Longitudinal Trends in Childhood Insulin Levels and Body Mass Index and Associations With Risks of Psychosis and Depression in Young Adults

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➕ **Supplemental content**

IMPORTANCE Cardiometabolic disorders often occur concomitantly with psychosis and depression, contribute to high mortality rates, and are detectable from the onset of the psychiatric disorders. However, it is unclear whether longitudinal trends in cardiometabolic traits from childhood are associated with risks for adult psychosis and depression.

OBJECTIVE To examine whether specific developmental trajectories of fasting insulin (FI) levels and body mass index (BMI) from early childhood were longitudinally associated with psychosis and depression in young adults.

DESIGN, SETTING, AND PARTICIPANTS A cohort study from the Avon Longitudinal Study of Parents and Children, a prospective study including a population-representative British cohort of 14 975 individuals, was conducted using data from participants aged 1 to 24 years. Body mass index and FI level data were used for growth mixture modeling to delineate developmental trajectories, and associations with psychosis and depression were assessed. The study was conducted between July 15, 2019, and March 24, 2020.

EXPOSURES Fasting insulin levels were measured at 9, 15, 18, and 24 years, and BMI was measured at 1, 2, 3, 4, 7, 9, 10, 11, 12, 15, 18, and 24 years. Data on sex, race/ethnicity, paternal social class, childhood emotional and behavioral problems, and cumulative scores of sleep problems, average calorie intake, physical activity, smoking, and alcohol and substance use in childhood and adolescence were examined as potential confounders.

MAIN OUTCOMES AND MEASURES Psychosis risk (definite psychotic experiences, psychotic disorder, at-risk mental state status, and negative symptom score) depression risk (measured using the computerized Clinical Interview Schedule–Revised) were assessed at 24 years.

RESULTS From data available on 5790 participants (3132 [54.1%] female) for FI levels and data available on 10 463 participants (5336 [51.0%] female) for BMI, 3 distinct trajectories for FI levels and 5 distinct trajectories for BMI were noted, all of which were differentiated by mid-childhood. The persistently high FI level trajectory was associated with a psychosis at-risk mental state (adjusted odds ratio [aOR], 5.01; 95% CI, 1.76-13.19) and psychotic disorder (aOR, 3.22; 95% CI, 1.11-9.90) but not depression (aOR, 1.38; 95% CI, 0.75-2.54). A puberty-onset major increase in BMI was associated with depression (aOR, 4.46; 95% CI, 2.38-9.87) but not psychosis (aOR, 1.98; 95% CI, 0.56-7.79).

CONCLUSIONS AND RELEVANCE The cardiometabolic comorbidity of psychosis and depression may have distinct, disorder-specific early-life origins. Disrupted insulin sensitivity could be a shared risk factor for comorbid cardiometabolic disorders and psychosis. A puberty-onset major increase in BMI could be a risk factor or risk indicator for adult depression. These markers may represent targets for prevention and treatment of cardiometabolic disorders in individuals with psychosis and depression.

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Cardiometabolic disorders often occur concomitantly with depression and schizophrenia,[1] leading to a reduced quality of life, increased health care costs,[2] and a shortened life expectancy.[3,4] Traditionally, this comorbidity has been attributed to chronic lifestyle factors (eg, physical inactivity or smoking) or the adverse effects of psychotropic medications.[5] However, meta-analyses report altered glucose-insulin homeostasis in relatively young, drug-naive patients with first-episode psychosis.[6,7] Similarly, reports from population-based longitudinal studies suggest a bidirectional association between depression and cardiovascular disease.[8,9] Together, this evidence suggests that cardiometabolic and psychiatric conditions may share pathophysiologic mechanisms. However, 2 key issues remain.

First, existing studies have predominantly included prevalent depression or psychosis cases and so cannot appropriately test the direction of association between cardiometabolic and psychiatric phenotypes.[10] Second, most longitudinal studies have included one-off measures of cardiometabolic indices, overlooking dynamic temporal changes in these markers.[11,12] Longitudinal repeated measurements could provide a more reliable measure of underlying homeostatic mechanisms and could identify population subgroups. For example, aberrant trajectories of childhood body mass index (BMI) are associated with adult cardiometabolic disorders.[13] Although cardiometabolic function encompasses a broad range of parameters, 2 pathways—insulin sensitivity and adiposity—are of particular interest regarding psychosis and depression. Genetic studies have indicated associations of BMI with depression[14] and fasting insulin (FI) levels with schizophrenia.[15] However, to our knowledge, no studies have examined whether FI level and BMI trajectories from childhood are associated with adult psychosis and depression.

Using data from the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort, we aimed to (1) delineate longitudinal trajectories of FI level and BMI based on repeated measurements in individuals between ages 1 and 24 years, (2) examine the characteristics of identified trajectories, and (3) test associations with risks of psychosis and depression at 24 years in the total sample and by sex. We hypothesized that altered cardiometabolic development from childhood would be associated with increased risks for depression and psychosis in adulthood.

Methods

Cohort and Sample

The ALSPAC initially recruited 14 541 pregnant residents in southwest England, with expected delivery dates between April 1, 1991, and December 31, 1992, resulting in 14 062 live births.[16-18] An additional 913 participants were recruited subsequently. Participants received financial compensation. Data were collected and managed using REDCap (University of Bristol[19,20]). Modeling of the trajectories was performed using 5790 participants for FI levels and 10 463 participants for BMI (eFigure 1 in the Supplement). Missing exposure data were handled using full-information maximum likelihood estima-

Key Points

Question Are longitudinal trends in insulin levels and body mass index from childhood associated with adult depression and psychosis?

Findings This cohort study of repeated-measure data from age 1 to 24 years in up to 10 463 individuals identified trajectories of fasting insulin levels and body mass index. Persistently high fasting insulin levels from age 9 years were associated with psychosis at 24 years, and puberty-onset body mass index increase was associated with depression at 24 years.

