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Childhood Adoption and Mental Health in Adulthood: The Role of Gene-Environment Correlations and Interactions in the UK Biobank

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ABSTRACT

BACKGROUND: Being adopted early in life, an indicator of exposure to early-life adversity, has been consistently associated with poor mental health outcomes in adulthood. Such associations have largely been attributed to stressful environments, e.g., exposure to trauma, abuse, or neglect. However, mental health is substantially heritable, and genetic influences may contribute to the exposure to childhood adversity, resulting in potential genetic confounding of such associations.

METHODS: Here, we explored associations between childhood adoption and mental health–related outcomes in midlife in 243,797 UK Biobank participants (*n* adopted = 3151). We used linkage disequilibrium score regression and polygenic risk scores for depressive symptoms, schizophrenia, neuroticism, and subjective well-being to address potential genetic confounding (gene-environment correlations) and gene-environment interactions. As outcomes, we explored depressive symptoms, bipolar disorder, neuroticism, loneliness, and mental health–related socioeconomic and psychosocial measures in adoptees compared with nonadopted participants.

RESULTS: Adoptees were slightly worse off on almost all mental, socioeconomic, and psychosocial measures. Each standard deviation increase in polygenic risk for depressive symptoms, schizophrenia, and neuroticism was associated with 6%, 5%, and 6% increase in the odds of being adopted, respectively. Significant genetic correlations between adoption status and depressive symptoms, major depression, and schizophrenia were observed. No evidence for gene-environment interaction between genetic risk and adoption on mental health was found.

CONCLUSIONS: The association between childhood adoption and mental health cannot fully be attributed to stressful environments but is partly explained by differences in genetic risk between adoptees and those who have not been adopted (i.e., gene-environment correlation).

Keywords: Childhood adversity, Depressive symptoms, Gene-environment interplay, Neuroticism, Polygenic risk scores, Schizophrenia

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Childhood adversity has been consistently associated with poor mental health in adulthood (1). Being adopted early in life is an indicator of exposure to early-life adversity, as adoptees likely have been exposed to more life stressors preadoption, including worse prenatal (e.g., maternal substance abuse, stress, health problems) and postnatal (e.g., lower socioeconomic status, neglect, abuse) environments, and to the likely stressful adoption process itself. Individuals adopted in early life are at increased risk for developmental and neurobiological difficulties and mental health problems in childhood (2), the latter persisting well into adulthood (3). While effect sizes are small and findings somewhat mixed, increased risks have been reported relatively consistently for depression, anxiety, personality disorders, neuroticism, behavioral disorders, and possibly substance (ab)use (3). Such associations have largely been attributed to early-life preadoption adversity (i.e., environmental factors).

However, genetic factors may also contribute to the higher risk of mental disorders among adoptees (4). Mental health problems, such as depression, anxiety, and schizophrenia, are all moderately heritable (5–8). Such problems may be prevalent in the biological parents of adoptees, possibly contributing to the adoption in the first place. Owing to their heritability, these problems could also result in increased genetic risk for mental health problems in the adoptees. Thus, the overrepresentation of these disorders in adoptees could partly be explained by increased genetic risk rather than solely being due to preadoptive and adoption-related stress. This is an example of passive gene-environment correlation (rGE), in which an individual's genetic predisposition (for mental health problems) is correlated with the childhood environment she or he is born into (increased adversity). Another possible scenario could be gene-by-environment (G×E) interaction, in which genetic

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vulnerability moderates the effect of adversity (i.e., the environment) on mental health as proposed by the diathesis-stress model (9).

Little is known about such interplay between genetic risk for mental health problems (nature) and childhood adversity (nurture). Candidate G×E research exploring stress and mental health has shown mixed results (10–12), partly owing to low power, lack of confirmed main effects, and poorly measured environment (10,13–15). A recent, and by far the largest, candidate-gene study could neither replicate previously reported interactions nor find any new interactions between candidate genes for depression and (childhood) adversity and concluded that previous findings would likely be false positives (15). However, a confounding factor is recall bias of childhood trauma when assessed self-reported, retrospectively, and simultaneously with mental health. Types of bias include effects of infantile amnesia (poor memories of events occurring during infancy), low ability to interpret family situations (e.g., socioeconomic hardship), and mental health at time of assessment, all affecting reliable recall of early stressful life events (16). In line with this, a recent systematic review and meta-analysis has shown that different groups of individuals are identified based on prospective compared with retrospective measures of childhood maltreatment, suggesting little agreement between the two, emphasizing the importance of a valid and objective indicator of early-life stress (17).

