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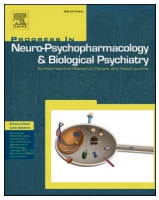

Polygenic risk for neuroticism is associated with externalizing symptoms in 2-year-old boys

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ABSTRACT

Recent advances in genome-wide association studies have enabled the estimation of genetic risk of complex traits, including neuroticism, with polygenic risk scores (PRS). Neuroticism PRS has been associated with psychiatric disorders and symptoms in adults, but studies in children are scarce. We studied whether neuroticism PRS, and its subscales, worry PRS and depressive affect PRS, were associated with externalizing and internalizing symptoms in 2-year-olds. We also examined parental neuroticism PRSs' association with children's externalizing and internalizing symptoms and whether parental depressive symptoms mediated the effect. Participants from two Finnish birth cohorts, CHILD-SLEEP and FinnBrain Birth Cohort Study, who had DNA and data on Brief Infant-Toddler Social and Emotional Assessment (BITSEA) available were included in the study ($N = 806$ and $N = 987$, respectively). PRSs were calculated based on GWAS data from UK Biobank. Child's neuroticism PRS, and its subscale worry PRS, were positively associated with externalizing symptoms in 2-year-old boys, but not in girls. Mother's depressive symptoms mediated the association between maternal neuroticism PRS and externalizing and internalizing symptoms in boys, but not in girls. Our results suggest that neuroticism PRS, and its subscale worry PRS, are associated with externalizing symptoms in already as young as 2-year-old boys, and, that subclinical symptoms of maternal depression that are based on genetic disposition, have an effect on boy's internalizing and externalizing symptoms. As we did not find any associations in girls, our study supports the suggestion that girls and boys may differ in how genetic and environmental factors contribute to their development.

1. Introduction

Neuroticism is a moderately stable, heritable personality trait characterized by a tendency to experience negative feelings. It has been shown to predispose to many health issues, including psychiatric disorders (Widiger and Oltmanns, 2017). The heritability of neuroticism has been evaluated to be as high as 40–50% (Vukasović and Bratko, 2015), although the SNP-based heritability, which is based on additive effects of genetic variants, is considerably lower, around 10% (Okbay et al., 2016). Large genome-wide association studies (GWAS) in recent years have shown that neuroticism is extremely polygenic, and that the genetic risk for neuroticism – like basically all complex behavioral traits

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– is best estimated by the joint effect of thousands of genetic loci (de Moor et al., 2015; Okbay et al., 2016; Nagel et al., 2018). Polygenic risk scores (PRS), which utilize published GWAS results and summarize the cumulative effect of numerous risk alleles into one score (Wray et al., 2021), are now widely used in estimating the genetic risk for complex traits, including neuroticism. However, PRSs for different psychiatric disorders and traits, including neuroticism, overlap and are somewhat difficult to disentangle, due to significant genetic correlations between them (Nagel et al., 2018; Okbay et al., 2016).

In adults, neuroticism PRS has been associated with higher likelihood of psychiatric disorders, including anxiety, phobias and Major Depressive Disorder (Docherty et al., 2018; de Moor et al., 2015), and with higher depressive symptoms (Kwong et al., 2021). In addition, it has been associated with many health-related PRSs, including PRS for triglycerides and PRS for coronary artery disease (Docherty et al., 2018). In children, however, there are fewer studies. In two recent studies, neuroticism PRS was associated with general psychopathology (Neumann et al., 2021) and case-control status in a clinical psychiatric child and adolescent sample (Jansen et al., 2021).

Psychiatric symptoms can be classified into internalizing (e.g. anxiety, depression and withdrawal) and externalizing (e.g. aggression, impulsivity and rule-breaking behavior) ones to define, study and understand socioemotional problems and psychopathology in young children (Achenbach, 1966). Neuroticism as a trait, or negative emotionality – a temperament trait that has been argued to resemble neuroticism in young children – is suggested to play an important role in the etiology and maintenance of internalizing and externalizing symptoms in childhood (Muris and Ollendick, 2005). As genetic factors have been shown to explain around 50% of variability in internalizing and externalizing symptoms (van der Valk et al., 2003), the possible role of neuroticism PRS as a genetic risk factor for these symptoms becomes plausible. So far, the association has been examined in two studies, which found neuroticism PRS to be associated with internalizing symptoms and psychopathology in children aged four years and older (Neumann et al., 2021; Akingbuwa et al., 2020). However, to our knowledge, there are no studies performed in younger children. Neither has its two distinct subscales, worry and depressed affect, which show considerable genetic differences (Nagel et al., 2018), been examined in adults or children.

As neuroticism PRS in adults is associated with depressive symptoms (Kwong et al., 2021), and depressive symptoms of mothers (Goodman et al., 2011; Pietikäinen et al., 2020) and fathers (Ramchandani et al., 2005) are associated with internalizing and externalizing symptoms in children, we examined, for the first time, also the effect of parental neuroticism PRS on child's internalizing and externalizing symptoms and if the parental symptoms mediated the association.

