Developmental Trajectory and Genetic Markers of Body Weight in Offspring of Parents with Mood Disorders

by

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Abstract

Individuals with mood disorders have a greater risk of experiencing metabolic health issues, including increased weight. When parents transmit risk of developing a mood disorder to their children, they also transmit this metabolic risk. We examined the timeframe over which offspring of parents with mood disorders began to display increased weight compared to offspring of unaffected parents. We found that females over age twelve with a family history of mood disorders showed a marked increase in body weight compared to females without a family history. We then investigated the relationship between the genetic predisposition to mood disorders and body weight, as well as the relationship between the genetic predisposition to metabolic traits and depressive symptoms. No association was found between mood disorder polygenic scores and body mass index nor between metabolic polygenic scores and depressive symptoms. These findings strengthen our understanding of how markers of metabolic health manifest in youth at risk for developing mood disorders.

List of Abbreviations Used

BMI	Body Mass Index
CRP	C-Reactive Protein
FORBOW	Families Overcoming Risk and Building Opportunities For Wellbeing
GRCh-37, 38	Genome Reference Consortium Human Build 37, 38
GWAS	Genome-Wide Association Study
LD	Linkage Disequilibrium
MAF	Minor Allele Frequency
MFQ	Mood and Feelings Questionnaire
PCA	Principal Components Analysis
PC-AiR	Principal Components Analysis In A Related Sample
pT	P-value Threshold
SCID-5	Scheduled Clinical Interview For the DSM-5
SES	Socioeconomic Status
SNP	Single Nucleotide Polymorphism
WtH	Waist-To-Height
zBMI	BMI Age-Adjusted Z-Score

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Chapter 1: Introduction

1.1 Overview

Mental illness and physical illness are connected. Mood disorders in particular are strongly linked to metabolic issues which contribute to a disproportionate level of morbidity and mortality later in life. Mood disorders are typically diagnosed in late adolescence or early adulthood, and metabolic diseases are typically detected much later. It is not yet known whether earlier indications of metabolic ill health, such as increased body weight, can be detected in at-risk youth. Individuals with a family history of mood disorders are susceptible to developing both mood disorders and increased weight. This thesis will examine when in development the difference in body weight begins for those at risk for developing mood disorders compared to those without family history. Furthermore, metabolic traits and mood disorders are highly heritable, and this thesis will investigate the genetic underpinnings of body weight, systemic inflammation, bipolar disorder, major depressive disorder, and their relationship to weight and depressive phenotypes.

1.1.1 What are mood disorders?

Mood disorders comprise a group of psychiatric illnesses that includes major depressive disorder and bipolar disorder. Mood disorders tend to onset in adolescence or early adulthood, with the majority of cases beginning between ages 15 – 25.[1] Approximately 30% of people are affected by depression and 4% are affected by bipolar disorder respectively at some point in their life.[2]

Mood disorders are among the leading causes of disease-related burden globally.[3] They have serious impacts on an individual's quality of life, causing social and economic burden.[4,5] Functional impairments, loss of employment, and increased healthcare costs are all detrimental effects faced by individuals with mood disorders.[6] People with bipolar disorder have shorter expected lifespans by 10 – 16 years[7] and those with depression have shorter lifespans by 9 – 15 years.[8]

1.1.2 Familial transmission of mood disorders

Children of parents with a mood disorder are at increased risk of developing one themselves.[9,10,11,12,13,14,15] Two-thirds of them will develop one by the time they are thirty-five years old.[16] Offspring of parents with depression are 2.4 times more likely to develop depression than offspring of parents who have no severe mental illness. Likewise, offspring whose parents have bipolar disorder are four times more likely to develop bipolar disorder compared to controls. The risk conferred to offspring of parents with mood disorders is also transdiagnostic[17]; four times as many children of parents with bipolar disorder develop depression as controls and five times as many children of depressed parents develop bipolar disorder compared to controls.[18] Rates of depression in offspring of parents with bipolar disorder and rates of bipolar disorder in parents with depression are two times and five times greater than in controls respectively.[18] Studying the transmission of the risk of mood disorders as a category allows us to capture this transdiagnostic risk in a way that disorder-specific methods do not.

1.1.3 Benefit of a high-risk cohort

Affected parents transmit risk for developing a mood disorder to their children through genetic and environmental factors. In addition to their increased risk of developing a mood disorder, these offspring face higher rates of anxiety, substance use disorder, functional impairments, and suicide.[19] Longitudinally studying offspring with high familial risk can help us separate factors that cause disorders from their consequences. Using a sample in which the concentration of risk is much greater than the general population, data is collected without knowing whether the individual will develop a diagnosis; outcomes based on differing levels of genetic risk for a disorder can then be examined.[20] Familial high-risk studies are valuable as they are enriched for both genetic and environmental risk, and can be combined with genetic methods to develop a better understanding of the role of genetics in the development of mood disorders.[21]

1.2 Connection between mood disorders and metabolic traits

One of the major contributors to decreased lifespan in individuals living with mood disorders is an increased risk of physical health issues.[22] Depression that onsets during childhood or adolescence increases risk for mortality as well as a litany of somatic conditions in adulthood, including autoimmune, endocrine, circulatory, and metabolic issues.[23] One major cause of mortality and morbidity in individuals with mood disorders is their substantial risk of developing metabolic issues including system inflammation and increased body weight.[24,25]

C-reactive protein (CRP) is a biomarker of inflammation that is produced by the liver. It increases acutely in response to infection or injury and declines quickly once the issue is remedied. In some chronic conditions, however, CRP levels remain slightly elevated.[26] Low-grade inflammation, evidenced by increased CRP levels, is seen in a quarter of all depression patients.[27] Increased CRP is also associated with increased severity of depressive symptoms.[26] There are sex differences seen in the relationship between CRP levels and depressive symptoms; increased CRP was associated with greater symptom severity in females but not males.[28]

Increased body weight is an additional metabolic health factor to consider in individuals living with mood disorders. Obesity is one of the strongest predictors of metabolic risk.[29] People with obesity and mood disorders are more likely to have other physical comorbidities compared to individuals who are obese with no mood disorder.[30] Individuals diagnosed with a mood disorder are more likely to develop obesity than the general population,[27] and inversely, individuals that are overweight or obese also have increased risk of depressive and manic symptoms.[31,32] The risk of developing depression is especially high in obese individuals who have other metabolic conditions such as type 2 diabetes or high serum CRP levels.[33,34] A number of studies have shown that obesity and mood disorders do not simply co-occur; they have a bidirectional relationship where each influences the presentation of the other.[27,35] The reciprocal relationship between obesity and depression exists in both sexes but is much stronger in females.[36] Interestingly, obese individuals who have depressive symptoms also have significantly higher CRP levels than non-obese depressed individuals.[37]

1.2.1 Co-transmission of mood and metabolic conditions

Metabolic issues are co-transmitted with mood disorders from parent to child. Maternal mental health can have a far-reaching impact on metabolic health in offspring. Depression in mothers during pregnancy is associated with high levels of CRP in offspring at age twenty-five.[38] In addition, high maternal weight before and during pregnancy is associated with increased rates of depression in offspring.[39,40] Depression and obesity show positive familial co-aggregation, such that having one increases chances of having the other within a family.[41] In individuals with a lifetime depression diagnosis and in their siblings, high BMI is associated with atypical and somatic profiles of depressive symptoms.[42] First-degree relatives of individuals with bipolar disorder have increased rates of metabolic diseases including type 2 diabetes, hypertension, and hyperlipidemia.[43]

1.2.2 Developmental trajectory of mood and body weight

Prospective studies have shown that depression in adolescence leads to a 70% increased risk of becoming obese, while obesity in adolescence confers a 40% increased risk of depression.[36] Children with depressive symptoms between ages 6 – 19 have been shown to have an increased likelihood of being overweight compared to peers without depressive symptoms.[44] The relationship between obesity and depression is more pronounced in adolescent females than males.[36,45,46] It is not yet known when in development individuals at risk for mood disorders begin to display increased body weight.

1.3 Genetic risk prediction

Most complex traits are polygenic. This means that a large number of variants across the genome influence the development of the trait, each with a tiny individual effect that does not reach genome-wide significance.[47] One way to index the polygenicity of traits is using polygenic scoring.

1.3.1 Polygenic scores to measure genetic risk

Polygenic scoring is growing into a promising measure in psychiatry research because it is one of the few available validated biomarkers and its predictive ability is increasing. It can be used to estimate an individual's genetic risk for a trait without family history information and unlike family history, it is separate from environmental factors.[21] However, polygenic scoring is not yet strong enough to inform clinical decisions.[48] One area where polygenic scores have utility is in early intervention, where they could help identify individuals at-risk for developing psychiatric disorders before onset.

To create polygenic scores, we begin by conducting a genome-wide association study (GWAS) to identify genetic variants (specifically single nucleotide polymorphisms, SNPs) associated with a given trait, such as body mass index (BMI), schizophrenia, or intelligence. Summary statistics are obtained from the GWAS, which contain a list of each genetic variant and an effect size indexing its influence on the chosen trait. These effect sizes must be obtained from an independent cohort from the test sample to ensure the scores are valid. Scores are then derived by weighting each variant present by its effect size to create a score measuring one individual's genetic predisposition to a chosen trait based on which relevant genetic variants they possess in their genome.[49]

One issue with polygenic scoring is that most GWASes have been conducted in populations with European ancestry.[49,50] The transferability of polygenic scores made from these GWASes to other populations is limited, as scores that come from European GWAS samples are biased by genetic drift with unpredictable directionality. While GWASes are growing to include more diverse populations, it is not yet enough to create accurate polygenic scores for mixed ethnicity samples.[51] Given these concerns, this thesis will be using individuals of European ancestry for all genetic analyses.

1.3.2 Genetics of mood disorders

Mood disorders are highly heritable; twin studies have shown that additive genetic variation makes up 35 – 45% of variance in risk of major depressive disorder and 65 – 70% variance in risk of bipolar disorder.[52] Genome-wide genotype data from common SNPs has shown that depression and bipolar disorder share a moderate genetic correlation of 0.47 and significant polygenic overlap based on risk scores.[53,54] Additionally, a meta-analysis has found fifteen genetic loci novel to mood disorders by examining depression and bipolar cohorts.[55]

Polygenic scores can be informative in understanding an individual's genetic predisposition to developing a mood disorder. Individuals with bipolar disorder have a significantly higher bipolar disorder polygenic scores than healthy controls. Interestingly, offspring of parents with bipolar disorder also show elevated bipolar polygenic scores compared to offspring of unaffected parents; the bipolar polygenic score predicts risk of developing bipolar disorder in offspring beyond the prediction based on parental diagnosis alone.[56] Moreover, the polygenic score for depression is positively associated with mood disorder diagnosis[57] and explains up to 3.2% of phenotypic variance.[58]

1.3.3 Shared genetics between metabolic traits and mood disorders

As with mood disorders, metabolic health risk is heritable and can be predicted genetically. There is a strong positive correlation between BMI in biological parents and children, but no correlation between BMI in adopted parents and children – this suggests that the intergenerational transmission of body weight is primarily genetic.[59]

Twenty-four pleiotropic genes have been identified to be shared between cardiometabolic and mood disorder risk; these indicate a potential shared biological pathway.[60] The genetic risk associated with body weight and CRP are also both highly polygenic.[61,62]

BMI has a heritability of 31 – 90%.[63] The polygenic score for BMI explains 14% of the variance in BMI. Depression shares 12% of its genetic component with obesity.[64] It shares at least seventeen loci with bipolar disorder and thirty-two with depression, over half of which are associated with increased BMI for both disorders, while just under half are associated with decreased BMI.[65]

While high serum CRP levels are indicative of mood disorder risk, they are influenced by recent disease, so polygenic scores indexing risk for high serum CRP levels can more reliably show an individual's lifetime CRP levels.[24] A genome-wide association study identified distinct variants associated with CRP that combined explained 11% of variance in the phenotype. Almost all variants remain significantly associated with CRP after adjusting for BMI, which suggests that these variants affect CRP levels independently of BMI.[61] CRP levels have a genetic correlation with depressive symptoms that is comparable to the genetic correlation between BMI and depressive symptoms.[66] Though increased serum CRP is associated with mood disorder history, it seems that the polygenic risk for CRP is not associated with mood disorder history or depression polygenic score.[24,67] However, CRP polygenic scores are associated with depression symptom severity and with the presence of somatic depression symptoms such as fatigue and appetite disturbances.[68,69]

1.4 Objectives

This thesis investigated the relationship between the metabolic traits of body weight and CRP and mood disorder risk. We studied the effect of family history of mood disorders on trends in offspring BMI over the developmental period. In addition, we explored the genetic elements of the metabolic-mood connection through the use of mood disorder polygenic scores to predict BMI and by using metabolic polygenic scores to predict depressive symptoms.

Chapter 2: Developmental trajectory of body weight by mood disorder risk

2.1 Introduction

People living with major mood disorders are substantially more likely to develop metabolic ill health than people without mood disorders.[70] Longitudinal studies have shown a connection between adolescent obesity and adult depression and vice versa, but it is unknown when in development this relationship arises.[35]

The increased risk of metabolic issues associated with mood disorders seems to begin early and act bidirectionally. Depressed mood predicts obesity a year later in adolescents,[35,71] and in obese adolescents, depressive symptoms exacerbate future weight gain.[72] Overweight and obese status predict earlier onset of depression and worse clinical outcomes, while a diagnosis of depression also increases risk of developing obesity.[31] Adolescents with bipolar disorder also have higher rates of overweight and obesity than those without major psychiatric illnesses, and overweight or obese status is associated with increased severity of their psychiatric symptoms.[73,74]

In both children and adults, the relationship between mood disorders and increased weight is stronger in females. Obesity is associated with the diagnosis of major depressive disorder in adult females but not males.[75] Additionally, in females depression in early adolescence predicts onset of obesity in late adolescence and obesity that develops in late adolescence predicts onset of depression in early adulthood.[76] In late adolescence and adulthood, females with a lifetime history of a mood disorder have an increased risk of obesity compared to controls while males do not show this increased risk.[77]

A commonly used measure of obesity is BMI, a ratio of the individual's height and weight. A BMI of 30 or greater is considered obese. A 30 year longitudinal study showed that adult females with a baseline BMI of 30 or more have significantly increased odds of getting a diagnosis of major depressive disorder. Individuals with a BMI of 25 and above (considered overweight) also have increased odds of developing depression, though these odds are attenuated after adjusting for other risk factors including age, education, and financial strain.[78] It is not only obese or overweight status that predicts depressive symptoms, rather it is the continuous spectrum of weight. Even in children who are not obese, depressive symptoms predict increased BMI.[79]

In adults, the BMI cut points for overweight and obesity are consistent over age and sex, but this is not the case in children. To use BMI as a measure in children, we must compare their scores to an external reference standard that accounts for both age and sex. BMI z-scores are the ideal way to do this to capture adiposity at a given time point, and they can be calculated from BMI-for-age growth charts.[80]

Though BMI is the most commonly used measure of obesity, other measures that reflect body shape may be more informative of health risks as BMI can overestimate obesity.[81,82] Measures of central adiposity, including waist circumference, waist-to-hip ratio, and waist-to-height (WtH) ratio are better predictors of obesity-related cardiovascular risk than BMI.[83] WtH ratio correlates well with intra-abdominal fat[84], which is a stronger indicator of long-term morbidity and mortality than BMI which more closely describes peripheral fat distribution.[85] WtH ratio is also more accurate than BMI for measuring cardiometabolic risk in adults and children.[86,87] WtH ratio is elevated in children ages 9 – 10 with a history of depression, especially in females.[88]

Body weight and mood disorders are both heritable. As such, parents with these conditions will pass their genetic risk on to offspring. Offspring of parents with major mood disorders have several-fold increased risks of developing a major mood disorder themselves.[18] Prospective studies of high-risk offspring provide the opportunity to examine the development of increased body weight and its relationship with familial risk for mood disorders. By following offspring prospectively, we were able to examine the emergence of the association between body mass and familial mood disorder risk. The Families Overcoming Risk and Building Opportunities for Wellbeing study (FORBOW) is an accelerated longitudinal cohort that covers a wide range of offspring ages, enabling us to get a picture of an extended developmental period. This allows us to study changes in BMI over a long developmental period and examine the directionality of risk factors.

