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Research paper

Polygenic risk for depression predicting temperament trajectories over 15 years – A general population study

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ABSTRACT

Background: A great number of case-control and population-based studies have shown that depression patients differ from healthy controls in their temperament traits. We investigated whether polygenic risk for depression predicts trajectories of temperament traits from early adulthood to middle age.
Methods: Participants came from the population-based Young Finns Study (n = 2212). The calculation for Polygenic risk for depression (PRS) was based on the most recent genome-wide association study. Temperament traits of Harm Avoidance, Novelty Seeking, Reward Dependence, and Persistence were assessed with the Temperament and Character Inventory in 1997, 2001, 2007, and 2012 (participants being 24–50-year-olds). As covariates, we used depressive symptoms as assessed by a modified version of the Beck Depression Inventory, psychosocial family environment from parent-filled questionnaires, and socioeconomic factors from adulthood.
Results: High PRS predicted higher Persistence from early adulthood to middle age ($p = 0.003$) when controlling for depressive symptoms, psychosocial family environment, and socioeconomic factors. PRS did not predict trajectories of Novelty Seeking ($p = 0.063$–0.416 in different models) or Reward Dependence ($p = 0.531$–0.736). The results remained unaffected when participants with diagnosed affective disorders were excluded. Additionally, we found an interaction between PRS and depressive symptoms when predicting the Harm Avoidance subscale Anticipatory Worry, indicating that the association of Anticipatory Worry with depressive symptoms is stronger in individuals with higher (vs. lower) PRS.
Limitations: There was some attrition due to the long follow-up.
Conclusions: High polygenic risk for major depression may predict differences in temperament trajectories among those who have not developed any severe affective disorders.

1. Introduction

Accumulating evidence has shown an association between temperament traits and depression. When temperament traits are considered one at a time, the most consistent finding from case-control and general population studies has been higher Harm Avoidance in depression patients when compared to healthy controls (Lim et al., 2018; Zaninotto et al., 2016). This finding is also evident in our dataset, i.e., in the Young Finns Study (Josefsson et al., 2011). Further, it seems that a current depressive state may transiently modify certain temperament traits: a meta-analysis concluded that high Harm Avoidance is associated both with a trait-like liability to depression and with current depressive states

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(Kampman and Poutanen, 2011). In clinical samples, a consistent decrease in Harm Avoidance has been reported during effective depression treatment (Kampman and Poutanen, 2011).

When interactions among temperament traits are considered, there are significant interactions between Harm Avoidance and Persistence (Cloninger et al., 2012). When considered alone, high Persistence is associated with increases in both positive and negative emotions, but in combination with Harm Avoidance it leads to negative perfectionism and reduced resilience to stress with increased anxiety and/or depression (Cloninger et al., 2012; Eley et al., 2013). More generally, low resilience with increased risk of depression and/or anxiety depends a personality configuration of high Harm Avoidance, high Persistence, and the character trait of low Self-directedness, which leads to susceptibility to discouragement from loss or failure (Cloninger et al., 2012). The role of Persistence in the regulation of distress in response depends on known specific brain circuitry that regulates behavioral responses to negative reinforcement (Cloninger et al., 2012; Gusnard et al., 2003).

Previous literature has demonstrated a strong genetic background of both temperament traits and depression. According to recent evidence, temperament is strongly influenced by >700 genes that modulate associative conditioning by molecular processes for synaptic plasticity and long-term learning and memory (Cloninger et al., 2019; Zwir et al., 2020). Regarding depression, the most recent GWAS on depression identified a total of 102 independent variants, including genes and gene pathways related to synaptic structure and neurotransmission, for example (Howard et al., 2019). Polygenic risk for depression (PRS) is estimated to explain ca. 5–10 % of the variation in the case-control status of depression (Halldorsdottir et al., 2019; Howard et al., 2018), with a standard deviation increase in polygenic risk for depression being associated with a 30 % increase in the hazard of depression (Musliner et al., 2019). The polygenic risk for depression correlates with depression severity in epidemiological cohorts (Halldorsdottir et al., 2019; Kwong et al., 2021). It is unknown, however, whether a high polygenic risk for depression predicts temperament traits linked to an increased liability to depression.

