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Research paper

Maternal depression and the polygenic p factor: A family perspective on direct and indirect effects

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ABSTRACT

Within-family studies typically assess indirect genetic effects of parents on children, however social support theory points to a critical role of partners and children on women's depression. To address this research gap and account for the high heterogeneity of depression, we calculated a general psychiatric factor using eleven major psychiatric polygenic scores (polygenic p), in up to 25,000 parent-offspring trios from the Norwegian Mother, Father and Child Cohort Study (MoBa). Multilevel modeling of trio polygenic p was used to distinguish direct and indirect genetic effects on mothers depression during pregnancy (gestational age 17 and 30 weeks), infancy (6 months, 18 months) and early childhood (3 years, 5 years, and 8 years). We found mothers polygenic p predicts their depression symptoms (b = 0.092; 95 % CI [0.087,0.098]), outperforming prediction using a single major depressive disorder polygenic score (b = 0.070, 95 % CI [0.066,0.075]). Jointly modeling trio polygenic p revealed indirect genetic effects of fathers (b = 0.022, 95 % CI [0.014,0.030]) and children (b = 0.021, 95 % CI [0.010,0.037]) on mothers' depression. Our results support the generalizability of polygenic effects across mental health and highlight the role of close family members on women's depression.

1. Introduction

Depression is a debilitating mood disorder characterised by persistent feelings of sadness, hopelessness, and a loss of pleasure in activities that were previously rewarding (American Psychiatric Association, 2013). Depression is most common in women of childbearing age (Cox et al., 1993; Kuehner, 2017), with 33–40 % of women having their first depressive episode during pregnancy or the postpartum period (Wisner et al., 2013). Maternal depression has a global prevalence of 17.22 % [95 % CI 16.00,18.51](Wang et al., 2021) and is one of the major contributors to pregnancy related morbidity and mortality (Gelaye et al., 2016).

The myriad of physical, emotional, and behavioural effects of maternal depression are not limited to mothers but extend to their offspring and partners and have more recently been shown to be bidirectional (Burke, 2003). For example, maternal depression poses an increased risk to children, including, higher rates of infanticide, reduced maternal sensitivity (Letourneau et al., 2012), and poor cognitive and social development (Goodman et al., 2011), while children's externalising and internalising symptoms can directly influence parental mental health (Ahmadzadeh et al., 2019; McAdams et al., 2015). Maternal depression puts an additional strain on intimate partner relationships resulting in increased conflicts and higher rates of divorce, which cripple women's social support, in turn, increasing their risk of maternal depression. In cases where mothers develop maternal depression, their partners are twice as likely to reach diagnostic criteria (Burke, 2003), compromising the buffering effects of partners on children's developmental outcomes (Burke, 2003; Vakrat et al., 2018). Together the evidence for mother, partner and child effects of maternal depression supports its reconceptualization as a family-wide problem where consideration of the entire family unit is essential for better understanding causes and developing effective treatments (Letourneau et al., 2012).

Maternal depression aggregates within families with genetic

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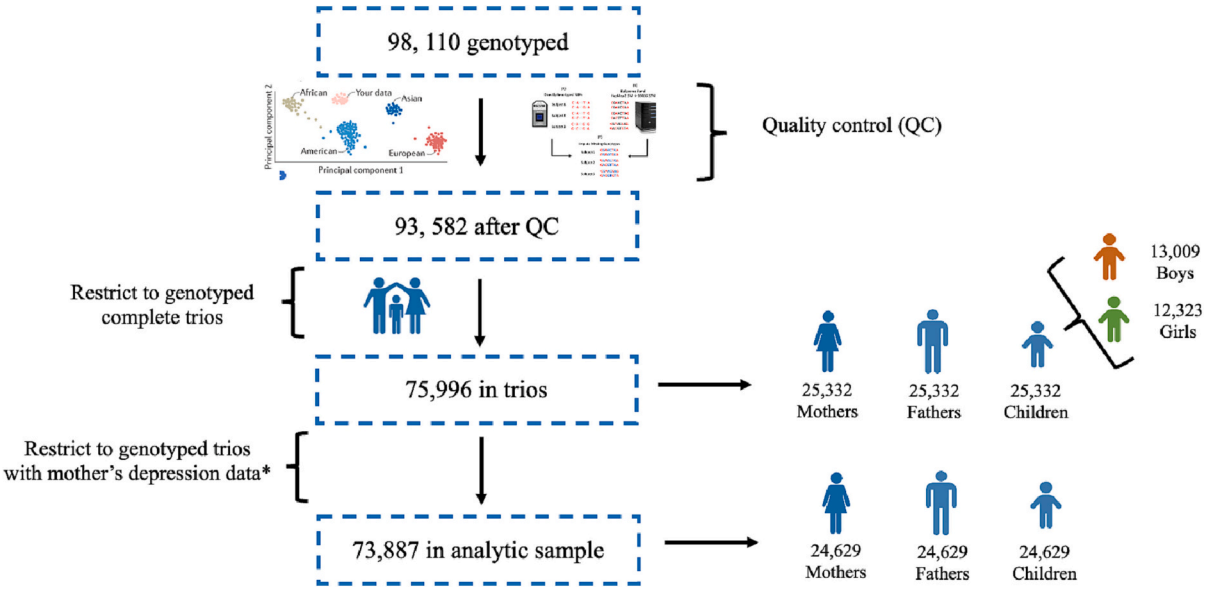

