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Title: Association of aetiological factors for hypomanic symptoms, bipolar disorder and other severe mental illnesses: twin and polygenic risk score analysis

Running head: Hypomania, bipolar disorder and other severe mental illnesses

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**Key points**

**Question:** What is the specific and shared genetic and environmental architecture of subsyndromal hypomania and bipolar disorder [BD], schizophrenia and major depressive disorder in young adults?

**Finding:** Higher heritability estimates for hypomania were found for males (59%) compared to females (29%). Moderate genetic (.40) and non-shared environmental correlations (.41) between hypomania and BD were detected. Hypomania was significantly associated with the polygenic risk scores for schizophrenia and major depressive disorder [MDD] but not for BD.

**Meaning:** The aetiology of subsyndromal hypomania overlaps with BD, MDD and schizophrenia, indicating that it may be a continuous trait for psychiatric disorders reflected at its extreme.
Abstract

Importance: Subsyndromal hypomanic symptoms are relatively common in the general population and are linked to the onset of bipolar disorder. Little is known about their aetiology and whether this is shared with the aetiology of bipolar disorder or other mental illnesses.

Objective: This is the first twin study to examine the genetic and environmental architecture of hypomanic symptoms in a non-clinical youth sample, and compare estimates at varying severity levels and their relationship with diagnosed bipolar disorder. Associations between hypomania and polygenic risk scores [PRS] for bipolar disorder, major depressive disorder and schizophrenia were also investigated.

Design, Setting and Participants: This study used phenotypic and genetic data from the Child and Adolescent Twin Study in Sweden.

Main Outcomes and Measures: Hypomanic symptoms were assessed using the parent-rated Mood Disorders Questionnaire when the twins were 18. Bipolar disorder diagnosis and/or lithium prescription were ascertained from national registries for residents of Sweden. PRS for psychiatric disorders were calculated using independent discovery genetic data.

Results: 8,568 twin pairs aged 18 (54.7% females) were included in the study. The hypomania heritability estimate was 59% (95% Confidence Intervals [CI] 52%-64%) for males and 29% (95% CI 16%-44%) for females. Unique environmental factors accounted for 41% (95% CI 36%-47%) of the hypomania variance in males and 45% (95% CI 40%-50%) in females. Shared environmental factors were only detected for females and explained 26% (95% CI 13%-38%) of the variance. The heritability estimates were fairly consistent across
different hypomania severity groups. Moderate genetic (.40, 95% CI .21-.58) and shared environmental (.41, 95% CI .03-.75) correlations between hypomania and diagnosed bipolar disorder were found. Hypomania was significantly associated with the PRS for schizophrenia and major depressive disorder but not bipolar disorder (bipolar I or II).

Conclusions and Relevance: Higher heritability for hypomania was found for males compared to females. The results highlight the shared aetiologies between hypomanic symptoms, bipolar disorder, major depression and schizophrenia in youths. Future research should focus on identifying specific shared genetic and environmental factors. These findings support a possible dimensional model of bipolar disorder, with hypomania representing a continuous trait underlying the disorder.

Key words: Hypomania, bipolar disorder, genetic, twin study, adolescence, polygenic risk score.
Introduction

Understanding the early manifestations of bipolar disorder [BD] are critical for the development of effective prevention and intervention. One approach to tackle this issue is to study subsyndromal hypomania (symptoms that do not meet diagnostic criteria for hypomaniac/mania episodes) in community samples during adolescence and early adulthood. This approach holds great promise since hypomanic and manic episodes are BD’s defining feature¹. Moreover, subsyndromal hypomanic symptoms are linked to manic and hypomaniac episodes and BD onset². Focusing on this developmental period is particularly informative for understanding BD’s aetiology since its onset typically occurs between 15-24 years.³ Questions concerning the relationship between BD and hypomanic symptoms in non-clinical populations remain⁴, such as: do hypomania and BD lie on the same phenotypic continuum, with the disorder representing the extreme end? Understanding the aetiological relationship between these phenotypes will help address this and related questions.

