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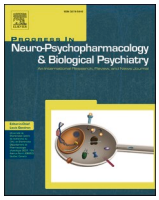

Polygenic risk scores for mood and related disorders and environmental factors: Interaction effects on wellbeing in the UK biobank

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ABSTRACT

Mood disorders have a genetic and environmental component and interactions (GxE) on the risk of psychiatric diseases have been investigated. The same GxE interactions may affect wellbeing measures, which go beyond categorical diagnoses and reflect the health-disease continuum.

We evaluated GxE effects in the UK Biobank, considering as outcomes subjective wellbeing (feeling good and functioning well) and objective measures (education and income). We estimated the polygenic risk scores (PRSs) of major depressive disorder, bipolar disorder, schizophrenia, and attention deficit hyperactivity disorder. Stressful/traumatic events during adulthood or childhood were considered as E variables, as well as social support. The addition of the PRSxE interaction to PRS and E variables was tested in linear or multinomial regression models, adjusting for confounders.

We included 33 k–380 k participants, depending on the variables considered. Most PRSs and E factors showed additive effects on outcomes, with effect sizes generally 3–5 times larger for E variables than PRSs. We found some interaction effects, particularly when considering recent stress, history of a long illness/disability/infirmity, and social support. Higher PRSs increased the negative effects of stress on wellbeing, but they also increased the positive effects of social support, with interaction effects particularly for the outcomes health satisfaction, loneliness, and income ($p <$ Bonferroni corrected threshold of 1.92e-4). PRSxE terms usually added ~0.01–0.02% variance explained to the corresponding additive model.

PRSxE effects on wellbeing involve both positive and negative E factors. Despite small variance explained at the population level, preventive/therapeutic interventions that modify E factors could be beneficial at the individual level.

1. Introduction

Mood disorders are leading causes of disability on a global scale (Vos et al., 2020), because of their high prevalence, typical recurrent/chronic course, and strong association with wellbeing and functioning in important areas of life (Pasman et al., 2023).

Mood disorders include major depressive disorder (MDD) and bipolar disorder (BP), both of which have a polygenic component (heritability of ~40–50% and 80%, respectively, in twin studies (Kendler et al., 2018) (Barnett and Smoller, 2009)). As noted, mood disorders are highly correlated with measures of wellbeing, such as life satisfaction, general happiness, feelings of loneliness, and activity limitations, on a phenotypic and genetic level (Strine et al., 2009) (Okbay et al., 2016) (Gao et al., 2017). Evaluating wellbeing in categories at risk is important for prevention strategies aiming to reduce the rate of full-blown mood disorders (Yüksel and Bahadir-Yilmaz, 2019).

Given the polygenic architecture of mood disorders, polygenic risk scores (PRSs) have been used to estimate mood disorders risk, but also to explore the genetic overlap with other conditions, including wellbeing-related and other traits. For example, the PRS of MDD was associated with a number of traits and medical conditions (Agerbo et al., 2021) (Fang et al., 2022) (Machlitt-Northen et al., 2022). However, MDD and BP are complex disorders, as environmental exposures are well known to influence the risk of disease in conjunction with genetic factors (Hoang et al., 2018). Previous studies investigated the interaction between genetic and environmental factors (GxE) on the risk of mood disorders,

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focusing on childhood traumatic experiences, with heterogeneous results. In two studies, the effect of MDD PRS on the risk of MDD was increased in those with a history of trauma vs no trauma (Coleman et al., 2020) (Peyrot et al., 2014), while another study reported an opposite effect (N. Mullins et al., 2016) and a meta-analysis found no interaction (Peyrot et al., 2018). Interestingly, positive environmental factors such as healthy lifestyle may also show an interaction with MDD PRS. One study found a stronger protective effect of healthy lifestyle in those with higher MDD PRS (Cao et al., 2021), and another study suggested a similar result for physical exercise, despite not testing directly a possible deviation from an additive effect (Choi et al., 2020). In general, an additive model (i.e., deviation from additivity) was suggested to better capture the biological mechanism of GxE effects (N. Mullins et al., 2016). Evidence of BP PRS x E interaction is scarcer (Park et al., 2020).

The diagnosis of mood and other psychiatric disorders follows a categorical approach, based on satisfying a minimum number of criteria over a certain time (American Psychiatric Association, 2013). The consequent heterogeneity among individuals with the same diagnosis has been long discussed, as well as the need to use residual categories in those who manifest a significant impairment in wellbeing but do not fall within any of the standard categories. Individuals with a history of trauma, particularly during childhood, often develop complex repercussions on their wellbeing, which may not lay within a diagnosis of MDD or another specific psychiatric disorder (Beilharz et al., 2020). These issues have consequences both on a clinical and research perspective. Reductions in wellbeing and functioning are in this sense a central characteristic across all psychiatric disorders, but they vary within a continuum, with mental illness being on one extreme of this spectrum, and a complex variability of shades in the middle (Santini et al., 2020). Wellbeing/functioning have cross-diagnostic importance, but they also are key predictors of health in general (not limited to mood or psychiatric disorders), disability, and life expectancy (Zaninotto and Steptoe, 2019).