Polygenic risk scores (PRSs)—a measure of the combined impact of all genotyped single nucleotide polymorphisms (18)—may be preferable to candidate genes to test for G×E effects (19). To our knowledge, only 5 studies have investigated G×E interaction between childhood adversity and genetic risk on mental health using PRSs, showing very mixed results (20–24). In all but one study, early-life adversity was self-reported and assessed simultaneously with mental health, making the assessment subjective and prone to hindsight and recall bias, resulting in low validity and substantial measurement error (16).

The aims of the present study were to 1) explore associations between childhood adoption (i.e., early adversity) and mental health–related outcomes in midlife in a large, population-based, genetically informative sample of more than 240,000 individuals; 2) assess rGE by comparing genetic risk for mental health—as indicated by PRSs for depressive symptoms, schizophrenia, neuroticism, and subjective well-being—between adopted and nonadopted participants, as well as investigate possible genetic correlations between childhood adoption and mental health–related phenotypes using genome-wide association study (GWAS) summary statistics; and 3) explore potential G×E interactions between childhood adoption and genetic risk on mental health–related outcomes.

METHODS AND MATERIALS

Sample

The UK Biobank (UKB) is a large database of approximately 500,000 individuals 39 to 73 years of age (25). After exclusions (Figure 1), the final sample size was 243,480 (54.4% women), of which 3151 individuals had been adopted in childhood. Genetic information was based on phase 2 imputed genotypes (see Supplement). The current study was conducted under UKB application 22224 and was approved by the Regional Ethical Review Board, Stockholm (Dnr: 2017/2348-32).

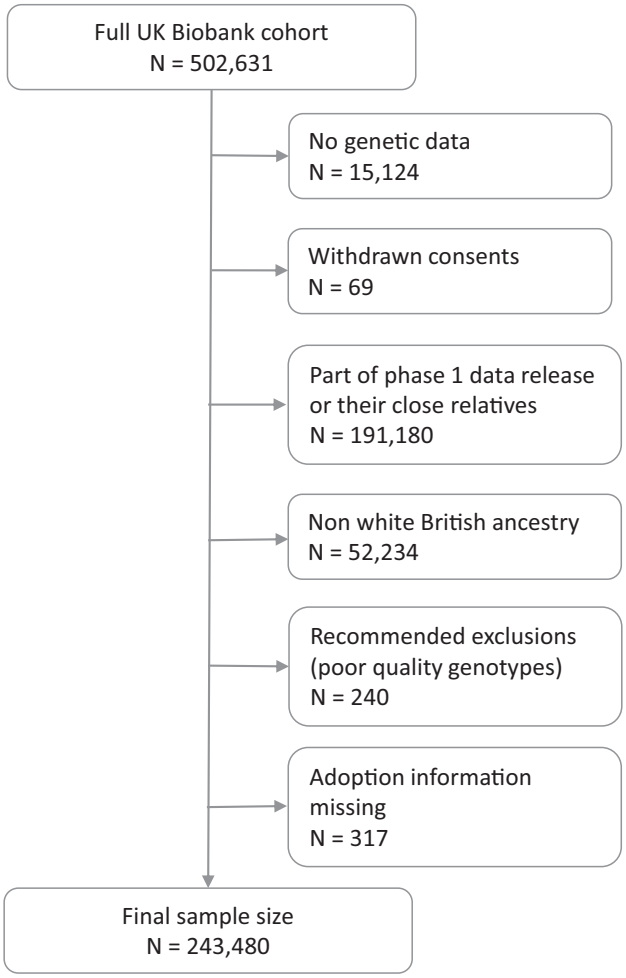

Figure 1. Flowchart indicating sample exclusions.

Phenotype Assessment

The question “Were you adopted as a child?” was used as an objective indicator of exposure to early childhood adversity. A total of 3151 individuals had been adopted in childhood. Participants who responded "Do not know" or "Prefer not to answer" to this question were removed from the analysis (n = 317).

Mental Health. Depressive symptoms were measured based on two self-reported items tapping into depressed mood ("How often have you felt down, depressed or hopeless?") and disinterest ("How often have you had little interest or pleasure in doing things?") in the past 2 weeks, as done in previous studies (26,27). The items were rated on 4-point Likert-type scale ranging from 0 (not at all) to 3 (nearly every day) and summed to a scale of 0 to 6.

Probable lifetime major depression status was based on the UKB item 20126, which contains information on major depression (probable single episode, probable recurrent severe major depression, and probable recurrent moderate major depression) and bipolar (type I and type II) status based on self-report items on the symptoms and duration of respective disorders (28). For the current analysis, all major depression subtypes were combined to indicate any probable lifetime major depression, and all bipolar cases were set to missing.

Whether the individual had ever seen a doctor for nerves, anxiety, tension, or depression was based on a single item, "Have you ever seen a general practitioner (GP) for nerves, anxiety, tension or depression?"