Heritability estimates within a similar range have been reported for BD (57%-85%)⁵,⁶ and pediatric BD phenotypes (75%)⁷, but no studies on subsyndromal hypomania in youths exist. Heritability estimates vary by BD type and severity, with a higher estimate of 57% for BD-I (diagnosed with a lifetime manic episode) compared to 46% for BD-II⁸ (diagnosed with both hypomaniac and major depressive episodes¹), which may be more closely related to subsyndromal hypomania. There is evidence that overlapping and distinct genetic factors influence different BD subtypes, thus there is value in examining them separately.⁸ But these results do not reveal whether there is any genetic overlap between subsyndromal hypomania and BD.

Preliminary evidence indicates that common genetic variants for BD captured using polygenic risk scores [PRS] are not significantly associated with hypomaniac symptoms⁹-¹¹,
though weak associations have been detected with more severe hypomania symptom profiles. These initial findings need to be replicated. Given the phenotypic and genetic overlap between BD and other psychiatric disorders, including major depressive disorder [MDD] and schizophrenia, it would be useful to consider whether these cross-phenotypic relationships are mirrored for hypomanic symptoms. Significant associations between BD and the schizophrenia and MDD (particularly for BD-II) PRS have been reported previously. But there are no studies examining the association between hypomania in non-clinical youth samples and schizophrenia and MDD PRS warranting further investigation.

PRS only capture additive effects of common genetic variants, which account for 15.6%-18.6% of BD’s genetic variance on the liability scale. The heritability parameter estimated using twin data covers the entire genetic variance (common and rare genetic factors), and can be used to examine genetic covariance between two or more phenotypes.

This is the first twin study to examine the aetiology of hypomaniac symptoms in young adults and its relationship to that of BD and other serious mental illnesses, combined with PRS analyses. Specifically, this study will examine the genetic and environmental architecture of hypomaniac symptoms at age 18 focusing on a continuous hypomania measure and subgroups based on extreme symptom levels (top 10%, 5% and 1%). Secondly, the extent to which the genetic and environmental risk factors for BD are associated with hypomania will be investigated. Finally, the polygenic overlap between hypomania and BD, schizophrenia and MDD will be explored.
Method

Participants

Each year since 2004, families of Swedish twins aged 9 or 12 years are invited to participate in the Child and Adolescent Twin Study in Sweden (CATSS)\textsuperscript{17} and are followed-up at 15 and 18 years.\textsuperscript{17} A total of 8,568 twin pairs participated in CATSS at age 18 with available parent-rated hypomania data (Supplementary Figure 1). A higher proportion of females with fewer neurodevelopmental/psychiatric diagnoses and parents with higher educational qualifications completed age 18 follow-up compared to those that declined to participate. Parents and twins provided consent prior to participation. CATSS was approved by the Regional Ethical Review Board in Stockholm (2016/2135-31).

Measures

Hypomanic symptoms were assessed by the parent-rated Mood Disorder Questionnaire (MDQ)\textsuperscript{18} when the twins were 18 years. The MDQ’s 13 yes/no items relate to the presence of symptoms based on DSM-IV criteria for a hypomanic or manic episode.\textsuperscript{18,19} Additional items enquire whether symptoms occur during the same period (episode) and impact functioning (impairment). The parent-rated MDQ has good sensitivity (.72) and specificity (.81) in identifying adolescent BD.\textsuperscript{18,20} Individuals were categorized as ‘high-risk’ of BD if at least 7 MDQ items were endorsed, clustered in the same period and caused moderate/severe impairment.\textsuperscript{21}

BD cases were identified using two approaches. First, via BD diagnosis (ICD-10 codes: F30-F31) up to age 24, identified using the Swedish National Patient Register [NPR]\textsuperscript{22}, which documents all specialist inpatient and outpatient care delivered to residents of Sweden. Second, through lithium prescriptions using the Prescribed Drug Register\textsuperscript{23}, which records
all medication prescriptions for residents of Sweden since 2005. NPR was also used to identify participants with a MDD (F32-F34) or schizophrenia (F20) diagnosis.

**Genetic information**

DNA was extracted from saliva samples provided at study enrolment and genotyped using the Illumina PsychChip. Standard quality control and imputation procedures were applied (details provided elsewhere\(^{24}\)). A total of 11,081 samples passed quality control assessment; 2,495 MZ twins were then imputed based on their genotyped co-twin. A total of 13,456 participants were included in genetic analyses, following imputation, quality control and exclusions (Supplementary Figure 1).