In the current study, we compared the trends in BMI z-scores (zBMI) over age between offspring of parents with mood disorders and controls to find an age range where the trends diverge. We also considered the impact of sex differences on the effect of familial risk of mood disorders on the trajectory of weight development. We hypothesized that individuals at high familial risk would display increases in weight (measured with zBMI) compared to control offspring beginning in adolescence. In addition, we expected weight increases to be most pronounced in females at high familial risk.

2.2 Methods

2.2.1 Participants

We recruited a cohort enriched for individuals with high familial risk for severe mental illness in Nova Scotia.[89] We included participants ages 3 – 20 and excluded participants with incomplete information on weight or height. Participants who were capable to give written informed consent to participate in the study did so, and those who were not provided assent and a parent or guardian provided written informed consent on their behalf. All study procedures described here were approved by the Research Ethics Board of the Nova Scotia Health Authority.

Participants were split into two groups: offspring who had at least one parent with a major mood disorders and comparison control offspring whose parents did not have major mood disorder diagnoses. Parents with mood disorders were recruited through referrals from adult mental health services by clinicians treating patients with severe mental illness. Parents of control participants were healthy individuals who were matched on demographic factors to parents with a mood disorder. Control parents were recruited through referral of acquaintances living in the same neighbourhoods as affected parents with children the same age, or by contacting parents of children who attended the same schools as children of affected parents.

2.2.2 Parental diagnosis psychopathology

We assessed parental diagnosis using the Structured Clinical Interview of the DSM-5 (SCID-5).[90] Offspring were assigned high familial risk status if they had at least one biological parent with a diagnosis of major depressive disorder or bipolar disorder or if they had multiple second-degree relatives with these disorders. Control offspring were individuals whose parents had no lifetime diagnosis of major depressive disorder or bipolar disorder.

2.2.3 Physical measurements

Height (in centimeters), weight (in kilograms), and waist circumference (in centimeters) of participants were measured during their annual assessment done by researchers blind to parental diagnosis. BMI was calculated using the formula (weight in kg)/(height in m)^2 while WtH ratio was calculated as (waist circumference in cm)/(height in cm).[91] Height and weight were collected using an HS-250 Brecknell measurement scale and waist circumference was measured with a measuring tape. BMI was transformed to age- and sex-adjusted z-scores based on reference data from the Centre for Disease Control using the growthcleanr package created for use in R by Daymont and colleagues.[92]

2.2.4 Statistical analysis

We explored the effect of age on zBMI in individuals with high and low familial mood risk, with age as the independent variable, zBMI as the dependent variable, and familial risk status as a covariate. We aimed to examine the development of zBMI over age without making assumptions about the shape of the trajectory, so we chose to test this relationship using non-parametric local-linear kernel regression with 500 bootstrap replications using the npregress package in STATA SE 16.[93] Nonparametric regression models the mean zBMI conditional on the covariates but does not make assumptions about the functional form of the relationship (unlike linear regression). Reported effect estimates are the averages of derivatives for continuous covariates (such as age) and averages of contrasts for factor covariates (such as group).

In addition, we conducted non-parametric kernel regressions of age on zBMI with high risk status as a covariate separately by sex to determine sex-specific effects. We did this for all ages, and also separated both males and females into two groups: below age twelve and above age twelve. This allowed us to better understand when in development we start to see differences between high risk and control groups. Age twelve was used as our cut-off because depressive symptoms are known to begin with pubertal onset, and twelve is a midpoint between average pubertal onset of females and males.[94] Though puberty onset is more predictive of depressive symptom onset than age, we did not have information on pubertal onset of enough participants to rely on this alone.[95]

2.2.5 Sensitivity analysis

We accounted for having repeated measurements from the same individual and for including related individuals in the sample by running a separate sensitivity analysis where we conducted the same tests as above using a subset of our sample only including one measurement from one individual per family to separate out the effect of relatedness and multiple measurements of the same individual in our results.

In the primary results, we did not include socioeconomic status (SES) as a covariate because having a mental illness tends to have a negative effect on SES; individuals with severe mental illness, including major depressive disorder and bipolar disorder, are more likely to have trouble finding jobs, are likely to live in lower income neighbourhoods, etc.[96,97] However, to ensure our results were not completely explained by SES, we conducted sensitivity analyses using nonparametric kernel regression with SES as a covariate. SES was measured as a sum of five binary indicators of SES: mother's education of high school or above, father's education of high school or above, home ownership, annual household income of greater than $60 000 per year, and a bedrooms to people ratio above 0.9. As such, participants could have a range of SES scores from zero to six.

2.2.6 Waist-to-height supplementary analysis

Both WtH ratio and zBMI were used as a measure of obesity, and their results were compared. The calculation for WtH ratio is waist circumference/height. All primary and sensitivity analyses conducted were the same as was described above for zBMI. These analyses accounted for family clusters, multiple assessments of the same individual, and SES.

2.3 Results

2.3.1 Demographic characteristics

A total of 64.9% of our final sample had high familial risk for major mood disorders. Over the whole group of 441 participants, we gathered BMI measurements from 1633 assessments and WtH measurements from 997 assessments. Due to this smaller number of assessments, WtH measurements were not used in the primary analysis, but we compared its relationship to familial mood risk status in supplemental analysis.

We also found that there was a significant difference in SES between the high familial risk group and controls, such that individuals with family history of mood disorders were more likely to have a lower SES. We did not include SES as a covariate in our main model because individuals with mood disorders tend to have lower SES, often as a result of the disorder.[96,97] The parents of our high mood risk participants are affected by this, so including SES in the model would remove some of the effect that having a high familial risk of mood disorders has on zBMI. Even so, we believe it is an important factor to consider and chose to include SES as a covariate in sensitivity analyses. Demographic characteristics of participants are displayed in Table 2.1.

We fully excluded data from 65 individuals from all analyses; these were cases where we did not have information on the individual's weight, height, or both. Of our excluded assessments, 66.7% were in the high familial mood risk group, and 49.8% were female. There were significant differences between included and excluded individuals on age and SES. Comparison of excluded and included participants is shown in Table 2.2.

Table 2.1 Demographic characteristics of participants. Differences between groups were tested using chi-squared (x^2) tests for categorical variables and t-tests for continuous variables. * is used to denote statistically significant differences between groups.

	High familial risk (n participants = 286)	Control (n participants = 155)	X^2	p-value
BMI measurements, n	1109	524		
Number of female participants with BMI (%)	149 (52.1)	77 (49.7)	0.24	0.627
Number of female BMI measurements (%)	557 (50.2)	253 (48.3)	0.54	0.464
Participants with WtH available	228 (79.7)	132 (85.2)		
Number of WtH measurements	642 (64.4)	355 (35.6)		
Number of female WtH measurements (%)	338	167	2.87	0.646
SES by category, n of measurements – not participants (%)*			54.31	1.8×10^{-10}
0	35 (3.2)	12 (2.3)		
1	128 (11.5)	18 (3.4)		
2	199 (17.9)	62 (11.8)		
3	274 (24.7)	126 (24.0)		
4	329 (29.7)	207 (39.5)		
5	144 (13.0)	99 (18.9)		
Ethnicity (Number of observations from individuals of European ancestry) (%)	1004 (90.5)	475 (90.6)	0.0057	0.940
			t-statistic	p-value
Age, mean (SD)*	12.1 (3.9)	11.2 (3.4)	-5.03	5.55×10^{-7}
BMI, mean (SD)*	20.5 (5.3)	19.1 (4.2)	-5.46	5.73×10^{-8}
WtH, mean (SD)*	0.469 (0.067)	0.450 (0.059)	-3.46	5.77×10^{-4}

Figure 2.1 Mean BMI for participants by familial mood risk status and sex. A shows participants below age twelve and B shows participants above age twelve. Error bars represent the standard deviation about the mean.

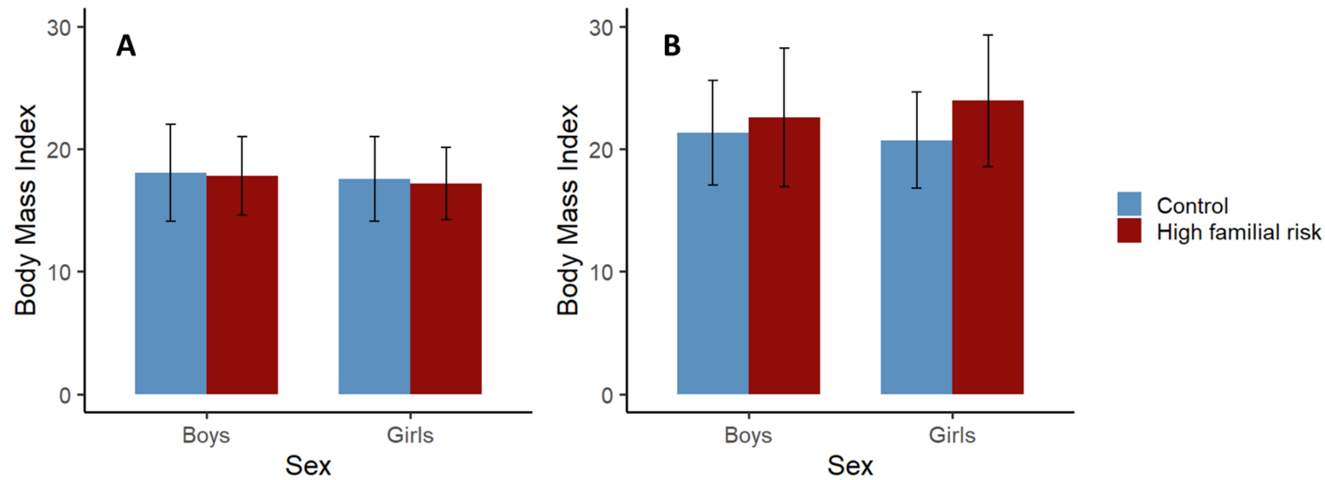


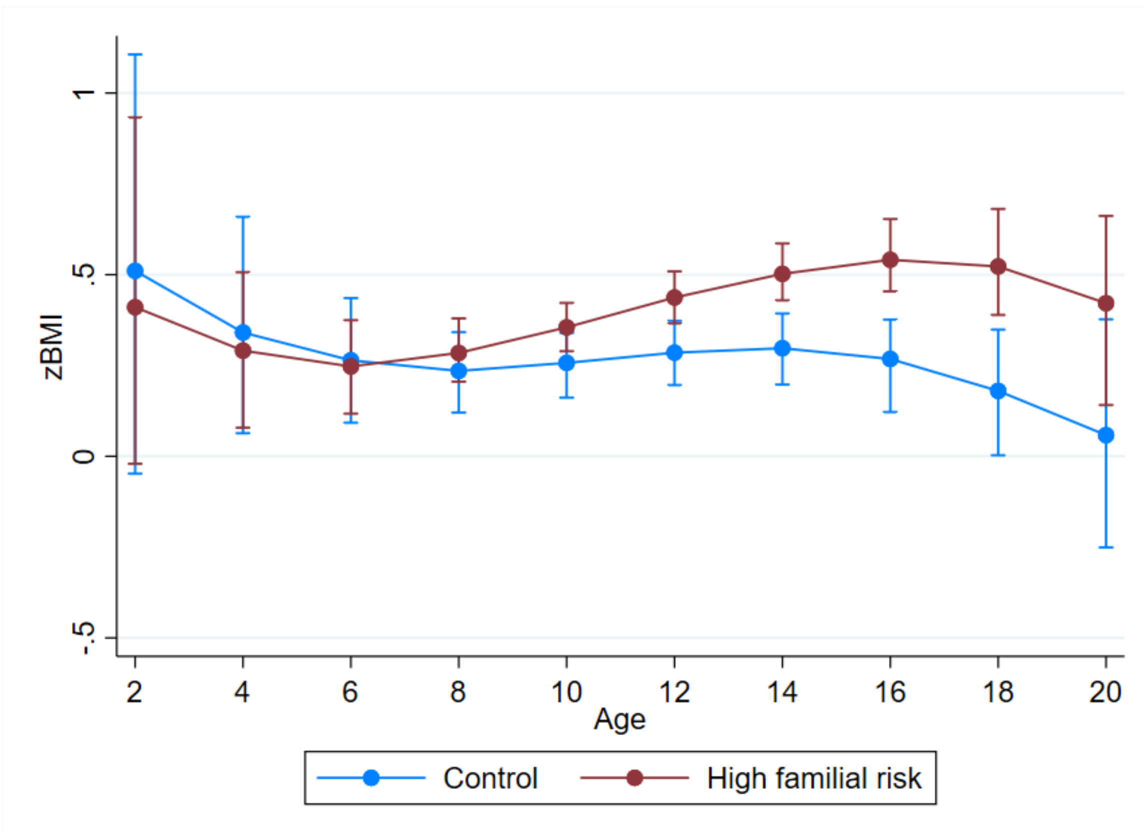
Table 2.2 Demographic characteristics of included and excluded participants. Differences between groups were tested using chi-squared (x^2) tests for categorical variables and t-tests for continuous variables. * is used to denote statistically significant differences between groups.

	Included in analysis (n = 441)	Excluded from analysis (n = 65)	X^2	p-value
Number of individuals at high familial risk (%)*	286 (64.9)	33 (50.8)	7.85	0.020
Female participants (%)	226 (61.5)	25 (38.5)	3.70	0.054
SES, number of participants by category (%)*			15.56	0.008
0	20 (4.5)	5 (7.7)		
1	36 (8.2)	14 (21.5)		
2	75 (17.0)	7 (10.8)		
3	111 (25.2)	18 (27.7)		
4	149 (33.8)	14 (21.5)		
5	50 (11.3)	7 (10.8)		
			t-statistic	p-value
Age, mean (SD)*	9.96 (4.07)	6.92 (5.25)	5.40	1.0×10^{-5}

2.3.2 Effect of parental mood disorder diagnosis on BMI

Over 1633 assessments of 441 participants with available weight and height measurements, zBMI was significantly higher in individuals at high familial risk for mood disorders compared to controls (β = 0.15, 95% CI 0.03 to 0.27, *p*=0.010; see Figure 2.1). Full regression results are shown in Appendix B, Table B.1.

Figure 2.2 Effect of mood disorder risk status on offspring zBMI in all offspring, as modeled by non-parametric regression estimates. Error bars represent the standard error of the mean at each two-year age interval.



2.3.3 Sex-specific analysis

In sex-stratified analyses, we found that females with high familial mood risk showed a significantly higher zBMI than controls (β = 0.25, 95% CI 0.08 to 0.42, *p* = 0.003; see Appendix B Table B.2) while males with high familial mood risk did not have a significantly different zBMI from controls (β = 0.05, 95% CI -0.11 to 0.21, p = 0.575; see Appendix B Table B.3).

Figure 2.3 Effect of mood disorder risk status on offspring zBMI in females, as modeled by non-parametric regression estimates. Error bars represent the standard error of the mean at each two-year age interval.