Whether the individual had ever seen a psychiatrist for nerves, anxiety, tension, or depression was based on a single item, "Have you ever seen a psychiatrist for nerves, anxiety, tension or depression?"

Probable bipolar disorder status was based on self-report and defined as having either of the two types of probable lifetime bipolar disorders (type I [mania] and type II [hypomania]) (28).

Neuroticism was measured with a 12-item Eysenck Personality Questionnaire Revised–Short Form (29). The number of positive answers (yes [1] vs. no [0]) were summed.

Feelings of loneliness were assessed with a single item, “Do you often feel lonely?” from the Eysenck Personality Questionnaire Revised–Short Form (29).

Psychosocial Factors. Subjective well-being (life satisfaction index) was based on 5 items capturing various aspects of life satisfaction—“In general, how satisfied are you with: (1)…the work that you do?; (2)…your health?; (3)…your family relationships?; (4)…your friendships?; (5)…your financial situation?"—and assessed on 6-point Likert-type scales ranging from 1 (extremely satisfied) to 6 (extremely unsatisfied). Items were reversed, with a higher score indicating more satisfaction, and then summed.

Happiness was assessed with a single item, "In general how happy are you?" with response options on a 6-point Likert-type scale ranging from 1 (extremely happy) to 6 (extremely unhappy). As most participants indicated being happy, the score was dichotomized, with moderately to extremely happy coded as 1 and moderately to extremely unhappy coded as 0.

For documenting recent stressful life events (SLEs), participants were asked whether they had experienced any of the following events in the past 2 years: 1) serious illness, injury, or assault to yourself; 2) serious illness, injury, or assault of a close relative; 3) death of a close relative; 4) death of a spouse/partner; 5) marital separation/divorce; or 6) financial difficulties. Reported events were summed (range, 0–6) and then 3 categories were created based on the number of events reported: 0, 1, and ≥2 events (see Supplemental Table S1 for the full SLE score).

Socioeconomic Factors and Health Behavior. Education was coded dichotomously indicating educational attainment above the compulsory age of 16 years: compulsory was coded as 0 and above compulsory was coded as 1.

Household income was assessed with the item "What is the average total income before tax received by your household?" Responses were given on a 5-point scale ranging from 0 (less than £18,000) to 4 (greater than £100,000).

Smoking status included 3 categories: never smoked, previous smoker, and current smoker.

Polygenic Risk Scores

Four PRSs were calculated using GWAS summary statistics for depressive symptoms, neuroticism, subjective well-being, and schizophrenia (26,30). As the discovery and target samples were partly overlapping, i.e., the UKB interim release genetic data were used in some discovery samples (26), all individuals in the interim release and their relatives up to the third degree were removed from the target sample (*n* removed = 191,092). Overlap between the discovery and target samples would violate the independent target sample requirement. PRSs for each trait were computed under 7 *p*-value thresholds ranging from 5×10^{-8} to .5 (–score command in Plink 2.0 alpha, https://www.cog-genomics.org/plink/2.0/) and standardized for further analysis. For each trait, the *p*-value threshold with the highest variance explained for the corresponding trait was selected for subsequent analyses (Figure 2). Owing to the large genetic overlap between bipolar disorder and schizophrenia (31,32), probable bipolar disorder status was used as mental health indicator and to validate the PRS for schizophrenia because of the low prevalence of schizophrenia (0.17%). See the Supplement for details on PRS calculation, validation, and selection. The number of linkage disequilibrium (LD)–pruned single nucleotide polymorphisms included in each PRS are reported in Supplemental Table S2.

Data Analyses

Phenotypic Analyses. Comparisons between adopted and nonadopted individuals on the mental health indicators and socioeconomic and psychosocial factors (i.e., smoking, life satisfaction, and recent SLEs) were carried out using logistic regression for binary outcomes, linear regression for continuous outcomes, and multinomial logistic regression for categorical outcomes. Adjustments were made for sex and age at testing. Further adjustments for educational level and household income were tested as secondary analysis. False discovery rate correction at .05 was used to account for all phenotypic tests.