Fig. 1. Depiction of the flow of individuals from the original 98,110 genotyped MoBa participants to the analytical sample of 24,629 parent-child trios with longitudinal depression data.
Note * = the number of individuals with maternal depression and genotype trio data at the first time point (i.e., 17 weeks' gestation). Sample sizes vary across the 7 time points, with the smallest sample size (n = 11,341 trios) at the final time point (i.e., 8 years), given study attrition.

influences (heritability) estimated at approximately 37 % using the twin design (Sullivan et al., 2000). Decades of social support theories indicate a role of close family members in depression in general, and maternal depression specifically (Séguin et al., 1995). For example, while the self-doubt, negative biases, and guilt associated with impaired mother-child relationships has a profound effect on depressed mothers' attachment models and views of relationships (Burke, 2003; Lefkovics et al., 2014), strong perceived social support is associated with reduced symptoms and less postpartum relapse (Wang et al., 2011). Particularly relevant to social support theories is recent evidence that the genomes of close relatives can also impact an individual's environment (Jami et al., 2021; Kong et al., 2018). These so-called 'indirect genetic effects' emerge when a trait in an index person (mother) is influenced by the genome of a person external to them (partner or child). For example, if child's genetic risk for psychopathology influences maternal depression symptoms above and beyond mothers own genetic risk, this would suggest an environmentally mediated effect of the child's genetically influenced behavior on the mother.

We have previously demonstrated bidirectional familial effects (i.e., mothers depression impacting child developmental outcomes, and child psychopathology increasing mothers depression) using twin and adoption studies (Gjerde et al., 2017; McAdams et al., 2015). In the present study, we extend this work by capitalising on genotype parent-offspring data to identify familial effects on maternal depression using DNA alone. Polygenic scores (PGS), which serve as an individual specific measurement of genetic propensity to a trait (Lewis and Vassos, 2020), can be used to investigate genetic effects, by aggregating maternal depression associated variants identified in genome-wide association studies (GWAS). When genotype data is available for mothers, fathers, and children, their joint inclusion can help to identify genetic effects working within families. Previously this approach has been used to assess indirect genetic effects of parents' mental health and cognitive abilities on children's neurodevelopmental outcomes (Cheesman et al., 2022b, 2022a; Demange et al., 2022; Pingault et al., 2022), in the present study we instead evaluate the effects of children and fathers on mothers, which to the best of our knowledge has not been done for maternal depression. We exploit genetic correlations and symptom overlap across psychiatric disorders (Bulik-Sullivan et al., 2015), to calculate a 'polygenic p' factor from 11 different psychiatric GWAS summary statistics. This general liability may better capture the heterogeneity and polygenicity in depression symptoms to boost prediction (Mullins and Lewis, 2017).

Based on consistent observation of high levels of comorbidity, and phenotypic and genetic correlations across psychiatric disorders, researchers have begun to consider whether most psychiatric disorders are unified by a single general psychiatric liability dimension 'p'(Lahey et al., 2012), which parallels the general intelligence factor 'g'(Gottfredson, 1998). Literature supports 'p', which explains a significant proportion of psychiatric symptom variability, is heritable, correlates highly with personality traits, associates with level of life impairment and has been detected in adolescence as well as adulthood (Allegrini et al., 2020; Caspi et al., 2014; Gjerde et al., 2023; Rosenström et al., 2019).

A *polygenic* p factor emerges when using PGS, as demonstrated using principal component analysis of 8 psychiatric PGS in an independent UK based sample of over 7000 individuals (Selzam et al., 2018). In separate analyses from this same UK sample, polygenic p reliably predicted phenotypic p, the first principal component that emerged from diverse questionnaire assessments of psychiatric disorders, across child development, as young as age 7 (Allegrini et al., 2020). Most literature on the polygenic p-factor has been preoccupied with demonstrating that it emerges using different factorial models, and less on its utility as a method of better capturing variation in heterogeneous disorders, which is the aim of the present study. Little is known to what extent the polygenic p factor predicts maternal depression and whether indirect genetic effects influence depression during the first years of parenthood. Depression's unique characteristic as a highly prevalent (Hasin et al., 2005) and moderately heritable disorder means that genetic differences between those with depression and those without are likely small. Coupled with its female preponderance(Kuehner, 2017), there is argument for focusing on depression in a population sample of women during the first years of parenthood, arguably a period of increased stress exposure, depression vulnerability, and potentially, signal for detection. When considering indirect effects, it is also likely that differences, in for example partners' mental health, could be particularly salient during the first years of parenthood when intimate relationships are especially needed to adjust to the new challenges of motherhood, yet this has yet to be formally tested (Burke, 2003).

We resolve the gaps in the literature by using a polygenic p factor

measured in genotyped mother-father-child trios to 1) Test whether a polygenic p factor can reliably predict depression in mothers above and beyond prediction using a single depression PGS and 2) Illuminate the relative indirect contribution of father and child polygenic p factors to mothers depression during pregnancy, infancy and early childhood. Our trio polygenic p method is maximised by using multilevel modeling where we allow for each mother to have her own individual slope that can vary as a function of time of depression measurement.