To date, findings have suggested an association between familial risk for depression and candidate genes for depression with temperament traits. First, a sib-pair study showed that temperament traits are related to the familiality of depression (Farmer et al., 2003). Second, candidate gene studies have reported correlations between temperament traits and polymorphisms related to serotonin transporter (5-HTTLPR), dopamine receptor (DRD4), monoamine oxidase (MAO-A) (Serretti et al., 2006), and brain-derived neurotrophic factor (BDNF) (Jiang et al., 2005) that, in turn, are related to depression (Karg et al., 2011; Liu et al., 2016; López León et al., 2005; Verhagen et al., 2010). The results from candidate gene studies, however, have not been replicated in all studies (Munafò et al., 2009; Tsuchimine et al., 2013). Furthermore, twin studies have shown that genetic factors explain a moderate to substantial portion of the relationship between personality and depressive symptoms and that TCI temperament traits and depression share a common genetical basis (Yuh et al., 2009; Ono et al., 2002; Yuh et al., 2008). To the best of our knowledge, no study has investigated whether polygenic risk for depression predicts temperament traits.

The present study investigated whether polygenic risk for depression predicts the developmental trajectories of temperament traits from early adulthood to middle age. We used the population-based Young Finns data with a 15-year prospective follow-up of Harm Avoidance, Novelty Seeking, Reward Dependence, and Persistence (participants being 24–50-year-olds). The data provided possibilities for taking into consideration a variety of potential confounders, such as psychosocial family environment, adulthood socioeconomic factors, and current depressive symptoms (Fig. 1).

2. Methods

2.1. Participants

The participants came from the Young Finns Study (YFS), which is an ongoing prospective follow-up study. The YFS started in 1980 (baseline study), and the participants have been followed since then. The sampling was designed to include a population-based sample of non-institutionalized Finnish children, representative with regard to sex (male vs. female), rural vs. urban environment, and Eastern vs. Western regions in Finland. The sample consisted of six age cohorts (born in 1962, 1965, 1968, 1971, 1974, or 1977). Altogether 4320 subjects were invited, and 3596 of them participated in the baseline study. The design of the YFS is described with further details elsewhere (Akerblom et al., 1985; Raitakari et al., 2008).

Measurements of temperament traits and depressive symptoms were conducted in 1997, 2001, 2007, and 2012, adulthood socioeconomic factors in 2011, and childhood family environment in 1980. In the present study, we included all the participants with data available on study variables and necessary covariates, varying between 1076 and 2212 in the analyses. The participants were aged between 20 and 35 years in 1997, between 24 and 39 years in 2001, between 30 and 45 years in 2007, and between 35 and 50 years in 2012, respectively.

The YFS has been carried out in accordance with the Declaration of Helsinki, and the study design has been approved by the ethical committees of all Finnish Universities with a medical faculty (Universities of Helsinki, Turku, Tampere, Kuopio, and Oulu). All the participants or their parents (participants aged <18 years) provided informed consent before participation.

2.2. Measures

2.2.1. Polygenic risk score for depression (PRS)

Genomic DNA was extracted from peripheral blood leukocytes using a commercially available kit and Qiagen BioRobot M48 Workstation according to the manufacturer's instructions (Qiagen, Hilden, Germany). Genotyping was done for 2556 samples using custom build Illumina Human 670k BeadChip atWelcome Trust Sanger Institute. Genotypes were called using the Illuminus clustering algorithm. Samples that failed Sanger genotyping pipeline QC criteria (i.e., duplicated samples, heterozygosity, low call rate, or Sequenom fingerprint discrepancy) were excluded from the analysis. Similarly, samples with sex discrepancy, low genotyping call rate (< 0.95), and possible relatedness (pi-hat > 0.2) were excluded from the analysis. Short Nucleotide Polymorphisms (SNPs) were excluded based on Hardy-Weinberg equilibrium test ($p \leq$ 1e-06), failed missingness test (call rate < 0.95) and failed frequency test (minor allele frequency < 0.01). After quality control, 546,677 genotyped SNPs were available for further analysis. Genotype imputation was performed using Minimac3 (Das et al., 2016) and 1000G phase3

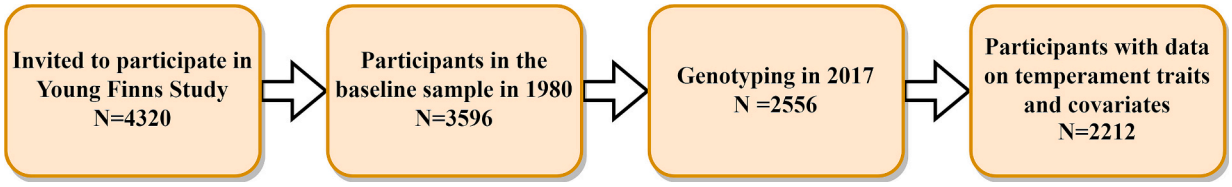

Fig. 1. An illustration of participant inclusion in the present study.

reference set on Michigan Imputation Server. A total of 102 SNPs related to clinical diagnosis of depression were identified using genomic data from a recent genome-wide meta-analysis of 807,553 individuals from the UK Biobank, 23andMe, and the Psychiatric Genomics Consortium PGC (p-value $<5 \times 10–8$) (Howard et al., 2019) were used for calculation of weighted polygenic risk score (PRS) for depression using Plink software (Purcell et al., 2007). For analyses, PRS was multiplied by 100 to have an appropriate scale.

