Supplementary Material

Autism polygenic scores are associated with trauma and self-harm

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Section 1: Brief literature support for mediators used in the analyses

1.1 Depression/depressive symptoms and Anxiety/anxiety symptoms

A history of psychiatric illness is the primary risk factor for SSBI, with the effect size being larger than any of the other socio-demographic factors. There has been consistent support for this in nation-wide studies[1,2]. Specifically, in autism, one study has demonstrated that a history of psychiatric illness is, in line with the general population, the single biggest risk factor for suicide[3]. A handful of studies have provided greater resolution by investigating specific risk factors for suicide among psychiatric conditions. A meta-analysis of autopsy reports of more than 3,000 individuals who died by suicide identified that affective disorders including depressive disorders were the most common diagnostic category among individuals who had died by suicide (diagnosed in 43.2% of individuals who had died by suicide)[4]. These results have been supported by other meta-analyses and systematic reviews[5,6]. Longitudinal studies of suicidal ideation have suggested that depressive symptoms/depression were the best predictors of suicidal ideation[7,8]. One study has demonstrated that depressive symptoms mediate the risk between autistic traits and SSBI[9]. In clinical and cross-sectional studies there is some support for anxiety as a risk factor for SSBI[10–12]. This is significant even after controlling for a number of co-morbid conditions[13].This has also been supported by longitudinal studies that have controlled for other co-morbid conditions[11,14]. Both anxiety and depression are elevated in autistic individuals[15,16]. Compared to the general populations, autistic individuals are 4-times more likely to experience depression[17]. Similarly, approximately 40% of children and adolescents with autism are have a co-morbid anxiety disorder[18].

1.2 Social factors

Loneliness and social isolation have been strongly linked to SSBI. Two prominent models link positive social support to reduced SSBI. The buffering hypothesis suggests positive social supports buffers the deleterious effect of stressors. In contrast, the main effects model suggests that being better integrated in a social network will increase healthy behaviours through conformity to social norms[19]. In a meta-analysis of more than 300,000 participants, Holt-Lunstad and colleagues[19], participants with stronger social relationships had a 50% percent increase in survival. Several studies have demonstrated that social isolation and reduced social relationship satisfaction are risk factors for SSBI[20–22]. Specifically, the availability of nation-wide registers in Scandinavian countries allows for large-scale interrogation of risk factors for SSBI limiting potential confounding factors in other cohort designs such as healthy volunteer bias. In a nation-wide longitudinal study from Denmark, being single was the second biggest risk factor for suicide after psychiatric illness[1]. These results were replicated in a nation-wide study in Sweden: the unadjusted Hazards Ratio was 1.59 for unmarried women and 1.75 for unmarried men[2]. Autistic individuals, on average, tend to report increased loneliness and feeling socially excluded[23], and have difficulties in forming and maintaining friendships[24,25]. In one study, autistic traits were positively correlated with increased loneliness and perceived social support[26]. The same study identified that the effects of autistic traits on depression are partly mediated by loneliness and satisfaction with social support[26]. In this study we investigate two metrics of social support – family relationship satisfaction and friendship satisfaction. We additionally also investigate two quantitative

measures of social support – Number of confiding relationships and frequency of friendship/family visits.

1.4 Job satisfaction

A few studies have investigated the role of job satisfaction/employment in SSBI. In a nation-wide register study from Denmark, unemployment modestly increased the risk for suicide ($1.14 < OR < 1.24$), with the risk increasing as the percentage of time being unemployed increased[1]. A smaller study in Sweden reported higher OR for unemployment as a risk factor for suicide ($1.93 < OR < 3.86$)[27]. In a larger, nation-wide study in Sweden, adjusted Hazard Ratios for suicide were 1.97 for unemployed men and 1.66 for unemployed women[2]. Unemployment is a significant issue in the autism community. According to a survey conducted by the National Autistic Society in the UK, only 16% of autistic adults are in full time employment , and less than a third are employed in some paid work (See: https://www.autism.org.uk/get-involved/media-centre/news/2016-10-27-employment-gap.aspx). A cross-sectional study in Germany identified that late-diagnosed autistic adults were disadvantaged at the job market[28].

1. Qin P, Agerbo E, Mortensen PB. Suicide Risk in Relation to Socioeconomic, Demographic, Psychiatric, and Familial Factors: A National Register–Based Study of All Suicides in Denmark, 1981–1997. *Am J Psychiatry*. 2003;160(4):765-772. doi:10.1176/appi.ajp.160.4.765

2. Crump C, Sundquist K, Sundquist J, Winkleby MA. Sociodemographic, psychiatric and somatic risk factors for suicide: a Swedish national cohort study. *Psychol Med*. 2014;44(02):279-289. doi:10.1017/S0033291713000810

3. Hirvikoski T, Mittendorfer-Rutz E, Boman M, Larsson H, Lichtenstein P, Bölte S. Premature mortality in autism spectrum disorder. *Br J Psychiatry*. 2016;208(3):232-238. doi:10.1192/bjp.bp.114.160192

4. Arsenault-Lapierre G, Kim C, Turecki G. Psychiatric diagnoses in 3275 suicides: a meta-analysis. *BMC Psychiatry*. 2004;4(1):37. doi:10.1186/1471-244X-4-37

5. Cavanagh JTO, Carson AJ, Sharpe M, Lawrie SM. Psychological autopsy studies of suicide: a systematic review. *Psychol Med*. 2003;33(3):395-405..