2. Methods

2.1. Sample

The Norwegian Mother, Father and Child Cohort Study (MoBa) (Magnus et al., 2006) is a population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health. Participants were recruited from all over Norway from 1999 to 2008. The women consented to participation in 41 % of the pregnancies. The cohort includes approximately 114,500 children, 95,200 mothers and 75,200 fathers. The current study is based on version 12 of the quality-assured data files released for research in 2016. The establishment of MoBa and initial data collection was based on a license from the Norwegian Data Protection Agency and approval from The Regional Committees for Medical and Health Research Ethics. The MoBa cohort is currently regulated by the Norwegian Health Registry Act. The current study was approved by The Regional Committees for Medical and Health Research Ethics (#2013/863). Analyses were restricted to a subset of the 98,110 genotyped parent-child trios from the full MoBa dataset with available self-report depression questionnaire data for mothers during pregnancy (17- and 30-weeks' gestation) and the first 8 years after birth (6 months, 18 months, 36 months, 5 years, and 8 years). Descriptive characteristics on the study sample were obtained from the Medical Birth Registry (MBRN), a national health registry containing information about all births in Norway as well as the father's questionnaire, administered between 2015 and 2016. The genotyped trios represented predominately cohabitating families, with 87 % of mothers living with the father of the genotyped child at 8 years. Only 0.01 % of father's report having never lived with their child. Further demographic descriptors of the sample are reported in the Supplementary Material. A flow chart depicting the analytical sample is displayed in Fig. 1.

2.2. Genotype quality control

The current MoBa genomic dataset comprises imputed genetic data for 98,110 individuals (~32,000 parent-offspring trios), derived from nine batches of participants, who make up four study cohorts. Within each batch, parent and offspring genetic data were quality controlled separately. Pre-imputation quality control criteria is described in detail in the supplementary material. We conducted post-imputation quality control, retaining SNPs meeting the following criteria: imputation quality score (INFO) ≥ 0.8 in all batches, non-duplicated (by position or name), call rate > 98 %, minor allele frequency (MAF) > 1 %, Hardy-Weinberg equilibrium (HWE) $p < 0.001$, not associated with genotyping batch at the genome-wide level, and not causing a mendelian error. We removed individuals with the following criteria: heterozygosity outliers (F-het $\pm$ 0.2), call rate < 98 %, reported sex mismatching SNP-based sex, duplicates (identified using PLINK's (Chang et al., 2015) –genome command as having pihat ≥ 0.98, and distinguished from monozygotic twins through linkage to unique IDs in the population register, plus age, sex, and kinship information within MoBa), individuals with excessive numbers of close relatives (cryptic relatedness) and mendelian errors. To minimise environmental confounding, we identified a sub-sample of individuals with European ancestries via principal component analysis using the 1000 Genomes reference; thresholds for exclusion of outliers were based on visual inspection of a plot of principal components 1 and 2. The final numbers of individuals and SNPs passing quality control were 93,582 and 6,797,215, respectively. Principal components of genetic ancestry were computed for all participants using PLINK's –within and –pca-clusters commands, based on an LD-pruned version of the final QC genotype data.

2.3. Calculation of trio polygenic scores

We selected 11 traits for construction of the polygenic p factor based on previous literature (Allegrini et al., 2020; Selzam et al., 2018) and on their public availability through the Psychiatric Genomics Consortium (PGC), which provided some standardization in the format of summary statistics. The included traits were: Major Depressive Disorder (MDD (Howard et al., 2019)), neuroticism (Nagel et al., 2018), anxiety (Purves et al., 2020), Post Traumatic Stress Disorder (PTSD(Nievergelt et al., 2019)), Attention Deficit Hyperactivity Disorder (ADHD(Demontis et al., 2019), Autism Spectrum Disorder (ASD)(Grove et al., 2019), anorexia (Watson et al., 2019), schizophrenia (Pardiñas et al., 2018), bipolar disorder(Stahl et al., 2019), Alcohol Use Disorders (AUD)(Sanchez-Roige et al., 2019) and Obsessive Compulsive Disorder (OCD (Arnold et al., 2018)). Prior to analyses we performed standard quality control removing any MoBa participants present in the 11 psychiatric GWAS summary statistics ($n = 250$). We then calculated polygenic scores (PGS) in line with published guidelines (Choi et al., 2020), for the MoBa genotyped trios (mother, father, child) as the weighted (by the original GWAS identified effect size estimate) sum of all (pvalue threshold $= 1$) single nucleotide polymorphisms (SNPs). Polygenic scores and the resulting polygenic p factor were standardised to have a mean of 0 and standard deviation of 1. PGS were computed using the statistical software PRSice-2(Choi and O'Reilly, 2019).