Boys and girls may differ in the genetic architecture of traits (Bernabeu et al., 2021), and, furthermore, have different sensitivity to environmental exposures, with mostly boys showing more sensitivity to environmental adversities (DiPietro and Voegtline, 2017). The reasons for the differences are not yet fully understood, but the possibility of sex differences in psychosocial development already in early childhood needs to be considered. Accordingly, we analyzed girls and boys separately in this study.

We examined 1) whether neuroticism PRS is associated with internalizing and externalizing symptoms already in as young as 2-year-old children, and 2) the role of the two subscales, worry PRS and depressed affect PRS, in these associations. We also studied 3) the effect of parental neuroticism PRS on children's internalizing and externalizing symptoms and whether parental depressive symptoms mediated the effect. We analyzed girls and boys separately, because of the emerging evidence that the effects of both genetic and environmental factors might differ in the two sexes. The study questions were analyzed in two independent Finnish birth cohorts.

2. Methods

2.1. Study samples

The study utilizes data from two Finnish birth cohorts, CHILD-SLEEP (CS) and FinnBrain Birth Cohort Study (FB) (www.finnbrain.fi), which have been systemically recruited during pregnancy and do not have overlapping families or individuals. The recruitment and study protocols have been described in more detail earlier (CS: Paavonen et al., 2017; FB: Karlsson et al., 2018). The ethics committees of Pirkanmaa Hospital District (CS) and the Hospital District of Southwest Finland (FB) have approved the study protocols and written informed consent has been obtained from all the parents. The study samples consist of the children that participated in the 2-year follow-ups and who had DNA and questionnaire data available (CS: $N = 806$; FB: $N = 987$). Ethnicity of all the participants included in the study was white.

2.2. Measures

Child externalizing and internalizing symptoms were assessed as a part of the 2-year follow-up by the Brief Infant-Toddler Social and Emotional Assessment (BITSEA) (Briggs-Gowan et al., 2004). BITSEA includes 42 items, of which 7 items assess externalizing and another 14 items internalizing symptoms, evaluated on a three-level rating scale. The possible ranges of the scores were 0–14 for externalizing and 0–28 for internalizing symptoms. Distributions of the scales are presented in Figs. S2 and S3 (see supplementary information). In CS the questionnaires were rated mostly by mother (69%), by mother and father together (30%), or by father (1%), and in FB separately by both mothers and fathers. For our main analyses we used the maternal assessments in FB. In supplementary analyses we used the paternal assessments in the FB sample (see supplementary information).

Maternal and paternal depressive symptoms were measured using the Finnish, shortened version (Kohout et al., 1993) of the Center for Epidemiological Studies Depression Scale (CES—D) (Radloff, 1977) (CS) and the Finnish version of the Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987) (FB) at the 2-year follow-ups. Both scales contain 10 items rated on a four-level rating scale. Ratings were summarized to one score ranging from 0 to 30 (higher scores reflecting more depressive symptoms). For CS, a dichotomous trajectory variable indicating continuously high/low depressive symptoms over two years (measurements at prenatal phase, 3 months, 8 months, and 2 years of child's age; see details Kiviruusu et al., 2020) was available and used as a covariate in the regression analyses. For the FB cohort similar variable was not available and depressive symptoms at the 2-year follow-up were used as a continuous score. Continuous scores (2-year follow-up) were used in the path analyses for both samples.

Neuroticism PRS. DNA samples extracted from umbilical blood were genotyped with Illumina Infinium PsychArray (CS, FB) and Illumina Infinium Global Screening Array (FB). Markers were removed for missingness (> 5%) and Hardy–Weinberg equilibrium (p-value $<1 \times 10^{-6}$). Individuals were checked for missing genotypes (> 5%), relatedness (identical by descent calculation, PI_HAT >0.2) and population stratification (multidimensional scaling). Genotyped data of both cohorts were pre-phased with Eagle 2.3.5 (Loh et al., 2016) and imputed with Beagle 4.1 (Browning and Browning, 2016) using the Finnish population-specific SISu v2 imputation reference panel. MDS plots for both cohorts are presented in Figs. S4 and S5 (see supplementary information).

Neuroticism PRS and the subscales depressed affect PRS and worry PRS were based on published GWAS summary statistics (Nagel et al., 2018, we used data on UK Biobank only). We used PRSice program (Euesden et al., 2015) to estimate the PRSs for the studied individuals. We accounted for LD by using the LD-clumping commands (−-clump-kb 500, −-clump-p 1.000000 and –clump-r2 0.250000). We used the p-value threshold of 0.1 ($N = 113{,}522$ SNPs) in our analyses, because it

was one of the best-fit p-value thresholds for neuroticism calculated with PRSice in the original GWAS study (Nagel et al., 2018), and it has been used also in other studies (Ahrens et al., 2022). We analyzed other thresholds (0.001, 0.05, 0.3, 0.5 and 1) in supplementary analyses (see supplementary information). PRS scores were normally distributed in both samples (CS and FB) and available for $N = 820$ (CS) and $N = 1044$ (FB) children and for $N = 188$ (CS) and $N = 122$ (FB) participants' parents.