In studies performed in the general population, wellbeing is usually assessed through life evaluations, using questions about life satisfaction, happiness, and sense of direction/purpose (Helliwell, 2019) (VanderWeele et al., 2020). Measures of wellbeing can reflect the hedonic component of wellbeing, i.e., feeling happy, or the eudaimonic perspective, i.e., feelings of self-realisation, fulfilment, and functioning well; an evaluative dimension of satisfaction with life can be considered (VanderWeele et al., 2020). While these measures focus on the subjective component, others are objective indicators, such as educational attainment and income. These can be easily collected at population level and add relevant information that complements the evaluation of subjective wellbeing.

Similar to other complex traits, subjective wellbeing has a significant genetic component (heritability estimates from 23% to 47%), which is highly correlated with depressive symptoms and neuroticism (Jamshidi et al., 2020) (Okbay et al., 2016) (Baselmans et al., 2019). Interestingly, no significant genetic correlation was found between wellbeing and physical traits, such as body mass index and coronary artery disease (Okbay et al., 2016), consistent with the observation that chronic physical disorders have lower impact on wellbeing than depression (Beekman et al., 2002). The contribution of environmental variables to wellbeing has been studied particularly in relation to work-related stress (Zhou et al., 2020), neighborhood safety, green spaces and pollution, social cohesion and satisfaction with governance and politics (Bjørndal et al., 2023).

To the best of our knowledge, there are no studies that tested the possible interaction between the PRS of psychiatric disorders and environmental variables on wellbeing. Testing this hypothesis is relevant, as discussed above, because of the importance of wellbeing, which has value beyond diagnosis. In this study, we tested the additive contribution and possible interaction effects of the PRSs of mood and related disorders with environmental factors on measures of wellbeing, using the UK Biobank (UKB) study. We considered all the mentioned subjective components of wellbeing, as well as objective measures (educational attainment and income). For the relationship between wellbeing and mood disorders, we considered the PRSs of MDD and BP. We also calculated the PRSs of schizophrenia (SCZ) and attention-deficit hyperactivity disorder (ADHD), as these are genetically correlated with mood disorders (Niamh Mullins et al., 2021) (Wray et al., 2018). In addition, the PRSs of SCZ and ADHD were associated with wellbeing in the general population and in people with depression, and with treatment outcomes in MDD and BP, suggesting that they may be particularly relevant in relation to wellbeing and important related variables such as treatment outcomes in patients (Fabbri et al., 2023) (Fabbri et al., 2022) (Fanelli et al., 2021) (International Consortium on Lithium Genetics (ConLi+Gen) et al., 2018).

2. Methods

2.1. Sample

UKB is a prospective health study of >500,000 individuals recruited from across the United Kingdom except Northern Ireland, aged between 40 and 69 at baseline (2006–2010). This study was established to identify the genetic and nongenetic determinants of diseases of middle and old age. UKB has collected and continues to collect medical history, environmental, lifestyle, activity, multimodal imaging, genetic and other biomarker data. It combines extensive and detailed assessment of exposures with follow-up and characterisation of many different health-related outcomes. These are obtained through linkage with electronic health records (hospital inpatient and primary care records) and many self-reported variables (touch-screen questionnaire at baseline, and online questionnaires during follow-up) (Conroy et al., 2019). Therefore, the UKB combines detailed individual-level information including biomarkers relevant for studying health-related outcomes in a well-powered sample. Nevertheless, the data should be interpreted taking in account the modality of collection and completeness. For example, the mental health questionnaire was administered online between 2016 and 2017, with inclusion of ~31% of all participants (Davis et al., 2020).

2.2. Outcomes

We studied measures of wellbeing in the following areas, to reflect the different subjective components of wellbeing as well as objective indicators:

- Subjective wellbeing: general happiness (data field 20,458), health satisfaction (data field 4548), belief that own life is meaningful (data field 20,460), friendship and family relations satisfaction (data fields 4570 and 4559, respectively), feelings of loneliness (data field 2020), financial and job satisfaction (data fields 4581 and 4537, respectively).
- Objective indicators of wellbeing: household income (data field 738) and qualifications (data field 6138).

Most measures of subjective wellbeing were measured on a Likert scale with six values, and they were part of the mental-health questionnaire or collected during the touchscreen questionnaire at recruitment (Davis et al., 2020). A detailed description of these nine wellbeing variables and their coding is provided in Supplementary Table 1.

2.3. Predictors

Polygenic risk scores (PRS) of MDD, BD, SCZ, and ADHD were calculated, using GWAS summary statistics described in Table 1.

The following seven environmental factors were considered for possible interaction with each PRS (see Supplementary Table 2 for a description of their coding):

Table 1
description of the GWAS summary statistics used to estimate the polygenic risk scores.

