analysis. b, Backward analysis.

Legend: Poverty is a latent variable built using HI as the unit identification, so that an increase in the indicator's load stands for increased income; the regression coefficients have therefore been reversed to facilitate interpretation of the effect of poverty. The effect estimates on the x axis are log-odds for binary traits (that is, for mental disorders) and unstandardized linear regression coefficients for continuous traits (that is, for poverty); the error bars represent 95% CIs.

Table 13: results of bidirectional MR of poverty against mental disorder

MR	N SNP	IVW, B (95% CI)	IVW p-value	IVW Q(df)	Q p-value†	WM, B (95% CI)	WM p-value	MR-Egger, B (95% CI)	MR-Egger p-value	Egger intercept p-value	Steiger Test p-value‡	MR-PRESSO	Mean F
Fw: PF on ADHD	77	0.330 (0.287; 0.373)	**1.28×10^{-51}**	243 (76)	**2.95×10^{-64}**	0.219 (0.142; 0.295)	**2.28×10^{-8}**	-0.232 (-0.568; 0.104)	0.180	**0.001**	**6.71×10^{-50}**	DT; p=0.418	40.8
Bw: ADHD on PF	22	0.402 (0.348; 0.455)	**1.24×10^{-48}**	102 (21)	**1.05×10^{-12}**	0.349 (0.245; 0.453)	**4.48×10^{-11}**	0.143 (-0.569; 0.856)	0.723	0.448	**3.37×10^{-39}**	GT; p=0.853	38.3
Fw: PF on AN	77	-0.192 (-0.254; -0.129)	**1.90×10^{-9}**	160 (76)	**5.50×10^{-6}**	-0.191 (-0.290; -0.092)	**1.50×10^{-4}**	-0.420 (-0.858; 0.018)	0.064	0.415	**8.32×10^{-17}**	DT; p=0.786	40.4
Bw: AN on PF	2	-0.001 (-0.038; 0.035)	0.947	7 (1)	**0.008**	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [b]	NR [c]	NR [c]
Fw: PF on ANX	79	0.229 (0.101; 357)	**4.59×10^{-4}**	82 (78)	0.362	0.158 (-0.028; 0.344)	0.096	-0.066 (-0.720; 0.587)	0.842	0.369	**3.20×10^{-9}**	GT; p=0.270	40.6
Bw: ANX on PF	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]
Fw: PF on ASD	79	-0.025 (-0.087; 0.038)	0.443	199 (78)	**4.54×10^{-9}**	-0.020 (-0.123; 0.082)	0.698	-0.477 (-0.899; -0.054)	**0.030**	**0.035**	**7.12×10^{-6}**	DT; p=0.981	40.3
Bw: ASD on PF	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]

Fw: PF on BD	79	-0.003 (-0.045; 0.039)	0.889	264 (78)	**9.93×10^{-26}**	-0.033 (-0.045; 0.039)	0.389	-0.247 (-0.631; 0.137)	0.211	0.206	NR [b]	DT; p=0.163	40.3
Bw: BD on PF	36	-0.091 (-0.133; -0.049)	**1.93×10^{-5}**	233 (35)	**1.29×10^{-29}**	-0.011 (-0.091; 0.069)	0.783	-0.052 (-0.638; 0.534)	0.863	0.909	**7.24×10^{-224}**	DT; p=0.110	39.2
Fw: PF on MDD	78	0.115 (0.074; 0.156)	**3.45×10^{-8}**	150 (77)	**7.91×10^{-6}**	0.089 (0.022; 0.157)	**0.010**	-0.013 (-0.271; 0.246)	0.924	0.325	**3.65×10^{-57}**	DT; p=0.824	40.0
Bw: MDD on PF	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]
Fw: PF on OCD	78	-0.202 (-0.355; -0.049)	**0.010**	96 (78)	0.067	-0.145 (-0.378; 0.088)	0.221	0.296 (-0.443; 1.04)	0.434	0.325	0.051	GT; p=0.141	40.0
Bw: OCD on PF	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]
Fw: PF on PTSD	79	0.140 (0.073; 0.207)	**3.79×10^{-5}**	118 (78)	**0.013**	0.114 (0.010; 0.217)	**0.031**	-0.108 (-0.461; 0.245)	0.511	0.163	**1.52×10^{-94}**	DT; p=0.952	40.3
Bw: PTSD on PF	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]
Fw: PF on SZ	79	0.110 (0.074; 0.145)	**1.36×10^{-9}**	547 (78)	**2.95×10^{-64}**	0.127 (0.056; 0.198)	**4.22×10^{-4}**	0.079 (-0.462; 0.304)	0.689	0.323	**7.79×10^{-77}**	DT; p=0.333	40.3

Bw: SZ on PF	176	0.082 (0.061; 0.102)	**1.41× 10^{-14}**	706 (175)	**4.84× 10^{-63}**	0.050 (0.012; 0.088)	**9.37× 10^{-3}**	0.006 (-0.156; 0.169)	0.922	0.352	**$<1^{-1000}$**	DT; p=0.351	45.6

Abbreviations: Fw: forward analysis; Bw: backward analysis; PF: poverty factor; ADHD: attention deficit hyperactivity disorder; AN: anorexia nervosa; ANX: anxiety disorder; ASD: autism spectrum disorder; BD: bipolar disorder; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; PTSD: post-traumatic stress disorder; SZ: schizophrenia; MR: mendelian randomization; SNP: single nucleotide polymorphism; IVW: inverse variance weighted (fixed effect); B: effect estimates are log-odds for binary traits (i.e., for mental disorders) and unstandardized regression coefficient for continuous traits (i.e., for poverty); 95% CI: 95% confidence interval; Q: Cochran's Q measure of heterogeneity; df: degree of freedom; WM: weighted median; DT: distortion test; GT: global test.

Legend:

P-value threshold for SNP selection <5e-8.

Poverty is a latent variable built using household income as unit identification, therefore an increase in the indicator's load stands for increased income, therefore the regression coefficients have been reversed to facilitate interpretation of the effect of poverty.

[a] The Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) test identifies possible bias from horizontal pleiotropy. The test consists of three parts, (1) the MR-PRESSO global test which detects horizontal pleiotropy, (2) the outlier corrected causal estimate which corrects for the detected horizontal pleiotropy and (3) the MR-PRESSO distortion test which estimates if the causal estimate is significantly different (at $p<0.05$) after adjustment for outliers. We conduct all three stages (with the argument NbDistribution=1000, namely using1000 simulation form the null distribution to compute empirical p-values) and present the outlier adjusted causal estimates (OACE) when both global and distortion tests are significant.

[b] We did not run Steiger Test if none of the MR analysis resulted significant (NR: not reported in the cell).

[c] Not enough SNP to perform MR (NR: not reported in the cell).

[†] Based on chi^2 test.

[‡] Based on t-test.

All statistical tests were two-sided. The p-values were not adjusted for multiple testing, therefore p-value<0.05 was considered significant (and reported in bolded text).

Steiger test indicated that the causal direction between the exposure and outcome was correct in all the analyses. Cochran's Q heterogeneity statistics was significant in all the analyses (except for the effect of PF on ANX and PF on OCD), which is suggestive of pleiotropy. Furthermore, we looked at MR-Egger intercept, which was significantly deviating from 0 in the analysis of PF against ADHD (p=0.001) and of PF against ASD (p=0.035), suggesting that pleiotropy was unbalanced in these relationships. The MR-Egger causal effect, which provides a better estimate in case of unbalanced pleiotropy than IVW MR, yielded uncertain results for the effect of PF on ADHD (B=-0.232 [95%CI: -0.568; 0.104]) and evidence of inverse relationship between PF and ASD (B=-0.477 [95%CI: -0.899; -0.0.54], Egger's intercept p=0.035). MR-PRESSO did not detect bias in the estimates due to horizontal pleiotropy in all the estimates. CAUSE analysis confirmed the causal effect of PF on ADHD bidirectionally, and unidirectionally on AN, MDD, and PTSD. No significant difference between the sharing and the causal model was found for the effect of PF on SZ bidirectionally. The results of CAUSE are presented in Supplementary Table 9.

Leave-one-out analyses, both in forward and backward directions, showed that the direction of the effect of each SNP is consistent with the direction of the overall causal estimate. In addition, for most of the analyses, a change in the estimations of less than 10% was obtained by leaving out each SNP, suggesting that none of the genetic variants were overly influential. Finally, to test if our results were robust to bias due to reverse causality, we repeated the MR analyses on a subset of SNPs selected through Steiger filtering. This sensitivity analysis confirmed the results of the main analysis, except for the effect of PF on OCD that was no longer significant after Steiger filtering (B=-0.013 [95%CI: -0.199; 0.173]). The results are presented in Supplementary Table 10.

To further explore whether the effect of poverty on mental disorder is driven by specific indicators, we performed bidirectional univariable MR using each of the poverty indicators (i.e., HI, OI, and SD) as the exposure. The results are presented in Figure 10, Supplementary Tables 11-13 (HI), 14-16 (OI), 17-19 (SD). The HI GWAS had a higher level of power than OI and SD GWASs, as indicated by the number of SNPs selected for the analyses (~50, ~30, and ~10, respectively).

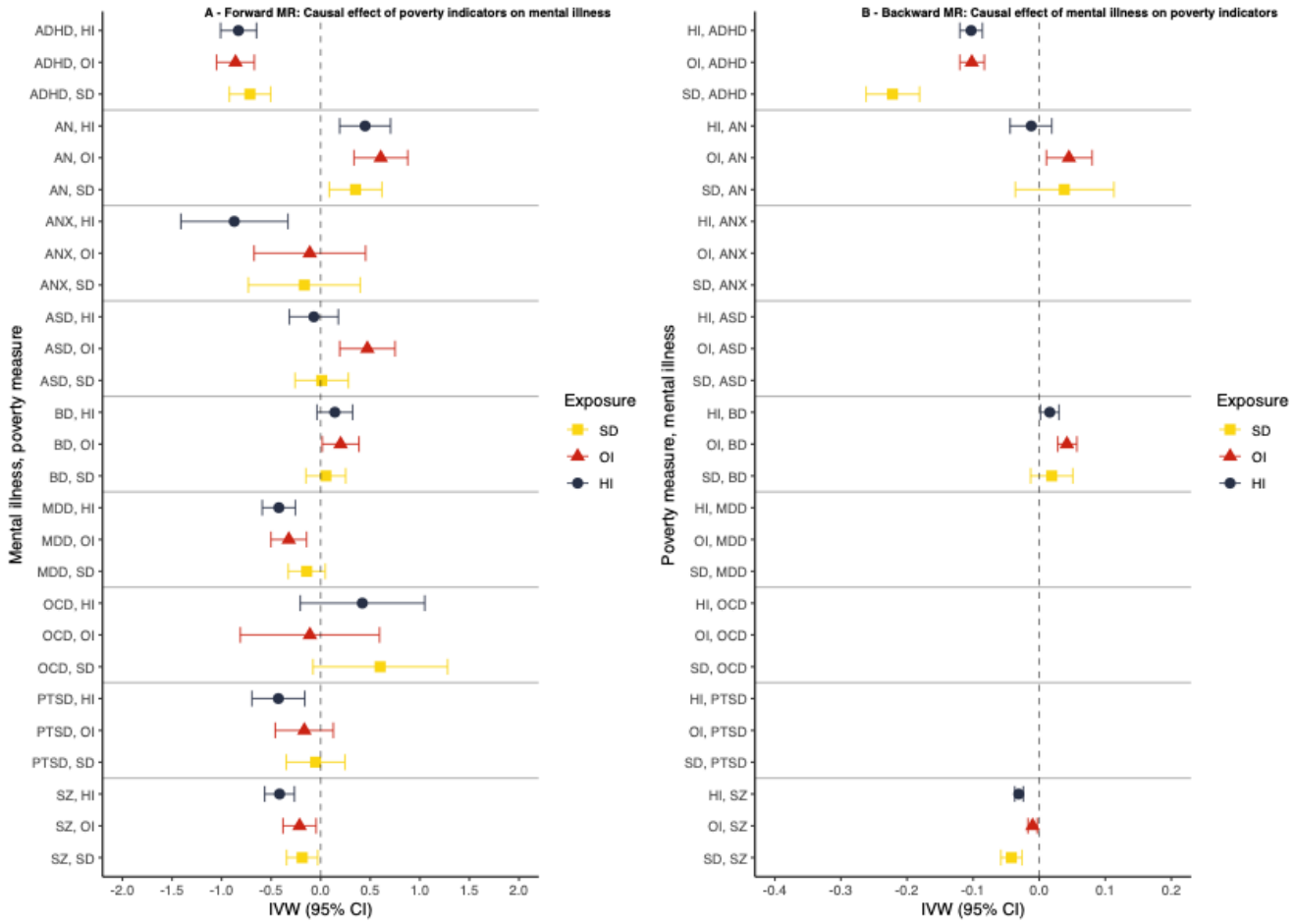


Figure 10: Results of univariable bidirectional MR analysis for each poverty measure against mental disorder. a, Forward analysis. b, Backward analysis.

Legend: To have a consistent direction of the effect, the SD effect has been reversed. The effect estimates on the x axis are log-odds for binary traits (that is, for mental disorders) and unstandardized linear regression coefficients for continuous traits (that is, for the poverty indicators); the error bars represent 95% CIs. Missing results are due to an insufficient number of SNPs selected for the MR analysis.

Overall, the direction of the associations obtained using the poverty common factor was consistent with those obtained for each indicator, where bidirectional causal effects of poverty on some mental disorders was observed. Specifically, using HI as a poverty measure, we found evidence of bidirectional effect with ADHD (B=-0.830 [95%CI: -1.01; -0.647]; B=-0.103 [95%CI: -0.120; -0.086], IVW forward and backward respectively) and SZ (B=-0.415 [95%CI: -0.565; -0.265]; B=-0.031 [95%CI: -0.037; -0.024], IVW forward and backward respectively), and unidirectional causal effect to MDD (B=-0.422 [95%CI: -0.589; -0.255]) and AN (B=0.448 [95%CI: 0.191; 0.704]). However, the

effect of HI on ADHD was biased by high heterogeneity and unbalanced pleiotropy (Egger's intercept p<0.001), with MR-Egger estimate yielding inconsistent results (B=0.606 [95%CI: -0.684; 1.90]). The bidirectional effect of OI on ADHD (B=-0.859 [95%CI: -1.05; -0.669]; B=-0.102 [95%CI: -0.120; -0.083], IVW forward and backward respectively) and unidirectionally to AN (B=-0.187 [95%CI: -0.344; -0.030]) and MDD (B=-0.322 [95%CI: -0.502; -0.143]) were confirmed also using OI as a measure of poverty. The effect of OI on SZ was also confirmed bidirectionally (B=-0.187 [95%CI: -0.344; -0.030]; B=-0.010 [95%CI: -0.017; -0.003]), but sensitivity analyses using CAUSE and Steiger filtering selection detected potential bias due to pleiotropy in the forward analysis. Notably, also the effect of OI and ADHD changed after Steiger filtering, with evidence of pleiotropy (Egger's intercept, p=0.033) and not significant MR-Egger estimate (B=0.094 [95%CI: -1.36; 1.55]). Backward analyses using OI as the outcome, confirmed the effect of BD on poverty using IVW but not WM methods (B=0.042 [0.028; 0.057]; B=0.020 [95%CI: -0.005; 0.046], IVW and WM respectively) as found using the common factor poverty; but novel evidence was found to the causal effect of AN to OI (B=0.045 [95%CI: 0.011; 0.080]), not replicated using the poverty common factor or other measures of poverty. Finally, using SD as a measure of poverty, the bidirectional effect on SZ (B=0.213 [95%CI: 0.046; 0.380]; B=0.042 [95%CI: 0.026; 0.058], IVW forward and backward respectively) and the unidirectional effect to AN (B=-0.352 [95%CI: -0.618; -0.087]) were confirmed. The bidirectional effect of SD on ADHD was also replicated (B=0.713 [95%CI: 0.504; 0.922]; B=0.222 [95%CI: 0.181; 0.262], IVW forward and backward respectively), with stronger evidence for the reverse effect as indicated by Steiger test (forward, p=0.079; backward, p<0.001). However, by applying the Steiger filtering selection, the effect of SD on ADHD held strong (B=0.557 [95%CI: 0.331; 0.784]). None of the other effects of SD remained significant after Steiger filtering, which is consistent with potential bias due to reverse causation in the relationship between SD and mental disorder.

4.3.3. Bidirectional univariable MR of household income categories against mental disorder

To explore the shape of the relationship between HI and mental health, and specifically to answer the question whether there is a particular HI threshold at which the effect of HI on mental health kicks-in, we used GWAS data for the HI categories and investigated the effect of each category on the considered mental disorders. That led to the creation of 4 dichotomous dummy variables, consisting of: (1) low HI (LHI): cases were those <£18k, controls were those ≥£18k; (2) low-mid HI (LMHI): cases were those <£29.99k, controls were those ≥£29.99k; (3) mid-high HI (MHHI): cases were those >£52k,

controls were those ≤£52k; (4) high HI (HHI): cases were those >£100k, controls were those ≤£100k. For each of these bidirectional univariable MR was performed.

As can be seen in Figure 11 and Supplementary Tables 20-23, we found a significant causal effect of being in the lowest HI class on ANX (B=0.628 [95%CI: 0.095; 1.16]), BD (B=0.306 [95%CI: 0.125; 0.487]), MDD (B=0.351 [95%CI: 0.189; 0.513]), PTSD (B=0.506 [95%CI: 0.253; 0.759]), and bidirectionally on ADHD (forward, B=0.610; [95%CI: 0.415; 0.805]; backward, B=0.210 [95%CI: 0.170; 0.250]) and SZ (forward, B=0.648 [95%CI: 0.488; 0.808]; backward, B=0.082 [95%CI: 0.066; 0.098]). In the LMHI class, the direction of the associations observed in the LHI was maintained, and interestingly, the effect size decreased, consistent with our leading hypothesis of more deleterious effect of poverty on mental health at very low levels of income. Exceptions were AN, ASD, and OCD for which being in the LMHI class resulted to be protective (B=-0.309 [95CI: -0.526; -0.091], B=-0.268 [95%CI: -0.488; -0.047], B=-0.774 [95%CI: -1.34; -0.212], respectively). The analyses in the higher classes (i.e., MHHI and HHI) showed that with each incremental increase or decrease of income there is a corresponding effect on mental disorder. For instance, AN and ASD - but not OCD – resulted causally associated with higher incomes, with stronger evidence for AN ($B_{MHHI \rightarrow AN}$=0.371 [95%CI: 0.193; 0.550]; $B_{MHHI \rightarrow ASD}$=0.480 [95%CI: 0.303; 0.658]; $B_{HHI \rightarrow AN}$=0.333 [95%CI: 0.065; 0.600]; $B_{HHI \rightarrow ASD}$=0.094 [95%CI: -0.121; 0.308]), whereas the association with ADHD, MDD, PTSD, and SZ resulted with opposite sign, confirming the causal relationship with lower income. Notably, ADHD and SZ showed a consistent bidirectional pattern across income levels, where a lower income was causally related to, and resulted also causal factors for lower incomes. This evidence is supporting a vicious circle between poverty and severe mental disorder that reiterates.

The effect of the HI levels on BD showed a U-shape distribution, resulting causally associated with both low and high HI ($B_{LHI \rightarrow BD}$=0.306 [95%CI:0.125; 0.487]; $B_{MHHI \rightarrow BD}$=0.179 [95%CI: 0.053; 0.304]; $B_{HHI \rightarrow BD}$=0.608 [95%CI: 0.423; 0.792]). However, these associations were not replicated using the WM method, and MR-PRESSO detected significant distortion in the estimate due to pleiotropy in the relationship between BD and MHHI, with outlier adjusted causal estimates (OACE) resulting not significant (OACE=0.002 [95%CI: -0.039; 0.042]).

The estimate of the causal effect using WM method, was consistent in the magnitude for LHI to ADHD and SZ forward and backward, unidirectionally on ANX, MDD, PTSD, and for MHHI and HHI on ASD.

Q statistics were suggestive of high levels of heterogeneity in most of the analyses, however, MR-Egger showed significant intercept and causal effect only for the relationship between MHHI and BD

(B=1.69 [95%CI: 0.376; 3.00]; Egger's intercept p=0.033). Steiger test indicated that the causal direction between the exposure and outcome was correct in all the analyses except those on ASD (p=0.994 and p=0.057 respectively for the association with MLHI and MHHI).

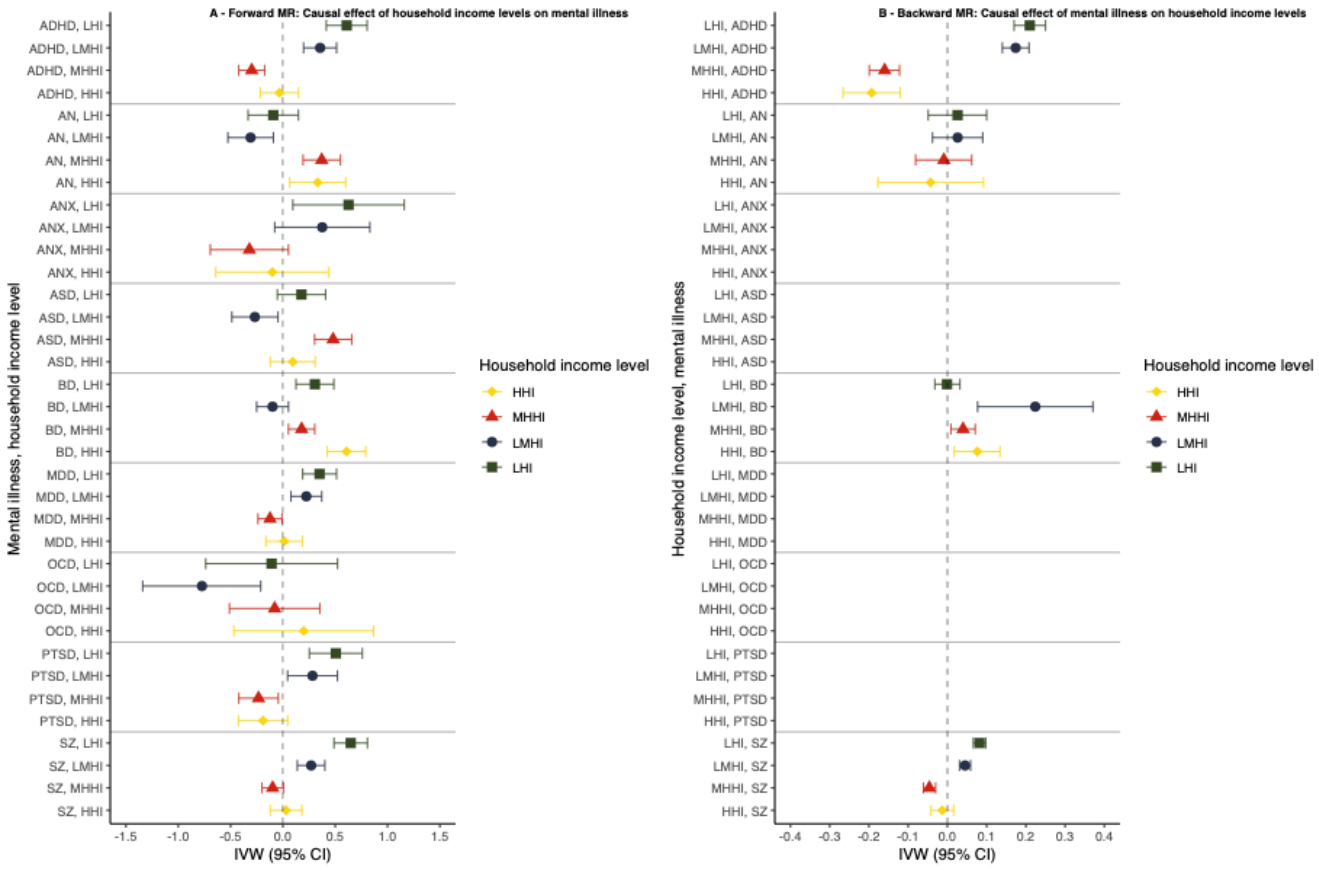


Figure 11: Results of univariable bidirectional MR analysis of HI levels against mental disorder. a, Forward analysis. b, Backward analysis.

Legend: For LHI, cases <£18,000 and controls ≥£18,000; for LMHI, cases <£29,999 and controls ≥£29,999; for MHHI, cases >£52,000 and controls ≤£52,000; and for HHI, cases >£100,000 and controls ≤£100,000. The effect estimates on the x axis are log-odds for both the forward and backward analyses given that all traits are binary; the error bars represent 95% CIs. Missing results are due to an insufficient number of SNPs selected for the MR analysis.

The MR analyses on a subset of SNPs selected through Steiger filtering confirmed a stronger causal effect played by the lowest HI level on ADHD, MDD, PTSD, and SZ. The protective effect of MHHI on ASD also was confirmed. Interestingly, the effects observed in the main analysis were not confirmed

for BD and AN, yielding evidence of reverse causation rather than direct causality for these associations. The results can be found in Supplementary Table 24.