2.3. Statistical analysis

We had three aims in our study 1) to analyze the association between child neuroticism PRS and externalizing and internalizing symptoms in 2-year-old children 2) to analyze which of the two subscores of neuroticism PRS, worry PRS or depressed affect PRS (or both), was associated with internalizing or externalizing symptoms in the case of significant findings in Aim 1, and 3) to examine the effects of parental neuroticism PRS on children's externalizing and internalizing symptoms. We analyzed non-response using *t*-tests for independent samples to evaluate whether children having missing data on externalizing and internalizing symptoms differed from children with non-missing data on neuroticism PRS. Aims 1 and 2. We examined the associations between *children's neuroticism PRS* and externalizing and internalizing symptoms in two separate regression models, with the first three principal components calculated from genetic data to control for population stratification and maternal depressive symptoms as covariates. Age was not a covariate, because all the children were 2-year-olds. We analyzed boys and girls separately, because of the emerging evidence of differential associations by child's sex in both genetic and environmental effects. We ran the analyses separately in the two birth cohorts, CS and FB, because ethical permissions prevented us to combine the data sets, and used meta-analysis to combine the results. We interpreted only the results of the meta-analysis. We did not adjust our analyses for multiple testing, because our main aim was to analyze two pre-determined research hypotheses (Aim1). In the case of significant findings in Aim 1, we analyzed the associations between *worry PRS* and *depressed affect PRS*, and externalizing and internalizing symptoms in children, with similar procedure. To gain further insight into the significant associations, we ranked boys according to their score on the neuroticism PRS and calculated a mean value of externalizing symptoms using a sliding window (width = 100) for the PRS to smoothen the data. We repeated the procedure with worry PRS and performed these analyses separately in the two datasets, CS and FB. We used IBM SPSS 26 for the regression analyses. The meta-analysis was performed with R 4.1.1 using the package "meta" (version 4.12–0) and fixed-effects model.

We examined the effect of *parent's neuroticism PRS* on children's externalizing and internalizing symptoms in a path model (Fig. 1) including direct and indirect paths from mother's and father's neuroticism PRSs to child's externalizing or internalizing symptoms. We performed a multiple group analysis with two groups, CS and FB, and ran the analyses separately for boys and girls. More detailed description of the fitting procedure is presented in supplementary information. We assessed the following model fit indices using the conventional thresholds for theses indices: χ^2 test not significant, CFI (robust), TLI (robust) > 0.95, RMSEA <0.06 and SRMR <0.08 (Hu and Bentler, 1999). Our data sets deviated significantly from multivariate normality, and we used the robust maximum-likelihood estimation and standardized variables. We used R 4.1.1 and the package "lavaan" (version 0.6–9) for the path analyses, and the package "MVN" (version 5.9) to test multivariate normality of the data.

3. Results

Boys had higher scores on externalizing symptoms ($p < 0.001$) than girls in both samples: boys had 0.23 (CS) and 0.35 (FB) standard deviations higher scores than girls (Table 1). The correlations between externalizing and internalizing symptoms were $r = 0.20$, $p < 0.001$ (CS boys), $r = 0.36$ $p < 0.001$ (CS girls), $r = 0.32$ $p < 0.001$ (FB boys) and $r = 0.24$ $p < 0.001$ (FB girls). There were no differences between the sexes in any of the PRSs or principal components calculated from genetic data in either of the samples (all Bonferroni-corrected *p*-values >0.1). Neuroticism PRS was significantly associated with missing data in both CS and