Trait	Reference	Description
Schizophrenia	Trubetskoy et al. (2022)	76,755 cases and 243,649 control
Major depressive disorder	Wray et al. (2018) (excluding UK Biobank and 23andMe)	45,591 cases and 97,674 controls
Bipolar disorder	Mullins et al. (2021)	41,917 cases and 371,549
Attention-deficit hyperactivity disorder	Demontis et al. (2019)	20,183 cases and 35,191 controls

1. Illness, injury, bereavement, stress in last 2 years (data field 6145), coded as binary variable (1 = at least one event; 0 = none).
2. Long-standing illness, disability, or infirmity (data field 2188), coded as 1 = yes and 0 = no.
3. Traumatic/stressful events during adulthood, calculated considering the following items, similarly to the approach taken in a previous study (Pitharouli et al., 2021) (Supplementary Table 2):
   i. Been in a confiding relationship as an adult (data field 20,522).
   ii. Physical violence by partner or ex-partner as an adult (data field 20,523).
   iii. Belittlement by partner or ex-partner as an adult (data field 20,521).
   iv. Sexual interference by partner or ex-partner without consent as an adult (data field 20,524).
4. Traumatic/catastrophic events during adulthood, calculated considering the following items, similarly to the approach of a previous study (Pitharouli et al., 2021) (Supplementary Table 2):
   i. Victim of sexual assault (data field 20,531).
   ii. Victim of physically violent crime (data field 20,529).
   iii. Been in serious accident believed to be life-threatening (data field 20,526).
   iv. Witnessed sudden violent death (data field 20,530).
   v. Diagnosed with life-threatening illness (data field 20,528).
   vi. Been involved in combat or exposed to warzone (data field 20,527).
5. Childhood trauma, calculated considering these items, in line with a previous study (Pitharouli et al., 2021) (Supplementary Table 2):
   i. Felt loved as a child (data field 20,489).
   ii. Physically abused by family as a child (data field 20,488).
   iii. Felt hated by family member as a child (data field 20,487).
   iv. Sexually molested as a child (data field 20,490).
   v. Someone to take to doctor when needed as a child (data field 20,491).
6. Adopted as a child (data field 1767), coded as 1 = yes and 0 = no.
7. A measure of social support, calculated as the sum of frequency of friend/family visits (data field 1031, coded in accordance with a previous study (Bralten et al., 2021)) and leisure/social activities (coded as 1 = one or more activity and 0 = none).

2.4. Statistical analysis

PRSs were calculated for the traits of interest by using non-strand ambiguous single nucleotide polymorphisms (SNPs) available in the HapMap3 data. These SNPs were selected from the base summary statistics and imputed genome-wide data in UKB (details of genotyping, quality control and imputation are described in the Supplementary Methods). Variant weights were estimated using PRS-CS-auto, with standard parameters (Ge et al., 2019); we then calculated PRSs using the estimated variants weights and the score function in PLINK 2.0 (Chang et al., 2015).

We tested the interaction between the described PRSs and environmental factors on the outcomes of interest, by using linear regression models or multinomial regression models. Linear regression appears appropriate to test GxE interactions, as previous studies suggested that an additive model (i.e., deviation from additivity) reflects better biological interaction (Knol et al., 2007). However, multinomial regression (i.e., deviation from multiplicativity) was used for the outcome variables describing qualifications and household income, since these were coded as factors, being represented by categories that cannot be conceptualized on a continuous or Likert scale (see Supplementary Table 1 for details).

Rather than testing both additive and multiplicative hypotheses of interaction, and increase multiple testing burden, we preferred to focus on the more supported hypothesis of a deviation from additivity effect, whenever this was compatible with the coding of the dependent variable (always true, except for qualifications and household income, as previously noted).

In all models we included an interaction term (Y ~ PRS + E + PRS x E + covariates), and as covariates we considered age at recruitment, sex, Townsend deprivation index (data field 189), and the first six ancestry principal components, in line with previous studies (Fabbri et al., 2022). When considering qualifications as outcome, we tested only models including childhood trauma and adoption as environmental factors, as other environmental variables were referred to adulthood and had no rationale for testing.

This study was focused on PRSxE interaction effects, however, for comparison and to check individual effects of PRSs and E variables, we also fitted models including only the additive effects of each PRS and E factor, with the same covariates (Y ~ PRS + E + covariates).

To make regression coefficients comparable, we scaled continuous variables by subtracting the mean and dividing by two times the standard deviation, while dichotomous variables were centered by subtracting the mean, as suggested by a previous study (Gelman, 2008).

We calculated the variance explained (R^2 or Nagelkerke's R^2 as appropriate) for a baseline model of only covariates, and then for four further models adding (1) each PRS, (2) each environmental factor, (3) each PRS and each environmental factor, and finally (4) a model with each PRS, each environmental factor, and their interaction. Our primary interest was the estimate and *p*-value for the interaction term in model (4). We considered as significant the Bonferroni corrected alpha level of 1.92e-4 (nine outcomes tested for seven E variables * four PRSs (i.e., 9 * 28 = 252) and one outcome [qualifications] tested for two E variables * four PRSs (i.e., 8): 0.05/260 = 1.92e-4).

As sensitivity analysis, where a significant PRSxE interaction was observed, we checked if the result was potentially affected by interactions between the PRS and the covariates, or the environmental factor and the covariates, by adding these interaction terms in the corresponding regression model, in line with a previous study (Keller, 2014). For these analyses, we considered the interaction of each PRS and environmental factor with Townsend deprivation index and ancestry principal components, as these vary geographically and may have interactions that impact on the PRSxE effect.

For all analyses, we acknowledge the use of the King's Computational Research, Engineering and Technology Environment (CREATE) (King's College London, 2023).

