Polygenic risk for schizophrenia, disordered eating behaviours and body mass index in adolescents

Francesca Solmi, Marina Carbo Mascarell, Stanley Zammit, James B. Kirkbride and Glyn Lewis

Background
Recent studies suggest psychotic and eating disorders can be comorbid and could have shared genetic liability. However, this comorbidity has been overlooked in the epidemiological literature.

Aims
To test whether polygenic risk scores (PRS) for schizophrenia are associated with disordered eating behaviours and body mass index (BMI) in the general population.

Method
Using data from the Avon Longitudinal Study of Parents and Children and random-effects logistic and linear regression models, we investigated the association between PRS for schizophrenia and self-reported disordered eating behaviours (binge eating, purging, fasting and excessive exercise) and BMI at 14, 16 and 18 years.

Results
Of the 6920 children with available genetic data, 4473 (64.6%) and 5069 (73.3%) had at least one disordered eating and one BMI outcome measurement, respectively. An s.d. increase in PRS was associated with greater odds of having binge eating behaviours (odds ratio, 1.36; 95% CI 1.16-1.60) and lower BMI (coefficient, −0.03; 95% CI, −0.06 to −0.01).

Conclusions
Our findings suggest the presence of shared genetic risk between schizophrenia and binge eating behaviours. Intermediate phenotypes such as impaired social cognition and irritability, previously shown to be positively correlated in this sample with schizophrenia PRS, could represent risk factors for both phenotypes. Shared genetic liability between binge eating and schizophrenia could also explain higher rates of metabolic syndrome in individuals with schizophrenia, as binge eating could be a mediator of this association in drug-naïve individuals. The finding of an association between greater PRS and lower BMI, although consistent with existing epidemiological and genetic literature, requires further investigation.

Declaration of interest
None.

Keywords
ALSPAC; schizophrenia; genetics; eating disorders.

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Sample
We used data from the Avon Longitudinal Study of Parents and Children (ALSPAC), an ongoing birth cohort study of children born in Avon (Bristol, UK) between 1 April 1991 and 31 December 1992, who were alive at 1 year of age (n = 13 988, 99.5% of all live births). More details on the ALSPAC sample is available in previous publications and on the study website (www.bristol.ac.uk/alspac), which also contains details of all the available data in a fully...
Thresholds ranging from $1 \times 10^{-3}$ to 0 were used to identify SNPs (range, 0 to 1) weighted by the logarithm of its odds ratio for schizophrenia in the Psychiatric Genomics Consortium sample. In our main analyses, we used PRS derived from a set of SNPs selected as this threshold best discriminates schizophrenia liability. To account for the need to balance true and false associations, in sensitivity analyses, we further re-run our models including the second-born twin (twin B, N = 202) to explore if this resulted in any changes. We further restricted analyses to participants of White ethnicity as current PRS have sufficient discriminant validity in individuals of European ancestry. All participants gave their informed consent to participate in the study. The ALSPAC ethics and law committee and the local research ethics committees approved this study.

### Exposure

PRS are a continuous variable capturing the cumulative effect of risk alleles for a disorder in a given individual. Although PRS are not yet able to predict clinical presentations of disorders, they have increasingly been recognised as valid biomarkers and used to identify intermediate behavioural phenotypes or correlates of clinical disorders. The derivation of PRS for schizophrenia in this sample has been previously described in detail. Briefly, PRS were calculated using training set data from the second schizophrenia GWAS of the Psychiatric Genomics Consortium, the largest genetics consortium devoted to the study of psychiatric disorders.

For each ALSPAC child, a total score was derived by adding the number of risk alleles in each single nucleotide polymorphism (SNP) (range, 0–2) weighted by the logarithm of its odds ratio for schizophrenia in the Psychiatric Genomics Consortium sample. In our main analyses, we used PRS derived from a set of SNPs selected using a $P$-value threshold of 0.05, as in previous ALSPAC studies, as this threshold best discriminates schizophrenia liability. To account for the need to balance true and false associations, in sensitivity analyses, we used scores derived from a broad range of $P$-value thresholds ranging from $1 \times 10^{-8}$ to 0.5, as in previous investigations. PRS were standardised to achieve a continuous variable with a mean of 0 and an s.d. of 1. Squared PRS terms were also used to test for non-linear associations as well as quintiles of PRS.