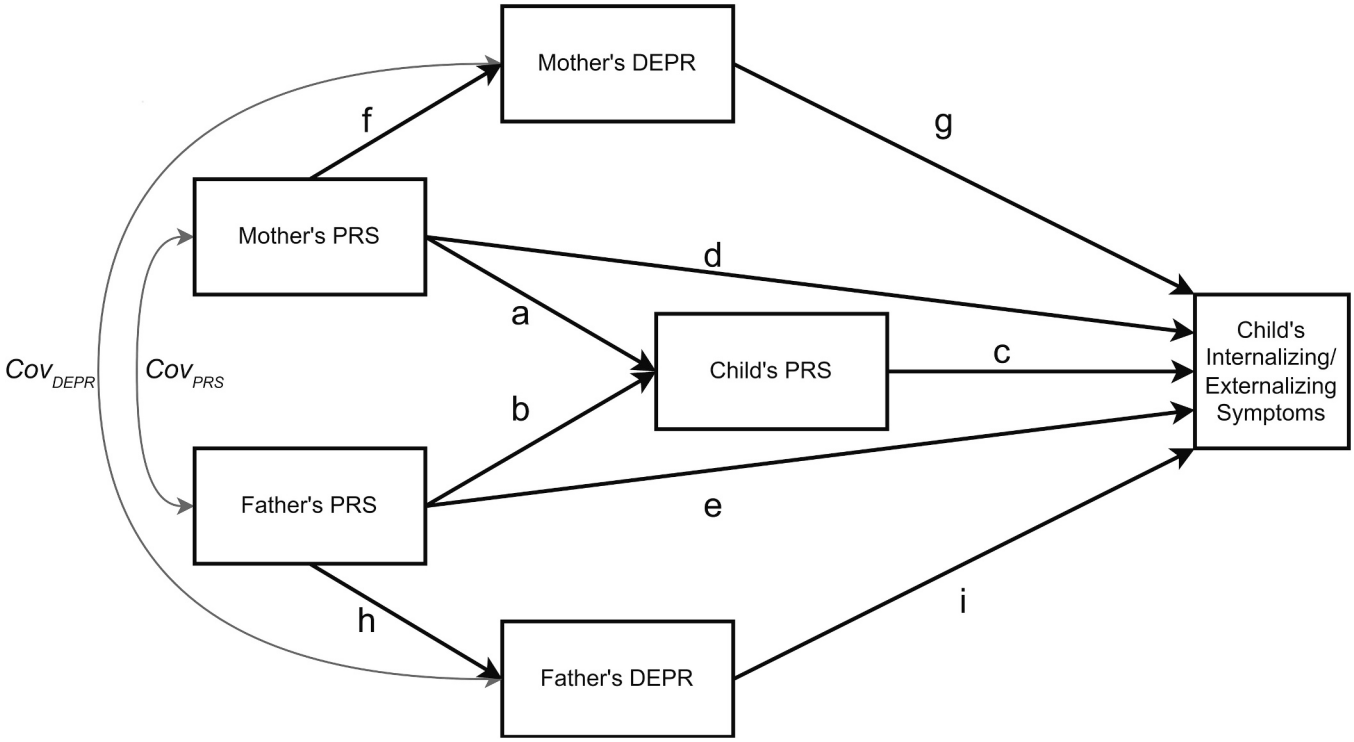

Fig. 1. Estimated paths (marked with letters *a* to *i*) and covariances (Cov_{PRS} and Cov_{DEPR}). Abbreviations: PRS = neuroticism PRS, DEPR = depression score.

Table 1
Description of the study samples CHILD-SLEEP ($N = 940$) and FinnBrain ($N = 1444$).

Variable	ChildSleep					FinnBrain				
	Girls $N = 446$		Boys $N = 494$		p[a]	Girls $N = 671$		Boys $N = 773$		p[a]
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Internalizing symptoms	3.9[b]	2.9	3.6[c]	2.9	0.07	3.4	2.6	3.4	2.4	0.52
Externalizing symptoms	2.8	2.1	3.3	2.2	4.8×10^{-4}	2.2	1.8	2.9[d]	2.1	2.0×10^{-11}
Maternal depression[s]	5.8[g]	4.0	5.4[h]	4.0	0.13	4.6[i]	4.3	4.6[j]	4.3	0.98
Maternal depression profile over two years	17.2% high[e]		13.7% high[f]		0.14	–	–	–	–	–
Paternal depression[s]	4.6[k]	3.3	4.9[l]	3.6	0.29	4.1[m]	4.1	3.7[n]	3.7	0.21
Internalizing symptoms (assessed by father)	–	–	–	–	–	3.2[o]	2.4	3.0[p]	2.4	0.18
Externalizing symptoms (assessed by father)	–	–	–	–	–	2.1[q]	1.6	2.5[p]	2.0	0.003

Note. Descriptives are presented for all subjects having data on internalizing and externalizing symptoms. Genetic data were available for $N = 820$ (CS) and $N = 1046$ (FB).
There were some missing data on study variables (marked with letters b to q). N for the variables were [b]445, [c]491, [d]772, [e]442, [f]481, [g]431, [h]460, [i]630, [j]737, [k]374, [l]394, [m]278, [n]303, [o]289, [p]317, [q]288. N for having all the study variables was $N = 806$ (CS) and $N = 987$ (FB).
[a] p-value for testing the statistical difference between boys and girls (*t*-test for continuous variables, X2 test for categorical variables).
[s] Measured by CES-D (CS) and EPDS (FB).

FB so that children with missing values on externalizing or internalizing symptoms had higher scores on neuroticism PRS compared to the children with non-missing data ($p = 0.01$ for all *t*-tests).

Regression analyses examining the association between *children's neuroticism PRS* and externalizing and internalizing symptoms revealed an association between neuroticism PRS and externalizing symptoms in boys (β (meta-analysis) $= 0.08$, $p = 0.01$) but not in girls (Table 2). Internalizing symptoms were not associated with neuroticism PRS in either sex. We then analyzed which of the two subscales, *worry PRS or depressed affect PRS*, or both were associated with externalizing symptoms in boys (Table 3) and found worry PRS, but not depressed affect PRS, to be associated with externalizing symptoms (β (meta-analysis) $=$ 0.09, $p = 0.01$). The results remained the same using other p-value thresholds (0.05, 0.3, 0.5 and 1) for the neuroticism and worry PRSs (Tables S1 and S2 in supplementary information). Externalizing symptoms plotted as a function of the neuroticism PRS and the worry PRS in boys are presented in Figs. 2a and b, respectively.

Path analyses examining the effect of *parental neuroticism PRSs* on children's externalizing and internalizing symptoms resulted in acceptable values on the fit indices indicating a good fit between the models and data in all models (Table S3). In boys (Fig. 3a and b), there was a significant mediation effect of maternal neuroticism PRS on both externalizing and internalizing symptoms through mother's depression scores (estimated path coefficient for the mediation path $fg = 0.09$, $p =$ 0.04 for externalizing, and $fg = 0.07$, p = 0.04 for internalizing symptoms). There was no such mediation effect with paternal neuroticism PRS. There were no direct associations of parental neuroticism PRSs on boys externalizing or internalizing symptoms, although there was some disagreement in the two samples: mother's neuroticism PRS was positively associated with internalizing symptoms in CS boys ($d = 0.26$, $p =$ 0.02), but not in FB boys, and negatively associated with externalizing symptoms in FB boys ($d = -0.46$, $p = 0.002$), but not in CS boys.