3. Results

The analyses included between ~380 K and 33 K participants, depending on the variables considered; a description of the available data with the respective numbers is in Supplementary Table 3.

3.1. Effects of E variables and PRSs

As expected, we found that the PRSs and E factors of interest showed strong associations with most measures of wellbeing (Supplementary Table 4). In most cases, E factors had larger effect sizes on outcomes than PRSs. For example, standardised regression coefficients were between 3.4 and 9.9 times larger for the E variable stress event in the last two

years than PRSs when considering loneliness as outcome, and generally considering all analyses they were 3–5 times larger (Supplementary Table 4).

Both childhood (particularly childhood trauma) and adulthood E variables showed strong associations with the wellbeing outcomes (Supplementary Table 4), while most PRSxE interactions involved current or recent environmental factors rather than childhood events. We indeed found PRSxE effects when considering stressful life events in the last two years and history of a long illness, disability, or infirmity. These environmental variables interacted with the PRSs of MDD, ADHD, BP, and/or SCZ on the level of loneliness, health satisfaction, family relationship satisfaction, financial satisfaction, and household income (see Table 2 for significant interaction effects, Supplementary Table 4 for all results). Specifically, higher PRSs appeared to increase the risk of worse outcomes when exposed to these stress factors, with an effect that was more than additive (interaction *p* values between 1.89e-4 and 2.15e-10; Table 2, Fig. 1). Interestingly, when having social support, the same groups showed a stronger protective effect, particularly for the PRS of MDD, BP, and SCZ, with an effect that was more than additive (interaction p values between 1.08e-4 and 2.13e-6; Table 2 and Fig. 2). These findings suggest that higher PRSs for mood disorders and related PRSs may predispose to a higher sensitivity to both positive and negative environmental factors, with interaction effects. However, in the case of household income, the PRS of BP was associated with an increased probability of being in the two groups with the highest income, and negative E factors had an opposite effect. When considering the interaction, a higher BP PRS increased the risk of being in the low income groups in the presence of stress factors (interaction p values of 1.17e-4 and 5.57e-5 for comparisons 52 K–100 K vs <18 K and > 100 K vs <18 K, respectively; Table 2, Supplementary Table 4, Supplementary Fig. 1).

Adulthood traumatic/catastrophic events showed no interaction with any PRS, while adulthood stressful life events (high vs none) interacted with MDD PRS on loneliness (p = 1.61E-4, Table 2, and Supplementary Table 4).

For childhood events (trauma and adoption), there was no interaction, but a result that was very close to the significance threshold, between the PRS of ADHD and adoption on qualifications (p = 3.56e-4, Supplementary Table 4). The direction suggested that the PRS of ADHD may decrease more the probability of having a University/College degree (vs no qualification) in those without a history of adoption vs adoptees (Supplementary Fig. 2).

An overview of all the results is reported in Supplementary Table 4 (effects of the variables PRSs and environmental factors separately and interaction term, as well as additive only models).

3.2. Variance explained and sensitivity analyses

The variance explained by each full model (with the interaction term), but also by PRS + covariates, environmental factor + covariates, PRS + environmental factor + covariates (additive model), and covariates alone is in Supplementary Table 5. Significant models including the PRSxE term explained from 2% and 41% of the variance, depending on the outcome; in all cases however, most of the variance was

Table 2
significant PRS x environmental effects on the outcomes of interest. For linear regression models, the regression coefficient and standard error (SE) are reported, while for multinomial regression models (household income and qualifications), effect estimates are presented as natural log risk ratio of inclusion in each category relative to the reference category (see Supplementary Table 1), with their 95% confidence interval (CI). All main effects (PRS, E) were statistically significant (see Supplementary Table 4), except for three BP PRS in the household income tests (shown with ^). The number of participants included in each test is reported. in Abbreviations: PRS = polygenic risk score; E = environmental variable; MDD = major depressive disorder; ADHD = attention-deficit hyperactivity disorder; BP = bipolar disorder; SCZ = schizophrenia.

