Autism polygenic scores are associated with trauma and self-harm

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Abstract

Importance: Autistic individuals experience significantly elevated rates of childhood trauma, and self-harm and suicidal behaviour and ideation (SSBI). It is unclear if polygenic scores for autism are associated the likelihood of experiencing these adverse mental health outcomes, and variables that may mediate and moderate this.

Objective: To investigate if polygenic scores for autism are associated childhood trauma and SSBI and identify variables that mediate and moderate these effects.

Design, setting, and participants: Using data from the UK Biobank ($105{,}222 < N < 105{,}638$), we applied polygenic scores for autism, and tested for association with childhood traumatic events and SSBI.

Exposure: Polygenic scores for autism, derived from an independent GWAS of autism. Sex and childhood trauma were moderators. Depression and anxiety symptoms, social relationships and job satisfaction were mediators.

Main outcomes and measures: Childhood trauma scores, self-harm ideation scores, and self-harm scores.

Results: Polygenic scores for autism were significantly associated with childhood trauma scores (max R^2 = 0.083%, P < $2x10^{-16}$), and self-harm ideation scores (max R^2 = 0.098%, P < $2x10^{-16}$), and self-harm scores (max R^2 = 0.12%, P < $2x10^{-16}$). Male sex significantly negatively moderated the effect of polygenic scores on childhood trauma scores (Beta = -0.025±0.005, P = $1.59x10^{-5}$) and self-harm scores (Beta = -0.015±0.005, P = 0.007). Childhood trauma scores significantly positively moderated the effect of polygenic scores on self-harm ideation scores (Beta = 0.007±0.002; P = 0.008). Depressive symptoms, and quality and frequency of social interactions were significant mediators of the effect of polygenic scores on autism, with the proportion of effect mediated ranging from 0.23 (95% CI: 0.34 – 0.12) for depression to 0.02 (95% CI: 0.03 – 0.01) for frequency of social interaction.

Conclusion and relevance: Our results suggest the risk for SSBI and childhood trauma is partly associated with polygenic scores for autism and point to significant gene-by-environment interactions, with sex and childhood traumatic experiences moderating the effects of SSBI. Finally, our results also identify significant mediators of the effect of polygenic scores on SSBI.

Key points

Question: Are adults with higher autism polygenic scores for autism more likely to experience childhood traumatic events and self-harm and suicidal behaviour and ideation (SSBI) and what are the variables that moderate and mediate this association between polygenic score and SSBI?

Findings: In the UK Biobank (28,177 < N < 105,638), polygenic scores for autism are significantly associated with childhood traumatic events and SSBI. Sex and childhood

traumatic events significantly moderated the effects of polygenic scores on SSBI. Depressive symptoms, and quality and frequency of social interactions mediated the effects of polygenic scores on SSBI.

Meaning: Higher polygenic scores for autism increase adverse childhood and adult events.

Introduction

A growing body of research has identified that autistic individuals have elevated rates of self-harm (with or without suicidal intent) and suicidal behaviour and ideation (SSBI),[1–6]. Between 10–66% of autistic individuals have contemplated suicide[2,5], 35% had planned or attempted suicide[2], and autistic individuals are 7.5 times more likely than individuals from the general population to have died by suicide[1]. In addition, there is a positive association between autistic traits and SSBI[3,7]. Suicide is one of the leading causes of mortality in autistic individuals, with the relative risk being higher for autistic women than autistic men[1] (a reversal of the sex ratio in the general population)[8]. In fact, for autistic women without a learning difficulty, suicide is the leading cause of mortality[1]. Clearly there is an urgent need to understand and address SSBI in autistic individuals. However, despite this, only a handful of studies have investigated the variables that contribute and mediate this[3,9,10]. These studies have identified variables such as the stress of camouflaging in autism, depression, lack of social support and unmet support needs, all contributing SSBI in autistic individuals. There is no question that these environmental factors and the stigma that might drive a person to camouflage their autism are all important contributing factors to SSBI in autism. Depressive symptoms also mediate the effect between social autistic traits and self-harm behaviour[3]. However, to date, there has been no large-scale investigation of other variables that might mediate the effects of autism/autistic traits on SSBI.

A separate line of research has identified that autistic individuals are more prone to traumatic episodes during childhood[11–15]. For instance, 18% of autistic children are likely to have been physically abused, and 16% likely to have been sexually molested[16]. Individuals who have a higher number of autistic traits are also more likely to experience childhood abuse than individuals who have lower scores[13,17]. Childhood trauma and the related sequalae are associated with poorer mental and physical health in later life[18–21], and increased

mortality[22–24]. Specifically, childhood trauma is a significant risk factor for SSBI[19,25–27]. Childhood trauma accounts for 16-50%[28] of variance in suicidal ideation, and 64-80%[29] of the variance in suicide attempts, though these studies were conducted in relatively modest sample sizes. In a larger nation-wide registry study of Danish children born in 1966, childhood abuse had the second largest effect on suicide attempt, the first being a history of psychiatric illness[26]. Thus, childhood trauma is both elevated in autism and, in the general population, is an important risk factor for SSBI. However, it is unclear if elevated childhood trauma interacts with the liability for autism to increase the risk for SSBI i.e. a stress-diathesis model for SSBI[30].