In girls (Figs. 3c and d), parental neuroticism PRSs were not associated with girls' externalizing or internalizing symptoms, neither directly, nor indirectly. However, there was some disagreement in the results in the two samples: In CS, mother's neuroticism PRS was associated with her depressive symptoms and, the depressive symptoms were associated with girl's internalizing symptoms. But the mediation path (form maternal neuroticism PRS to girl's internalizing symptoms) was not significant, $fg = 0.06$, $p = 0.07$. In FB girls, mother's neuroticism PRS was not associated with her depression scores.

4. Discussion

In our study of two population-based birth cohorts, we found that neuroticism PRS and the subscale worry PRS were positively associated with externalizing symptoms in 2-year-old boys. The finding was not dependent on the choice of the PRS threshold. In particular, low genetic risk for neuroticism was associated with less externalizing symptoms, while in the high end of the PRS score the association flattened. However, children excluded from the analysis based on missing data on externalizing symptoms had significantly higher scores on neuroticism PRS than the children included. Accordingly, the effect of high neuroticism PRS might not be fully captured in this study. We did not find any associations in girls.

The finding in boys was as we hypothesized: lower scores on neuroticism PRS were associated with less externalizing symptoms. We expected similar findings on internalizing symptoms too, but such associations were not found. In previous research, neuroticism PRS has been associated with internalizing symptoms and psychopathology in older children (aged 4 years or more) (Neumann et al., 2021; Akingbuwa et al., 2020), although not in all studies (Ensink et al., 2020). In our study, the participants were 2-year-olds, and at that age externalizing symptoms are easier to identify than internalizing symptoms, and they might be also over reported (Clarke-Stewart et al., 2003). Furthermore, internalizing and externalizing symptoms might not be completely distinguishable at the age of 2 years. The cognitive development that is required for the full expression of internalizing symptoms is not yet

Table 2
Results of four separate regression analyses examining associations between neuroticism PRS and externalizing and internalizing symptoms in boys and girls. Regression coefficients (β) are presented for CHILD-SLEEP, FinnBrain and meta-analysis. The first three principal components and maternal depression were used as covariates.

Variable		CHILD-SLEEP			FinnBrain			Meta-analysis		
		β	std error	p	β	std error	p	β	95%CI	p
Boys	Externalizing	0.12	0.05	0.01	0.05	0.04	0.21	0.084	0.02; 0.15	0.01**
	Internalizing	−0.01	0.05	0.84	0.04	0.04	0.38	0.02	−0.04; 0.08	0.58
Girls	Externalizing	−0.05	0.05	0.29	0.00	0.04	0.98	−0.02	−0.08; 0.04	0.53
	Internalizing	0.03	0.05	0.50	−0.07	0.05	0.17	-0.02	−0.08; 0.05	0.62

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 3
Results of two separate regression analyses on externalizing symptoms in boys. Regression coefficients (β) are presented for CHILD-SLEEP, FinnBrain and meta-analysis. The first three principal components and maternal depression were used as covariates.

Neuroticism PRS subscale	CHILD-SLEEP			FinnBrain			Meta-analysis		
	β	std error	p	β	std error	p	β	95% CI	p
Worry	0.11	0.05	0.03	0.08	0.05	0.10	0.09	0.02; 0.15	0.01**
Depressed Affect	0.08	0.05	0.13	−0.03	0.05	0.57	0.02	−0.05; 0.09	0.54