4.3.4. MVMR of poverty factor and cognitive ability against mental disorder

Like other measures of socioeconomic status, genetic effects are unlikely to influence poverty directly. Rather, genetic effects are likely to influence poverty through intermediary traits (such as health, personality, intelligence, and other characteristics) that are themselves heritable [203]. Previous studies have shown that cognitive ability (referred to as general cognitive function, performance, or as intelligence) is one likely causal factor in income differences [203] as well as being genetically associated with mental disorder [89]. MVMR was used to estimate the effect of poverty on each mental disorder, while controlling for CA. First, bidirectional univariable MR of CA on mental disorder was performed, finding evidence supporting a bidirectional inverse causal relationship between CA and ADHD (B=-0.638 [95%CI:-0.720; -0.556]; B=-0.151 [95%CI:-0.172; -0.131], forward and backward direction, respectively) and SZ (B=-0.297 [95%CI:-0.365; -0.228]; B=-0.055 [95%CI:-0.063; -0.047], forward and backward direction, respectively), unidirectional negative causal effect of CA on MDD and PTSD (B=-0.140 [95%CI:-0.215; -0.065] and B=-0.139 [95%CI:-0.264; -0.013], respectively) and unidirectional causal effect of CA on AN and ASD (B=0.306 [95%CI:0.190; 0.422] and B=0.310 [95%CI:0.193; 0.427], respectively). The results are displayed in Supplementary Tables 25-26. MVMR analysis yielded results supporting a causal effect of PF on ADHD, AN, ANX, MDD, OCD, PTSD, and SZ, beyond CA. Still, the effect of PF on mental disorder decreased when including CA in the model. These results suggest that the univariable MR results of P on mental disorder are slightly biased by CA, a direct effect of PF on ADHD, AN, and ANX remains, nonetheless. The results of MVMR are shown in Table 14.

Table 14: Multivariable Mendelian Randomization results of poverty and cognitive ability on mental illness

MVMR	**N SNP**	**IVW B (95% CI)**	**IWV p-value**
Outcome: ADHD	203		
Exposure 1: PF		0.232 (0.169; 0.295)	**7.28×10^{-13}**
Exposure 2: CA		-0.477 (-0.612; -0.342)	**4.31×10^{-12}**

Outcome: AN	205		
Exposure 1: PF		-0.109 (-0.183; -0.035)	**0.004**
Exposure 2: CA		0.149 (-0.008; 0.306)	0.062
Outcome: ANX	207		
Exposure 1: PF		0.114 (0.007; 0.221)	**0.036**
Exposure 2: CA		-0.344 (-0.571; -0.117)	**0.003**
Outcome: ASD	208		
Exposure 1: PF		0.022 (-0.054; 0.099)	0.564
Exposure 2: CA		0.217 (0.054; 0.379)	**0.009**
Outcome: BD	208		
Exposure 1: PF		0.020 (-0.044; 0.085)	0.538
Exposure 2: CA		0.006 (-0.132; 0.144)	0.931
Outcome: MDD	208		
Exposure 1: PF		0.076 (0.030; 0.123)	**0.001**
Exposure 2: CA		-0.091 (-0.190; 0.008)	0.071
Outcome: OCD	208		
Exposure 1: PF		-0.202 (-0.340; -0.0.064)	**0.004**
Exposure 2: CA		0.320 (0.024; 0.615)	**0.034**
Outcome: PTSD	208		
Exposure 1: PF		0.111 (0.048; 0.173)	**4.90×10^{-4}**
Exposure 2: CA		-0.160 (-0.294; -0.027)	**0.019**
Outcome: SZ	208		
Exposure 1: PF		0.092 (0.018; 0.167)	**0.015**
Exposure 2: CA		-0.297 (-0.457; -0.136)	**2.94×10^{-4}**

Abbreviations: MVMR: multivariable Mendelian randomization; SNP: single nucleotide polymorphism; IVW: multivariable mendelian randomization via inverse variance weighted method (random effects); B: effect estimates are log-odds; 95% CI: 95% confidence intervals; ADHD: attention deficit hyperactivity disorder; PF: poverty factor; CA: cognitive ability; AN: anorexia nervosa; ANX: anxiety disorder; ASD: autism spectrum disorder; BD: bipolar disorder; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; PTSD: post-traumatic stress disorder; SZ: schizophrenia

Legend: Poverty is a latent variable built using household income as unit identification, therefore an increase in the indicator's load stands for increased income, therefore the regression coefficients have been reversed to facilitate interpretation of the effect of poverty. All statistical tests are two-sided. The

p-values were not adjusted for multiple testing, therefore p-value<0.05 was considered significant (and reported in bolded text).

Importantly, and unlike the univariable models, the inclusion of CA in a MVMR model produced highly dissimilar results comparing between the poverty factor and each indicator of poverty. First, the inclusion of CA in a MVMR model removed the effect of HI on mental disorder. Second, for both OI and SD some significant effects remained where OI demonstrated a direct effect on ASD and SD showed a direct effect on AN. The results of these additional MVMR models are shown in Supplementary Tables 27-29. Taken together these results support the idea that the majority of the genetic effects that link poverty to mental disorder do act on CA. However, by utilizing a general factor of poverty the resulting increase in statistical power facilitated the discovery of genetic effects acting to link poverty to mental health independent of the effects of CA. Therefore, while cognitive ability is correlated with poverty, it does not fully account for the observed genetic effects on mental health. These findings, when considered alongside the results of the MR of PF and CA, point to CA fitting as an upstream component in the complex causal pathway linking poverty to mental disorder.
Figure 12 displays the directed acyclic graph (DAG) showing the most robust causal relationships identified across the MR methods used to examine the effects of poverty and cognitive ability on mental disorders.

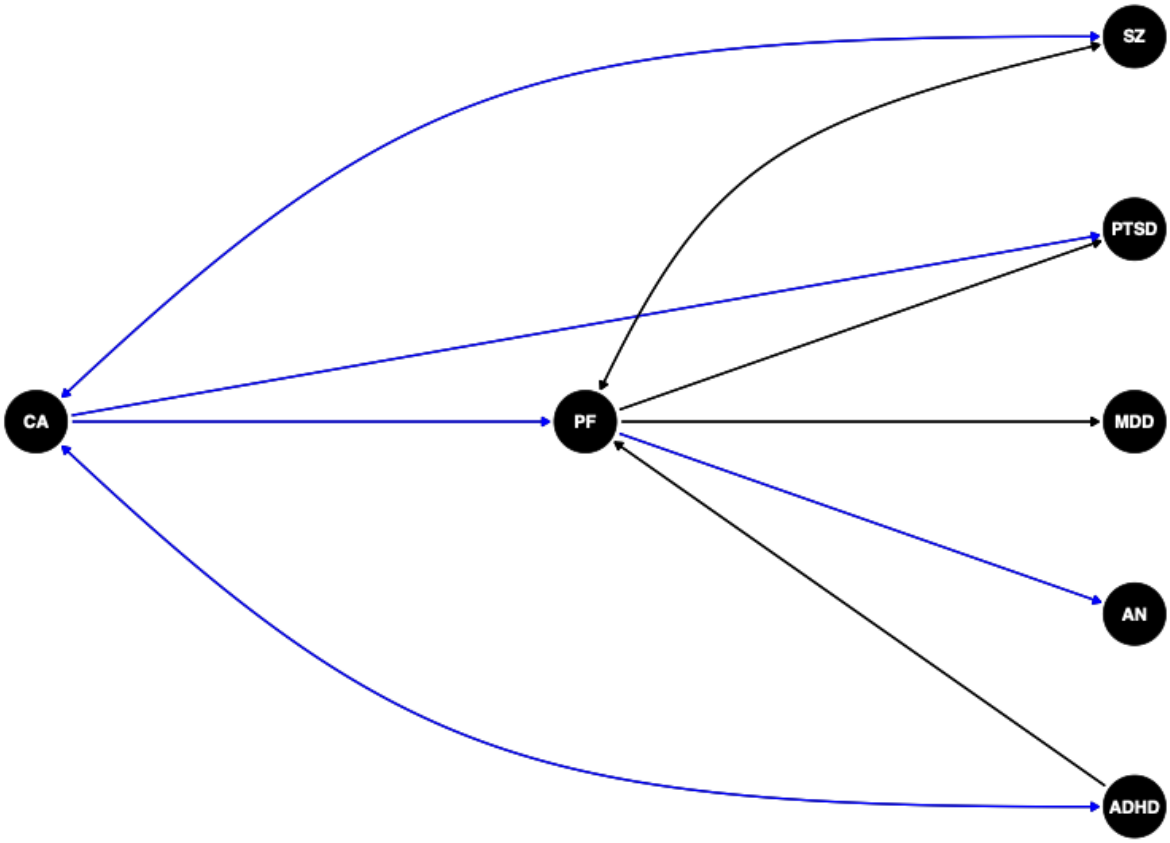


Figure 12: Directed acyclic graph of the most robust causal relationships between poverty, mental disorders, and cognitive ability.

Abbreviations: CA: cognitive ability; PF: poverty factor; ADHD: attention deficit and hyperactivity disorder; AN: anorexia nervosa; MDD: major depressive disorder; PTSD: post-traumatic stress disorder; SZ: schizophrenia.

Legend: The arrows are from the exposure to the outcome; double-headed arrows indicate bidirectional causal relationships. Black edges represent positive causal effect; blue edges represent negative causal effect.

5. Discussion

This dissertation set out to investigate gene-environment influences on mental disorders using psychiatric genetic epidemiology study designs. Specific focus was on CM and poverty, two well-established risk factors yet complex to measure and often intertwined with other contextual influences. By incorporating genetic data into cohort and registry-based analyses, this work yielded robust

evidence supporting the existence of rGE between genetic risk to SZ and CM in shaping at-risk mental states to psychosis, and causal effect of abuse on SZ and of poverty on MDD and SZ.
The evidence generated can be highly relevant to inform primary prevention actions aimed at reducing the incidence of mental disorders and improving mental health for all.

TRAIL study:

This study demonstrated that schizophrenia genetic risk (SZ-PRS) is associated with a greater exposure to childhood maltreatment (CM) and psychotic like experiences (PLE) in a population-based cohort of young adults (N=1262) and replicated these findings in an independent sample (N=1740). Moreover, CM mediated the effect of schizophrenia genetic risk on psychotic-like experiences in both cohorts. Our data suggest that around 15% of PLE can be explained by our set of predictors (SZ-PRS, CM, and cannabis use), and up to one-third of the effect of schizophrenia genes on PLE is exerted through increased exposure to CM. That indicates synergy between genes and environment in shaping mental health phenotypes, such as those linked to high-risk to psychosis [72,204–207].
The reported relationship of CM with PLE echoes previous research showing that CM is associated with multidimensional psychopathology in the general population [13,208–211]. Our data confirm that CM is one of the strongest components of the exposome (the dense network of environmental exposures) that contribute to psychosis proneness [212,213]. From that perspective, the observation that CM is also associated with SZ-PRS in two independent, population-based, cohorts is very relevant. Previous research already reported a link between SZ-PRS and CM, with indirect influence on emotional, attention, and thought problems in children [88]. The current study extends the relationship between SZ-PRS and CM to early adulthood and finds evidence of a role as mediator of genetic risk to PLE for CM. These findings are consistent with a pleiotropic influence of schizophrenia genes. From a clinical perspective, PLE may be viewed as the expression of a shared genetic vulnerability that works through several pathways/mechanisms, among which we collected the strongest evidence for CM and cannabis. The reported mediations by CM and cannabis use are robust to the adjustment for other candidate mediators, including neuroticism and tobacco smoking. Adjustment for personality traits is relevant as they have been demonstrated to influence self-reported measures. Particularly, neuroticism has been suggested to increase the likelihood of individuals to recall CM [200]. However, adjusting the model for the potential influence of neuroticism did not change the role played by CM. If more frequent reporting of PLE was entirely due to increased neuroticism, including neuroticism in the model would have

attenuated or even nullified our findings. Our data suggest that the mediations do not act through changed reporting, but instead is likely to reflect truly increased levels of PLE.

In agreement with previous studies, we confirm that tobacco smoking is related to PLE and cannabis use [201,202,214]. However, the adjustment for nicotine exposure did not alter the mediation by CM. Unexpectedly, the effect of tobacco smoking on PLE had opposite directions in the two cohorts: in the discovery sample, tobacco consumption increased PLE, similarly to cannabis; in the replication sample tobacco consumption resulted in less PLE, but the adjustment increased the indirect effect of SZ-PRS on PLE through cannabis use. The reason for the discrepancies in the role of tobacco between the cohorts is unclear. It may be attributable on the different patterns of use between countries [214,215] but, in the absence of further data, any speculation is premature.

By comparing CM subtypes, we found that emotional neglect and emotional abuse are the strongest mediators of the relationship between the genetic risk to schizophrenia and PLE. That evidence complements previous findings from prominent G×E research that placed these among the most relevant exposures for the development of schizophrenia in people with high load of SZ-PRS [43]. Emotional abuse was also identified as a particularly strong risk factor for PLE in studies of high-risk populations [216,217]. The strong role of emotional abuse (and to lesser extent neglect) may be in part explained also by the fact that these types of CM are the most frequently endorsed which translates into a higher statistical power.

Finally, concerning the PLE dimensions, we found that the direct effect of SZ-PRS on delusions and hallucinations (i.e., the positive dimension of the CAPE) was not significant, although the indirect effect through the mediation pathway of CM and cannabis was. In contrast, the CAPE negative dimension (consisting of social withdrawal and blunting) was strongly influenced by the whole set of predictors, including SZ-PRS. The fact that SZ-PRS correlates with negative symptoms but not to the positive ones is in line with previous studies conducted on people with schizophrenia [218,219]. One possible explanation is that people inherit a genetic vulnerability to schizophrenia that makes them more introversive, emotionally blunted, and disorganized. Then, the exposure to relevant environmental risk factors (like cannabis and CM) leads to the expression of positive PLE (such as delusion and hallucination). Therefore, the differences in the effect of SZ-PRS on specific psychotic symptom dimensions may be explained as rGE.

REM study:

This study presents data from three large cohort studies that shows that childhood abuse, neglect, and their combination all significantly contribute to an increased risk of SZ, BD, and MDD. However, childhood abuse and neglect differ in the strength of their relation to diagnosis and clinical symptom profile. Abuse was significantly stronger related to higher odds of developing SZ compared to its impact on MDD and BD. Neglect was most strongly associated with risk for BD and MDD.

The strong association between CM abuse aligns with the mediation effect of abuse subtypes in the pathway from genetic risk to SZ and PLE found in the TRAIL study.

Differences between childhood abuse and neglect were also present across diagnosis at the symptom-level. Childhood abuse was associated with a significantly higher risk of suicide attempts, feelings of worthlessness or guilt, delusions and hallucinations, whereas neglect was significantly related to agitation and reduced need for sleep. Differential effects of child abuse and neglect at the symptom level were most prominent for symptoms of psychosis whereby abuse strongly increased the risk of delusions and hallucinations, in contrast to neglect.

In addition to the distinction between the effects of childhood abuse and neglect alone, this study also shows that experiencing both childhood abuse and neglect (combined CM) is related to higher odds of MDD or BD than the mere additive effect of child abuse plus neglect. Accumulation of stressful life events has been noted before as a risk factor for MDD [220], and is consistent with the stress resilience model whereby symptoms of psychiatric disorders develop when the impact of adversity exceeds resilience thresholds [94,221–223]. On the symptom-level, combined maltreatment showed the same pattern, with higher risks for a multitude of symptoms, compared to abuse and neglect alone. Consequently, combined maltreatment exceeds a dose-response relationship and can be seen as a more detrimental type of CM for the risk for BD and MDD. Table 15 summarizes the effect of CM types on symptom level psychopathology.

Table 15: Summary of all statistically significant associations between type of childhood maltreatment and symptoms of depression, mania, and psychosis, with a significance level of $\alpha=0.05$

Psychopathology	Abuse	Neglect	Combined

Depressive symptoms	Worthlessness/Guilt ↑ Suicide attempt ↑	Agitation ↑	Depressive mood ↑ Weight gain/increased appetite ↑ Hypersomnia ↑ Agitation ↑ Retardation ↑ Worthlessness/Guilt ↑ Returning thoughts of death ↑ Suicide attempt ↑
Manic symptoms		Reduced need for sleep ↑	Exaggerated confidence ↓ Reduced need for sleep ↑
Psychotic symptoms	Delusions ↑ Hallucinations ↑	Delusions ↓	

Another consideration on the differential relations between CM type and psychopathology is related to recent evidence of rGE [20,224]. In the relation between CM and SZ for instance, genetic liability to SZ has been associated with CM [225] and CM has been found to act as a mediator in the relation between genetic risk for SZ and the occurrence of PLE. For the current study, the joint effect of both environmental experiences and genetic vulnerability underlying the development of psychopathology [200,224] is very relevant and the results therefore should be viewed considering the broader social context in which CM occurs [107,226]. CM subtypes are likely associated with many potential confounders such as life stresses, parental psychopathology, and substance abuse [227], which occur more frequently in households with lower socio-economic status [227–229]. Differential influences of abuse and neglect may well be related to specific environmental circumstances, similarly as childhood neglect has been associated with antisocial personality disorder of the caretaker [230] and neuroticism of the child [231].

The MONEY study provided support of a causal relationship between poverty and some mental disorders. Jointly modeling different indicators of poverty using GSEM, and subsequent MR, provided convergent evidence supporting bidirectional causal effects of poverty and ADHD/SZ, a unidirectional causal effect of poverty on MDD and an inverse causal relationship between poverty and AN. Notably, the evidence of causal relationship between poverty and ADHD was influenced by unbalanced pleiotropy. These findings, in two Western ancestry samples, complement the available evidence on social inequalities in mental health collected across different countries, samples, and study designs

[82,129,133,137], including previous MR studies focusing on MDD, household income, and unemployment [232–234]. However, this research adds evidence that the relationship between poverty and mental disorder is valid across different measures of poverty and extends the investigation to a wider range of mental disorders.

This study primarily builds on genetic evidence and therefore warrants caution with respect to the conceptualization of poverty and mental disorders. Moreover, whilst poverty and other measures of socioeconomic status are heritable traits, it is very unlikely that there are direct genetic effects. Genetic associations with socioeconomic traits are likely the result of vertical pleiotropy. Vertical pleiotropy describes instances where one trait is causally associated with a second trait. In these cases, the genetic effects that act on the first trait will also be detected as being associated on the second [235]. In that context, MR can best be viewed as a way to approximately randomly assign heritable traits that give rise to income differences. Two key candidates of such underlying traits are intelligence and personality. For example, intelligence may lead to both educational advantage and socioeconomic success as well as healthier behaviors and lead to good mental health [236–240]. In this study we adjusted for cognitive ability and made two additional observations. First, when controlling for CA the causal effect of the general factor of poverty reduced by around 30% compared with univariate estimates, indicating the CA was a contributor to the causal association between poverty and mental disorders. Second, when examining each of the indicators of poverty separately, the effect of HI and OI on mental disorders were no longer statistically significant after controlling for CA. For SD, most of the evidence of a direct causal effect of poverty was absent after adjusting for CA however, higher SD remained in an inverse association with AN. The higher power obtained by using the common factor of poverty rather than the individual indicators likely facilitated the detection of the influence of heritable poverty traits above and beyond the role of CA and enabled detection of the causal role of poverty on mental health.

Of note is the vast literature showing that health characteristics (e.g., obesity), physical appearance, and mental state can influence economic outcomes including employment opportunities or wages [241–243]. Therefore, our results of a causal effect of poverty on mental disorder should not be taken as proof supporting genetic determinism, but rather as epidemiological evidence of the detrimental effects of poverty and socio-economic inequalities on mental health, regardless of the mechanisms.

The causal relationship between poverty and mental disorder is likely to involve material, psychological, behavioral, and biological pathways. For example, those with the heritable traits linked to lower levels of poverty may be more able to move away from stressful

environments/jobs/neighborhoods and so place themselves at a lower risk of disorder [92]. Furthermore, the level of development of the welfare system may be a material mediator to the health-damaging effects of income losses [244,245]. Psychosocial mechanisms are a result of the interaction between people's social environment and their feelings: living on low income is stressful, and at the same time people in disadvantaged situations may have fewer resources to cope with difficult circumstances. Increasingly, biological research is providing evidence showing how experiences such as social defeat can "get under the skin" causing biochemical changes in the body and brain and increasing the risk of developing mental health problems [246,247]. Other contributing factors to the relation between poverty and mental disorder are the negative health behaviors that are more prevalent in socially disadvantaged groups [248], likely as a consequence of the higher financial cost of healthy behaviors. For example, a healthy diet is more expensive than processed foods and joining a gym or sporting clubs can be costly. Moreover, unhealthy behaviors such as smoking or drinking alcohol may be used as coping strategies for stressful situations [249].

5.1. Limitations

The results presented in this dissertation should be interpreted in the light of its limitations. For all the studies, all participants originate from Western countries, which may reduce the generalizability of the findings. In relation to this, the MONEY study used data from genetic studies conducted in populations of European ancestry from high income countries. Generalizability to populations from other ancestries, and to low- and middle-income countries, is therefore uncertain [250]. Particularly, this raises questions about the specificity and universality of the effects of poverty on mental health in different cultures and contexts with different political and social systems.

Specific for the TRIAL study, the cross-sectional design study limited the capability to address causality, and the implementation of a rigorous multiple mediation path analysis approach might have only partially bridged this limitation. Also, residual confounding cannot be ruled out. Future research should adopt prospective designs, particularly assessing the transition rates from a non-clinical high-risk state to clinical phenotypes.

For the TRIAL and REM studies, the selection of retrospective self-reported measure of trauma is always of concern even though the use of a frequently used validated tool, with verification questions, and the analysis of neuroticism (that may influence reporting) may have partially alleviated this problem in the TRIAL study.

Fourth, in line with most studies implementing PRS, the conclusions of the TRIAL study are based on small effect sizes. Even though our results are based on the latest release of the PGC, SZ-PRS explain only a limited portion of the schizophrenia phenotype (i.e., around 7%), therefore in this study the contribution of SZ-PRS to PLE and CM are rather modest (1.4% and 1.1%, respectively).

In the REM study, limitations that are mostly related to the use of data from three separate cohort studies. Consequently, the analyses were restricted to MDD, BD, and SZ and particularly disorders such as post-traumatic stress disorder (PTSD), anxiety disorders or personality disorders [251–253] were not taken into account. As another consequence of this approach, symptom level information on psychosis was not present for the MDD cases. Whereas diagnostic classifications according to the DSM were made using completed validated diagnostic clinical assessments, the presence or absence of a particular symptom was defined based on harmonization of the CIDI, CASH and SCID items. Also, the analysis of multiple symptoms and diagnosis constitute an element of multiple testing that was not adjusted for. The most important limitation of REM study is that although possible residual confounding or collider bias is minimized by the facts that all cohorts were recruited in a similar way, and the analysis procedure included MR, bias related to reverse causation cannot be ruled out. Also, it should be noted that the MR analyses are preliminary as they are based on a different assessment of CM, and that the forward analysis could only be based on a small selection of SNPs with a sub-genome wide significant threshold. The lack of association between the CM types and MDD and BD may therefore reflect the limited power of the MR analyses. In the analysis of abuse against SZ, there is evidence of pleiotropy. This could be explained by increased variance due to the small selection of SNPs in the forward analysis, since the suggestion for pleiotropy disappears in the follow-up analysis including a larger selection of SNPs.

The limitations that should be considered when interpreting the results of the MONEY study are the followings. First, for ANX, ASD, MDD, OCD, and PTSD, GWAS sample sizes were relatively small, precluding their use as exposure variables for investigating the impact of these disorders on poverty. This is due to the insufficient number of SNPs retained following the selection, clumping, and harmonization steps. For the SNPs selection, we used the threshold of $p<5\times10^{-8}$, which is recommended by MR guidelines to ensure the validity of the relevance MR assumption [79]. We could have relaxed this threshold to include additional SNPs, but this could introduce bias. Therefore, we refrained from performing those MR analyses and trust that future, more powerful GWAS on these conditions yield more suitable instruments for MR, bridging this gap. Second, it is well acknowledged that psychiatric phenotypes are complex and heterogeneous, which generally translates to low power.

