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The association between birth weight, ponderal index, psychotropic medication, and type 2 diabetes in individuals with severe mental illness

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A sub-optimal environment in fetal life is an important risk factor for the inherent risk of type 2 diabetes. ∗ The “thrifty phenotype hypothesis” describes that inadequate fetal nutrition imposes mechanisms of nutritional thrift upon the individuals through early permanent alterations of the neuroendocrine system. This alteration leads to increased susceptibility to a wide range of diseases, including both neuropsychiatric diseases and type 2 diabetes. The main pathological pathway is hypothesized to be through prenatal insulin resistance and impaired glucose metabolism which through epigenetic changes may lead to an abnormal glucose metabolism in young people predisposing them to metabolic disorders such as type 2 diabetes. These epigenetic modifications may also lead to abnormal brain development which in turn may influence systems crucial to development of neuropsychiatric disease and thus provide a link between metabolic impairment and psychiatric disease. Accordingly, research has shown a predisposition towards metabolic disturbances (i.e. impaired glucose metabolism) in drug-naïve patients (to obviate the potential confounding by psychotropic medication) and furthermore, patients with severe mental illness have been
shown to have two to three times higher risk of type 2 diabetes compared with the general population. Due to this, it has been suggested that individuals with impaired fetal growth might be especially vulnerable to development of metabolic disturbances and weight change associated with the use of some psychotropic drugs. Indeed, a recent study reported that abnormal birth weight was an independent risk factor for diabetes onset in clozapine-treated patients with schizophrenia emphasizing the importance of the risk factor in this population.

Since antipsychotic medications appeared in the 1960s, and especially after the introduction of second-generation antipsychotics, a number of studies have associated the use of psychotropic medication with development of type 2 diabetes in patients with severe mental illness. From a clinical perspective, it is important to identify if certain groups of patients are at greater risk of developing type 2 diabetes when receiving psychotropic medication.

Commonly used measures of impaired fetal growth have been low birth weight, low ponderal index (a weight-height related parameter mainly used to assess the pattern of fetal growth), and small-for-gestational-age, which have all been associated with metabolic diseases. However, no study has explored the role of fetal growth markers on the association between the use of psychotropic medication and type 2 diabetes.

In this study, we aimed to test the hypothesis that individuals with low or high birth weight or ponderal index have especially high risk of type 2 diabetes after receiving psychotropic medication.

2. Methods

2.1. Population

All individuals born in Denmark between 1973 and 1983 (N = 675,455) were identified in the Danish Medical Birth Register, which was established in 1973 and comprises birth information on all live-born children and their parents. This cohort was linked to the Civil Registration System, the Danish Psychiatric Central Research Register, the Danish National Patient Register, the Danish National Prescription Registry and the Education Register, using the personal identification number as key, in order to obtain information on sociodemographics, vital status, medical diagnoses, and medication use. Based on this data linkage, we identified individuals with severe mental illness defined as a hospital contact with a diagnosis of schizophrenia, depression, or bipolar disorder on or after the age of 10 years in the Danish Psychiatric Central Research Register or the Danish National Patient Register. The two registers hold information on admissions to psychiatric or somatic wards from 1969 and 1977, respectively, and information from emergency rooms and outpatient clinics from 1995. Diagnoses have been coded according to the 8th revision of the International Classification of Diseases (ICD-8) from 1969 to 1995, and the 10th revision (ICD-10) from 1995 and onwards. Selected codes are shown in Fig. 1.

Fig. 1. Flow chart of included individuals.
2.2. Psychotropic medication

Data on any prescription on psychotropic medication since 1995 was retrieved from the Danish National Prescription Registry. The inclusion of psychotropic medication was based on a screening of psychopharmacological agents available during the study period and their potential influence on glucose tolerance or body weight.\textsuperscript{2,4,25} Psychotropic medications were categorized into antipsychotic, mood stabilizing, or antidepressant medication. For mood stabilizing medication, valproate, lamotrigine and lithium were included. Anatomical therapeutic chemical (ATC) classification system codes are shown in Fig. 1. In supplementary analysis, tricyclic antidepressants and mirtazapine were included as a measure of “obesity-causing antidepressant medication”. We also explored combinations of drugs in four categories (no use of psychotropic medication; use one class; used two classes; or used all three classes) and seven categories (antipsychotics only; antipsychotics and mood stabilizers; antipsychotics and antidepressants; mood stabilizers only; mood stabilizers and antidepressants; antidepressants only; and no psychotropic medication).