### Outcomes

Data on disordered eating behaviours (binge eating, fasting, purging and excessive exercise) in the previous 12 months was self-reported in postal questionnaires by adolescents at approximately 14, 16 and 18 years of age, using a modified version of the Youth Risk Behaviour Survey. We considered each of the disordered eating behaviours under investigation as present (yes/no) if they had occurred at least once in the previous year. Binge eating was defined as having ever eaten large amounts of food in a short period of time while usually experiencing a sense of loss of control over the amount of food eating. We defined purging adolescents as those who had ever self-induced vomit or used laxatives for weight loss, and fasting adolescents as those who had ever fasted for an entire day to lose weight. We considered excessive exercise as exercising frequently for weight loss even when sick, or finding it difficult to do school work (age 14 years) or feeling guilty when not exercising (age 16 and 18 years), as these dimensions (as opposed to amount of exercise undertaken, for instance) have been shown to better capture eating disorder psychopathology. Objective measurements of height and weight were collected in clinic visits when adolescents were approximately 13, 15 and 17 years of age. From these measures we derived a continuous standardised measure of BMI, which was standardised at ages 13 and 15 years by age- and gender-specific z-scores derived from the updated Stata package zanthro, as recommended in the literature.

### Confounders

In our analyses, we accounted for population stratification by conducting principal component analyses and adjusting our models for population principal components as covariates. We also described our sample in relation to a number of child and family characteristics, including child’s gender, maternal age, marital status (single/ married/divorced, widowed or separated) and education (compulsory/non-compulsory education).

### Data analysis

To take in to account the repeated nature of our outcome measurements, we used random-effects logistic and linear multilevel regressions (Stata commands \texttt{xtlogit} and \texttt{xtreg}, respectively), which allowed us to model repeated follow-up time points nested within individuals. In our models, we further added a linear variable for age (age 14, 16 and 18 years) to model the effect of time, as well as population principal components to account for population stratification. We tested for non-linear associations with a quadratic term for PRS. To further explore non-linearity and dose-response patterns of these associations, we divided PRS scores in quintiles and re-run our models with this variable as our main exposure. As sensitivity analyses, we tested for these associations using continuous measures of PRS derived from risk alleles associated with schizophrenia at different $P$-value thresholds, as previously done. We conducted all analyses on Stata version 13 for Windows.

### Sample

In total, 6920 children had available genetic data. Of these, 4473 (64.6%) and 5069 (73.3%) had data available at least at one time point on all disordered eating variables and one BMI outcome measurement, respectively. Across outcome measurements, between 26.8% ($n = 1851$, BMI) and 34.5% ($n = 2387$, binge eating) did not have any outcome data available, and between 24.8% ($n = 1718$, excessive exercise) and 42.8% ($n = 2961$, BMI) had data at all three time points. Proportions of children with two time points of data available varied between 16.6% ($n = 1151$, BMI) and 21.0% ($n = 1454$, excessive exercise), and that of children with only one time point available ranged between 13.8% ($n = 957$, BMI) and 19.4% ($n = 1345$, fasting and excessive exercise; data available from authors).

As shown in Table 1, just over half of our sample were girls (54.9%) and most children had a married mother (84.3%) who had completed compulsory education (52.2%) and was, on average, 29.4 years of age.