This is reflected by the relatively modest effects of each poverty indicator on mental disorders. Third, it is essential to acknowledge the potential influence of the dynastic effect, wherein characteristics transmitted across generations, such as the association between a parent's genotype and offspring phenotype, is a known source of bias in MR studies as it violates the second assumption (i.e., independence) [254]. Detecting the exact magnitude of bias resulting from this effect is challenging as current sample sizes preclude such analyses today. Future studies examining the causal link between poverty and mental health outcomes in a MR framework will be better placed to assess any influence of dynastic effects on the causal estimates identified. We also advise triangulation of our findings using complementary research methods in future studies. Fourth, it should be noted that previous research pointed out that UK Biobank participants are on average healthier and live in less socioeconomically deprived areas than the UK average [255]. This could introduce potential selection bias in MR studies using UK Biobank data, inflating the risk of Type I error [256,257]. However, the impact of selection bias is particularly strong when the selection effect is large, for instance, when studying disease progression, secondary diseases, or specific subpopulations, such as elderly people [256]. In the context of our research, the selection effect is likely to be low. Furthermore, there is evidence that UK Biobank is sufficiently large and heterogeneous to provide valid scientific inferences of associations between exposures and health conditions, which is in line with the aim of our research [255]. Fifth, the selection of SNPs associated with the latent factor poverty was performed in the UK Biobank, leading to the potential risk of overestimation of the SNP-phenotype association due to winner's curse bias. However, the impact of this bias is generally not substantial in large samples, as the UK Biobank [258]. Other limitations of MR concern temporality and linearity: MR is thought to provides estimates of lifetime risk and assumes linear effects. Although the use of MR on HI levels and the inclusion of mental disorders with onsets across the whole person's lifespan (e.g., ranging from ADHD and ASD to MDD and ANX) may have mitigated these limitations, future studies should particularly focus on assessing if there are critical windows or acute reactions to poverty exposure. Finally, the genetic variants captured by our measure of poverty are likely to have pleiotropic effects [259]. However, to break the assumptions of MR it is not sufficient for the genetic variants in the instrumental variable to have pleiotropic effects [260]. The genetic variants used as instrumental variables must have horizontally pleiotropic effects mediated via mechanisms other than those captured by poverty. Should genetic variants have vertically pleiotropic effects, e.g., SNP→neuron→intelligence→education→poverty→health→mental disorder, then our MR derived causal estimates will not be biased. Furthermore, should the SNPs affect other phenotypes, but these phenotypes do not affect outcome, then these effects will not bias our MR

estimates. It is possible that the genetic variants identified in our poverty GWAS do have horizontally pleiotropic effects, however, it is unclear what mechanisms would mediate such effects (e.g., personality). In the current study we investigate potentially pleiotropic effects using MVMR to examine the role of CA [261]. Future research should use MVMR to investigate the role of other traits that link poverty to mental health outcomes.

5.2. Implications for research and practice

This research has direct implications for research as the data generated for the poverty GWAS have been made publicly available and can be integrated in future investigations (see Data availability section). Additionally, this research confirmed that psychiatric genetic epidemiology methods can be applied to research questions related to pathogenesis of mental disorders, to ultimately identify environmental risk factor to target in preventive interventions.

In the TRIAL study, mediation by CM of the relationship between SZ-PRS and PLE point out that rGE plays a role in genetic estimates of psychosis risk. Three potential rGE mechanisms can explain the relation between SZ-PRS and CM [108]: 1-passive rGE, 2-evocative rGE and 3-active rGE. (1) Passive rGE refers to the association between a person's genotype and the behavior of genetically related individuals. Parental mental health and parental history of CM are confirmed risk factor for maltreating offspring [262,263]. A person's genetic risk is reflective of parents' genetic risk, and a higher genetic load for schizophrenia in parents might have influenced their children's environment to increase the likelihood of CM. (2) Evocative rGE occurs when a person's genetically driven behavior elicits responses from others. Previous research highlighted sub-clinical psychiatric manifestation of emotional and behavioral problems in children with higher SZ-PRS [264–267] which might have exposed them to harder punishments by caretakers. (3) Active rGE occurs when people's life experiences are directly influenced by their own genetically determined behaviors, such as thrill-seeking or risk-taking behaviors.

Regardless the rGE mechanism involved in this study, CM account for up to 30% of the effect of SZ-PRS on PLE. Simulations pointed out that mediation through CM becomes a significant mechanism in participants within the top 40% of SZ-PRS. The question is warranted whether such a threshold may provide guidance for tailoring preventative strategies. For instance, resources may be allocated for counselling of children and adolescents targeting those with the highest genetic risk and coaching their

caretakers on positive parenting skills [268]. This might offer an opportunity for attenuating the risk of mental health disorder. Indeed, previous research confirmed that fostering safe and stable relationship between intimate partners and between mothers and children is effective in reducing the intergenerational transmission of abuse in families [269]. Addressing parental mental health and parental history of childhood abuse in case of passive rGE would help to provide individualized support and to plan early interventions, such as early education about lifestyle and parenting skills [270]. However, considering that the contribution of SZ-PRS is low and other more intuitive factors (such as help seeking behavior and educational problems) are likely to be stronger risk factors, preventive approaches based on SZ-PRS should be further explored in future research with larger sample size.

One of the most consistent findings of the REM study is the strong relation of abuse with SZ and positive psychotic symptoms. A strong relation between abuse and SZ fits previous reports of a threefold increase in psychosis risk and hallucinations in patients with a history of child abuse [117,271–273] and warrants the question about a possible causal relation between child abuse (and not neglect) and SZ.

The findings from the MR analyses lend further support for this hypothesis, even when based on a limited numbers of SNPs due to the modest discovery set of the UK Biobank (N=143,473). Such a relation would be of great importance to further promote public prevention programs and could provide a personalized treatment perspective for individuals suffering from SZ with a history of abuse. Considering that a history of CM has a negative influence on prognosis and treatment outcomes [274], the question is warranted to what extent individual trauma-focused therapy might decrease their burden [275,276], even in the absence of post-traumatic stress disorder. Another prospect of an increased understanding of the CM-SZ relationship could be the development of predictive models for antipsychotic treatment outcomes, as has previously been done for MDD [277]. A clinical hypothesis could be that SZ patients with a history of CM are less likely to respond to antipsychotics and more likely to trauma-focused therapy as compared to patients without such CM history. More fundamentally, these findings could be a starting point for etiology research into a distinct abuse-SZ pathway. One possible direction for such studies could be the revisiting of molecular pathways linking CM to dopaminergic function specified by CM type [105]. Previous research suggests several other psychological, social, and biological pathways from childhood adversity to SZ [226,278], that could be refined by specifying CM type.

In addition to pinpointing the relevance of gene-environment effects, the current study underlines the importance of differentiating in the type of adverse childhood experiences with respect to their effects on mental health. Previous research already indicated the relevance of CM even within diagnostic category by reporting clinical and neurobiological differences between maltreated and non-maltreated individuals with the same primary DSM-5 diagnosis [279,280]. The current study underscores the potential for such refinements. A subdivision within diagnoses based on the effects of childhood adversities may contribute to developing alternative, transdiagnostic approaches in future research. Besides child abuse and neglect, subdividing CM experiences into emotional and physical trauma could also be further investigated [281]. Ultimately, further differentiating the effects of various CM types might open doors to targeted therapy and prediction models.

The findings reiterate the need to further unravel the role of poverty in mental disorders and the way to use this insight to advance mental health for all. The choice of which action to take to address the problem is a political matter, but attention is warranted considering increasing income inequalities worldwide [282], as well as increasing incidence of mental disorders [6,283].
Previous studies examining antipoverty programs reported positive and sustained effects on mental health [284], including reduction of depression and suicide rates [137,285,286]. For example, a recent RCT found that cash incentives provided to low-income individuals led to meaningful improvements in depression [287]. Additionally, specific economic interventions such as family assets, employment support, and rental assistance may be effective in enhancing the mental health of program beneficiaries [288,289]. However, it is important to note that previous quasi-experimental research using natural experiments, such as on the lottery winner population, provided supportive evidence for small association between SES and mental health [290], and qualitative studies showed that receiving money could be perceived as a debt or burdensome responsibility [291,292], which may contribute to increased stress [293,294]. Therefore, further research is necessary to identify the factors within economic support interventions (e.g., microcredit, loans, personal health budgets) that influence mental health outcomes. Early studies that combined antipoverty interventions, such as financial incentives and financial mentoring programs, appeared more effective in improving mental health compared to providing financial incentives alone [286]. Given these complexities, policymakers could consider policies that can be beneficial both for individuals living in poverty and those living with severe mental disorders. Policymakers should also consider a key finding of this study about the effect of cognitive ability in the causal pathway linking poverty to mental disorder. CA is closely associated with educational attainment

and occupational status, which are often regarded as socio-economic status variables relevant to health [237,238,240]. Although the genetic relationship between CA and mental disorder differs from the genetic relationship between education and mental disorder [89,295], educational attainment is a likely causal factor in CA differences [296–298] and is a more straightforward target for interventions than CA. Thus, future research should explore strategies aimed at facilitating individuals' participation in education, which may lead to better mental health [22,130,299].

6. Conclusions

Environmental risk factors are in part genetic and therefore the traditional division between genes and environment needs revision. Using psychiatric genetic epidemiology designs, the research presented in this dissertation has refined the evidence base on key environmental risk factors for mental health. CM and poverty emerged as critical risk factors for severe mental disorders like SZ, MDD, BD, and ADHD. These findings can inform future research into targeted primary prevention interventions to improve mental health for all.

7. Data availability

The variance-covariance matrix and the codes for replicating the analyses of the TRAIL study can be accessed here: https://github.com/MattiaMarchi/SEM_Sz-PRS-CM_PLE
The summary statistics of the seven GWAS generated for the MONEY study can be accessed from the GWAS catalog at the following link: https://www.ebi.ac.uk/gwas/publications/38987359
The codes for generated for the MONEY study can be accessed here:
https://github.com/MattiaMarchi/Common-factor-GWAS---MR

8. Acknowledgements

The three studies presented in this dissertation have all been published and are available open access at the following permanent links:
- TRAIL study: Marchi et al. Translational Psychiatry (2022) 12, 219-229.
https://doi.org/10.1038/s41398-022-01975-1

- REM study: Alkema et al. Psychological Medicine (2024) 54, 1598-1609. https://doi.org/10.1017/S0033291723003471
- MONEY study: Marchi et al. Nature Human Behaviour (2024) 8, 1771-1783. https://doi.org/10.1038/s41562-024-01919-3

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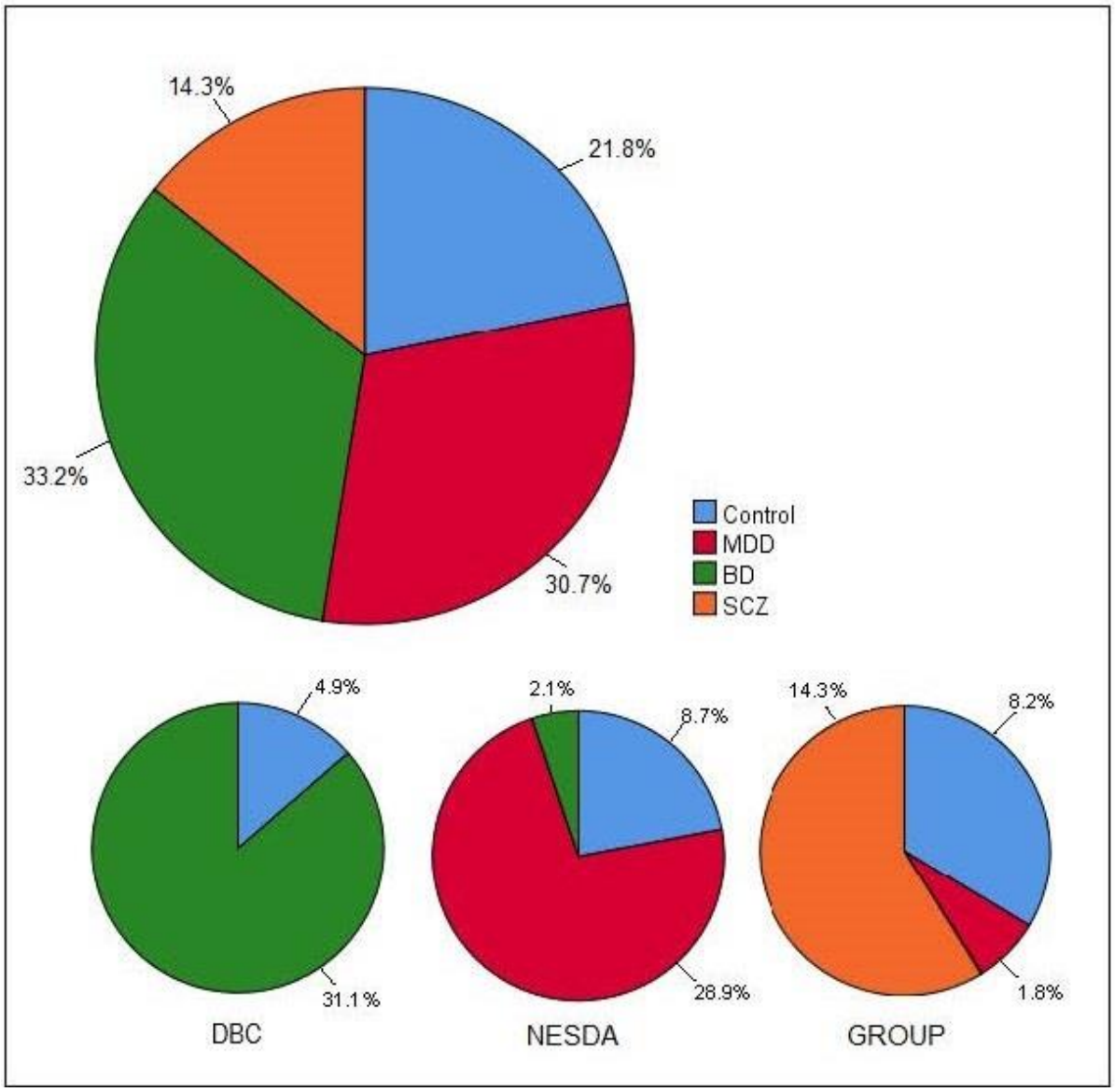
10. Appendix

The Childhood Trauma Questionnaire: *each item was answered on a Likert scale from 1 (never) to 5 (very often).*

Item Nr.	25-items English version	Reply
1	I didn't have enough to eat.	
2	I knew there was someone to take care of me and protect me.	
3	People in my family called me things like "stupid", "lazy" or "ugly".	
4	My parents were too drunk or high to take care of the family.	
5	There was someone in my family who helped me feel that I was important or special.	
6	I had to wear dirty clothes.	
7	I felt loved.	
8	I thought that my parents wished I had never been born.	
9	I got hit so hard by someone in my family that I had to see a doctor or go to the hospital.	
10	People in my family hit me so hard that it left me with bruises or marks.	
11	I was punished with a belt, a board, a cord, or some other hard object.	
12	People in my family looked out for each other.	
13	People in my family said hurtful or insulting things to me.	
14	I believe that I was physically abused.	
15	I got beaten so badly that it was noticed by someone like a teacher, neighbor, or doctor.	
16	I felt that someone in my family hated me.	
17	People I my family felt close to each other.	
18	Someone tried to touch me in a sexual way or tried to make me touch them.	
19	Someone threatened to hurt me or tell lies about me unless I did something sexual with them.	
20	Someone tried to make me do sexual things or watch sexual things.	
21	Someone molested me.	
22	I believe that I was emotionally abused.	
23	There was someone to take me to the doctor if I needed it.	
24	I believe that I was sexually abused.	
25	My family was a source of strength and support.	



Supplementary Figure 1: *Distribution of diagnosis categories per cohort in the REM study*

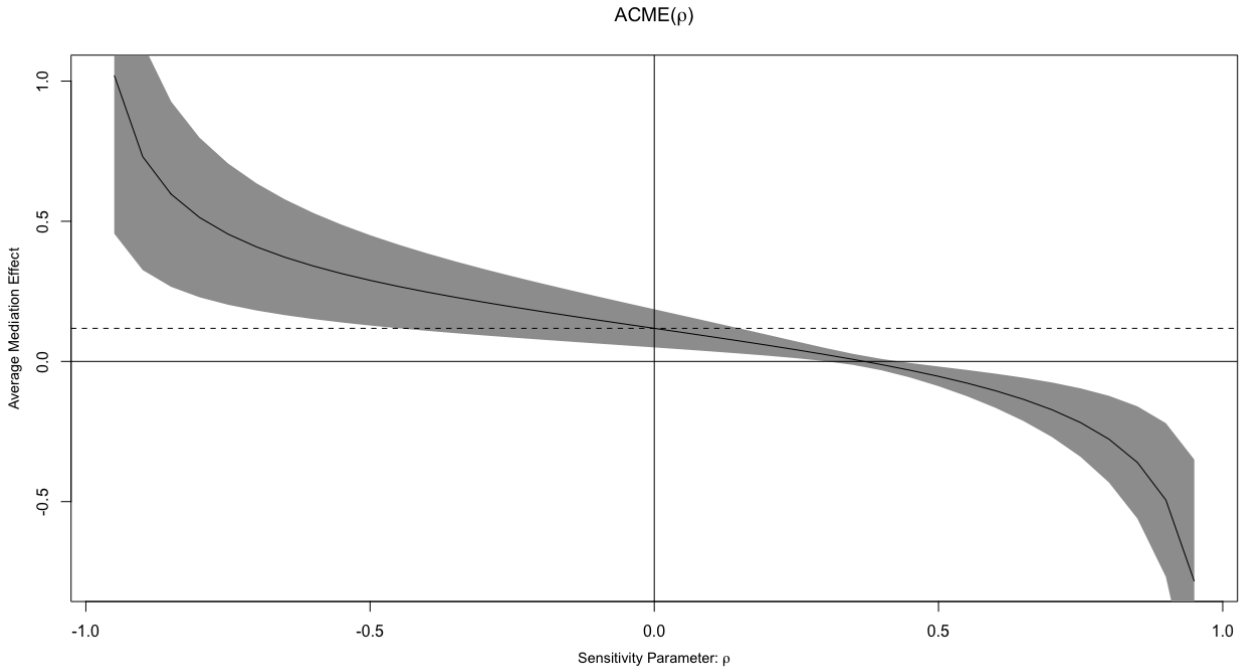
Legend: Distribution of cases in percentages (%) of major depressive disorder (MDD), bipolar disorder (BD), schizophrenia (SCZ) and participants without psychiatric diagnosis (controls) in the total dataset (large pie chart) and specified for each cohort study (three smaller pie charts) used for the composite dataset: the Dutch Bipolar Cohort (DBC), the Netherlands Study of Depression and Anxiety (NESDA) and the Genetic Risk and Outcome in Psychosis (GROUP) study.

TRAIL study

Supplementary Table 1: *Variance of PLE phenotype explained by the SZ-PRS selected from the LASSO*

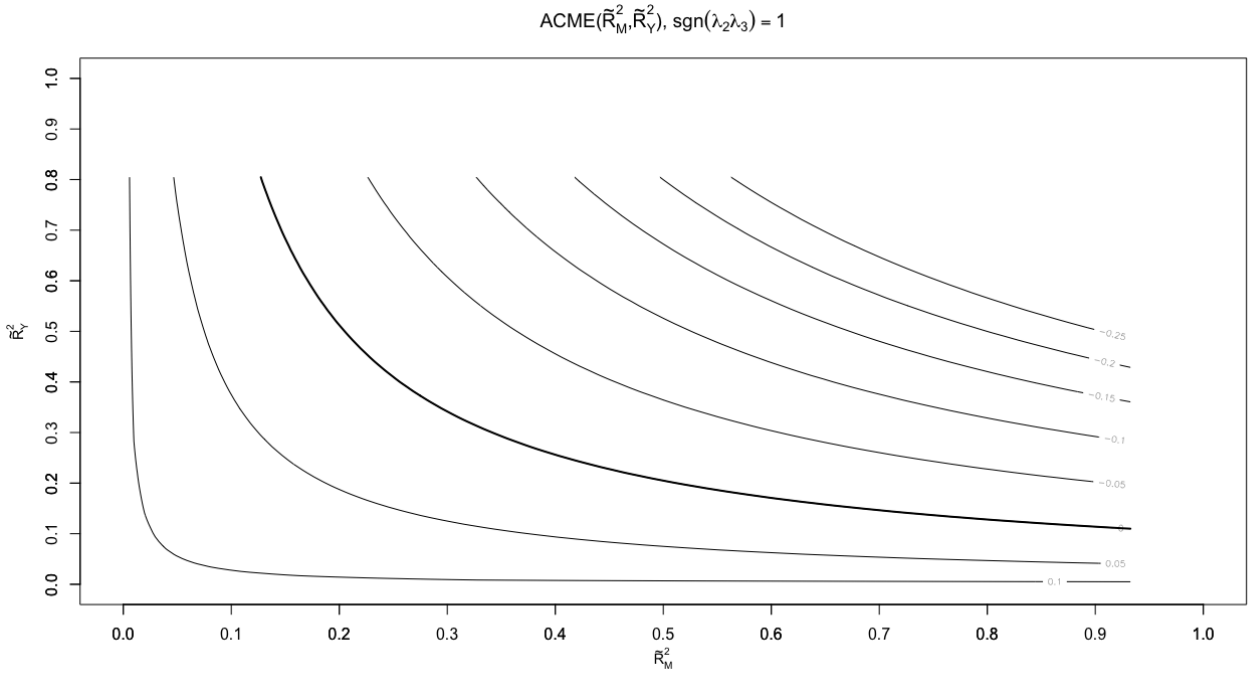
SZ-PRS pt	Unstandardized estimate (95% CI)	p-value	R^2
0.2	0.348 (0.190; 0.506)	<0.001	0.0139
0.5	0.328 (0.181; 0.475)	<0.001	0.0143
1	0.326 (0.180; 0.471)	<0.001	0.0142

Abbreviations: SZ-PRS pt: schizophrenia polygenic risk score p-value threshold; 95% CI: 95% confidence interval



Supplementary Figure 2: *Causal mediation effect of CM as function of the sensitivity parameter (ρ)*

Abbreviations: ACME: average causal mediation effect of CM.



Supplementary Figure 3: *Explanatory power of a confounder on the causal mediation effect of CM*

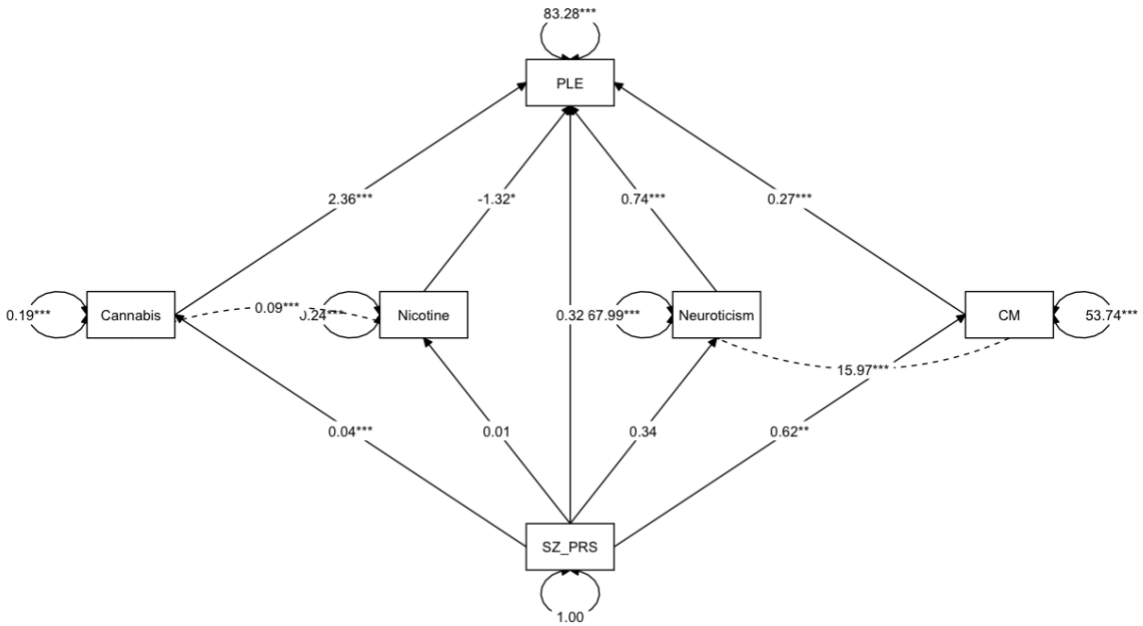
Abbreviations: ACME: average causal mediation effect of CM.

Supplementary Table 2: *Results of parallel four-mediator model in the replication sample (IMAGEN cohort)*

Regressions	**Unstandardized estimate (95% CI)**	**Standardized coefficient**	**p-value**
Direct effects			
Outcome model: PLE (R^2=0.371)			
SZ-PRS	0.324 (-0.207; 0.855)	0.028	0.231
CM	0.270 (0.188; 0.352)	0.172	<0.001
Cannabis use	2.36 (0.989; 3.74)	0.089	0.001
Neuroticism	0.740 (0.673; 0.806)	0.531	<0.001
Nicotine	-1.32 (-2.53; -0.11)	-0.056	0.032
Mediator model: CM (R^2=0.007)			
SZ-PRS	0.618 (0.185; 1.05)	0.084	0.005
Mediator model: Cannabis use (R^2=0.009)			
SZ-PRS	0.041 (0.017; 0.065)	0.094	0.001

Mediator model: Neuroticism (R^2=0.002)			
SZ-PRS	0.343 (-0.117; 0.803)	0.042	0.144
Mediator model: Nicotine (R^2=0.001)			
SZ-PRS	0.008 (-0.019; 0.035)	0.016	0.568
Covariances			
CM – Neuroticism	16.0 (12.2; 19.7)	0.264	<0.001
Cannabis – Nicotine	0.091 (0.078; 0.104)	0.431	<0.001
Indirect effects (proportion mediated)			
CM (20.1%)	0.167 (0.039; 0.294)	0.014	0.010
Cannabis (11.6%)	0.097 (0.017; 0.177)	0.008	0.018
Neuroticism (30.6%)	0.254 (-0.087; 0.595)	0.022	0.145
Nicotine (-1.3%)	-0.011 (-0.048; 0.027)	-0.001	0.581
Sum	0.507 (0.111; 0.903)	0.044	0.012
Total effect	0.831 (0.178; 1.48)	0.072	0.013

Abbreviations: 95% CI: 95% bias-corrected bootstrap confidence interval; PLE: psychotic-like experiences; CM: childhood maltreatment; SZ-PRS: schizophrenia polygenic risk score at p-value threshold 0.5.