2.3. Diabetes

Type 2 diabetes was defined by a diagnosis of type 2 diabetes derived according to ICD-10 codes from the Danish National Patient Register using E11, E13, or E14 codes (Fig. 1). Type 2 diabetes was further defined by the first prescription of oral antidiabetic medication using ATC code A10B. As metformin is also used by women suffering from polycystic ovary syndrome (PCOS),\textsuperscript{26} women with a diagnosis of PCOS in the Danish National Patient Register did not receive a diagnosis of type 2 diabetes when retrieving metformin, similar for women diagnosed with gestational diabetes (n = 10).

Type 1 diabetes was defined as an ICD-10 diagnosis of E10 or use of insulin (ATC code A10A) before age 35, and patients with type 1 diabetes were excluded if present at baseline or censored if diagnosed during follow-up.

2.4. Birth weight and ponderal index

Birth weight and ponderal index were obtained from the Danish Medical Birth Register and were used as proxy measurements for fetal growth. Birth weight was categorized into three categories: \(<2500: \text{low birth weight; } 2500–3900: \text{normal birth weight (reference); and } \geq 4000 \text{g: high birth weight as done in previous analyzes.}^2\textsuperscript{7} \text{Ponderal index, calculated as birth weight [kg]/birth length [meters],}^2\textsuperscript{8} \text{was also included because it is theoretically assumed to measure fetal growth and hereby discriminate between intrauterine well-fed (high ponderal index) and disproportionate growth restricted newborns (low ponderal index).}^2\textsuperscript{8} \text{Ponderal index was analyzed as a three-category variable (1st quintile; 2nd–4th quintile; 5th quintile) as done previously.}^2\textsuperscript{7} \text{Individuals with missing information on birth weight were excluded. We furthermore restricted the population to singleton pregnancies because multiple pregnancies have different patterns of fetal growth.}

2.5. Covariates

Covariates were chosen a priori, based on the available data and previous research findings of associations with diabetes and/or psychotropic medications. From the Danish Medical Birth Register, we included maternal age in years (categorized as \(<20, 20–34.9, \text{and } \geq 35 \text{years of age). Maternal educational level at age 10 of the child (the participant) was used as a proxy measure for participant’s social position. Maternal educational level included from the Education Register was categorized as basic (7–10 years: primary school with or without finals), middle (9–12 years: middle and secondary school, or skilled training in industry, trade and craft), high (\(>12 \text{years: secondary school final, medium length or higher education), or missing. Missing information on education was assigned a fixed number, as missingness was not assumed to be missing completely at random but rather associated with being in the older age groups. Sex was included as a binary variable. Further information on ethnicity was retrieved from the civil registration system and categorized as Danish, Western or non-Western origin using the coding develop by Statistics Denmark.

Since obesity is a risk factor for diabetes, a diagnosis of obesity before or at study entry was identified in the Danish National Patient Register using IDC-8 code 277.99 and ICD-10 codes E66.0–66.9. We also included information on family history of type 2 diabetes defined by whether the mother had type 2 diabetes at baseline.

2.6. Statistical analyzes

Stata version 15 was used for all statistical analyzes.

First, the association between use of psychotropic medication and type 2 diabetes was analyzed using Cox proportional hazards regression models with age as the underlying time scale, calculating hazard ratios (HRs) with 95% confidence intervals (CI). Individuals were followed from age at first diagnosis of severe mental illness until first diagnosis of type 2 diabetes or end of follow-up (December 31st, 2018, when individuals were between 35 and 46 years old). Psychotropic medication was included as a time-dependent variable with change of exposure status to exposed at the first prescription of psychotropic medication. Individuals with use of psychotropic medication before baseline were considered exposed from the time of inclusion. Three different levels of adjustment were used: a crude model (age-adjusted, since age was the underlying time scale); a model 1, which was further adjusted for gender, maternal age, maternal education, sub-diagnosis, premorbid obesity and maternal diabetes; and a model 2, which was further adjusted for use of either antidepressant/mood stabilizing medication (for antipsychotics), antipsychotic/antidepressant medication (for mood stabilizing medication), or antipsychotic/mood stabilizing medication (for antidepressants). The proportional hazards assumption was tested graphically by plotting –log (–log(survival)) vs. log (follow-up time). No violations were identified.