Regarding the effect size of PRS when predicting depression-related outcomes, it has been found that polygenic risk scores for major depression predict suicide attempt in major depressive disorder (R^2 = 0.3 %) and bipolar disorder (R^2 = 0.2 %) (Mullins et al., 2019) and insomnia in major depressive patients ($R^2 = 1.75^{-3}$) (Melhuish Beaupre et al., 2021). A meta-analysis showed that polygenic risk for major depression was associated with non-response (OR = 1.10, p = 0.013, pseudo-R^2 = 0.2 %) and non-remission (OR = 1.14, p = 0.004, pseudo-R2 = 0.6 %) in patients with major depressive disorder (Fanelli et al., 2021). Our longitudinal data was analyzed with multilevel models that cannot estimate traditional R^2 values. However, if using simple regression analyses (predicting depression-related outcomes at one time point by the PRS), high PRS predicted higher depressive symptoms as measured with the Beck Depression Inventory (B = 5.483, p = 0.015, R^2 change = 0.8 %), the modified version of the Beck Depression Inventory (B = 0.527, p = 0.027, R^2 change = 0.9 %) and also higher exhaustion symptoms (B = 0.284, p = 0.044, R^2 change = 0.7 %) when controlling for age, sex, socioeconomic factors, and early family environment. Those estimates are slightly higher than in previous studies but are still likely to be underestimates because of a smaller sample size and lower statistical power than in our main analyses with multilevel models.

2.2.2. Temperament traits

Temperament traits were measured using the Temperament and Character Inventory (Cloninger et al., 1994). The inventory contains four temperament dimensions: Novelty Seeking, Harm Avoidance, Reward Dependence, and Persistence. Novelty Seeking consists of 40 statements which can be divided to four subscales: Exploratory Excitability, Impulsiveness, Extravagance, and Disorderliness. Harm Avoidance has 35 statements and consists of four subscales: Anticipatory Worry, Fear of Uncertainty, Shyness, and Fatigability. Despite the subscales of Harm Avoidance and depressive symptoms having apparent nominal overlap, their pairwise correlations (as measured by the same questionnaires used in this study) are not very high (r = 0.23–0.61) (Elovainio et al., 2004). Reward Dependence consists of 24 statements and has subscales for Sentimentality, Attachment, and Dependence. Persistence consists of 8 questions and has no subscales in the questionnaire used for this study. All the statements were self-rated using a five-point Likert scale (1 = definitively false, 5 = definitively true).

Temperament measurements were done in 1997, 2001, 2007, and 2012. For each measurement year, we calculated a mean score of all items of each scale for participants who had answered to at least 50 % of the items. The mean scores were standardized with the mean and standard deviation of the year 1997 measurement for the analyses to stabilize the scales of the growth curves of the temperament traits.

2.2.3. Depressive symptoms

Depressive symptoms were controlled for in the analyses since they are known to result in temporary changes in some temperament traits (Kampman and Poutanen, 2011). On the other hand, since depressive symptoms also correlate with genetic liability to depression, we included depressive symptoms only in one model (and reported the results also when not considering depressive symptoms). Depressive symptoms were assessed using a modified Beck Depression Inventory (mBDI) (Elovainio et al., 2006; Katainen et al., 1999). The original BDI consists of 21 sets of four statements with increasing severities, from which each participant chooses the most descriptive of his/her situation. The modified questionnaire consists of 21 statements (e.g., "I feel discouraged about the future" and "It takes an extra effort to get started at doing something") that are the second mildest statements from the original BDI questionnaire and are rated with a five-point Likert-scale (1 = definitively false, 5 = definitively true). The modified scale does not include cut-off values to diagnose a major depressive disorder but is designed to better capture mild and subclinical depressive symptoms in a non-clinical population. The modified scale of the BDI has been used also previously (e.g., Rosenström et al., 2012; Elovainio et al., 2015; Saarinen et al., 2018). We calculated a mean score of the answers for participants who had answered to at least 50 % of the items (i.e., the mean score ranged between 1 and 5). The questionnaire had good internal reliability in every measurement year (Cronbach's α = 0.886–0.913).