Supplementary Figure 4: *Path diagram of parallel four-mediator model in the replication sample (IMAGEN cohort).*

Legend: the estimates reported are the unstandardized regression coefficients. *p<0.05; **p<0.01; ***p<0.001.

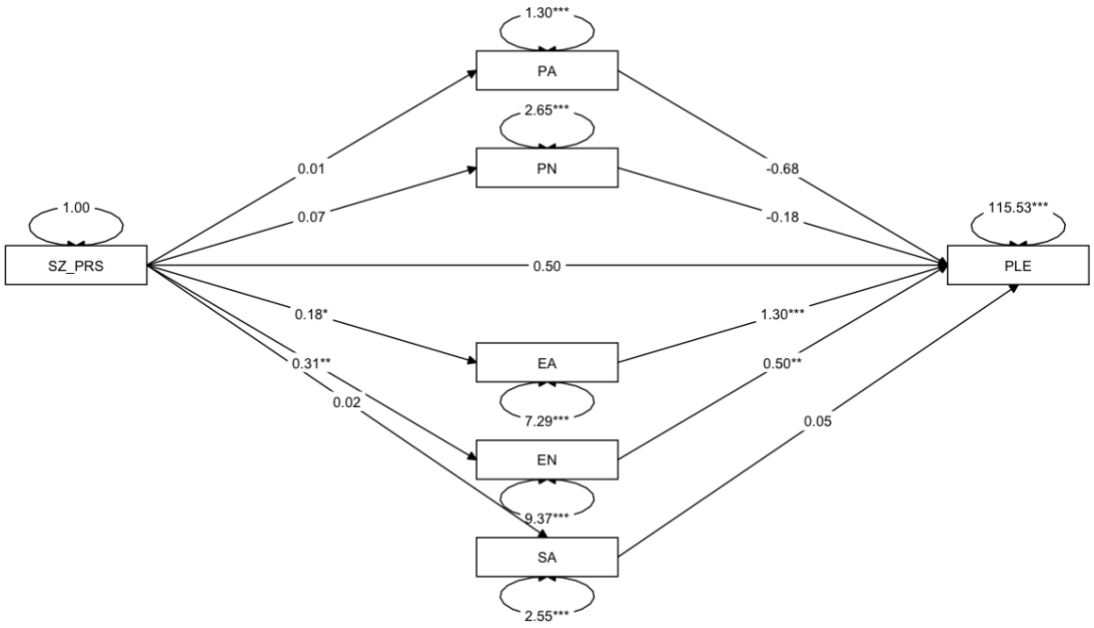
Abbreviations: SZ-PRS: schizophrenia polygenic risk score at p-value threshold 0.5; CM: childhood maltreatment; PLE: psychotic-like experiences.

Supplementary Table 3: *Results of parallel multiple mediation analysis according to the trauma subtype in the replication sample (IMAGEN cohort)*

Regressions	**Unstandardized estimate (95% CI)**	**Standardized coefficient**	**p-value**
Direct effects			
Outcome model: PLE (R^2=0.123)			
SZ-PRS	0.499 (-0.128; 1.13)	0.043	0.119
Sexual abuse	0.046 (-0.396; 0.488)	0.006	0.840
Physical abuse	-0.684 (-1.45; 0.085)	-0.068	0.081
Emotional abuse	1.30 (0.947; 1.66)	0.307	<0.001
Physical neglect	-0.183 (-0.669; 0.302)	-0.026	0.459
Emotional neglect	0.496 (0.200; 0.792)	0.133	0.001
Mediator model: Sexual abuse (R^2<0.001)			
SZ-PRS	0.024 (-0.071; 0.119)	0.015	0.619
Mediator model: Physical abuse (R^2<0.001)			
SZ-PRS	0.013 (-0.054; 0.081)	0.012	0.699
Mediator model: Emotional abuse (R^2=0.005)			
SZ-PRS	0.184 (0.024; 0.343)	0.068	0.024
Mediator model: Physical neglect (R^2=0.002)			
SZ-PRS	0.074 (-0.023; 0.171)	0.045	0.136
Mediator model: Emotional neglect (R^2=0.010)			
SZ-PRS	0.305 (0.123; 0.487)	0.099	0.001

Indirect effects (proportion mediated)			
Sexual abuse (0.1%)	0.001 (-0.010; 0.013)	<0.001	0.852
Physical abuse (-1.0%)	-0.009 (-0.057; 0.038)	-0.001	0.705
Emotional abuse (27.5%)	0.239 (0.020; 0.458)	0.021	0.032
Physical neglect (-1.6%)	-0.014 (-0.053; 0.026)	-0.001	0.505
Emotional neglect (17.4%)	0.151 (0.023; 0.280)	0.013	0.021
Sum	0.369 (0.126; 0.612)	0.032	0.003
Total effect	0.868 (0.211; 1.53)	0.076	0.010

Abbreviations: 95% CI: 95% bias-corrected bootstrap confidence interval; PLE: psychotic-like experiences; SZ-PRS: schizophrenia polygenic risk score at p-value threshold 0.5.



Supplementary Figure 5: *Path diagram of parallel multiple mediation analysis according to the trauma subtype in the replication sample (IMAGEN cohort).*

Legend: the estimates reported are the unstandardized regression coefficients. *p<0.05; **p<0.01; ***p<0.001.

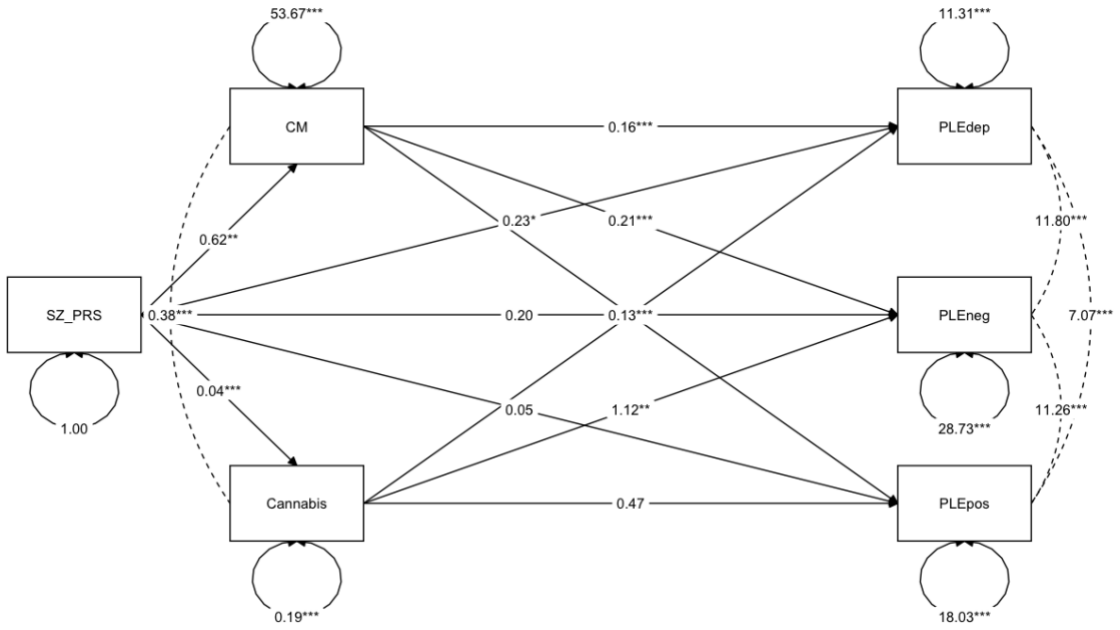
Abbreviations: SZ-PRS: schizophrenia polygenic risk score at p-value threshold 0.5; PLE: psychotic-like experiences; PS: physical abuse; PN: physical neglect; EA: emotional abuse; EN: emotional neglect; SA: sexual abuse.

Supplementary Table 4: *Results of multiple outcome parallel mediation model in the replication sample (IMAGEN cohort)*

Regressions	**Unstandardized estimate (95% CI)**	**Standardized coefficient**	**p-value**
Direct effects			
Outcome model: PLE depression (R^2=0.117)			
SZ-PRS	0.233 (0.037; 0.429)	0.065	0.020
CM	0.158 (0.130; 0.187)	0.325	<0.001
Cannabis use	0.222 (-0.238; 0.681)	0.027	0.345
Outcome model: PLE negative (R^2=0.089)			
SZ-PRS	0.199 (-0.113; 0.511)	0.035	0.211
CM	0.205 (0.159; 0.252)	0.269	<0.001
Cannabis use	1.12 (0.387; 1.85)	0.086	0.003
Outcome model: PLE positive (R^2=0.052)			
SZ-PRS	0.051 (-0.195; 0.298)	0.012	0.683
CM	0.128 (0.092; 0.165)	0.216	<0.001
Cannabis use	0.468 (-0.109; 1.04)	0.047	0.112
Mediator model: CM (R^2=0.007)			
SZ-PRS	0.616 (0.183; 1.05)	0.084	0.005
Mediator model: Cannabis use (R^2=0.009)			
SZ-PRS	0.041 (0.017; 0.065)	0.095	0.001
Covariances			
ELA – Cannabis use	0.383 (0.185; 0.582)	0.121	<0.001
Indirect effects (proportion mediated)			
CM ~ PLE depression (11.4%)	0.098 (0.026; 0.169)	0.027	0.007
CM ~ PLE negative (14.8%)	0.127 (0.003; 0.220)	0.023	0.008
CM ~ PLE positive (9.2%)	0.079 (0.019; 0.139)	0.018	0.010
Cannabis ~ PLE depression (1.0%)	0.009 (-0.011; 0.029)	0.003	0.363
Cannabis ~ PLE negative (5.3%)	0.046 (0.006; 0.087)	0.008	0.025
Cannabis ~ PLE positive (2.2%)	0.019 (-0.007; 0.046)	0.004	0.151

Sum CM (35.2%)	0.303 (0.082; 0.524)	0.068	0.007
Sum Cannabis (8.7%)	0.075 (-0.001; 0.150)	0.015	0.052
Total	0.378 (0.141; 0.614)	0.083	0.002
Total effect	0.861 (0.200; 1.52)	0.195	0.011

Abbreviations: 95% CI: 95% bias-corrected bootstrap confidence interval; PLE: psychotic-like experiences; CM: childhood maltreatment; SZ-PRS: schizophrenia polygenic risk score at p-value threshold 0.5.



Supplementary Figure 6: *Path diagram of multiple outcome parallel mediation model in the replication sample (IMAGEN cohort).*

Legend: the estimates reported are the unstandardized regression coefficients. *p<0.05; **p<0.01; ***p<0.001.

Abbreviations: SZ-PRS: schizophrenia polygenic risk score at p-value threshold 0.5; CM: childhood maltreatment; PLE: psychotic-like experiences (pos: positive; neg: negative; dep: depression).

REM study

Supplementary Table 5: *Relation of childhood maltreatment type and mental disorder in a non-adjusted logistic regression model.*

Mental disorder	OR (95%CI) Abuse	OR (95%CI) Neglect	OR (95%CI) Combined
MDD	1.78 [1.24-2.56]*	2.66 [2.06-3.42]*	4.92 [3.65-6.64]*
BD	1.98 [1.39-2.82]*	2.86 [2.23-3.67]*	4.64 [3.44-6.25]*
SZ	3.17 [2.17-4.63]*	1.74 [1.27-2.39]*	3.39 [2.40-4.80]*

Abbreviations: BD: bipolar disorder; MDD: major depressive disorder; OR: odds ratio; SZ: schizophrenia; 95%CI: 95% confidence interval.

Legend: *Significant with α=0.05

Supplementary Table 6: *Results of bidirectional MR of abuse, neglect and combined CM against BD, MDD, and SZ with p-value threshold: 3e-06 for forward analyses, 5e-08 for backward analyses.*

MR	N SNP	IVW (95% CI)	p-value	IVW Q (df)	Q p-value	WM (95% CI)	p-value	MR-Egger (95% CI)	p-value	Egger intercept p-value*	Steiger Test p-value [b]	MR-PRESSO [a]	Mean F
Fw: Abuse on BD	6	-0.013 (-0.096; 0.070)	0.757	5.53 (5)	0.355	-0.003 (-0.115; 0.109)	0.963	-0.077 (-0.638; 0.483)	0.800	0.764	NR[b]	GT; p=0.377	23.1
Bw: BD on Abuse	35	0.085 (-0.023; 0.193)	0.123	33.9 (34)	0.473	0.074 (-0.084; 0.233)	0.357	-0.073 (-0.662; 0.516)	0.809	0.595	NR[b]	GT; p=0.445	39.4
Fw: Neglect on BD	8	-0.003 (-0.069; 0.063)	0.929	17.4 (7)	**0.015**	0.043 (-0.050; 0.135)	0.366	0.178 (0.045; 0.312)	0.039	0.021	**<0.001**	DT; p=0.403	23.5
Bw: BD on Neglect	35	0.002 (-0.118; 0.121)	0.976	52.2 (34)	**0.024**	-0.061 (-0.244; 0.123)	0.517	-1.04 (-1.76; -0.316)	**0.008**	0.007	**<0.001**	DT; p=0.673	39.4
Fw: Combined on BD	8	-0.055 (-0.116; 0.005)	0.074	11.5 (7)	0.117	-0.028 (-0.112; 0.056)	0.512	-0.110 (-0.302; 0.083)	0.307	0.563	NR[b]	GT; p=0.119	23.5
Bw: BD on combined	35	-0.010 (-0.138; 0.119)	0.881	41.1 (34)	0.188	0.013 (-0.177; 0.202)	0.896	-0.772 (-1.50; -0.047)	0.044	0.044	**<0.001**	GT; p=0.184	39.4
Fw: Abuse on MDD	7	0.001 (-0.077; 0.076)	0.993	1.44 (6)	0.963	0.024 (-0.068; 0.116)	0.611	0.032 (-0.237; 0.301)	0.827	0.822	NR[b]	GT; p=0.967	23.2

Bw: MDD on Abuse	0	NR[c]	NR[c]	NR[c]	NR[c]	NR[c]	NR[c]	NR[c]	NR[c]	NR[c]	NR[c]	NR[c]	NR[c]
Fw: Neglect on MDD	8	0.037 (-0.027; 0.100)	0.256	8.58 (7)	0.284	0.037 (-0.054; 0.129)	0.456	-0.021 (-0.159; 0.117)	0.776	0.795	NR[b]	GT; p=0.320	23.4
Bw: MDD on Neglect	0	NR[c]	NR[c]	NR[c]	NR[c]	NR[c]	NR[c]	NR[c]	NR[c]	NR[c]	NR[c]	NR[c]	NR[c]
Fw: Combined on MDD	9	-0.058 (-0.112; -0.006)	**0.030**	3.34 (8)	0.911	-0.036 (-0.106; 0.034)	0.308	0.021 (-0.079; 0.122)	0.689	0.418	**<0.001**	GT; p=0.920	23.2
Bw: MDD on Combined	0	NR[c]	NR[c]	NR[c]	NR[c]	NR[c]	NR[c]	NR[c]	NR[c]	NR[c]	NR[c]	NR[c]	NR[c]
Fw: Abuse on SZ	6	0.112 (0.045; 0.180)	**0.001**	7.50 (5)	0.186	0.099 (-0.008; 0.191)	0.132	0.174 (-0.321; 0.669)	0.528	0.815	**<0.001**	GT; p=0.196	23.1
Bw: SZ on Abuse	176	0.105 (0.052; 0.159)	**<0.001**	181 (175)	0.353	0.128 (0.047; 0.210)	**0.002**	0.251 (0.040; 0.462)	**0.021**	0.165	**<0.001**	GT; p=0.341	45.6
Fw: Neglect on SZ	6	-0.025 (-0.076; 0.025)	0.323	43.2 (7)	**<0.001**	0.016 (-0.058; 0.090)	0.667	0.150 (-0.050; 0.351)	0.193	0.091	NR[b]	DT; p=0.196	23.5
Bw: SZ on Neglect	176	0.086 (0.028; 0.145)	**0.004**	196 (175)	0.133	0.120 (0.031; 0.209)	**0.008**	0.121 (-0.123; 0.364)	0.333	0.776	**<0.001**	GT; p=0.127	45.6
Fw: Combined on SZ	8	0.017 (-0.035; 0.050)	0.514	8.10 (7)	0.324	0.034 (-0.037; 0.104)	0.349	0.074 (-0.059; 0.206)	0.317	0.391	NR[b]	GT; p=0.315	23.3

Bw: SZ on combined	176	0.105 (0.042; 0.169)	**0.001**	156 (175)	0.844	0.116 (0.022; 0.210)	**0.015**	0.201 (-0.045; 0.448)	0.111	0.431	<**0.001**	GT; p=0.853	45.6

Abbreviations: Abbreviations: Fw: forward analysis; Bw: backward analysis; BD: bipolar disorder; MDD: major depressive disorder; SZ: schizophrenia; MR: mendelian randomization; SNP: single nucleotide polymorphism; IVW: inverse variance weighted (fixed effect); 95% CI: 95% confidence interval; Q: Cochran's Q measure of heterogeneity; df: degree of freedom; WM: weighted median; DT: distortion test; GT: global test.

Legend: effect estimates are log-odds.

[a] The Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) test identifies possible bias from horizontal pleiotropy. The test consists of three parts, (1) the MR-PRESSO global test which detects horizontal pleiotropy, (2) the outlier corrected causal estimate which corrects for the detected horizontal pleiotropy and (3) the MR-PRESSO distortion test which estimates if the causal estimate is significantly different (at $p<0.05$) after adjustment for outliers. We conduct all three stages (with the argument NbDistribution=1000, namely using1000 simulation form the null distribution to compute empirical p-values) and present the outlier adjusted causal estimates (OACE) when both global and distortion tests are significant.

[b] We did not run Steiger Test if none of the MR analysis resulted significant (NR: not reported in the cell).

[c] Not enough SNP to perform MR (NR: not reported in the cell).

All statistical tests were two-sided. The p-values were not adjusted for multiple testing, therefore p-value<0.05 was considered significant (and reported in bolded text).

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Supplementary Table 7: *Factor loading of each poverty indicator used for the estimation of the latent poverty factor*

Regression	**Unstandardized B (SE)**	**Standardized B (SE)**	**p-value**
PF~HI	0.280 (0.007)	1,00 (0.028)	**5.061×10^{-295}**
PF~SD	-0.127 (0.004)	-0.733 (0.025)	**5.230×10^{-198}**
PF~OI	0.261 (0.008)	0.862 (0.025)	**6.194×10^{-260}**

Abbreviations: PF: poverty common factor; HI: household income; SD: social deprivation; OI: occupational income; B: linear regression coefficient; SE: standard error.

Legend: Linear regression was used for testing the factor loadings of each indicator on the common factor. The p-values are two-sided and not adjusted for multiple testing, therefore p-value<0.05 was considered significant (and reported in bolded text).

Supplementary Table 8: *Odds Ratio of univariable forward Mendelian randomization analysis of poverty against mental disorder*

MR: method	**OR (95% CI)**	**p-value**
PF → ADHD:		
IVW	1.39 (1.33; 1.45)	**1.28×10^{-51}**
WM	1.24 (1.15; 1.34)	**2.28×10^{-8}**
MR-Egger	0.794 (0.565; 1.10)	0.180
PF → AN:		
IVW	0.826 (0.775; 0.877)	**1.90×10^{-9}**
WM	0.826 (0.746; 0.910)	**1.50×10^{-4}**
MR-Egger	0.658 (0.424; 1.02)	0.064
PF → ANX:		
IVW	1.26 (1.11; 1.43)	**4.59×10^{-4}**
WM	1.17 (0.971; 1.41)	0.096
MR-Egger	0.935 (0.488; 1.80)	0.842
PF → ASD:		
IVW	0.980 (0.917; 1.04)	0.443
WM	0.980 (0.885; 1.09)	0.698
MR-Egger	0.621 (0.406; 0.943)	**0.030**
PF → BD:		

IVW	0.997 (0.952; 1.04)	0.889
WM	0.971 (0.901; 1.04)	0.389
MR-Egger	0.775 (0.532; 1.15)	0.211
PF → MDD:		
IVW	1.12 (1.08; 1.17)	**3.45×10^{-8}**
WM	1.09 (1.02; 1.17)	**0.010**
MR-Egger	0.990 (0.763; 1.28)	0.924
PF → OCD:		
IVW	0.820 (0.699; 0.952)	**0.010**
WM	0.862 (0.685; 1.09)	0.221
MR-Egger	1.34 (0.641; 2.82)	0.434
PF → PTSD:		
IVW	1.15 (1.08; 1.23)	**3.79×10^{-5}**
WM	1.12 (1.01; 1.24)	**0.031**
MR-Egger	0.901 (0.630; 1.28)	0.163
PF → SZ:		
IVW	1.12 (1.08; 1.16)	**1.41×10^{-14}**
WM	1.14 (1.06; 1.22)	**9.37×10^{-3}**
MR-Egger	0.926 (0.629; 1.36)	0.922

Abbreviations: MR: Mendelian randomization; OR: Odds Ratio; 95% CI: 95% confidence intervals; P: poverty; ADHD: attention deficit hyperactivity disorder; AN: anorexia nervosa; ANX: anxiety disorder; ASD: autism spectrum disorders; BD: bipolar disorder; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; PTSD: post-traumatic stress disorder; SZ: schizophrenia; IVW: inverse variance weighted (fixed effect); WM: weighted median.

Legend: Poverty is a latent variable built using household income as unit identification, therefore an increase in the indicator's load stands for increased income, therefore the ORs have been reversed to facilitate interpretation of the effect of poverty. All statistical tests were two-sided. The p-values were not adjusted for multiple testing, therefore p-value<0.05 was considered significant (and reported in bolded text).

Supplementary Table 9: *CAUSE results of the relations between poverty and mental disorder*

Model 1	**Model 2**	**Δ ELPD**	**SE Δ ELPD**	**z-score**	**p-value**[†]
Fw: PF on ADHD					
Null	Sharing	-67.54	9.89	-6.83	**8.49×10^{-12}**

Null	Causal	-74.39	10.94	-6.80	**1.46×10^{-11}**
Sharing	Causal	-6.85	1.34	-5.12	**3.06×10^{-7}**
Bw: ADHD on PF					
Null	Sharing	-4.26	1.78	-2.40	**0.016**
Null	Causal	-9.60	3.77	-2.55	**0.011**
Sharing	Causal	-5.34	2.01	-2.65	**0.008**
Fw: PF on AN					
Null	Sharing	-9.37	3.49	-2.69	**0.007**
Null	Causal	-13.61	5.00	-2.72	**0.006**
Sharing	Causal	-4.24	1.67	-2.54	**0.011**
Bw: AN on PF					
Null	Sharing	0.39	0.15	2.62	**0.009**
Null	Causal	0.60	0.98	0.61	0.540
Sharing	Causal	0.21	0.84	0.25	0.803
Fw: PF on ANX					
Null	Sharing	-0.41	1.11	-0.36	0.715
Null	Causal	-0.64	2.02	-0.32	0.750
Sharing	Causal	-0.24	1.03	-0.23	0.818
Bw: ANX on PF					
Null	Sharing	0.17	0.04	4.09	**4.31×10^{-5}**
Null	Causal	0.81	0.22	3.70	**2.16×10^{-4}**
Sharing	Causal	0.65	0.19	3.41	**0.001**
Fw: PF on ASD					
Null	Sharing	0.52	0.07	7.04	**1.92×10^{-12}**
Null	Causal	1.38	0.11	12.99	**1.39×10^{-38}**
Sharing	Causal	0.86	0.03	25.23	**1.88×10^{-140}**
Bw: ASD on PF					
Null	Sharing	0.48	0.04	10.65	**1.74×10^{-26}**
Null	Causal	1.26	0.06	21.68	**3.17×10^{-104}**
Sharing	Causal	0.78	0.04	21.17	**1.81×10^{-99}**
Fw: PF on BD					
Null	Sharing	0.47	0.09	5.20	**1.99×10^{-7}**
Null	Causal	1.27	0.50	2.53	**0.011**
Sharing	Causal	0.81	0.43	1.89	0.059
Bw: BD on PF					
Null	Sharing	0.44	0.04	12.51	**6.58×10^{-36}**
Null	Causal	1.28	0.05	26.16	**7.58×10^{-151}**

Sharing	Causal	0.84	0.02	41.95	**$<1^{-1000}$**
Fw: PF on MDD					
Null	Sharing	-9.90	3.72	-2.66	**0.008**
Null	Causal	-13.68	5.09	-2.69	**0.007**
Sharing	Causal	-3.78	1.51	-2.50	**0.013**
Bw: MDD on PF					
Null	Sharing	0.01	0.36	0.04	0.968
Null	Causal	-1.16	1.81	-0.64	0.521
Sharing	Causal	-1.18	1.45	-0.81	0.418
Fw: PF on OCD					
Null	Sharing	-0.36	0.95	-0.38	0.707
Null	Causal	-1.11	2.19	-0.51	0.612
Sharing	Causal	-0.75	1.29	-0.59	0.558
Bw: OCD on PF					
Null	Sharing	0.29	0.05	5.83	**5.54×10^{-9}**
Null	Causal	0.97	0.36	2.70	**0.007**
Sharing	Causal	0.67	0.32	2.08	**0.037**
Fw: PF on PTSD					
Null	Sharing	-12.72	4.22	-3.01	**0.003**
Null	Causal	-16.75	5.58	-3.00	**0.003**
Sharing	Causal	-4.03	1.51	-2.68	**0.007**
Bw: PTSD on PF					
Null	Sharing	0.19	0.06	3.39	**0.001**
Null	Causal	0.65	0.58	1.12	0.264
Sharing	Causal	0.46	0.52	0.87	0.384
Fw: PF on SZ					
Null	Sharing	-1.08	0.96	-1.12	0.261
Null	Causal	-4.24	2.87	-1.48	0.140
Sharing	Causal	-3.16	1.92	-1.65	0.100
Bw: SZ on PF					
Null	Sharing	-1.78	1.30	-1.36	0.173
Null	Causal	-5.03	3.24	-1.55	0.121
Sharing	Causal	-3.25	1.95	-1.67	0.095

Abbreviations: MR: mendelian randomization; ELPD: expected log pointwise posterior density; 95%CI: 95% confidence interval; SE: standard error; Fwd: forward MR; Bwd: backward MR; P: latent factor poverty; ADHD: attention deficit hyperactivity disorder; AN: anorexia nervosa; ANX: anxiety

disorder; ASD: autism spectrum disorder; BD: bipolar disorder; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; PTSD:
post-traumatic stress disorder; SZ: schizophrenia.
Legend: † Based on t-test. The p-values are two-sided and not adjusted for multiple testing, therefore p-value<0.05 was considered significant (and reported in bolded text).