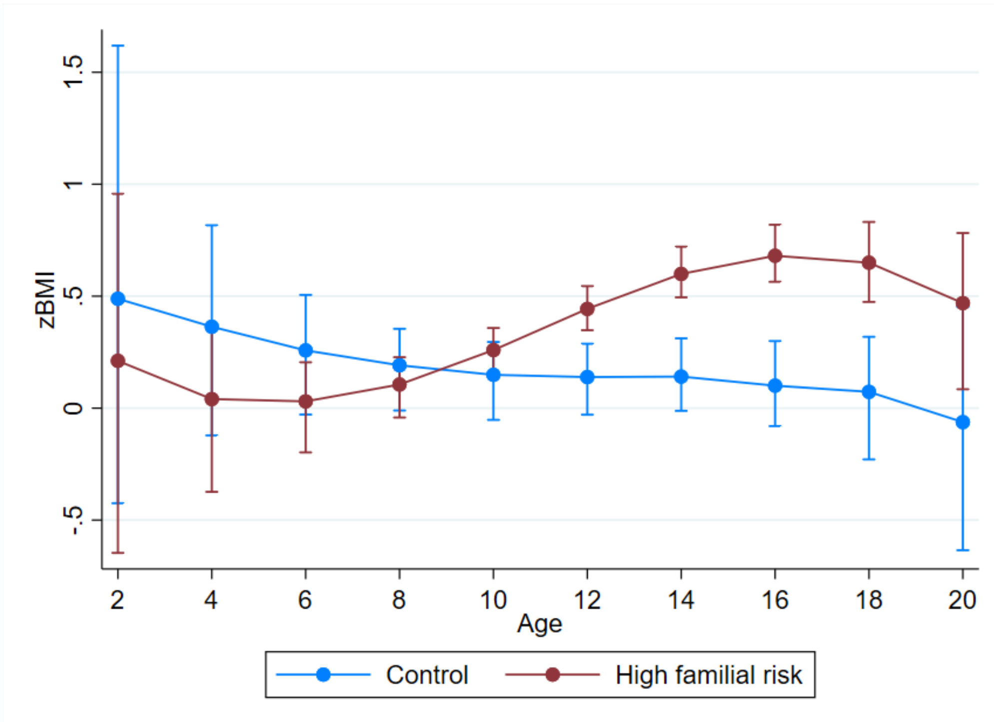
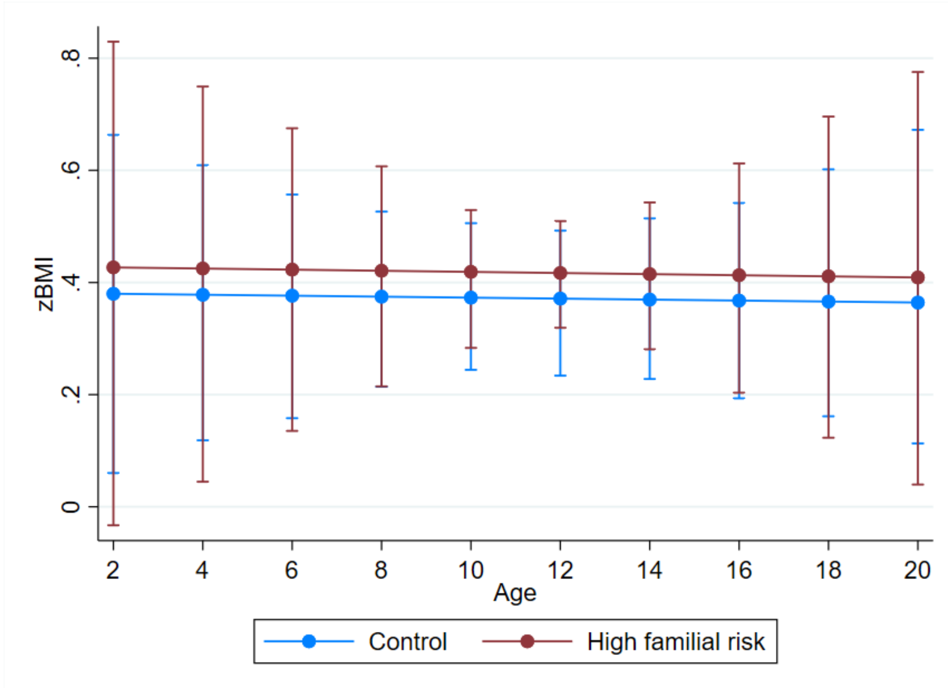


Figure 2.4 Effect of mood disorder risk status on offspring zBMI in males, as modeled by non-parametric regression estimates. Error bars represent the standard error of the mean at each two-year age interval.



2.3.4 Age-stratified analysis

When separated into younger (3-12 years) and older (13-20 years) age groups, we found that younger females at high familial mood risk did not show a significant difference in zBMI from controls (β = -0.11, 95% CI -0.31 to 0.12, $p = 0.333$; see Appendix B Table B.4), and older females at high familial risk had a significantly higher zBMI than controls (β = 0.60, 95% CI 0.38 to 0.85, $p < 0.0001$; see Appendix B Table B.5).

Younger males with high familial mood risk did not show a significantly different zBMI from controls (β = 0.02, 95% CI = -0.19 to 0.23, $p = 0.873$; see Appendix B Table B.6). Older males at high familial mood risk showed a numerical increase in zBMI compared to controls that did not reach statistical significance ($\beta = 0.10$, 95% CI -0.13 to 0.34, $p = 0.381$; see Appendix B Table B.7).

2.3.5 Waist-to-height ratio analysis

In the full sample of individuals who had WtH measurements available, we found that there was a significantly higher WtH in individuals with high familial mood risk compared to controls ($\beta = 0.014$, 95% CI = 0.0069 to 0.022, $p < 0.0001$).

In females, we found that those with high familial mood risk had a significantly increased WtH ratio compared to controls ($\beta = 0.023$, 95% CI = 0.012 to 0.033, $p < 0.0001$). In younger females, those with high familial mood risk did not show a significant difference in WtH ratio compared to controls ($\beta = -0.002$, 95% CI = -0.019 to 0.016, $p = 0.797$), but in the older females, those with a family history of mood disorders showed a marked increase in WtH ratio compared to controls ($\beta = 0.037$, 95% CI = 0.025 to 0.052, $p < 0.0001$).

In males, we found that those with high familial mood risk had no significant difference in WtH ratio compared to controls ($\beta = 0.006$, 95% CI = -0.007 to 0.017, $p = 0.351$). Both younger ($\beta = 0.001$, 95% CI = -0.016 to 0.019, $p = 0.911$) and older males ($\beta = 0.012$, 95% CI = -0.003 to 0.029, $p = 0.119$) showed no difference in WtH ratio between individuals with familial mood risk and controls. See Appendix B Tables B.8 to B.14 for full regression results.

These results show the same trends as our analyses using zBMI as a metric for body composition. WtH ratios are more representative of abdominal obesity particularly in youth, but BMI is used more widely in the literature and is useful for comparison to other studies.

2.3.6 Sensitivity analysis

2.3.6.1 Family clustering and repeated measurements

When only one zBMI measurement per family was retained, the full sample showed a nominal difference between high risk and control groups, with individuals at high familial risk showing higher zBMIs. Females at high familial mood risk showed a significantly increased zBMI compared to controls, but males did not. Younger females did not show a significant difference, while older females did. In both younger and older males, there were no significant differences between groups. See Appendix B Tables B.15 – B.21 for full regression results.

Using one WtH measurement per family, we found similar results to the reduced zBMI sample analysis; in the full sample there was a numerical increase in WtH ratio in individuals at high familial mood risk, a significant increase in WtH ratio of females at high familial mood risk, and no difference between groups in males. When separated by age group, we found that older and younger females as well as younger males showed no significant differences in WtH ratio between groups, but older males at high familial mood risk did show a significantly higher WtH ratio than controls. This change in results could be related to the greatly reduced sample size associated with this sensitivity analysis, especially when stratifying by both age and sex. See Appendix B Tables B.22 – B.28 for full regression results.

2.3.6.2 Socioeconomic status

We also ran sensitivity analyses to ascertain whether the main results detailed above were affected by SES. After including SES in our model in addition to age and familial mood risk status, we found that our results were mainly unchanged. In the full sample, individuals at high familial mood risk showed a numerical increase in zBMI compared to controls. Females at high familial mood risk still had a significantly higher zBMI than controls, driven by the significantly increased zBMI in females at high familial mood risk age twelve and above. Males also showed the same trend as the primary model. Neither younger nor older males showed any significant difference in zBMI associated with high risk status. Sensitivity analysis of WtH ratio showed the same trends as the primary model as well. See Appendix B Tables B.29 to B.35 for full regression results.

2.4 Discussion

2.4.1 Summary of results

This study found that familial mood risk influenced the trajectory of zBMI from childhood to early adulthood. Participants with a family history of mood disorders tended to have greater zBMIs than those without a family mood history. Sex- and age-stratified analysis showed that this effect was driven by females above the age of 12. These results seem to be robust to sensitivity analysis accounting for SES, family clustering, and repeated measurements.

In WtH analyses, we found the same trends as in zBMI; older females with familial mood risk had a significantly increased WtH ratio compared to controls, while other age and sex categories did not show this difference. In sensitivity analyses accounting for

SES, we found results were mainly unchanged. In sensitivity analyses accounting for family clustering and multiple measurements, we found that there was still a significant difference between females with high familial mood risk compared to controls, but the increased WtH ratio seen between all high risk offspring compared to controls became statistically non-significant. There was still a significant difference between older females with high mood risk compared to controls, and a new significant increase in WtH ratio was found between older high risk males and controls. This new result could mean that WtH ratios are able to pick up on a difference between family high risk and control older males which is masked by family clustering and multiple measurements. However, it is important to bear in mind that this sensitivity analysis was done in a much smaller sample (n = 98) compared to the full WtH sample of males (n = 492), and as a result has reduced statistical power.

2.4.2 Clinical implications

Our results show that individuals with high familial risk for developing mood disorders are more likely to develop a higher weight in adolescence, particularly females. These findings are consistent with studies that have shown a connection between mood disorder diagnosis and higher weight.

We found that adolescent females are at greatest risk of developing an increased zBMI or WtH ratio based on their familial mood history; females at this age are twice as likely to experience depression onset as males[98], and familial risk is the best predictor.[99] Bipolar disorder often first presents with a depressive episode, with mania or hypomania appearing years later.[100] Adolescent females seem to be at greatest risk for metabolic health issues based on their mood disorder risk. Early identification of metabolic risk allows us to pinpoint a window of opportunity for early intervention on a potentially modifiable risk factor that may provide a chance to decrease severity of future psychiatric illness.[73]

2.4.3 Strengths of the study

To our knowledge, this is the first study to examine the differences in trajectory of body mass and composition over childhood and adolescence between individuals with and without family history of a mood disorder. This study benefitted from a cohort enriched with offspring of parents with mood disorders; two-thirds of the sample, much higher than the population average, had parents with mood disorders.[101]

The sample also had researcher-measured waist circumferences, heights, and weights. This allowed us to avoid the concern of self-report bias as individuals tend to inaccurately report their physical measurements. Men and women both overestimate their own height, but differ in their biases when it comes to weight. Men tend to overestimate weight while women underestimate theirs.[102]

2.4.4 Limitations of the study

This study was limited in a number of ways. First, we excluded 65 individuals from analysis because we did not have complete weight or height information from them. These individuals were different from our main sample in a few key ways: they had lower SES, they were younger, and a larger proportion of them were high risk. This may have occurred for a few reasons. Younger participants by nature have had fewer annual assessments, and therefore we have had fewer opportunities to collect their weight and height measurements. It has been shown that both study participation and positive metabolic health outcomes are associated with SES, such that individuals who participate more in research studies tend to be physically healthier and of higher SES status. [103,104] This combined with the fact that a greater proportion of the individuals with missing data were in the high mood risk group suggests that our excluded group may be especially vulnerable to developing physical health issues. It will be important to try to obtain physical measurements from these participants in future assessments and compare them to the main sample.

Next, weight of offspring may have been affected by parental lifestyle choices, which may have been influenced by their disorder and its severity. This study did not consider lifestyle factors that could impact the developmental trajectory of body composition including sleep quality, activity levels, or food habits, all which have been shown to affect mood disorder severity and body weight.[105,106,107,108]

Additionally, repeated measures and inclusion of related individuals were accounted for in a separate sensitivity analyses in a subset of data with one measurement per family. Ideally, these variables would have been included in the main model, but it was not possible to include random effects variables in models run through the npregress function in Stata SE 16. As they were not included in the main model, we were not able to quantify the effect of family clustering and multiple measurements. Moving forward, it would be useful to use a nonparametric regression method that allowed for inclusion of random effects variables, perhaps by using the Bayesian nonparametric regression model outlined by Ryu and Mallick which allows for random effects covariates to be modelled nonlinearly.[109]

2.4.5 Future directions

There is still more work to be done to understand the development of increased weight in at-risk youth. One important step is to separate out genetic and environmental influences affecting youth with high familial mood risk: how much of the impact of familial mood risk on physique is dependent on shared genetics with the affected parent and how much is related to shared environment?

Now that it is established that weight differences begin to appear in adolescence, further predictors of comorbid metabolic and mood disorders can be examined in future studies, potentially including serum CRP levels.

It has been recommended that individuals diagnosed with major mood disorders should be screened for metabolic risk factors.[110] Both behavioural and pharmacological interventions have showed promise for decreasing metabolic issues such as obesity and pre-diabetes symptoms in individuals with mood disorders. Our findings suggest that screening individuals with familial mood risk may be helpful as they show increased weight beginning in adolescence.

2.5 Conclusion

We found that offspring of parents with mood disorders had an increased zBMI and WtH ratio compared to controls with unaffected parents. This increase was driven by high-risk adolescent females, the group most at risk for developing mood disorders. It is important to address risk factors in this group who are particularly vulnerable to developing both mood and metabolic issues.

Adolescent females face immense pressure related to body image and weight, and individuals at risk for depression are prone to being highly self-critical, so it is important to be sensitive and compassionate when addressing this topic, especially in the context of intervention.[111,112]

Chapter 3: Polygenic influences on mood and body weight among youth at familial risk for mood disorders

3.1 Introduction

Individuals with mood disorders are more likely to develop metabolic ill health.[26] Metabolic diseases and mood disorders both have a high burden of disease,[113] and having metabolic comorbidities worsens illness in individuals with mood disorders (including increased severity of mood symptoms, treatment resistance, and functional impairments).[26,114,115,32] Obesity in particular is associated with increased severity of bipolar disorder.[116]

Experiencing either a mood disorder or metabolic condition is predictive of having the other, with a diagnosis of major depressive disorder increasing the risk of metabolic diseases like type 2 diabetes and metabolic disease diagnosis increasing risk of depression onset.[117] One meta-analysis showed a strong relationship between depression and metabolic syndrome.[118] Females with bipolar disorder are at higher risk of developing increased weight, blood glucose, and insulin than controls.[119] Depressive symptoms are also associated with increased levels of CRP, a marker of metabolic health that indicates systemic inflammation.[26] Obesity, a metabolic risk factor, shows a bidirectional relationship with depression where obesity increases the risk for depression and depression increases the risk of future obesity.[33]

Major depressive disorder and bipolar disorder are highly heritable, as are metabolic conditions like increased body weight and type 2 diabetes.[18,120] Metabolic issues and mood disorders can be co-transmitted; higher polygenic risk scores for cardiometabolic traits are associated with increased risk for bipolar disorder.[121] BMI shares a number of genetic variants with mood disorders, and CRP levels have a genetic correlation with depressive symptoms.[66]

The genetic risk associated with both mood disorders and metabolic issues is highly polygenic.[60] As such, polygenic scoring is an effective way of capturing the overall genetic liability to each trait. High polygenic scores for BMI are associated with overweight and obese status, while high depression and bipolar disorder polygenic scores are strongly associated with the respective diagnoses.[122,123,124] BMI and CRP polygenic scores are associated with depressive symptoms in both clinical and general populations.[69]

Associations between genetic liability for mood disorders and metabolic traits like BMI and CRP have been shown in individuals with mood disorders themselves, but it has not yet been studied how this genetic risk relates to body weight and depressive symptoms in offspring of parents with major mood disorders.