2.4. Computation of trio polygenic p factors

A 'polygenic p' factor representing general genetic liability to psychiatric disorders was calculated by performing an exploratory factor analysis with a bi-factor geomin rotation on eleven psychiatric PGS for complete mother, father, child trios. Evidence for the p factor has previously emerged using Principle Components Analyses (PCA), which seeks to extract linear composites from observed correlated variables. Here, we use the bi-factor solution to test a theoretical model of latent *genetic* structures that could account for the observed comorbidity between current psychiatric constructs and that can act both directly (mothers on their own depressive symptoms) and indirectly (father and child general genetic propensity on mothers' depressive symptoms). We relied on Bayesian Information Criterion (BIC) as an index of relative model quality, given increased performance for complex biometric models and large sample sizes (Markon and Krueger, 2004). Exploratory factor analysis for the polygenic p factor was performed in Mplus 8.5 with geomin orthogonal bi-factor rotation (Browne, 2001; Muthén and Muthen, 2017; Muthén and Muthén, 1998). Further details on the construction of the polygenic p factor including model fit statistics and comparisons across mental health indices within MoBa and between MoBa and the population average, have been published elsewhere (Ayorech et al., 2023; Rosenström et al., 2019). With this approach we obtained a separate polygenic p factor for mothers, fathers, and children, which we could jointly model to separate direct (mother) and indirect (father and child) genetic effects on mothers depression, while simultaneously controlling for the shared genetic relatedness between family members.

Studies of direct and indirect genetic effects are typically conducted with children as the focal individual, such that parental polygenic score effects are regressed out of child polygenic score effects, revealing direct effects of genes that are free from the selection processes such as assortative mating or population stratification that parents introduce. In the present study, we fixed child effects to occur after birth by multiplying the child polygenic p factor by a dummy variable taking the values of 0 when mothers were pregnant and 1 when they were not

Table 1
Models used to test effect of mother, father, and child polygenic p on mothers' depression.

Model	Fixed effect	Interactions with time	Random effect
1.	Mothers' polygenic p		–
2.	Mothers' polygenic p, parity, pregnancy, time		Mothers' ID
3.	Mothers' polygenic p, parity, pregnancy, time		Mothers' ID,time
4.	Mothers' polygenic p, parity, pregnancy, time	Mothers' polygenic p	Mother's ID,time
5.	Mother' polygenic p, Fathers' polygenic p, Child polygenic p, parity, pregnancy, time	Mothers' polygenic p	Mother's ID,time
6.	Mothers' polygenic p, Fathers' polygenic p, Child polygenic p, parity, pregnancy, time	Mothers', Fathers' and, Child polygenic p	Mother's ID,time

Note. Pregnancy here reflects concurrent pregnancy therefore allowing for mothers to be pregnant with the index child for whom we have genotype data and subsequent pregnancies across 7 measurement timepoints of 17- and 30-weeks' gestation, 6 months, 18 months, 3 years, 5 years, and 8 years.

pregnant to reflect our conceptualisation of child effects on mothers depression occurring only after the child is born. We could then test for indirect effects of child genes on mothers depression during the first 8 years of life. Fathers' genes were free to influence maternal depression across all measured years.

2.5. Measures

2.5.1. Depression

A validated short version of the Hopkins Symptoms Checklist (SCL) was used to assess depressive symptoms in mothers during pregnancy (17 and 30 weeks' gestation) and after birth when the child was 6 months, 18 months, 36 months, 5 years and 8 years (Tambs and Røysamb, 2014). The correlations between the SCL depression scores and the original SCL are high (0.92) and the scale shows good alpha reliability (0.82) (Tambs and Røysamb, 2014). The SCL depression items assessed the extent to which mothers felt hopeless about the future, felt blue, worried too much, or felt everything was an effort, assessed on a 4-point Likert scale ranging from "not at all, bothered," to "extremely bothered". For each measurement timepoint, MoBa mothers received a depression score calculated as the mean of SCL depression items, requiring at least 50 % of the items to be non-missing. We then divided the SCL score by 1.85, which is the cut for depression according to this scale. As a result, SCL scores above 1 indicate meeting threshold for depression diagnosis. Further descriptive statistics on the SCL are available in the Supplementary.

2.5.2. Time

Time was calculated by taking the original assessment timepoints obtained from the questionnaire data (17 weeks, 30 weeks, 6 months, 18 months, 3 years, 5 years, and 8 years) and converting them to reflect the number of months between measurements then dividing these values by 12 to reflect change in years. The values for time became −0.5, −0.25, 0.5, 1, 1.5, 2 and 3.

2.5.3. Statistical analyses

We sought to distinguish the direct effect of polygenic psychiatric risk in women from the indirect effect of close family members, while simultaneously accounting for the clustering of our longitudinal measures across time and pregnancy status. This was achieved using 6 separate models with increasing complexity, as described below.

First, we captured the population average direct effect of mothers general genetic liability to psychiatric disorders (polygenic p) on their depression scores using a generalised linear model with a sandwich estimator for repeated measurement (Model 1). To account for data clustering, we performed a series of linear mixed-effect, or multilevel, models with random effects for mother ID and then mother ID and time (Model 2 and 3) and compared their fit statistics. We then investigated whether direct genetic effects of mothers polygenic p on depression change during the first 8 years of their child's life by adding interactions between mothers polygenic p factor and time (Model 4). The indirect effect of familial psychiatric risk on mothers depression was investigated by adding father and child PGS to the Model (Model 5). By simultaneously modeling mother, father, and child genetics, we could identify the main effect of each family member while accounting for their shared genes. Finally, we tested for interactions between father and child PGS and time (Model 6). Multilevel models were performed in R Studio (Team, 2020) version 4.0.3 using the lme4 (Bates et al., 2014) package version 1.1.26, with model comparisons made using the anova () command. All tested models are summarised in Table 1.