As sensitivity analyzes for unmeasured confounding, E-values were calculated using the \textit{evalu-calculate.com}. An E-value is defined as the minimum strength of association that an unmeasured confounder would need to have with both exposure and outcome to fully explain the exposure-outcome association beyond the confounders already included in the model. Thus, a large E-value implies that considerable unmeasured confounding is needed to explain the effect estimate.\textsuperscript{29} To provide an example, for a hazard ratio of 1.86 with an E-value of 3.12, the observed hazard ratio of 1.86 could be completely explained by an unmeasured confounder that was associated with both the exposure and outcome by a hazard ratio of 3.12.

Next, to study whether birth weight or ponderal index modified the association between psychotropic medication and type 2 diabetes, individuals were stratified into categories of birth weight and ponderal index, respectively. Potential interactions were tested by including an interaction term (birthweight*psychotropic medication and birthweight*ponderal index, respectively) into the model. The models with and without the interaction terms were compared using a likelihood ratio test. Finally, use of psychotropic medication is related to mortality and competing risk may influence the risk estimates because individuals who die are no longer at risk of type 2 diabetes. Thus, in supplementary analyzes we used competing risk regression to calculate the cumulative incidence of type 2 diabetes by type of psychotropic medication use, to explore whether any difference could be explained by competing mortality risk.

3. Results

After exclusion of individuals with missing information on birth weight (n = 1372), twins or triplets (n = 13,246), individuals without
severe mental illness (n = 623,461), or type 1 diabetes (n = 416), leading to a total of 36,957 individuals with a register-based hospital diagnosis of schizophrenia (n = 7762), bipolar disorder (n = 1928), or depression (n = 23,087) to be included in the study. The baseline characteristics of the population are shown in Table 1. Individuals were born between 1973 and 1983 and had a mean age of 29.2 years (range 10.4–45.7 years) at the time of study entry. When examining the use of psychotropic medication, 22,675 (61.4%) received antipsychotic medication either before or during follow-up; 9428 (25.5%) received mood stabilizers, while 32,645 (88.3%) received antidepressant medication. Overlap between different sub-diagnoses and different medication use is shown in Supplementary Fig. 1. When examining birth weight, 6655 (18.0%) had a birth weight < 2500 g, while 3837 (10.4%) had a birth weight ≥ 4000 g. For ponderal index, 7874 (21.3%) had a ponderal index in the lowest quintile, while 7184 (19.4%) had a ponderal index in the highest quintile.

### 3.1. Psychotropic medication and type 2 diabetes

During follow-up, a total of 1575 (4.2%) received a diagnosis of type 2 diabetes. Mean follow-up was 9.3 years (range 0.0–34.8). Individuals were censored at death (n = 1405), emigration (n = 530), or a diagnosis of type 1 diabetes (n = 118).

In the crude (age-adjusted) models, use of antipsychotic medication was associated with an 86% higher rate of type 2 diabetes (HR 1.86; 95% CI 1.70–1.95; E-value 7.04) than in patients with depression (HR 1.48; 95% CI 1.29–1.70; E-value: 2.32), while there was no differences in risk for mood stabilizing or antidepressant medication. The HRs for bipolar disorder were imprecisely estimated as the number of outcomes was small (n = 34).