Meaning This study's findings suggest that changes in insulin sensitivity and adiposity starting from childhood may have disorder-specific associations with psychosis and depression and represent targets for prevention and treatment of cardiometabolic disorders in people with psychosis and depression.

tion (eMethods in the Supplement). Data were deidentified. The ALSPAC Ethics and Law Committee and local research ethics committees provided ethical approval for the ALSPAC cohort study. Ethical approval for the present study was obtained via the ALSPAC Executive Committee. Consent for biological samples was collected in accordance with the Human Tissue Act of 2004 covering England, Wales and Northern Ireland. Informed consent for all collected data was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort study.

Measurement of Exposures

Fasting insulin levels were measured at ages 9 (n = 894), 15 (n = 3484), 18 (n = 3286), and 24 (n = 3253) years, using an ultrasensitive automated microparticle enzyme immunoassay (Mercodia), which does not cross-react with proinsulin. Sensitivity of the immunoassay was 0.07 mU/L, and interassay and intraassay coefficients of variation were less than 6%. Fasting blood samples were drawn at 9 AM after a 10-hour fast, then spun and stored at −80 °C. There was no evidence of freeze-thaw cycles during storage.

Body mass index, calculated as weight in kilograms divided by height in meters squared, was measured at 1 (n = 1236), 2 (n = 1036), 3 (n = 1050), 4 (n = 1018), 7 (n = 8200), 9 (n = 7633), 10 (n = 7465), 11 (n = 7100), 12 (n = 6704), 15 (n = 5415), 18 (n = 5061), and 24 (n = 3975) years.

Psychiatric Outcomes at Age 24 Years

Psychotic experiences (PEs) were identified through the semistructured Psychosis-Like Symptom Interview[21] conducted by trained psychology graduates and coded per the definitions in the Schedules for Clinical Assessment in Neuropsychiatry, version 2.0.[22] The Psychosis-Like Symptom Interview had good interrater (intraclass correlation: 0.81; 95% CI, 0.68-0.89) and test-retest (0.9; 95% CI, 0.83-0.95) reliability. Psychotic experiences occurring in the past 6 months covered the 3 main positive symptom domains: hallucinations, delusions, and thought

interference. After cross-questioning, interviewers rated PEs as absent, suspected, or definite. We included cases of definite PEs; the comparator group comprised individuals with suspected or absent PEs.

Cases of at-risk mental state were identified by mapping Psychosis-Like Symptom Interview data to Comprehensive Assessment of At-Risk Mental State (CAARMS) criteria.[23] Cases were defined as participants meeting CAARMS criteria for attenuated psychosis (symptoms not reaching the psychosis threshold owing to levels of intensity or frequency) or brief limited intermittent psychosis (frank psychotic symptoms that resolved spontaneously within 1 week).

Cases of psychotic disorder were defined[21] as definite PEs that were not attributable to sleep or fever, had occurred more than once per month during the previous 6 months, and were very distressing or negatively impactful on social/occupational functioning, and led to seeking of professional help. We also included participants meeting the criteria for CAARMS psychotic disorder (threshold psychotic symptoms occurring for >1 week).

Ten questions from the Community Assessment of Psychic Experiences questionnaire[24] were administered covering interest, motivation, emotional reactivity, pleasure, and sociability. Participants rated each item as 0 (never), 1 (sometimes), 2 (often), and 3 (always). We recoded the variables by scoring always and often as 1 and never and sometimes as 0, and then summed the values to result in a possible total score of 0 to 10.

Depression was measured using the computerized Clinical Interview Schedule–Revised.[25] The interview assesses symptoms of depression occurring in the past week and provides a diagnosis of depressive episode based on the *International Statistical Classification of Diseases, Tenth Revision* criteria, which we used as a binary outcome (codes F32.0-32.2). We also included a Clinical Interview Schedule–Revised depression severity score, comprising scores for mood, thoughts, fatigue, concentration, and sleep, as a continuous outcome.

For assessment of potential confounders, we included sex at birth, race/ethnicity, paternal social class, childhood emotional and behavioral problems (measured using the Strength and Difficulties Questionnaire[26] at age 7 years), and cumulative scores of smoking, physical activity, alcohol use, substance use, sleep problems, and average calorie intake between ages 7 and 24 years (eMethods in the Supplement).

Statistical Analysis

We standardized (*z* transformed) FI levels and BMI separately in males and females and then combined the sex-stratified *z* scores for each variable at each time point to delineate trajectories using curvilinear growth mixture modeling[27] (eMethods in the Supplement). We used *z* scores to measure the relative change in FI levels and BMI because BMI increases in all young people during early life. Because the sample size for FI levels at age 9 years was smaller, we repeated growth mixture modeling without age-9-years data and compared the characteristics of the resultant trajectories. Analyses were conducted using MPlus, version 8 (Muthén & Muthén), and R, version 3.6.0 (R Project for Statistical Computing). Two-tailed

P values were corrected for multiple testing using the Holm-Bonferroni method[28] for the 6 psychiatric outcomes. A corrected *P* value <.05 was used as the threshold for significance. We estimated how participants overlapped between BMI and FI level trajectories (the most common and highest risk) using the φ correlation coefficient.

We used the 3-step method[29] to estimate associations of sociodemographic, lifestyle, and clinical factors with trajectory membership (eMethods in the Supplement). The 3-step method allows class separation unaffected by auxiliary variables, retains and includes information on class uncertainty, and is robust when entropy is greater than 0.60. Multinomial regression was used to estimate odds ratios (ORs) and 95% CIs for the associations of sociodemographic and lifestyle factors with FI level and BMI trajectories compared with the most common trajectory. We considered time-invariant (sex, ethnicity, social class at birth, family history of cardiovascular disease, gestational age, birth weight, and perinatal stressful life events) and time-variant (physical activity and smoking in adolescence and early adulthood) factors. Odds ratios represent the increase in the risk of membership of a particular trajectory category per SD increase in factor. Next, we examined the clinical phenotype of trajectories at 24 years, examining mean levels of commonly measured clinical and biochemical factors for participants grouped by most-likely trajectory membership (eMethods in the Supplement). Next, we used logistic regression to estimate the association of trajectory membership with an age-appropriate cardiometabolic outcome: metabolic syndrome at 24 years (eMethods in the Supplement).