Outcome	PRS x E variables	N participants included	Estimate	SE or CI	p
Loneliness	MDD PRS x stress event last two years	376,732	0.0156	2.50E-03	3.20E-10
	ADHD PRS x stress event last two years	376,732	0.0158	0.0025	2.15E-10
	MDD PRS x longstanding disability/illness/infirmity	370,525	0.0166	0.0026	3.94E-10
	BP PRS x longstanding disability/illness/infirmity	370,525	0.0141	0.0026	8.89E-8
	ADHD PRS x longstanding disability/illness/infirmity	370,525	0.0143	0.0026	7.21E-8
	SCZ PRS x longstanding disability/illness/infirmity	370,525	0.0117	0.0026	9.36E-6
	MDD PRS x adulthood stress (high vs none)	88,131	0.0198	0.0053	1.61E-4
Health satisfaction	ADHD PRS x stress event last two years	127,697	−0.0222	0.0055	5.83E-5
	MDD PRS x longstanding disability/illness/infirmity	125,391	−0.0271	0.0055	8.63E-7
	ADHD PRS x longstanding disability/illness/infirmity	125,391	−0.0260	0.0055	2.46E-6
	SCZ PRS x longstanding disability/illness/infirmity	125,391	−0.023	0.0055	2.92E-5
	MDD PRS x social support	127,117	0.0232	0.0055	2.74E-5
	SCZ PRS x social support	127,117	0.0261	0.0055	2.13E-6
	BP PRS x social support	127,117	0.0212	0.0055	1.08E-4
Family relationship satisfaction	SCZ PRS x longstanding disability/illness/infirmity	124,590	−0.0221	0.0059	1.89E-4
Financial satisfaction	MDD PRS x stress event last two years	127,540	−0.0307	0.0054	9.79E-9
	ADHD PRS x stress event last two years	127,540	−0.0303	0.0053	1.48E-8
Household income 31 K–52 K vs <18 K	MDD PRS x stress event last two years	158,666	0.8954	0.8583-0.9341	3.10E-7
	BP PRS x stress event last two years^	158,666	0.906	0.8685-0.9451	4.74E-6
	ADHD PRS x stress event last two years	158,666	0.9012	0.8639-0.9402	1.45E-6
	BP PRS x longstanding disability/illness/infirmity^	155,533	0.9095	0.8699-0.9509	2.95E-5
Household income 52 K–100 K vs <18 K	MDD PRS x stress event last two years	140,952	0.8864	0.8465-0.9283	3.02E-7
	BP PRS x stress event last two years^	140,952	0.9134	0.8723-0.9565	1.17E-4
	ADHD PRS x stress event last two years	140,952	0.8779	0.8383-0.9194	3.30E-8
	MDD PRS x longstanding disability/illness/infirmity	138,423	0.9092	0.8649-0.9558	1.89E-4
Household income >100 K vs <18 K	BP PRS x stress event last two years	90,386	0.8685	0.811-0.9302	5.57E-5

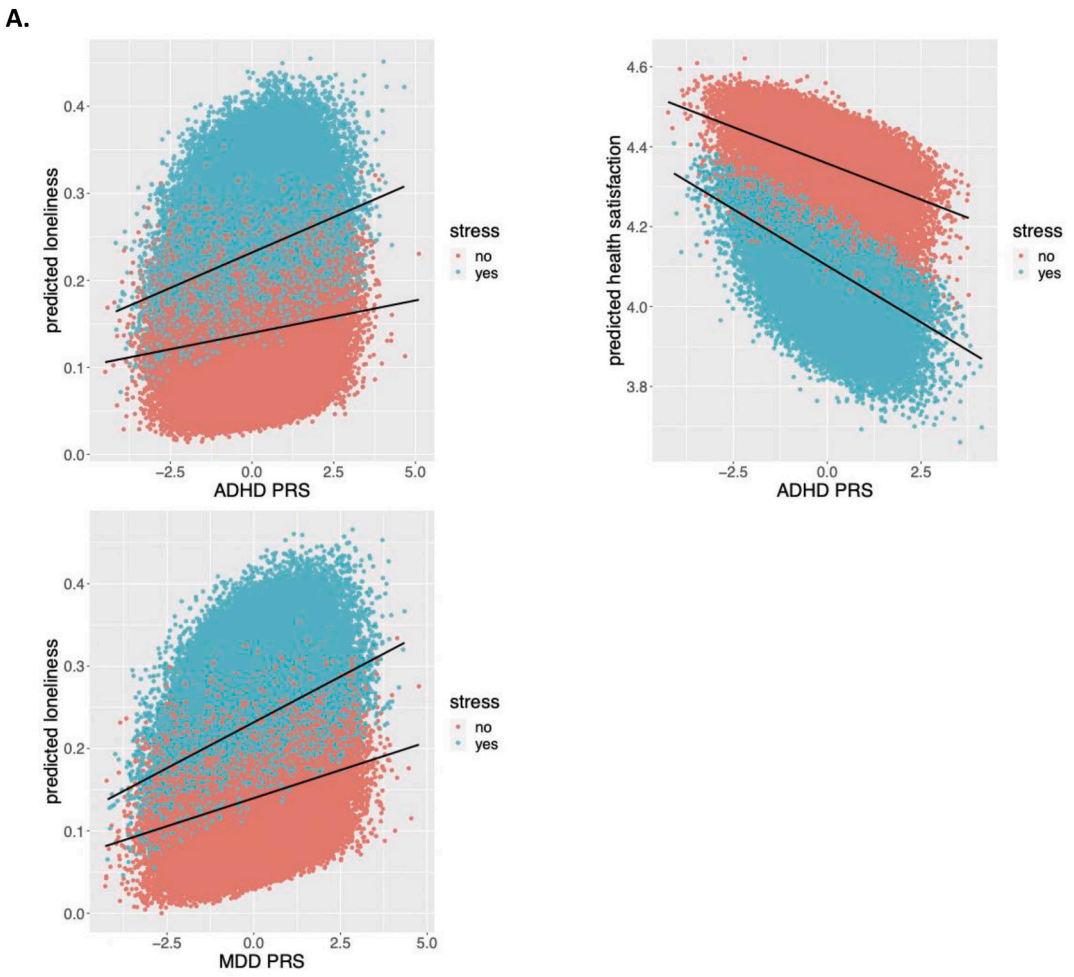

Fig. 1. significant interactions between the PRSs of interest and negative environmental factors on loneliness and health satisfaction. Two negative environmental factors are considered (A. stressful life events in the last two years; B. history of a long illness, disability, or infirmity). The posterior distribution of Y derived from the regression models is represented. Black lines represent regression lines.

ascribable to the covariates and environmental factors. In general, most PRSs added ~0.03–0.15% to R2 vs the E + covariates model, and most PRSxE terms added ~0.01–0.02% vs the PRS + E + covariates (additive only) model.