6. Yoshimasu K, Kiyohara C, Miyashita K, Stress Research Group of the Japanese Society for Hygiene TSRG of the JS for. Suicidal risk factors and completed suicide: meta-analyses based on psychological autopsy studies. *Environ Health Prev Med*. 2008;13(5):243-256. doi:10.1007/s12199-008-0037-x

7. Garrison CZ, Addy CL, Jackson KL, McKeown RE, Waller JL. A longitudinal study

of suicidal ideation in young adolescents. *J Am Acad Child Adolesc Psychiatry*. 1991;30(4):597-603. doi:10.1097/00004583-199107000-00011

8. Prinstein MJ, Nock MK, Simon V, Aikins JW, Cheah CSL, Spirito A. Longitudinal trajectories and predictors of adolescent suicidal ideation and attempts following inpatient hospitalization. *J Consult Clin Psychol*. 2008;76(1):92-103. doi:10.1037/0022-006X.76.1.92

9. Culpin I, Mars B, Pearson RM, et al. Autistic traits and suicidal thoughts, plans, and self-Harm in late adolescence: population-based cohort study. *J Am Acad Child Adolesc Psychiatry*. 2018;57(5):313-320.e6. doi:10.1016/J.JAAC.2018.01.023

10. Karakoç Demirkaya S, Tutkunkardaş MD, Mukaddes NM. Assessment of suicidality in children and adolescents with diagnosis of high functioning autism spectrum disorder in a Turkish clinical sample. *Neuropsychiatr Dis Treat*. 2016;e 12:2921-2926. doi:10.2147/NDT.S118304

11. Sareen J, Cox BJ, Afifi TO, et al. Anxiety Disorders and Risk for Suicidal Ideation and Suicide Attempts. *Arch Gen Psychiatry*. 2005;62(11):1249. doi:10.1001/archpsyc.62.11.1249

12. Cox BJ, Direnfeld DM, Swinson RP, Norton GR. Suicidal ideation and suicide attempts in panic disorder and social phobia. *Am J Psychiatry*. 1994;151(6):882-887. doi:10.1176/ajp.151.6.882

13. Nepon J, Belik S-L, Bolton J, Sareen J. The relationship between anxiety disorders and suicide attempts: findings from the National Epidemiologic Survey on Alcohol and Related Conditions. *Depress Anxiety*. 2010;27(9):791-798. doi:10.1002/da.20674

14. Boden JM, Fergusson DM, John Horwood L. Anxiety disorders and suicidal behaviours in adolescence and young adulthood: findings from a longitudinal study. *Psychol Med*. 2007;37(03):431. doi:10.1017/S0033291706009147

15. Strang JF, Kenworthy L, Daniolos P, et al. Depression and anxiety symptoms in children and adolescents with autism spectrum disorders without intellectual disability. *Res Autism Spectr Disord*. 2012;6(1):406-412. doi:10.1016/j.rasd.2011.06.015

16. Kim JA, Szatmari P, Bryson SE, Streiner DL, Wilson FJ. The Prevalence of anxiety and mood problems among children with autism and Asperger Syndrome. *Autism*. 2000;4(2):117-132. doi:10.1177/1362361300004002002

17. Hudson CC, Hall L, Harkness KL. Prevalence of depressive disorders in individuals with autism spectrum disorder: a Meta-Analysis. *J Abnorm Child Psychol*. March

2018:1-11. doi:10.1007/s10802-018-0402-1

18. van Steensel FJA, Bögels SM, Perrin S. Anxiety disorders in children and adolescents with autistic spectrum disorders: a meta-analysis. *Clin Child Fam Psychol Rev*. 2011;14(3):302-317. doi:10.1007/s10567-011-0097-0

19. Holt-Lunstad J, Smith TB, Layton JB. Social relationships and mortality risk: A meta-analytic review. Brayne C, ed. *PLoS Med*. 2010;7(7):e1000316. doi:10.1371/journal.pmed.1000316

20. Santini ZI, Koyanagi A, Tyrovolas S, Haro JM. The association of relationship quality and social networks with depression, anxiety, and suicidal ideation among older married adults: Findings from a cross-sectional analysis of the Irish Longitudinal Study on Ageing (TILDA). *J Affect Disord*. 2015;179:134-141. doi:10.1016/j.jad.2015.03.015

21. Chang Q, Chan CH, Yip PSF. A meta-analytic review on social relationships and suicidal ideation among older adults. *Soc Sci Med*. 2017;191:65-76. doi:10.1016/j.socscimed.2017.09.003

