Genetic architecture and risk of childhood maltreatment across five psychiatric diagnoses

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Key points

Question: Are there differences in the genetic architecture of childhood maltreatment exposed children across psychiatric diagnoses?

Findings: Polygenic score analyses demonstrated that a high polygenic load of ADHD and education-decreasing variants are associated with childhood maltreatment risk across psychiatric diagnoses, and genetics can be used to stratify individuals into risk groups with significant different risks of childhood maltreatment.

Meaning: Genetics combined with information on other risk factors, can be used to identify vulnerable individuals at increased risk for childhood maltreatment.

Abstract

Importance: Childhood Maltreatment (CM) is associated with psychiatric disorders. Underlying mechanisms are complex and involve genetics.

Objective: To investigate the polygenic architecture of CM exposed individuals across psychiatric conditions, and if genetics modulates absolute CM risk in the presence of high-impact risk factors such as parental psychiatric diagnoses.

Design and participants: The population-based case-cohort iPSYCH was used to analyse 13 polygenic scores (PGS) in CM-exposed individuals across five psychiatric ICD-10 diagnoses benchmarked against controls. Individuals were stratified into PGS quantiles, and absolute CM risk was calculated using Cox regression. Sex-specific analyses were also performed.

Main outcome and measures:

PGSs were generated using summary statistics from genome-wide association studies of phenotypes representing psychiatric disorders, CM, educational attainment, and substance use, and tested for their association with CM across psychiatric disorders.

Results: This study included 102,856 individuals (47,938 females, 54,918 males) 8-35 years old. We analysed 2,179 CM-exposed individuals across individuals with attention deficit hyperactivity disorder (ADHD; N=22,674), autism (N=18,941), schizophrenia (N=6,103), bipolar disorder (N=3,061), depression (N=28,896) and controls (N=34,689). PGSs for ADHD and educational attainment were associated with CM across all psychiatric diagnoses. The absolute CM risk was increased in the highest PGS groups, e.g., for ADHD the absolute CM risk was 5.6% in the highest ADHD-PGS quartile while only 3,3% in the lowest ADHD-PGS quartile (hazard rate ratio quantile-4 vs quantile-1 = 1.81; CI = 1.47 – 2.22). CM risk was more than twice as high for children with psychiatric diagnosed parents (5.7%) than for children with non-diagnosed parents (2.5%), but even in the presence of this risk factor individuals could still be stratified into risk groups based on their genetics. No genetic differences between CM exposed males and females were observed, but striking sex-differences in absolute CM risk, which reached 5.6% for females in the highest ADHD-PGS quartile while it was 2.0% for males.

Conclusions and relevance: Individuals with high a ADHD-PRS and/or low educational attainment-PRS are at elevated risk of CM. Extra attention should be given to CM-high-risk individuals across all five psychiatric diagnoses i.e. females with a high ADHD-PGS and/or a parent diagnosed with a psychiatric disorder.

Introduction

Childhood maltreatment (CM), here defined as exposure to physical, sexual or emotional abuse or/and deprivation or severe neglect during childhood, occurs frequently, but a reliable prevalence estimate is difficult to obtain due to differences in age groups, methods, and instruments used to collect data on CM[1,2]. CM is associated with acute and chronic problems in wellbeing and cognitive and socio-emotional development across the lifespan[3].

While CM itself (the actual abuse or neglect), is not directly inherited in a genetic sense, genetic factors may influence a child's risk of experiencing CM; family studies indicate that genetic influences could account for between 6.4% and 62.5% of the variation in risk, with highest heritability for severe physical abuse. CM results from a complex interplay between genetic predispositions and environmental factors, including cultural differences in acceptability of CM[4], that shapes a child's vulnerability to maltreatment.

Common genetic variants explain a part of the heritability. A recent genome-wide association study (GWAS) meta-analysis of childhood maltreatment (N=185,414) has identified 14 genome-wide significant loci and estimated the variance explained by common genetic variants, i.e., the single nucleotide polymorphism (SNP) heritability (h^2_{SNP}) to 0.093 for CM[5].