Autism is highly heritable, with twin and family-based estimates identifying heritability estimates between 60-90%[31–34]. There is compelling evidence that autism can be modelled as the extreme end of subclinical manifestations of autism, termed autistic traits, which are normally distributed in the general population[35–38]. Whilst *de novo* protein truncating variants in specific genes and CNVs are robustly associated with autism[39–42], the majority of the heritability (11-49%)[43–45] is attributable to common genetic variants. In studies of the general population, polygenic scores derived from genome-wide association studies (GWAS) of autism, which represent the underlying liability for autism, are associated with a number of normally distributed traits in the general population: social and communication difficulties in childhood[46], autistic traits[47], and cognitive aptitude[48].

Both trauma[49,50] and SSBI[51,52] are heritable – possibly due to heritable personality traits such as social naivete or risk-taking behaviour, or through the environment, where specific personality traits elicit specific adverse behaviour from family or friends (for example, introverted children are more likely to be bullied)[53]. Twin and adoption studies have demonstrated that, on average, approximately a quarter of variance in stressful life events and parenting behaviour can be explained by the child's genetics[49]. Given the significant

heritability of autism, it thus becomes pertinent to investigate if polygenic scores for autism are associated with adverse childhood and adult outcomes in autism. An advantage of using polygenic scores is that they are less likely to be confounded by socio-economic factors which can influence rates of autism diagnosis[54–57].

In this study, we address these questions using data on SSBI, childhood traumatic events, and potential mediating variables from the UK Biobank and link these to polygenic scores for autism in more than 100,000 individuals. Specifically, we investigate four questions: 1. Are polygenic scores for autism associated with childhood traumatic events? 2. Are polygenic scores for autism associated with SSBI in adulthood? 3. Do sex and childhood traumatic events moderate the effect of autism polygenic scores on SSBI (a gene-by-environment model)? 4. Do specific social and neuropsychiatric variables mediate the effects of polygenic scores for autism on SSBI?

Methods

Participants: Participants were a maximum of 105,638 individuals from the UK Biobank[58] (Year of birth: 1936 to 1970), who were unrelated to each other, and of European ancestry[59]. We excluded participants whose genetic sex did not match their reported sex, or were outliers for genetic heterozygosity. We further excluded participants who had not completed the mental health questionnaire[60], resulting in the final sample of 105,638 participants (44% males).

Phenotypes: The phenotypes used in the study are measures of childhood trauma and self-harm behaviour[60]. We constructed three phenotype scales to quantify childhood trauma and SSBI.

1. *Childhood trauma (N = 105,638)*: We constructed a childhood trauma score from the total score of 5 questions. Each of these questions were scored from 0 to 4, with options ranging from 'never true' to 'very often true'. We excluded participants who reported 'prefer not to answer'. For two of the positive items, we inverse scored it to capture trauma. Total scores ranged from 0 to 20, with higher scores representing higher trauma. We refer to this phenotype as 'childhood trauma score' throughout the results. The items included are:
    a. Felt loved as a child (inverse scored)
    b. Someone to take me to the doctor as a child (inverse scored)
    c. Sexually molested as a child
    d. Physically abused by family as a child
    e. Felt hated by family member as a child

2. *SSBI (N = 105,222)*: We used 4 questions of SSBI which were measured on different scales. The first two items had three options: 'No', 'Yes, Once', 'Yes, more than once'. The third item had four options: 'Not at all', 'Several days', 'More than half the days', 'Nearly every day'.
    a. Ever thought life was not worth living (range: 0 – 2)
    b. Ever contemplated self-harm (range: 0 – 2)
    c. Recent thoughts of suicide or self-harm (range: 0 – 3)
    d. Ever attempted self-harm (binarized: 1 = yes, 0 = no)

Given the range in scores, we constructed two scales, the first being the self-harm ideation scale, which was created by summing up the scores for the first three items. The total score on the self-harm ideation scale ranges from 0 to 7. We refer to this phenotype as 'self-

harm ideation score'. We created a second scale by including all items. For this, we binarized scores for all four items with 1 representing 'yes' and 0 representing 'no'. Thus, the total score on the self-harm scale ranged from 0 to 4. We refer to this phenotype as 'self-harm score'. For both measures, we excluded participants who chose 'Prefer not to answer'. Total scores were created only for participants who responded to all the items included in the scores.