Supplementary Table 10: *Results of univariable bidirectional Mendelian Randomization of poverty against mental disorder, after Steiger filtering*

MR	N SNP	IVW, B (95% CI)	IVW p-value	WM, B (95% CI)	WM p-value	MR-Egger, B (95% CI)	MR-Egger p-value	Egger intercept p-value	Mean F
P on ADHD	72	0.283 (0.239; 0.327)	**3.62×10^{-36}**	0.181 (0.105; 0.256)	**2.92×10^{-6}**	-0.210 (-0.497; 0.078)	0.157	**1.91×10^{-5}**	40.8
P on AN	71	-0.147 (-0.212; -0.082)	**9.34×10^{-6}**	-0.170 (-0.267; -0.073)	**6.27×10^{-4}**	-0.420 (-0.799; -0.041)	**0.034**	0.147	40.6
P on ANX	68	0.158 (0.022; 0.294)	**0.023**	0.135 (-0.070; 0.339)	0.197	0.226 (-0.448; 0.900)	0.514	0.997	42.1
P on ASD	67	-0.025 (-0.094; 0.044)	0.473	-0.020 (-0.124; 0.084)	0.703	-0.446 (-0.774; -0.117)	**0.010**	**0.010**	39.6
P on BD	58	-0.014 (-0.064; 0.036)	0.577	-0.036 (-0.109; 0.038)	0.344	0.165 (-0.081; 0.410)	0.194	0.074	39.1
P on MDD	76	0.101 (0.060; 0.143)	**1.49×10^{-6}**	0.082 (0.018; 0.146)	0.012	0.043 (-0.204; 0.289)	0.735	0.549	40.1
P on OCD	49	-0.013 (-0.199; 0.173)	0.893	-0.010 (-0.263; 0.244)	0.941	-0.211 (-0.509; 0.931)	0.569	0.581	43.2
P on PTSD	79	0.140 (0.073; 0.207)	**3.79×10^{-5}**	0.114 (0.012; 0.215)	**0.028**	-0.108 (-0.461; 0.245)	0.551	**0.020**	40.3
P on SZ	76	0.071 (0.035; 0.108)	**1.18×10^{-4}**	0.125 (0.055; 0.194)	**4.24×10^{-4}**	-0.057 (-0.407; 0.294)	0.752	**0.003**	40.2

Abbreviations: P: poverty; ADHD: attention deficit hyperactivity disorder; AN: anorexia nervosa; ANX: anxiety disorder; ASD: autism spectrum disorders; BD: bipolar disorder; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; PTSD: post-traumatic stress disorder; SZ: schizophrenia; MR: mendelian randomization; SNP: single nucleotide polymorphism; IVW: inverse variance

weighted (fixed effect); B: effect estimates are log-odds; 95% CI: 95% confidence interval; WM: weighted median; NR: not reported because not enough SNP to perform MR.

Legend: Poverty is a latent variable built using household income as unit identification, therefore an increase in the indicator's load stands for increased income, therefore the regression coefficients have been reversed to facilitate interpretation of the effect of poverty. All statistical tests were two-sided. The p-values were not adjusted for multiple testing, therefore p-value<0.05 was considered significant (and reported in bolded text).

Supplementary Table 11: *Results of univariable bidirectional Mendelian Randomization of household income against mental disorder*

MR	**N SNP**	**IVW, B (95% CI)**	**IVW p-value**	**IVW Q(df)**	**Q p-value**[†]	**WM, B (95% CI)**	**WM p-value**	**MR-Egger, B (95% CI)**	**MR-Egger p-value**	**Egger intercept p-value**	**Steiger Test p-value**[‡]	**MR-PRESSO**	**Mean F**
Fw: HI on ADHD	46	-0.830 (-1.01; -0.647)	**5.91×10^{-19}**	125 (45)	**1.92×10^{-9}**	-0.560 (-0.863; -0.256)	**2.91×10^{-4}**	0.606 (-0.684; 1.90)	0.362	**0.030**	**5.62×10^{-53}**	DT; p=0.215	36.7
Bw: ADHD on HI	23	-0.103 (-0.120; -0.086)	**4.28×10^{-33}**	75.2 (22)	**9.84×10^{-9}**	-0.079 (-0.108; -0.049)	**2.37×10^{-7}**	0.019 (-0.159; 0.197)	0.836	0.185	**2.10×10^{-53}**	DT; p=0.572	39.2
Fw: HI on AN	50	0.448 (0.191; 0.704)	**0.001**	100 (49)	**2.50×10^{-5}**	0.370 (-0.041; 0.781)	0.078	0.990 (-0.710; 2.69)	0.259	0.524	**3.67×10^{-16}**	DT; p=0.149	37.2
Bw: AN on HI	4	-0.012 (-0.044; 0.019)	0.444	9 (3)	**0.027**	-0.005 (-0.043; 0.034)	0.817	0.268 (-0.187; 0.722)	0.367	0.348	NR [b]	GT; p=0.093	31.9
Fw: HI on ANX	48	-0.872 (-1.41; -0.331)	**0.002**	48 (47)	0.434	-0.497 (-1.31; 0.312)	0.229	-0.091 (-3.00; 2.82)	0.951	0.594	**5.61×10^{-9}**	GT; p=0.427	37.3

Bw: ANX on HI	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]
Fw: HI on ASD	54	-0.069 (-0.316; 0.178)	0.583	134 (53)	**6.80×10^{-9}**	-0.095 (-0.508; 0.319)	0.654	0.801 (-0.850; 2.45)	0.346	0.292	NR [b]	DT; p=0.909	37.5
Bw: ASD on HI	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]
Fw: HI on BD	47	0.143 (-0.037; 0.322)	0.120	207 (46)	**3.64×10^{-22}**	0.063 (-0.242; 0.368)	0.685	1.31 (-0.347; 2.97)	0.128	0.163	NR [b]	DT; p=0.093	37.2
Bw: BD on HI	36	0.016 (0.002; 0.030)	**0.020**	189 (35)	**5.82×10^{-23}**	0.018 (-0.005; 0.042)	0.122	-0.015 (-0.188; 0.158)	0.869	0.726	**1.58×10^{-260}**	DT; p=0.098	39.2
Fw: HI on MDD	50	-0.422 (-0.589; -0.255)	**7.37×10^{-7}**	72 (49)	**0.017**	-0.297 (-0.561; -0.032)	**0.027**	-0.435 (-1.29; 0.423)	0.325	0.975	**4.71×10^{-54}**	DT; p=0.725	36.9
Bw: MDD on HI	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]
Fw: HI on OCD	50	0.420 (-0.206; 1.05)	0.189	48 (49)	0.499	0.301 (-0.633; 1.23)	0.528	0.079 (-2.42; 2.58)	0.951	0.784	NR [b]	GT; p=0.514	36.9
Bw: OCD on HI	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]

Fw: HI on PTSD	54	-0.427 (-0.693; -0.161)	**0.002**	66 (53)	0.113	-0.306 (-0.708; 0.096)	0.135	-0.317 (-1.59; 0.952)	0.626	0.861	**1.66×10^{-84}**	GT; p=0.112	37.5
Bw: PTSD on HI	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]
Fw: HI on SZ	47	-0.415 (-0.565; -0.265)	**5.81×10^{-8}**	338 (46)	**5.41×10^{-45}**	-0.432 (-0.733; -0.130)	**0.005**	-0.146 (-1.77; 1.48)	0.861	0.739	**3.44×10^{-56}**	DT; p=0.431	37.2
Bw: SZ on HI	176	-0.031 (-0.037; -0.024)	**7.19×10^{-19}**	603 (175)	**1.91×10^{-47}**	-0.025 (-0.037; -0.012)	**0.001**	-0.018 (-0.067; 0.031)	0.477	0.597	**$<1^{-1000}$**	DT; p=0.240	45.6

Abbreviations: Fw: forward analysis; Bw: backward analysis; HI: household income; ADHD: attention deficit hyperactivity disorder; AN: anorexia nervosa; ANX: anxiety disorder; ASD: autism spectrum disorders; BD: bipolar disorder; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; PTSD: post-traumatic stress disorder; SZ: schizophrenia; MR: mendelian randomization; SNP: single nucleotide polymorphism; IVW: inverse variance weighted (fixed effect); B: effect estimates are log-odds for binary traits (i.e., for mental disorder) and unstandardized regression coefficient for continuous traits (i.e., for household income); 95% CI: 95% confidence interval; Q: Cochran's Q measure of heterogeneity; df: degree of freedom; WM: weighted median; DT: distortion test; GT: global test.

Legend:

P-value threshold for SNP selection <5e-8.

[a] The Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) test identifies possible bias from horizontal pleiotropy. The test consists of three parts. (1) the MR-PRESSO global test which detects horizontal pleiotropy. (2) the outlier corrected causal estimate which corrects for the detected horizontal pleiotropy and (3) the MR-PRESSO distortion test which estimates if the causal estimate is significantly different (at p<0.05) after adjustment for outliers. We conduct all three stages (with the argument NbDistribution=1000. namely using1000 simulation form the null distribution to compute empirical p-values) and present the outlier adjusted causal estimates (OACE) when both global and distortion tests are significant.

[b] We did not run Steiger Test if none of the MR analysis resulted significant (NR: not reported in the cell).

[c] Not enough SNP to perform MR (NR: not reported in the cell).

† Based on chi2 test.

‡ Based on t-test.

All statistical tests were two-sided. The p-values were not adjusted for multiple testing, therefore p-value<0.05 was considered significant (and reported in bolded text).

Supplementary Table 12: *Results of univariable bidirectional Mendelian Randomization of household income against mental disorder, after Steiger filtering*

MR	**N SNP**	**IVW, B (95% CI)**	**IVW p-value**	**WM, B (95% CI)**	**WM p-value**	**MR-Egger, B (95% CI)**	**MR-Egger p-value**	**Egger intercept p-value**	**Mean F**
HI on ADHD	44	-0.698 (-0.885; -0.511)	**2.54×10^{-13}**	-0.549 (-0.856; 0.243)	**5.53×10^{-4}**	0.366 (-0.716; 1.45)	0.511	**0.022**	36.8
HI on AN	47	0.315 (0.045; 0.585)	**0.022**	0.301 (-0.101; 0.702)	0.142	-0.018 (-1.29; 1.25)	0.978	0.315	36.1
HI on ANX	43	-0.473 (-1.04; 0.097)	0.104	-0.206 (-1.01; 0.596)	0.615	0.619 (-2.41; 3.65)	0.690	0.075	37.8
HI on ASD	44	-0.044 (-0.321; 0.233)	0.754	-0.092 (-0.500; 0.317)	0.660	0.791 (-0.362; 1.94)	0.186	**4.88×10^{-4}**	36.2
HI on BD	36	0.148 (-0.058; 0.354)	0.160	0.083 (-0.219; 0.386)	0.589	0.547 (-0.476; 1.57)	0.302	**0.021**	36.7
HI on MDD	48	-0.354 (-0.524; -0.183)	**4.63×10^{-5}**	-0.288 (-0.549; -0.027)	**0.031**	-0.650 (-1.42; 0.116)	0.103	0.930	37.1
HI on OCD	29	0.043 (-0.820; 0.734)	0.913	-0.284 (-1.35; 0.785)	0.602	0.322 (-2.91; 3.56)	0.847	0.578	40.3

HI on PTSD	54	-0.427 (-0.693; -0.161)	**0.002**	-0.306 (-0.708; 0.096)	0.135	-0.317 (-1.59; 0.952)	0.626	0.861	37.5
HI on SZ	44	-0.214 (-0.370; -0.059)	**0.007**	-0.405 (-0.695; -0.114)	**0.006**	-0.374 (-1.82; 1.07)	0.615	0.207	36.9

Abbreviations: HI: household income; ADHD: attention deficit hyperactivity disorder; AN: anorexia nervosa; ANX: anxiety disorder; ASD: autism spectrum disorders; BD: bipolar disorder; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; PTSD: post-traumatic stress disorder; SZ: schizophrenia; MR: mendelian randomization; SNP: single nucleotide polymorphism; IVW: inverse variance weighted (fixed effect); B: effect estimates are log-odds; 95% CI: 95% confidence interval; WM: weighted median; NR: not reported because not enough SNP to perform MR.

Legend: All statistical tests were two-sided. The p-values were not adjusted for multiple testing, therefore p-value<0.05 was considered significant (and reported in bolded text).

Supplementary Table 13: *CAUSE results of the relations between household income and mental disorder*

Model 1	**Model 2**	**Δ ELPD**	**SE Δ ELPD**	**z-score**	**p-value**[†]
Fw: HI on ADHD					
Null	Sharing	-26.00	5.93	-4.39	**1.13×10^{-5}**
Null	Causal	-31.83	7.26	-4.38	**1.19×10^{-5}**
Sharing	Causal	-5.83	1.53	-3.80	**1.45×10^{-4}**
Bw: ADHD on HI					
Null	Sharing	-17.77	4.47	-3.98	**6.89×10^{-5}**
Null	Causal	-23.53	6.00	-3.92	**8.85×10^{-5}**
Sharing	Causal	-5.76	1.60	-3.61	**3.06×10^{-4}**
Fw: HI on AN					
Null	Sharing	-4.18	2.04	-2.05	**0.040**
Null	Causal	-8.41	3.89	-2.17	**0.030**
Sharing	Causal	-4.24	1.90	-2.24	**0.025**
Bw: AN on HI					
Null	Sharing	0.45	0.06	7.08	**1.44×10^{-12}**
Null	Causal	1.15	0.54	2.15	**0.032**
Sharing	Causal	0.70	0.48	1.44	0.150
Fw: HI on ANX					
Null	Sharing	-1.54	1.86	-0.83	0.407
Null	Causal	-2.04	2.70	-0.75	0.453
Sharing	Causal	-0.50	1.21	-0.41	0.682
Bw: ANX on HI					
Null	Sharing	0.09	0.04	2.12	**0.034**
Null	Causal	0.62	0.36	1.70	0.089
Sharing	Causal	0.53	0.33	1.57	0.116
Fw: HI on ASD					
Null	Sharing	0.49	0.07	7.16	**8.07×10^{-13}**
Null	Causal	1.39	0.26	5.32	**1.04×10^{-7}**
Sharing	Causal	0.90	0.21	4.20	**2.67×10^{-5}**
Bw: ASD on HI					
Null	Sharing	-0.51	0.62	-0.83	0.407
Null	Causal	-3.19	2.44	-1.31	0.190
Sharing	Causal	-2.68	1.84	-1.46	0.144
Fw: HI on BD					

Null	Sharing	0.44	0.11	4.12	**0.001**
Null	Causal	1.03	0.70	1.48	0.069
Sharing	Causal	0.59	0.61	0.98	0.327
Bw: BD on HI					
Null	Sharing	0.43	0.03	13.18	**1.14×10^{-39}**
Null	Causal	1.35	0.11	11.76	**6.27×10^{-32}**
Sharing	Causal	0.92	0.11	8.19	**2.61×10^{-16}**
Fw: HI on MDD					
Null	Sharing	-11.26	4.00	-2.82	**0.005**
Null	Causal	-15.12	5.31	-2.85	**0.004**
Sharing	Causal	-3.86	1.54	-2.50	**0.012**
Bw: MDD on HI					
Null	Sharing	-0.51	0.62	-0.83	0.407
Null	Causal	-3.19	2.44	-1.31	0.190
Sharing	Causal	-2.68	1.84	-1.46	0.144
Fw: HI on OCD					
Null	Sharing	-0.10	0.72	-0.14	0.889
Null	Causal	-0.55	1.94	-0.28	0.779
Sharing	Causal	-0.45	1.25	-0.36	0.719
Bw: OCD on HI					
Null	Sharing	0.27	0.08	3.30	**0.001**
Null	Causal	0.92	0.52	1.77	0.077
Sharing	Causal	0.65	0.45	1.44	0.150
Fw: HI on PTSD					
Null	Sharing	-6.47	3.09	-2.09	**0.037**
Null	Causal	-8.97	4.47	-2.00	**0.046**
Sharing	Causal	-2.50	1.53	-1.64	0.101
Bw: PTSD on HI					
Null	Sharing	0.18	0.10	1.74	0.082
Null	Causal	0.24	0.91	0.26	0.795
Sharing	Causal	0.06	0.81	0.07	0.944
Fw: HI on SZ					
Null	Sharing	-1.55	0.91	-1.70	0.089
Null	Causal	-6.27	3.00	-2.09	**0.037**
Sharing	Causal	-4.73	2.10	-2.25	**0.024**
Bw: SZ on HI					
Null	Sharing	-2.78	1.61	-1.73	0.084

Null	Causal	-6.76	3.53	-1.91	0.056
Sharing	Causal	-3.98	1.94	-2.05	**0.040**

Abbreviations: MR: mendelian randomization; ELPD: expected log pointwise posterior density; 95%CI: 95% confidence interval; SE: standard error; Fwd: forward MR; Bwd: backward MR; HI: household income; ADHD: attention deficit hyperactivity disorder; AN: anorexia nervosa; ANX: anxiety disorder; ASD: autism spectrum disorder; BD: bipolar disorder; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; PTSD: post-traumatic stress disorder; SZ: schizophrenia.

Legend: † Based on t-test. The p-values are two-sided and not adjusted for multiple testing, therefore p-value<0.05 was considered significant (and reported in bolded text).

Supplementary Table 14: *Results of bidirectional MR of occupational income against mental disorder*

MR	N SNP	IVW, B (95% CI)	IVW p-value	IVW Q(df)	Q p-value[†]	WM, B (95% CI)	WM p-value	MR-Egger, B (95% CI)	MR-Egger p-value	Egger intercept p-value	Steiger Test p-value[‡]	MR-PRESSO	Mean F
Fw: OI on ADHD	33	-0.859 (-1.05; -0.669)	**7.75×10^{-19}**	100 (32)	**6.68×10^{-9}**	-0.572 (-0.891; -0.253)	**5.61×10^{-4}**	0.132 (-1.54; 1.80)	0.878	0.243	**1.18×10^{-45}**	DT; p=0.560	40.3
Bw: ADHD on OI	23	-0.102 (-0.120; -0.083)	**2.93×10^{-27}**	113 (22)	**2.92×10^{-14}**	-0.102 (-0.135; -0.069)	**3.30×10^{-11}**	-0.052 (-0.297; 0.192)	0.679	0.692	**3.69×10^{-33}**	DT; p=0.598	39.2
Fw: OI on AN	34	0.606 (0.337; 0.879)	**1.10×10^{-5}**	72 (33)	**1.50×10^{-4}**	0.437 (-0.007; 0.882)	0.054	2.51 (0.635; 4.39)	**0.013**	0.051	**1.50×10^{-16}**	DT; p=0.392	40.4
Bw: AN on OI	4	0.045 (0.011; 0.080)	**0.009**	5 (3)	0.204	0.048 (0.002; 0.094)	**0.042**	-0.056 (-0.500; 0.388)	0.827	0.696	**1.05×10^{-17}**	GT; p=0.299	31.9
Fw: OI on ANX	32	-0.110 (-0.672; 0.453)	0.702	39 (31)	0.163	-0.129 (-0.920; 0.661)	0.749	0.767 (-2.36; 3.89)	0.634	0.578	NR [b]	GT; p=0.164	40.6
Bw: ANX on OI	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]
Fw: OI on ASD	33	0.471 (0.192; 0.750)	**0.001**	82 (32)	**3.22×10^{-6}**	0.340 (-0.142; 0.822)	0.167	2.36 (0.281; 4.44)	**0.034**	0.078	**5.50×10^{-6}**	DT; p=0.200	40.3

Bw: ASD on OI	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]
Fw: OI on BD	34	0.201 (0.016; 0.386)	**0.033**	136 (33)	**2.12×10^{-14}**	0.137 (-0.187; 0.461)	0.407	1.88 (0.135; 3.63)	**0.043**	0.063	**3.43×10^{-4}**	DT; p=0.096	40.4
Bw: BD on OI	36	0.042 (0.028; 0.057)	**1.90×10^{-8}**	147 (35)	**3.26×10^{-15}**	0.020 (-0.005; 0.046)	0.116	0.068 (-0.099; 0.235)	0.431	0.763	**7.03×10^{-206}**	DT; p=0.174	39.2
Fw: OI on MDD	33	-0.322 (-0.502; -0.143)	**4.37×10^{-4}**	83 (32)	**3.05×10^{-6}**	-0.125 (-0.420; 0.171)	0.408	0.309 (-1.10; 1.72)	0.671	0.376	**9.81×10^{-40}**	DT; p=0.849	40.3
Bw: MDD on OI	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]
Fw: OI on OCD	33	0.600 (-0.078; 1.28)	0.083	34 (32)	0.362	0.530 (-0.453; 1.51)	0.290	-2.15 (-5.44; 1.13)	0.208	0.103	NR [b]	GT; p=0.361	40.3
Bw: OCD on OI	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]
Fw: OI on PTSD	33	-0.051 (-0.347; 0.245)	0.736	53 (32)	**0.012**	-0.271 (-0.717; 0.176)	0.235	-0.407 (-2.26; 1.44)	0.669	0.702	NR [b]	DT; p=0.934	40.3
Bw: PTSD on OI	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]

Fw: OI on SZ	34	-0.187 (-0.344; -0.030)	**0.020**	278 (33)	**2.06×10^{-40}**	-0.176 (-0.489; 0.138)	0.272	0.202 (-2.07; 2.48)	0.863	0.734	**3.65×10^{-54}**	DT; p=0.818	40.4
Bw: SZ on OI	176	-0.010 (-0.017; -0.003)	**0.008**	512 (175)	**9.74×10^{-35}**	-0.008 (-0.021; 0.005)	0.228	0.005 (-0.044; 0.055)	0.830	0.526	**$<1^{-1000}$**	DT; p=0.065	45.6

Abbreviations: Fw: forward analysis; Bw: backward analysis; OI: occupational income; ADHD: attention deficit hyperactivity disorder; AN: anorexia nervosa; ANX: anxiety disorder; ASD: autism spectrum disorder; BD: bipolar disorder; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; PTSD: post-traumatic stress disorder; SZ: schizophrenia; MR: mendelian randomization; SNP: single nucleotide polymorphism; IVW: inverse variance weighted (fixed effect); B: effect estimates are log-odds for binary traits (i.e., for mental illnesses) and unstandardized regression coefficient for continuous traits (i.e., for occupational income); 95% CI: 95% confidence interval; Q: Cochran's Q measure of heterogeneity; df: degree of freedom; WM: weighted median; DT: distortion test; GT: global test.

Legend:

P-value threshold for SNP selection <5e-8.

[a] The Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) test identifies possible bias from horizontal pleiotropy. The test consists of three parts, (1) the MR-PRESSO global test which detects horizontal pleiotropy, (2) the outlier corrected causal estimate which corrects for the detected horizontal pleiotropy and (3) the MR-PRESSO distortion test which estimates if the causal estimate is significantly different (at $p<0.05$) after adjustment for outliers. We conduct all three stages (with the argument NbDistribution=1000, namely using1000 simulation form the null distribution to compute empirical p-values) and present the outlier adjusted causal estimates (OACE) when both global and distortion tests are significant.