#### Table 1

Baseline characteristics of 36,957 individuals with severe mental illness, born between 1973 and 1983.

| Covariate                          | All (n = 36,957) | Antipsychotic medication | Mood stabilizing medication | Antidepressant medication |
|------------------------------------|------------------|--------------------------|-----------------------------|---------------------------|
|                                    | No (%)           | Yes (%)                  | No (%)                      | Yes (%)                   | No (%)                      | Yes (%)                   |
| Number (%)                         | 36,957           | 14,282 (38.6)            | 22,675 (61.4)               | 27,529 (74.5)             | 9428 (25.5)                 | 3412 (11.7)               | 32,645 (88.3)             |
| Women, n (%)                       | 21,146 (57.2)    | 9177 (43.3)              | 11,969 (56.7)               | 15,174 (71.0)             | 5972 (28.0)                 | 1598 (7.5)                | 19,548 (59.9)             |
| Maternal age, n (%)                | 20–49 years      | 1120 (7.8)               | 2137 (9.4)                  | 2466 (9.0)                | 791 (8.4)                   | 390 (9.0)                 | 2861 (8.8)                |
| Gestational age, n (%)             | <32 weeks        | 39 (0.6)                 | 62 (0.6)                    | 76 (0.6)                  | 25 (0.6)                    | 17 (0.87)                 | 84 (0.59)                 |
| Maternal education, n (%)          | 10 years         | 604 (4.7)                | 1088 (4.7)                  | 1360 (4.6)                | 374 (3.97)                  | 188 (4.4)                 | 1366 (4.6)                |
| Maternal history of type 2 diabetes, n (%) | 20–49 years | 1120 (7.8)               | 2137 (9.4)                  | 2466 (9.0)                | 791 (8.4)                   | 390 (9.0)                 | 2861 (8.8)                |
| Ethnicity n (%)                    | Danish           | 36,108 (97.7)            | 14,080 (97.5)               | 26,980 (73.0)             | 11,173 (30.2)               | 4399 (11.9)               | 26,980 (73.0)             |
|                                    | Western          | 6204 (17.6)              | 173 (2.7)                   | 713 (1.7)                 | 470 (1.1)                   | 268 (0.7)                 | 6204 (17.6)               |
|                                    | Non-Western      | 2765 (19.4)              | 173 (2.7)                   | 713 (1.7)                 | 470 (1.1)                   | 268 (0.7)                 | 2765 (19.4)               |
|                                    | Obesity at baseline, % | 487 (4.7)              | 113 (4.2)                   | 491 (2.4)                 | 91 (4.0)                    | 40 (1.0)                  | 487 (4.7)                 |
|                                    | Schizophrenia    | 1459 (10.2)              | 91 (4.0)                    | 91 (4.0)                  | 40 (1.0)                    | 40 (1.0)                  | 1459 (10.2)               |
|                                    | Bipolar disorder | 713 (5.0)                | 427 (1.2)                   | 914 (3.3)                 | 4385 (12.0)                 | 4385 (12.0)               | 713 (5.0)                 |
|                                    | Depression       | 1267 (32.4)              | 672 (17.4)                  | 8555 (29.1)               | 2857 (30.3)                 | 2857 (30.3)               | 1267 (32.4)               |
|                                    | Birth weight, n (%) | <2500 g                 | 4715 (18.5)                 | 14,080 (27.3)             | 26,980 (73.0)               | 26,980 (73.0)             | <2500 g                   |
|                                    | 2500-3999 g      | 4715 (18.5)              | 14,080 (27.3)               | 26,980 (73.0)             | 26,980 (73.0)               | 26,980 (73.0)             | 2500-3999 g               |
|                                    | 4000+            | 4715 (18.5)              | 14,080 (27.3)               | 26,980 (73.0)             | 26,980 (73.0)               | 26,980 (73.0)             | 4000+                      |
| Ponderal index, n (%)              | 1st quintile     | 7874 (21.3)              | 2955 (20.7)                 | 4919 (21.7)               | 5822 (21.2)                 | 5822 (21.2)               | 7874 (21.3)               |
|                                    | 2nd-4th quintile | 21,726 (58.8)            | 8407 (58.9)                 | 13,319 (58.7)             | 16,151 (58.7)               | 16,151 (58.7)             | 21,726 (58.8)             |
|                                    | 5th quintile     | 7184 (19.4)              | 2860 (20.0)                 | 4324 (19.1)               | 5426 (19.7)                 | 5426 (19.7)               | 7184 (19.4)               |
|                                    | Unknown          | 173 (0.5)                | 60 (0.4)                    | 113 (0.5)                 | 130 (0.5)                   | 43 (0.5)                  | 22 (0.5)                  |