22. Lasgaard M, Goossens L, Elklit A. Loneliness, depressive symptomatology, and suicide ideation in adolescence: Cross-Sectional and longitudinal analyses. *J Abnorm Child Psychol*. 2011;39(1):137-150. doi:10.1007/s10802-010-9442-x

23. Deckers A, Muris P, Roelofs J. Being on your own or feeling lonely? Loneliness and other social variables in youths with autism spectrum disorders. *Child Psychiatry Hum Dev*. 2017;48(5):828-839. doi:10.1007/s10578-016-0707-7

24. Kasari C, Locke J, Gulsrud A, Rotheram-Fuller E. Social networks and friendships at school: Comparing children with and without ASD. *J Autism Dev Disord*. 2011;41(5):533-544. doi:10.1007/s10803-010-1076-x

25. Rotheram-Fuller E, Kasari C, Chamberlain B, Locke J. Social involvement of children with autism spectrum disorders in elementary school classrooms. *J Child Psychol Psychiatry*. 2010;51(11):1227-1234. doi:10.1111/j.1469-7610.2010.02289.x

26. Hedley D, Uljarević M, Foley K-R, Richdale A, Trollor J. Risk and protective factors underlying depression and suicidal ideation in Autism Spectrum Disorder. *Depress Anxiety*. 2018;35(7):648-657. doi:10.1002/da.22759

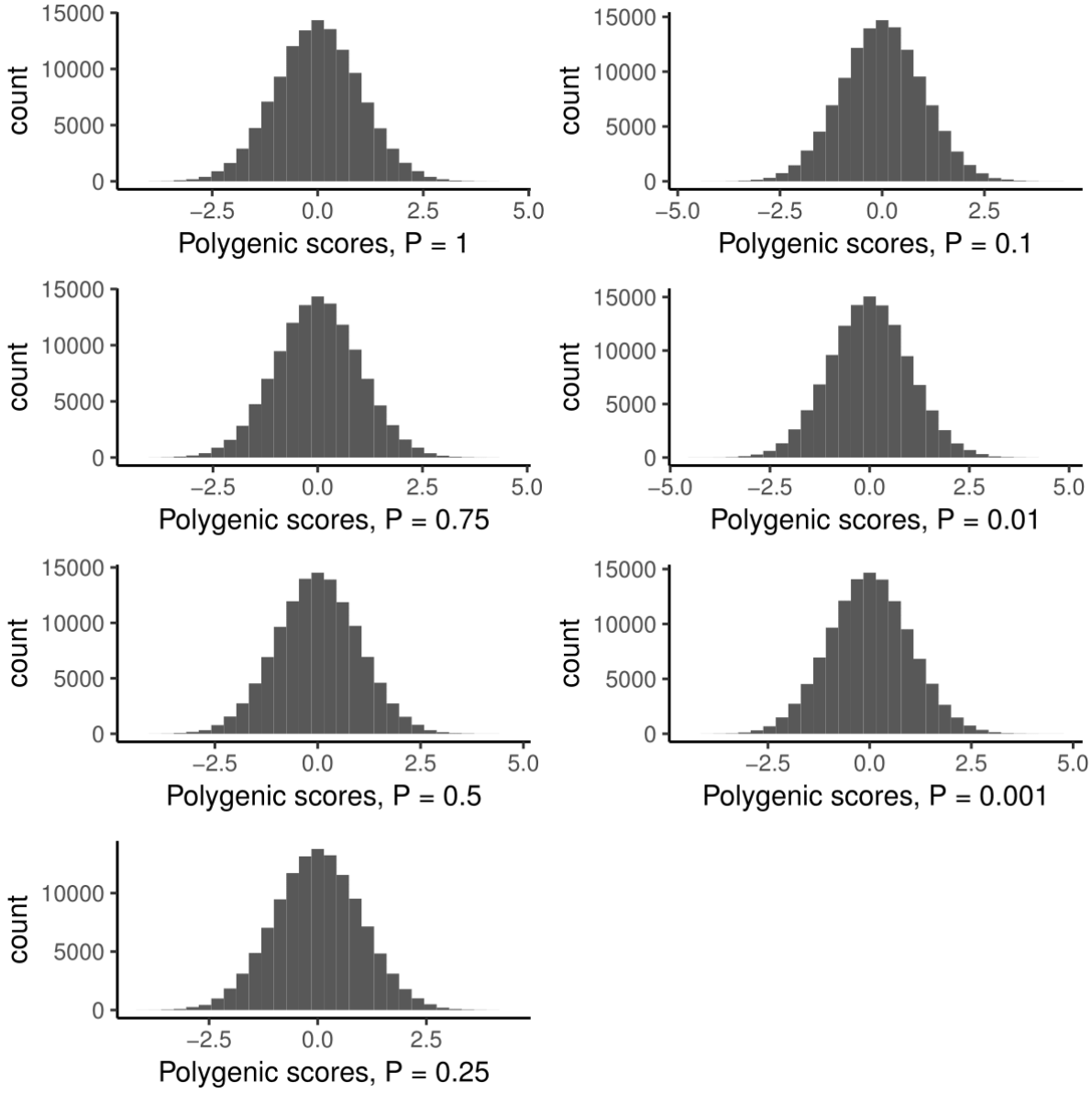
27. Johansson S-E, Sundquist J. Unemployment is an important risk factor for suicide in contemporary Sweden: an 11-year follow-up study of a cross-sectional sample of 37 789 people. *Public Health*. 1997;111(1):41-45. doi:10.1038/SJ.PH.1900317