2.2.4. Socioeconomic factors in adulthood

Socioeconomic factors were included in the covariates since they may act as confounding variables when predicting the TCI temperament traits (Al-Halabí et al., 2010). Socioeconomic factors in adulthood included the participant's educational level, occupational status, and annual income level. These covariates were all self-reported. Educational level is composed of three levels (1 = comprehensive school, 2 = high school or occupational school, 3 = academic level), as was occupational status (1 = manual worker, 2 = lower-grade non-manual worker, 3 = higher-grade non-manual worker). Annual income consisted of 13 levels (1 $\leq$ 5000€, 13 $\geq$ 60,000€). All the socioeconomic variables were treated as continuous in the analyses.

2.2.5. Childhood psychosocial environment

Finally, we adjusted the analyses for the qualities of childhood family environment since parental care-giving and home environment are found to significantly predict the TCI temperament traits in adulthood (Josefsson et al., 2013b). All the childhood environmental characteristics were assessed with questionnaires presented to the parents in 1980. In case there were missing values in 1980, we imputed them using data from the closest possible follow-up point (in 1983). The cumulative score of stressful life events included the following factors: changes of residence, changes of school, parental divorce (parents living together or separated), mother's or father's death, mother's or father's hospitalization within the past 12 months, and child's hospitalization due to sickness or accident. The cumulative score of adverse socioeconomic circumstances included the following factors: parents' occupational status, educational level, family income, unstable employment situation, and overcrowded apartment. The cumulative score of unfavourable emotional family atmosphere included the following factors: emotional distance between the child and parent, parental intolerance toward the child, strict discipline toward the child, parental life dissatisfaction, mother's or father's mental disorder, and mother's or father's frequent alcohol intoxication. The cumulative scores have been used also previously (Saarinen et al., 2022) and are described with further details in the **Supplementary Methods**. To summarize, each cumulative risk score was calculated as a total score of single risk factors (each risk factor was first standardized by age cohort (M = 0, SD = 1 within each age cohort). In this way, the cumulative risk scores could have also negative values (if a participant had on average a lower exposure to risk factors than the other participants in his/her age cohort).

2.3. Statistical analyses

All analyses were conducted using SPSS 28 (SPSS Inc., Chicago, IL, USA). First, attrition analyses were done by comparing the study variables between included (n = 2212) and dropped-out (n = 1384) participants using independent samples t-tests, Mann-Whitney U tests, and chi-square tests.

We used linear mixed models with maximum likelihood estimation to investigate the linear connections between PRS and trajectories of temperament traits. In the analyses, we used full-information maximum

likelihood estimation and, thus, included all the participants who had data available on the follow-up variables in at least one measurement year (data available on temperament traits and depressive symptoms in 1997, 2001, 2007, and/or 2012). Missing values in the covariates measured only once (i.e., qualities of early family environment in 1980 and adulthood socioeconomic factors in 2011) resulted in listwise deletion. Thus, the analysis sample varied between 1076 and 2212 in the analyses.

Statistical assumptions for linear mixed models were found to be approximately fulfilled. Linear mixed models estimate fixed and random effects. Fixed effects can be interpreted similarly to regression coefficients (i.e., group-level estimates), while random effects refer to individual-level variance in the intercept and residual variance. We estimated a separate linear mixed model for the trajectory of each temperament trait. PRS was included in the fixed effects (i.e., the main effect of PRS on a temperament trait over the follow-up). Fixed effects included also the intercept and different sets of covariates in three models. Model 1 was adjusted for age, age squared, and sex, because polygenic risk scores have been previously shown to have age-dependent effects (Saarinen et al., 2022). The fixed effect of age estimates the linear change in a temperament trait over age, while the fixed effect of age^2 estimates the quadratic change in a temperament trait over age. These age-effects were included since the TCI temperament traits are known to display linear and quadratic changes over age (Josefsson et al., 2013a). Subject id (grouping variable) and intercept were used as random effects in all the models (i.e., we allowed the intercept to vary between the participants). We did not include PRS in the random effects (i.e., we did not allow the regression coefficient of PRS to vary between different participants when predicting TCI traits) because the statistical fit of the models reduced if adding the random effect of PRS.

We also ran two other models with further covariates (fixed effects). Model 2 was additionally adjusted for the three cumulative scores of psychosocial family environment that have been previously found to predict depressive symptoms in this dataset (Elovainio et al., 2015). Model 3 was additionally adjusted for adulthood socioeconomic factors and current depressive symptoms because, first, socioeconomic factors are shown to associate with depressive symptoms in this dataset (Elovainio et al., 2012) and, second, current depressive symptoms are known to result in temporary changes in temperament traits (Kampman and Poutanen, 2011).