This project examined the co-transmission of genetic risk for mood disorders and increased body mass in individuals at high familial risk for mood disorders. We aimed to find out how the genetic susceptibility to mood disorders affects BMI as well as how the genetic predisposition to increased BMI and CRP levels affects depressive symptoms. We also investigated how having a family history of mood disorders can impact these relationships.

We first asked whether the genetic predisposition to depression and bipolar disorder, indexed by polygenic scores, influenced BMI in a cohort enriched for individuals with high familial risk for mood disorders. We then considered the effect of metabolic genetic liability, using the BMI and CRP polygenic scores, on depressive symptoms in this group. We hypothesized that polygenic scores for depression and bipolar disorder would show a positive relationship with BMI, and that polygenic scores for BMI and CRP would be positively associated with depressive symptom severity.

3.2 Methods

3.2.1 Participants

We recruited a cohort of children and youth aged 6 to 26 years enriched for individuals with high familial risk for mood disorders in Nova Scotia.[89] We included 297 participants who had provided a saliva sample and excluded 91 participants of non-European ethnicity. Participants who could give written informed consent to participate in the study did so, and those who could not provided assent and their parent or guardian provided written informed consent on their behalf.

Participants were split into two groups: offspring at high familial risk for major mood disorders and comparison control offspring with low familial risk for major mood disorders. Parents of high risk participants were recruited through referrals from adult mental health services by clinicians treating patients with severe mental illness, while parents of control participants were healthy individuals matched on neighbourhood and demographic factors to parents of the high risk participants, and recruited through acquaintance and school-based referral. All study procedures described here were approved by the Research Ethics Board of the Nova Scotia Health Authority.

3.2.2 Parental diagnosis

We assessed parental diagnosis using the SCID-5.[90] Offspring were assigned high familial risk status if they had at least one biological parent with a diagnosis of major depressive disorder or bipolar disorder, or if they had multiple second-degree relatives with these disorders. Control offspring were individuals whose parents had no lifetime diagnosis of major depressive disorder or bipolar disorder.

3.2.3 Offspring depressive symptom assessment

Participants underwent annual assessments, with separate teams assessing parents and offspring. Researchers assessing offspring were blind to parent diagnosis and researchers assessing parents were blind to offspring diagnosis. Depressive symptoms were assessed using the Mood and Feelings Questionnaire (MFQ)[125] self or parent report.

3.2.4 Physical measurements of participants

Height (in centimeters), weight (in kilograms), and waist circumference (in centimeters) of participants were measured by researchers annually during their FORBOW assessment. Offspring assessments were done by researchers blind to parental diagnosis.

3.2.5 Saliva sample collection and DNA extraction

Participants provided a saliva sample using the Oragene kit (DNA Genotek Inc, Kanata, ON) which keeps samples stable at room temperature for up to 5 years. Saliva was stored at room temperature until DNA was extracted according to kit instructions.

First, samples were mixed gently by inversion and incubated in an air incubator overnight at 50 degrees Celsius to ensure DNA was released and nucleases were permanently inactivated. Samples were then mixed with prepIT•L2P and vortexed to precipitate impurities and inhibitors. The mixture was then incubated on ice for ten minutes and centrifuged at room temperature for five minutes at 15 000 x *g* to separate out the pellet containing impurities. The clear supernatant was retained and transferred to a fresh tube while the pellet was discarded. 100% ethanol was added to the supernatant and mixed gently via inversion. Samples were then allowed to sit at room temperature for ten minutes to allow DNA to precipitate completely. Next, samples were centrifuged at room temperature for two minutes at 15 000 x *g* to separate out the DNA pellet. The supernatant was discarded without disturbing the DNA pellet. 70% ethanol was added to the DNA pellet to further clear impurities then removed carefully without disturbing the pellet. The DNA pellet was dissolved in TE buffer solution to preserve DNA and protect it from degradation. The solution was vortexed to mix completely and incubated at room temperature overnight. Samples were kept at -20 degrees Celsius for long-term storage.

DNA samples were quantified using a Nanodrop spectrophotometer. Only samples with a concentration of 50 ng/uL or above and a 260/280 ratio of 1.7 – 2.0 were retained. We made sure DNA had not degraded by running a subset of 8 random samples on a 1% ethidium bromide gel, and excluded samples that appeared degraded in imaging from further processing.

3.2.6 Genotyping

Genome-wide genotyping was done using the Illumina Infinium Global Screening Array-24 BeadChip for SNPs using DNA extracted from saliva as detailed above. All genetic data was aligned against the Genome Reference Consortium Human Build 37

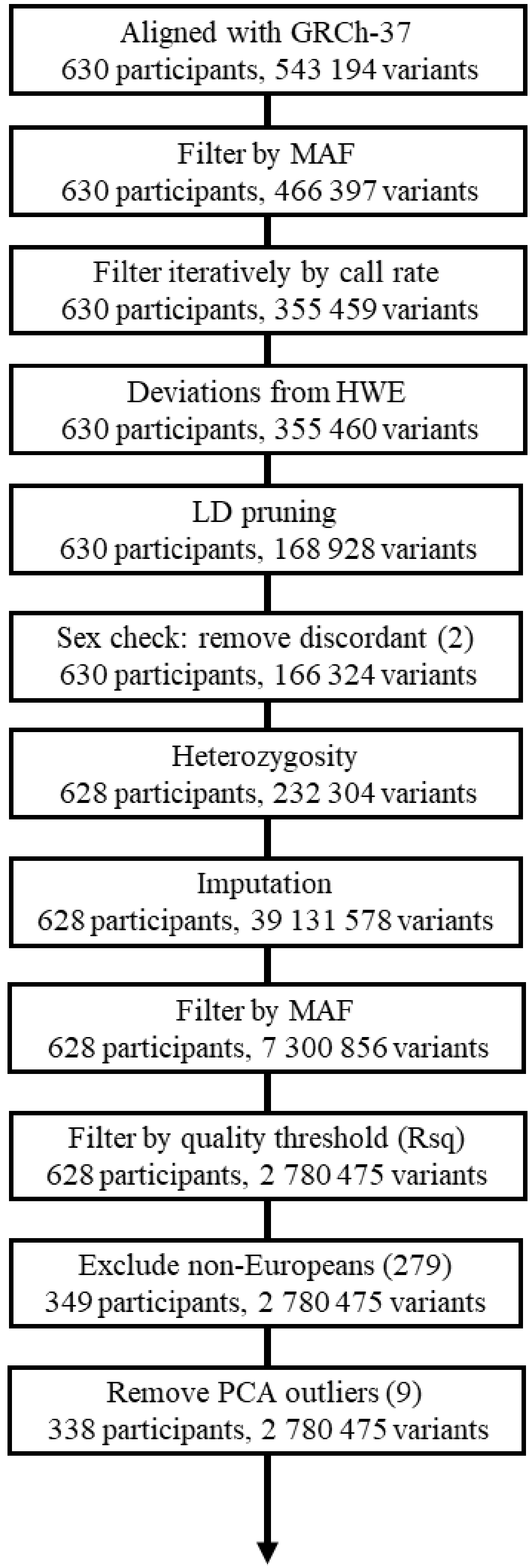
(GRCh37). If genotyping data was aligned to a different reference build, it was converted to GRCh37 using the procedure detailed in Appendix A Fig A.1.

3.2.7 Genetic data processing

A genetic quality control pipeline was followed to retain only the variants and individuals that have reliable high-quality genetic data. We followed the process for genetic quality control and imputation outlined by Coleman et al.[126] PLINK 1.9 was used for this process.[127] See Figure 3.1 below for the variants and individuals analysed and excluded at each step. Before imputation, quality control steps were conducted to remove the following: variants that had a minor allele frequency (MAF) of less than 1%, variants with a missing call rate more than 5%, individuals with a genotyping rate lower than 95%, variants that failed the Hardy-Weinberg equilibrium test at a significance level of $p < 10 \times 10^{-10}$, participants with discordant self-reported and genetic sex, and participants with heterozygosity values greater than 4 standard deviations above the sample mean.[128]

Data was imputed using minimac3 on the Michigan Imputation Server. We used the Haplotype Reference Consortium r1.1 2016 as the reference panel and phasing was done using Eagle v2.3. After imputation, further steps of quality control were done, including pruning variants with a MAF below 1% and imputation quality (measured with R^2) of below 0.30.

Figure 3.1 Genetic quality control and imputation pipeline (HWE = Hardy-Weinberg Equilibrium



3.2.8 Ethnicity and population stratification

All populations of humans show genetic structure (variation in how genetically similar people are to one another, caused by a history of migration, population mixing, and geographic separation). Different populations have differences in their genetic structure which may correlate with patterns of phenotypic variation, leading to population stratification (erroneous associations to be found between genetic variants and phenotypic traits). Population stratification can introduce huge bias into polygenic scoring.[129] One way to deal with this is by applying principal component analysis (PCA) to our genome-wide SNP genotype data. Dimension reduction is performed to construct principal components (PCs), such that the first PC explains the greatest variance in the data and each subsequent PC explains less and less of the variance and must be independent of the other PCs. PCA can be used to model differences in ancestry between individuals to avoid spurious correlations between variants and traits of interest while maintaining sufficiently high power to detect true associations.[130] In addition, some variants show departure from the Hardy-Weinberg equilibrium because of population stratification, and these were removed during the quality control process. [131]

The top few PCs typically reflect population structure among the individuals in the sample, but when a sample includes related individuals, this acts as a confound and the top PCs constructed from standard PCA are reflective of family clusters instead. To calculate PCs that are robust to containing related individuals in the sample, we used a method of PCA in Related Samples (PC-AiR). PC-AiR accounts for the relatedness in the samples by measuring kinship coefficients and pairwise ancestry divergence to create a subset of individuals that are ancestry-representative of the full sample and contains mutually unrelated individuals. The unrelated subset is used to run a standard PCA, then the PC values for the excluded individuals are predicted based on their genetic relatedness.[132] Outliers that were 4 standard deviations above or below the mean for the top 4 PCs were removed. See Appendix Figure A.2 for the full PC-AiR protocol (https://bioconductor.org/packages/devel/bioc/vignettes/GENESIS/inst/doc/pcair.html). The top 10 PCs calculated with this method were used as covariates in the polygenic score statistical analyses to account for population stratification. All individuals of non-European ancestry were excluded from polygenic score analysis.

3.2.9 Constructing polygenic scores

We created polygenic scores for genetic liability to depression, bipolar disorder, BMI, and CRP using the clumping and thresholding method with the PRSice2 software.[133] Clumping was done to remove SNPs that were in linkage disequilibrium (LD) with one another and compile a list of independent SNPs with an $r^2 < 0.1$ within any 500 kb window.

The GWAS used for each trait were chosen based on their size and the quality of their measurement of the phenotype. Since genetic prediction of complex traits benefits from including a large number of variants that do not reach genome-wide significance, we chose a significance threshold for variant effect sizes that balanced having a large proportion of causal variants (true with more stringent thresholds) with having a greater total number of variants included (as true with a more lenient threshold). P-value thresholds (pT) were chosen according to which threshold explained the most phenotypic variance in its original GWAS. The depression polygenic score was constructed at pT=0.05, the bipolar disorder polygenic score at pT=0.1, the BMI polygenic score at pT=0.005, and the CRP polygenic score at pT=0.05.[61,62,134,58] To calculate polygenic scores, each allele that met the pT was weighted by the effect size of its association with each phenotype (detailed in the summary statistics from the reference GWAS). Polygenic scores were all standardized via conversion to z-scores using R version 4.2.1.[135,136]

3.2.10 Statistical analysis

We tested the effect of the depression polygenic score and bipolar polygenic score on BMI and the effect of BMI polygenic score and CRP polygenic score on current depressive symptoms using mixed-effects linear regression and controlling for sex, age, family identifier, SES, familial mood risk status, and the first ten ancestry informative PCs. Analyses were also split by familial risk status to investigate whether there was a differential effect of polygenic scores on BMI or depressive symptoms based on family history of mood disorders.

We also tested the effects of the depression polygenic score on depressive symptoms and the effect of the BMI polygenic score on BMI to check whether the polygenic scores have the expected positive relationships with their related phenotypes. These analyses were also run using mixed-effects linear regression and controlling for sex, age, family identifier, SES, familial mood risk status, and the first ten PCs.

SES was scored as a sum of five binary indicators of SES: mother's education of high school or above, father's education of high school or above, home ownership, annual household income of greater than $60,000 a year, and a bedroom to people ratio above 0.9. Participants could have a range of SES scores from 0 – 5.

We accounted for including related family members in the sample by including family identifiers as random effects variables in the model. All regressions were run using the lme4 package in R 4.2.1.[137]

3.3 Results

3.3.1 Demographic characteristics

We gathered data from 297 participants, 67.3% of whom were at high familial risk for major mood disorders. The high familial mood risk and control groups had no significant differences in number of participants, SES, or BMI, but the control group was younger on average. See Appendix B Figure B.2 for a visual breakdown of SES by high risk status.

Table 3.1 Demographic characteristics of participants (* denotes a significant difference between groups)

	High familial risk	Control	X^2	p-value
Participants, n	200	97		
Females, n (%)	110 (55)	46 (47)	1.504	0.2201
SES by category, n of measurements – not participants (%)			6.2345	0.2841
0	5 (2.5)	3 (3.1)		
1	20 (10)	4 (4.1)		
2	39 (19.5)	12 (12.4)		
3	45 (22.5)	25 (25.8)		
4	58 (29.0)	34 (35.1)		
5	33 (16.5)	19 (19.6)		
			t-statistic	p-value
Age, mean (SD)*	15.4 (4.3)	13.9 (3.1)	-3.517	0.000514
BMI, mean (SD)*	22.6 (6.0)	20.9 (4.6)	-2.7482	0.006446

3.3.2 Mood disorder polygenic scores and BMI

We found that the depression polygenic score showed a non-significant weakly positive correlation with BMI (β=0.34, 95% CI -0.24 – 0.92, *p*=0.250) after correcting for age, sex, family high risk status, family identifier, SES, and the first ten principal components. The bipolar disorder polygenic score showed a non-significant negative relationship with BMI (β=-0.28, , 95% CI -0.86 – 0.29, *p*=0.334). See Appendix B Table B.36 and B.37 for full regression results.