Note, the UK Biobank also includes the following question: 'Ever attempted suicide'. We excluded the item from the scale as it was completed by only 3,971 individuals after quality control. We also excluded the item 'Contemplated self-harm in past year', as this was completed by 23,192 participants.

Mediators of self-harm

We further considered the effects of 7 measures as mediators of polygenic scores for autism and self-harm:

1. *Depressive symptoms* ($39{,}479 < N < 39{,}551$): We developed a depressive symptoms score based on items in the UK Biobank that mapped onto the DSM-5 criteria for Major Depressive Disorder[61]. All items were recoded to 0 and 1. Scores ranged from 0 to 8 with 8 being the highest score. The included items are:
    a. Prolonged feelings of sadness
    b. Prolonged loss of interest in normal activities
    c. Changes in sleep
    d. Feelings of tiredness during worst episode of depression
    e. Feelings of worthlessness during worst period of depression
    f. Difficulty concentrating during worst depression

g. Thoughts of death during worst depression

h. Weight change during worst episode of depression

2. *Anxiety symptoms* (28,177 < N < 28,231): We developed an anxiety symptoms score based on items in the UK Biobank that mapped onto the DSM-5[61] criteria for Generalized Anxiety Disorder. All items were recoded to 0 and 1. Scores ranged from 0 to 7. The items included are:

    a. Difficulty stopping worrying during worst period of anxiety

    b. Multiple worries during worst period of anxiety

    c. More irritable than usual during worst period of anxiety

    d. Keyed up or on edge during worst period of anxiety

    e. Easily tired during worst period of anxiety

    f. Difficulty concentrating during worst period of anxiety

    g. Frequent trouble falling or staying asleep during worst period of anxiety

3. *Friendship and family relationship dissatisfaction* (56,704 < N < 56,842): This was measured using the question – 'In general how satisfied are you with your friendships/family relationships?'. Participants could choose between extremely happy (coded 0) to extremely unhappy (coded 5). Data was collected across three instances, and we used the earliest instance for each participant aggregating data across all three instances.

4. *Job dissatisfaction* (30,533 < N < 30,575): This was measured using the question – 'In general how satisfied are you with the work that you do?'. Participants could choose between extremely happy (coded 0) to extremely unhappy (coded 5). We excluded participants who responded with 'I am not employed' as the UK Biobank is an ageing cohort and it is difficult to distinguish retired participants from unemployed

participants. Data was collected across three instances, and we used the earliest instance for each participant aggregating data across all three instances.

5. *Frequency of friendship/family visits* (117,616 < N < 117,772): This was measured using the question – 'How often do you visit friends or family or have them visit you?' Participants could choose from extremely happy (coded 1) to no friends/family outside household (coded 7). Data was collected across three instances, and we used the earliest instance for each participant aggregating data across all three instances.
6. *Confiding relationship* (115,402 < N < 115,553): This was measured using the question: 'Since I was sixteen... I have been in a confiding relationship'. Participants could choose from never true (coded 0) to very often true (coded 4) .

Previous research has provided support for all these variables influencing SSBI, which is provided in **Supplementary Note Section 1**. We note that, typically for mediation analyses, a temporal ordering is required with the independent variable (polygenic scores) occurring before the mediating variable, which in turn occurs before the dependent variable (SSBI). Whilst polygenic scores are largely immutable and occur at the time of conception, due to the cross-sectional nature of the current data available in the UK Biobank, we are unable to clearly demonstrate the causal nature of the mediator in the current study. However, collecting longitudinal data in large numbers is difficult, and variables of interest should be prioritized to prevent participant fatigue. In such instances, a cross-sectional mediation analysis is helpful to prioritize variants for further analysis, justifying the mediation analysis in the current dataset. Mediation analyses were conducted using the Mediation package in R using 1000 simulations. **Supplementary Figures 1 - 5** provides frequency histograms of all variables used in the analyses.