Finally, to correct for multiple testing, we used false discovery rate (FDR) correction with Benjamini-Hochberg procedure to correct the *p*-values of the main analyses (Benjamini & Hochberg, 1995). Also, we calculated Nagelkerke's pseudo-R^2 values for each model (multilevel models cannot estimate traditional R^2 values). Although pseudo-R^2 values cannot be directly interpreted as the percentage of explained variance, pseudo-R^2 values can provide useful information when making comparisons between different models.

3. Results

The mean, standard deviation, frequency, and measurement range of the study variables are presented in Table 1.

Results of the attrition analyses showed that the included participants scored slightly lower in Novelty Seeking (3.03 vs 2.97, $p < 0.001$, Cohen's d = 0.16) and Harm Avoidance (2.67 vs 2.61, $p = 0.011$, Cohen's d = 0.11), and higher in Reward Dependence (3.24 vs 3.32, $p < 0.001$, Cohen's d = −0.20) than dropped-out participants. There was no attrition bias in Persistence. Women were more likely to participate than men (55.7 % vs 44.3 %, $p \leq 0.001$). Included participants were more likely to have academic-level education (23 % vs 5.8 %, $p = 0.001$) and to be in upper-grade non-manual work (26.9 % vs 7.7 %, p = 0.001) than dropped-out participants but had approximately similar adulthood income.

Table 1
Descriptive statistics of study variables.

	Mean (*SD*)	Frequency (%)	Measurement range
Age (1997)	27.56 (5.04)		20–35
Sex (Male)		981 (44.3)	
Polygenic risk for depression	−0.08 (0.08)		min = −0.35, max = 0.29
Novelty Seeking[a]			
1997	3.03 (0.40)		1–5
2001	2.99 (0.40)		1–5
2007	2.93 (0.38)		1–5
2012	2.88 (0.38)		1–5
Harm Avoidance[a]			
1997	2.65 (0.49)		1–5
2001	2.59 (0.53)		1–5
2007	2.60 (0.51)		1–5
2012	2.60 (0.52)		1–5
Reward Dependence[a]			
1997	3.36 (0.44)		1–5
2001	3.36 (0.44)		1–5
2007	3.31 (0.44)		1–5
2012	3.30 (0.43)		1–5
Persistence[a]			
1997	3.22 (0.55)		1–5
2001	3.21 (0.56)		1–5
2007	3.26 (0.54)		1–5
2012	3.19 (0.54)		1–5
Depressive symptoms			
1997	2.12 (0.65)		1–5
2001	2.06 (0.66)		1–5
2007	2.07 (0.66)		1–5
2012	2.04 (0.66)		1–5
Cumulative scores of family environment (1980)			
Stressful life events	−0.01 (0.40)		min = −0.50, max = 2.24
Adverse socioeconomic circumstances	−0.03 (0.65)		min = −1.35, max = 2.93
Unfavourable emotional family atmosphere	−0.02 (0.44)		min = −1.66, max = 2.69
Educational level (2011)			
Comprehensive school		217 (9.8)	
Occupational school or high school		818 (37.0)	
Academic level		562 (25.4)	
Occupational status (2011)			
Manual worker		274 (12.4)	
Lower-grade non-manual worker		581 (26.3)	
Upper-grade non-manual worker		627 (28.3)	
Income level (2011)	7.40 (3.05)		1–13

[a] Standardized with the mean and standard deviation of 1997 for analyses.

3.1. Main analyses: the main effect of PRS on temperament trajectories

The results of the linear mixed models can be seen in Table 2 (see **Supplementary Tables 1–4** for further details). The fixed effect of PRS on the trajectory of Harm Avoidance was non-significant in all of the models: in Model 1 ($p = 0.448$, adjusted for age, age^2, and sex), in Model 2 ($p = 0.535$, additionally adjusted for cumulative scores of psychosocial family environment and adulthood socioeconomic factors), in Model 3 ($p = 0.228$, additionally adjusted for depressive symptoms). Similarly, PRS did not have any significant fixed effect on the trajectory of Novelty Seeking (p = 0.063, $p = 0.399$, $p = 0.416$ in Models 1–3, respectively) or Reward Dependence ($p = 0.531$, $p = 0.736$, $p = 0.672$ in Models 1–3, respectively). Finally, we found that PRS had a positive association (fixed effect) with Persistence when controlling for adulthood socioeconomic factors (B = 0.939, $p = 0.003$, Model 2) and when also controlling for depressive symptoms (B = 0.931, p = 0.003, Model 3) but not in Model 1 when those factors were non-controlled ($p = 0.520$). This finding is illustrated in Fig. 2. Nagelkerke's pseudo-R^2 values ranged between 0.58 and 0.59 in Models 1–3 when predicting Persistence, between 0.70 and 0.71 when predicting Novelty Seeking or Reward Dependence, and between 0.70 and 0.79 when predicting Harm Avoidance.