Figure 3.2 Relationship between depression polygenic score and BMI (PGS = polygenic score)

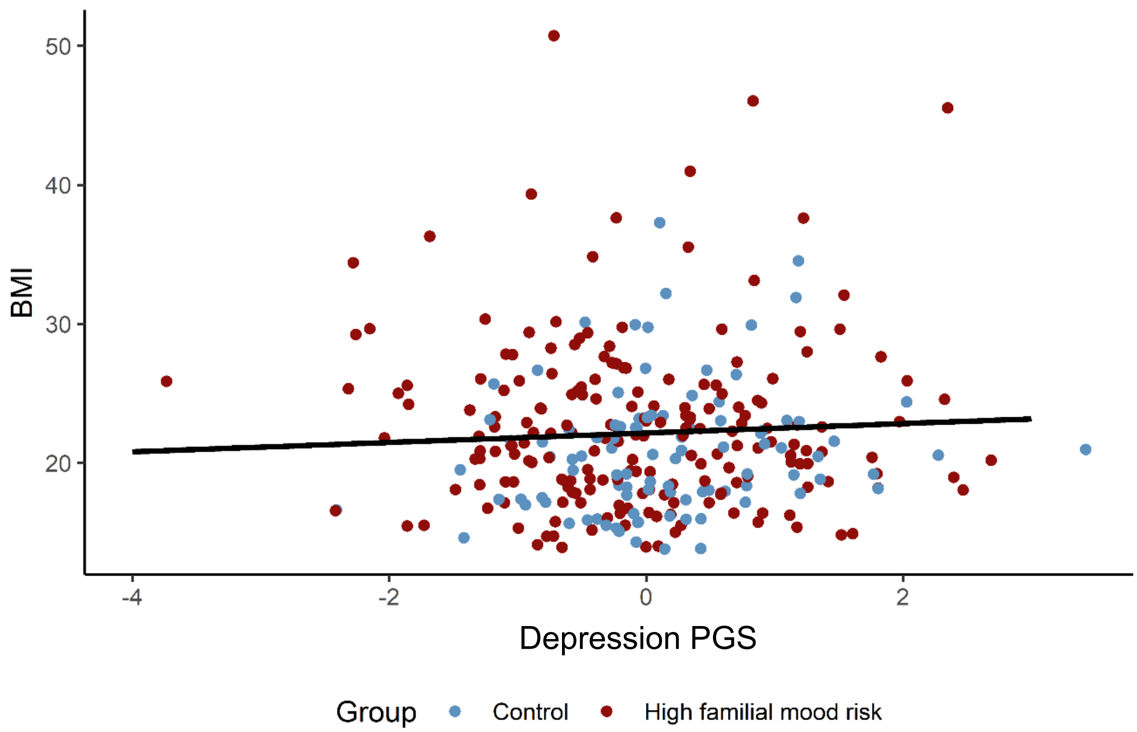
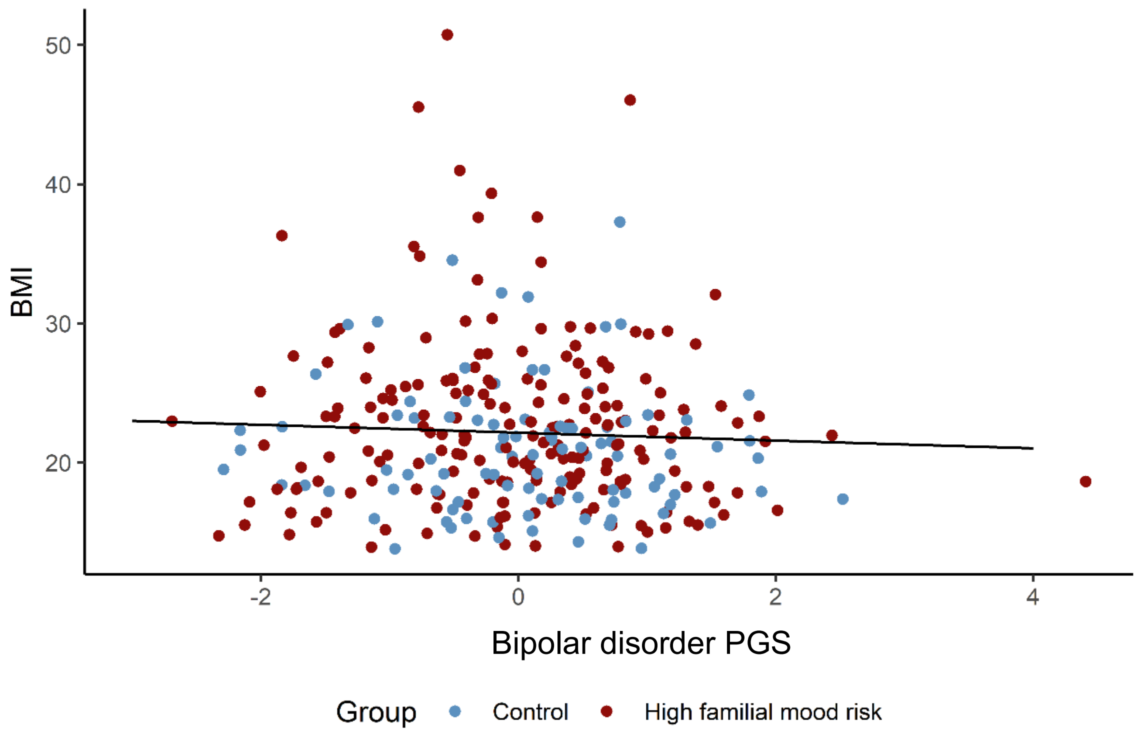


Figure 3.3 Relationship between bipolar disorder polygenic score and BMI (PGS = polygenic score)



When we considered the individuals with high familial mood risk and controls separately, we found that the depression polygenic score was non-significantly positively correlated with BMI in the high familial risk group (β=0.23, 95% CI -0.49 – 0.96, *p*=0.525) and had a non-significant positive correlation with BMI in the controls (β=0.51, 95% CI -0.48 – 1.51, *p*=0.306). The bipolar disorder polygenic score showed a non-significant negative relationship with BMI in the high familial risk group (β=-0.37, 95% CI -1.11 – 0.36, *p*=0.377) and a non-significant positive relationship with BMI in the control group (β=0.09, 95% CI =-0.93 – 1.10, *p*=0.867). See Appendix B Table B.38 – B.41 for full regression results.

Figure 3.4 Relationship between depression polygenic score and BMI, separated by mood risk status (PGS = polygenic score)

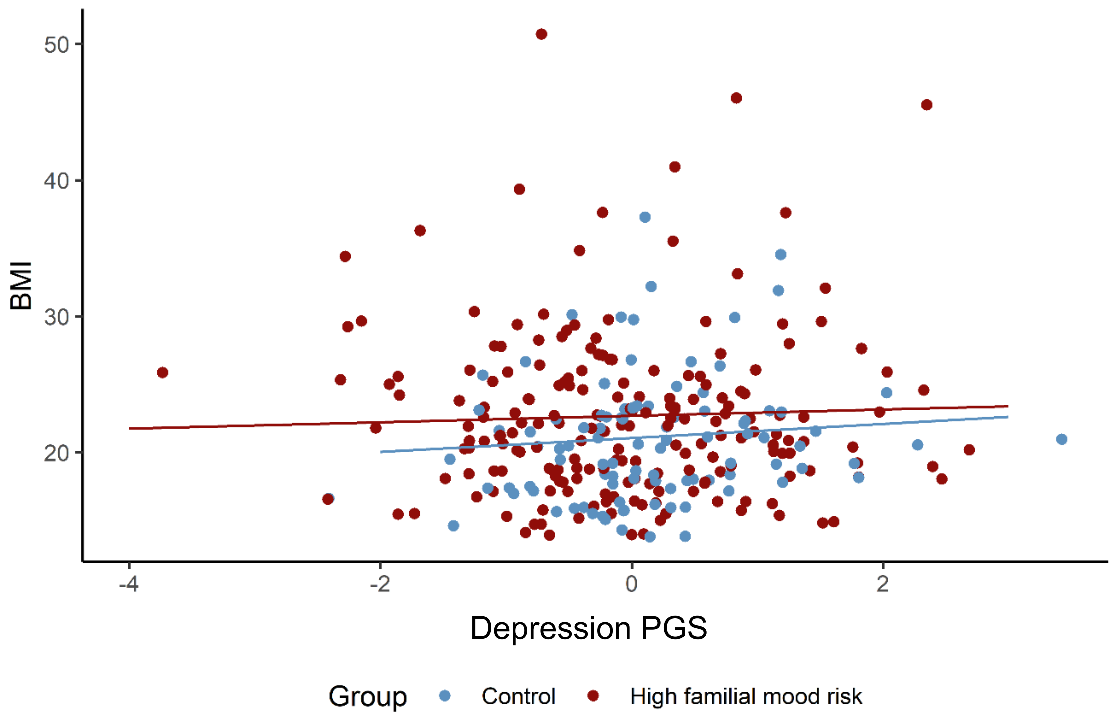
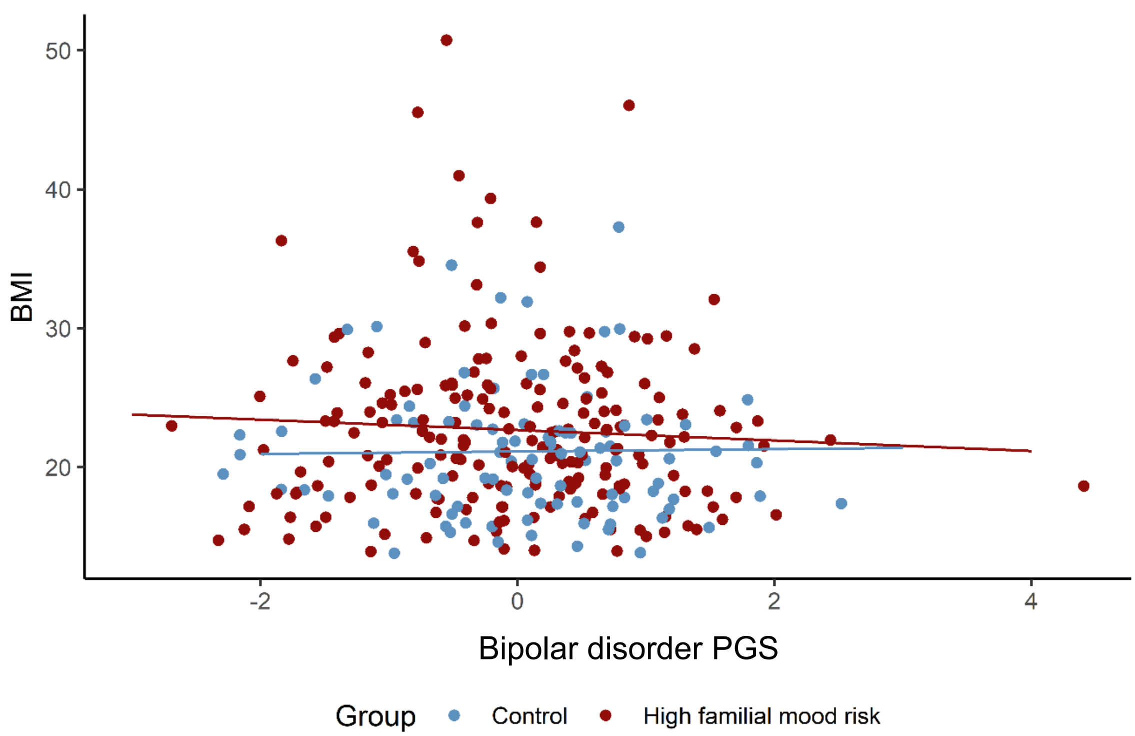


Figure 3.5 Relationship between bipolar disorder polygenic score and BMI, separated by mood risk status (PGS = polygenic score)



3.3.3 Metabolic polygenic scores and depressive symptoms

We found that the BMI polygenic score showed a slight non-significant negative relationship with depressive symptom severity (β=-0.02, 95% CI -0.15 – 0.11, *p*=0.746) after correcting for age, sex, family identifier, family high risk status, SES, and the first ten principal components. The CRP polygenic score showed a weak non-significant positive relationship with depressive symptoms (β=0.05, 95% CI -0.07 – 0.18, *p*=0.411). See Appendix B Table B.42 and B.43 for full regression results.

Figure 3.6 Relationship between BMI polygenic score and depressive symptoms (PGS = polygenic score)

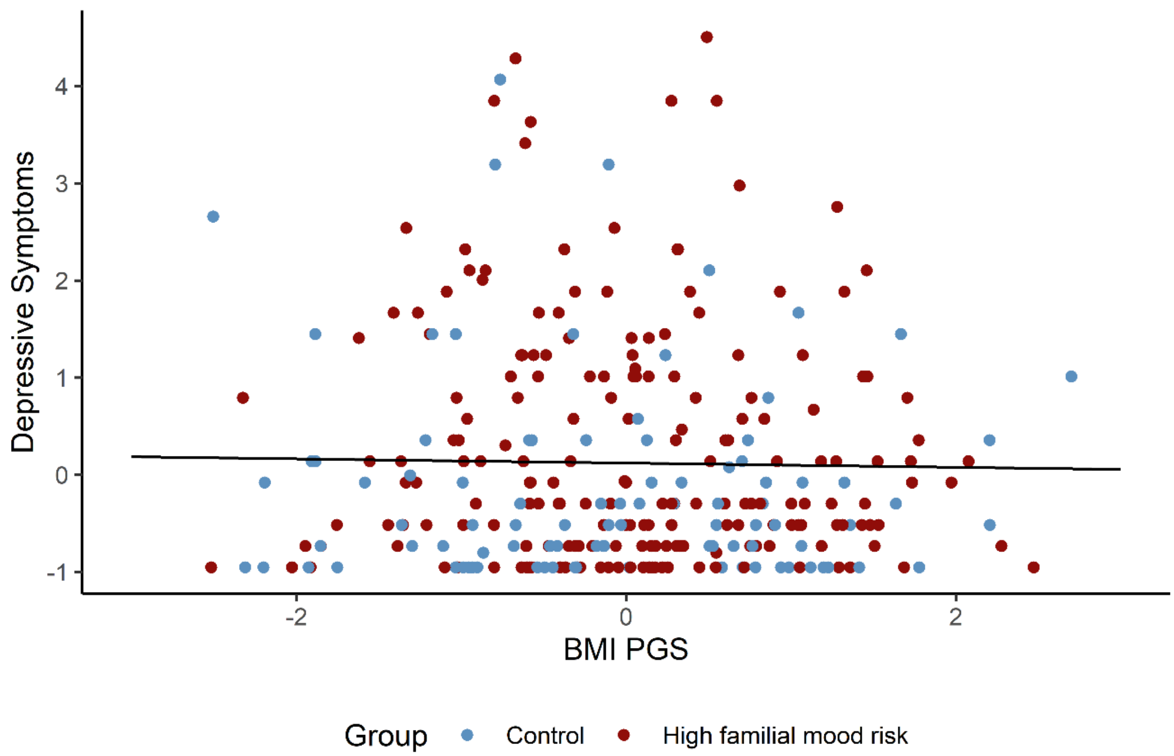
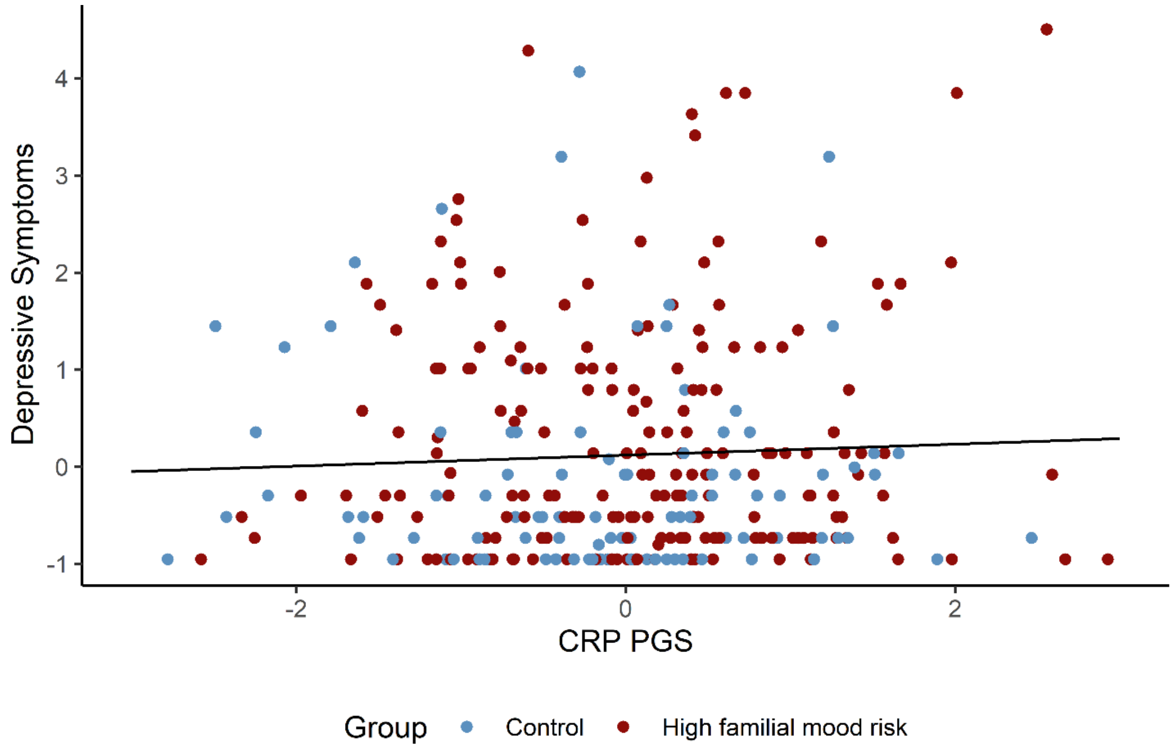