PRS for five disorders were calculated for each participant. PRS were derived from publicly available GWAS summary statistics for BD, BD-I, BD-II\(^{15}\), MDD\(^{25}\) and schizophrenia\(^{26}\), independent of CATSS. The PRS-cs approach\(^ {27} \) was used for PRS scoring (see Supplementary Materials). PRS were calculated using PLINK, by scoring the number of the risk alleles for the respective illness weighted by their effect size, for each individual. Scores were standardized using z-score transformations. Principal component analysis was used to derive covariates to account for population stratification.

**Statistical analyses**

The MDQ was positively skewed and therefore log-transformed. Participants were split into high-risk and low-risk groups based on MDQ cut-off described above.\(^ {21}\) Logistic regression models within a generalized estimating equations [GEE] framework were undertaken to compare the rates of BD diagnosis among those in the high-risk group compared to the remaining sample, controlling for sex and birth year. Differences in hypomania score
between those with and without a BD diagnosis was tested using a linear regression model with GEE framework controlling for sex and birth year. GEE were used to account for the use of twins, to calculate robust standard errors and were implemented in the drgee package of R. A 1-sided $P < .05$ was considered to test statistical significance.

**Twin analyses**

The classic twin method was utilised to examine the degree genetic and environmental factors influence individual phenotypes (hypomania and BD diagnosis) as well as the degree to which they are shared between them. Phenotypic variance can be partitioned into additive genetic (A), shared (C; common to both twins) and unique (E; differ across twins and measurement error) environmental influences. This is based on the assumption that identical or monozygotic (MZ) twins share 100% of their segregating DNA code relative to non-identical or dizygotic twins (DZ) who share approximately half. Higher twin pair correlations among MZ compared to DZ twins suggests genetic influences on a trait. The general principles of the twin design are described in detail elsewhere.

DeFries-Fulker extreme analyses was used to contrast the degree to which the genetic and environmental factors influence differing hypomania severity by focusing on the aetiology of the mean difference of extreme scores and the whole population. A significant group heritability estimate suggests that there is a genetic link between the extreme groups and full sample. A joint categorical-continuous bivariate model was used to estimate the genetic correlation between BD and hypomania, and the degree to which overlapping genetic and environmental influences explained their association.
Polygenic risk score analyses

To test associations between hypomania (symptoms and high-risk group) and each of the PRS, GEEs were performed with robust SEs based on clustering related individuals; 10 principal components were used as covariates in these analyses (Supplementary Materials).
Results

Parent-rated hypomanic symptoms using the MDQ were available for 8,568 twin pairs (Table 1). Females reported significantly more hypomanic symptoms compared to males ($\beta=0.11$, $se=0.04$, $p=0.014$). A total of 64 participants (0.8%) were categorised as high-risk for BD using published MDQ cut-offs21; and 54 (0.3%) received a BD diagnosis or lithium prescription. BD cases had a significantly higher hypomania score compared to the rest of the sample ($\beta=3.01$, $se=0.73$, $p<0.001$). A significantly greater proportion of the high-risk group (14%) had a BD diagnosis relative to the remaining sample (0.27%) (OR=1.32, 95% Confidence Intervals [CI] 1.13-1.55, $p<0.001$).

Twin analyses

Table 2 presents twin correlations for hypomanic symptoms and BD diagnosis. Since there were sex differences for hypomania twin correlations, the parameters were estimated separately for males and females in subsequent analyses. MZ correlations were higher than DZ correlations suggesting genetic contributions to hypomania and BD. MZ correlations were less than 1 indicating non-shared environmental influences.

Supplementary Tables 1 and 2 present the fit statistics for the univariate twin models. ACE models were chosen as best fitting, with sex differences observed for hypomania. BD was highly heritable with non-shared environmental factors explaining the remaining variance (Figure 1). Genetic influences explained most of the hypomania variance in males (59%), with non-shared environmental factors accounting for the rest (41%). In contrast, for females non-shared environmental factors accounted for the majority of the
hypomania variance (45%) with genetic and shared environmental factors explaining 29% and 26%, respectively.