[b] We did not run Steiger Test if none of the MR analysis resulted significant (NR: not reported in the cell).

[c] Not enough SNP to perform MR (NR: not reported in the cell).

† Based on chi2 test.

‡ Based on t-test.

Supplementary Table 15: *Results of univariable bidirectional Mendelian Randomization of occupational income against mental disorder, after Steiger filtering*

MR	N SNP	IVW, B (95% CI)	IVW p-value	WM, B (95% CI)	WM p-value	MR-Egger, B (95% CI)	MR-Egger p-value	Egger intercept p-value	Mean F
OI on ADHD	32	-0.780 (-0.972; -0.587)	**1.91×10^{-15}**	-0.556 (-0.890; 0.222)	**0.001**	0.094 (-1.36; 1.55)	0.900	**0.033**	40.6
OI on AN	34	0.608 (0.337; 0.879)	**1.10×10^{-5}**	0.437 (-0.007; 0.882)	0.054	2.51 (0.635; 4.39)	**0.013**	**0.001**	40.4
OI on ANX	31	0.004 (-0.566; 0.575)	0.988	-0.102 (-0.961; 0.757)	0.816	0.164 (-2.83; 3.16)	0.915	0.713	40.9
OI on ASD	29	0.125 (-0.179; 0.428)	0.421	0.104 (-0.363; 0.571)	0.664	2.04 (-0.054; 4.03)	0.054	**0.010**	38.9
OI on BD	29	-0.134 (-0.338; 0.071)	0.201	-0.091 (-0.397; 0.215)	0.561	0.445 (-0.905; 1.79)	0.524	**0.024**	38.7
OI on MDD	33	-0.322 (-0.502; -0.143)	**4.37×10^{-4}**	-0.125 (-0.420; 0.171)	0.408	0.309 (-1.10; 1.72)	0.671	0.376	40.3
OI on OCD	25	0.107 (-0.672; 0.885)	0.788	-0.075 (-1.18; 1.03)	0.894	-1.37 (-4.75; 2.02)	0.437	0.590	40.6
OI on PTSD	33	-0.051 (-0.347; 0.245)	0.736	-0.271 (-0.717; 0.176)	0.235	-0.407 (-2.26; 1.44)	0.669	0.702	40.3
OI on SZ	33	0.082 (-0.240; 0.077)	0.313	-0.172 (-0.497; 0.153)	0.299	1.24 (-0.700; 3.19)	0.219	**0.001**	40.6

Abbreviations: OI: occupational income; ADHD: attention deficit hyperactivity disorder; AN: anorexia nervosa; ANX: anxiety disorder; ASD: autism spectrum disorders; BD: bipolar disorder; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; PTSD: post-traumatic stress disorder; SZ: schizophrenia; MR: mendelian randomization; SNP: single nucleotide polymorphism; IVW: inverse variance weighted (fixed effect); B: effect estimates are log-odds; 95% CI: 95% confidence interval; WM: weighted median; NR: not reported because not enough SNP to perform MR.

Legend: All statistical tests were two-sided. The p-values were not adjusted for multiple testing, therefore p-value<0.05 was considered significant (and reported in bolded text).

Supplementary Table 16: *CAUSE results of the relations between occupational income and mental disorder*

Model 1	**Model 2**	**Δ ELPD**	**SE Δ ELPD**	**z-score**	**p-value**[†]
Fw: OI on ADHD					
Null	Sharing	-15.39	4.06	-3.79	**1.51×10^{-4}**
Null	Causal	-21.30	5.72	-3.72	**1.99×10^{-4}**
Sharing	Causal	-5.91	1.72	-3.44	**5.82×10^{-4}**
Bw: ADHD on OI					
Null	Sharing	-11.42	3.31	-3.45	**5.61×10^{-4}**
Null	Causal	-17.32	5.04	-3.44	**5.82×10^{-4}**
Sharing	Causal	-5.91	1.76	-3.36	**7.79×10^{-4}**
Fw: OI on AN					
Null	Sharing	-7.83	3.41	-2.30	**0.021**
Null	Causal	-10.22	4.62	-2.21	**0.027**
Sharing	Causal	-2.39	1.47	-1.62	0.105
Bw: AN on OI					
Null	Sharing	0.29	0.24	1.24	0.215
Null	Causal	0.17	1.26	0.14	0.889
Sharing	Causal	-0.12	1.04	-0.12	0.904
Fw: OI on ANX					
Null	Sharing	-2.19	2.13	-1.03	0.303
Null	Causal	-2.86	2.97	-0.96	0.337
Sharing	Causal	-0.66	1.26	-0.53	0.596
Bw: ANX on OI					
Null	Sharing	0.09	0.10	0.86	0.390
Null	Causal	0.82	0.42	1.96	0.050
Sharing	Causal	0.73	0.34	2.16	**0.031**
Fw: OI on ASD					
Null	Sharing	0.38	0.21	1.83	0.067
Null	Causal	0.63	1.07	0.59	0.555
Sharing	Causal	0.24	0.87	0.28	0.779
Bw: ASD on OI					
Null	Sharing	0.34	0.14	2.39	**0.017**
Null	Causal	0.58	0.90	0.65	0.516
Sharing	Causal	0.24	0.77	0.32	0.749
Fw: OI on BD					

Null	Sharing	0.46	0.07	6.39	**1.66×10^{-10}**
Null	Causal	1.38	0.09	16.01	**1.09×10^{-57}**
Sharing	Causal	0.91	0.02	36.68	**1.52×10^{-294}**
Bw: BD on OI					
Null	Sharing	0.08	0.59	0.13	0.447
Null	Causal	-0.13	1.69	-0.08	0.469
Sharing	Causal	-0.21	1.13	-0.19	0.427
Fw: OI on MDD					
Null	Sharing	-0.69	0.95	-0.73	0.465
Null	Causal	-2.62	2.63	-1.00	0.317
Sharing	Causal	-1.93	1.71	-1.13	0.258
Bw: MDD on OI					
Null	Sharing	0.24	0.21	1.14	0.254
Null	Causal	0.06	1.25	0.05	0.960
Sharing	Causal	-0.18	1.04	-0.17	0.865
Fw: OI on OCD					
Null	Sharing	0.39	0.24	1.61	0.107
Null	Causal	0.72	1.07	0.67	0.503
Sharing	Causal	0.33	0.84	0.39	0.697
Bw: OCD on OI					
Null	Sharing	0.24	0.05	4.39	**1.13×10^{-5}**
Null	Causal	0.80	0.41	1.92	0.055
Sharing	Causal	0.56	0.37	1.52	0.129
Fw: OI on PTSD					
Null	Sharing	-1.71	1.63	-1.05	0.294
Null	Causal	-3.60	3.04	-1.18	0.238
Sharing	Causal	-1.89	1.56	-1.21	0.226
Bw: PTSD on OI					
Null	Sharing	0.27	0.03	8.54	**1.34×10^{-17}**
Null	Causal	1.05	0.13	7.92	**2.38×10^{-15}**
Sharing	Causal	0.78	0.12	6.75	**1.48×10^{-11}**
Fw: OI on SZ					
Null	Sharing	0.467	0.03	16.1	**2.55×10^{-58}**
Null	Causal	1.32	0.05	25.5	**1.97×10^{-143}**
Sharing	Causal	0.849	0.04	19.4	**7.72×10^{-84}**
Bw: SZ on OI					
Null	Sharing	-0.88	2.61	-0.34	0.734

Null	Causal	0.03	2.38	0.01	0.992
Sharing	Causal	0.92	0.55	1.68	0.093

Abbreviations: MR: mendelian randomization; ELPD: expected log pointwise posterior density; 95%CI: 95% confidence interval; SE: standard error; Fwd: forward MR; Bwd: backward MR; OI: occupational income; ADHD: attention deficit hyperactivity disorder; AN: anorexia nervosa; ANX: anxiety disorder; ASD: autism spectrum disorder; BD: bipolar disorder; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; PTSD: post-traumatic stress disorder; SZ: schizophrenia.

Legend: † Based on t-test. The p-values are two-sided and not adjusted for multiple testing, therefore p-value<0.05 was considered significant (and reported in bolded text).

Supplementary Table 17: *Results of bidirectional MR of social deprivation against mental disorder*

MR	**N SNP**	**IVW, B (95% CI)**	**IVW p-value**	**IVW Q(df)**	**Q p-value**[†]	**WM, B (95% CI)**	**WM p-value**	**MR-Egger, B (95% CI)**	**MR-Egger p-value**	**Egger intercept p-value**	**Steiger Test p-value**[‡]	**MR-PRESSO**	**Mean F**
Fw: SD on ADHD	7	0.713 (0.504; 0.922)	**2.20×10^{-11}**	17 (6)	**0.001**	0.629 (0.298; 0.960)	**2.12×10^{-4}**	-0.157 (-3.25; 2.94)	0.925	0.603	0.079	DT; p=0.083	32.1
Bw: ADHD on SD	23	0.222 (0.181; 0.262)	**2.93×10^{-27}**	41 (22)	**0.009**	0.193 (0.129; 0.257)	**5.67×10^{-9}**	0.259 (-0.061; 0.579)	0.128	0.819	**5.95×10^{-78}**	DT; p=0.464	39.2
Fw: SD on AN	10	-0.352 (-0.618; -0.087)	**0.009**	21 (9)	**0.014**	-0.293 (-0.658; 0.072)	0.115	0.302 (-2.90; 3.51)	0.858	0.697	0.170	DT; p=0.100	32.8
Bw: AN on SD	4	-0.038 (-0.113; 0.036)	0.314	4 (3)	0.303	-0.052 (-0.146; 0.042)	0.277	-0.403 (-1.15; 0.342)	0.400	0.436	NR [b]	GT; p=0.352	31.9
Fw: SD on ANX	9	0.165 (-0.399; 0.730)	0.566	5 (8)	0.731	0.261 (-0.471; 0.992)	0.485	0.904 (-3.63; 5.44)	0.708	0.757	NR [b]	GT; p=0.709	33.0
Bw: ANX on SD	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]
Fw: SD on ASD	9	-0.010 (-0.279; 0.258)	0.939	21 (8)	**0.009**	0.218 (-0.200; 0.635)	0.308	-0.466 (-4.35; 3.42)	0.821	0.823	NR [b]	DT; p=0.290	33.1
Bw: ASD on SD	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]

Fw: SD on BD	8	-0.052 (-0.252; 0.148)	0.607	67 (7)	**5.18×10^{-12}**	-0.131 (-0.427; 0.164)	0.384	1.02 (-3.04; 5.09)	0.639	0.618	NR [b]	DT; p=0.756	31.8
Bw: BD on SD	36	-0.019 (-0.051; 0.013)	0.244	105 (35)	**6.99×10^{-9}**	-0.004 (-0.060; 0.052)	0.884	0.023 (-0.284; 0.330)	0.885	0.787	NR [b]	DT; p=0.096	39.2
Fw: SD on MDD	8	0.141 (-0.046; 0.328)	0.138	12 (7)	0.103	1.00 (-0.075; 0.475)	0.155	0.370 (-1.80; 2.54)	0.749	0.842	NR [b]	GT; p=0.125	33.4
Bw: MDD on SD	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]
Fw: SD on OCD	8	0.109 (-0.593; 0.811)	0.761	10 (7)	0.177	0.201 (-0.773; 1.18)	0.685	-1.19 (-8.68; 6.31)	0.767	0.744	NR [b]	GT; p=0.206	33.4
Bw: OCD on SD	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]
Fw: SD on PTSD	9	0.165 (-0.127; 0.458)	0.268	10 (8)	0.273	0.190 (-0.228; 0.609)	0.373	1.38 (-1.37; 4.12)	0.358	0.412	NR [b]	GT; p=0.287	33.1
Bw: PTSD on SD	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]
Fw: SD on SZ	8	0.213 (0.046; 0.380)	**0.012**	62 (7)	**1.10×10^{-10}**	0.314 (0.015; 0.614)	**0.040**	2.03 (-0.993; 5.05)	0.236	0.278	0.277	DT; p=0.999	31.8

Bw: SZ on SD	176	0.042 (0.026; 0.058)	**3.57×10^{-7}**	402 (175)	**8.73×10^{-20}**	0.020 (-0.007; 0.048)	0.147	-0.043 (-0.137; 0.052)	0.376	0.071	**$<1^{-1000}$**	DT; p=0.836	45.6

Abbreviations: Fw: forward analysis; Bw: backward analysis; SD: social deprivation; ADHD: attention deficit hyperactivity disorder; AN: anorexia nervosa; ANX: anxiety disorder; ASD: autism spectrum disorder; BD: bipolar disorder; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; PTSD: post-traumatic stress disorder; SZ: schizophrenia; MR: mendelian randomization; SNP: single nucleotide polymorphism; IVW: inverse variance weighted (fixed effect); B: effect estimates are log-odds for binary traits (i.e., for mental illnesses) and unstandardized regression coefficient for continuous traits (i.e., for social deprivation); 95% CI: 95% confidence interval; Q: Cochran's Q measure of heterogeneity; df: degree of freedom; WM: weighted median; DT: distortion test; GT: global test.

Legend:

P-value threshold for SNP selection <5e-8.

[a] The Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) test identifies possible bias from horizontal pleiotropy. The test consists of three parts, (1) the MR-PRESSO global test which detects horizontal pleiotropy, (2) the outlier corrected causal estimate which corrects for the detected horizontal pleiotropy and (3) the MR-PRESSO distortion test which estimates if the causal estimate is significantly different (at $p<0.05$) after adjustment for outliers. We conduct all three stages (with the argument NbDistribution=1000, namely using1000 simulation form the null distribution to compute empirical p-values) and present the outlier adjusted causal estimates (OACE) when both global and distortion tests are significant.

[b] We did not run Steiger Test if none of the MR analysis resulted significant (NR: not reported in the cell).

[c] Not enough SNP to perform MR (NR: not reported in the cell).

[†] Based on chi2 test.

[‡] Based on t-test.

Supplementary Table 18: *Results of univariable bidirectional Mendelian Randomization of social deprivation against mental disorder, after Steiger filtering*

MR	N SNP	IVW, B (95% CI)	IVW p-value	WM, B (95% CI)	WM p-value	MR-Egger, B (95% CI)	MR-Egger p-value	Egger intercept p-value	Mean F
SD on ADHD	6	0.557 (0.331; 0.784)	**1.36×10^{-6}**	0.526 (0.205; 0.847)	**0.001**	0.326 (-1.95; 2.60)	0.793	0.088	31.8
SD on AN	9	-0.188 (-0.470; 0.093)	0.189	-0.281 (-0.664; 0.102)	0.150	-0.761 (-3.10; 1.57)	0.543	0.299	33.0
SD on ANX	9	0.165 (-0.399; 0.730)	0.566	0.261 (-0.486; 1.01)	0.494	0.904 (-3.63; 5.44)	0.708	0.355	33.0
SD on ASD	7	0.028 (-0.276; 0.332)	0.855	0.169 (-0.240; 0.579)	0.418	-1.19 (-4.27; 1.89)	0.483	**0.027**	33.3
SD on BD	5	-0.124 (-0.374; 0.127)	0.334	-0.152 (-0.462; 0.158)	0.337	-0.418 (-1.90; 1.07)	0.620	0.880	32.3
SD on MDD	8	0.141 (-0.046; 0.328)	0.138	0.200 (-0.060; 0.460)	0.132	0.370 (-1.80; 2.54)	0.749	0.888	33.4
SD on OCD	2	-0.422 (1.84; 0.995)	0.559	NR	NR	NR	NR	NR	33.0
SD on PTSD	9	0.165 (-0.127; 0.458)	0.268	0.190 (-0.232; 0.612)	0.377	1.38 (-1.37; 4.12)	0.358	0.424	33.1
SD on SZ	7	0.084 (-0.091; 0.259)	0.345	0.247 (-0.059; 0.553)	0.114	1.18 (-1.76; 4.12)	0.468	0.686	32.1

Abbreviations: SD: social deprivation; ADHD: attention deficit hyperactivity disorder; AN: anorexia nervosa; ANX: anxiety disorder; ASD: autism spectrum disorders; BD: bipolar disorder; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; PTSD: post-traumatic stress disorder; SZ: schizophrenia; MR: mendelian randomization; SNP: single nucleotide polymorphism; IVW: inverse variance weighted (fixed effect); B: effect estimates are log-odds; 95% CI: 95% confidence interval; WM: weighted median; NR: not reported because not enough SNP to perform MR.

Legend: All statistical tests were two-sided. The p-values were not adjusted for multiple testing, therefore p-value<0.05 was considered significant (and reported in bolded text).

Supplementary Table 19: *CAUSE results of the relations between social deprivation and mental disorder*

Model 1	**Model 2**	**Δ ELPD**	**SE Δ ELPD**	**z-score**	**p-value**[†]
Fw: SD on ADHD					
Null	Sharing	-19.58	5.15	-3.80	**1.45×10^{-4}**
Null	Causal	-24.85	6.50	-3.82	**1.33×10^{-4}**
Sharing	Causal	-5.27	1.54	-3.43	**6.04×10^{-4}**
Bw: ADHD on SD					
Null	Sharing	-40.14	7.96	-5.05	**4.42×10^{-7}**
Null	Causal	-45.66	9.11	-5.01	**5.44×10^{-7}**
Sharing	Causal	-5.52	1.56	-3.54	**4.00×10^{-4}**
Fw: SD on AN					
Null	Sharing	0.36	0.09	3.98	**6.89×10^{-5}**
Null	Causal	0.94	0.57	1.64	0.101
Sharing	Causal	0.57	0.49	1.18	0.238
Bw: AN on SD					
Null	Sharing	0.53	0.07	7.61	**2.74×10^{-14}**
Null	Causal	1.34	0.15	9.09	**9.90×10^{-20}**
Sharing	Causal	0.82	0.11	7.40	**1.36×10^{-13}**
Fw: SD on ANX					
Null	Sharing	0.35	0.33	1.09	0.276
Null	Causal	1.00	0.82	1.23	0.219
Sharing	Causal	0.65	0.51	1.27	0.204
Bw: ANX on SD					
Null	Sharing	0.14	0.07	2.12	**0.034**
Null	Causal	0.61	0.76	0.80	0.424
Sharing	Causal	0.46	0.70	0.67	0.503
Fw: SD on ASD					
Null	Sharing	0.45	0.08	5.84	**5.22×10^{-9}**
Null	Causal	1.26	0.22	5.67	**1.43×10^{-8}**
Sharing	Causal	0.81	0.19	4.32	**1.56×10^{-5}**
Bw: ASD on SD					
Null	Sharing	0.38	0.09	4.41	**1.03×10^{-5}**
Null	Causal	1.09	0.51	2.14	**0.032**
Sharing	Causal	0.72	0.46	1.56	0.119

Fw: SD on BD					
Null	Sharing	-1.00	0.76	-1.30	0.192
Null	Causal	-4.61	2.73	-1.69	0.091
Sharing	Causal	-3.61	1.97	-1.83	0.067
Bw: BD on SD					
Null	Sharing	0.01	0.50	0.01	0.499
Null	Causal	-1.01	2.03	-0.50	0.309
Sharing	Causal	-1.01	1.54	-0.66	0.256
Fw: SD on MDD					
Null	Sharing	-2.55	1.65	-1.55	0.121
Null	Causal	5.44	3.40	-1.60	0.110
Sharing	Causal	-2.89	1.80	-1.61	0.107
Bw: MDD on SD					
Null	Sharing	-0.86	0.93	-0.92	0.358
Null	Causal	-3.39	2.77	-1.23	0.219
Sharing	Causal	-2.53	1.87	-1.36	0.174
Fw: SD on OCD					
Null	Sharing	0.48	0.18	2.67	**0.008**
Null	Causal	1.40	0.37	3.84	**1.23×10^{-4}**
Sharing	Causal	0.93	0.20	4.60	**4.22×10^{-6}**
Bw: OCD on SD					
Null	Sharing	0.23	0.07	3.40	**0.001**
Null	Causal	0.99	0.20	4.90	**9.58×10^{-7}**
Sharing	Causal	0.76	0.15	5.03	**4.90×10^{-7}**
Fw: SD on PTSD					
Null	Sharing	-3.57	2.40	-1.49	0.136
Null	Causal	-4.38	3.39	-1.29	0.197
Sharing	Causal	-0.81	1.17	-0.69	0.490
Bw: PTSD on SD					
Null	Sharing	0.16	0.07	2.15	**0.032**
Null	Causal	0.74	0.65	1.14	0.254
Sharing	Causal	0.59	0.59	1.00	0.317
Fw: SD on SZ					
Null	Sharing	-0.77	0.64	-1.19	0.234
Null	Causal	-4.27	2.66	-1.61	0.107
Sharing	Causal	-3.50	2.02	-1.74	0.082
Bw: SZ on SD					

Null	Sharing	-4.63	2.41	-1.92	0.055
Null	Causal	-7.90	3.99	-1.98	**0.048**
Sharing	Causal	-3.28	1.63	-2.01	**0.044**

Abbreviations: MR: mendelian randomization; ELPD: expected log pointwise posterior density; 95%CI: 95% confidence interval; SE: standard error; Fwd: forward MR; Bwd: backward MR; SD: social deprivation; ADHD: attention deficit hyperactivity disorder; AN: anorexia nervosa; ANX: anxiety disorder; ASD: autism spectrum disorder; BD: bipolar disorder; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; PTSD: post-traumatic stress disorder; SZ: schizophrenia.

Legend: † Based on t-test. The p-values are two-sided and not adjusted for multiple testing, therefore p-value<0.05 was considered significant (and reported in bolded text).

Supplementary Table 20: *Results of univariable bidirectional Mendelian randomization of low household income against mental disorder*

MR	N SNP	IVW, B (95% CI)	IVW p-value	IVW Q(df)	Q p-value[†]	WM, B (95% CI)	WM p-value	MR-Egger, B (95% CI)	MR-Egger p-value	Egger intercept p-value	Steiger Test p-value[‡]	MR-PRESSO	Mean F
Fw: LHI on ADHD	8	0.610 (0.415; 0.805)	**8.25×10^{-10}**	8 (7)	0.338	0.569 (0.286; 0.853)	**1.98×10^{-4}**	0.695 (-0.288; 1.68)	0.215	0.867	**1.41×10^{-9}**	GT; p=0.364	33.5
Bw: ADHD on LHI	23	0.210 (0.170; 0.250)	**8.16×10^{-25}**	44 (22)	**0.004**	0.203 (0.136; 0.270)	**2.96×10^{-9}**	-0.042 (-0.353; 0.268)	0.792	0.120	**2.24×10^{-64}**	GT; p=0.444	39.2
Fw: LHI on AN	11	-0.092 (-0.333; 0.148)	0.452	16 (10)	0.106	0.018 (-0.329; 0.365)	0.919	-0.094 (-1.58; 1.39)	0.904	0.998	NR [b]	GT; p=0.102	33.7
Bw: AN on LHI	4	0.026 (-0.049; 0.100)	0.500	7 (3)	0.067	0.016 (-0.073; 0.106)	0.725	-0.519 (-1.52; 0.484)	0.417	0.396	NR [b]	GT; p=0.133	31.9
Fw: LHI on ANX	10	0.628 (0.095; 1.16)	**0.021**	6 (9)	0.734	0.700 (0.016; 1.38)	**0.045**	0.300 (-3.08; 3.68)	0.866	0.852	**0.012**	GT; p=0.767	33.6
Bw: ANX on LHI	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]
Fw: LHI on ASD	12	0.177 (-0.053; 0.408)	0.132	45 (11)	**5.29×10^{-6}**	0.228 (-0.145; 0.602)	0.231	0.407 (-1.82; 2.63)	0.727	0.840	NR [b]	DT; p=0.575	33.5
Bw: ASD on LHI	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]

Fw: LHI on BD	9	0.306 (0.125; 0.487)	**0.001**	13 (8)	0.106	0.159 (-0.108; 0.427)	0.243	-0.545 (-1.42; 0.332)	0.263	0.092	0.462	GT; p=0.141	33.7
Bw: BD on LHI	36	-0.001 (-0.032; 0.032)	0.983	91 (35)	**7.10×10^{-7}**	0.029 (-0.023; 0.081)	0.275	0.125 (-0.158; 0.407)	0.394	0.384	NR [b]	DT; p=0.215	39.2
Fw: LHI on MDD	10	0.351 (0.189; 0.513)	**2.23×10^{-5}**	13 (9)	0.175	0.398 (0.058; 0.558)	**0.016**	0.880 (0.082; 1.68)	**0.006**	0.218	**3.57×10^{-8}**	GT; p=0.207	33.5
Bw: MDD on LHI	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]
Fw: LHI on OCD	10	-0.108 (-0.738; 0.522)	0.737	11 (9)	0.306	0.293 (-0.536; 1.12)	0.488	0.593 (-2.60; 3.78)	0.725	0.670	NR [b]	GT; p=0.309	33.5
Bw: OCD on LHI	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]
Fw: LHI on PTSD	12	0.506 (0.253; 0.759)	**8.99×10^{-5}**	8 (11)	0.672	0.511 (0.167; 0.855)	**0.004**	0.412 (-0.769; 1.59)	0.510	0.877	**2.51×10^{-15}**	GT; p=0.716	33.5
Bw: PTSD on LHI	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]
Fw: LHI on SZ	9	0.648 (0.488; 0.808)	**2.13×10^{-15}**	58 (8)	**9.92×10^{-8}**	0.400 (0.102; 0.699)	**0.009**	-0.151 (-2.16; 1.86)	0.887	0.452	0.421	DT; p=0.783	33.7

Bw: SZ on LHI	176	0.082 (0.066; 0.098)	**6.18× 10^{-24}**	439 (175)	**6.98× 10^{-24}**	0.071 (0.045; 0.098)	**3.31× 10^{-8}**	0.115 (0.016; 0.214)	**0.024**	0.511	**<1^{-1000}**	DT; p=0.543	45.6

Abbreviations: Fw: forward analysis; Bw: backward analysis; LHI: low household income (<£18,000); ADHD: attention deficit hyperactivity disorder; AN: anorexia nervosa; ANX: anxiety disorder; ASD: autism spectrum disorder; BD: bipolar disorder; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; PTSD: post-traumatic stress disorder; SZ: schizophrenia; MR: mendelian randomization; SNP: single nucleotide polymorphism; IVW: inverse variance weighted (fixed effect); B: effect estimates are log-odds; 95% CI: 95% confidence interval; Q: Cochran's Q measure of heterogeneity; df: degree of freedom; WM: weighted median; DT: distortion test; GT: global test.