* Some individuals have more than one sub-diagnosis.
Any antidepressant medication

| HR (95% CI) | HR (95% CI) | HR (95% CI) |
|-------------|-------------|-------------|
| 1 [reference]| 1.86 (1.67-2.07)| 1.68 (1.49-1.90)|
| 1 [reference]| 1.35 (1.21-1.53)| 1.41 (1.25-1.59)|
| 1 [reference]| 1.73 (1.46-2.06)| 2.00 (1.68-2.39)|

Any mood stabilizing medication

| HR (95% CI) | HR (95% CI) | HR (95% CI) |
|-------------|-------------|-------------|
| 1 [reference]| 1.98 (1.95-2.00)| 1.80 (1.68-2.00)|
| 1.35 (1.19-1.52)| 1.28 (1.19-1.40)| 1.21 (1.07-1.37)|

Any antipsychotic medication

| HR (95% CI) | HR (95% CI) | HR (95% CI) |
|-------------|-------------|-------------|
| 1 [reference]| 1.77 (1.73-1.82)| 1.77 (1.73-1.82)|

Fig. 2. Associations between psychotropic medication and type 2 diabetes in 34,851 men and women with a diagnosis of schizophrenia, bipolar disorder, or depression.

3.2. Birth weight/ponderal index, psychotropic medication, and the risk of type 2 diabetes

Compared to individuals with a normal birth weight (2600-3900 g), individuals with a low (<2500 g) birth weight had higher rates of type 2 diabetes (HR 1.13; 95% CI 1.01–1.28; E-value 1.51), whereas a high birth weight (>4000 g) was not associated with a higher rate (Supplementary Table 3). Across all categories of birth weight, individuals who received antipsychotic or antidepressant medication had higher risk of diabetes than individuals who did not receive those medications (Fig. 3). Only individuals receiving mood stabilizing medication with a birth weight ≥4000 g did not have higher risk than non-users with a similar high birth weight. The highest rates of type 2 diabetes were identified in individuals with a low birth weight using antipsychotic medication (HR<sub>antipsychotics</sub> 1.98; 95% CI 1.66–2.35; E-value 3.37), mood stabilizing medication (HR<sub>mood stabilizers</sub> 1.72; 95% CI 1.38–2.13; E-value 2.83), or antidepressant medication (HR<sub>antidepressants</sub> 2.44; 95% CI 1.93–3.08; E-value 4.31) compared to non-users with a normal birth weight, who had the lowest rates. There were no interactions between birth weight and any of the medications on the development of type 2 diabetes (all log-likelihood ratio test for interaction had p-values >0.05).

Ponderal index was also associated with the risk of type 2 diabetes, especially a ponderal index in the 5th quintile showed higher rate of diabetes compared to the 2nd to 4th quintile (HR 1.26; 95% CI 1.11–1.43; E-value 1.83) (Supplementary Table 3). Across all categories of ponderal index, individuals receiving psychotropic medication had higher rates of diabetes compared to non-users (Supplementary Fig. 3), suggesting that both psychotropic medication and ponderal index are risk factors for development of type 2 diabetes. However, as for birth weight, there were no interactions between ponderal index and any of the medications on the development of type 2 diabetes (all log-likelihood ratio test for interaction had p-values >0.05).

Analyses including interaction with number of psychotropic medications used showed no interaction with birth weight for type 2 diabetes. The highest rates of type 2 diabetes were identified in individuals with low birth weight using all three types of medications (HR 5.32; 95% CI 3.49–8.12; E-value 10.11), followed by individuals with normal or high birth weight using all three types of medications. Similar findings were identified in the analyses stratified by ponderal index (Table 2). The interaction analyzes with combinations of medications had few observations in several categories, which led to imprecise estimations.

When examining only tricyclic antidepressants and/or mirtazapine, results were similar, albeit with slightly lower estimates (Supplementary Table 4). For birth weight, the highest rates of type 2 diabetes were identified in individuals with low birth weight using tricyclic antipsychotics or mirtazapine (HR 1.59; 95% CI 1.34–1.88; E-value 2.56), followed by individuals with normal or high birth weight using tricyclic antipsychotics or mirtazapine (HR 1.35; 95% CI 1.19–1.52; E-value 2.04) and (HR1.31; 95% CI 1.31–1.02; 1.68; E-value 1.31) compared to non-users with normal birth weight. For ponderal index, the highest rates were similarly identified in individuals with low birth weight using tricyclic antidepressants or mirtazapine (HR 1.61; 95% CI 1.36–1.80; E-value 2.6) compared to non-users with normal birth weight.