### Results

<table>
<thead>
<tr>
<th>Gender</th>
<th>Male</th>
<th>Female</th>
<th>Polygenic risk score, mean (s.d.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age</td>
<td>2019 (45.14%)</td>
<td>2454 (54.86%)</td>
<td>-0.04 (1.00)</td>
</tr>
<tr>
<td>Maternal education</td>
<td>327 (52.19%)</td>
<td>2135 (47.85%)</td>
<td>-0.08 (0.98)</td>
</tr>
<tr>
<td>Marital status</td>
<td>21 (4.53%)</td>
<td>0.00 (0.98)</td>
<td>Correlation</td>
</tr>
<tr>
<td>Marital status</td>
<td>29.44 (4.45)</td>
<td>0.05</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sample characteristics and polygenic risk score distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>--------</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Maternal education</td>
</tr>
<tr>
<td>Compulsory</td>
</tr>
<tr>
<td>Non-compulsory</td>
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<tr>
<td>Marital status</td>
</tr>
</tbody>
</table>
showed an association between genetic risk of schizophrenia and disordered eating behaviours. In particular, we found that higher schizophrenia PRS were associated with greater odds of binge eating, a behaviour that is central to the diagnoses of bulimia nervosa and binge eating disorder, but that can also occur in individuals with anorexia nervosa of the binge-purge type. We also observed some evidence of an association between greater schizophrenia PRS and lower BMI. These patterns of associations were largely consistent across a range of PRS training-set P-value thresholds.

**Table 2** Twelve-month prevalence of disordered eating behaviours at ages 14, 16 and 18 years

<table>
<thead>
<tr>
<th>Time points</th>
<th>Binge eating, n (%)</th>
<th>Purging, n (%)</th>
<th>Fasting, n (%)</th>
<th>Excessive exercise, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 14 years</td>
<td>N = 3879</td>
<td></td>
<td>N = 3875</td>
<td>N = 3860</td>
</tr>
<tr>
<td>Age 14 years</td>
<td>48 (1.2%)</td>
<td>62 (1.6%)</td>
<td>240 (6.2%)</td>
<td>80 (2.1%)</td>
</tr>
<tr>
<td>Age 16 years</td>
<td>N = 3296</td>
<td></td>
<td>N = 3282</td>
<td>N = 3338</td>
</tr>
<tr>
<td>Age 16 years</td>
<td>124 (3.8%)</td>
<td>197 (6.0%)</td>
<td>439 (13.4%)</td>
<td>88 (2.7%)</td>
</tr>
<tr>
<td>Age 18 years</td>
<td>N = 2232</td>
<td></td>
<td>N = 2228</td>
<td>N = 2220</td>
</tr>
<tr>
<td>Age 18 years</td>
<td>97 (4.4%)</td>
<td>141 (6.4%)</td>
<td>261 (11.5%)</td>
<td>93 (3.7%)</td>
</tr>
</tbody>
</table>

a Sample sizes vary slightly across outcomes at each time point because of different patterns of missing data across questions used to derive them.

Schizophrenia PRS and disordered eating behaviours

As shown in Table 3, in logistic regression models, we found strong evidence that a 1 s.d. increase in PRS for schizophrenia was associated with a 1.36 increase in the odds of binge eating (95% CI 1.16–1.60, P < 0.0001). Greater PRS were not associated with purging behaviours (odds ratio, 1.03; 95% CI 0.88–1.21; P = 0.71), fasting (odds ratio, 1.02; 95% CI 0.91–1.15; P = 0.73) or excessive exercise (odds ratio, 1.09; 95% CI 0.95–1.26; P = 0.19). Finally, an s.d. increase in PRS was associated with a −0.03 s.d. decrease in BMI (95% CI −0.06 to −0.01; P = 0.02), although evidence of this association was moderate to weak. We did not find any evidence of non-linear relationships when using quadratic PRS terms.

When we investigated these associations using quintiles of PRS, we observed that children in the top three quintiles had the highest odds of binge eating and lower BMI (see Table 4).

**Sensitivity analyses**

When we used PRS derived from SNPs with different P-value thresholds in the GWAS sample, our findings were overall consistent, although associations became more prominent at larger P-value thresholds (findings shown in Supplementary Figs 1 and 2). Including the other twin (twin B) in our sample did not alter our findings in relation to binge eating (odds ratio, 1.38; 95% CI 1.17–1.62; P < 0.0001) or BMI (coefficient, −0.03; 95% CI −0.06 to −0.01; P = 0.02; data available from authors).