PRS Analyses to Address rGE. To test for differences in genetic risk between adopted and nonadopted individuals (rGE), multivariate logistic regression models were applied with each of the 4 PRSs as independent variable predicting adoption status. Considering potential genetic overlap between the mental health variables, all PRSs were also included in the same model (if significant). Subsequently, to assess how much of the effect of adoption status on mental health was explained by differences in genetic risk, multivariate linear/logistic regression models were fitted with adoption status and the respective PRS as independent variables added stepwise to predict mental health outcomes. We then assessed the change in effect size of adoption on mental health from the model with

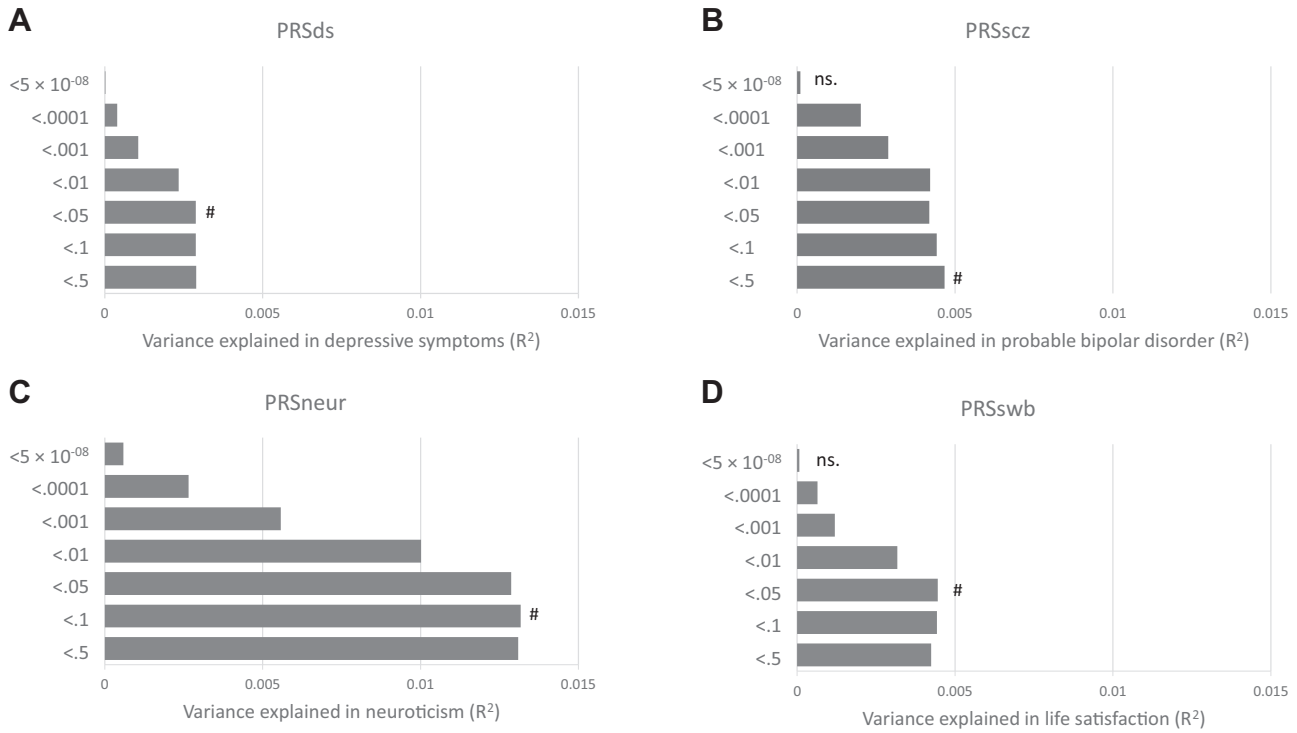

Figure 2. Variance explained in depressive symptoms, probable bipolar disorder, neuroticism, and life satisfaction by the respective polygenic risk scores under 7 *p*-value cutoff thresholds. #The *p*-value threshold selected for subsequent analyses. ns., nonsignificant association; PRSds, polygenic risk score for depressive symptoms; PRSneur, polygenic risk score for neuroticism; PRSscz, polygenic risk score for schizophrenia; PRSswb, polygenic risk score for subjective well-being.

adoption as the sole predictor, to the model with both adoption and genetic risk.

LD Score Regression to Explore rGE. Genetic correlations between childhood adoption and mental health were assessed using LD score regression (LDSC) in LD Hub. GWAS summary statistics of adoption ("Were you adopted as a child" in the full UKB sample of 360,450 with 5158 adoptees) were extracted from http://www.nealelab.is/uk-biobank (GWAS sample sizes in Supplemental Table S3). At the LD Hub Test Center (33,34) the following categories were selected for further testing: psychiatric diseases, personality traits, education, smoking behavior, UK Biobank traits to explore the genetic correlations between adoption status, and a selection of mental health–related variables. The genetic correlations are reported together with the standard error, unadjusted *p* values, and false discovery rate correction.