4. Discussion

In this study of 36,957 individuals born between 1973 and 1983 with a register-based diagnosis of schizophrenia, bipolar disorder, or depression, we found that the use of antipsychotic, mood stabilizing, and antidepressant medication was associated with higher rates of type 2 diabetes. The risk increased with number of different types of medication used. Individuals with a birth weight below 2500 g had a higher rate of type 2 diabetes, whereas for ponderal index, especially individuals with a high ponderal index had a higher rate of diabetes. Yet, neither birth weight nor ponderal index modified the association between psychotropic medication and diabetes risk.

Our findings that antipsychotic medication was a risk factor for type 2 diabetes are in accordance with many previous studies, including a previous Danish register-based study. This and other studies have indicated that the risk of metabolic dysregulation or type 2 diabetes are highest for second-generation antipsychotics especially olanzapine and clozapine. For antidepressants, previous studies find conflicting results. In 2013, two meta-analyses of 8 and 12 studies reported a 19% and 49% higher rate of incident diabetes, respectively, in individuals using antidepressants. Selective serotonin reuptake inhibitors and tricyclic antidepressants had even higher rates. As a consequence, the association may be explained by confounding by indication (i.e. that the association observed may be due to psychotropic medication being a proxy for severe mental illness). Thus, to reduce the potential of confounding by indication, our study population was restricted to individuals with a severe mental illness. Our study indicated that the risk of type 2 diabetes increased with the number of different types of medication used, which might be an indicator of disease severity. Contrary to what we expected, the risk of type 2 diabetes was lower when examining only tricyclic...
The association between low birth weight and type 2 diabetes is well-documented. In a large meta-analysis including 4 million participants in 49 studies, the authors reported that each kg increase in birth weight was associated with a 22% reduction in the risk of developing type 2 diabetes. Furthermore, binary analysis showed that participants with a birth weight lower than 2500 g had a higher risk of type 2 diabetes than individuals with a birth weight above 2500 g with an odds ratio of 1.45 (95% CI 1.33–1.59). In our analysis, individuals with severe mental illness with a birth weight below 2500 g had a HR for diabetes of 1.13 (95% CI 1.01–1.27) compared to individuals with a normal birth weight. A recent meta-analysis supports this finding by identifying a non-linear and L-shaped association between birth weight and type 2 diabetes, with the highest risk among individuals with low birth weight and a less steep association with increasing birth weight. In our analyses, we further found that especially high ponderal index, i.e. with a high weight compared to height, was associated with increased rates of type 2 diabetes. This could be partly explained by mothers with gestational diabetes having increased risk of giving birth to infants large-for-gestational-age. Unfortunately, it was not possible to adjust for maternal gestational diabetes in the present study, because this information was not available when the present cohort was born.

We did not find that birth weight modified the association between psychotropic medication and type 2 diabetes. Both psychotropic medication and low birth weight were individual risk factors and, as such, individuals with low birth weight and use of psychotropic medication had the highest risk of type 2 diabetes (but the combined risk was not higher than expected from the risk estimates for each risk factor). For ponderal index, the risk was highest in individuals who received psychotropic medication and had a high ponderal index, but, again, there was no interaction between ponderal index and psychotropic medication use on the development of type 2 diabetes. Interestingly, we did not find that individuals with a lower ponderal index had significantly increased risk of type 2 diabetes, even if the point estimates tended to point towards a slightly increased risk (HR 1.12 [95% CI 0.82–1.15]). The validity of the ponderal index to capture intrauterine growth restriction has previously been questioned. A study of 2504 pregnancies showed that birth weight was a better predictor of thinness, abdominal circumference, and organ asymmetry and thus a better marker of intrauterine growth restriction than ponderal index. The possible low validity of the ponderal index as an indicator of fetal growth could explain why we did not find any association between low ponderal index and type 2 diabetes. A previous study reported that birth weight was positively associated with weight gain after antipsychotic treatment with olanzapine in antipsychotic-naïve patients. However, using a non-linear approach, the weight gain seemed higher in both individuals with high and low birth weight and none of the participants in that study had a birth weight lower than 2500 g or higher than 4000 g. No previous large-scale study using type 2 diabetes as outcome has tested for possible interactions between weight or ponderal index and use of psychotropic medication.