Using the 3-step method, logistic regression was used to estimate ORs and 95% CIs for binary outcomes per trajectory, compared with the most common trajectory. Linear regression for continuous outcomes was used to estimate β coefficients and 95% CIs representing the SD increase in the risk of outcomes per trajectory. We tested associations for the total sample and separately by sex before and after adjusting for potential confounders. Regression models for negative symptoms were additionally adjusted for depressive symptoms, and vice versa.
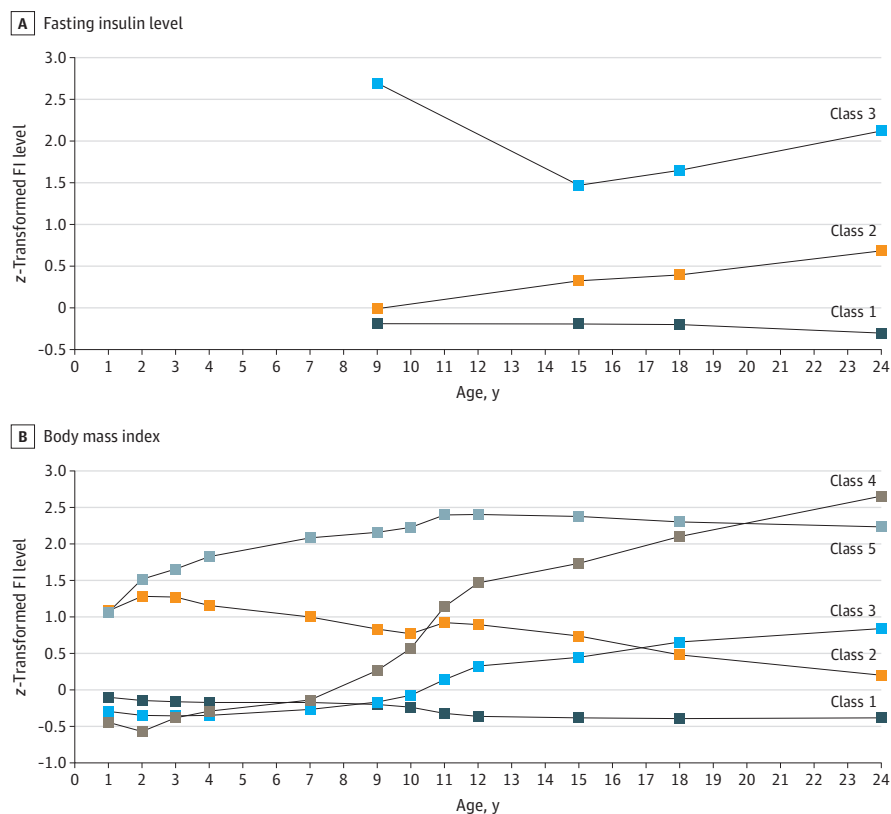
Results

Trajectories of FI Levels and BMI

Based on 5790 participants (2658 [45.9%] male, 3132 [54.1%] female), the 3-trajectory solution for FI levels was optimum, representing stable average (class 1: 4939 [77.8%]), minor increase (class 2: 693 [19.0%]), and persistently high (class 3: 158 [3.1%]) trajectories between ages 9 and 24 years (**Figure 1**A; eTable 1 and eFigure 2 in the Supplement). The trajectories were similar after excluding age-9-years data (eFigure 3 in the Supplement).

Based on 10 463 participants (5336 [51.0%] female, 5127 [49.0%] male) included in the analysis of BMI, the 5-trajectory solution was optimum, representing stable average (class 1: 8383 [71.1%]), gradually decreasing (class 2: 949 [7.0%]), puberty-onset minor increase (class 3: 668 [14.5%]), puberty-onset major increase (class 4: 174 [1.9%]), and persistently high

Figure 1. Fasting Insulin Levels and Body Mass Index Trajectories in the Avon Longitudinal Study of Parents and Children

A, Fasting insulin levels measured at ages 9 to 24 years in 5790 participants. Class 1 (stable average) comprised 77.8% of the sample; class 2 (minor increase), 19.0%; and class 3 (persistently high), 3.1%. B, Body mass index measured at ages 1 to 24 years in 10 463 participants. Class 1 (stable average) comprised 71.1% of the sample; class 2 (gradually decreasing), 7.0%; class 3 (puberty-onset minor increase), 14.5%; class 4 (puberty-onset major increase), 1.9%; and class 5 (persistently high), 5.5%. Trajectories were delineated using growth mixture modeling at 4 time points for fasting insulin and 12 time points for body mass index. Nodes in the graph represent mean z scores for fasting insulin level or body mass index at each time point for each developmental trajectory.

(class 5: 289 [5.5%]) BMI trajectories between ages 1 and 24 years (Figure 1B; eTable 2 and eFigure 4 in the Supplement).

The stable average FI level and BMI trajectories were statistically significantly correlated (r_φ = 0.233, P < .001), as were the persistently high trajectories (r_φ = 0.092, P < .001).

Both deviating FI level trajectories were associated with lower social class, family history of cardiometabolic disease, lower physical activity, and smoking in adolescence and early adulthood. Lower birth weight and more perinatal stressful life events were associated with the persistently high trajectory compared with the stable average trajectory (eTable 3 in the Supplement). The persistently high trajectory cohort also had mean FI, high-density lipoprotein cholesterol, triglyceride, and C-reactive protein levels outside of UK reference ranges at 24 years (eTable 4 in the Supplement). Deviating FI level trajectories were associated with metabolic syndrome at 24 years (adjusted OR [aOR] for the persistently high trajectory, 9.21; 95% CI, 3.77-20.15) (eTable 5 in the Supplement).