**Hypomania and BD aetiological overlap**

There was a moderate phenotypic correlation between hypomania and BD ($r=0.38$, 95% CI: 0.29-0.47). The limited number of BD cases (N=54) meant joint models with hypomania were not able to consider males and females separately. Cross-trait cross-twin correlations are shown in Table 2 and are higher for MZ compared DZ twins suggesting a genetic contribution to the covariance between hypomania and BD. Figure 1 shows the moderate genetic (.40, 95% CI .21-.58) and non-shared environmental (.41, 95% CI .03-.75) correlation between hypomania and BD using an AE model. The hypomania-BD phenotypic correlation was found to be mainly explained by genetic factors (72%, 95% CI 41%-98%) with a smaller contribution from non-shared environmental factors (28%, 95% CI 2%-59%). Results were similar when an ACE model was applied (Supplementary Table 3).

The hypomania-MDD correlation was small ($r=0.12$, 95% CI: 0.04-0.20) and only 30 schizophrenia cases were identified, which prohibited the exploration of the relationships between these disorders and hypomania using twin methods.

**Hypomania extreme analyses**

AE models showed the best fit for the DeFries-Fulker analyses. Significant group heritability was found in the DeFries-Fulker analyses, which suggests a genetic link between severe levels of hypomania and variation in hypomanic symptoms in the whole sample (Table 3). Similar heritability estimates were found across each of the hypomania severity groups, although slightly lower in the top 1% group.
PRS analyses

The schizophrenia and MDD PRS were significantly associated with hypomanic symptoms but not when the high-risk group was considered (Table 4). No significant associations were detected between any of the BD PRS and hypomania.
Discussion

To our knowledge this is the first twin study to examine the specific and shared aetiology of hypomanic symptoms, BD, MDD and schizophrenia, in a non-clinical youth sample, combined with a polygenic approach. We found higher heritability for hypomania among males (59%) compared to females (29%). Common environmental factors were only found to influence hypomania for females (26%), but unique environmental influences accounted for a similar degree of the variance for males (41%) and females (45%). Significant group heritability was detected when groups with more severe levels of hypomania were examined, this suggests that similar genetic factors influence low and more severe levels of hypomania. Moderate genetic and non-shared environmental correlations between hypomania and BD were found. The small correlation between hypomania and MDD and the restricted number of schizophrenia diagnoses prohibited using twin analyses to assess the shared aetiology between these phenotypes. The PRS for schizophrenia and MDD but not BD were significantly associated with subsyndromal hypomania.

This investigation provides a novel contribution by examining the aetiology of subsyndromal hypomania in a community sample of young adults. The heritability estimate we found of 59% for males parallels the results for BD in adults (range: 59% - 85%) but is higher than what is reported for adult BD-II (46%). Our results for females were more curious where environmental influences accounted for the majority of the hypomania variance and genetic factors explained 29%. Various environmental factors have been implicated in the aetiology of BD and hypomania, including childhood maltreatment. Research shows that females are at greater risk of experiencing such trauma relative to males, which could explain the diminished role of genetic factors at this developmental
stage. Future studies are needed to replicate our findings and assess any developmental changes in the hypomania aetiology.

Phenotypic continuums between psychiatric disorders (e.g., MDD) and their respective subthreshold symptoms (e.g., depressive symptoms) that are more frequently observed in the general population, are used to understand the early manifestations, developmental trajectories and aetiology of such disorders.\textsuperscript{35,36} Such research is critical for the development of effective prevention and intervention.\textsuperscript{37} Research in this space concerning BD is emerging and gaining momentum.

Our findings partly address this issue showing a moderate genetic (.40) and non-shared environmental (.41) correlation between subsyndromal hypomania and BD for the first time. The genetic correlation is lower but not that dissimilar to those reported for depressive symptoms and MDD in the same sample (.53-.58).\textsuperscript{10} Our work adds to the validity of a hypomania continuum of BD, when combined with research showing links between hypomania and bipolar-related risk factors (e.g., childhood maltreatment).\textsuperscript{33}

Caution should be taken when applying the hypomania continuum to BD given that the disorder is not characterised by one symptom dimension, unlike MDD. For instance, BD patients commonly experience psychosis\textsuperscript{38} and depressive episodes, with the latter included in the BD-II diagnostic criteria.\textsuperscript{1} Thus, a BD quantitative trait model may be best explained as the intersection of extremes of multiple symptom dimensions. Our results suggest that hypomania would be one such symptom dimension. Depressive symptoms and psychotic-like experiences may represent other dimensions to consider, but need to be empirically tested.