The interactions between environmental factors and the PRSs of interest did not always remain significant (Bonferroni correction) after including PRS x covariates and environmental factors x covariates interaction terms in the regression models (Supplementary Table 6: 15/26 [58%] PRSxE interactions remained significant). Most of the PRSxE interactions on loneliness and financial satisfaction/household income remained significant. However, interactions not reaching the Bonferroni adjusted p threshold were in the same direction as in the main analyses and showed p values with an order of magnitude of 10^{-3} - 10^{-4}.

4. Discussion

We tested the interaction of the PRSs of mood and related disorders with stressful life events and social support on various measures of wellbeing. The rationale was to study the PRSxE effects on outcome measures that are relevant independent from satisfying the diagnostic criteria for a psychiatric diagnosis.

Our results highlighted individual effects of PRSs and E factors on the outcomes, with additive and in some cases interaction effects. We identified several interactions of PRSs with current or recent environmental factors, specifically stressful life events and history of a long illness, disability, or infirmity, and social support. Traumatic/catastrophic events during adulthood or childhood had strong effects on wellbeing, larger than PRSs, but no interaction effects. For example, the effect size of childhood trauma on general happiness was ~5 times larger than the effect of MDD PRS, and almost 8 times larger when considering the belief that one's own life is meaningful as outcome.

Overall, our findings showed that the PRSs of interest were associated with worse wellbeing in those exposed to negative environmental factors, particularly when considering recent stress factors and long history of illness/disability/infirmity as E factors, and loneliness, health satisfaction, and income as outcomes. At the same time, PRSs were associated with better wellbeing in the presence of social support, i.e., a favourable environmental variable, with a more than additive or multiplicative effect. When considering social support, it is interesting to note that the significant PRS x social support effects were found for the outcome health satisfaction, suggesting that this E factor can have a relevant impact on general health, as previously found (Heinze et al., 2015). Generally, PRSs and E factors added ~0.1–0.2% and ~ 1–4% to the variance explained by covariates only, respectively; PRSxE terms added ~0.01–0.02% to the variance explained by additive models including PRS + E + covariates. Although PRSs and PRSxE explained only small fractions of the variance at the population level, these effects might be meaningful for individuals with very high risk or protective factors, e.g., those at one tail of the PRS distribution, as previously suggested (Lewis and Vassos, 2020).