Deviating BMI trajectories were associated with lower social class, family history of cardiometabolic disease, more perinatal stressful life events, lower physical activity, and smoking in adolescence and early adulthood compared with the stable average trajectory. Higher birth weight was associated

with the gradually decreasing and persistently high trajectories, whereas lower birth weight was weakly associated with both puberty-onset increase trajectories (eTable 6 in the Supplement). Deviating BMI trajectories were also associated with mean values of waist circumference and FI, high-density lipoprotein cholesterol, and C-reactive protein levels outside of UK reference ranges at 24 years (eTable 7 in the Supplement). All deviating BMI trajectories were associated with metabolic syndrome at 24 years (aOR for the persistently high trajectory, 10.62; 95% CI, 5.89-19.13) (eTable 5 in the Supplement).

Associations of FI and BMI Trajectories With Psychiatric Outcomes

The persistently high FI level trajectory was associated with the psychosis at-risk mental state (aOR, 5.01; 95% CI, 1.76-13.19), psychotic disorder (aOR, 3.22; 95% CI, 1.11-9.90), and negative symptoms (adjusted β, 0.07; 95% CI, 0.01-0.13) at age 24 years. Fasting insulin level trajectories were not associated with depression (aOR, 1.38; 95% CI, 0.75-2.54) (Table 1; Figure 2A; eTable 8 in the Supplement).

The puberty-onset major increase trajectory of BMI was associated with a higher risk of a depressive episode (aOR, 4.46;

Table 1. Psychosis and Depressive Outcomes at Age 24 Years Associated With Fasting Insulin Level Trajectories From Age 9 to 24 Years

Trajectory and outcome at 24 y	Sample, No.	Odds ratio (95% CI)		P value[b]
		Unadjusted	Adjusted[a]	
Definite PE				
Class 1: stable average	4939	1 [Reference]	1 [Reference]	
Class 2: minor increase	693	1.48 (0.98-2.24)	1.31 (0.56-3.35)	.31
Class 3: persistently high	158	1.88 (1.05-3.60)	1.50 (0.98-2.41)	.33
Psychosis at-risk mental state				
Class 1: stable average	4939	1 [Reference]	1 [Reference]	
Class 2: minor increase	693	1.59 (0.20-8.02)	1.36 (0.32-5.76)	>.99
Class 3: persistently high	158	6.33 (1.97-20.30)	5.01 (1.76-13.19)	.006
Psychotic disorder				
Class 1: stable average	4939	1.00 [reference]	1.00 [Reference]	
Class 2: minor increase	693	1.85 (0.70-4.88)	1.23 (0.55-2.74)	>.99
Class 3: persistently high	158	4.74 (1.67-13.42)	3.22 (1.11-9.90)	.05
Depressive episode				
Class 1: stable average	4939	1 [Reference]	1 [Reference]	
Class 2: minor increase	693	1.26 (0.73-2.67)	1.36 (0.57-2.81)	.88
Class 3: persistently high	158	1.31 (0.81-4.32)	1.38 (0.75-2.54)	.69

Abbreviation: PE, psychotic experience.

[a] Adjusted for sex, ethnicity, social class, Strength and Difficulties Questionnaire (measured at 7 years) findings, and cumulative scores for smoking, physical activity, alcohol and substance use, sleep problems, and calorie intake.

[b] P values adjusted for multiple testing using the Holm-Bonferroni method.

95% CI, 2.38-9.87) and depressive symptoms (adjusted β, 0.08; 95% CI, 0.03-0.14) at age 24 years. The puberty-onset minor increase trajectory was weakly associated with depressive symptoms at 24 years (adjusted β, 0.06; 95% CI, 0.01-0.11). Body mass index trajectories were not associated with psychosis outcomes (aOR for psychotic disorder in the puberty-onset major increase trajectory, 1.98; 95% CI, 0.56-7.79) (Table 2 and Figure 2B; eTable 9 in the Supplement).