CM has been associated with childhood onset neurodevelopmental diagnoses[6] (e.g. attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) and psychiatric conditions with later onset e.g. schizophrenia (SCZ), bipolar disorder (BPD) and major depressive disorder (MDD)[7,8]. Exposure to CM might be associated with development of subsequent psychiatric conditions by its potential impact on brain structure[9,10] and methylation patterns[11]. It could also be hypothesized that for individuals genetically predisposed to a psychiatric condition, CM could increase the risk of symptom manifestation or severity[12].

Studies have also found support for a shared genetic risk component of CM and psychiatric disorders e.g. individuals with high polygenic scores (PGSs) for ADHD and SCZ, have higher risk of experiencing CM[13-15]. Parenting a child with symptoms of a neurodevelopmental

disorder (which in part is due to genetics) can be stressful, especially if the parents themselves are diagnosed with a psychiatric disorder, and thus might increase the risk of CM.

The aim of this study is to evaluate potential similarities or differences in the polygenic architecture of CM exposed individuals across five psychiatric conditions, and the extent to which the risk of CM is modulated by the polygenic risk load (i.e. the PGS). This was done by PGS analyses in the Danish iPSYCH cohort[16,17]. We demonstrate how we can stratify individuals with psychiatric diagnoses into CM risk groups by their PGS and identify striking sex differences and strong impact of parental diagnosis of psychiatric disorders on the absolute risk of CM.

Methods

The study was reported following STROBE guidelines. The iPSYCH study was approved by the Scientific Ethics Committee, Central Denmark Region (Case No 1-10-72-287-12) and the Danish Data Protection Agency. In accordance with Danish legislation, the Danish Scientific Ethics Committee has, for this study, waived the need for specific informed consent in biomedical research based on existing biobanks.

The iPSYCH cohort and phenotype definition

Included individuals come from the population-based case-cohort iPSYCH[16,17], generated from a baseline cohort of all children born in Denmark between May 1, 1981, and December 31, 2008, who were alive and resided in Denmark on their one-year birthday. Register codes with information until the 31/12/2016, were used to identify individuals in the cohort with an ICD-10 diagnosis of ADHD, ASD, MDD, SCZ and BPD and randomly selected population-based controls (eMethods).

ICD-10 register codes were used to identify children exposed to CM by codes indicating sexual or physical abuse, or severe neglect in childhood (eTable 1 and eMethods). Due to low sample

size of individuals with SCZ and BPD exposed to CM these two diagnoses were merged in the PGS analyses in the iPSYCH cohort (referred to as SCZ/BPD). Biological material from the individuals was obtained from the New Born Screening Biobank[18], and genotyped as outlined in the eMethods.

Genetic correlations and estimation of number of shared variants

Linkage Disequilibrium Score Regression (LDSC)[19] was used to estimate genetic correlations between CM and psychiatric disorders, using the largest available GWAS summary statistics of CM[5], ADHD[20], ASD[21], BPD[22], SCZ[23] and MDD[24]. LD scores and weights for the European population were obtained from the original LDSC package (see URLs).

The number of shared common variants between CM and the five psychiatric disorders were estimated using bivariate mixture modelling implemented in MiXeR[25] (See eMethods).

PGS analyses

We performed PGS analyses to evaluate if PGSs representing specific phenotypes could be used to differentiate CM exposed from non-exposed individuals across psychiatric disorders. We tested for differences in PGS load between CM exposed groups and non-exposed groups, only including individuals with homogenous genetic ancestry (see Supplement 1). PGSs for individuals in the iPSYCH cohort were calculated for 13 phenotypes, using LDpred2-auto[26] and weights derived from GWASs: CM[5], educational attainment (EA)[27] psychiatric diagnoses (ADHD[20], ASD (unpublished see eMethods), BPD[22], SCZ[23], MDD[24], Alcohol use disorder [AUD][28], cannabis use disorder [CUD][29], opioid use disorder [OUD][30]) and substance use (drinks per week [DrnWk][31]), cannabis use [CU][32], smoking initiation [SmokIni][31]), See eMethods.

Multivariate multivariable regression, described in detail in (REF[21]), was applied to evaluate the PGS load across groups benched-marked against population-based controls with no diagnosis of CM, ADHD, ASD, BPD, SCZ and MDD (See eMethods).