Genetic quality control and polygenic scores: We used genotype and imputed SNPs from the UK Biobank[59]. Imputed and genotyped SNPs were used with imputed dosages converted to hard-calls using Plink[62]. We restricted our analyses to SNPs with minor allele frequency > 1%, with an imputation $r^2 > 0.6$, with a genotyping rate > 90%, and did not have significant deviations from the Hardy-Weinberg Equilibrium defined by $P < 1 \times 10^{-6}$. We excluded individuals who were genetically related (KING-estimated kinship > 0.088, equivalent to third-degree relatives), were not of 'White British' ethnicity determined by genetic grouping (UKB Data-field 22006), who had discordant reported and genetic sex, who were outliers for genetic heterozygosity, and who had genotyping rate < 90%. Polygenic scores were constructed using PRSice 2[63]. Polygenic scores are weighted averages of common risk polymorphisms that represent an individual's inherited liability for a condition. Weights are assigned for each allele based on the regression Beta value of the GWAS (base dataset), and individuals are scored according to the number of risk alleles they have (0, 1, or 2). The base dataset was the largest autism GWAS based on 18,381 autistic individuals and 27,969 neurotypical individuals[43]. This cohort is independent of the participants from the UK Biobank in this study. Polygenic scoring was conducted using a clumping and thresholding algorithm, after clumping SNPs using an LD-based r^2 of 0.1 and a genomic distance of 250 kb. Note that this is a conservative threshold and radically minimizes the possibility of overcounting the effects. Polygenic scores were constructed for 7 thresholds (P = 1, 0.75, 0.5, 0.25, 0.1, 0.01, and 0.001) for the three primary phenotypes. These thresholds were chosen to balance the signal-to-noise ratio and as autism is highly polygenic[43]. Additionally, for each item in the three primary phenotypes, we conducted individual polygenic score-based regression analysis using the P-value threshold that explained the maximum variance for the primary phenotype that included the item. We used linear regression or logistic regression with the standardized polygenic score as the independent variable, the first 20 genetic

principle components, year of birth, sex, and genotyping batch as covariates in the model, all of which were standardized. For the variables that were significantly associated with polygenic scores for autism, we also investigated the average scores of the variables in the top and the bottom centiles of the polygenic scores uncorrected for any covariates.

For specific analyses, we modelled interaction between sex and polygenic scores, and childhood trauma scores and polygenic scores. We further conducted a series of mediation analyses to identify potential variables that mediate the association between autism polygenic scores and SSBI. All variables were standardized for both the moderation and the mediation analyses. For the moderation analysis with SSBI as the dependent variable, and all mediation analyses, we restricted our investigations to a polygenic score P-value threshold of 0.5 as this explained the maximum variance in SSBI. For the moderation analysis with childhood trauma as the dependent variable, we used a P-value threshold of 0.25 as this explained the maximum variance in childhood trauma.

Multiple testing correction: For each analysis conducted, we corrected for the multiple tests conducted by using Bonferroni correction. For the initial polygenic score regression analyses across the phenotypes, the Bonferroni corrected alpha was P = 0.002 to correct for the 21 tests conducted (7 P-value thresholds for 3 primary phenotypes). For each item-level analysis, the Bonferroni corrected alpha was P = 0.0055, to correct for the 9 tests conducted (9 individual item investigated at a specific P-value threshold for the polygenic scores). For the interaction analyses, the Bonferroni corrected alpha was P = 0.01 to account for the 5 tests conducted (3 sex*polygenic score interaction tests conducted, and two childhood trauma score*polygenic score interaction tests conducted at specific P-value threshold for the polygenic scores). Prior to the mediation analyses, we investigated if the mediator was

associated with either of the two SSBI phenotypes after accounting for the effects of the autism polygenic scores (Bonferroni alpha: P = 0.05/14 = 0.0035), and separately, if the autism polygenic scores were associated with the seven mediators (Bonferroni alpha: P = 0.05/7 = 0.007). Subsequently, we conducted mediation analysis only using the variables that were significantly associated with both the outcome (SSBI) and the treatment (polygenic scores). Thus, we conducted 8 tests in total (4 mediators tested for the two SSBI phenotypes), and identify significant results at a Bonferroni corrected alpha of P = 0.0625. These are conservative alpha thresholds as these tests are not necessarily independent of each other.

This study received ethical approval to access and work with de-identified data from the UK Biobank from the Cambridge Human Biology Research Ethics Committee.

Data and code availability: All code used in this analysis right from QC of the UK Biobank to generating the figures are available here: https://github.com/autism-research-centre/Autism_vulnerability_UKB. Please note, we provide all the analysis and steps in detail along with the results as a knitted document in the link above. Data is available from the UK Biobank to approved researchers.

Results

Autism polygenic scores are associated with childhood traumatic events

We first investigated if polygenic scores for autism are associated with childhood traumatic events. Polygenic scores at all 7 P-value thresholds were significantly associated with childhood trauma score. The variance explained was highest at P = 0.25 (R^2 = 0.083%, P < $2x10^{-16}$) (**Table 1**). Dividing the cohort into centiles based on the polygenic scores (P =

0.25), the top 1% had, on average, an 18% increase in childhood trauma scores compared to the bottom 1% (**Figure 1**).