**Discussion**

Using a large prospective cohort of British children, this study showed an association between genetic risk of schizophrenia and disordered eating behaviours. In particular, we found that higher schizophrenia PRS were associated with greater odds of binge eating, a behaviour that is central to the diagnoses of bulimia nervosa and binge eating disorder, but that can also occur in individuals with anorexia nervosa of the binge-purge type. We also observed some evidence of an association between greater schizophrenia PRS and lower BMI. These patterns of associations were largely consistent across a range of PRS training-set P-value thresholds.

**Strengths and limitations**

This study has a number of strengths. We used a large general population sample of adolescents whose disordered behaviours were self-reported across adolescence, thus avoiding sampling biases often associated with clinically diagnosed cases. The PRS we used were derived using findings from the largest schizophrenia GWAS to date. Our BMI measure was obtained from objective measurements, thus avoiding reporting biases, and standardised using age and gender growth curves. The detailed characterisation of the ALSPAC sample allowed us to investigate which specific disordered eating phenotypes might be underpinned by shared genetic liability with psychotic disorders. The use of repeated measurements across adolescence also allowed us to fully exploit the richness of the data-set, minimise the role of missing data and account for outcome clustering within individuals.

Several limitations should nevertheless be noted. Our disordered eating definitions were broad and some of the participants might have experienced these behaviours at a very low threshold. However, previous evidence in this sample has shown that even adolescents with broad disordered eating presentations experienced comorbidity and long-term outcomes comparable with those observed in full diagnoses. This finding is consistent with the idea that eating disorders, like other psychiatric disorders, occur on a continuum of severity and suggest that these definitions can be useful for future studies investigating the aetiology of and outcomes associated with these conditions. Our sample was also characterised by a notable degree of attrition, which was predicted by greater schizophrenia PRS. It is possible that collider (i.e. selection) bias, which occurs if selection into the study is conditional on the

**Table 3** Random-effects logistic and linear regression model results

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>PRS odds ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binge eating</td>
<td>1.36 (1.16–1.60)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Purging</td>
<td>1.03 (0.88–1.21)</td>
<td>0.71</td>
</tr>
<tr>
<td>Fasting</td>
<td>1.02 (0.91–1.15)</td>
<td>0.73</td>
</tr>
<tr>
<td>Excessive exercise</td>
<td>1.09 (0.95–1.26)</td>
<td>0.19</td>
</tr>
<tr>
<td>Body mass index</td>
<td>−0.03 (−0.06 to −0.01)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

PRS, polygenic risk score.
N = 4475.
N = 5069.
exposure and outcome measured, could have induced or prevented the observation of some of the associations under study. The PRS measure that we used was derived in an adult population and might not capture genetic liability to early-onset cases of schizophrenia. However, this measure has been extensively used to explore intermediate phenotypes in general population samples, hence our approach aligns with that of previous investigations. Finally, although they were derived from a large discovery data-set, it has been shown that the PRS measure we used only explain around 7% of the variance in schizophrenia. Hence, we cannot exclude that some of the associations that we did not observe were due to the limited predictive value of our exposure measure.

Comparisons with previous literature and interpretation of the findings

Although this is the first study to show an association between schizophrenia PRS and binge eating, this finding is consistent with those of previous epidemiological investigations in clinical and general population samples. For instance, McGrath et al have recently shown that individuals with lifetime psychotic symptoms had two to four times the odds of also experiencing bulimia nervosa and binge eating disorder, respectively, two eating disorders for whose diagnosis binge eating is a central criterion. A cross-sectional study of UK adults found that those who experience loss of control over eating (a symptom of binge eating) were more likely to report auditory hallucinations and other psychotic experiences. In this sample, psychotic experiences at 13 years were cross-sectionally associated with loss-of-control eating in adolescents, mirroring findings of adult populations showing that dysregulated eating behaviours can serve to regulate immediate emotional states. Longitudinal studies investigating the association between social cognition and irritability in childhood and disordered eating in the general population are therefore warranted, as these could be transdiagnostic markers of risk across multiple phenotypes.