The source of the genetic overlap between BD and hypomanic symptoms is unclear given that we and others have not found an association between hypomania and the BD
Several reasons may explain this result. Firstly, the hypomania-BD genetic overlap may not be due to common genetic variation captured in PRS but rare genetic factors included in the twin heritability parameter used here. Secondly, the BD PRS is calculated using adults with BD who experience more severe symptomatology, we focused on subsyndromal hypomania in youths. Finally, the BD PRS explains 15.6%-18.6% of the BD genetic variance on the liability scale. Hence the lack of association between the BD PRS and hypomania provides a limited picture of their genetic overlap.

Previous studies have reported a significant association between schizophrenia and MDD PRS and BD diagnosis as well as hypomanic/manic episodes (schizophrenia PRS only). We extend these findings by showing a link with hypomania at the subsyndromal level. The divergent associations between the BD PRS (15.6%-18.6%) and the schizophrenia (24%) and MDD (8.7%) PRS with hypomania do not seem to be attributable to the degree to which they explain the genetic variance for their respective disorders on the liability scale.

Our findings have important research and clinical implications. Firstly, our work underscores the importance of studying subsyndromal hypomania in its own right given its association with the diagnosis and aetiology of several psychiatric disorders. Other studies have found that hypomania in youths is associated with adverse outcomes, including suicidality and other psychopathological symptoms. Hypomania prevention and intervention strategies need to be developed to avoid progression to clinical disorders. Secondly, the hypomania-BD link reported here highlights the potential for using hypomania to identify high-risk BD groups who may benefit most from prevention and intervention efforts.

The strengths of this investigation include utilisation of a large, longitudinal genetically informative sample, national registries and a multi-method approach, but there
are some limitations. First, a limited number of participants received a BD and schizophrenia diagnosis, which means the hypomania-BD results should be interpreted cautiously and the hypomania-schizophrenia relationship could not be examined using the twin method. This also prevented the examination of the sensitivity and specificity of subsyndromal hypomania in predicting later psychiatric diagnoses. Future studies should consider exploring such relationships in a sample who have passed through the typical age of BD and schizophrenia onset. Second, hypomania was assessed with the parent-rated MDQ, since studies have shown that parent-report is more accurate in assessing adolescent hypomania than self- and teacher-ratings. Also the MDQ is one of the best validated and discriminating BD instruments for youths. But late adolescence/early adulthood marks a transitional period into independence where parents are not fully aware of their children’s behaviour and emotions. Future studies should use self-report instruments particularly in older samples. The MDQ does not enquire about symptom duration, a key component of the diagnostic criteria for hypomanic/manic episodes; this would be useful to incorporate in our ‘high-risk’ group classification. Finally, BD cases were identified using official diagnoses and lithium prescription. Lithium is predominantly used to treat BD but can be used for treatment-resistant depression and hypomania that does not meet BD diagnostic criteria. Therefore, some BD cases may have been misclassified here.

**Conclusion**

This is the first twin study in a non-clinical sample of young adults to investigate the specific and shared aetiology of subsyndromal hypomania and BD, MDD and schizophrenia, which also uses a PRS approach. Higher heritability estimates for hypomania were observed for males compared to females. Moderate genetic and non-shared environmental
correlations between hypomania and BD were found. We found this genetic overlap was not explained by common genetic factors using the BD PRS. Hypomania was significantly associated with schizophrenia and MDD PRS. These results suggest a shared aetiology between subsyndromal hypomania and BD, MDD and schizophrenia. The findings are also relevant to exploring a BD dimensional model, providing preliminary support for hypomania representing a quantitative trait underlying this disorder. More research is needed however for firm conclusions to be drawn.
Disclosures and acknowledgements

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References


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41. Hosang GM, Cardno AG, Freeman D, Ronald A. Characterization and structure of


Figure Legend

Figure 1. Genetic and environmental univariate estimates and bivariate correlations for hypomanic symptoms at age 18 and bipolar disorder (diagnosis and lithium prescription) at age 24 years. Panel A: Genetic and environmental influences on hypomania at age 18 for males; Panel B: Genetic and environmental influences on hypomania at age 18 for females. Panel C: Genetic and environmental influences for bipolar disorder and/or lithium prescription up to age 24 years. Panel D: Joint-continuous model estimates for hypomania at 18 years and bipolar disorder/lithium prescription up to age 24 years.