When genetic data for parent-offspring trios are all included in the model, we can interpret the effect of mothers polygenic p factor on mothers depression as a 'direct' genetic effect and the effect of father and child polygenic p factor on mothers depression as 'indirect' genetic effects, as depicted in Fig. 2.

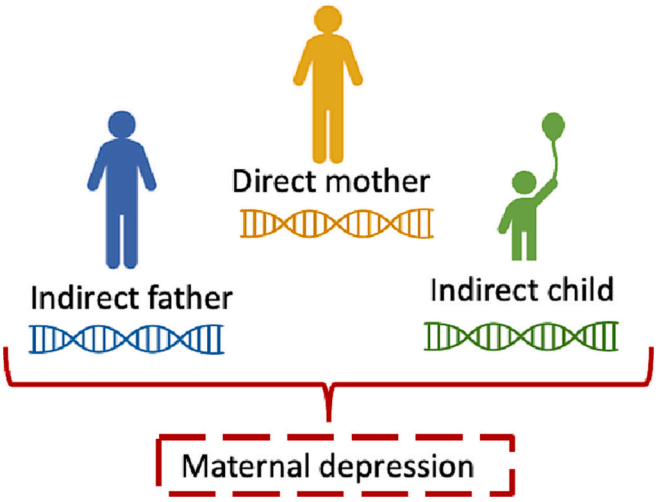

Fig. 2. Direct and indirect effects of trio (mother, father, child) polygenic p factor genes on mothers maternal depression. Stippled red box indicates the cumulative effect of familial general genetic propensity to psychiatric disorders on mothers depression, supporting the reconceptualizing of maternal depression as a family-wide problem. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2.5.4. Covariates

As our primary research interest was to investigate the genetic effects operating through family members for whom we have genotype data, we included mothers parity and whether they were pregnant with any successive pregnancies, as covariates in all models. Parity was taken as the highest reported number of previous deliveries obtained either by i) mother self-report, or ii) as registered by the MBRN. Parity was coded as 0 = 'primiparous', 1 = 'one previous birth', 2 = 'two previous births', 3 = 'three previous births', and 4 = '4 or more previous births. Sample sizes for each of the parity groups are available in Table S1. Current pregnancy was captured using questionnaire data across each of the 7-depression measurement timepoints, indicating whether mothers were currently pregnant. Inclusion of these covariates renders all child genetic effects as interpretable as those of the pregnancy for which we have genotypic data.

Table 2
Factor loadings for each of the eleven psychiatric polygenic scores on the polygenic p factor.

Polygenic scores[a]	Loading on p factor
Major depressive disorder	0.742
Neuroticism	0.531
Anxiety disorder	0.500
Post-traumatic stress disorder	0.220
Attention deficit hyperactivity disorder	0.197
Autism spectrum disorder	0.168
Anorexia	0.154
Schizophrenia	0.131
Bipolar disorder	0.118
Alcohol use disorders	0.114
Obsessive compulsive disorder	0.053

Note:
[a] References for each of the genome-wide association studies used to calculate the polygenic scores are provided here: (Arnold et al., 2018; Demontis et al., 2019; Grove et al., 2019; Howard et al., 2019; Nagel et al., 2020; Nievergelt et al., 2019; Purves et al., 2020; Sanchez-Roige et al., 2019; Stahl et al., 2019; Watson et al., 2019).

3. Results

3.1. A polygenic p factor emerges from polygenic scores of 11 psychiatric GWAS

Our exploratory factor analysis with a bifactor solution revealed a single general psychopathology factor for which each of the eleven PGS loaded significantly (Table 2). Full details regarding computation of the polygenic p factor and model selection can be found in the Supplementary Materials and online (Ayorech et al., 2023).

3.2. A polygenic p factor capturing general genetic liability to any psychiatric disorder reliably predicts maternal depression (Model 1)

Results from a simple linear regression indicate mothers polygenic p factor predicts depression symptom scores (b = 0.092, 95 % CI [0.087,0.098]). The p factor prediction outperforms the depression symptom prediction when using the Major Depressive Disorder polygenic scores alone (b = 0.070, 95 % CI [0.066,0.075]).

3.3. The polygenic p factor effect remains when considering the observed longitudinal structure of the data (Model 2)

The results from the simple linear regression are replicated when using a multilevel model, where the intercept is allowed to vary for each mother (b = 0.088, 95 % CI [0.079, 0.095]).

3.4. Adding a random slope for time improves model fit statistics (Model 2 and 3)

Our BIC statistics indicate that model fit improved when the mothers polygenic p factor effect was allowed to also vary across time (X^2 = 963.14, $p < 0.001$). Adding a random slope for time introduces an interaction with time and varying slopes of time over mother ID.