We performed three analyses: (**I**) we tested if CM has a common variant risk component by comparing the PGS load of CM exposed individuals to non-exposed individuals within each psychiatric diagnosis (ADHD vs ADHD+CM, MDD vs MDD+CM, ASD vs ASD+CM, SCZ/BPD vs SCZ/BPD+CM) (**II**) we tested if the genetic risk component of CM differs across psychiatric diagnoses by comparing the PGS load of CM exposed individuals across psychiatric conditions (all pair-wise comparisons of: ADHD+CM, MDD+CM, ASD+CM, BIP/SCZ+CM) (**III**) We tested for potential differences in the PGS load between CM exposed females and males within each psychiatric diagnosis (ADHD+CM [females vs males], MDD+CM [females vs males], ASD+CM [females vs males], BPD/SCZ+CM [females vs males]). Each analysis was corrected using Bonferroni correction, number of tests corrected for are noted in the eTable legends.

Two sensitivity analyses were conducted (I) we tested for PGS differences between those with CM reported before 18 years of age versus those with CM reported retrospectively after 18 years of age. (II) We tested for PGS differences between CM exposed individuals having at least one parent with a psychiatric diagnosis versus those with parents without a psychiatric diagnosis (details in eMethods).

Hazard rate ratio and absolute risk of maltreatment across psychiatric disorders

Cox regression was performed to estimate the relative hazard rate ratio (HRR) and absolute risk of CM within individuals with ADHD, SCZ/BPD and MDD (ASD was not included due to low number of CM exposed individuals with ASD) stratified into PGS-quantiles (see eMethods).

We estimated relative and absolute risk of CM separately for females and males with psychiatric diagnoses, for individuals having one or both parents diagnosed with a psychiatric disorder, and for individuals having parents without a psychiatric diagnosis (parental psychiatric diagnoses considered were SCZ, MDD, BPD, ADHD and any substance use disorder (ICD10 F10-F19; acute intoxication excluded). To reach a sufficient sample size, individuals with MDD, ASD, ADHD, BIP and SCZ were pooled, and the five psychiatric diagnoses were included as covariates in the regression models.

For comparison the relative and absolute risk of CM in the general Danish population was assessed by running a Cox model on the population-based controls stratified into PGS tertials. This analysis was also run separately for males and females.

Results

Genetic overlap of CM and psychiatric disorders

MiXeR analyses, using published GWAS summary statistics, estimated that there exist 10,042 (standard error [s.e.] = 787) common variants associated with CM, which is comparable to what was observed for the five psychiatric disorders (eTable 2). CM demonstrated significant genetic correlations (r_g) with the five psychiatric conditions ranging from $r_g = 0.27$ (s.e. = 0.03; $P = 4.65x10^{-20}$) for CM vs BPD to $r_g = 0.59$ (s.e. = 0.03, $P = 7.08x10^{-100}$) for CM vs ADHD (eTable 3), suggesting a common variant genetic overlap of CM with the five psychiatric conditions. This was further supported by MiXeR analyses that identified a substantial overlap in the number of shared influencing variants. Almost all CM influencing variants overlap with MDD (95%) and SCZ (90%), while the lowest overlap was observed with BPD (55%) (Figure 1), the fraction of shared variants with concordant directions of effect on the phenotypes was high ranging from 64% (CM and SCZ) to 76% (CM and ADHD) (eTable 2).

PGS differences among CM exposed and non-exposed individuals in iPSYCH

In iPSYCH 2,179 individuals had an ICD-10 code indicating exposure to CM, with a significant overrepresentation among individuals with psychiatric diagnoses, ranging from 2% (ASD) to 4.8% (SCZ) compared to the population-based controls (0.4%) (Table 1).

The CM-PGS, calculated for individuals in iPSYCH using the published CM GWAS[5] as base, was significantly higher in all individuals with a psychiatric diagnosis compared to controls whether exposed to CM or not, supporting a genetic overlap between CM and psychiatric disorders. The CM-PGS was higher in CM exposed individuals compared to non-exposed individuals, however only significant within MDD ($P = 1.78x10^{-9}$, Figure 2.a., eTable 4).