28. Frank F, Jablotschkin M, Arthen T, et al. Education and employment status of adults with autism spectrum disorders in Germany - a cross-sectional-survey. *BMC Psychiatry*. 2018;18(1):75. doi:10.1186/s12888-018-1645-7

Section 2: Number of SNPs at each P-value threshold

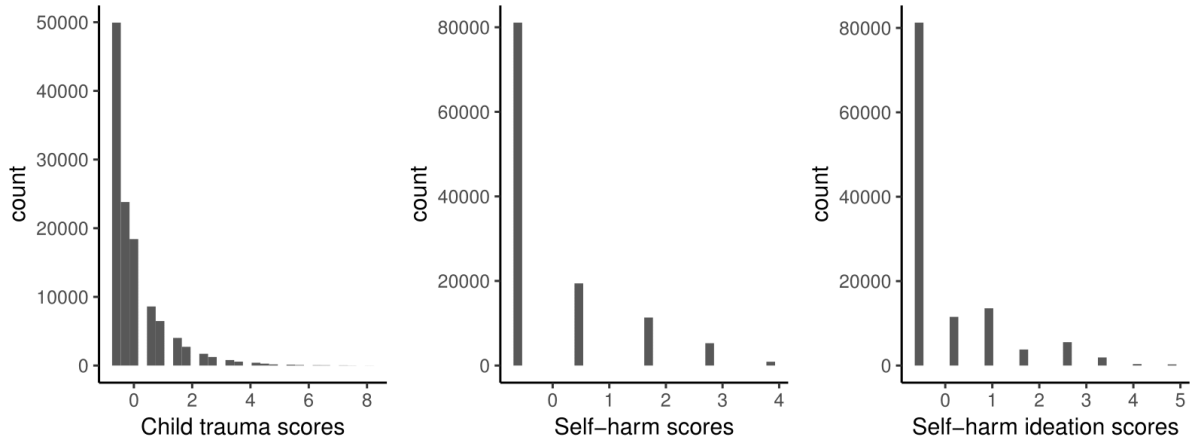
Threshold	N SNPs
0.001	1329
0.01	7958
0.1	48036
0.25	95196
0.5	153806
0.75	194514
1	220650

Supplementary Figure 1: Histograms of polygenic scores



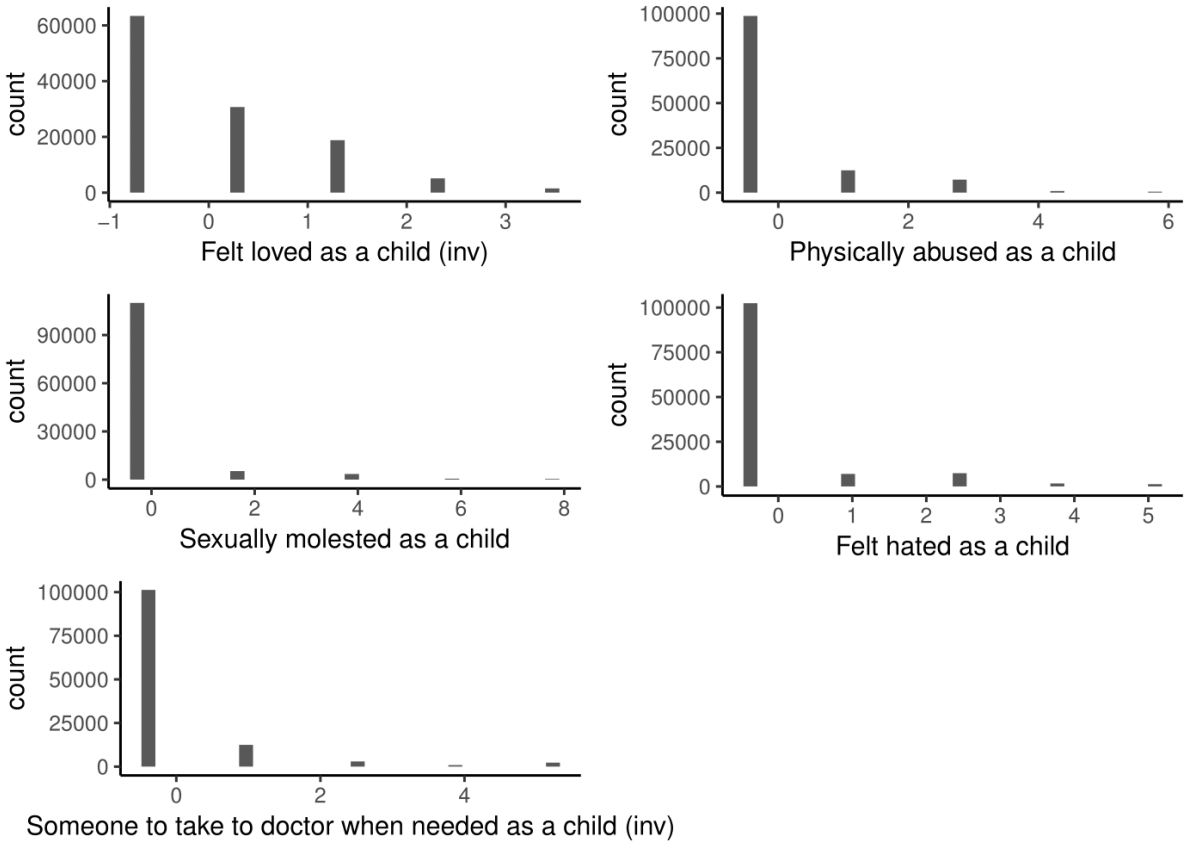
Frequency histogram of standardized autism polygenic scores in the UK Biobank.