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

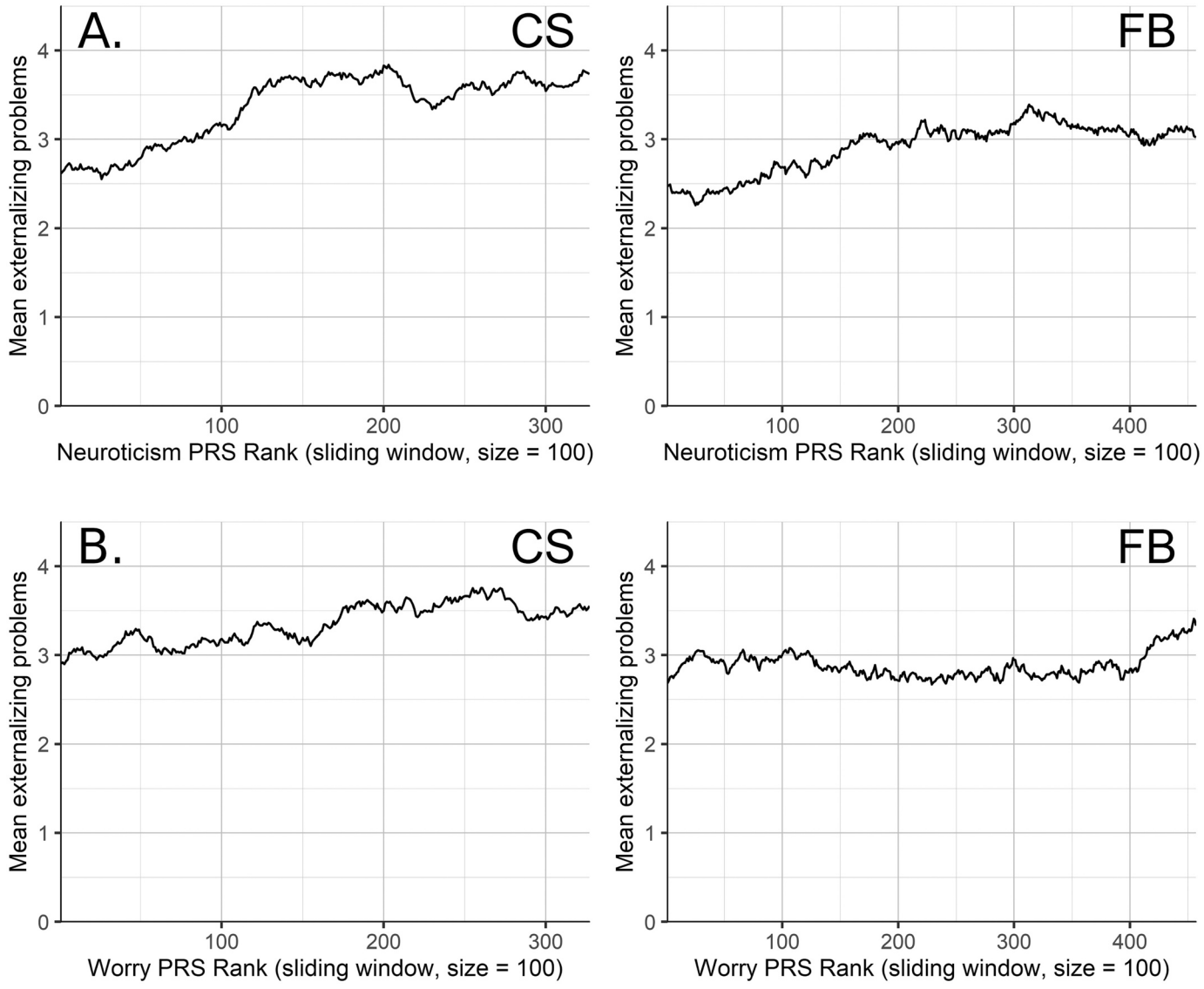

Fig. 2. Externalizing symptoms as a function of a. neuroticism PRS and b. worry PRS using a sliding window of size = 100 in boys.

achieved at the age of 2 years, and, accordingly, internalizing symptoms, for example anxiety, might be more easily expressed by externalizing behavior. This raises the question of whether the validity of internalizing symptoms measured at the age of 2 years is as good as a molecular genetic study would require.

In addition to total neuroticism PRS, boys' externalizing symptoms associated also with the subscale worry. To our knowledge, this was the first study to analyze the two subscales of neuroticism PRS, hence the analysis was exploratory in nature. Nagel et al. (2018) showed that worry PRS and depressed affect PRS had markedly different genetic correlations with other traits: worry PRS was genetically linked with schizophrenia, bipolar disorder, and anorexia, while depressed affect PRS was more related to depression. While there is no previous research on the worry PRS in children, our results could be considered as in line with the findings on genetically related schizophrenia PRS, which has been associated with externalizing and internalizing behavior in 3- to 6-year-olds (Riglin et al., 2017; Ensink et al., 2020; Jansen et al., 2018).

We did not find any associations in girls. Because of the reasons discussed above, possible associations between internalizing symptoms and neuroticism PRS might not be easily found in 2-year-olds. Regarding externalizing symptoms, girls and boys differed already at the basic rate: boys had more externalizing symptoms in both samples. This is in line with previous literature; boys tend to have higher scores on externalizing behavior than girls (Rescorla et al., 2012). On the other hand,