When evaluating psychiatric disorder PGSs, the ADHD- and MDD-PGSs were significantly higher in CM exposed individuals compared to non-exposed individuals within all five psychiatric diagnoses (except the MDD-PGS within SCZ/BPD; Figure 2.b., eTable 4). No differences in exposed vs non-exposed individuals were observed for the SCZ-, BPD- and ASD-PGSs. Results for Substance use disorders and substance use PGSs (Figure 2.c, eTable 4) are described in the eResults.

The EA-PGS was significantly lower in individuals exposed to CM compared to non-exposed individuals across all the psychiatric diagnoses (P-values ranging from $3.36x10^{-5}$ [SCZ/BPD] to $9.86x10^{-12}$ [ADHD], eTable 4, Figure 2.a). Interestingly, we observed a significant difference in ASD for the EA-PGS, which demonstrated a strong negative association in individuals with ASD exposed to CM and a positive association with ASD in non-CM exposed individuals (Figure 2.a).

Sensitivity analyses did not detect any differences in the PGS load between those with CM reported in childhood compared to those with CM reported retrospectively in adulthood (eFigure 1 and 2; eTable 5 and 6).

When comparing the PGS load in those exposed to CM across all psychiatric diagnoses no strong differences in the genetic architecture were observed (eFigure 3, eTable 7). However,

CM exposed individuals with ADHD stood out, since this group demonstrated significantly higher ADHD-, EA- and SmokIni-PGSs compared to the CM exposed groups of the other diagnoses (eFigure 3, eTable 7).

Absolute risk of CM across genetic risk groups

When estimating the absolute CM risk within individuals with ADHD, MDD and SCZ/BPD, stratified into PGS quantiles, we observed a general increased risk of CM with increasing PGS load (eTable 8) e.g., for ADHD the highest HRR for CM was observed for individuals in the lowest (1^{st}) EA-PGS quantile compared to the highest (4^{th}) quantile (HRR = 2.11, s.e. = 0.11, P = $3.94x10^{-12}$). Among individuals with ADHD the absolute CM risk reached 7% in the lowest EA-PGS quantile, which was significantly higher than observed in the group with the highest EA-PGS quantile where the absolute risk reached 3% (Figure 3). For both MDD and SCZ/BPD the highest absolute CM risk was observed in the highest ADHD-PGS quantile reaching an absolute risk of 5%, which for both disorders were significantly higher than observed for the lowest ADHD-PGS quantile (3%; Figure 3).

The ADHD- and EA-PGSs were also able to stratify the population-based controls into risk groups with a significant higher HRR in the high genetic risk groups compared to the other groups and the absolute risk reached 1.2% in the highest ADHD- and $EA_{decreasing}$-PGS tertiles (Figure 3; eTable 8).

Sex-stratified analyses and impact on risk of parental psychiatric diagnosis

There were no significant differences in the PGS load between females (N = 29,808) and males (N = 36,076) with psychiatric disorders exposed to CM, implying a similar common variant risk load across the two sexes (eFigure 3, eTable 9), but sex-specific absolute CM risk differences were striking. The absolute CM risk reached 5.5% among females with psychiatric diagnoses in the highest ADHD-PGS quartile (Figure 4.a), while it only reached 2% for males

in the highest ADHD-PGS quartile (Figure 4.b). The maximum CM risk for males was lower than observed for females in the lowest ADHD-PRS quartile (3.2%) and at a similar level as observed for population-based females in the highest ADHD-PGS tertile (1.6%) (Figure 4.a. and b).

Among individuals with psychiatric diagnoses, having at least one parent diagnosed with a psychiatric disorder (N = 16,493) the absolute CM risk reached 5,7% in the highest ADHD-PGS tertile. This was considerably higher than observed for those with a psychiatric diagnosis but no diagnosed parents (N = 49,470), where the risk reached 2.5%. No differences in PGS load were observed between those with diagnosed parents compared to those with non-diagnosed parents (eTable 12).

Discussion

This study sheds light on the genetic architecture of CM across five major psychiatric disorders. We found evidence for CM being highly polygenic (~10,000 influencing variants) with a large proportion of the common CM influencing variants being shared with ADHD, ASD, MDD, BPD and SCZ - and the majority with concordant direction of increasing effects. This finding was reflected in the PGS analyses demonstrating an association of the CM-PGS with psychiatric diagnoses, supporting previous findings of shared genetics between CM and psychiatric conditions[14,15,33]. The CM-PGS was further increased in CM exposed individuals across psychiatric diagnoses, suggesting that the genetic architecture underlying CM in the general population (i.e. the individuals analysed in the training GWAS[5]) also associate with CM in individuals with psychiatric diagnoses.