Supplementary Figure 2: Histograms of the three primary variables included in the study



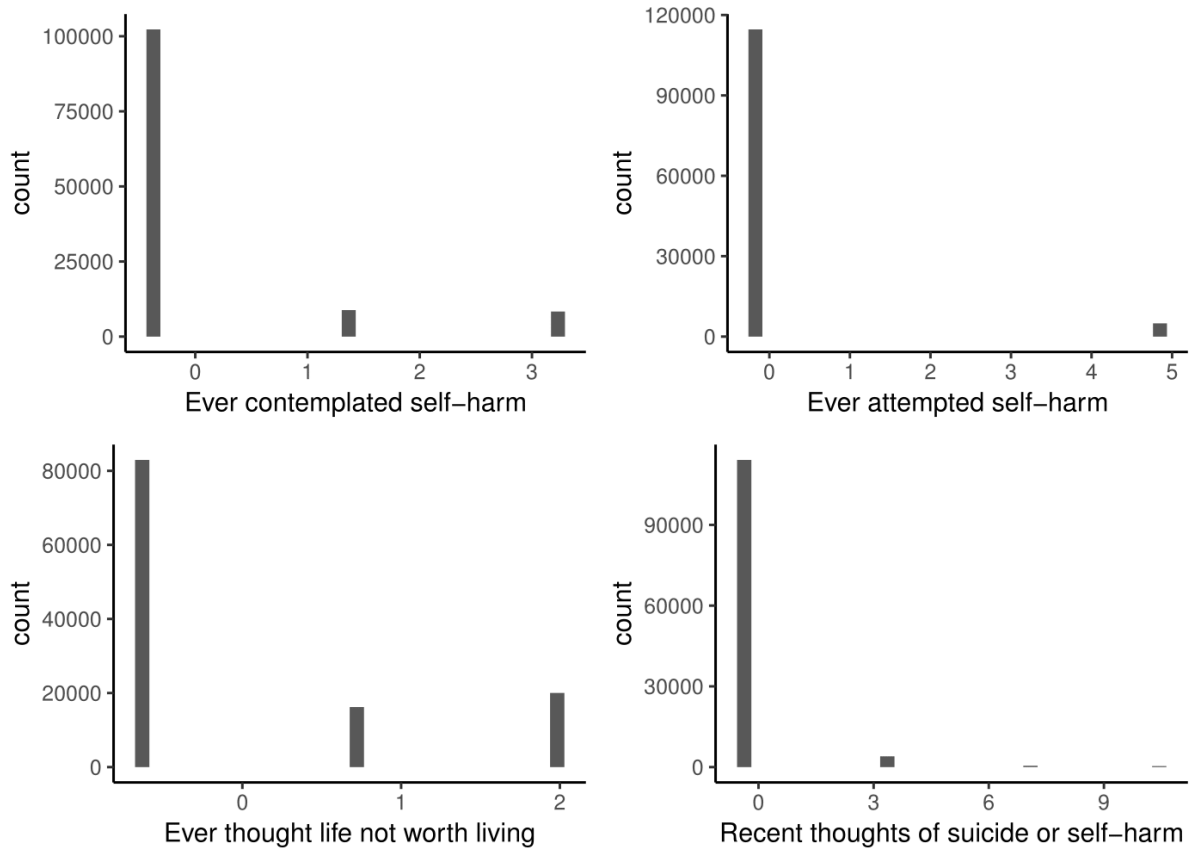
Frequency histogram of the three primary variables (standardized) included in the study.