Legend:

P-value threshold for SNP selection <5e-8.

The phenotypes are analyzed as binary cases (coded as 1) and controls (coded as 0). Do note that this leads to change in the direction of effect when comparing across some of the traits. LHI = class 1 (i.e., HI<£18,000, cases) vs classes 2,3,4,5 (controls)

[a] The Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) test identifies possible bias from horizontal pleiotropy. The test consists of three parts, (1) the MR-PRESSO global test which detects horizontal pleiotropy, (2) the outlier corrected causal estimate which corrects for the detected horizontal pleiotropy and (3) the MR-PRESSO distortion test which estimates if the causal estimate is significantly different (at p<0.05) after adjustment for outliers. We conduct all three stages (with the argument NbDistribution=1000, namely using1000 simulation form the null distribution to compute empirical p-values) and present the outlier adjusted causal estimates (OACE) when both global and distortion tests are significant.

[b] We did not run Steiger Test if none of the MR analysis resulted significant (NR: not reported in the cell).

[c] Not enough SNP to perform MR (NR: not reported in the cell).

[†] Based on chi2 test.

[‡] Based on t-test.

All statistical tests were two-sided. The p-values were not adjusted for multiple testing, therefore p-value<0.05 was considered significant (and reported in bolded text).

Supplementary Table 21: *Results of univariable bidirectional Mendelian randomization of low-mid household income against mental disorder*

MR	**N SNP**	**IVW, B (95% CI)**	**IVW p-value**	**IVW Q(df)**	**Q p-value**[†]	**WM, B (95% CI)**	**WM p-value**	**MR-Egger, B (95% CI)**	**MR-Egger p-value**	**Egger intercept p-value**	**Steiger Test p-value**[‡]	**MR-PRESSO**	**Mean F**
Fw: LMHI on ADHD	15	0.356 (0.198; 0.513)	**9.85×10^{-6}**	57 (14)	**3.45×10^{-7}**	0.161 (-0.075; 0.398)	0.181	-1.00 (-3.51; 1.51)	0.448	0.304	**3.23×10^{-16}**	DT; p=0.115	35.8
Bw: ADHD on LMHI	23	0.174 (0.140; 0.208)	**3.56×10^{-23}**	74 (22)	**1.66×10^{-7}**	0.166 (0.107; 0.226)	**3.90×10^{-8}**	-0.015 (-0.373; 0.343)	0.936	0.304	**1.84×10^{-60}**	DT; p=0.852	39.2
Fw: LMHI on AN	17	-0.309 (-0.526; -0.091)	**0.005**	40 (16)	**0.001**	-0.222 (-0.542; 0.099)	0.176	-1.35 (-4.23; 1.53)	0.373	0.486	**0.001**	DT; p=0.160	35.3
Bw: AN on LMHI	4	0.026 (-0.038; 0.090)	0.426	8 (3)	**0.047**	0.023 (-0.056; 0.102)	0.564	-0.652 (-1.29; -0.014)	0.183	0.171	NR [b]	GT; p=0.103	31.9
Fw: LMHI on ANX	17	0.376 (-0.078; 0.831)	0.105	9 (16)	0.930	0.189 (-0.387; 0.765)	0.520	-0.884 (-4.80; 3.03)	0.664	0.535	NR [b]	GT; p=0.952	35.3
Bw: ANX on LMHI	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]

Fw: LMHI on ASD	18	-0.268 (-0.488; -0.047)	**0.017**	55 (17)	**7.54×10^{-6}**	-0.374 (-0.753; 0.005)	0.053	-2.15 (-5.04; 0.746)	0.165	0.217	0.994	DT; p=0.275	33.4
Bw: ASD on LMHI	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]
Fw: LMHI on BD	16	-0.099 (-0.251; 0.053)	0.201	95 (15)	**1.84×10^{-13}**	0.067 (-0.352; 0.217)	0.643	-2.40 (-5.36; 0.553)	0.133	0.146	NR [b]	DT; p=0.255	35.6
Bw: BD on LMHI	36	-0.030 (-0.058; -0.003)	**0.032**	138 (35)	**4.45×10^{-14}**	-0.030 (-0.076; 0.017)	0.208	-0.001 (-0.302; 0.301)	0.999	0.844	**1.19×10^{-269}**	DT; p=0.226	39.2
Fw: LMHI on MDD	17	0.224 (0.077; 0.371)	**0.003**	19 (16)	0.281	0.204 (-0.004; 0.411)	0.054	-0.159 (-1.39; 1.07)	0.803	0.547	**4.83×10^{-19}**	GT; p=0.278	33.5
Bw: MDD on LMHI	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]
Fw: LMHI on OCD	17	-0.774 (-1.34; -0.212)	**0.007**	11 (16)	0.795	-0.833 (-1.57; -0.097)	**0.027**	-0.350 (-4.75; 4.05)	0.878	0.852	0.249	GT; p=0.781	33.5
Bw: OCD on LMHI	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]
Fw: LMHI on PTSD	17	0.283 (0.045; 0.521)	**0.020**	24 (16)	0.087	0.285 (-0.071; 0.640)	0.117	-0.485 (-2.89; 1.92)	0.698	0.537	**2.10×10^{-24}**	GT; p=0.096	35.3
Bw: PTSD on LMHI	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]

Fw: LMHI on SZ	16	0.270 (0.138; 0.401)	**5.84×10^{-5}**	122 (15)	**2.81×10^{-18}**	0.117 (-0.132; 0.366)	0.357	-0.273 (-3.42; 2.87)	0.867	0.738	**2.58×10^{-16}**	DT; p=0.361	35.6
Bw: SZ on LMHI	176	0.045 (0.031; 0.059)	**1.84×10^{-10}**	436 (175)	**5.35×10^{-24}**	0.041 (0.018; 0.063)	**6.01×10^{-4}**	0.032 (-0.052; 0.117)	0.455	0.768	**$<1^{-1000}$**	DT; p=0.775	45.6

Abbreviations: Fw: forward analysis; Bw: backward analysis; LMHI: low-mid household income (≤£30,999); ADHD: attention deficit hyperactivity disorder; AN: anorexia nervosa; ANX: anxiety disorder; ASD: autism spectrum disorder; BD: bipolar disorder; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; PTSD: post-traumatic stress disorder; SZ: schizophrenia; MR: mendelian randomization; SNP: single nucleotide polymorphism; IVW: inverse variance weighted (fixed effect); B: effect estimates are log-odds; 95% CI: 95% confidence interval; Q: Cochran's Q measure of heterogeneity; df: degree of freedom; WM: weighted median; DT: distortion test; GT: global test.

Legend:

P-value threshold for SNP selection <5e-8.

The phenotypes are analyzed as binary cases (coded as 1) and controls (coded as 0). Do note that this leads to change in the direction of effect when comparing across some of the traits. LMHI = cases: classes 1 (i.e., HI<£18,000) and 2 (i.e., £18,000≤HI≤£29,000) vs controls: classes 3,4,5.

[a] The Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) test identifies possible bias from horizontal pleiotropy. The test consists of three parts, (1) the MR-PRESSO global test which detects horizontal pleiotropy, (2) the outlier corrected causal estimate which corrects for the detected horizontal pleiotropy and (3) the MR-PRESSO distortion test which estimates if the causal estimate is significantly different (at p<0.05) after adjustment for outliers. We conduct all three stages (with the argument NbDistribution=1000, namely using1000 simulation form the null distribution to compute empirical p-values) and present the outlier adjusted causal estimates (OACE) when both global and distortion tests are significant.

[b] We did not run Steiger Test if none of the MR analysis resulted significant (NR: not reported in the cell).

[c] Not enough SNP to perform MR (NR: not reported in the cell).

† Based on chi2 test.

‡ Based on t-test.

All statistical tests were two-sided. The p-values were not adjusted for multiple testing, therefore p-value<0.05 was considered significant (and reported in bolded text).

Supplementary Table 22: *Results of univariable bidirectional Mendelian randomization of mid-high household income against mental disorder*

MR	**N SNP**	**IVW, B (95% CI)**	**IVW p-value**	**IVW Q(df)**	**Q p-value†**	**WM, B (95% CI)**	**WM p-value**	**MR-Egger, B (95% CI)**	**MR-Egger p-value**	**Egger intercept p-value**	**Steiger Test p-value‡**	**MR-PRESSO**	**Mean F**
Fw: MHHI on ADHD	20	-0.298 (-0.422; -0.174)	**2.65×10^{-6}**	49 (19)	**1.91×10^{-4}**	-0.112 (-0.312; 0.088)	0.272	-0.198 (-1.11; 0.709)	0.674	0.827	**1.27×10^{-26}**	OACE: -0.182 (-0.342; -0.023); p=0.038	36.4
Bw: ADHD on MHHI	23	-0.160 (-0.199; -0.122)	**3.68×10^{-16}**	45 (22)	**0.002**	-0.155 (-0.216; -0.093)	**3.63×10^{-7}**	0.027 (-0.280; 0.333)	0.867	0.238	**3.20×10^{-70}**	DT; p=0.549	39.2
Fw: MHHI on AN	20	0.371 (0.193; 0.550)	**4.59×10^{-5}**	49 (19)	**2.98×10^{-4}**	0.281 (-0.018; 0.581)	0.066	1.05 (-0.224; 2.33)	0.123	0.297	**2.95×10^{-4}**	OACE: 0.181 (-0.058; 0.420); p=0.156	36.6
Bw: AN on MHHI	4	-0.009 (-0.081; 0.062)	0.803	7 (3)	0.066	0.036 (-0.052; 0.124)	0.425	0.314 (-0.811; 1.44)	0.639	0.628	NR [b]	GT; p=0.130	31.9

Fw: MHHI on ANX	20	-0.320 (-0.694; 0.053)	0.093	15 (19)	0.691	-0.098 (-0.583; 0.389)	0.694	-0.951 (-3.27; 1.36)	0.431	0.595	NR [b]	GT; p=0.722	36.4
Bw: ANX on MHHI	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]
Fw: MHHI on ASD	21	0.480 (0.303; 0.658)	**1.11×10^{-7}**	36 (20)	**0.015**	0.393 (0.093; 0.692)	**0.010**	0.345 (-0.763; 1.45)	0.549	0.809	0.057	DT; p=0.208	36.2
Bw: ASD on MHHI	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]
Fw: MHHI on BD	19	0.179 (0.053; 0.304)	**0.005**	125 (18)	**9.94×10^{-18}**	0.028 (-0.208; 0.264)	0.816	1.69 (0.376; 3.00)	**0.022**	**0.033**	0.187	DT; p=0.092	36.8
Bw: BD on MHHI	36	0.040 (0.009; 0.071)	**0.011**	133 (35)	**2.56×10^{-13}**	0.030 (-0.020; 0.081)	0.239	0.025 (-0.308; 0.357)	0.885	0.927	**2.14×10^{-267}**	OACE: 0.002 (-0.039; 0.042); p=0.943	39.2
Fw: MHHI on MDD	21	-0.123 (-0.238; -0.008)	**0.036**	34 (20)	**0.025**	-0.070 (-0.245; 0.105)	0.433	0.474 (-0.178; 1.13)	0.171	0.082	**3.29×10^{-23}**	DT; p=0.256	36.2
Bw: MDD on MHHI	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]
Fw: MHHI on OCD	21	-0.079 (-0.511; 0.353)	0.720	23 (20)	0.265	-0.065 (-0.679; 0.549)	0.836	-0.399 (-2.63; 1.83)	0.729	0.776	NR [b]	GT; p=0.271	36.2

Bw: OCD on MHHI	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]
Fw: MHHI on PTSD	21	-0.233 (-0.421; -0.044)	**0.016**	25 (20)	0.184	-0.195 (-0.471; 0.080)	0.165	-0.080 (-1.06; 0.900)	0.874	0.758	**1.75×10^{-30}**	GT; p=0.197	36.2
Bw: PTSD on MHHI	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]
Fw: MHHI on SZ	20	-0.098 (-0.201; 0.005)	0.063	143 (19)	**7.85×10^{-21}**	-0.171 (-0.376; 0.033)	0.100	-0.236 (-1.60; 1.12)	0.738	0.841	NR [b]	DT; p=0.574	36.4
Bw: SZ on MHHI	176	-0.046 (-0.061; -0.030)	**6.73×10^{-9}**	432 (175)	**1.53×10^{-23}**	-0.039 (-0.066; -0.012)	**0.005**	0.018 (-0.077; 0.112)	0.707	0.172	**$<1^{-1000}$**	DT; p=0.431	45.6

Abbreviations: Fw: forward analysis; Bw: backward analysis; MHHI: mid-high household income (≥ £52,000); ADHD: attention deficit hyperactivity disorder; AN: anorexia nervosa; ANX: anxiety disorder; ASD: autism spectrum disorder; BD: bipolar disorder; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; PTSD: post-traumatic stress disorder; SZ: schizophrenia; MR: mendelian randomization; SNP: single nucleotide polymorphism; IVW: inverse variance weighted (fixed effect); B: effect estimates are log-odds; 95% CI: 95% confidence interval; Q: Cochran's Q measure of heterogeneity; df: degree of freedom; WM: weighted median; DT: distortion test; GT: global test.

Legend:

P-value threshold for SNP selection <5e-8.

The phenotypes are analyzed as binary cases (coded as 1) and controls (coded as 0). Do note that this leads to change in the direction of effect when comparing across some of the traits. MHHI = controls: classes 1, 2, and 3 vs cases: classes 4 (i.e., £52,000 ≤HI≤£100,000) and 5 (i.e., HI>£100,000)

[a] The Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) test identifies possible bias from horizontal pleiotropy. The test consists of three parts, (1) the MR-PRESSO global test which detects horizontal pleiotropy, (2) the outlier corrected causal estimate which corrects for the detected horizontal pleiotropy and (3) the MR-PRESSO distortion test which estimates if the causal estimate is significantly different (at $p<0.05$) after adjustment for outliers. We conduct all three stages (with the argument NbDistribution=1000, namely using1000 simulation form the null distribution to compute empirical p-values) and present the outlier adjusted causal estimates (OACE) when both global and distortion tests are significant.

[b] We did not run Steiger Test if none of the MR analysis resulted significant (NR: not reported in the cell).

[c] Not enough SNP to perform MR (NR: not reported in the cell).

[†] Based on chi2 test.

[‡] Based on t-test.

All statistical tests were two-sided. The p-values were not adjusted for multiple testing, therefore p-value<0.05 was considered significant (and reported in bolded text).

Supplementary Table 23: *Results of univariable bidirectional Mendelian randomization of high household income against mental disorder*

MR	N SNP	IVW, B (95% CI)	IVW p-value	IVW Q(df)	Q p-value[†]	WM, B (95% CI)	WM p-value	MR-Egger, B (95% CI)	MR-Egger p-value	Egger intercept p-value	Steiger Test p-value[‡]	MR-PRESSO	Mean F
Fw: HHI on ADHD	2	-0.033 (-0.216; 0.149)	0.720	0.4 (2)	0.513	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [b]	NR [c]	45.1
Bw: ADHD on HHI	23	-0.193 (-0.266; -0.120)	**1.87×10^{-7}**	42 (22)	**0.007**	-0.211 (-0.322; -0.100)	**2.26×10^{-4}**	0.085 (-0.464; 0.633)	0.765	0.324	**1.81×10^{-85}**	DT; p=0.982	39.2

Fw: HHI on AN	2	0.333 (0.065; 0.600)	**0.015**	2 (1)	0.195	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	0.183	NR [c]	45.1
Bw: AN on HHI	4	-0.043 (-0.177; 0.092)	0.535	2 (3)	0.544	-0.036 (-0.196; 0.125)	0.663	-0.113 (-1.36; 1.13)	0.875	0.921	NR [b]	GT; p=0.581	31.9
Fw: HHI on ANX	2	-0.101 (-0.641; 0.440)	0.715	0.004 (1)	0.949	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [b]	NR [c]	45.1
Bw: ANX on HHI	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]
Fw: HHI on ASD	3	0.094 (-0.121; 0.308)	0.392	40 (2)	**1.85×10^{-9}**	0.509 (0.163; 0.855)	**0.004**	-4.07 (-6.29; 1.85)	0.173	0.167	**0.031**	NR [c]	46.8
Bw: ASD on HHI	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]
Fw: HHI on BD	2	0.608 (0.423; 0.792)	**1.01×10^{-10}**	1 (1)	0.283	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	**0.015**	NR [c]	45.1
Bw: BD on HHI	36	0.076 (0.017; 0.134)	**0.011**	87 (35)	**2.65×10^{-6}**	0.066 (-0.026; 0.159)	0.158	0.065 (-0.443; 0.573)	0.803	0.968	**1.53×10^{-282}**	DT; p=0.117	39.2
Fw: HHI on MDD	2	0.013 (-0.163; 0.188)	0.889	2 (1)	0.219	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	45.1

Bw: MDD on HHI	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]
Fw: HHI on OCD	2	0.199 (-0.469; 0.866)	0.560	2 (1)	0.180	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	45.1
Bw: OCD on HHI	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]
Fw: HHI on PTSD	3	-0.190 (-0.425; 0.046)	0.114	1 (2)	0.569	-0.157 (-0.453; 0.139)	0.300	-0.887 (-2.40; 0.626)	0.456	0.528	NR [b]	NR [c]	46.8
Bw: PTSD on HHI	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]
Fw: HHI on SZ	2	0.030 (-0.121; 0.182)	0.693	14 (1)	**2.18×10^{-4}**	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	45.1
Bw: SZ on HHI	176	-0.013 (-0.042; 0.016)	0.395	295 (175)	**3.49×10^{-8}**	0.002 (-0.049; 0.052)	0.950	0.095 (-0.051; 0.242)	0.205	0.138	NR [b]	DT; p=0.195	45.6

Abbreviations: Fw: forward analysis; Bw: backward analysis; HHI: high household income (> £100,000); ADHD: attention deficit hyperactivity disorder; AN: anorexia nervosa; ANX: anxiety disorder; ASD: autism spectrum disorder; BD: bipolar disorder; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; PTSD: post-traumatic stress disorder; SZ: schizophrenia; MR: mendelian randomization; SNP: single nucleotide polymorphism; IVW: inverse variance weighted (fixed effect); B: effect estimates are log-odds; 95% CI: 95% confidence interval; Q: Cochran's Q measure of heterogeneity; df: degree of freedom; WM: weighted median; DT: distortion test; GT: global test.

Legend:

P-value threshold for SNP selection <5e-8.

The phenotypes are analyzed as binary cases (coded as 1) and controls (coded as 0). Do note that this leads to change in the direction of effect when comparing across some of the traits. HHI = cases: class 5 (i.e., HI>£100,000) vs controls: classes 1,2,3,4.

[a] The Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) test identifies possible bias from horizontal pleiotropy. The test consists of three parts, (1) the MR-PRESSO global test which detects horizontal pleiotropy, (2) the outlier corrected causal estimate which corrects for the detected horizontal pleiotropy and (3) the MR-PRESSO distortion test which estimates if the causal estimate is significantly different (at p<0.05) after adjustment for outliers. We conduct all three stages (with the argument NbDistribution=1000, namely using1000 simulation form the null distribution to compute empirical p-values) and present the outlier adjusted causal estimates (OACE) when both global and distortion tests are significant.

[b] We did not run Steiger Test if none of the MR analysis resulted significant (NR: not reported in the cell).

[c] Not enough SNP to perform MR (NR: not reported in the cell).

[†] Based on chi2 test.

[‡] Based on t-test.

All statistical tests were two-sided. The p-values were not adjusted for multiple testing, therefore p-value<0.05 was considered significant (and reported in bolded text).

Supplementary Table 24: *Results of univariable bidirectional Mendelian randomization analysis of household income levels against mental disorder, after Steiger filtering*

MR	N SNP	IVW, B (95% CI)	IVW p-value	WM, B (95% CI)	WM p-value	MR-Egger, B (95% CI)	MR-Egger p-value	Egger intercept p-value	Mean F
LHI on ADHD	8	0.610 (0.415; 0.805)	**8.25×10^{-10}**	0.569 (0.278; 0.861)	**1.17×10^{-4}**	0.695 (-0.288; 1.68)	0.215	0.744	33.5

LMHI on ADHD	14	0.238 (0.075; 0.401)	**0.004**	0.156 (-0.088; 0.399)	0.209	-1.62 (-3.18; 0.057)	0.065	0.170	36.0
MHHI on ADHD	19	-0.246 (-0.373; -0.118)	**1.57×10^{-4}**	-0.111 (-0.311; 0.090)	0.279	0.375 (-0.476; 1.23)	0.400	0.428	36.5
HHI on ADHD	2	-0.033 (-0.216; 0.149)	0.720	NR	NR	NR	NR	NR	45.1
LHI on AN	10	0.005 (-0.247; 0.256)	0.972	0.028 (-0.310; 0.365)	0.871	0.217 (-0.970; 1.40)	0.729	0.807	34.0
LMHI on AN	15	-0.096 (-0.330; 0.138)	0.421	-0.078 (-0.401; 0.244)	0.634	-1.34 (-3.15; 0.468)	0.170	0.130	34.9
MHHI on AN	17	0.137 (-0.062; 0.336)	0.178	0.212 (-0.072; 0.496)	0.143	0.429 (-0.624; 1.48)	0.437	0.921	34.8
HHI on AN	2	0.333 (0.065; 0.600)	**0.015**	NR	NR	NR	NR	NR	45.1
LHI on ANX	9	0.509 (-0.061; 1.08)	0.080	0.677 (-0.070; 1.42)	0.076	0.437 (-2.96; 3.83)	0.808	0.377	33.5
LMHI on ANX	16	0.285 (-0.184; 0.754)	0.233	0.174 (-0.421; 0.769)	0.566	-0.608 (-4.54; 3.32)	0.766	0.022	35.5
MHHI on ANX	19	-0.286 (-0.662; 0.089)	0.135	-0.096 (-0.604; 0.411)	0.710	-0.400 (-2.79; 1.99)	0.747	0.097	36.8
HHI on ANX	2	-0.101 (-0.641; 0.440)	0.715	NR	NR	NR	NR	NR	45.1
LHI on ASD	8	0.213 (-0.066; 0.492)	0.135	0.274 (-0.127; 0.675)	0.180	-0.739 (-1.90; 0.423)	0.259	0.459	33.8
LMHI on ASD	9	0.003 (-0.311; 0.318)	0.980	-0.110 (-0.522; 0.302)	0.602	-1.10 (-3.49; 1.29)	0.396	0.287	32.7
MHHI on ASD	16	0.240 (0.034; 0.445)	**0.023**	0.136 (-0.160; 0.430)	0.367	0.230 (-0.618; 1.08)	0.603	0.004	35.6

HHI on ASD	0	NR	NR	NR	NR	NR	NR	NR	NR
LHI on BD	6	0.073 (-0.154; 0.300)	0.528	0.068 (-0.210; 0.345)	0.633	-0.146 (-0.995; 0.702)	0.752	0.554	32.5
LMHI on BD	11	-0.001 (-0.190; 0.190)	0.998	-0.004 (-0.286; 0.279)	0.980	0.876 (-1.17; 2.92)	0.424	0.988	32.5
MHHI on BD	14	-0.042 (-0.197; 0.114)	0.598	-0.140 (-0.375; 0.094)	0.241	0.211 (-0.746; 1.17)	0.673	0.247	33.0
HHI on BD	0	NR	NR	NR	NR	NR	NR	NR	NR
LHI on MDD	10	0.351 (0.189; 0.513)	**2.23×10^{-5}**	0.308 (0.072; 0.544)	**0.011**	0.880 (0.082; 1.68)	0.063	0.942	33.5
LMHI on MDD	16	0.224 (0.077; 0.371)	**0.003**	0.204 (-0.005; 0.412)	0.056	-0.026 (-1.35; 1.30)	0.970	0.650	35.6
MHHI on MDD	21	-0.123 (-0.238; -0.008)	**0.036**	-0.070 (-0.240; 0.100)	0.420	0.474 (-0.178; 1.13)	0.171	0.526	36.2
HHI on MDD	2	0.013 (-0.163; 0.188)	0.889	NR	NR	NR	NR	NR	45.1
LHI on OCD	8	0.119 (-0.592; 0.830)	0.743	0.272 (-0.590; 1.13)	0.536	-0.417 (-3.55; 2.72)	0.803	0.064	33.5
LMHI on OCD	9	-0.036 (-0.793; 0.722)	0.927	0.095 (-0.863; 1.05)	0.846	1.60 (-3.87; 7.07)	0.584	0.781	35.9
MHHI on OCD	12	0.072 (-0.478; 0.621)	0.798	0.231 (-0.514; 0.976)	0.544	0.753 (-1.82; 3.33)	0.579	0.726	39.0
HHI on OCD	0	NR	NR	NR	NR	NR	NR	NR	NR
LHI on PTSD	12	0.506 (0.253; 0.759)	**8.99×10^{-5}**	0.511 (0.167; 0.854)	**0.004**	0.412 (-0.769; 1.59)	0.510	0.949	33.5
LMHI on PTSD	17	0.283 (0.045; 0.521)	**0.002**	0.285 (-0.064; 0.633)	0.109	-0.485 (-2.89; 1.92)	0.698	0.508	35.3

MHHI on PTSD	21	-0.233 (-0.421; -0.044)	**0.016**	-0.195 (-0.475; 0.084)	0.171	-0.080 (-1.06; 0.900)	0.874	0.506	36.2
HHI on PTSD	3	-0.189 (-0.425; 0.046)	0.114	-0.157 (-0.452; 0.139)	0.298	-0.887 (-2.40; 0.626)	0.456	0.695	46.8
LHI on SZ	8	0.491 (0.320; 0.662)	**1.87×10^{-8}**	0.382 (0.088; 0.675)	**0.011**	0.300 (-1.45; 2.05)	0.749	0.447	33.5
LMHI on SZ	15	0.145 (0.009; 0.282)	**0.037**	0.110 (-0.141; 0.360)	0.391	-0.212 (-2.84; 2.42)	0.877	0.325	35.2
MHHI on SZ	19	-0.023 (-0.129; 0.083)	0.665	-0.170 (-0.380; 0.040)	0.112	-0.331 (-1.53; 0.868)	0.596	0.454	36.3
HHI on SZ	2	0.030 (-0.121; 0.182)	0.693	NR	NR	NR	NR	NR	45.1

Abbreviations: MR: Mendelian randomization; B: effect estimates are log-odds; 95% CI: 95% confidence intervals; HI: household income; ADHD: attention deficit hyperactivity disorder; AN: anorexia nervosa; ANX: anxiety disorder; ASD: autism spectrum disorders; BD: bipolar disorder; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; PTSD: post-traumatic stress disorder; SZ: schizophrenia; IVW: inverse variance weighted (fixed effect); WM: weighted median; NR: not reported because not enough SNP to perform MR.