Risk factors for low birth weight include maternal lifestyle factors such as smoking or drug abuse, and if the association between low birth weight and type 2 diabetes is causal, interventions to reduce these factors in pregnant women might lower the risk of type 2 diabetes, both in individuals with and without severe mental illness. As the highest risk of psychotropic medication induced type 2 diabetes was seen in individuals with the lowest birth weight, attention towards this factor could be considered along with other important risk factors for diabetes when prescribing psychotropic medication.

This study has several strengths and limitations. One strength is the large nationwide sample of all individuals born in Denmark between 1973 and 1983 and with a hospital contact with severe mental illness. Including only individuals with these severe mental illnesses is likely to limit confounding by indication when investigating psychotropic medication induced a risk factor for type 2 diabetes. By linking individual data using the Danish personal identification number, we were able to gather information from several registers, including birth data, all prescriptions of psychotropic drugs (which can only be obtained by prescription in Denmark), data on hospital contacts with psychiatric disease or diabetes, as well as death, emigration, country of origin, maternal education, and somatic comorbidity. However, it is a limitation that the register data did not include information on BMI or lifestyle during the life course and, thus, on the risk of unmeasured confounding. This was

| Table 2 | Association between number of different psychotropic medications and type 2 diabetes in the study population and by different categories of birth weight and ponderal index. |
|---------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Number of medication used | No. total | No. T2D | HR (95% CI) |
| All study members | No psychotropic medication | 2043 | 46 | 1 [reference] |
| One type | 12,512 | 470 | 2.08 (1.54–2.83) |
| Two types | 14,970 | 737 | 3.05 (2.26–4.12) |
| Three types | 7432 | 322 | 3.79 (2.77–5.17) |
| Birth weight | 2500 g | | |
| No | 324 | 10 | 1.32 (0.64–2.70) |
| One type | 2103 | 98 | 2.36 (1.57–3.56) |
| Two types | 2483 | 169 | 4.12 (2.79–5.36) |
| Three types | 1173 | 80 | 5.32 (3.49–8.12) |
| 2600–3900 g | No | 1455 | 30 | 1 [reference] |
| One type | 8545 | 324 | 2.16 (1.49–3.15) |
| Two types | 8741 | 488 | 3.42 (2.36–4.95) |
| Three types | 4717 | 224 | 4.20 (2.86–6.16) |
| >4000 g | No | 222 | 6 | 1.38 (0.57–3.33) |
| One type | 1233 | 48 | 2.17 (1.37–3.42) |
| Two types | 1426 | 80 | 3.83 (2.52–5.83) |
| Three types | 672 | 18 | 2.35 (1.30–4.22) |
| Ponderal index | 1st quintile | No | 392 | 15 | 2.10 (1.07–4.10) |
| One type | 2598 | 107 | 2.63 (1.63–4.25) |
| Two types | 3116 | 194 | 4.93 (3.11–7.82) |
| Three types | 1507 | 88 | 5.95 (3.65–9.69) |
| 2nd–4th quintile | No | 1208 | 20 | 1 [reference] |
| One type | 7237 | 262 | 2.65 (1.68–4.17) |
| Two types | 8443 | 401 | 4.19 (2.67–6.57) |
| Three types | 4077 | 183 | 5.12 (3.22–8.13) |
| 5th quintile | No | 428 | 11 | 1.89 (0.90–3.96) |
| One type | 2463 | 99 | 3.46 (2.14–5.61) |
| Two types | 2755 | 141 | 5.34 (3.34–8.53) |
| Three types | 1268 | 50 | 5.15 (3.06–8.66) |
evaluated using E-value, where a large E-value implies that considerable unmeasured confounding is needed to explain the effect estimate. In the present study the identified E-values were generally quite large (range: 1.3 to 10), which indicate that unmeasured confounding for most of the associations should be rather large to explain the identified associations.