Supplementary Figure 3: Histograms of individual level child trauma items



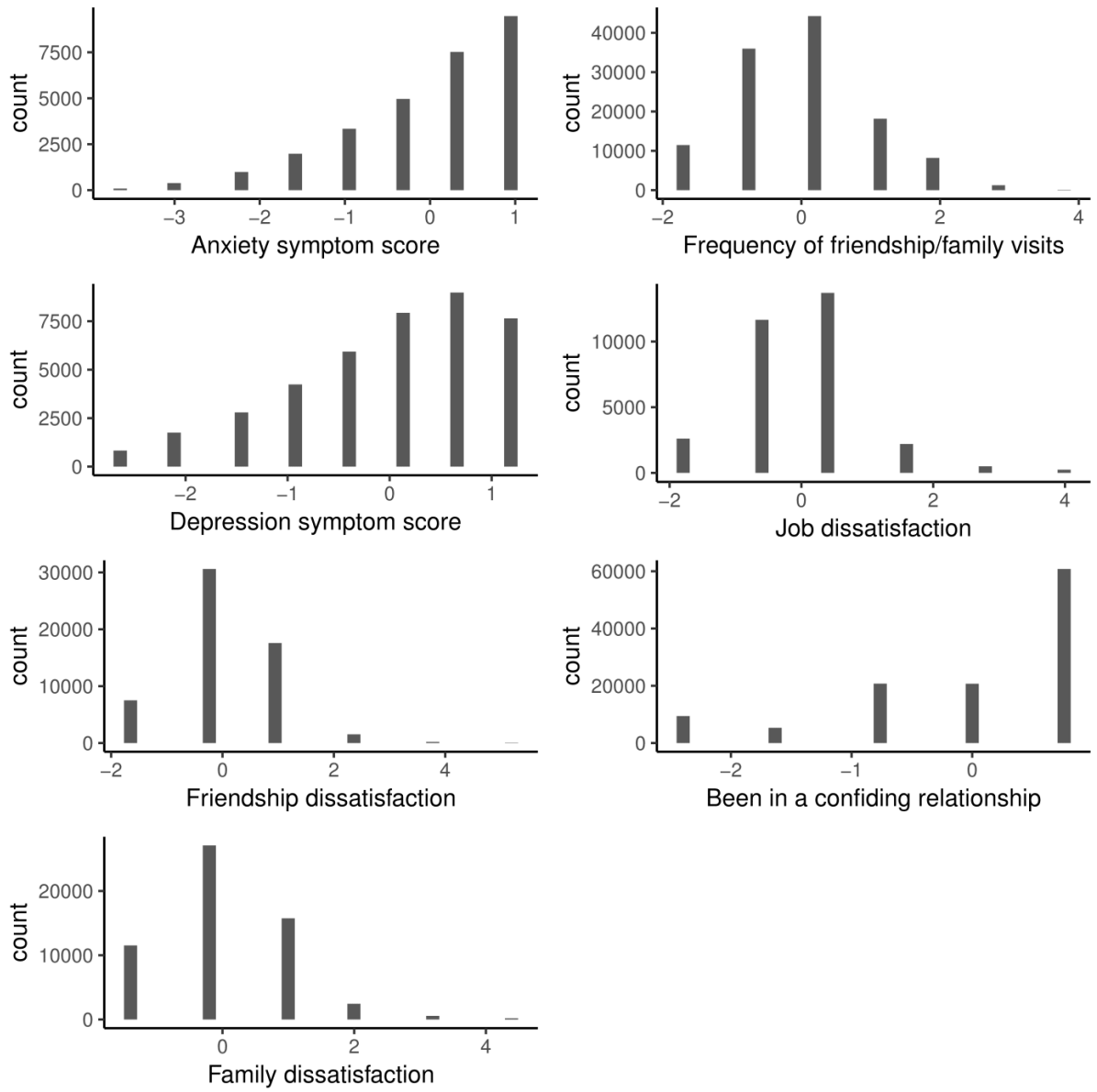
Frequency histogram of the five individual items included in the child trauma phenotype. All variables have been standardized.