PRS Analyses to Address G×E. To test for G×E, an interaction term between adoption status and the respective PRS was added in addition to the two main effects (i.e., adoption and PRS) predicting mental health. All models were adjusted for age, age^2, sex, and 15 principal components. To adjust for potential effects of covariates on the interaction, we also included adjustments for all covariate × PRS and covariate × adoption status interactions, as previously suggested (35). Bonferroni correction at a significance level of .01 was used to account for similar tests across four phenotypes (.05/4). In all analyses, relatedness in the sample was dealt with by applying a "sandwich" estimator using Family ID (see Supplement). Statistical analyses were conducted in Stata/IC 15.0 (StataCorp, College Station, TX).

RESULTS

Phenotypic Analyses

Adoptees were more likely to be men and current smokers, and reported lower education and income levels, more symptoms of depression, higher neuroticism, and more loneliness (Table 1). Adoptees also reported more SLEs in the past 2 years and less satisfaction with their health and financial status (for descriptive information on the full sample and adoption nonresponders, see Supplemental Table S4). There were no significant differences between adopted and nonadopted individuals for happiness, life, work, family relationship, and friendship satisfaction. Adjustment for education and income levels did not significantly change the results (data not shown). The rate of adoption was constant across age deciles (see Supplemental Table S6).

Genetic Analyses

Each standard deviation increase in the PRSs for depressive symptoms, schizophrenia, and neuroticism was associated with 6% (odds ratio [OR], 1.06; 95% confidence interval [CI], 1.03–1.10; $p < .01$), 5% (OR, 1.05; 95% CI, 1.01–1.09; $p = .01$), and 6% (OR, 1.06; 95% CI, 1.02–1.10; $p < .01$) increase in the

Table 1. Socioeconomic, Mental and Somatic Health, and Psychosocial Outcomes in Adopted and Nonadopted Individuals

		Not Adopted		Adopted in Childhood		
	Range	*n*	Mean ± SD or *n* (%)	*n*	Mean ± SD or *n* (%)	*p* Value[a]
Female	0–1	240,329	130,869 (54.45)	3151	1638 (51.98)	.01[b]
Age, Years	39–72	240,329	56.89 ± 8.01	3151	56.83 ± 8.45	.89
Socioeconomic Factors						
Education level (>compulsory)	0–1	198,316	157,098 (79.22)	2516	1946 (77.34)	.01[b]
Household income	1–5	206,836	2.635 ± 1.19[c]	2692	2.439 ± 1.18[c]	<001[b]
Mental Health						
Depressive symptoms	0–6	225,973	0.533 ± 1.06	2955	0.639 ± 1.19	<001[b]
Seen a doctor for nerves, anxiety, tension, or depression	0–1	238,836	81,852 (34.7)	3126	1208 (38.64)	<001[b]
Seen a psychiatrist for nerves, anxiety, tension, or depression	0–1	239,406	26,663 (11.14)	3132	479 (15.29)	<001[b]
Probable lifetime MDD	0–1	56,842	15,203 (26.75)	687	189 (27.51)	.39
Probable bipolar disorder	0–1	42,274	635 (1.50)	512	14 (2.73)	.03[b]
Neuroticism	0–12	195,145	4.105 ± 3.25	2525	4.379 ± 3.37	<001[b]
Loneliness	0–1	236,718	41,324 (17.46)	3100	718 (23.16)	<001[b]
Psychosocial Factors						
Smoking	0–2	239,402		3134		
Never			132,416 (55.31)		1424 (45.44)	Ref.
Former			85,553 (35.74)		1243 (39.66)	<001[b]
Current			21,433 (8.95)		467 (14.90)	<001[b]
Happiness	0–1	78,903	75,615 (95.83)	993	944 (95.07)	.27
Life satisfaction sum score	0–23	53,035	15.57 ± 2.73	652	15.53 ± 2.97	.89
Work satisfaction	0–1	54,005	48,825 (90.41)	663	606 (91.40)	.27
Health satisfaction	0–1	78,922	68,955 (87.37)	994	839 (84.41)	.006[b]
Family relationships satisfaction	0–1	78,491	73,745 (93.95)	977	906 (92.73)	.13
Friendship satisfaction	0–1	78,343	75,974 (96.98)	987	960 (97.26)	.50
Financial satisfaction	0–1	78,811	69,081 (87.65)	991	831 (83.85)	<.001[b]
Stressful life events	0–2	238,901		3116		
0			135,628 (56.77)		1645 (52.79)	Ref.
1			76,701 (32.11)		1054 (33.83)	.001[b]
≥2			26,572 (11.12)		417 (13.38)	<.001[b]

A higher score indicates "more" of the phenotype.
MDD, major depressive disorder.
[a]Based on logistic, linear, or multinomial regressions with adoption as the predictor, adjusted for age and sex.
[b]False discovery rate significant.
[c]Household income level 2 and 3 (closest to the mean) equal £18,000 to £30,999 and £31,000 to £51,999, respectively.

odds of being adopted, respectively (Figure 3). The PRS for subjective well-being was not associated with adoption (OR, 0.90; 95% CI, 0.95–1.02; p = .44). When all 3 associated PRSs were included in the model, all remained nominally significant predictors of childhood adoption, with the PRS for schizophrenia having the largest effect (OR, 1.05; 95% CI, 1.01–1.09; p = .02), followed by the PRSs for depressive symptoms (OR, 1.05; 95% CI, 1.01–1.09; p = .02) and neuroticism (1.04; 1.00–1.08; p = .04). Sensitivity analysis without related individuals showed similar results (Supplemental Table S5).