Insert Figure 1 and Table 1 here

To investigate the deeper association between polygenic scores and individual trauma, we ran individual regression models using a threshold of P = 0.25 for each of the 5 items that were included in the childhood trauma score. For three of the five measures (inverse-scored 'felt loved as a child', 'felt hated as a child', and 'physically abused'), polygenic scores were significantly and positively associated with the traumatic event testing (**Table 2**). Of the three, the variance explained was the highest for 'felt loved as child' (R^2 = 0.089%, P < $2x10^{-16}$) and the lowest for physically abused (R^2 = 0.058%, P = $6.2x10^{-13}$). We identified a nominal positive association between the item 'sexually molested' and polygenic scores for autism (R^2 = 0.004%, P = 0.011), but the P-value was not statistically significant after correcting for multiple testing, and the variance explained is small. There was no significant association between inverse-scored item 'being taken to the doctor' and polygenic scores for autism. For the three significant items, we also divided into centiles and compared the effects between the bottom 1% and the top 10% (**Supplementary Figure 6)**. The top 1% reported 40%, 16%, and 34% increase in scores for the items 'felt hated as a child', 'felt loved as a child' (inverse scored), and 'physically abused' compared to the bottom 1% respectively.

Insert Table 2 here

Autism polygenic scores are associated with self-harm behaviours

We next investigated if polygenic scores for autism are associated with self-harm ideation scores and self-harm scores. Polygenic scores across all 7 P-value thresholds were significantly and positively associated with both self-harm ideation and self-harm scores (**Table 1**). The variance explained for self-harm ideation was highest at P = 0.5 (R^2 = 0.098%, P < $2x10^{-16}$). Similarly, for total self-harm scores, the variance explained was highest at P = 0.5 (R^2 = 0.12%, P < $2x10^{-16}$). Dividing the cohort into centiles based on polygenic scores (P = 0.5) , the top 1% reported a 39% increase in self-harm scores and an 34% increase in self-harm ideation scores compared to the bottom 1% **(Supplementary Figure 7)**.

At an item level, polygenic scores for autism (P-value threshold = 0.5) were significantly associated with three of the four items ('thought life not worth living', 'contemplated self-harm', and 'ever attempted self-harm') (**Table 2**). For these three items, the variance explained was on average higher than the average variance explained for individual childhood traumatic experience. The highest variance explained was for 'thought life not worth living' (Nagelkerke's pseudo R^2 = 0.15%, P < $2x10^{-16}$). Polygenic scores were only nominally associated with the item 'recent thoughts of suicide or self-harm' (Nagelkerke's pseudo R^2 = 0.007%, P = 0.017). Compared to the bottom 1%, the top 1% had a 54%, 136%, and 30% increase in scores on 'contemplate self-harm', 'ever attempted self-harm', and 'think life was not worth living' respectively. In other words, in this cohort, at the bottom 1%, 31 out of 1000 individuals are likely to ever attempt self-harm, which increases to 73 out of 1000 at the top 1%.

Sex and childhood trauma moderate the effect of polygenic scores on SSBI

We investigated if sex moderates the effect of polygenic scores on childhood trauma scores and SSBI using an interaction model. Across all three measures, the main effect of sex and polygenic scores were significant (**Table 3**). Female sex was significantly and positively associated with higher childhood trauma and SSBI. Sex significantly interacted with polygenic scores for childhood trauma score ($Beta_{Males}$ = -0.025±0.005, P = $1.59x10^{-5}$), and self-harm score ($Beta_{Males}$ = -0.015±0.006, P = $6.8x10^{-3}$). We observed a nominally significant interaction between self-harm ideation and sex, but this is no longer significant after correcting for the multiple tests conducted ($Beta_{Males}$ = -0.014±0.006, P = 0.014). Further, childhood trauma significantly moderated the effects of polygenic scores on self-harm score (Beta =$7.24x10^{-3}$±$2.76x10^{-3}$, P = $8.8x10^{-3}$), but was only nominally moderated the effect on self-harm ideation (Beta =$6.74x10^{-3}$±$2.76x10^{-3}$, P = 0.014). The main effects were of polygenic scores for autism and for childhood trauma were significant in both self-harm score and self-harm ideation (**Table 3**).

Insert Table 3 here

Social variables and depression mediate the effect of polygenic scores on SSBI

Finally, we investigated if seven different variables mediate the relationship between polygenic scores for autism and SSBI. We first investigated if these variables are significantly associated with SSBI. After multiple testing correction (Bonferroni corrected alpha = 0.0035), all variables were significantly associated with the two SSBI phenotypes (**Supplementary Table 1**). However, after correcting for multiple tests (Bonferroni corrected alpha = 0.007) polygenic scores for autism were significantly associated only with friendship dissatisfaction, family relationship dissatisfaction, depression scores, and frequency of social interactions (**Supplementary Table 2**). After Bonferroni correction, all four variables

significantly mediated the relationship between polygenic scores four autism and the two SSBI phenotypes (**Supplementary Table 3**). The proportion of effect mediated was highest for depression (23%) and lowest for frequency of social interactions (2%).