In general, the PGS load of CM exposed individuals across psychiatric diagnoses were similar suggesting a consistent underlying genetic architecture of CM in both childhood (ADHD, ASD) and adult-onset conditions (MDD, SCZ/BPD). In line with this result, we did not find any genetic differences between those with CM reported in childhood and those with CM

reported retrospectively in adulthood. Thus, from a genetic point of view, the group of individuals who reported CM retrospectively, do not differ (genetically) from those where CM was reported in childhood. This contrasts previous research suggesting a difference[34], but in these studies the retrospective measurement was interview or questionnaire, which might differ from the register codes based on clinical assessment used in this study.

The ADHD- and EA-PGSs were significantly increased in CM exposed children compared to non-exposed children across all psychiatric diagnoses. Thus, it could be hypothesized that the common variant risk influencing CM involves a combination of variants having a negative impact on educational attainment and are associated with externalizing impulsive behaviours. This is in line with findings that childhood learning disabilities, and neurodevelopmental conditions increase CM risk[3]. Likewise, behaviours and symptoms associated with ADHD have previously been linked to CM risk in children with ADHD[35,36] and in non-diagnosed children[37].

Several studies have investigated the association of CM and with depression[38,39], and in this context it is worthwhile to note that the ADHD-PGS predicted CM within individuals with MDD better than the MDD-PGS. This suggests that the link between CM and MDD is influenced to a larger extent by ADHD genetics (which strongly overlaps MDD genetics[20]) than genetic factors being more MDD specific. This is in line with a study of a US urban birth cohort of more than 3,000 children that found childhood adverse experiences to be stronger associated with externalizing- than internalizing problematic behaviours at nine years of age[40].

There could be several ways in which the PGS load affect CM risk. A previous study found an association of increased ADHD-PGS with externalizing and impulsive behaviours in non-diagnosed individuals[41], and it could therefore be hypothesised that children with high ADHD-PGS loads demonstrate more disruptive externalizing behaviours that could increase CM risk. It is important to emphasize that we do not suggest that an individual is ever responsible for their exposure to CM.

The genome of a child represents the genetics of the parents, and thus it could also be hypothesised that a high ADHD-PGS reflects a high parental genetic liability for ADHD and other psychiatric conditions, which might be associated with less parental resources potentially increasing CM risk. This hypothesis was elucidated by our analyses showing that the absolute CM risk was more than doubled for children with diagnosed parents compared to those with non-diagnosed parents, suggesting that parental psychiatric disorders have a large impact on CM risk. However, we also observed that individuals with diagnosed parents still could be stratified into risk groups based on their genetics, and that the PGS load in CM exposed individuals with diagnosed parents was not different from children with non-diagnosed parents. These observations suggest that the genetics of the child and parental psychiatric diagnosis affect CM risk rather independently. In line with other findings suggesting family history to partly confer risk that is not captured by PGSs[42]. Thus, genetics of the child modulate CM risk even in the presence of a high-risk factor like having a diagnosed parent.

There were no differences in the genetic risk between males and females exposed to CM, while we found strikingly higher absolute risk of CM for females than for males. This implies the existence of environmental factors that puts females at greater risk for CM than males. In particular CM due to sexual abuse was more frequent among females than males in the iPSYCH cohort, which has also been reported by others[1] and reflects the World Health Organization reporting a three times higher prevalence of childhood sexual abuse among females than males[43]. We would like to highlight that the absolute CM risks reported in this study are based on a population-based sample with minimal ascertainment bias that includes all individuals diagnosed with ADHD, MDD and SCZ/BPD born in Denmark from 1981 to 2008 and therefore provide solid evidence of a higher CM risk for females, at least in the Danish population.