When both predictors, adoption and the respective PRS for each phenotype, were added to the prediction model stepwise, the attenuation of the adoption effect on the mental health indicators was minimal (Table 2).

LDSC analyses revealed positive genetic correlations between childhood adoption and depressive symptoms, major depressive disorder, schizophrenia, and smoking behavior and a negative correlation with educational attainment (Table 3). No genetic overlap with neuroticism and subjective well-being was detected.

There were no interactions between the PRSs and adoption status on mental health outcomes in adulthood (Table 2).

DISCUSSION

To our knowledge, the present study is the largest exploring the association between childhood adoption, as an indicator of childhood adversity, and mental health in adulthood, and the first using a genetically informative sample. Findings showed that adoptees were somewhat worse off on mental health–related measures, in part reflecting differences in genetic risk captured by PRSs for depressive symptoms, schizophrenia, and neuroticism between adoptees and those not adopted.

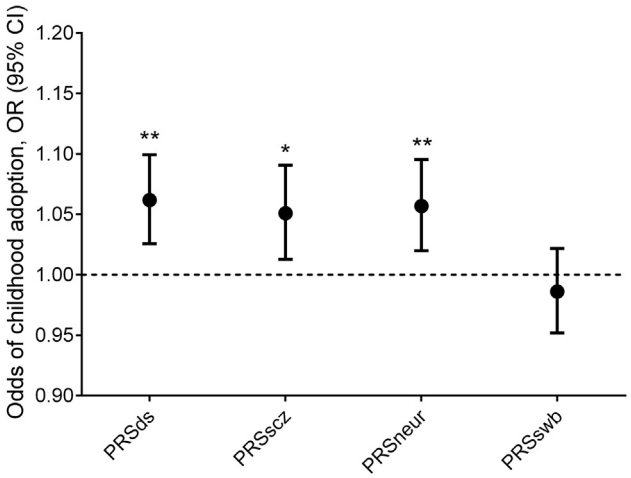

Figure 3. Change in odds for childhood adoption by 1 SD polygenic risk score change. *$p < .01$; **$p < .005$. CI, confidence interval; OR, odds ratio; PRSds, polygenic risk score for depressive symptoms; PRSneur, polygenic risk score for neuroticism; PRSscz, polygenic risk score for schizophrenia; PRSswb, polygenic risk score for subjective well-being.

Phenotypic Differences

Adoptees were more likely to be men and to smoke, had lower education and socioeconomic status, and reported more stressful life events, loneliness, and mental health problems in adulthood. However, adoptees were as happy and satisfied with their life overall, although they were somewhat less satisfied with their health and financial situation, in keeping with the somewhat lower income in this group. Although significant, overall, the phenotypic differences between adopted and nonadopted individuals were found to be small. These findings are largely in agreement with previous literature describing small but consistent differences in the mental health of adoptees compared with nonadopted individuals (2,3). As the adoptive families are normally highly selected, children are generally adopted into better-than-average rearing environments, which could compensate and minimize any differences in the eventual mental health and psychosocial outcomes of the adoptees.

Genetic Differences

Using PRSs, we found that adoptees had an increased genetic risk for depressive symptoms, schizophrenia, and neuroticism, but not for subjective well-being, suggesting that the observed differences in mental health may at least partly be due to increased genetic risk rather than solely to environmental exposure to SLEs (i.e., adoption-related experiences). These findings were further supported by LDSC results, which showed that childhood adoption was genetically correlated with higher risk for depressive symptoms, major depressive

Table 2. Main Effects and Interaction of PRS and Adoption on Depressive Symptoms, Probable Bipolar Disorder, Neuroticism, and Life Satisfaction