Figure 3.7 Relationship between CRP polygenic score and depressive symptoms (PGS = polygenic score)



When we separated participants by mood disorder risk status, we found that the BMI polygenic score was non-significantly negatively correlated with depressive symptoms in the high familial risk group (β=-0.04, 95% CI -0.23 – 0.14, *p*=0.631) and positively correlated in the controls (β=0.04, 95% CI -0.15 – 0.22, *p*=0.676). The CRP polygenic score showed a non-significant positive correlation with depressive symptoms in high mood risk offspring (β=0.13, 95% CI -0.04 – 0.29, *p*=0.95) and a non-significant negative correlation in controls (β=-0.16, 95% CI -0.35 – 0.04, *p*=0.11). See Appendix B Table B.44 and B.47 for full regression results.

Figure 3.8 Relationship between BMI polygenic score and depressive symptoms, separated by mood risk status (PGS = polygenic score)

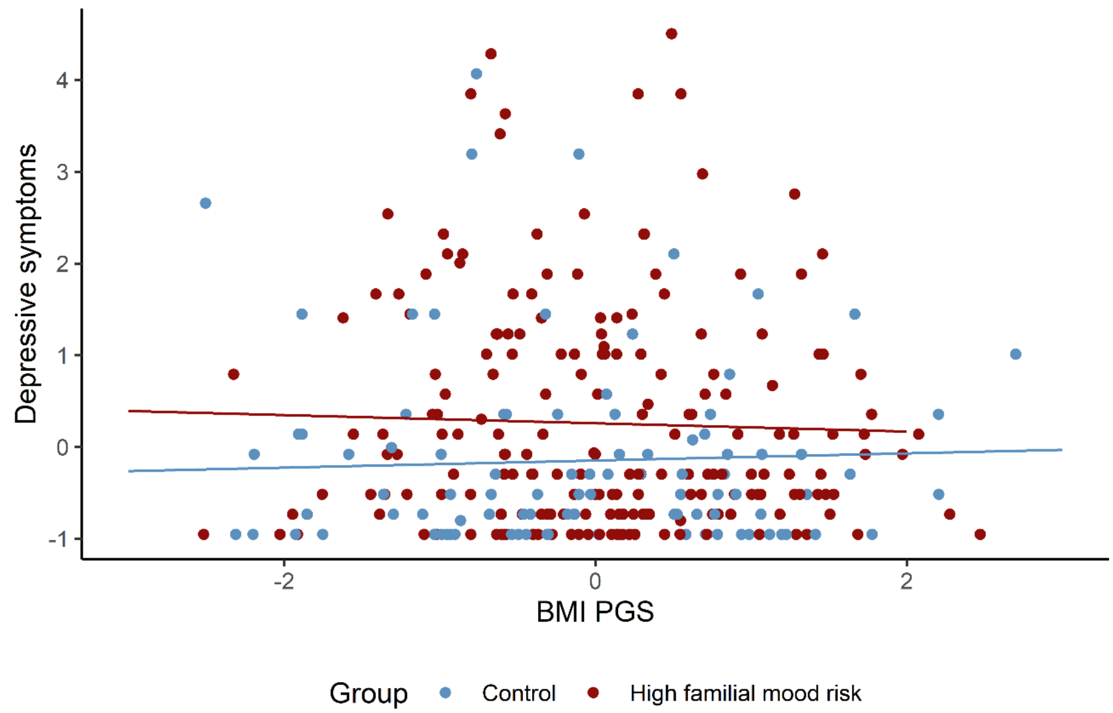
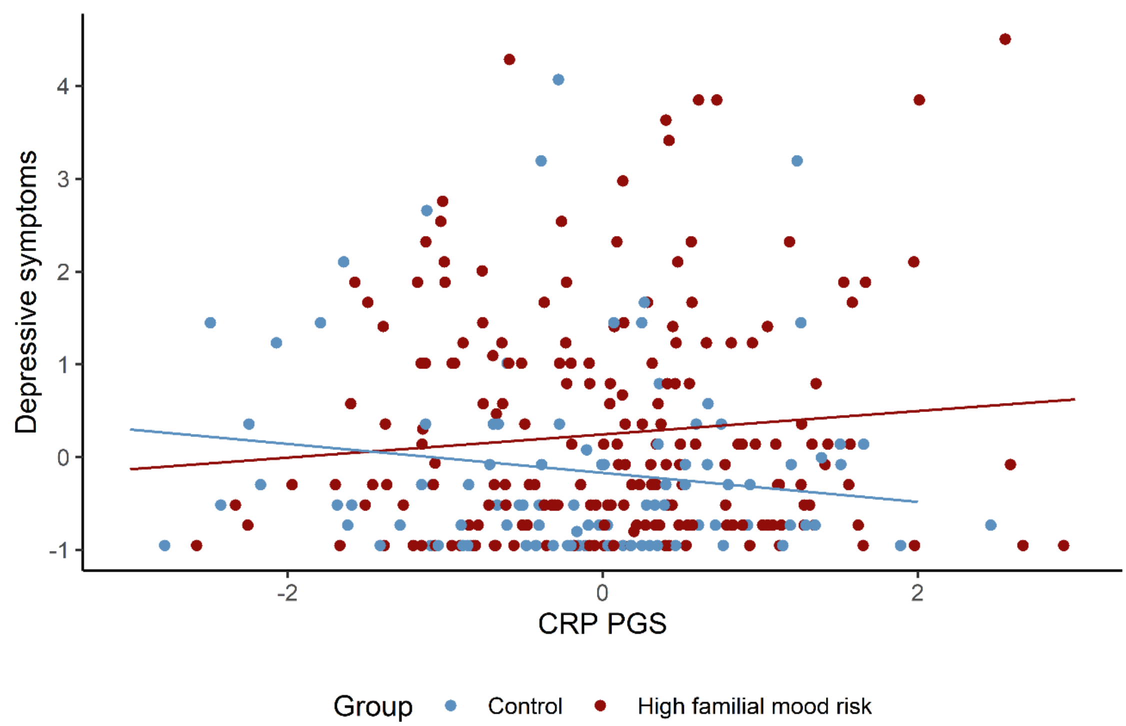


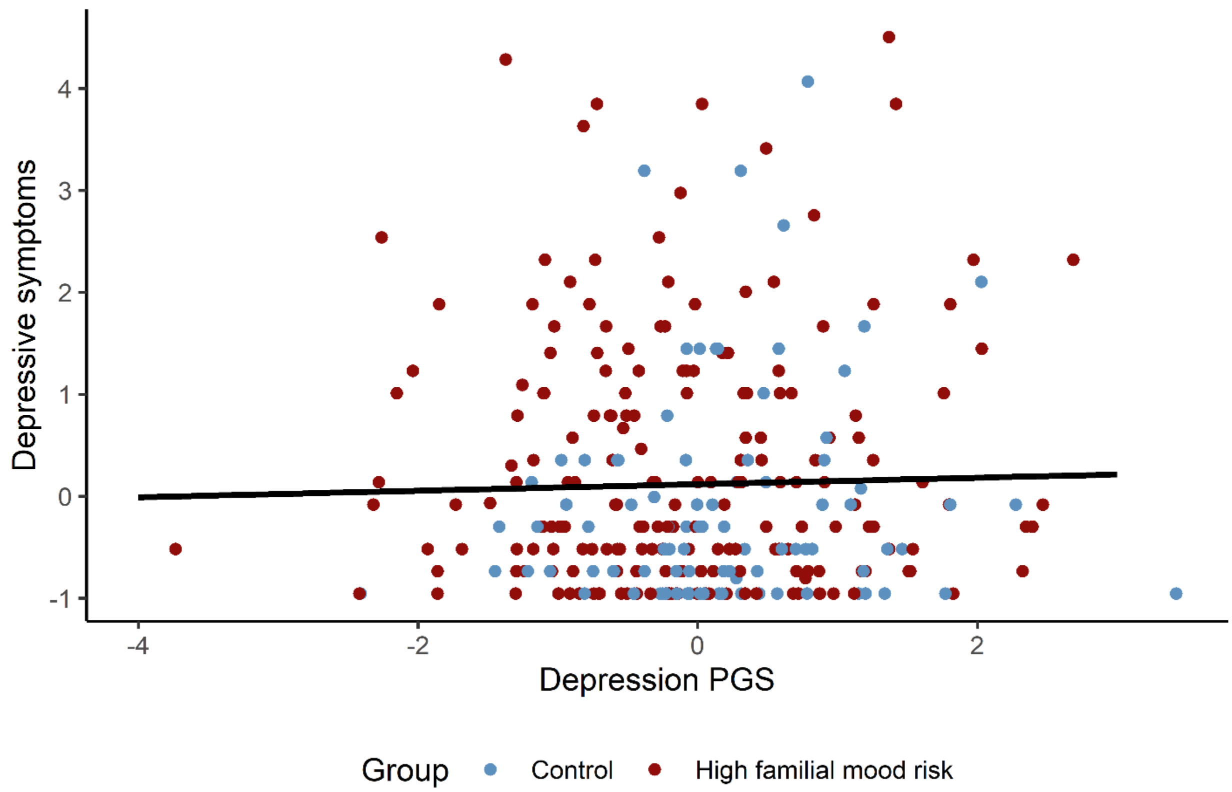
Figure 3.9 Relationship between CRP polygenic score and depressive symptoms (PGS = polygenic score)



3.3.4 Depression polygenic score and depressive symptoms

Depression polygenic scores showed a non-significant positive association with depressive symptom severity (β=0.03, 95% CI -0.10 – 0.16, *p*=0.627) after correcting for age, sex, family identifier, family high risk status, SES, and the first ten principal components.

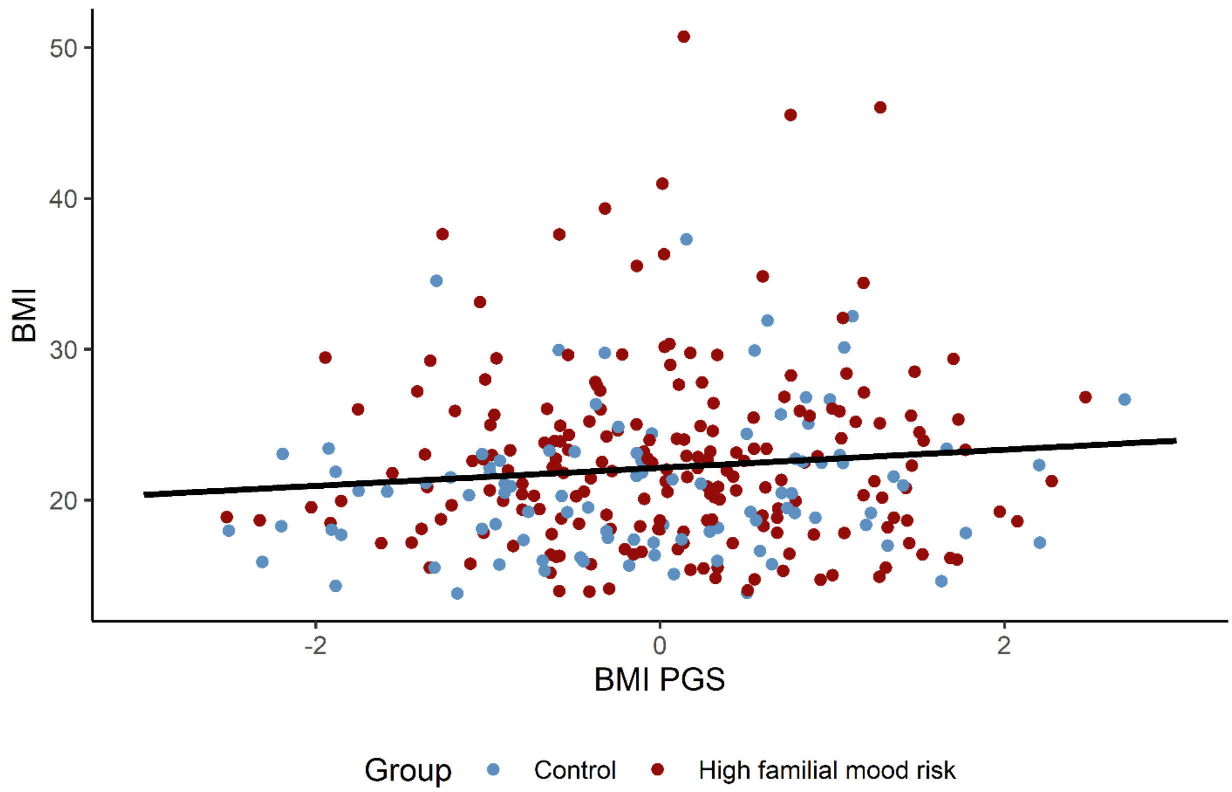
Figure 3.10 Relationship between depression polygenic score and depressive symptoms (PGS = polygenic score)



3.3.5 BMI polygenic score and BMI

The BMI polygenic score was positively associated with participant BMI (β=0.60, 95% CI 0.01 – 1.18, *p*=0.045) after correcting for age, sex, family identifier, family high risk status, SES, and the first ten principal components.

Figure 3.11 Relationship between BMI polygenic score and BMI (PGS = polygenic score)



3.4 Discussion

3.4.1 Summary of results

We examined the relationship between mood disorder polygenic scores and body weight as well as the relationship between metabolic polygenic scores and depressive symptoms. We found no significant effect of depression and bipolar disorder polygenic scores on BMI and no significant effect of BMI and CRP polygenic scores on depressive symptoms. As such, we were not able to support our hypotheses that the mood disorder polygenic scores would be positively associated with BMI or that the metabolic polygenic scores would be positively associated with depressive symptom severity.

When examining the relationship between the depression polygenic score and depressive symptom severity, we found that they were not significantly associated. However, we did find that the BMI polygenic score was significantly associated with participant BMI.