Sex-Stratified Associations of Risks for Psychiatric Outcomes

For FI trajectories, the pattern of association with risks for psychiatric outcomes in sex-stratified analysis was similar to the primary analysis. For example, point estimates for the association between the persistently high FI trajectory and psychotic disorder were similar in males (aOR, 3.94; 95% CI, 1.10-11.96) compared with females (aOR, 2.50; 95% CI, 0.57-11.09), and 95% CIs overlapped. There was no association between persistently high FI and depression in males (aOR, 0.95; 95% CI, 0.22-4.12) or females (aOR, 1.50; 95% CI, 0.76-2.96) (Figure 3; eTable 10 and eTable 11 in the Supplement). For BMI, point estimates for depression for both puberty-onset increase trajectories were larger in females. For example, for the puberty-onset major increase trajectory, the association for females (aOR, 6.28; 95% CI, 2.14-18.44) was stronger than for males (aOR, 2.23; 95% CI, 0.41-12.72). There was no significant association of BMI trajectories with psychosis outcomes. For example, there was no association between puberty-onset major BMI increase and psychotic disorder for males (aOR, 1.62; 95% CI, 0.71-3.98) or females (aOR, 2.60; 95% CI, 0.66-8.21) (Figure 3; eTable 12 and eTable 13 in the Supplement).
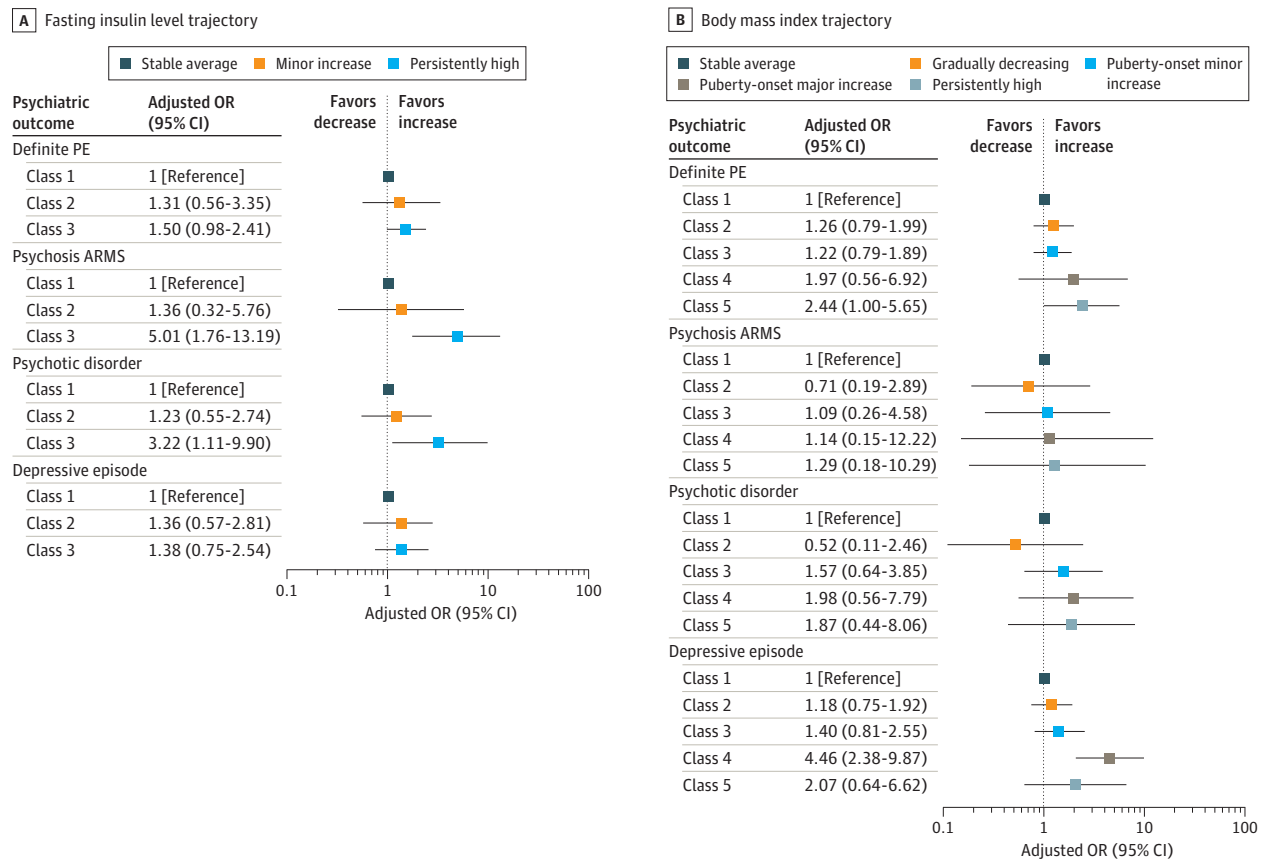
Discussion

We delineated FI level and BMI trajectories from early life, using prospective repeated measurements in a large population-representative birth cohort, and report distinct associations with psychosis and depression measured in adulthood. After adjusting for a number of relevant confounders, we found that persistently high FI levels from mid-childhood appeared to be associated with an increased risk of psychosis outcomes at age 24 years, while BMI increases around the age of puberty onset were associated with depression at age 24 years. Associations of BMI and FI level trajectories with cardiometabolic risk factors, such as social class, ethnicity, smoking, physical activity, and adult metabolic syndrome, suggest face validity to the identified trajectories. Although the last data point for BMI and FI levels overlapped with the outcome assessment, the trajectories were differentiated by mid-childhood, suggesting a temporal association between exposure and outcome. Evidence for the association of puberty-onset BMI increase and adult depression remained after adjusting for childhood emotional and behavioral problems, suggesting that a reverse direction of association may not fully explain this finding. Although the same adjustment may be less capable of ruling out reverse direction of the association between persistently high FI levels and psychosis, it is unlikely that many participants had experienced psychosis before age 9 years, and so a reverse direction of association is unlikely.

We found consistent evidence for an association between FI level trajectories and psychosis outcomes. Effect sizes were largest in the persistently high trajectory, consistent with a dose-response relationship, and point estimates were larger in more clinically relevant outcomes. Our findings complement meta-analyses reporting altered glucose-insulin homeostasis in first-episode psychosis.[6,7] Moreover, our results suggest that disruptions to glucose-insulin homeostasis detectable at first-episode psychosis in adults may begin in childhood. The point estimates partly attenuated after adjustment for confounders, suggesting that malleable lifestyle factors, such as smoking, physical activity, and diet, should remain targets for reducing the risk of incident cardiometabolic disorders in

Figure 2. Associations of Fasting Insulin Levels and Body Mass Index Trajectories With Psychosis and Depressive Outcomes in the Avon Longitudinal Study of Parents and Children

Adjusted odds ratios (ORs) and 95% CIs showing associations of fasting insulin (A) and body mass index (B) trajectories from childhood with risk of psychosis and depression outcomes at age 24 years after adjusting for sex, ethnicity, social class, childhood emotional and behavioral problems, and cumulative scores of smoking, physical activity, alcohol and substance use, sleep problems, and calorie intake. ARMS indicates at-risk mental state; PE, psychotic experiences.

young people with psychosis. We also found that participants classified into the persistently high FI level trajectory, who had the highest risk of psychosis, had mean BMI and fasting plasma glucose values within reference ranges at age 24 years. Therefore, the risk of incident cardiometabolic disorders in these individuals may not be detected in psychosis early-intervention services, since commonly measured physical indices may not identify them. Consequently, careful assessment and clinical considerations are needed to minimize the risk of cardiometabolic disorders in these individuals.

Our findings suggest that altered glucose-insulin homeostasis could be a shared mechanism for psychosis and type 2 diabetes, which could be genetic and/or environmental in origin. People with comorbid schizophrenia and type 2 diabetes have a higher genetic predisposition for both disorders compared with controls,[30] and genetic predisposition for schizophrenia is associated with insulin resistance in patients with schizophrenia.[31] In addition, we found that the persistently high FI trajectory, which had the strongest associations with psychosis outcomes, was also associated with lower birth weight and perinatal stressful life events. We noted similar patterns of associa-

tion in BMI trajectories that were associated with depression. These findings are consistent with the fetal programming hypothesis,[32] which posits that disruption in early-life development can have broad influences on adult health.