Next, we investigated whether the association of PRS with TCI traits could be modified by age. For that purpose, we added the age*PRS interaction effect and the age^2*PRS interaction effect (to examine whether the connection of PRS with TCI traits could change over age in a linear or curvilinear manner). This analysis was done because previous studies have reported such interactions between age and polygenic risk scores when predicting psychological development (Saarinen et al., 2023; Saarinen et al., 2022). We did not find any significant interaction effects of age*PRS or age^2*PRS when predicting temperament traits. Thus, participants' age (participants were 24–50-year-olds during the follow-up) did not modify the association of PRS on trajectories of temperament traits. The interaction between PRS and sex was non-significant when predicting temperament traits.

The results remained unaffected when including only participants without diagnosed affective disorders (n = 1053–2015, see **Supplementary Methods** for collection of psychiatric diagnoses). That is, PRS did not predict Harm avoidance (p = 0.235–0.854 in Models 1–3), Reward Dependence (p = 0.477–0.721), or Novelty Seeking (p = 0.054–0.362). High PRS predicted a higher curve of Persistence in Models 2 and 3 ($p = 0.004$).

Since the subscales of the TCI traits are shown to have different associations with depressive symptoms (Elovainio et al., 2004), we next examined the effect of PRS on the trajectories of the subscales of Novelty Seeking (i.e., Exploratory Excitability, Impulsiveness, Extravagance, and Disorderliness), Harm Avoidance (i.e., Anticipatory Worry, Fear of Uncertainty, Shyness, and Fatigability), and Reward Dependence (i.e., Sentimentality, Attachment, and Dependence). The models used here were otherwise identical to the ones used in the main analyses. High PRS was associated with slightly lower Fatigability in Model 3 (B = −0.498, $p = 0.033$), but this prediction did not survive after FDR correction for multiple testing. There were no significant associations of PRS with the other subscales of Novelty Seeking (p = 0.197–0.956 in Models 1–4), Harm Avoidance (p = 0.058–0.990), or Reward Dependence (p = 0.251–0.990).

3.2. Additional analyses: the interaction between PRS and depressive symptoms on temperament trajectories

In additional analyses, we investigated whether depressive symptoms modify the relationship between PRS and temperament trajectories (i.e., we added the interaction of PRS*depressive symptoms to the model). This was done because there is evidence for depression-induced changes in the TCI traits (Kampman and Poutanen, 2011) and because previous studies (Goldberg et al., 2014; Salminen et al., 2023) give references that depressive states might result in stronger changes of TCI traits in those with higher (vs. lower) genetic liability to depression. The interaction was significant when predicting Anticipatory Worry (B = 0.763, $p = 0.010$) but nonsignificant when predicting any other main scale or subscale (p = 0.099–0.521). This finding is illustrated in Fig. 3.

4. Discussion

This was the first study to examine the relationship between polygenic risk for depression (PRS) and trajectories of TCI temperament traits. As a main result, high PRS predicted an elevated trajectory of Persistence from early adulthood to middle age when controlling for a broad set of covariates. PRS did not have any main effect on Novelty seeking, Reward Dependence, or their subscales. These findings remained regardless of including or excluding participants with diagnosed affective disorders, or controlling for depressive symptoms or not. Additionally, we found an interaction between PRS and depressive symptoms when predicting Harm Avoidance subscale Anticipatory Worry, indicating that the association of Anticipatory Worry with depressive symptoms is stronger in individuals with higher PRS.

High PRS predicted higher Persistence from early adulthood to middle age. This association seems not to be explained by genetic overlap because the SNPs linked to Persistence in previous studies in which genes were questionably assumed to act independently of one another (Service et al., 2012) have no overlap with the SNP's included in our polygenic risk score for depression. The scale of Persistence partially measures trait perfectionism (items such as “I am more of a perfectionist than most people”; “Usually I work harder than most people, because I

Table 2
Fixed effect of PRS when predicting the trajectories of the TCI traits with polygenic risk for depression (PRS) using linear mixed models.