Discussion

Whilst autism is typically or should be diagnosed in childhood, increasing research has focussed on the long-term mental and physical health of autistic individuals throughout adulthood. Specifically, a growing body of literature shows that autistic adults are at higher risk for SSBI[1–6]. These studies are all limited in that they have tested relatively small cohorts, and have typically relied on clinical groups. We extend these results by modelling the underlying genetic liability for autism using polygenic scores in more than 100,000 individuals. We find that polygenic scores for autism are significantly associated with both childhood traumatic events and SSBI, demonstrating that there is a continuous increase in both childhood traumatic events and SSBI along a gradient of increasing polygenic scores for autism.

Our results clearly suggest that children with elevated polygenic scores are particularly vulnerable to traumatic events, in particular, physical abuse, feeling that they were not loved, and feeling that they were hated. Whilst trauma is thought to be a largely environmental factor, we propose three hypotheses by which polygenic scores may contribute to childhood abuse. The first hypothesis is that elevated polygenic scores for autism may lead to difficulties in social interaction, communication, and socially inappropriate behaviour[47,64], which may evoke abusive behaviours from parents, caregivers, and peers, leading to greater childhood trauma. Second, social naivete among autistic children may contribute to higher exposure to potentially dangerous situations which may lead to greater incidence of trauma.

Finally, evaluating an event as being traumatic depends on an individual's assessment of the event. Some autistic individuals may be hypersensitive to perceiving an event as traumatic. These hypotheses are in line with twin studies that have identified a significant heritability for childhood and adult traumatic events, which are predominantly environmental factors[49].

Consistent with previous literature[1–6], we also demonstrate the polygenic scores for autism are associated with SSBI and several individual items that contributed to the scores. Dividing the cohort into centiles of polygenic scores demonstrates a sharp increase in SSBI between the top and bottom 1%. The sharpest increase is in the category 'ever attempted self-harm'. Here, the 1% with the highest polygenic scores for autism is 2.3 times more likely to ever attempt self-harm compared to the bottom 1%. The risk of SSBI in autistic teenagers and adults likely occurs because they have experienced exclusion by society, bullying by their peers, ridicule by their teachers, late diagnosis and therefore an absence of early support for their disability, and a lack of life-long support, given that autism is a life-long condition. There is growing evidence of high rates of such vulnerability in autistic adults[65].

Whilst it is well established that childhood trauma contributes to SSBI in later life in the typical population, it is unclear how this interacts with autism or autistic traits. Our results suggest that there is a significant interaction between polygenic scores for autism and childhood trauma to contribute to increased SSBI, providing evidence for a gene-by-environment interaction. Thus, for individuals with high polygenic scores for autism, this represents a 'double hit'. Not only do high polygenic scores contribute to high SSBI in adulthood, these scores also contribute to higher childhood trauma, which also increases the risk for SSBI. Childhood trauma may represent a modifiable risk factor if we are able to identify who is at greater risk for childhood trauma. Thus, it is important to provide support to children with elevated autistic traits or elevated autism polygenic scores, to minimize the risk for childhood trauma and later SSBI.

Our results also suggest that females with elevated polygenic scores are more vulnerable to both childhood trauma and self-harm. In the general population, whilst more males complete suicide than women[8], the trend is reversed in autistic individuals[1]. However in both autistic individuals[2] and the general population[66], females report greater suicidal ideation. One potential mechanism that may explain the moderating effect of sex on SSBI is camouflaging, where autistic individuals may adopt methods to conceal their social difficulties. More autistic women than men are thought to camouflage[67], and emerging evidence suggests that this leads to elevated depression, anxiety, and SSBI[9,68–70]. Both the interaction terms represent a diathesis-stress model[30] where a dispositional vulnerability (polygenic scores for autism) interacts with a stress (childhood trauma or factors associated with female sex such as camouflaging) to contribute to higher SSBI.

Finally, we also investigated variables mediating the association between polygenic scores for autism and SSBI. We identified that depressive symptoms, quality of social relationships (friendship satisfaction and family relationship satisfaction) and frequency of social relationships significantly mediate a small proportion of the effect. Whilst these provide a model for further investigation, we caution against further interpretation of these results. Mediators must typically have temporal precedence over the dependent variable, which we were unable to clearly establish in this study. Well defined longitudinal studies in relatively large cohorts are needed to clearly establish causal mediation and our results prioritize variables for these investigations.

We acknowledge that this study has a few limitations that must be borne in mind when interpreting the results. First, the UK Biobank has a volunteer bias as participants are likely to be healthier, better educated and more affluent than the general population[71]. As such, the rates of self-harm behaviour and childhood trauma may be lower than that in the general population. Second, whilst the GWAS used to construct polygenic scores for autism

is the largest to date, it still captures only 2.5% of the total variance compared to a SNP heritability of 11%[43]. Third, childhood trauma has been measured retrospectively and this could introduce bias in the measurement of childhood trauma. Using a dataset that better reflects the general population and increasing the variance explained by autism polygenic scores may improve the estimates obtained from this study.