Supplementary Figure 4: Histograms of individual level SSBI items



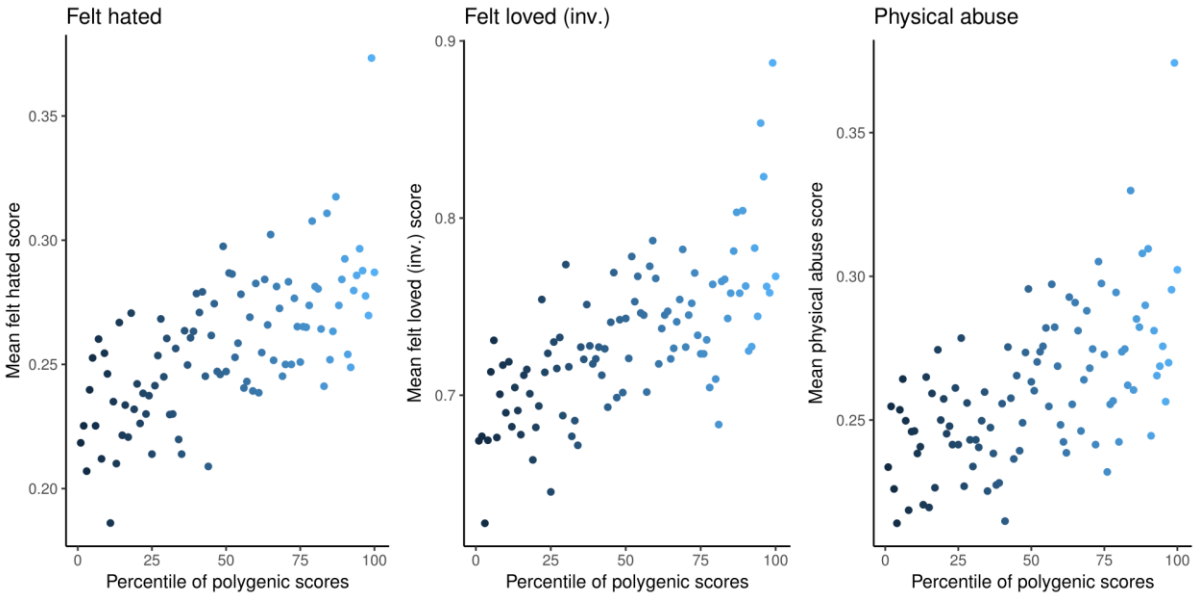
Frequency histogram of the five individual items included in the SSBI phenotypes. All variables have been standardized.

Supplementary Figure 5: Histograms of mediating variables



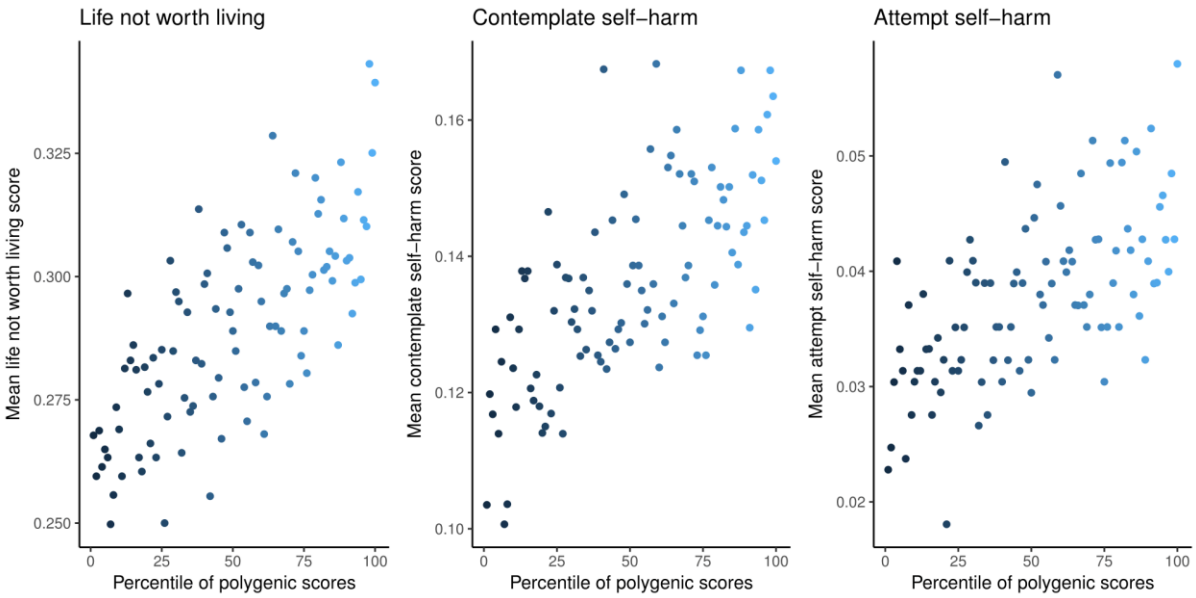
Frequency histogram of the seven mediating variables (standardized). .

Supplementary Figure 6: Scores on individual childhood trauma items based on centiles of polygenic scores



This figure provides the scores of three individual trauma items 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. Please note, 'Felt loved' is inverse scored.

Supplementary Figure 7: Scores on individual SSBI items based on centiles of polygenic scores



This figure provides the scores of three individual SSBI item 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.