	Model 1 (n = 2211)			Model 2 (n = 1076)			Model 3 (n = 1076)		
	B	*SE*	*p*	B	*SE*	*p*	B	*SE*	*p*
Harm Avoidance									
PRS	0.187	0.247	0.448	−0.207	0.333	0.535	−0.327	0.271	0.228
Novelty Seeking									
PRS	−0.428	0.230	0.063	−0.274	0.325	0.399	−0.264	0.325	0.416
Reward Dependence									
PRS	−0.133	0.212	0.531	0.099	0.293	0.736	0.123	0.291	0.672
Persistence									
PRS	0.147	0.229	0.520	**0.939**	**0.317**	**0.003**	**0.931**	**0.317**	**0.003**

SE = standard error.
Bolded values indicate statistical significance after Benjamini-Hochberg correction for multiple testing.
Model 1 was adjusted for age and sex.
Model 2 was additionally adjusted for the cumulative scores of psychosocial family environment and socioeconomic factors in adulthood.
Model 3 was additionally adjusted for depressive symptoms.
Note: The sample size varied between the models due to different amounts of missing values in the covariates.

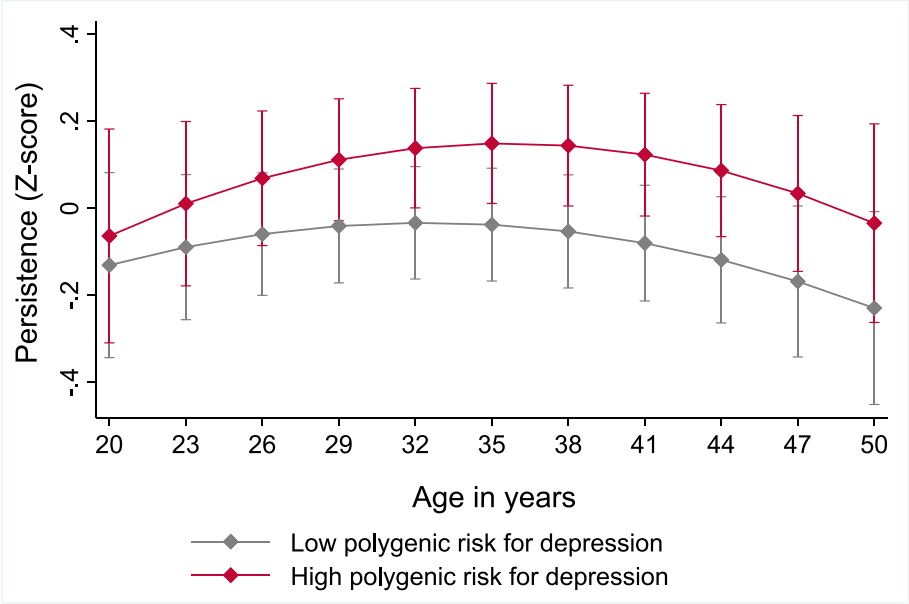

Fig. 2. Model-predicted trajectory of Persistence separately for participants with low PRS (−1 standard deviation) and high PRS (+1 standard deviation). Note: Adjusted for sex, psychosocial family environment, socioeconomic factors, and depressive symptoms.

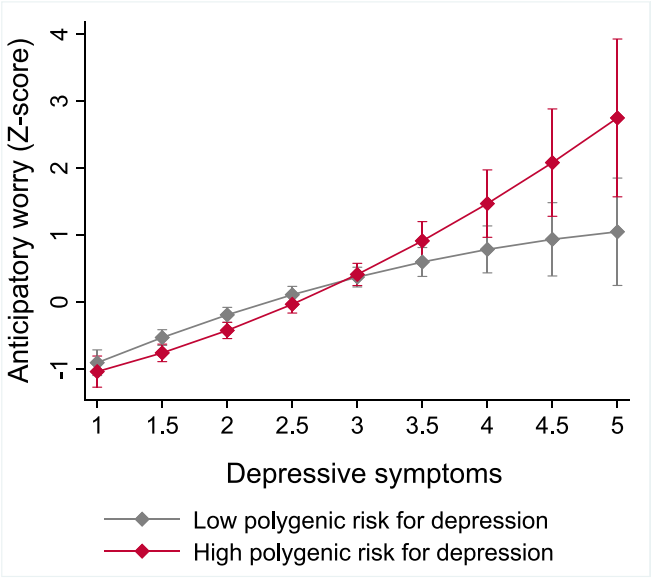

Fig. 3. Model-predicted trajectory of Anticipatory Worry at different levels of depressive symptoms separately for participants with low PRS (−1 standard deviation) and high PRS (+1 standard deviation).

want to succeed as well as possible"). High perfectionism has been linked to various forms of psychopathology, but most significantly to depression (Limburg et al., 2017) and anxiety disorders (Cloninger et al., 2012). Interestingly, high Persistence has previously been associated with greater health and overall happiness in combination with low Harm Avoidance and high Self-Directedness (Cloninger et al., 2012). However, such trait profiles were outside of the scope of our study but remain a topic for future studies. Finally, we found the association between PRS and Persistence only after controlling for adulthood socioeconomic status. This is in line with previous studies showing that low adulthood socioeconomic status correlates with higher polygenic risk for major depression (Machlitt-Northen et al., 2022) and higher depressive symptoms (Ridley et al., 2020).