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Table 1: Effect of polygenic scores for autism across the three primary phenotypes

Beta	SE	Z	P	P-threshold	R^2 (%)	Phenotype
2.86E-02	2.88E-03	9.931	<2.2E-16	1	0.0811	Childhood trauma
2.85E-02	2.88E-03	9.883	<2.2E-16	0.75	0.0803	Childhood trauma
2.87E-02	2.88E-03	9.951	<2.2E-16	0.5	0.0814	Childhood trauma
2.89E-02	2.88E-03	10.029	<2.2E-16	0.25	0.0827	Childhood trauma
2.71E-02	2.88E-03	9.395	<2.2E-16	0.1	0.0725	Childhood trauma
2.27E-02	2.88E-03	7.877	3.39E-15	0.01	0.0507	Childhood trauma
1.31E-02	2.88E-03	4.531	5.89E-06	0.001	0.0162	Childhood trauma
3.08E-02	2.87E-03	10.73	<2.2E-16	1	0.094	Self-harm ideation
3.10E-02	2.87E-03	10.809	<2.2E-16	0.75	0.095	Self-harm ideation
3.14E-02	2.87E-03	10.962	<2.2E-16	0.5	0.098	Self-harm ideation
2.91E-02	2.87E-03	10.152	<2.2E-16	0.25	0.084	Self-harm ideation
2.76E-02	2.87E-03	9.632	<2.2E-16	0.1	0.075	Self-harm ideation
2.57E-02	2.87E-03	8.968	<2.2E-16	0.01	0.065	Self-harm ideation
1.51E-02	2.86E-03	5.267	1.39E-07	0.001	0.022	Self-harm ideation
3.37E-02	2.87E-03	11.752	<2.2E-16	1	0.112	Self-harm score
3.39E-02	2.87E-03	11.824	<2.2E-16	0.75	0.113	Self-harm score
3.43E-02	2.87E-03	11.975	<2.2E-16	0.5	0.116	Self-harm score
3.26E-02	2.87E-03	11.369	<2.2E-16	0.25	0.105	Self-harm score
3.07E-02	2.87E-03	10.703	<2.2E-16	0.1	0.093	Self-harm score
2.72E-02	2.87E-03	9.49	<2.2E-16	0.01	0.073	Self-harm score
1.73E-02	2.87E-03	6.03	1.64E-09	0.001	0.029	Self-harm score

This table provides the result of the polygenic score analyses for the three primary phenotypes at various 7 different P-value thresholds. For each analysis we report the regression coefficient (Beta) and the accompanying standard errors (SE), Z-score (Z) and P-value of the Z-score (P). Variance explained (R^2) is provided in percentages.

Table 2: Effect of polygenic scores on individual phenotypic items

Item	Beta	SE	Z	P	P-threshold	R^2 (%)	Category
Felt loved as child	3.01E-02	2.89E-03	10.41	<2.2E-16	0.25	0.089	Childhood trauma
Sexually molested as a child	7.27E-03	2.88E-03	2.52	0.011	0.25	0.004	Childhood trauma
Physically abused as a child	2.43E-02	2.88E-03	8.44	<2.2E-16	0.25	0.058	Childhood trauma
Felt hated as a child	2.57E-02	2.87E-03	8.94	<2.2E-16	0.25	0.065	Childhood trauma
Taken to the doctor as a child	1.97E-04	2.88E-03	0.06	0.945	0.25	-0.0008	Childhood trauma
Ever Thought life not worth living	3.09E-02	2.86E-03	10.79	<2.2E-16	0.5	0.146	SSBI
Ever contemplated self-harm	2.97E-02	2.86E-03	10.40	<2.2E-16	0.5	0.135	SSBI
Ever attempted self-harm	2.45E-02	2.88E-03	8.50	<2.2E-16	0.5	0.093	SSBI
Recent thoughts of suicide and self-harm	6.89E-03	2.90E-03	2.38	0.017	0.5	0.007	SSBI