Due to a low sample size, our statistical power was limited and these results may not be conclusive. There was high dispersion in BMI and depressive symptoms, and this may have also limited our statistical power. We are currently working on gathering further genetic samples and increasing our sample size through collaboration with similar cohorts enriched with familial mood risk.

3.4.2 Clinical implications

For the most part, our results showed effects that were not statistically significant, but we discovered some interesting trends. The depression polygenic score was positively correlated with BMI in both risk groups. The bipolar disorder polygenic score was negatively correlated with BMI in offspring with high familial mood risk and positively correlated with BMI in the control group. Familial risk for depression is associated with increased BMI,[41] and has a small genetic correlation of -0.06 with bipolar disorder, and a significant genetic correlation of 0.12 with major depressive disorder.[65] The trends in our data follow the pattern of positive correlation between BMI and depression and negative correlation between BMI and bipolar disorder. There may be a mood disorder-specific effect of genetic risk on BMI. Additionally, it is possible that the genetic component of mood disorder risk influences BMI differently in individuals with familial risk and those without. Further studies in our cohort will examine this connection further.

The BMI polygenic score had a negative correlation with depressive symptoms in all participants. While the association between increased weight and mood symptoms is well documented[27,31,32], one study found that increase BMI had a protective effect against depressive symptoms.[138] This study examined middle-aged Chinese individuals, a very different demographic from our current study, so the applicability of these results to our sample may be limited. It is more likely that an increased sample is required to discover the true relationship between the BMI polygenic score and depressive symptoms in at-risk youth.

There was a positive correlation between the CRP polygenic score and depressive symptoms, but when separated by risk status, the CRP polygenic score showed opposing results in offspring with high familial risk and controls. The CRP polygenic score was positively associated with depressive symptoms in high risk offspring but negatively associated with them in controls. Individuals with mood disorders, especially those with higher BMIs[139], tend to have elevated CRP levels, so it was expected that those with increased genetic risk for elevated CRP would have more depressive symptoms.[26,29] The opposite trend in controls suggests that there may be a stronger non-genetic influence on the relationship between CRP levels and depressive symptoms if parents do not have a mood disorder.

We found that the BMI polygenic score was predictive of measured BMI, as expected based on previous studies showing the predictive capacity of obesity and BMI polygenic scores.[62,140] The relationship between the depression polygenic score and depressive symptoms did not reach statistical significance, but it was slightly positive. Previous research has shown that the depression polygenic score is associated with depression symptom severity, but that it explains a small proportion of the variance in symptoms (0.95 – 1.7%).[141,142,143] The small effect of the depression polygenic score on depressive symptoms may explain why, though we see a positive trend, we did not find a statistically significant association in our sample.

3.4.3 Strengths of the study

This study was conducted in a sample where two-thirds of the participants carry genetic risk for mood disorders, passed on from a biological parent with a mood disorder diagnosis. Due to the high proportion of individuals with mood disorder risk, these results can be applied to both clinical and community populations with reasonable accuracy.

The prospective design of this study meant that we were able to collect data on antecedents of mood disorders in a particularly vulnerable cohort. We avoided sources of bias associated with retrospective studies of health (such as selection bias), and were able to separate precursors from consequences of the disorder.

3.4.4 Limitations of the study

One major limitation to this study is that we were unable to include a number of individuals in statistical analysis because we could only retain individuals of European ethnicity for polygenic scoring. This decrease in sample size of 91 individuals of non-European ethnicity would have lowered our statistical power, meaning we would not be able to detect smaller effect sizes. An analysis of mood and metabolic polygenic scores and their relationship to weight and depressive symptom phenotypes may be worth pursuing in a larger dataset that will be able to detect smaller effect sizes. A new round of genotyping is currently in progress that will greatly increase our sample size.

Another limitation to this study is that the samples used in the original GWASes are very different from ours in terms of demographics and how the traits are quantified. For example, a majority of the participants in the CRP GWAS are middle-aged or older. Polygenic scores derived from these GWAS summary statistics may not be representative of the true polygenic risk our participants (children, adolescents, and young adults) have.

3.4.5 Future directions

One opportunity for moving forward is a disorder-specific analysis. It is possible that these polygenic scores may influence phenotypic traits differently based on parental mood diagnosis. Though they share genetic risk, there are differences in the genetic architecture of bipolar disorder and depression, and their effects on BMI have been shown to be in the opposite directions. A useful future step might be to consider the effects of mood and metabolic polygenic scores on phenotypes of interest separately in offspring of parents with major depressive disorder and bipolar disorder.

It has been shown that childhood adversity has a negative effect on metabolic health in individuals with mood disorders.[144] Another avenue to pursue further is the impact of childhood adversity on the relative role of genetics in determining metabolic health in youth at risk for mood disorders.

3.5 Conclusion

Screening for genetic risk can aid individualized gene-based health recommendations. Children of parents with mood disorders are at increased risk for physical and mental illness, and understanding the genetic relationship between mood and metabolic health could help us identify those in need of preventative interventions.

Chapter 4: General Conclusions

4.1 Objectives

The goals of this thesis were to identify developmental differences in the trajectory of body weight between offspring of parents with mood disorder and offspring of unaffected parents, and to examine the genetic underpinnings of the relationship between mood disorder risk and metabolic traits using polygenic scoring.

4.2 Summary of results

We found that individuals at high familial risk for mood disorders tended to have a higher zBMI. This effect was driven by females at high familial risk who, beginning in adolescence, had a significantly higher zBMI than control offspring. These effects were replicated using WtH ratio as a measure of body composition.

When we looked at the polygenic scores indexing mood disorder risk, we found that the depression and bipolar polygenic scores had no significant effects on BMI, but the depression polygenic score was weakly associated with increasing BMI in all individuals, regardless of familial mood risk and the bipolar disorder polygenic score was weakly associated with decreasing BMI in all individuals.

Metabolic polygenic scores also showed no significant effects on depressive symptoms. The BMI polygenic score was associated with decreasing depressive symptoms in all offspring, and the CRP polygenic score appeared to differentially affect depressive symptoms based on family history of mood disorders. The CRP polygenic score was associated with increasing depressive symptoms in the high mood risk offspring and decreasing symptoms in the controls.

4.3 Future directions

We identified a period of development where adolescent females with a family history of mood disorders begin to show a significantly higher zBMI and WtH ratios compared to controls. Further work should consider the impact of early intervention on protecting against development of mood and metabolic conditions in this high-risk group. Additionally, education of youth on the relationship between mental and physical health with thoughtful consideration of the stigma associated with mental health conditions and increased body weight would be a great opportunity to empower youth to take charge of their own health.

In the study of developmental trends of zBMI we considered sex differences, but in future work it will be interesting and important to consider the effect of gender identity on zBMI. Are the differences between high mood risk and control offspring consistent with an individual's sex or gender when the two are different? Transgender individuals have elevated rates of mood disorders and may be particularly vulnerable to physical health issues as a result.[145]

Another interesting future step would be to study the disorder specificity of metabolic genetic risk. Is the effect of the BMI and CRP polygenic scores on depressive symptoms different in offspring of parents with major depressive disorder and bipolar disorder?

One way of explaining the increased rates of metabolic issues in those with increased mood disorder risk is an atypical subtype of depression that has been characterized by overeating and oversleeping. This subtype is transmitted from parent to child, and is preceded by increased BMI. Individuals with this subtype of depression seem at especially increased risk of developing physical health conditions and identifying them early could allow us to mitigate their risk.[146]

Obesity and metabolic disorders are associated with poor response to first-line mood disorder treatments.[147,114] A large body of research has shown the effectiveness of early intervention and prevention in youth with familial risk for mood disorders.[148] It is important to identify and address risk early as there is potential for implementing preventative measures.[149] Preventative interventions using psychoeducation and cognitive-behavioural therapy for youth at risk for depression have been shown to lower rates of depression onset and decrease depressive symptoms.[150] Early identification of individuals at risk of both metabolic issues and mood disorders could allow us to implement preventative measures or inform decisions on alternative treatments.

4.4 Conclusion

Studying precursors of mood disorders in offspring at high familial risk offers the opportunity to mitigate risk through prevention and early intervention in a particularly vulnerable group. Physical and mental health are intrinsically connected, and by identifying modifiable risk factors we may be able to ensure positive future health outcomes.

Appendix A: Supplemental Methods

Figure A.1 Conversion of genome coordinates from GRCh38 to GRCh37

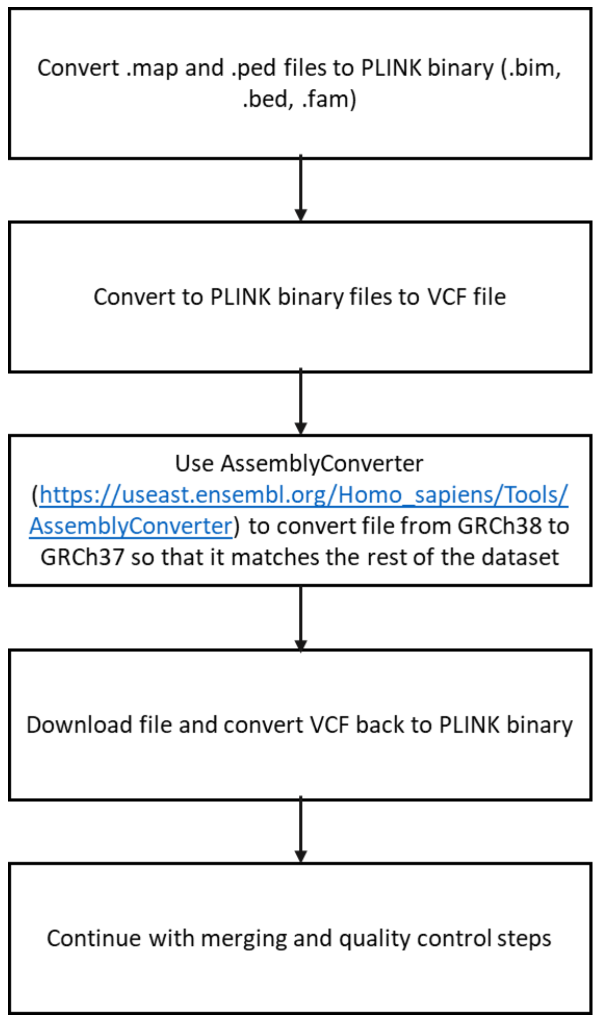
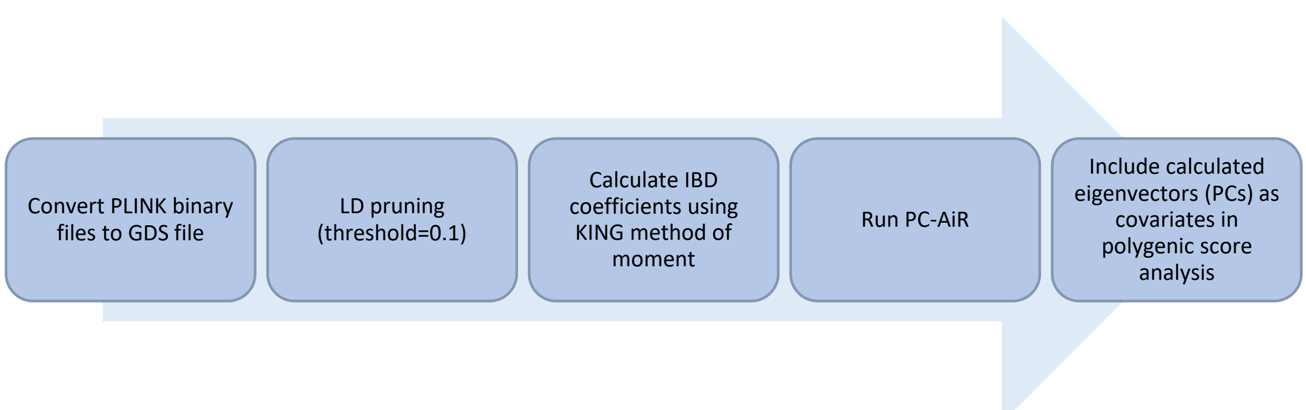


Figure A.2 PC-AiR protocol (IBD = identity by descent)



Appendix B: Supplemental Results

Figure B.1 SES breakdown for Chapter 2

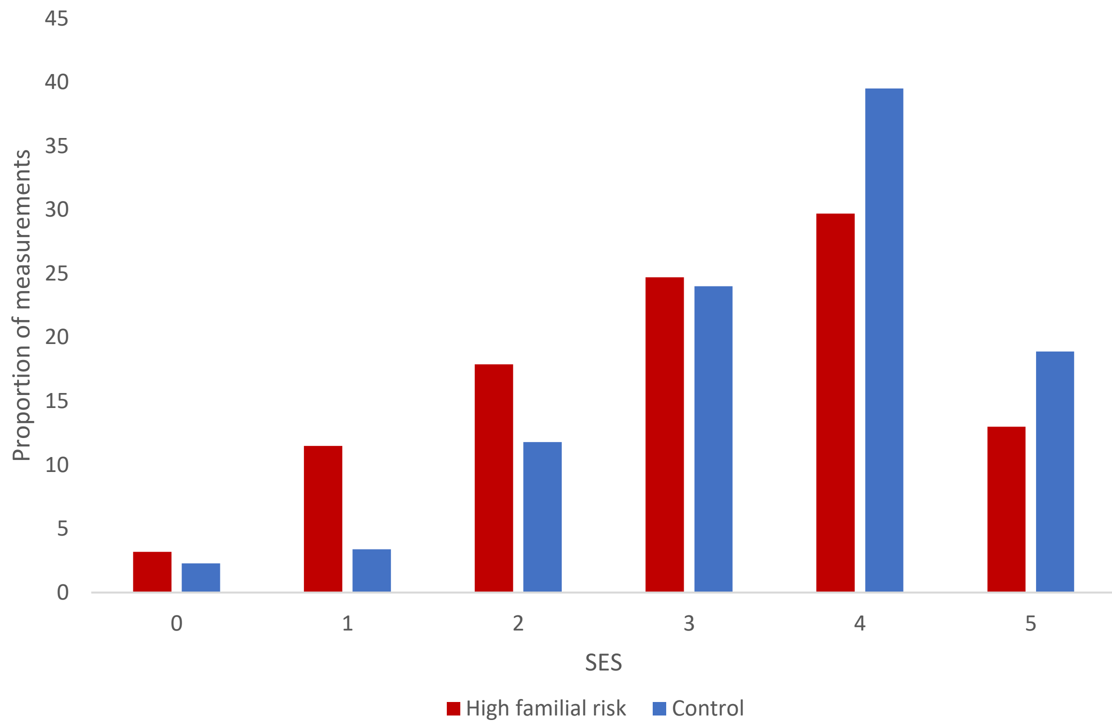


Table B.1 Regression results for zBMI in the full sample

	β	95% confidence interval		p-value
		Lower bound	Upper bound	
Familial mood risk status	0.15	0.03	0.27	0.010
Age	0.01	-0.01	0.03	0.145

Table B.2 Regression results for zBMI in females

	β	95% confidence interval		p-value
		Lower bound	Upper bound	
Familial mood risk status	0.25	0.08	0.42	< 0.0001
Age	0.04	0.03	0.06	0.003

Table B.3 Regression results for zBMI in males

	β	95% confidence interval		p-value
		Lower bound	Upper bound	
Familial mood risk status	0.05	-0.11	0.21	0.575
Age	-0.01	-0.03	0.03	0.948

Table B.4 Regression results for zBMI in younger females

	β	95% confidence interval		p-value
		Lower bound	Upper bound	
Familial mood risk status	-0.11	-0.31	0.12	0.333
Age	0.03	-0.02	0.07	0.304