	Adoption		PRS		PRS × Adoption		
	Beta/OR (95% CI)	*p* Value	Beta/OR (95% CI)	*p* Value	Beta/OR (95% CI)	*p* Value	Model R^2
Depressive Symptoms[a]							
Model 1[b]	0.10 (0.05 to 0.14)	<.001[c]	–		–		.0166
Model 2[b]	—		0.05 (0.05 to 0.06)	<.001[c]	–		.0193
Model 3[b]	0.09 (0.05 to 0.13)	<.001[c]	0.05 (0.05 to 0.06)	<.001[c]	–		.0194
Model 4[d]	0.16 (−1.14 to 0.45)	.300	0.13 (0.10 to 0.16)	<.001[c]	−0.01 (−0.05 to 0.03)	.513	.0197
Probable Bipolar Disorder[e]							
Model 1[b]	1.89 (1.11 to 3.25)	.020	–		–		.0129
Model 2[b]	—		1.25 (1.15 to 1.35)	<.001[c]	–		.0166
Model 3[b]	1.86 (1.09 to 3.20)	.024	1.25 (1.15 to 1.35)	<.001[c]	–		.0173
Model 4[d]	8.02 (0.25 to 262.60)	.242	0.48 (0.28 to 0.82)	.008[c]	1.32 (0.77 to 2.23)	.306	.0268
Neuroticism[a]							
Model 1[b]	0.09 (0.05 to 0.13)	<.001[c]	–		–		.0328
Model 2[b]	—		0.12 (0.11 to 0.12)	<.001[c]	–		.0458
Model 3[b]	0.08 (0.04 to 0.12)	<.001[c]	0.12 (0.11 to 0.12)	<.001[c]	–		.0460
Model 4[d]	0.05 (−0.22 to 0.32)	.706	0.14 (0.11 to 0.17)	<.001[c]	−0.01 (−0.05 to 0.03)	.775	.0462
Life Satisfaction[a]							
Model 1[b]	−0.017 (−0.10 to 0.07)	.693	–		–		.0317
Model 2[b]	–		0.07 (0.06 to 0.08)	<.001[c]	–		.0361
Model 3[b]	−0.014 (−0.10 to 0.07)	.746	0.07 (0.06 to 0.08)	<.001[c]	–		.0361
Model 4[d]	−0.56 (−1.07 to −0.06)	.028	0.07 (0.02 to 0.13)	.014	−0.06 (−0.14 to 0.02)	.162	.0370

Continuous outcome and PRS variables standardized (mean = 0 ± 1).
CI, confidence interval; OR, odds ratio; PRS, polygenic risk score.
[a]Beta is reported.
[b]Adjusted for sex, age, age^2, and 15 principal components.
[c]$p < .01$.
[d]Adjusted for sex, age, age^2, 15 principal components and interaction terms between adoption and all covariates, and PRS and all covariates.
[e]OR is reported, schizophrenia PRS in the model.

Table 3. Genetic Correlations Between Childhood Adoption and Mental Health Disorders/Traits

Disorder/Trait	r_g	SE	*p* Value
Mental Health			
Depressive symptoms	.45	.13	5×10^{-4}[a]
Major depressive disorder	.37	.15	.01[a]
Bipolar disorder	.08	.09	.37
Schizophrenia	.24	.07	.001[a]
Subjective well-being	−.15	.11	.17
Neuroticism	.12	.13	.37
Loneliness	.37	.09	6.36×10^{-5}[a]
Education			
College completion	−.50	.10	3.71×10^{-7}[a]
Smoking Behavior			
Ever vs. never smoked	.38	.11	5×10^{-4}[a]
Cigarettes smoked per day	.42	.16	.01[a]

r_g, genetic correlation.
[a]False discovery rate significant.

disorder, schizophrenia, college noncompletion, and smoking, but not with subjective well-being, and, contrary to our PRS results, not with neuroticism (although the correlations were in the expected direction). Together, these findings indicate that adoptees on average have a somewhat higher genetic predisposition for mental health problems, lower education attainment, and smoking. As these traits typically manifest in adolescence, it is unlikely that the child's genetic risk profile contributed to the child's being placed for adoption. More likely is that the biological parents of the adoptees (carriers of the same risk alleles) were at higher genetic risk for mental health problems, substance use (i.e., smoking), and lower educational attainment, traits that could possibly contribute to the circumstances leading to adopting out a child. This suggests passive rGE, in which the child's genetic predisposition (for mental health problems) is correlated with the environment that the child is born into (increased adversity owing to the parent's higher likelihood to experience mental health problems). As such, the well-known association between adoption and mental health, which has largely been attributed to stressful environmental factors in childhood (1,24), such as being exposed to trauma, abuse, or neglect, is likely better explained by a more complex model including a combination of genetic and environmental factors. It seems plausible that this finding may extend to general associations between childhood adversity—if experienced in the context of a biological family—and mental health outcomes, even if not resulting in an adoption. However, importantly, both genetic influences and adoption explain only a small part of individual differences in mental health on the population level, and the difference in genetic risk between adoptees and nonadoptees explained only a small fraction of the adoption effect. Our findings are in line with two recent studies using self-reported trauma measures reporting a small but significant association between major depression PRSs and childhood trauma (21) and between the PRSs for major depression and neuroticism with recent SLE exposure, respectively (36). However, the majority of studies exploring main effects of genetic risk and SLE exposure and their interaction on mental health outcomes did not assess potential gene-environment correlations [e.g., (24,37)].