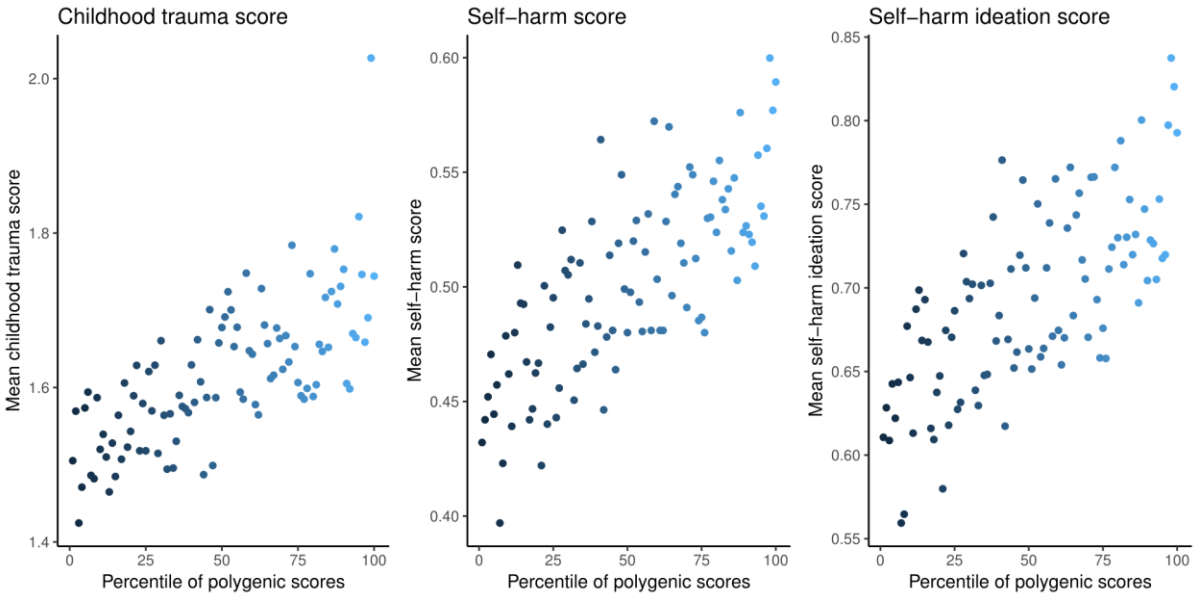
This table provides the result of the polygenic score analyses for the individual items at specific P-value thresholds. For each analysis we report the regression coefficient (Beta) and the accompanying standard errors (SE), Z-score (Z) and P-value of the Z-score (P-value). Variance explained (R^2) is provided in percentages. Please note, the variance explained for SSBI items is measured using Nagelkerke's pseudo-R^2 given that these were binary phenotypes.

Table 3: Interaction effects

Beta	SE	Z	P	P-threshold	Variable	Category
4.01E-02	3.88E-03	10.34	<2.2E-16	0.25	PGS	Childhood Truama Score
-7.14E-02	5.82E-03	-12.26	<2.2E-16	0.25	Sex (Male)	Childhood Truama Score
-2.50E-02	5.80E-03	-4.31	1.59E-05	0.25	PGS:Sex (Male)	Childhood Truama Score
3.77E-02	3.86E-03	9.77	<2.2E-16	0.5	PGS	Self-harm ideation score
-1.22E-01	5.78E-03	-21.11	<2.2E-16	0.5	Sex (Male)	Self-harm ideation score
-1.40E-02	5.76E-03	-2.43	0.014	0.5	PGS:Sex (Male)	Self-harm ideation score
4.13E-02	3.86E-03	10.70	<2.2E-16	0.5	PGS	Self-harm score
-1.49E-01	5.78E-03	-25.81	<2.2E-16	0.5	Sex (Male)	Self-harm score
-1.56E-02	5.76E-03	-2.70	0.006	0.5	PGS:Sex (Male)	Self-harm score
2.31E-02	2.75E-03	8.42	<2.2E-16	0.5	PGS	Self-harm ideation score
2.87E-01	2.77E-03	103.43	<2.2E-16	0.5	Childtrauma	Self-harm ideation score
6.74E-03	2.76E-03	2.44	0.014	0.5	PGS:Childtrauma	Self-harm ideation score
2.60E-02	2.75E-03	9.455	<2.2E-16	0.5	PGS	Self-harm score
2.84E-01	2.78E-03	102.36	<2.2E-16	0.5	Childtrauma	Self-harm score
7.24E-03	2.76E-03	2.61	0.008	0.5	PGS:Childtrauma	Self-harm score

This table provides the results of the interaction effect for the three primary phenotypes. For all three phenotypes, we tested the interaction between polygenic scores and sex. Additionally, for the two SSBI phenotypes, we tested the interaction between polygenic scores and childhood trauma. For each interaction, we report the two main effects and the interaction effect. For each analysis we report the regression coefficient (Beta) and the accompanying standard errors (SE), Z-score (Z) and P-value of the Z-score (P).

Figure 1: Scores on childhood trauma and SSBI based on centiles of polygenic scores



This figure provides the scores of three primary phenotypes against the percentile of polygenic scores after the cohort was divided into 100 groups based on polygenic scores. Each dot in the plot represents an average phenotypic score for that group.