Limitations

The strength of our study includes the use of genetic data linked to register data from childhood to adulthood in a population-based case-cohort. However, our study has some limitations. We identified CM based on ICD10 register codes and do not know the extent to which, our findings are valid for CM defined by other methods such as questionaries or interviews, nor if our findings extrapolate to genetic diverse groups. No comparable large population-based case-cohort exist for replication of our results, and thus we were not able to evaluate the generalizability of our findings. Additionally, we were not able to make any causal inferences since it was not possible to conclude if the psychiatric symptoms manifested before after the reporting of CM in the registries. Furthermore, the trajectories of cumulative absolute risk of CM reflect when the ICD10 codes were registered, so we cannot draw strong conclusions about trajectories of exact timing of CM. Finally, we cannot exclude unrecognized biases in clinical practice[36].

Conclusions

Our study identified a similar genetic CM risk component across psychiatric diagnoses involving ADHD associated variants. Our results show that being a female and having at least one parent with a psychiatric disorder are risk factors for CM, but also that genetics modulate CM risk even in the presence of these two strong risk factors suggesting that genetic data could add information when identifying children with increased vulnerability towards CM. Recognising and treating ADHD symptoms across psychiatric conditions early in life might be an important health strategy to reduce the population prevalence of CM.

Data sharing

iPSYCH data can be accessed after approval by the iPSYCH Data Access Committee and can only be accessed on the secured Danish server (GenomeDK [https://genome.au.dk]) as the data

are protected by Danish legislation. For data access and correspondence please contact: Ditte Demontis (ditte@biomed.au.dk) or Anders D. Børglum (anders@biomed.au.dk).

Author contributions

Ditte Demontis and Trine Tollerup Nielsen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Ditte, Helen, Edmund, Trine, Paraskevi

Acquisition, analysis, or interpretation of data: Trine, Ditte, Helen, Edmund, Paraskevi, Jakob, Christina, Thomas, Søren, Anders

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Supervision: Ditte, Helen, Edmund

Conflicts of interest

DD has received speaker fee from Medice Nordic and Takeda. ADB has received speaker fee from Lundbeck. ES-B has received speaker fee and travel support from Takeda and Medice.

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Table 1. Included individuals from the iPSYCH cohort

Phenotype	Total sample size	CM diagnosis	%CM	P-value psych vs control	%CM exposed individuals who are females	% CM exposed individuals who are males	%CM exposed females due to sexual abuse	%CM exposed males due to sexual abuse
ADHD	22,674	778	3.4	4.47×10^{-183}	47.7	52.3	52.6	13.8
ASD	18,941	376	2.0	1.33×10^{-77}	40.4	59.6	48.0	17.4
MDD	28,896	1,047	3.6	2.29×10^{-203}	87.3	12.7	73.9	28.6
BPD	3,064	79	2.6	4.28×10^{-57}	86.1	13.9	72.1	NA
SCZ	6,103	292	4.8	2.17×10^{-219}	74.0	26.0	72.7	22.4
Population - based controls	34,689	125	0.4	NA	71.2	28.8	58.4	22.2

Total number of individuals with the five analysed psychiatric diagnoses in the iPSYCH cohort, and number of individuals exposed to CM (CM diagnosis). Percentage of individuals exposed to CM (%CM) among those with psychiatric diagnoses and population-based controls (i.e. randomly selected individuals from the Danish population without ADHD, ASD, MDD, BPD, SCZ). The percentage of CM exposed individuals who are females (%CM exposed individuals who are females) and males (%CM exposed individuals who are males). The percentage of females and males exposed to CM caused by sexual abuse (%CM exposed females due to sexual abuse; %CM exposed males due to sexual abuse). Two-sided unadjusted P-value from testing if the proportion of CM exposed individuals within each psychiatric diagnosis is different than the proportion of CM exposed individuals in among the population-based controls (P-value psych vs control). NA = due to data protection, results based on counts below five are not available. Individuals can be counted more than once if they are diagnosed with more than one of the psychiatric disorders.