Our findings regarding the association of BMI trajectories with depression at age 24 years are in line with meta-analyses[33,34] suggesting an association between BMI and risk of depression. Similar trajectories of BMI have been linked with adult type 2 diabetes,[35] obesity,[36] and coronary heart disease.[37] The character and composition of BMI trajectories we identified are consistent with those of previous studies, although our length of follow-up was longer than the follow-up of most previous studies.[38]

Our findings provide further insights into the link between BMI and depression,[34] suggesting that puberty-onset increases in BMI specifically are associated with risk of adult depression. This finding, together with the lack of evidence for an association between persistently high BMI and depression, indicates that BMI might be a risk indicator for depression rather than a risk factor because individuals in the persistently high BMI trajectory would likely have been exposed to the "largest

Table 2. Psychiatric Outcomes at Age 24 Years Associated With BMI Trajectories From Age 1 to 24 Years

Trajectory and outcome at 24 y	Sample, No.	Odds ratio (95% CI)		P value[b]
		Unadjusted	Adjusted[a]	
Definite PE				
Class 1: stable average	8383	1 [Reference]	1 [Reference]	
Class 2: gradually decreasing	949	1.43 (0.82-1.96)	1.26 (0.79-1.99)	>.99
Class 3: puberty-onset minor increase	668	1.66 (0.87-2.55)	1.22 (0.79-1.89)	>.99
Class 4: puberty-onset major increase	174	3.56 (0.87-11.54)	1.97 (0.56-6.92)	>.99
Class 5: persistently high	289	3.21 (1.01-9.11)	2.44 (1.00-5.65)	.37
Psychosis at-risk mental state				
Class 1: stable average	8383	1 [Reference]	1 [Reference]	
Class 2: gradually decreasing	949	0.49 (0.10-3.21)	0.71 (0.19-2.89)	>.99
Class 3: puberty-onset minor increase	668	1.12 (0.23-5.43)	1.09 (0.26-4.58)	>.99
Class 4: puberty-onset major increase	174	1.32 (0.10-13.11)	1.14 (0.15-12.22)	>.99
Class 5: persistently high	289	1.55 (0.44-3.21)	1.29 (0.18-10.29)	>.99
Psychotic disorder				
Class 1: stable average	8383	1 [Reference]	1 [Reference]	
Class 2: gradually decreasing	949	0.44 (0.21-2.03)	0.52 (0.11-2.46)	>.99
Class 3: puberty-onset minor increase	668	1.97 (0.60-3.46)	1.57 (0.64-3.85)	>.99
Class 4: puberty-onset major increase	174	2.14 (0.65-6.21)	1.98 (0.56-7.79)	>.99
Class 5: persistently high	289	3.11 (0.53-13.22)	1.87 (0.44-8.06)	>.99
Depressive episode				
Class 1: stable average	8383	1 [Reference]	1 [Reference]	
Class 2: gradually decreasing	949	1.33 (0.77-1.88)	1.18 (0.75-1.92)	>.99
Class 3: puberty-onset minor increase	668	1.69 (0.90-3.21)	1.40 (0.81-2.55)	.31
Class 4: puberty-onset major increase	174	8.91 (4.21-17.12)	4.46 (2.38-9.87)	.006
Class 5: persistently high	289	3.01 (0.91-7.59)	2.07 (0.64-6.62)	.44

Abbreviations: BMI, body mass index; PE, psychotic experience.

[a] Adjusted for sex, ethnicity, social class, Strength and Difficulties Questionnaire (measured at 7 years), and cumulative scores for smoking, physical activity, alcohol and substance use, sleep problems, and calorie intake.

[b] P values adjusted for multiple testing using the Holm-Bonferroni method.