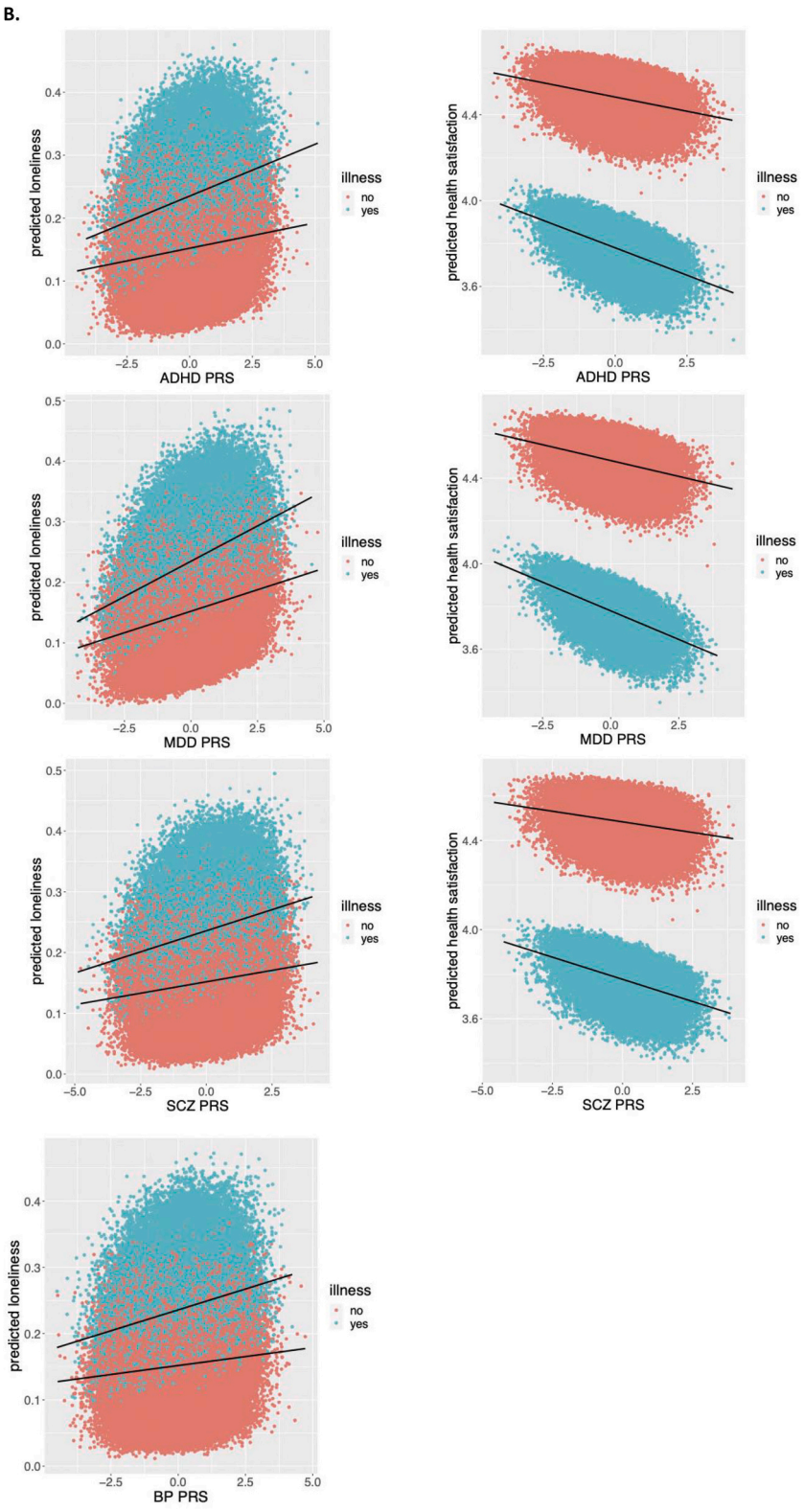

Fig. 1. (*continued*).

Two main theories of GxE interaction are the stress-diathesis model and the differential susceptibility framework (Musci et al., 2019). According to the first, individuals have a certain level of genetic risk factors for a disorder, and they manifest it when and if they experience stressful life events that by adding to the genetic factors reach a certain threshold. The differential susceptibility model is similar, but it adds that genetics may lead to increased susceptibility to both negative and positive environments (Musci et al., 2019), which is in line with our findings. However, most of the previous studies examined PRS interaction with stressful/traumatic events rather than protective environments (see Introduction). Regarding the use of a disease diagnosis as outcome in GxE studies, when assuming the differential susceptibility model we

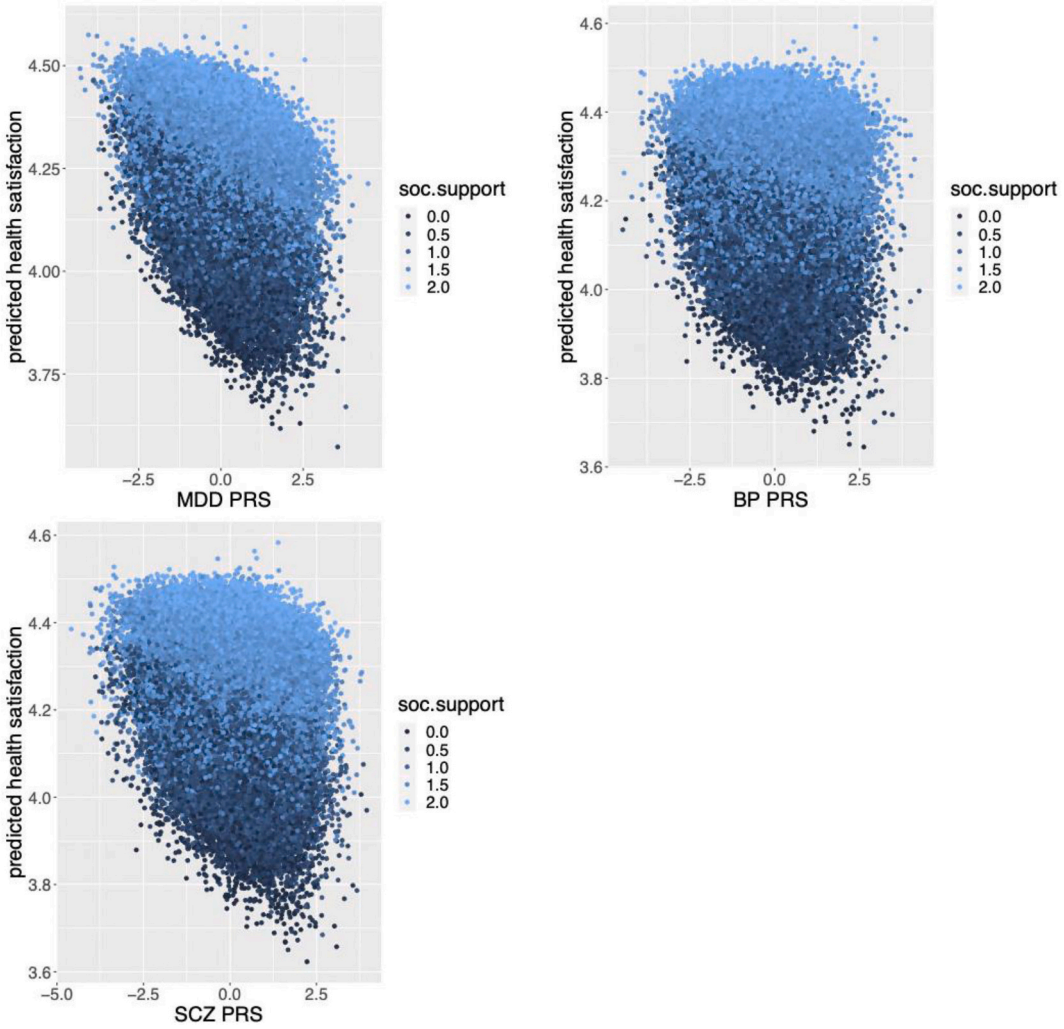

Fig. 2. significant interactions between PRSs and social support on the level of health satisfaction. The posterior distribution of Y derived from the regression models is represented.

suggest that the threshold over which a disease manifests is difficult to quantify, as it is not necessarily the same for all individuals/disorders. This appears a good reason to focus on measures of wellbeing and not only categorical diagnoses.