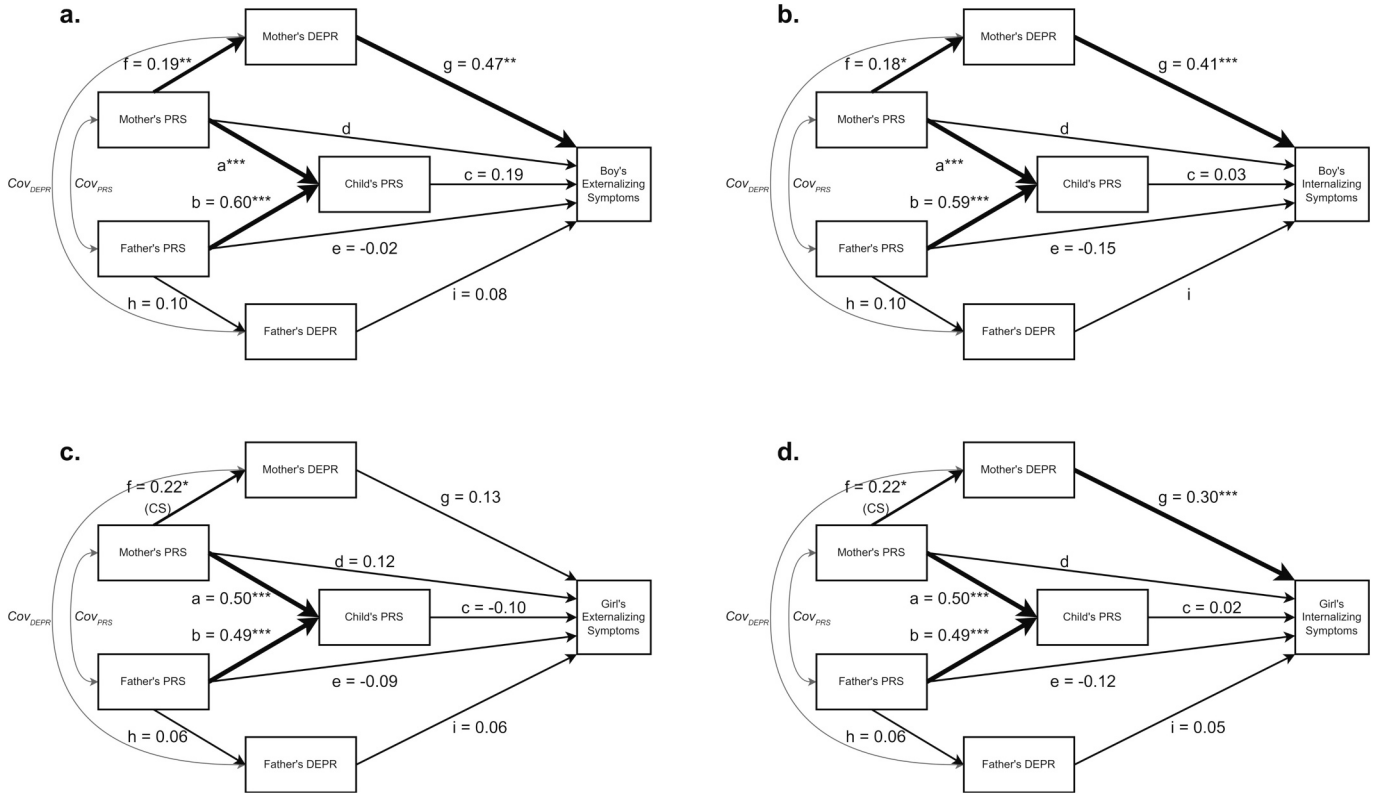

Fig. 3. Results of path models. Coefficients estimated from both samples (CS and FB) are shown. Covariance estimates in boys: $COV_{PRS} = 0.04$ (CS), $COV_{PRS} = 0.01$ (FB), $COV_{DEPR} = 0.24$* (CS), $COV_{DEPR} = 0.11$ (FB); and in girls: $COV_{PRS} = 0.04$ (CS), $COV_{PRS} = -0.13$ (FB); COV_{DEPR}.= 0.12 (CS), $COV_{DEPR} = -0.08$ (FB). Path estimates that differed in the two samples are presented below. a. Externalizing symptoms in boys (CS, $N = 90$ and FB, $N = 55$). a = 0.33*** (CS); a = 0.62 *** (FB); d = −0.02 (CS); d = −0.46** (FB). b. Internalizing symptoms in boys (CS, $N = 89$ and FB, N = 55). a = 0.33*** (CS), a = 0.62*** (FB); d = 0.26* (CS), d = −0.12 (FB); $i = 0.18$ (CS), $i = -0.14$ (FB). c. Externalizing symptoms in girls (CS, $N = 98$ and FB, $N = 67$). f = 0.22* (CS), f = −0.12 (FB). d. Internalizing symptoms in girls (CS, N = 98 and FB, N = 67). f = 0.22* (CS), f = −0.12 (FB); d = 0.16 (CS), d = −0.05 (FB). Abbreviations: PRS = polygenic risk score for neuroticism, DEPR = depression score, CS = CHILDSLEEP, FB = FinnBrain. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. Statistically significant paths are bolded.

genetic influences that affect behavior might be different for boys and girls. A study conducted by Rhee et al. (2007) suggested a higher genetic influence for boys than girls in internalizing and externalizing behavior. Gender differences with other PRSs have also been reported (Acosta et al., 2020). The possibility of gender differences in genetic influences is an interesting aspect that is worth of further research.

Our findings were based on the results of a meta-analysis of two birth cohorts. Although the meta-analysis examining the association between externalizing symptoms and neuroticism PRS (or worry PRS) in boys was significant, the association was not significant in both samples, but only in the CS sample. In the FB sample, the association was in the same direction but non-significant. However, with more liberal *p*-value thresholds for the PRS, the association between worry PRS and externalizing symptoms in boys was significant also in the FB sample (see supplementary information).