Supplementary Table 1: Effect mediators on the SSBI phenotypes

Self-harm ideation				
Phenotype	Beta	SE	Z	P
Anxiety symptoms	3.34E-01	7.42E-03	44.954	< 2E-16
Depression symptoms	5.12E-01	5.70E-03	89.795	< 2E-16
Friendship dissatisfaction	1.38E-01	4.13E-03	33.317	< 2E-16
Family relationship dissatisfaction	1.63E-01	4.11E-03	39.541	< 2E-16
Job dissatisfaction	1.36E-01	5.82E-03	23.312	< 2E-16
Frequency of friendship/family visit	5.01E-02	2.92E-03	17.142	< 2E-16
Confiding relationship	-1.11E-01	2.89E-03	-38.216	< 2E-16
Self-harm				
Phenotype	Beta	SE	Z	P
Anxiety symptoms	3.10E-01	7.17E-03	43.159	< 2E-16
Depression symptoms	4.97E-01	5.57E-03	89.267	< 2E-16
Friendship dissatisfaction	1.29E-01	4.13E-03	31.101	< 2E-16
Family relationship dissatisfaction	1.56E-01	4.11E-03	37.886	< 2E-16
Job dissatisfaction	1.19E-01	5.82E-03	20.428	< 2E-16
Frequency of friendship/family visit	4.74E-02	2.92E-03	16.228	< 2E-16
Confiding relationship	-1.08E-01	2.89E-03	-37.255	< 2E-16

Supplementary Table 2: Effect of polygenic scores on mediators

Phenotype	Beta	SE	Z	P
Anxiety symptoms	1.21E-02	5.85E-03	2.07	0.037
Depression symptoms	1.77E-02	4.82E-03	3.67	2.34E-04
Friendship dissatisfaction	1.43E-02	4.16E-03	3.43	6.03E-04
Family relationship dissatisfaction	1.99E-02	4.18E-03	4.75	2.00E-06
Frequency of friendship/family visit	1.34E-02	2.84E-03	4.71	2.43E-06
Job dissatisfaction	1.23E-02	5.66E-03	2.16	0.030
Confiding relationship	-5.63E-03	0.002924	-1.92	0.054

Supplementary Table 3: Mediation effects

	Depression symptoms				
	Estimate	95% CI Lower	95% CI Upper	P	Phenotype
ACME	0.00891	0.00409	0.01	< 2E-16	Self-harm ideation
ADE	0.0302	0.0199	0.04	< 2E-16	Self-harm ideation
Total Effect	0.03911	0.02708	0.05	< 2E-16	Self-harm ideation
Prop. Mediated	0.22628	0.12082	0.34	< 2E-16	Self-harm ideation
	Estimate	95% CI Lower	95% CI Upper	P	
ACME	0.00873	0.00415	0.01	< 2E-16	Self-harm
ADE	0.03256	0.02177	0.04	< 2E-16	Self-harm
Total Effect	0.04129	0.02963	0.05	< 2E-16	Self-harm
Prop. Mediated	0.21098	0.10659	0.32	< 2E-16	Self-harm
	Family dissatisfaction				
	Estimate	95% CI Lower	95% CI Upper	P	Phenotype
ACME	0.00304	0.00165	0	< 2E-16	Self-harm ideation
ADE	0.02928	0.0214	0.04	< 2E-16	Self-harm ideation
Total Effect	0.03231	0.02403	0.04	< 2E-16	Self-harm ideation
Prop. Mediated	0.09312	0.05244	0.14	< 2E-16	Self-harm ideation
	Estimate	95% CI Lower	95% CI Upper	P	
ACME	0.00298	0.00169	0	< 2E-16	Self-harm
ADE	0.03206	0.0246	0.04	< 2E-16	Self-harm
Total Effect	0.03504	0.02735	0.04	< 2E-16	Self-harm
Prop. Mediated	0.08549	0.04772	0.13	< 2E-16	Self-harm
	Friendship dissatisfaction				
	Estimate	95% CI Lower	95% CI Upper	P	Phenotype
ACME	0.001824	0.000648	0	< 2E-16	Self-harm ideation
ADE	0.030371	0.022244	0.04	< 2E-16	Self-harm ideation
Total Effect	0.032195	0.023946	0.04	< 2E-16	Self-harm ideation
Prop. Mediated	0.056995	0.019593	0.1	< 2E-16	Self-harm ideation
	Estimate	95% CI Lower	95% CI Upper	P	
ACME	0.001726	0.000589	0	0.004	Self-harm
ADE	0.033207	0.024808	0.04	< 2E-16	Self-harm
Total Effect	0.034933	0.026428	0.04	< 2E-16	Self-harm
Prop. Mediated	0.049687	0.017509	0.08	0.004	Self-harm
	Frequency of friendship/family visits				
	Estimate	95% CI Lower	95% CI Upper	P	Phenotype
ACME	0.000671	0.000393	0	< 2E-16	Self-harm ideation
ADE	0.03086	0.025251	0.04	< 2E-16	Self-harm ideation
Total Effect	0.031532	0.025898	0.04	< 2E-16	Self-harm ideation
Prop. Mediated	0.021101	0.012103	0.03	< 2E-16	Self-harm ideation
	Estimate	95% CI Lower	95% CI Upper	P	
ACME	0.000631	0.000359	0	< 2E-16	Self-harm
ADE	0.033841	0.028085	0.04	< 2E-16	Self-harm
Total Effect	0.034471	0.028772	0.04	< 2E-16	Self-harm
Prop. Mediated	0.018231	0.010644	0.03	< 2E-16	Self-harm