In some cases, the PRS of a psychiatric disorder can have a positive effect on wellbeing, with the exception of the top tail of the distribution (Gale et al., 2013). This is the case of BP PRS and both educational achievement and income (Niamh Mullins et al., 2021) (Wendt et al., 2021), in line with the observation that parental higher education and higher wealth are associated with increased risk of BP in the offspring (Tsuchiya et al., 2004). Our results confirmed the association between BP PRS and both qualifications and income (Supplementary Table 4), but they added that the presence of a current or recent stress event can reverse the effect on income.

When considering childhood events, we found no interaction. ADHD PRS x adoption was close to the significance threshold for an effect on qualifications, which was interesting because in line with previous evidence. ADHD PRS may decrease more the probability of having a University/College degree vs no qualification in nonadopted participants vs adoptees, despite not reaching the Bonferroni corrected alpha threshold, possibly because of the limited sample size included in this analysis. A previous study showed twice as much phenotypic variance in years of education explained by the education PRS in nonadopted individuals as in adoptees, confirming that genetic factors play a lower role in adoptees, and suggesting a mediating role of the home environment (Cheesman et al., 2020).

Our findings should be interpreted considering the limitations of this study. First, the measures of wellbeing were heterogenous in terms of their assessment and scale. We applied linear regression whenever possible, in line with the hypothesis that an additive interaction model better captures the biological mechanism of GxE interactions (Knol et al., 2007). However, the phenotypes qualifications and household income were measured using categories that could not be translated into a binary or Likert variable without applying an arbitrary and potentially misleading approach, therefore we opted for using multinomial regression (i.e., deviation from multiplicativity). We decided to not use linear regression for each pair of categories, as the distance/difference between each category and the reference category is expected to vary. Second, some phenotypes were relatively rare, particularly the variable adopted as a child (number of adoptees between 1264 and 5671, depending on the considered E variable), possibly explaining the lack of results surviving after multiple-testing correction. Third, UKB is not representative of the general UK population (Fry et al., 2017), and our analyses were limited to participants of European ancestry, which is the largest group in UKB. We decided to focus on the PRSs of four psychiatric disorders, as these showed a rationale for wellbeing modulation (see Introduction). Extending the analyses to other psychiatric disorders could have potentially added further insights, but we decided to focus on the selected ones, given the discussed rationale, and to limit the multiple-testing burden. Finally, environmental factors and covariates

explained most variance in wellbeing measures, and the addition of PRSs and PRSxE improved the variance marginally, but significantly, likely due to sample size. Co-variance between the analysed PRSs and E factors may have contributed to the marginal increase in R2 when adding PRSs and PRSxE to the models. However, disentangling this issue was beyond the aims of this study.

5. Conclusion

In conclusion, our results support that both positive and negative E factors have a strong effect on wellbeing measures, and some E factors interact with the PRSs of mood and related disorders on measures of wellbeing. Despite small contributions to the variance in outcomes at the population level, PRSxE effects might be relevant at the individual level, for example for people with very high level of risk factors or protective factors, in terms of PRSs or E variables. As people with high PRSs for psychiatric disorders appear more sensitive to the effects of environmental factors, they could benefit from prevention/therapeutic interventions based on their modification.

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Ethical standards

UK Biobank had obtained ethics approval from the Northwest Multicentre Research Ethics Committee (MREC) with approval number 11/NW/0382.

Declaration of generative AI in scientific writing

Generative artificial intelligence (AI) and AI-assisted technologies were not used in the writing process.

Author contributions

CF conceptualized the study, performed data analysis and wrote the original draft. CL and AS provided suggestions for data analysis, results interpretation and contributed to review & editing of the manuscript.

CRediT authorship contribution statement

Chiara Fabbri: Conceptualization, Formal analysis, Writing – original draft. **Cathryn M. Lewis:** Methodology, Writing – review & editing. **Alessandro Serretti:** Methodology, Writing – review & editing.

Declaration of competing interest

Chiara Fabbri was a speaker for Janssen.

Cathryn *M. Lewis* sits on the Scientific Advisory Board for Myriad Neuroscience, and she has been a consultant/speaker for SYNLAB and UCB.

Alessandro Serretti is or was a consultant/speaker for Abbott, Abbvie, Angelini, AstraZeneca, Clinical Data, Boehringer, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Innovapharma, Italfarmaco, Janssen, Lundbeck, Naurex, Pfizer, Polifarma, Sanofi, Taliaz and Servier.

Data availability

The UK Biobank resource is accessible to bona fide researchers for health-related research in the public interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2024.110972.

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