3.5. Time contributes to variance in the p factor prediction of maternal depression (Model 3) and interacts with polygenic risk (Model 4)

We observed a main effect of time (b = 0.146, 95 % CI [0.128,0.165]) indicating regardless of the other contributors in the model, time contributes to variation in mothers' depression scores. Mothers polygenic p factor interacted with time (b = 0.012; 95 % CI [0.004,0.019]), suggesting a small increase in the effect of mothers' general liability to psychiatric disorders on their own depression across the 8 measured childbearing years.

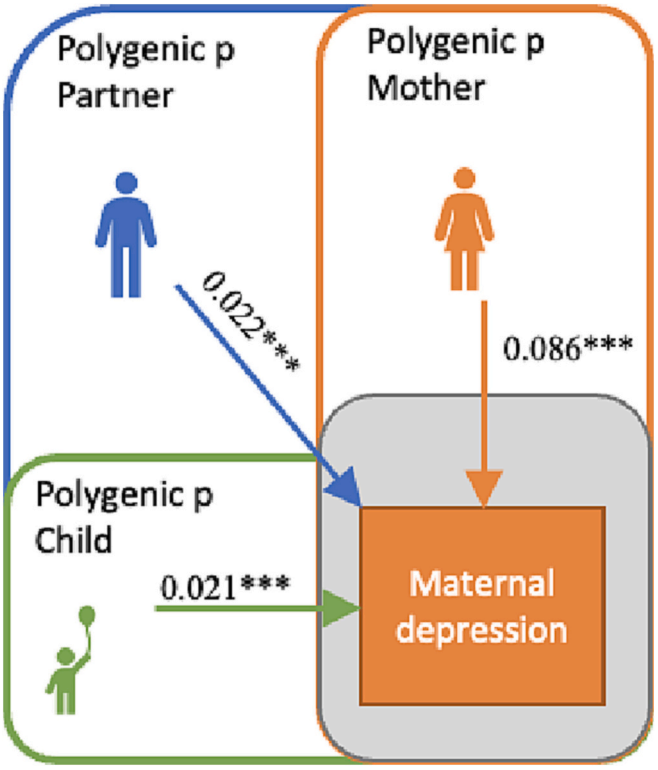

Fig. 3. Within family polygenic p effects on mothers depression.
*Note: *** reflects p value's < 0.001.*

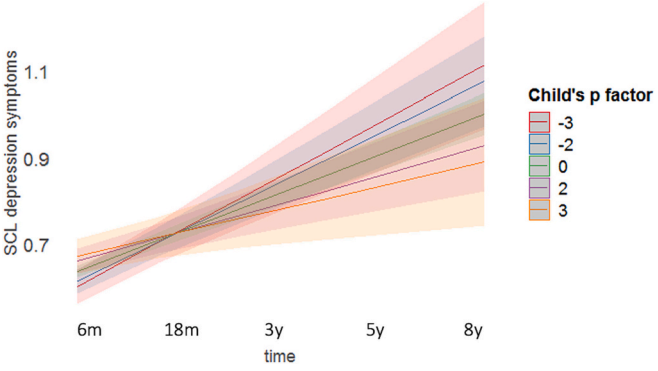

Fig. 4. Child p factor effect on mothers depression across the first 8 years of life.

3.6. Trio polygenic scores reveal the role of the family's general psychiatric liability on mothers depression (Model 5)

We demonstrate indirect genetic effects of children (b = 0.021, 95 % CI [0.010,0.037]) and fathers (b = 0.022, 95 % CI [0.014,0.030]) polygenic p on maternal depression symptoms (Fig. 3). Because all family members are included in the model, these estimates account for assortative mating between partners and shared genes between parents and offspring. As expected, direct effects of mothers polygenic p (b = 0.086,95 % CI [0.070,0.102]) on their own depression are stronger than indirect effects of fathers (b = 0.022, 95 % CI [0.014,0.030]) or children (b = 0.021, 95 % CI [0.010,0.037]).

3.7. The impact of time on depression differs as a function of child's genetic liability to psychiatric disorders (Model 6)

The interaction between mothers p factor and time did not survive

Table 3
Effect of covariates.

Covariate	Effect	[95 % CI]
Pregnancy	−0.036	[−0.059;-0.013]
Parity 1	0.007	[−0.004;0.019]
Parity 2	0.004	[−0.011;0.019]
Parity 3	−0.009	[−0.037;0.020]
Parity 4	0.005	[−0.045;0.055]

Note: Pregnancy here refers to the effect of subsequent pregnancies across the 7 time points, not the effect of being pregnant or not with the index child for whom we have genotype data.

the within-family analyses adjusting for father and child polygenic p (b = 0.004; 95 % CI [−0.011,0.018]). Instead, a small negative interaction between child p factor and time (b = −0.024, 95 % CI [−0.045,0.004]) emerged, although confidence intervals overlap with zero. The observed child effects are robust to population stratification, assortative mating and other selection factors introduced by parental genes (Fig. 4).

3.8. Effect of covariates

The effect of each of our covariates in our final multilevel model (model 6) is described in Table 3.