Legend: LHI: low household income, cases were those less than £18,000; LMHI: low-mid HI, cases were those less than £29,999; MHHI: mid-high HI, cases were those more than £52,000; HHI: high HI, cases were those more than £100,000.

All statistical tests were two-sided. The p-values were not adjusted for multiple testing, therefore p-value<0.05 was considered significant (and reported in bolded text).

Supplementary Table 25: *Results of bidirectional Mendelian randomization of cognitive ability against mental disorder*

MR	N SNP	IVW, B (95% CI)	IVW p-value	IVW Q(df)	Q p-value[†]	WM, B (95% CI)	WM p-value	MR-Egger, B (95% CI)	MR-Egger p-value	Egger intercept p-value	Steiger Test p-value[‡]	MR-PRESSO	Mean F
Fw: CA on ADHD	131	-0.638 (-0.720; -0.556)	**1.37×10^{-52}**	341 (130)	**7.02×10^{-21}**	-0.493 (-0.632; -0.354)	**1.78×10^{-11}**	-0.635 (-1.27; -0.005)	0.050	0.993	**$<1^{-1000}$**	DT; p=0.714	44.0
Bw: ADHD on CA	23	-0.151 (-0.172; -0.131)	**6.21×10^{-48}**	91 (22)	**2.16×10^{-10}**	-0.106 (-0.142; -0.071)	**1.33×10^{-8}**	-0.010 (-0.236; 0.256)	0.938	0.206	**2.61×10^{-25}**	OACE: -0.122 (-0.155; -0.090); **$p=5.93\times10^{-7}$**	39.2
Fw: CA on AN	137	0.306 (0.190; 0.422)	**2.28×10^{-7}**	291 (136)	**3.76×10^{-13}**	0.384 (0.197; 0.571)	**4.02×10^{-5}**	0.974 (0.223; 1.73)	**0.012**	0.076	**2.21×10^{-114}**	DT; p=0.874	43.9
Bw: AN on CA	3	-0.005 (-0.047; 0.038)	0.826	6 (2)	0.053	-0.008 (-0.072; 0.055)	0.795	-0.007 (-0.931; 0.917)	0.991	0.997	NR [b]	NR [c]	32.3
Fw: CA on ANX	137	-0.344 (-0.578; -0.110)	**0.004**	149 (136)	0.204	-0.159 (-0.499; 0.180)	0.358	-0.268 (-1.40; 0.865)	0.643	0.894	**6.32×10^{-66}**	GT; p=0.210	43.9
Bw: ANX on CA	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]
Fw: CA on ASD	138	0.310 (0.193; 0.427)	**2.09×10^{-7}**	338 (137)	**9.51×10^{-19}**	0.280 (0.087; 0.473)	**0.004**	0.552 (-0.274; 1.38)	0.193	0.556	**2.76×10^{-43}**	DT; p=0.553	43.8
Bw: ASD on CA	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]

Fw: CA on BD	134	0.003 (-0.078; 0.085)	0.934	491 (133)	**2.06×10^{-42}**	-0.120 (-0.265; 0.024)	0.102	0.147 (-0.573; 0.867)	0.689	0.689	NR [b]	DT; p=0.420	44.0
Bw: BD on CA	36	0.015 (-0.001; 0.032)	0.069	370 (35)	**2.04×10^{-57}**	0.024 (-0.006; 0.054)	0.119	-0.149 (-0.445; 0.147)	0.330	0.276	NR [b]	OACE: -0.003 (-0.030; 0.024); p=0.805	39.2
Fw: CA on MDD	138	-0.140 (-0.215; -0.065)	**2.66×10^{-4}**	279 (137)	**1.06×10^{-11}**	-0.103 (-0.225; 0.019)	0.099	-0.177 (-0.654; 0.301)	0.470	0.876	**2.64×10^{-283}**	DT; p=0.842	43.8
Bw: MDD on CA	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]
Fw: CA on OCD	138	0.272 (-0.012; 0.557)	0.061	192 (137)	**0.001**	0.186 (-0.259; 0.630)	0.414	-0.102 (-1.62; 1.41)	0.896	0.621	NR [b]	DT; p=0.848	43.8
Bw: OCD on CA	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]
Fw: CA on PTSD	136	-0.139 (-0.264; -0.013)	**0.030**	192 (135)	**0.001**	-0.207 (-0.396; -0.018)	**0.032**	0.220 (-0.458; 0.898)	0.525	0.289	**$<1^{-1000}$**	DT; p=0.172	43.9
Bw: PTSD on CA	0	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]	NR [c]
Fw: CA on SZ	134	-0.297 (-0.365; -0.228)	**2.92×10^{-17}**	986 (133)	**4.05×10^{-128}**	-0.149 (-0.289; -0.008)	**0.038**	-0.057 (-0.933; 0.819)	0.899	0.584	**$<1^{-1000}$**	DT; p=0.863	44.0

Bw: SZ on CA	175	-0.055 (-0.063; -0.047)	**2.23×10^{-39}**	1010 (174)	**6.49×10^{-114}**	-0.046 (-0.062; -0.030)	**9.05×10^{-9}**	-0.092 (-0.170; 0.014)	**0.023**	0.345	**1.86×10^{-286}**	OACE: -0.036 (-0.051; -0.022); **$p=4.87\times10^{-6}$**	45.6

Abbreviations: Fw: forward analysis; Bw: backward analysis; CA: cognitive abilities; ADHD: attention deficit hyperactivity disorder; AN: anorexia nervosa; ANX: anxiety disorder; ASD: autism spectrum disorder; BD: bipolar disorder; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; PTSD: post-traumatic stress disorder; SZ: schizophrenia; MR: mendelian randomization; SNP: single nucleotide polymorphism; IVW: inverse variance weighted (fixed effect); B: effect estimates are log-odds for binary traits (i.e., for mental illnesses) and unstandardized regression coefficient for continuous traits (i.e., for cognitive abilities); 95% CI: 95% confidence interval; Q: Cochran's Q measure of heterogeneity; df: degree of freedom; WM: weighted median; DT: distortion test; GT: global test.

Legend:

P-value threshold for SNP selection <5e-8.

[a] The Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) test identifies possible bias from horizontal pleiotropy. The test consists of three parts, (1) the MR-PRESSO global test which detects horizontal pleiotropy, (2) the outlier corrected causal estimate which corrects for the detected horizontal pleiotropy and (3) the MR-PRESSO distortion test which estimates if the causal estimate is significantly different (at $p<0.05$) after adjustment for outliers. We conduct all three stages (with the argument NbDistribution=1000, namely using1000 simulation form the null distribution to compute empirical p-values) and present the outlier adjusted causal estimates (OACE) when both global and distortion tests are significant.

[b] We did not run Steiger Test if none of the MR analysis resulted significant (NR: not reported in the cell).

[c] Not enough SNP to perform MR (NR: not reported in the cell).

[†] Based on chi2 test.

[‡] Based on t-test.

All statistical tests were two-sided. The p-values were not adjusted for multiple testing, therefore p-value<0.05 was considered significant (and reported in bolded text).

Supplementary Table 26: *Results of univariable bidirectional Mendelian Randomization of cognitive ability against mental disorder, after Steiger filtering*

MR	N SNP	IVW, B (95% CI)	IVW p-value	WM, B (95% CI)	WM p-value	MR-Egger, B (95% CI)	MR-Egger p-value	Egger intercept p-value	Mean F
CA on ADHD	131	-0.638 (-0.720; -0.556)	**1.37×10^{-52}**	-0.493 (-0.632; -0.354)	**4.05×10^{-11}**	-0.635 (-1.27; -0.005)	0.050	0.993	44.0
CA on AN	132	0.298 (0.180; 0.416)	**1.06×10^{-7}**	0.366 (0.170; 0.561)	**9.07×10^{-5}**	0.854 (0.183; 1.52)	**0.014**	0.147	44.0
CA on ANX	125	-0.109 (-0.353; 0.135)	0.380	-0.068 (-0.425; 0.288)	0.706	0.143 (-0.967; 1.25)	0.801	0.138	44.1
CA on ASD	116	0.102 (-0.026; 0.229)	0.117	0.172 (-0.021; 0.366)	0.081	0.557 (-0.096; 1.21)	0.097	0.076	44.3
CA on BD	112	-0.083 (-0.173; 0.006)	0.069	-0.138 (-0.283; 0.006)	0.061	-0.082 (-0.623; 0.460)	0.768	0.632	42.9
CA on MDD	137	-0.153 (-0.228; -0.078)	**6.79×10^{-5}**	-0.106 (-0.228; 0.016)	0.089	-0.098 (-0.557; 0.362)	0.677	0.282	43.9
CA on OCD	94	-0.013 (-0.354; 0.327)	0.940	-0.097 (-0.583; 0.389)	0.695	-0.125 (-1.57; 1.32)	0.866	0.855	44.8
CA on PTSD	136	-0.139 (-0.264; -0.013)	**0.030**	-0.207 (-0.406; -0.009)	**0.041**	0.220 (-0.458; 0.898)	0.525	0.498	43.9
CA on SZ	130	-0.209 (-0.279; -0.139)	**6.16×10^{-12}**	-0.140 (-0.276; -0.005)	**0.043**	0.161 (-0.624; 0.945)	0.689	**0.001**	44

Abbreviations: CA: cognitive abilities; ADHD: attention deficit hyperactivity disorder; AN: anorexia nervosa; ANX: anxiety disorder; ASD: autism spectrum disorders; BD: bipolar disorder; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; PTSD: post-traumatic stress disorder; SZ: schizophrenia; MR: mendelian randomization; SNP: single nucleotide polymorphism; IVW: inverse variance weighted (fixed effect); B: effect estimates are log-odds; 95% CI: 95% confidence interval; WM: weighted median; NR: not reported because not enough SNP to perform MR.

Legend: All statistical tests were two-sided. The p-values were not adjusted for multiple testing, therefore p-value<0.05 was considered significant (and reported in bolded text).

Supplementary Table 27: *CAUSE results of the relations between cognitive ability and mental disorder*

Model 1	**Model 2**	**Δ ELPD**	**SE Δ ELPD**	**z-score**	**p-value**[†]
Fw: CA on ADHD					
Null	Sharing	-69.24	9.79	-7.07	**1.55×10^{-12}**
Null	Causal	-76.54	10.84	-7.06	**1.67×10^{-12}**
Sharing	Causal	-7.30	1.21	-6.04	**1.54×10^{-9}**
Bw: ADHD on CA					
Null	Sharing	-22.00	4.75	-4.64	**3.48×10^{-6}**
Null	Causal	-28.89	6.27	-4.61	**4.03×10^{-6}**
Sharing	Causal	-6.89	1.57	-4.39	**1.13×10^{-5}**
Fw: CA on AN					
Null	Sharing	-0.01	0.53	-0.02	0.984
Null	Causal	-1.01	2.02	-0.50	0.617
Sharing	Causal	-1.00	1.50	-0.66	0.509
Bw: AN on CA					
Null	Sharing	0.46	0.07	6.83	**8.49×10^{-12}**
Null	Causal	1.35	0.07	18.32	**5.73×10^{-75}**
Sharing	Causal	0.89	0.02	40.41	**$<1^{-1000}$**
Fw: CA on ANX					
Null	Sharing	-7.02	3.68	-1.91	0.056
Null	Causal	-7.17	4.27	-1.68	0.093
Sharing	Causal	-0.14	1.38	-0.11	0.912
Bw: ANX on CA					
Null	Sharing	0.25	0.09	2.88	**0.004**
Null	Causal	1.08	0.30	3.61	**3.06×10^{-4}**
Sharing	Causal	0.83	0.25	3.35	**0.001**
Fw: CA on ASD					
Null	Sharing	-0.40	0.88	-0.46	0.646
Null	Causal	-1.88	2.43	-0.78	0.435
Sharing	Causal	-1.48	1.57	-0.94	0.347
Bw: ASD on CA					
Null	Sharing	0.31	0.17	1.88	0.060
Null	Causal	0.39	1.01	0.39	0.697
Sharing	Causal	0.08	0.85	0.09	0.928
Fw: CA on BD					
Null	Sharing	0.42	0.15	2.80	**0.003**

Null	Causal	0.79	0.98	0.81	0.210
Sharing	Causal	0.37	0.84	0.84	0.328
Bw: BD on CA					
Null	Sharing	0.45	0.07	5.98	**2.23×10^{-9}**
Null	Causal	1.09	0.52	2.08	**0.038**
Sharing	Causal	0.64	0.45	1.42	0.156
Fw: CA on MDD					
Null	Sharing	-7.83	2.96	-2.64	**0.008**
Null	Causal	-12.20	4.61	-2.65	**0.008**
Sharing	Causal	-4.38	1.68	-2.60	**0.009**
Bw: MDD on CA					
Null	Sharing	0.36	0.08	4.74	**2.14×10^{-6}**
Null	Causal	0.78	0.73	1.07	0.285
Sharing	Causal	0.42	0.66	0.64	0.522
Fw: CA on OCD					
Null	Sharing	-1.11	1.55	-0.72	0.471
Null	Causal	-1.66	2.54	-0.65	0.516
Sharing	Causal	-0.54	1.10	-0.50	0.617
Bw: OCD on CA					
Null	Sharing	0.28	0.03	8.40	**4.64×10^{-17}**
Null	Causal	1.05	0.11	9.63	**5.97×10^{-22}**
Sharing	Causal	0.77	0.10	8.08	**6.48×10^{-16}**
Fw: CA on PTSD					
Null	Sharing	-10.48	3.93	-2.67	**0.008**
Null	Causal	-13.58	5.18	-2.62	**0.009**
Sharing	Causal	-3.10	1.48	-2.09	**0.037**
Bw: PTSD on CA					
Null	Sharing	0.27	0.09	2.86	**0.004**
Null	Causal	0.77	0.63	1.23	0.219
Sharing	Causal	0.50	0.55	0.92	0.358
Fw: CA on SZ					
Null	Sharing	-6.54	2.36	-2.77	**0.006**
Null	Causal	-12.02	4.25	-2.83	**0.005**
Sharing	Causal	-5.48	1.90	-2.88	**0.004**
Bw: SZ on CA					
Null	Sharing	-5.95	2.35	-2.53	**0.011**
Null	Causal	-10.84	4.20	-2.58	**0.010**

Sharing	Causal	-4.89	1.86	-2.62	**0.009**

Abbreviations: MR: mendelian randomization; ELPD: expected log pointwise posterior density; 95%CI: 95% confidence interval; SE: standard error; Fwd: forward MR; Bwd: backward MR; CA: cognitive abilities; ADHD: attention deficit hyperactivity disorder; AN: anorexia nervosa; ANX: anxiety disorder; ASD: autism spectrum disorder; BD: bipolar disorder; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; PTSD: post-traumatic stress disorder; SZ: schizophrenia.

Legend: † Based on t-test. The p-values are two-sided and not adjusted for multiple testing, therefore p-value<0.05 was considered significant (and reported in bolded text).

Supplementary Table 28: *Multivariable Mendelian Randomization results of household income and cognitive ability on mental disorder*

Regression	**N SNP**	**IVW, B (95% CI)**	**IVW p-value**
Outcome: ADHD	192		
Exposure 1: HI		-0.124 (-0.326; 0.078)	0.230
Exposure 2: CA		-0.508 (-0.639; -0.376)	**4.10×10^{-14}**
Outcome: AN	201		
Exposure 1: HI		0.010 (-0.229; 0.250)	0.933
Exposure 2: CA		0.350 (0.202; 0.498)	**3.57×10^{-6}**
Outcome: ANX	199		
Exposure 1: HI		0.010 (-0.350; 0.370)	0.956
Exposure 2: CA		-0.260 (-0.475; -0.045)	**0.018**
Outcome: ASD	204		
Exposure 1: HI		0.196 (-0.047; 0.440)	0.114
Exposure 2: CA		0.273 (0.115; 0.432)	**0.001**
Outcome: BD	195		
Exposure 1: HI		0.049 (-0.164; 0.261)	0.654
Exposure 2: CA		-0.021 (-0.159; 0.117)	0.766
Outcome: MDD	204		
Exposure 1: HI		-0.029 (-0.177; 0.119)	0.701
Exposure 2: CA		-0.118 (-0.211; -0.025)	**0.013**
Outcome: OCD	204		
Exposure 1: HI		0.108 (-0.341; 0.558)	0.636
Exposure 2: CA		0.296 (0.013; 0.580)	**0.041**
Outcome: PTSD	204		

Exposure 1: HI		0.143 (-0.052; 0.338)	0.150
Exposure 2: CA		-0.077 (-0.206; 0.051)	0.236
Outcome: SZ	195		
Exposure 1: HI		0.085 (-0.167; 0.336)	0.510
Exposure 2: CA		-0.163 (-0.328; 0.002)	0.052

Abbreviations: SNP: single nucleotide polymorphism; IVW: multivariable mendelian randomization via inverse variance weighted method (random effects); B: effect estimates are log-odds; 95% CI: 95% confidence intervals; ADHD: attention deficit hyperactivity disorder; HI: household income; CA: cognitive abilities; AN: anorexia nervosa; ANX: anxiety disorder; ASD: autism spectrum disorder; BD: bipolar disorder; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; PTSD: post-traumatic stress disorder; SZ: schizophrenia.

Legend: All statistical tests were two-sided. The p-values were not adjusted for multiple testing, therefore p-value<0.05 was considered significant (and reported in bolded text).

Supplementary Table 29: *Multivariable Mendelian Randomization results of occupational income and cognitive ability on mental disorder*

Regression	**N SNP**	**IVW, B (95% CI)**	**IVW p-value**
Outcome: ADHD	163		
Exposure 1: OI		-0.189 (-0.427; 0.048)	0.118
Exposure 2: CA		-0.511 (-0.654; -0.368)	**2.36×10^{-12}**
Outcome: AN	165		
Exposure 1: OI		0.248 (-0.021; 0.517)	0.071
Exposure 2: CA		0.329 (0.166; 0.491)	**7.29×10^{-5}**
Outcome: ANX	164		
Exposure 1: OI		-0.032 (-0.425; 0.360)	0.872
Exposure 2: CA		0.121 (-0.600; -0.126)	**0.003**
Outcome: ASD	166		
Exposure 1: OI		0.393 (0.103; 0.682)	**0.008**
Exposure 2: CA		0.267 (0.094; 0.441)	**0.003**
Outcome: BD	166		
Exposure 1: OI		0.204 (-0.039; 0.447)	0.100
Exposure 2: CA		0.050 (-0.097; 0.196)	0.506
Outcome: MDD	166		
Exposure 1: OI		-0.079 (-0.258; 0.101)	0.389
Exposure 2: CA		-0.121 (-0.229; -0.014)	**0.027**

Outcome: OCD	166		
Exposure 1: OI		-0.133 (-0.657; 0.391)	0.618
Exposure 2: CA		0.201 (-0.114; 0.516)	0.210
Outcome: PTSD	166		
Exposure 1: OI		0.143 (-0.092; 0.378)	0.234
Exposure 2: CA		-0.183 (-0.326; -0.041)	**0.011**
Outcome: SZ	166		
Exposure 1: OI		-0.003 (-0.298; 0.291)	0.981
Exposure 2: CA		-0.229 (-0.406; -0.052)	**0.011**

Abbreviations: SNP: single nucleotide polymorphism; IVW: multivariable mendelian randomization via inverse variance weighted method (random effects); B: effect estimates are log-odds; 95% CI: 95% confidence intervals; ADHD: attention deficit hyperactivity disorder; OI: occupational income; CA: cognitive abilities; AN: anorexia nervosa; ANX: anxiety disorder; ASD: autism spectrum disorder; BD: bipolar disorder; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; PTSD: post-traumatic stress disorder; SZ: schizophrenia.

Legend: All statistical tests were two-sided. The p-values were not adjusted for multiple testing, therefore p-value<0.05 was considered significant (and reported in bolded text).

Supplementary Table 30: *Multivariable Mendelian Randomization results of social deprivation and cognitive ability on mental disorder*

Regression	**N SNP**	**IVW, B (95% CI)**	**IVW p-value**
Outcome: ADHD	152		
Exposure 1: SD		-0.135 (-0.317; 0.048)	0.147
Exposure 2: CA		-0.656 (-0.785; -0.528)	**1.80×10^{-23}**
Outcome: AN	161		
Exposure 1: SD		-0.240 (-0.448; -0.033)	**0.023**
Exposure 2: CA		0.342 (0.185; 0.499)	**1.90×10^{-5}**
Outcome: ANX	161		
Exposure 1: SD		0.083 (-0.223; 0.389)	0.593
Exposure 2: CA		-0.267 (-0.490; -0.44)	**0.019**
Outcome: ASD	162		
Exposure 1: SD		-0.354 (-0.587; -0.120)	**0.003**
Exposure 2: CA		0.235 (0.066; 0.404)	**0.007**
Outcome: BD	155		
Exposure 1: SD		0.088 (-0.124; 0.299)	0.416

Exposure 2: CA		-0.007 (-0.159; 0.145)	0.925
Outcome: MDD	162		
Exposure 1: SD		0.005 (-0.142; 0.152)	0.946
Exposure 2: CA		-0.129 (-0.229; -0.028)	**0.012**
Outcome: OCD	162		
Exposure 1: SD		-0.055 (-0.519; 0.409)	0.817
Exposure 2: CA		0.335 (0.023; 0.647)	**0.035**
Outcome: PTSD	162		
Exposure 1: SD		-0.053 (-0.244; 0.139)	0.588
Exposure 2: CA		-0.140 (-0.279; -0.002)	**0.047**
Outcome: SZ	155		
Exposure 1: SD		0.142 (-0.104; 0.387)	0.259
Exposure 2: CA		-0.218 (-0.395; -0.040)	**0.016**

Abbreviations: SNP: single nucleotide polymorphism; IVW: multivariable mendelian randomization via inverse variance weighted method (random effects); B: effect estimates are log-odds; 95% CI: 95% confidence intervals; ADHD: attention deficit hyperactivity disorder; SD: social deprivation measured with Towsend deprivation index; CA: cognitive abilities; AN: anorexia nervosa; ANX: anxiety disorder; ASD: autism spectrum disorder; BD: bipolar disorder; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; PTSD: post-traumatic stress disorder; SZ: schizophrenia. Legend: All statistical tests were two-sided. The p-values were not adjusted for multiple testing, therefore p-value<0.05 was considered significant (and reported in bolded text).