Table B.5 Regression results for zBMI in older females

	β	95% confidence interval		p-value
		Lower bound	Upper bound	
Familial mood risk status	0.60	0.38	0.85	< 0.001
Age	0.01	-0.06	0.05	0.910

Table B.6 Regression results for zBMI in younger males

	β	95% confidence interval		p-value
		Lower bound	Upper bound	
Familial mood risk status	0.02	-0.19	0.23	0.873
Age	0.01	-0.04	0.06	0.686

Table B.7 Regression results for zBMI in older males

	β	95% confidence interval		p-value
		Lower bound	Upper bound	
Familial mood risk status	0.10	-0.13	0.34	0.381
Age	0.78	-0.08	0.07	< 0.001

Table B.8 Regression results for WtH in the full sample

	β	95% confidence interval		p-value
		Lower bound	Upper bound	
Familial mood risk status	0.01	0.01	0.02	< 0.001
Age	0.001	-0.0004	0. 002	0.169

Table B.9 Regression results for WtH in females

	β	95% confidence interval		p-value
		Lower bound	Upper bound	
Familial mood risk status	0.02	0 .01	0.03	<0.001
Age	0.002	0.0004	0.004	0.013

Table B.10 Regression results for WtH in males

	β	95% confidence interval		p-value
		Lower bound	Upper bound	
Familial mood risk status	0 .01	-0.007	0.02	0.351
Age	-0.001	-0. 002	0.001	0.423

Table B.11 Regression results for WtH in younger females

	β	95% confidence interval		p-value
		Lower bound	Upper bound	
Familial mood risk status	-0.002	-0.02	0.02	0.797
Age	-0.003	-0.01	0.003	0.289

Table B.12 Regression results for WtH in older females

	β	95% confidence interval		p-value
		Lower bound	Upper bound	
Familial mood risk status	0.0373214	0.0250607	0.0519796	< 0.001
Age	0.0045523	0.000622	0.0078607	0.010

Table B.13 Regression results for WtH in younger males

	β	95% confidence interval		p-value
		Lower bound	Upper bound	
Familial mood risk status	0.001	-0.02	0.02	0.911
Age	0.01	0.0003	0.01	0.043

Table B.14 Regression results for WtH in older males

	β	95% confidence interval		p-value
		Lower bound	Upper bound	
Familial mood risk status	0.01	-0.003	0.03	0.119
Age	-0.001	-0.006	0.003	0.542

Table B.15 Regression results for sensitivity analysis of zBMI including one measurement per family

	β	95% confidence interval		p-value
		Lower bound	Upper bound	
Familial mood risk status	0.19	-0.08	0.51	0.208
Age	0.01	-0.03	0.05	0.594

Table B.16 Regression results for sensitivity analysis of zBMI including one measurement per family in females

	β	95% confidence interval		p-value
		Lower bound	Upper bound	
Familial mood risk status	0.49	0.05	0.90	0.023
Age	-0.01	-0.05	0.04	0.790

Table B.17 Regression results for sensitivity analysis of zBMI including one measurement per family in males

	β	95% confidence interval		p-value
		Lower bound	Upper bound	
Familial mood risk status	-0.14	-0.56	0.26	0.476
Age	0.02	-0.04	0.08	0.516

Table B.18 Regression results for sensitivity analysis of zBMI including one measurement per family in younger females

	β	95% confidence interval		p-value
		Lower bound	Upper bound	
Familial mood risk status	0.24	-0.41	0.89	0.458
Age	-0.02	-0.18	0.14	0.778

Table B.19 Regression results for sensitivity analysis of zBMI including one measurement per family in older females

	β	95% confidence interval		p-value
		Lower bound	Upper bound	
Familial mood risk status	0.73	0.21	1.25	0.004
Age	0.03	-0 .11	0.18	0.638

Table B.20 Regression results for sensitivity analysis of zBMI including one measurement per family in younger males

	β	95% confidence interval		p-value
		Lower bound	Upper bound	
Familial mood risk status	-0.35	-0.81	0.10	0.141
Age	0.09	-0.04	0.23	0.161

Table B.21 Regression results for sensitivity analysis of zBMI including one measurement per family in older males

	β	95% confidence interval		p-value
		Lower bound	Upper bound	
Familial mood risk status	0.15	-0.63	0.86	0.700
Age	-0.07	-0.36	0.24	0.644

Table B.22 Regression results for sensitivity analysis of WtH including one measurement per family

	β	95% confidence interval		p-value
		Lower bound	Upper bound	
Familial mood risk status	0.02	-0.001	0.04	0.071
Age	-0.002	-0.004	0.001	0.158

Table B.23 Regression results for sensitivity analysis of WtH including one measurement per family in females

	β	95% confidence interval		p-value
		Lower bound	Upper bound	
Familial mood risk status	0.03	0.001	0.05	0.029
Age	-0.002	-0.01	0.002	0.409

Table B.24 Regression results for sensitivity analysis of WtH including one measurement per family in males

	β	95% confidence interval		p-value
		Lower bound	Upper bound	
Familial mood risk status	0.02	-0.01	0.039	0.163
Age	.-0.003	-0.005	0.005	0.896

Table B.25 Regression results for sensitivity analysis of WtH including one measurement per family in younger females

	β	95% confidence interval		p-value
		Lower bound	Upper bound	
Familial mood risk status	0.01	-0.02	0.05	0.0619
Age	-0.003	-0.02	0.01	0.734

Table B.26 Regression results for sensitivity analysis of WtH including one measurement per family in older females

	β	95% confidence interval		p-value
		Lower bound	Upper bound	
Familial mood risk status	0.05	0.01	0.08	0.376
Age	0.004	-0.01	0.01	0.482

Table B.27 Regression results for sensitivity analysis of WtH including one measurement per family in younger males

	β	95% confidence interval		p-value
		Lower bound	Upper bound	
Familial mood risk status	-0.01	-0.05	0.01	0.374
Age	0.007	-0.005	0.02	0.286

Table B.28 Regression results for sensitivity analysis of WtH including one measurement per family in older males

	β	95% confidence interval		p-value
		Lower bound	Upper bound	
Familial mood risk status	0.04	-0.001	0.08	0.048
Age	-0.005	-0.03	0.01	0.615

Table B.29 Regression results for sensitivity analysis of zBMI including SES in the full sample

	β	95% confidence interval		p-value
		Lower bound	Upper bound	
Familial mood risk status	0.11	-0.01	0.23	0.060
Age	0.01	-0.01	0.03	0.092
SES	0.04	-0.01	0.08	0.154

Table B.30 Regression results for sensitivity analysis of zBMI including SES in females

	β	95% confidence interval		p-value
		Lower bound	Upper bound	
Familial mood risk status	0.24	0.09	0.40	0.003
Age	0.04	0.02	0.05	0.001
SES	0.04	-0.01	0.11	0.111

Table B.31 Regression results for sensitivity analysis of zBMI including SES in males

	β	95% confidence interval		p-value
		Lower bound	Upper bound	
Familial mood risk status	0.01	-0.15	0.18	0.870
Age	-0.01	-0.03	0.02	0.577
SES	0.02	-0.06	0.11	0.586

Table B.32 Regression results for sensitivity analysis of zBMI including SES in younger females

	β	95% confidence interval		p-value
		Lower bound	Upper bound	
Familial mood risk status	-0.10	-0.32	0.14	0.384
Age	0.03	-0.03	0.08	0.338
SES	0.07	-0.01	0.15	0.110

Table B.33 Regression results for sensitivity analysis of zBMI including SES in older females

	β	95% confidence interval		p-value
		Lower bound	Upper bound	
Familial mood risk status	0.57	0.34	0.78	< 0.001
Age	-0.01	-0.05	0.05	0.958
SES	0.02	-0.04	0.10	0.493

Table B.34 Regression results for sensitivity analysis of zBMI including SES in younger males

	β	95% confidence interval		p-value
		Lower bound	Upper bound	
Familial mood risk status	-0.01	-0.22	0.26	0.982
Age	0.01	-0.06	0.07	0.811
SES	0.07	-0.06	0.18	0.242

Table B.35 Regression results for sensitivity analysis of zBMI including SES in older males

	β	95% confidence interval		p-value
		Lower bound	Upper bound	
Familial mood risk status	0.08	-0.17	0.32	0.522
Age	-0.03	-0.09	0.04	0.382
SES	-0.05	-0.15	0.06	0.330

Figure B.2 SES breakdown for Chapter 3

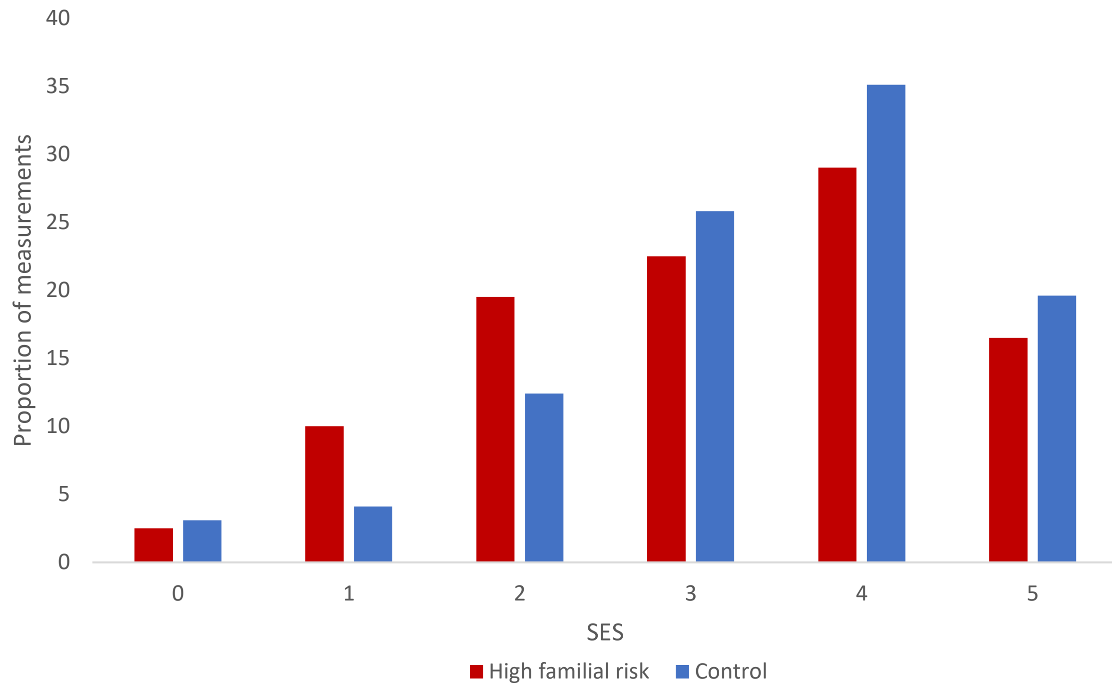


Table B.36 Mixed-effects linear regression results for depression polygenic score and BMI in all offspring

	β	95% confidence interval	p-value
Depression PGS	0.34	-0.24 – 0.92	0.25
Sex	-0.21	-1.28 – 0.87	0.707
Age	0.71	0.57 – 0.85	<0.001
Familial mood risk status	0.79	-0.66 – 2.25	0.285
SES	-0.01	-0.50 – 0.49	0.978

Table B.37 Mixed-effects linear regression results for bipolar polygenic score and BMI in all offspring

	β	95% confidence interval	p-value
Bipolar polygenic score	-0.28	-0.86 – 0.29	0.334
Sex	-0.26	-1.34 – 0.83	0.643
Age	0.71	0.57 – 0.85	<0.001
Familial mood risk status	0.73	-0.72 – 2.18	0.325
SES	0.01	-0.48 – 0.50	0.962

Table B.38 Mixed-effects linear regression results for depression polygenic score and BMI in high familial risk offspring

	B	95% confidence interval	p-value
Depression polygenic score	0.23	-0.49 – 0.96	0.525
Sex	-0.53	-1.98 – 0.92	0.47
Age	0.73	0.56 – 0.90	<0.001
SES	-0.06	-0.69 – 0.57	0.854

Table B.39 Mixed-effects linear regression results for depression polygenic score and BMI in control offspring

	β	95% confidence interval	p-value
Depression polygenic score	0.51	-0.48 – 1.51	0.306
Sex	0.08	-1.46 – 1.62	0.919
Age	0.63	0.36 – 0.90	<0.001
SES	0.35	-0.46 – 1.16	0.393

Table B.40 Mixed-effects linear regression results for bipolar polygenic score and BMI in high familial risk offspring

	β	95% confidence interval	p-value
Bipolar polygenic score	-0.37	-1.11 – 0.36	0.319
Sex	-0.64	-2.10 – 0.82	0.389
Age	0.73	0.56 – 0.90	<0.001
SES	-0.05	-0.67 – 0.58	0.884

Table B.41 Mixed-effects linear regression results for bipolar polygenic score and BMI in control offspring

	β	95% confidence interval	p-value
Bipolar polygenic score	0.09	-0.93 – 1.10	0.867
Sex	0.15	-1.40 – 1.70	0.847
Age	0.65	0.39 – 0.92	<0.001
SES	0.43	-0.40 – 1.26	0.303

Table B.42 Mixed-effects linear regression results for BMI polygenic score and depressive symptoms in all offspring

	β	95% confidence interval	p-value
BMI polygenic score	-0.02	-0.15 – 0.11	0.746
Familial mood risk status	0.56	0.31 – 0.80	<0.001
Sex	0.05	0.02 – 0.09	0.001
Age	0.26	-0.05 – 0.57	0.102
SES	-0.08	-0.18 – 0.03	0.154

Table B.43 Mixed-effects linear regression results for CRP polygenic score and depressive symptoms in all offspring

	β	95% confidence interval	p-value
CRP polygenic score	0.05	-0.07 – 0.18	0.411
Familial mood risk status	0.55	0.31 – 0.80	<0.001
Sex	0.06	0.02 – 0.09	0.001
Age	0.25	-0.07 – 0.56	0.123
SES	-0.08	-0.18 – 0.03	0.164

Table B.44 Mixed-effects linear regression results for BMI polygenic score and depressive symptoms in high familial risk offspring

	β	95% confidence interval	p-value
BMI polygenic score	-0.04	-0.23 – 0.14	0.631
Sex	0.49	0.17 – 0.81	0.003
Age	0.05	0.02 – 0.09	0.005
SES	-0.04	-0.17 – 0.10	0.613

Table B.45 Mixed-effects linear regression results for BMI polygenic score and depressive symptoms in control offspring

	β	95% confidence interval	p-value
BMI polygenic score	0.04	-0.04 – 0.29	0.676
Sex	0.66	0.28 – 1.03	0.001
Age	0.05	-0.01 – 0.12	0.11
SES	-0.15	-0.33 – 0.02	0.082

Table B.46 Mixed-effects linear regression results for CRP polygenic score and depressive symptoms in high familial risk offspring

	β	95% confidence interval	p-value
CRP polygenic score	0.13	-0.04 – 0.29	0.147
Sex	0.49	0.18 – 0.81	0.003
Age	0.06	0.02 – 0.10	0.003
SES	-0.03	-0.17 – 0.11	0.645

Table B.47 Mixed-effects linear regression results for CRP polygenic score and depressive symptoms in control offspring

	β	95% confidence interval	p-value
CRP polygenic score	-0.16	-0.35 – 0.04	0.109
Sex	0.69	0.31 – 1.06	<0.001
Age	0.05	-0.01 – 0.11	0.102
SES	-0.16	-0.33 – 0.01	0.069

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