dose" of BMI. Therefore, if BMI were the risk factor, one would have expected the largest effect size for depression in that trajectory. Consequently, environmental and/or genetic factors influencing BMI during puberty are likely to be important risk factors for depression. For instance, social stressors, such as bullying, may predispose to altered eating behaviors and an increased risk of depression in adolescents.[39] In addition, deviating childhood BMI trajectories have been associated with a greater risk of adolescent and adult eating disorders,[40] which are commonly comorbid with depression.[41] Also, the effects of estrogen may be relevant, since the associations of puberty-onset BMI increases and depression appeared to be stronger in females than males. Changes in estrogen levels are associated with depressive symptoms throughout life in women, including pregnancy,[42] menopause,[43] and puberty.[44] Estrogen is associated with obesity[45] and may explain the genetic correlation of age at menarche with adult obesity[46] and depression.[47] Further research is needed to identify factors influencing pubertal BMI increases, as they may represent important preventive targets for depression.
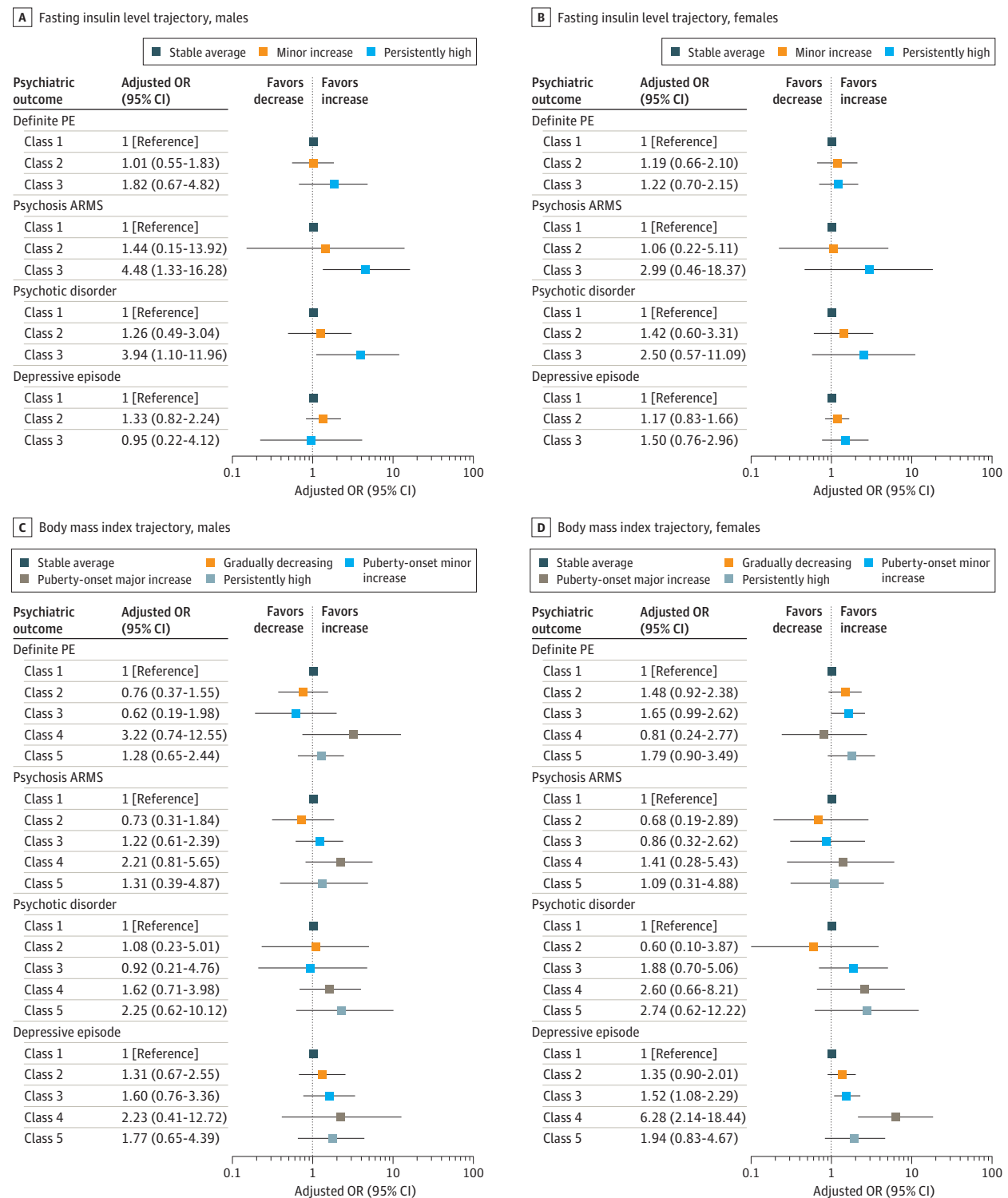
We did not find consistent evidence for associations of FI level trajectories with depression or of BMI trajectories with psychosis. Previous research has reported mixed findings regarding the association between insulin resistance and depression in young adults.[48,49] However, some estimates for the associations of BMI trajectories with psychosis outcomes in our analyses had wide 95% CIs, possibly owing to sample size. These particular findings require replication in larger samples of people with psychosis.

Strengths and Limitations

Strengths of the study include a longitudinal design with repeated measurements of BMI and FI levels between ages 1 and 24 years in a relatively large sample enabling a detailed examination of dynamic cardiometabolic changes from childhood to early adulthood. We included several relevant depression and psychosis outcomes, which allowed us to examine for specificity and for a biological gradient of evidence.

Limitations of the study include missing data. Although we used a robust method to handle missing data, full-information maximum likelihood may be biased in instances in which data were not missing at random.[50] However, the risk of bias in full-information maximum likelihood is no greater than the bias associated with traditional complete-case methods,[51] and full-information maximum likelihood permitted a larger sample size and therefore increased statistical power. Nevertheless, missing psychiatric outcome data may have affected our results. Furthermore, although we adjusted for a number of relevant potential confounders, residual confounding could still be an issue. For example, we could not account for psychological stress since data on cortisol levels were available only at age 9 years in a small subsection of the cohort. Therefore, further research is needed, such as mendelian randomization analysis, to examine for potentially unconfounded associations. In addition, the 95% CIs were relatively wide for the sex-stratified analysis, likely owing to reduced statistical power. Therefore, replication of our work in larger samples is required. In addition, the ALSPAC data set does not include *International Statistical*

Figure 3. Sex-Stratified Associations of Fasting Insulin Levels and Body Mass Index Trajectories With Psychosis and Depressive Outcomes in the Avon Longitudinal Study of Parents and Children

A Fasting insulin level trajectory, males

Legend: ■ Stable average ■ Minor increase ■ Persistently high

Psychiatric outcome	Adjusted OR (95% CI)
Definite PE	
Class 1	1 [Reference]
Class 2	1.01 (0.55-1.83)
Class 3	1.82 (0.67-4.82)
Psychosis ARMS	
Class 1	1 [Reference]
Class 2	1.44 (0.15-13.92)
Class 3	4.48 (1.33-16.28)
Psychotic disorder	
Class 1	1 [Reference]
Class 2	1.26 (0.49-3.04)
Class 3	3.94 (1.10-11.96)
Depressive episode	
Class 1	1 [Reference]
Class 2	1.33 (0.82-2.24)
Class 3	0.95 (0.22-4.12)

B Fasting insulin level trajectory, females

Legend: ■ Stable average ■ Minor increase ■ Persistently high

Psychiatric outcome	Adjusted OR (95% CI)
Definite PE	
Class 1	1 [Reference]
Class 2	1.19 (0.66-2.10)
Class 3	1.22 (0.70-2.15)
Psychosis ARMS	
Class 1	1 [Reference]
Class 2	1.06 (0.22-5.11)
Class 3	2.99 (0.46-18.37)
Psychotic disorder	
Class 1	1 [Reference]
Class 2	1.42 (0.60-3.31)
Class 3	2.50 (0.57-11.09)
Depressive episode	
Class 1	1 [Reference]
Class 2	1.17 (0.83-1.66)
Class 3	1.50 (0.76-2.96)

C Body mass index trajectory, males

Legend: ■ Stable average ■ Gradually decreasing ■ Puberty-onset minor increase ■ Puberty-onset major increase ■ Persistently high