4. Discussion

We calculated *polygenic p*, a factor capturing general genetic propensity to mental health problems, in 24,629 genotyped parent-offspring trios from the Norwegian mother, father and child cohort study (MoBa). Our key research aim was to distinguish the direct and indirect effects of general genetic risk for psychiatric disorders on mothers' depressive symptoms across the first 8 years of parenthood. We see improved prediction of mothers depression when the polygenic p factor is used when compared to the Major Depressive Disorder polygenic score alone. We find evidence of indirect genetic effects of father and child genes on mothers' depression symptoms, which is in line with a social support hypothesis of depression. Crucially, by incorporating longitudinal measures in our within-family analyses, we find evidence that the impact of indirect genetic effects on maternal depression can vary across time. Together, our results have implications for the reconceptualization of maternal depression as a family-wide problem and for the generalizability of polygenic effects across mental health.

4.1. General mental health variants capture risk that influences maternal depression

Given considerable symptomatic and genetic overlap across psychiatric disorders, a general psychopathology (p) factor was recently proposed and shown to reliably capture variance in the experiences of mental health problems across the lifespan (Martel et al., 2017; Rosenström et al., 2019). By extracting a general factor from eleven psychiatric polygenic scores, we demonstrate the capacity for polygenic p to predict maternal depression, improving on prediction using the major depression polygenic score alone. Although current polygenic score effect sizes are small in magnitude, this boost in prediction ($b = 0.070_{\text{major depression PGS}}$ to $b = 0.092_{\text{polygenic p}}$) suggests psychiatric traits with currently underpowered discovery samples can profit from success stories from other well powered GWAS. Our results highlight the added value of including diverse indexes of mental health symptomatology when seeking to boost depression prediction. By including father and child polygenic scores in the same model, we show that the effect of maternal polygenic risk on depression is mostly direct and not due to non-random mating or early heritable traits in the offspring.

4.2. Interpreting indirect genetic effects

Our trio polygenic p design controls for shared genes between family members to reveal each member's unique genetic effect. An important implication of this design is that any observed indirect effects are corrected for many of the biases that plague typical behavioural genetic studies including assortative mating and population stratification (Ayorech et al., 2023; Torvik et al., 2022). Assortative mating refers to non-random mate choice that results in similarities between partners that are larger than chance (Torvik et al., 2022). Population stratification refers to differences in allele frequencies between groups due to systematic differences in ancestry rather than association of genes with disease (Haworth et al., 2019). Because parents choose their mates and child genes are randomly allocated conditional on parental alleles, our indirect effect estimates when derived within-families, correct for these biases. Direct effects of an index person (i.e., mother) on their own trait (maternal depression) have a clear genetic pathway, from mothers' DNA variation to variation in their depressive symptoms. By contrast, indirect effects operate through the environment – i.e., genetic variation in fathers or offspring influence mothers' environments. For example, family members with a higher genetic propensity for mental health problems may create more stressful home environments, which would in turn impact maternal depressive symptoms. Evidence of indirect effects on mothers' depression have been demonstrated using an adoption design (McAdams et al., 2015), and now here with DNA alone. Importantly, compared to measured symptoms of general mental health, our polygenic p factor is not prone to reporter or selection bias and is normally distributed (Ayorech et al., 2023).

4.3. Fathers matter

A strength of the present study is that by indexing fathers risk for psychopathology using genetic data we in part circumnavigate biases common in questionnaire data where fewer if any measurement timepoints for fathers' depression symptom scores are typically available. Given polygenic scores harness the predictive power from the original GWAS discovery sample and can make useful predictions in sample sizes in the 100's rather than the 1000's needed in other genomic approaches, we highlight the utility of polygenic scores for smaller datasets where limited father phenotypic data are available. We found evidence for a small effect of fathers general psychiatric risk on mothers depressive symptoms, which supports social support theories of the impact of fathers on mothers mental health during the childbearing years (Burke, 2003).

As GWAS sample sizes increase, the predictive utility of psychiatric polygenic scores, when used in conjunction with known environmental risk factors, will be clinically relevant (Lewis and Vassos, 2020). For this reason, further interpretation of the implications of indirect effects of fathers' genes are warranted, especially as current polygenic scores capture only a fraction of the known genetic influence estimated from twin studies, and paternal effects are likely underestimated in the present study. Despite long standing evidence for an effect of fathers on mothers depression, few genetically sensitive studies include both partners (Paulson and Bazemore, 2010). Fathers may offer an untapped resource when it comes to interventions for maternal depression, given the greater evidence base on men's treatment response, and that reduction of fathers' symptoms prior to birth may provide an additional source of stability for mothers and children postpartum (Baylis, 2010). Although father effects were small in magnitude, it is noteworthy that they stood up to control for mother and child effects and emerged even with mothers reporting on the fathers' symptoms. This is relevant given previous studies have found stronger indirect father effects when fathers reported on their own mental health (Ahmadzadeh et al., 2019).

4.4. The importance of modeling indirect and direct genetic effects across time

We found small evidence that the indirect child effects varied across time. The strongest effects of child's general genetic risk for psychiatric disorders were observed at 6 months, which is also a period of heightened risk for post-partum depression. Indeed twin heritability estimates for post-partum depression (50 %)(Viktorin et al., 2016) are higher than for major depressive disorder (37 %) (Sullivan et al., 2000), which may in part reflect reduced heterogeneity in symptoms when restricted to women who have undergone the bio-psycho-social process of childbirth. Together, these results suggest depression GWAS may increase power by sampling mothers with symptoms specific to the first 6 month's post-partum.