Figure legends

Figure 1. Genetic overlap of CM and psychiatric conditions

Venn diagrams showing MiXeR results of the estimated number of variants shared between CM and psychiatric conditions. Circles represent shared variants (dark green), unique to CM (light blue) and unique to the other phenotype (light green). The number of shared variants (and standard errors) are shown in thousands. The size of the circles reflects the polygenicity of each phenotype, with larger circles corresponding to greater polygenicity. The estimated genetic correlation (r_g) between CM and each phenotype is shown below the corresponding Venn diagram, with an accompanying scale (−1 to +1) with red representing a positive genetic correlation. Bivariate results for CM and attention deficient hyperactivity disorder (ADHD), autism spectrum disorder (ASD), bipolar disorder (BPD), schizophrenia (SCZ), and major depressive disorder (MDD) are shown (see also eTable 2). Note: for CM vs ASD, the model had limited support, and the results should be interpreted with caution.

Figure 2. PGS load across CM exposed and non-exposed individuals with psychiatric diagnoses

PGS analyses across subgroups (x-axis) of individuals with BPD and SCZ with a CM diagnosis (BPD/SCZ+CM; N = 357) and without (BDP/SCZ = 8,526), individuals with ASD and a CM diagnosis (ASD+CM; N = 345) and without (ASD = 17,898), individuals with ADHD and a CM diagnosis (ADHD+CM; N = 604) and without (ADHD; N = 16,747), individuals with MDD and a CM diagnosis (MDD+CM; N = 748) and without (MDD; N = 20,975). The subgroups were benchmarked against a common population-based control group without CM, ADHD, SCZ, ASD, MDD and BPD (N = 34,564). Multivariable regression was performed for the following PGSs (listed above each plot): **(a)** childhood maltreatment (CM), educational attainment (EA) **(b)** attention deficient hyperactivity disorder (ADHD) autism spectrum disorders (ASD), major depressive disorder (MDD), bipolar disorder (BPD), schizophrenia (SCZ) **(c)** alcohol use disorders (AUD), cannabis use (CU), cannabis use disorder (CUD), drinks per week (DrnkWk), smoking initiation (SmoIni), opioid use disorder (OUD). On the y-axis the beta-coefficient from the multivariate regression for each dependent variable and the corresponding 95% confidence intervals are shown as vertical lines. Significant difference between betas for the CM subgroup against the non-exposed CM subgroup within each psychiatric diagnosis is indicated with a horizontal line with the P-value above, i.e., the Wald test of equal group effect (see also eTable 4). NS indicate no significant differences.

Figure 3. Absolute risk of CM in PGS quantiles of individuals with psychiatric diagnoses

Absolute risk of reported CM (with 95% CI) on the y-axis, over time on the x-axis among individuals with ADHD (**a** and **d,** N = 22,674), MDD (**b** and **e,** N = 28,896) and SCZ/BPD (**c** and **f,** N = 9,167). The individuals are stratified into quartiles (1q-4q) or tertiles (1q-3q) based on their ADHD-PGS (**a-c**) or EA-PGS (**d-f**). The coloured values at the right on the figures indicate absolute risk of CM reported by age 30. Absolute risk (95% CI) of CM among population-based controls stratified into tertiles based on their ADHD- or EA-PGS (N = 34,689), is shown in blue, and the blue values indicate absolute risk of CM at age 30 with the darkest blue value representing the risk in the highest PGS tertile and the lightest blue value the risk in the lowest PGS tertile.

Figure 4. Absolute CM risk in females and males and individuals with and without psychiatric diagnosed parents

Absolute risk of reported CM (with 95% CI) on the y-axis, over time on the x-axis among individuals stratified into quartiles (1q-4q) or tertiles (1q-3q) based on their ADHD-PGS: (**a**) among females with psychiatric diagnoses (N = 29,808), risk among population-based control females in blue (N = 18,130) (**b**) among males with psychiatric diagnoses

(N = 36,076), risk among population-based control males in blue (N = 18,842) (**c**) individuals with psychiatric diagnoses with at least one parent diagnosed with a psychiatric disorder (N = 16,493), risk among population-based controls in blue (N = 34,689) (**d**) individuals with psychiatric diagnoses with parents not diagnosed with a psychiatric disorder (N = 49,470), risk among population-based controls in blue (N = 34,689). The coloured values at the right on the figures indicate absolute risk of CM reported by age 30. The values in blue represent absolute risk at age 30 for population-based controls, with the darkest blue value representing the risk in the highest PGS tertile and the lightest blue value the risk in the lowest PGS tertile.

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