Psychiatric outcome	Adjusted OR (95% CI)
Definite PE	
Class 1	1 [Reference]
Class 2	0.76 (0.37-1.55)
Class 3	0.62 (0.19-1.98)
Class 4	3.22 (0.74-12.55)
Class 5	1.28 (0.65-2.44)
Psychosis ARMS	
Class 1	1 [Reference]
Class 2	0.73 (0.31-1.84)
Class 3	1.22 (0.61-2.39)
Class 4	2.21 (0.81-5.65)
Class 5	1.31 (0.39-4.87)
Psychotic disorder	
Class 1	1 [Reference]
Class 2	1.08 (0.23-5.01)
Class 3	0.92 (0.21-4.76)
Class 4	1.62 (0.71-3.98)
Class 5	2.25 (0.62-10.12)
Depressive episode	
Class 1	1 [Reference]
Class 2	1.31 (0.67-2.55)
Class 3	1.60 (0.76-3.36)
Class 4	2.23 (0.41-12.72)
Class 5	1.77 (0.65-4.39)

D Body mass index trajectory, females

Legend: ■ Stable average ■ Gradually decreasing ■ Puberty-onset minor increase ■ Puberty-onset major increase ■ Persistently high

Psychiatric outcome	Adjusted OR (95% CI)
Definite PE	
Class 1	1 [Reference]
Class 2	1.48 (0.92-2.38)
Class 3	1.65 (0.99-2.62)
Class 4	0.81 (0.24-2.77)
Class 5	1.79 (0.90-3.49)
Psychosis ARMS	
Class 1	1 [Reference]
Class 2	0.68 (0.19-2.89)
Class 3	0.86 (0.32-2.62)
Class 4	1.41 (0.28-5.43)
Class 5	1.09 (0.31-4.88)
Psychotic disorder	
Class 1	1 [Reference]
Class 2	0.60 (0.10-3.87)
Class 3	1.88 (0.70-5.06)
Class 4	2.60 (0.66-8.21)
Class 5	2.74 (0.62-12.22)
Depressive episode	
Class 1	1 [Reference]
Class 2	1.35 (0.90-2.01)
Class 3	1.52 (1.08-2.29)
Class 4	6.28 (2.14-18.44)
Class 5	1.94 (0.83-4.67)

Adjusted odds ratios (ORs) and 95% CIs showing associations of fasting insulin level trajectories in males (A) and females (B) and body mass index trajectories in males (C) and females (D) from childhood with risk of psychosis and depression outcomes at age 24 years after adjusting for sex, ethnicity, social class, childhood emotional and behavioral problems, and cumulative scores of smoking, physical activity, alcohol and substance use, sleep problems, and calorie intake. ARMS indicates at-risk mental state; PE, psychotic experience.

Classification of Diseases and *DSM* diagnoses of schizophrenia. However, our psychotic disorder outcome would likely meet the threshold for clinical intervention, and all our psychosis outcomes lie on the schizophrenia continuum.

Conclusions

We report that the cardiometabolic comorbidity of psychosis and depression may have distinct early-life origins. Disrupted insulin sensitivity from mid-childhood appeared to be associated with adult psychosis, and BMI increases starting around the time of puberty onset were associated with adult depression. Although residual confounding may be an issue, our results suggest that these cardiometabolic markers could be among shared risk factors and indicators for adult cardiometabolic and psychiatric disorders and may represent novel targets for prevention and treatment of cardiometabolic disorders in people with psychosis and depression.

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Author Contributions: Dr Perry had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Perry, Upthegrove, Jones, Khandaker.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Perry, Jones, Khandaker.
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Statistical analysis: Perry, Stochl.
Obtained funding: Perry, Upthegrove, Zammit, Jones, Khandaker.
Administrative, technical, or material support: Jones, Khandaker.
Supervision: Upthegrove, Wareham, Langenberg, Dunger, Jones, Khandaker.

Conflict of Interest Disclosures: Dr Perry reported receiving grants from the National Institute for Health Research (NIHR) during the conduct of the study. Dr Upthegrove reported receiving grants from the NIHR, UK Research and Innovation, EU Seventh Framework Programme, and personal fees from Sunovion outside the submitted work. Dr Winpenny reported receiving grants from the Medical Research Council during the conduct of the study. Dr Jones reported paid consulting for Recordati and Janssen outside the submitted work. No other disclosures were reported.

Funding/Support: Dr Perry received funding support from the NIHR (doctoral research fellowship DRF-2018-11-ST2-018). Dr Khandaker received funding support from the Wellcome Trust (intermediate clinical fellowship, grant 201486/Z/16/Z), the MQ: Transforming Mental Health (data science award, grant MQDS17/40), the Medical Research Council UK (MICA: Mental Health Data Pathfinder grant MC_PC_17213 and Therapeutic Target Validation in Mental Health grant MR/S037675/1), and the BMA Foundation (J Moulton grant 2019). Dr Jones received funding from the Medical Research Council and MQ: Transforming Mental Health (data science award, grant MQDS17/40), programmatic funding from NIHR (grant RP-PG- 0616-20003), and support from the Applied Research Collaboration East of England. Dr Upthegrove received funding support from the NIHR (HTA grant 127700) and Medical Research Council (Therapeutic Target Validation in Mental Health grant MR/S037675/1). Dr Zammit is supported by the NIHR Biomedical Research Centre at University Hospitals Bristol National Health Service (NHS) Foundation Trust and the University of Bristol. The UK Medical Research Council and Wellcome Trust (grant 102215/2/13/2) and the University of Bristol provide core support for the Avon Longitudinal Study of Parents and Children (ALSPAC). A comprehensive list of grants funding is available on the ALSPAC website (http://www.bristol.ac.uk/alspac/external/documents/grant-acknowledgements.pdf); this research was specifically funded by the Wellcome Trust (grant 08426812/Z/07/Z), Wellcome Trust & MRC (grant 217065/Z/19/Z), and the MRC (grant MR/M006727/1).

Role of the Funder/Sponsor: The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The views expressed in this publication are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health and Social Care.

Additional Contributions: We are grateful to all the families who took part in this study, the midwives for their help in recruiting the families, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists, and nurses.

Additional Information: Information about the data available in ALSPAC is available at http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/.

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