Previous studies have shown that Harm Avoidance has a strong genetic background (Service et al., 2012) and is linked to increased depressive symptoms (Elovainio et al., 2004) and dysphoria in this same dataset (Rosenström et al., 2014). The current study did not find any significant main effect of PRS on the trajectory of Harm Avoidance. This null finding may not be fully explained by a lack of statistical power since we observed a consistent and significant link between PRS and Persistence. Second, we used linear mixed models that are more sensitive to obtain also modest differences in longitudinal trajectories (Gelman and Hill, 2006). Third, a roughly similar sample size has been enough to obtain associations between polygenic risk scores and psychological development also previously (Saarinen et al., 2023).

We found, however, an interaction between PRS and depressive symptoms when predicting Anticipatory Worry and Shyness (subscales of Harm Avoidance), indicating that high PRS starts to predict higher Anticipatory Worry only at high levels of depressive symptoms. Previous research has demonstrated a two-way relationship between Harm Avoidance and depressive symptoms: high Harm Avoidance predicts an increased risk for depressive symptoms (Kampman and Poutanen, 2011), but also severe depressive symptoms or a high cumulative number of depressive episodes predict an increase in Harm Avoidance (Kampman and Poutanen, 2011; Nery et al., 2009). Our study further showed that the association of anticipatory worry with depressive symptoms is stronger in individuals with higher PRS.

This study had some limitations that are necessary to be taken into consideration. First, as is common in longitudinal studies, there was some degree of drop-out over the follow-up. Included (vs. dropped-out) participants were more likely to be women, to have an academic-level education and to be in upper-grade non-manual work, and to have lower Novelty Seeking and Harm Avoidance and higher Reward Dependence. Second, although PRS predicted depressive symptoms in this dataset, its predictive power was not very strong. As a recent review stated (Murray et al., 2021), polygenic risk scores do not, nor should they be expected to, fully predict for common complex conditions such as depression or personality traits. Nevertheless, our PRS was calculated based on the most recent GWAS study on clinical diagnosis of depression (Howard et al., 2019). A PRS consisting of SNPs related to non-clinical depressive symptoms might yield more generalizable results in a population-based dataset. As strengths, this study used a comparatively large population-based sample, including a 15-year follow-up of temperament traits with four different measurement times and an

extensive set of potential confounding variables. Additionally, this study utilized diagnostic data collected from the Finnish Care Register for Health Care.

In conclusion, previous studies have demonstrated an association between temperament dimensions (such as Harm Avoidance and Persistence) and depressive symptoms (Elovainio et al., 2004) and between temperament dimensions and neurotransmitter polymorphisms (Verhagen et al., 2010). Our study provided evidence that polygenic risk for major depression may predict differences in temperament trajectories, also among those without diagnosed affective disorders.

CRediT authorship contribution statement

Veikka Lavonius: Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Liisa Keltikangas-Järvinen:** Conceptualization, Data curation, Funding acquisition, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Binisha Hamal Mishra:** Formal analysis, Investigation, Methodology, Writing – review & editing. **Elina Sormunen:** Investigation, Methodology, Writing – review & editing. **Mika Kähönen:** Data curation, Investigation, Writing – review & editing. **Olli Raitakari:** Data curation, Funding acquisition, Methodology, Resources, Writing – review & editing. **Jarmo Hietala:** Data curation, Funding acquisition, Methodology, Resources, Writing – review & editing. **C. Robert Cloninger:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Terho Lehtimäki:** Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing. **Aino Saarinen:** Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

None.

Data availability

The Cardiovascular Risk in Young Finns (YFS) dataset comprises health-related participant data, and their use is therefore restricted under the regulations on professional secrecy (Act on the Openness of Government Activities, 612/1999) and on sensitive personal data (Personal Data Act, 523/1999, implementing the EU data protection directive 95/46/EC). Due to these legal restrictions, the data from this study cannot be stored in public repositories or otherwise made publicly available. However, data access may be permitted on a case by case basis upon request. Data sharing outside the group is done in collaboration with YFS group and requires a data-sharing agreement. Investigators can submit an expression of interest to the chairman of the publication committee (Prof. Mika Kähönen, Tampere University, Finland, mika.kahonen@tuni.fi).

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The funding sources had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2024.01.093.

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