The effects of child's polygenic liability inverted from 3 years until our final assessment at 8 years with lower general psychiatric risk in children associated with higher symptoms of maternal depression. Speculation on the mechanisms underlying this inversion require further longitudinal investigations, especially given our current understanding of how indirect genetic effects operate in this sample is largely based on early childhood (Cheesman et al., 2020; Eilertsen et al., 2021). It remains feasible for example, that as children reach adolescence, a key developmental period for the onset of mental health disorders, their mental health symptomatology can increase mothers' depressive symptoms.

The direction of mother, father and child effects on maternal depression has implications for genome-wide association studies which seek to estimate direct genetic effects on a phenotype, but also capture indirect genetic effects together with population stratification. Although population stratification can be largely accounted for using principal component analysis, indirect genetic effects remain uncontrolled in traditional GWAS of unrelated individuals. By conducting GWAS within family members, these indirect effects can be quantified. For example when a GWAS for depression was conducted both between families (standard approach with unrelated individuals) and within-families (using siblings), an up to 50 % shrinkage in effect size estimates was observed (Howe et al., 2022). We found time contributes more to depression symptom variation than our polygenic score, which isn't surprising given current polygenic scores underestimate genetic effects and depression variation is under less genetic influence compared to other psychiatric disorders (i.e, 37 % compared to ~80 % for schizophrenia). Because indirect genetic effects contribute to the environments depressed women experience, large within-family studies incorporating longitudinal assessments of maternal depression may help to elucidate the changing role of women's environments on their depression across time.

5. Limitations

The present study suffers from the following notable limitations.

5.1. Representativeness

A critical shift in genetic research and the discourse around its implications is occurring (Bien et al., 2019). Glaring biases in our research which is predominantly conducted by, with and for individuals of white European ancestry continue to limit the benefits of genomic discovery, largely excluding racialized individuals who make up the global majority. The present study is based on GWAS summary statistics from those of European ancestry and recent evidence suggest accuracy of polygenic score predictions decays with increasing genetic distance from the GWAS study cohort (Fatumo et al., 2022; Martin et al., 2019). Continuous collaborative GWAS' efforts to recruit and analyse data from samples from diverse ancestry will improve the generalisability of polygenic score findings.

5.2. Selection

Like all population studies, The Norwegian Mother, Father, and Child study suffers from selection biases, although evidence suggests that the impact of this selection bias is largely restricted to prevalence estimates obtained using the dataset and not to associations between exposures and outcomes(Nilsen et al., 2009). Only genotyped complete trios were included, however we show in separate analyses that the average polygenic p factor burden in these trios is similar to the population average(Ayorech et al., 2023). We indexed depression liability through genomic data rather than symptoms or clinical diagnoses, which partially buffers some of the selection biases as those with high genetic liability but who would not reach symptom criteria still can provide valuable information for risk prediction. Polygenic scores from 11 psychiatric GWAS yielded a predictive polygenic p factor, which is impressive for two reasons: 1) most GWAS samples select 'pure' cases which poorly represent the high levels of co-occurring conditions and comorbidities found outside of these strict study conditions; and 2) SNP's used to construct polygenic scores are based on averaged effects of depression symptoms across broad European context which may not so readily generalise to Norway.

5.3. Accuracy and magnitude of effect estimates

Our polygenic p factor underestimates the effects of general psychiatric risk. For example, when a p factor was derived from symptom scores from broad psychiatric disorders, twin and DNA based heritability estimates suggest effect sizes larger than what we observe(Allegrini et al., 2020; Neumann et al., 2016). As larger, more representative GWAS are conducted, we expect stronger signal for polygenic scores capturing genetic risk for mental disorders. Until then, rich longitudinal genotyped family datasets including depression symptom measurements can provide insights into how genetic variation contributes to differences both between and within-families.

6. Conclusion

Given evidence that many psychiatric disorders represent the extreme end of quantitative traits (Plomin et al., 2009), we capitalise on the world's largest population-based pregnancy cohort to test whether general genetic liability to *any* psychiatric disorder can be used to advance our knowledge of depression genetics. Through inclusion of parent-child trio genotypes and rich longitudinal data we demonstrate indirect effects of the family on maternal depression, supporting the need to consider women's entire support network when investigating the aetiology of their depression.

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CRediT authorship contribution statement

Z.A and E.Y conceived of the study. Z.A conducted the analyses and wrote the manuscript. All authors provided critical feedback and helped shape the research, analyses, and interpretations.

Role of the funding source

The funding sources had no role in the design of this study, its execution, analyses, interpretation of the data, or decision to submit results.

Conflict of interest

We declare no competing conflicts of interests in relation to the submitted work.

Data availability

MoBa data can be accessed by application to the Regional Committee for Medical and Health 494 Research Ethics in Norway and MoBa (https://www.fhi.no/en/studies/moba/for-forskere495artikler/research-and-data-access/). The consent given by the participants does not open for storage of data on an individual level in repositories or journals.

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