Parents' neuroticism PRSs were not directly associated with children's externalizing or internalizing symptoms. However, in boys, maternal depression scores mediated the effect of mothers' neuroticism PRS on externalizing or internalizing symptoms, but only when mother had rated the outcome. When father had assessed the child's symptoms (data only from FB, see supplementary information), these associations were weaker and non-significant, but father's depression scores were associated with girl's internalizing and externalizing symptoms. Studies show consistently that maternal depression and depressive symptoms are associated with internalizing and externalizing symptoms in children (Pietikäinen et al., 2020; Goodman et al., 2011), but the effect is stronger, if mother has assessed the child's behavior compared to other raters (Goodman et al., 2011). Here, our findings suggest that also subclinical symptoms of depression (that are based on genetic disposition) influence mother's perception of her son and how fathers perceive their daughters. The parents' negative understanding of their child could presumably have negative effect on the child-parent interaction, which could pose a cascade of negative consequences to the well-being of the child. Thus, our finding could have a clinical value in basic health care where professionals meet parents with light depressive symptoms.

The same mediation result was not found in girls, possibly due to the reasons discussed above. On the other hand, previous studies have suggested that girls and boys might differ on how environment influences their internalizing and externalizing symptoms. For example, in a study by Wang and Yan (2019) boys were more susceptible to mothers' depression by showing more stable patterns of internalizing and externalizing symptoms in the presence of maternal depression than girls.

While boy's neuroticism PRS was associated with externalizing problems in the regression analyses performed in this study, the same association was not statistically significant in the path analysis, which included also parental PRS and depressive symptoms (see Fig. 3a). However, the path coefficient was of similar (or greater) magnitude ($c = 0.19$) as betas in the regression analyses. The lack of significance is probably due to the small sample sizes in the path analyses ($N = 90$ (CS), $N = 55$ (FB)).

We found neuroticism and worry PRS to be associated with externalizing symptoms in boys. However, our results do not allow us to conclude on the mechanism operating behind this association. We cannot conclude whether higher genetic liability to neuroticism predisposes to externalizing behavior or whether it reflects more complicated mechanisms, including gene-environment correlations (Plomin et al., 1977). Our results could reflect a passive gene-environment

correlation, in which inherited neuroticism PRS was associated with parental behaviors linked with the same genetic liability, and which influence the child's externalizing behavior. An evocative gene-environment correlation is also plausible: genetic liability to neuroticism might evoke parental behaviors that affect the child's externalizing symptoms. Furthermore, both could operate at the same time, as has been shown in other studies (Wertz et al., 2020). The question was addressed to some extent in the path analysis and some indication of a passive gene-environment correlation was obtained: mother's neuroticism PRS was associated with her depression scores, which in turn seemed to affect the child's behavior. On the other hand, as parental depressive symptoms seemed to affect mostly on their assessment of their children, the interpretation is more complicated. We were not able to assess the possibility of an evocative gene-environment correlation in this path analysis with a limited number of participants.

4.1. Limitations

Children's neuroticism PRS was associated with missing data on externalizing symptoms, and models weighed with missingness might have resulted in more accurate estimates. Parent's depressive symptoms were measured with different scales in CS and FB, although both have been shown to be valid measures of depressive symptoms (González et al., 2017; Cox et al., 1996). Because the number of parents genotyped was limited, we had a quite small sample size in the path models, which may increase the risk for spurious parameter estimates. On the other hand, the parameter estimates were mostly based on two datasets, which decreases the likelihood of false positive findings. Finally, in the path models, causality cannot be confirmed, as the data concerning parents' and children's symptoms were cross-sectional. Furthermore, the path models included only parental depressive symptoms and not other potential environmental factors.

The neuroticism PRS was based on the UK Biobank sample, and it was not validated in Finnish people. Finns are known to differ genetically from other Europeans (Nelis et al., 2009), which may limit the validity of a PRS that is based on a non-Finnish sample. However, the PRS has been successfully used in other non-British European samples (Ahrens et al., 2022; Jansen et al., 2021), and other PRSs based on the UK Biobank have been used in Finnish samples, for example PRSs of LDL-cholesterol and triglycerides have been associated with coronary artery disease in Finland (Ripatti et al., 2020).

5. Conclusion

In summary, we found neuroticism PRS and the subscale worry PRS to be associated with externalizing symptoms in 2-year-old boys, suggesting that lower scores on neuroticism PRS are associated with less externalizing symptoms, although, the effect of high neuroticism PRS might not have been fully captured in this study due to attrition. We found mother's depressive symptoms to mediate the association between maternal neuroticism PRS and boy's externalizing and internalizing symptoms, and, as such, our results suggest that also subclinical symptoms of maternal depression that are based on genetic disposition, have an effect on child's internalizing and externalizing symptoms. There was a difference between girls and boys in our study, supporting the suggestion that girls and boys may differ in how genetic and environmental factors contribute to their development.

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Author statement

Conceptualization: JL, KK, JTP, MS, LK, HK, EJP, TP; Formal analysis: JL; Visualization: JL; Writing - Original Draft: JL, KK, HA, TP; Writing – Review & Editing: JL, KK, HA, JTP, SN, MS, AK, PP, HK, LK, EJP, TP; Resources: AK, PP, HK, LK, EJP, TP; Funding acquisition: HK, LK, EJP, TP.

Ethical statement

The ethics committees of Pirkanmaa Hospital District and the Hospital District of Southwest Finland have approved the study protocols, and the study procedure was in accordance with the Declaration of Helsinki. Written informed consent has been obtained from all the parents (participants of the data sets used in this study were newborn babies at the time of recruitment).

Declaration of Competing Interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2023.110720.

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