The observed association between PRS for schizophrenia and binge eating also raises a number of hypotheses regarding the observed presence of similar metabolic abnormalities shared by people with psychotic illnesses and binge eating disorder. In people with psychotic disorders, metabolic abnormalities may arise for several reasons, including use of antipsychotics. Nevertheless, impaired glycaemic control and insulin resistance have also been shown in adolescents with non-clinical psychotic experiences, as well as in drug-naïve individuals with schizophrenia and their first-degree relatives. Similar metabolic abnormalities are observed among individuals with binge eating disorder. Although more research is needed to disentangle temporal associations, our findings lend themselves to two possible interpretations, which will require further investigation. First, it is possible that metabolic abnormalities could represent shared risk factors for both of these phenotypes. Second, binge eating could represent a mediator in the association between psychotic experiences and dysglycaemia. This hypothesis is supported by recent findings showing that insulin resistance measured at age 9 years was not associated with greater psychotic experiences at age 13 years, but those with psychotic experiences at 18 years had, cross-sectionally, greater insulin resistance.

Table 4 Multilevel logistic and linear regression models for the association between quintiles of polygenic risk scores for schizophrenia and disordered eating and body mass index

<table>
<thead>
<tr>
<th>Quintile</th>
<th>Binge eating,^a odds ratio (95% CI)</th>
<th>Purging,^a odds ratio (95% CI)</th>
<th>Fasting,^a odds ratio (95% CI)</th>
<th>Excessive exercise,^a odds ratio (95% CI)</th>
<th>Body mass index,^b coefficient (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First quintile</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Second quintile</td>
<td>0.90 (0.51–1.38)</td>
<td>1.14 (0.69–1.88)</td>
<td>1.00 (0.70–1.44)</td>
<td>0.96 (0.61–1.50)</td>
<td>–0.08 (–0.16 to 0.01)</td>
</tr>
<tr>
<td>Third quintile</td>
<td>1.68 (1.00–2.83)</td>
<td>0.94 (0.56–1.58)</td>
<td>0.99 (0.66–1.57)</td>
<td>0.97 (0.62–1.52)</td>
<td>–0.10 (–0.19 to –0.01)</td>
</tr>
<tr>
<td>Fourth quintile</td>
<td>1.77 (1.05–2.98)</td>
<td>1.33 (0.80–2.19)</td>
<td>1.34 (0.94–1.92)</td>
<td>1.14 (0.73–1.76)</td>
<td>–0.08 (–0.17 to 0.01)</td>
</tr>
<tr>
<td>Fifth quintile</td>
<td>2.37 (1.41–3.96)</td>
<td>1.16 (0.69–1.96)</td>
<td>1.05 (0.72–1.52)</td>
<td>1.19 (0.67–1.87)</td>
<td>–0.12 (–0.21 to –0.03)</td>
</tr>
</tbody>
</table>

^b N = 4473.
^N = 5069.
18 years, suggesting that the latter could be a contributing factor in the onset of metabolic abnormalities.

In light of the observed association between PRS and binge eating, often associated with greater BMI, our finding that schizophrenia PRS predict lower BMI is difficult to interpret. This association, however, has been previously observed, and is in line with findings of genetic studies showing an inverse correlation between schizophrenia and BMI, and with those of epidemiological investigations showing that low BMI is a risk factor for schizophrenia. The pathophysiological mechanisms underpinning the association between genetic liability for schizophrenia and low BMI are unclear, particularly as clinically, overweight and obesity are more frequently observed in individuals with psychotic illnesses. Environmental factors associated with increased genetic risk (i.e. deprivation) could explain low BMI before disease onset, and the emergence of binge eating in adolescence could partially contribute to minimising any existing differences in BMI. Another hypothesis is that genetic risk for schizophrenia leads to both binge eating and low BMI via different risk pathways.

To our knowledge, this is the first study to show an association between polygenic risk for schizophrenia and disordered eating behaviours. Although replication of these results is needed, we find that PRS are associated with greater risk of binge eating behaviours. Future research should investigate the presence of shared intermediate phenotypes across these disorders, including the role of metabolic abnormalities, to improve early identification of at-risk children. From a clinical viewpoint, these findings further highlight the need to consider the co-occurrence of disordered eating behaviours, particularly binge eating, in individuals with psychotic illnesses, as this might account for the weight gain observed in this population.

References