G×E Interaction

The association between measured genetic risk and mental health outcomes was independent of adoption status, showing no significant evidence for G×E interaction. These findings are not consistent with the diathesis-stress model, which holds that the effect of stress on mental health outcomes is amplified in the genetically vulnerable (9). To our knowledge, the only previous study using an objective indicator of childhood adversity by comparing emotional health in twins reared apart/adopted separately to twins reared together by their biological parents, using the PRS for neuroticism as an indicator of genetic risk (20), found an interaction, but with a smaller association between genetic risk and emotional health in those reared apart. We did not observe such an interaction effect between adoption status and genetic risk, despite using a much larger sample. This could be due to several factors including small sample size (i.e., power) in the previous study among other differences in sample characteristics, measures, and study design.

Our findings are in line with two recent studies, which found no evidence for an interaction between a PRS for major depression and self-reported childhood trauma in adulthood (21) and in childhood/youth (24), respectively. Two studies (37,38), applying similar methods but using self-reported recent SLEs (in adulthood), reported a significant interaction effect in line with the diathesis-stress model. However, the interaction could be induced by the self-reported stress likely being correlated with both genetic risk for depression and the depression outcome, resulting in those who are at higher risk for depression and possibly experiencing depressive symptoms reporting (and subjectively experiencing) more life stress (i.e., recall bias) (37). This is in line with our finding that adoptees reported significantly more SLEs in adulthood than nonadoptees and highlights the importance of using objective indicators of (early) life adversity.

Limitations

Despite several advantages to the data and measures used here, there are also limitations. First, there was no information about the extent of trauma, i.e., circumstances preceding and leading to the adoption, age at adoption, exposure to foster care, or whether a stepparent adopted the child while living with one biological parent. Such factors may play a crucial role in gene-environment interplay and should be investigated in the future. Although historical data indicate that the rate of adoptions in the United Kingdom has declined while age at adoption has increased from the 1960s, we did not find an increase over time in reported adoptions in the UKB data (see Supplemental Table S6). However, the majority of those changes were reported to have taken place from the 1980s onward. As the vast majority of our sample was born in the 1950s and 1960s, our sample was quite homogeneous and may only be minimally affected by those changes in adoption rates and age over time. However, we cannot exclude that those adopted earlier in time and potentially at an earlier age

may be less aware of their adoption status. This would result in underreporting of adoption in the older part of the sample, which in turn could also explain the lack of change we find in adoption rates over time. Although the adoption status was also based on self-report, it is less likely that inaccuracy of the response to the adoption question is correlated with genetic and phenotypic outcomes compared with retrospectively self-reported SLEs. Nevertheless, potential false statements regarding the adoption status cannot be ruled out.

Second, many mental health phenotypes used in this study were based on only 1 or 2 items or only on a subset of the full sample—an inevitable shortcoming of large cohort studies. Further, PRSs explain only a small fraction of the total trait variance in respective phenotypes, not even close to single nucleotide polymorphism heritability estimates. However, with increased sample sizes of the discovery GWAS, PRSs will eventually start accounting for more genetic variance (39). As new and more powerful discovery GWASs become available, future studies should replicate and extend our findings including additional mental health–related PRSs and phenotypes.

Finally, although adoptees had a higher genetic risk for neuroticism, genetic correlation between adoption status and neuroticism based on LDSC results was not significant. This could be due to inherent differences between the PRS and LDSC approaches. While the first only relies on summary statistics for only one of the traits (i.e., mental health), the second is dependent on the availability of powerful GWAS for both traits of interest (i.e., mental health and adoption status). As there were only 5000 cases (adoptees) in the adoption GWAS, its power and hence the power of the LDSC approach may be somewhat limited. Further, the two types of analyses were conducted in somewhat different samples, which may potentially also contribute to the discordant findings. As such, replication would be desirable to confirm the genetic association between neuroticism and adoption status.

Conclusions

Adoptees are somewhat worse off in almost all explored mental health domains while also showing a higher genetic predisposition for mental health problems. This suggests that the well-known association between family-related childhood adversity, such as adoption, and mental health cannot fully be explained by the exposure to trauma, abuse, or neglect, but rather is due to a more complex combination of genetic risk and environmental factors (gene-environment correlation), in which higher parental genetic risk for mental health problems may result in both an increased genetic risk for the child and increased risk for the circumstances leading to an adoption.

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