(A) Additive genetic influences; (C) shared environmental factors; (E) non-shared environmental influences. Numbers in parentheses are 95% confidence intervals.
Table 1. Sample description

<table>
<thead>
<tr>
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<th>Overall N (%) or Mean (SD)</th>
<th>Male N (%) or Mean (SD)</th>
<th>Female N (%) or Mean (SD)</th>
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<tr>
<td></td>
<td>N individuals</td>
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<td></td>
<td>17136</td>
<td>7755 (45.3)</td>
<td>9381 (54.7)</td>
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<td>5162 (30.1)</td>
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<td>2705 (34.9)</td>
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<td>3212 (34.2)</td>
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<td>DZ opposite sex twins</td>
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<td>2849 (36.7)</td>
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<td>3208 (34.2)</td>
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<tr>
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<td>MDQ mean (SD)</td>
<td>0.79 (1.75)</td>
<td>0.73 (1.71)</td>
<td>0.84 (1.79)</td>
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<td>64 (0.8)</td>
<td>25 (0.7)</td>
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<td>Severity groups (N, %)</td>
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<td>838 (11.0)</td>
<td>358 (10.2)</td>
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<td>MDQ, 5%</td>
<td>363 (4.8)</td>
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<td>Bipolar disorder and/or Lithium prescription</td>
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<td>54 (0.3)</td>
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<td>Lithium prescription</td>
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Abbreviations: SD, standard deviation; MZ, monozygotic; DZ, dizygotic; MDQ, Mood Disorder Questionnaire
### Table 2. Phenotypic, twin and cross-trait cross twin correlations for hypomania and bipolar disorder

<table>
<thead>
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<td></td>
<td>$r_{ph}$</td>
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<td>Hypomania at age 18</td>
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<td>Cross-trait</td>
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</table>

*Abbreviations: $r_{ph}$ phenotypic correlation; MZ, monozygotic twin pairs; DZ, dizygotic twin pairs; MZM, monozygotic male twin pairs; DZM dizygotic male twin pairs; MZF, monozygotic female twin pairs; DZF dizygotic female twin pairs; DZOS dizygotic opposite sex twin pairs.*
**Table 3.** Extremes analyses for hypomania using DeFries Fulker analysis

<table>
<thead>
<tr>
<th>Model and parameters</th>
<th>Severity groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;10%</td>
</tr>
<tr>
<td>A</td>
<td>0.53 (0.47-0.60)</td>
</tr>
<tr>
<td>E (residual)</td>
<td>0.47 (0.40-0.53)</td>
</tr>
</tbody>
</table>

\(^a\)High-risk group= Mood Disorders Questionnaire score of at least 7 with symptoms clustered together in the same period and moderate to severe problems (e.g., work and legal problems).
Table 4. Association between hypomanic symptoms and polygenic risk scores for severe mental illnesses.

<table>
<thead>
<tr>
<th>PRS</th>
<th>Hypomanic symptoms</th>
<th>High-risk for bipolar disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beta</td>
<td>SE</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>0.017</td>
<td>0.03</td>
</tr>
<tr>
<td>Bipolar disorder I</td>
<td>-0.014</td>
<td>0.029</td>
</tr>
<tr>
<td>Bipolar disorder II</td>
<td>0.045</td>
<td>0.027</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>0.08</td>
<td>0.026</td>
</tr>
<tr>
<td>Major depressive disorder</td>
<td>0.09</td>
<td>0.027</td>
</tr>
</tbody>
</table>

Abbreviations: SE, standard error; OR, odds ratio; CI, confidence intervals