Another limitation of this study is that the National Prescription Registry only holds information on medical prescriptions from 1995. Consequently, we did not have any medical data on individuals before the age of 16–22 years. Another limitation is the lack of information on medication use in hospitals. Some individuals may receive psychotropic medication in outpatient clinics and not all medication is registered. Furthermore, we can only identify redeemed prescriptions of a psychotropic drug and not whether the patients take the medication. In fact, a review of adherence to antipsychotic medications in patients diagnosed with psychosis found a mean rate of adherence of 42%. A later systematic review showed that adherence was a problem especially in younger patients, and since our population was quite young, a certain degree of non-adherence would be expected. However, this is not likely to explain our results, since non-adherence would only tend to drive the association towards the null hypothesis. Furthermore, we cannot reject that individuals who were prescribed psychotropic medication had a different, potentially more thorough, screening for diabetes, which could explain the higher rates in these groups. As mentioned previously, we did not separate between the different antipsychotic medications because many patients shifted treatment during

| Medication use | No. total | No. T2D | HR (95 % CI) |
|---------------|----------|---------|-------------|
| Any use of antipsychotic medication | | | |
| BW ≤ 2500 g | No | 2,480 | 97 | 1.05 (0.84-1.32) |
| | Yes | 4,175 | 260 | 1.98 (1.66-2.35) |
| BW 2600-3900 g | No | 10,314 | 325 | 1 [reference] |
| | Yes | 16,151 | 741 | 1.67 (1.45-1.92) |
| BW ≥ 4000 g | No | 1,488 | 50 | 1.09 (0.81-1.47) |
| | Yes | 2,349 | 102 | 1.58 (1.26-1.99) |
| Any use of mood stabilizers | | | |
| BW ≤ 2500 g | No | 4,943 | 262 | 1.12 (0.98-1.30) |
| | Yes | 1,712 | 95 | 1.72 (1.38-2.13) |
| BW 2600-3900 g | No | 19,726 | 806 | 1 [reference] |
| | Yes | 6,739 | 260 | 1.44 (1.25-1.66) |
| BW ≥ 4000 g | No | 2,860 | 125 | 1.08 (0.89-1.30) |
| | Yes | 977 | 27 | 1.01 (0.68-1.48) |
| Any use of antidepressant medication | | | |
| BW ≤ 2500 g | No | 740 | 36 | 1.31 (0.90-1.92) |
| | Yes | 5,915 | 321 | 2.44 (1.93-3.08) |
| BW 2600-3900 g | No | 3,093 | 95 | 1 [reference] |
| | Yes | 23,372 | 971 | 2.15 (1.73-2.67) |
| BW ≥ 4000 g | No | 479 | 19 | 1.25 (0.76-2.05) |
| | Yes | 3,358 | 133 | 2.07 (1.58-2.70) |

Fig. 3. Association between psychotropic medication use and type 2 diabetes in different birth weight categories.
follow-up and it would complicate the analytical model to address this without determining on the future. Another limitation is the lack of information on gestational age, which was missing in the Medical Birth Register for more than half of the individuals included. Finally, since our population was quite young (mean age at baseline: 29.2 years) and because we only followed individuals for a mean of 10 years, we were only able to examine the onset of type 2 diabetes before the age of 45 and we did not differentiate between type 2 diabetes, or prediabetes.

5. Conclusion

Young adults with severe mental illness and low birth weight had the highest risk of type 2 diabetes. Use of antipsychotics was also associated with higher risk of type 2 diabetes, but neither birth weight nor ponderal index modified the association between psychotropic medication and type 2 diabetes. Therefore, our study does not support that indicators of nutritional thrift due to gestational malnourishment influence the dia-

betogenic effect of psychotropics.

Data approvals

The study was approved by the Danish Data Inspection. The data that support the findings of this study are available from Statistics Denmark. Restrictions apply to the availability of the data that were used under license for this study.

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CRediT authorship contribution statement

The data that support the findings of this study are available from Statistics Denmark. Restrictions apply to the availability of the data that were used under license for this study.

Declaration of competing interest

All authors report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jdiacomp.2020.108181.
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