# Psychiatric Morbidity in Women With Previous Gestational Diabetes Mellitus

## A Nationwide Register-Based Cohort Study

Christensen, Maria Hornstrup; Andersen, Marianne Skovsager; Rubin, Katrine Hass; Nohr, Ellen Aagaard; Aalders, Jori; Vinter, Christina Anne; Jensen, Dorte Moeller

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**Full title**

Psychiatric morbidity in women with previous gestational diabetes mellitus – a nationwide register-based cohort study

**Short running title**

Psychiatric morbidity after GDM

**Author list**

Maria Hornstrup Christensen[1,2,3], Marianne Skovsager Andersen[3,4], Katrine Hass Rubin[5,6], Ellen Aagaard Nohr[2,3], Jori Aalders[1,3], Christina Anne Vinter[1,2,3], Dorte Moeller Jensen[1,2,3]

**List of affiliations**

[1] Steno Diabetes Center Odense, Odense University Hospital, Denmark

[2] Department of Gynecology and Obstetrics, Odense University Hospital, Denmark

[3] Department of Clinical Research, University of Southern Denmark, Denmark

[4] Department of Endocrinology, Odense University Hospital, Denmark

[5] Research unit OPEN, Department of Clinical Research, University of Southern Denmark, Denmark

[6] OPEN - Open Patient data Explorative Network, Odense University Hospital, Denmark

**Author details**

Name: Maria Hornstrup Christensen

Highest academic degree: Master of Health Science

ORCID identifier: 0000-0002-4985-4491

Affiliations: [1] Steno Diabetes Center Odense, Odense University Hospital, Denmark

[2] Department of Gynecology and Obstetrics, Odense University Hospital, Denmark

[3] Department of Clinical Research, University of Southern Denmark, Denmark

Name: Marianne Skovsager Andersen

Highest academic degree: DMSc, PhD, Professor

ORCID identifier: 0000-0002-4603-9504

Affiliations: [3] Department of Clinical Research, University of Southern Denmark, Denmark

[4] Department of Endocrinology, Odense University Hospital, Denmark

Name: Katrine Hass Rubin
Highest academic degree: PhD, Associate professor
ORCID identifier: 0000-0001-5045-536X
Affiliations: [5] Research unit OPEN, Department of Clinical Research, University of Southern Denmark, Denmark
[6] OPEN - Open Patient data Explorative Network, Odense University Hospital, Denmark

Name: Ellen Aagaard Nohr
Highest academic degree: PhD, Professor
ORCID identifier: 0000-0001-7039-1105
Affiliations: [2] Department of Gynecology and Obstetrics, Odense University Hospital, Denmark
[3] Department of Clinical Research, University of Southern Denmark, Denmark

Name: Jori Aalders
Highest academic degree: PhD
ORCID identifier: 0000-0002-7207-8304
Affiliations: [1] Steno Diabetes Center Odense, Odense University Hospital, Denmark
[3] Department of Clinical Research, University of Southern Denmark, Denmark

Name: Christina Anne Vinter
Highest academic degree: PhD, Associate professor
ORCID identifier: 0000-0001-5084-6053
Affiliations: [1] Steno Diabetes Center Odense, Odense University Hospital, Denmark
[2] Department of Gynecology and Obstetrics, Odense University Hospital, Denmark
[3] Department of Clinical Research, University of Southern Denmark, Denmark

Name: Dorte Moeller Jensen
Highest academic degree: DMSc, PhD, Professor
ORCID identifier: 0000-0002-3298-9824

Affiliations: [1] Steno Diabetes Center Odense, Odense University Hospital, Denmark
[2] Department of Gynecology and Obstetrics, Odense University Hospital, Denmark
[3] Department of Clinical Research, University of Southern Denmark, Denmark

**Contact information of the corresponding author**

Name: Maria Hornstrup Christensen

E-mail: maria.hornstrup.christensen@rsyd.dk

Phone: +45 25388718

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**Twitter summary**

This nationwide register-based study from Denmark shows that women with previous gestational diabetes mellitus have an increased risk of developing psychiatric morbidity later in life.

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**Abbreviation list**

| | |
|---|---|
| aHR | Adjusted hazard ratio |
| BMI | Body mass index |
| CI | Confidence interval |
| GDM | Gestational diabetes mellitus |

| | |
|---|---|
| HR | Hazard ratio |
| IQR | Interquartile range |
| PCOS | Polycystic ovary syndrome |

**Abstract**

*Objective*

To investigate associations between previous gestational diabetes mellitus (GDM) and incident psychiatric morbidity. Additionally, to explore the role of subsequent diabetes mellitus development in psychiatric morbidity risk.

*Research design and methods*

A nationwide register-based cohort study including all women delivering in Denmark from 1997 to 2018 was conducted. GDM exposure was based on diagnosis code, whereas psychiatric morbidity outcome was based on diagnosis codes and psychopharmacological medication use. Multiple Cox regression and mediation analyses were performed.

*Results*

In a study population of 660,017 women, previous GDM was associated with increased risks of depression based on diagnosis code and/or medication use (adjusted hazard ratio [aHR] 1.22 [95% CI 1.18–1.27]), any psychiatric diagnosis (aHR 1.20 [95% CI 1.13–1.27]), and any psychopharmacological medication use (aHR 1.21 [95% CI 1.17–1.25]). Moreover, risks of depressive and anxiety disorders, as well as antidepressant and antipsychotic medication use were

increased, with aHRs ranging from 1.14 [95% CI 1.05–1.25] to 1.32 [95% CI 1.22–1.42]. No associations were found regarding substance use disorders, psychotic disorders, bipolar disorders, postpartum psychiatric disease, and anxiolytic medication use. Psychiatric morbidity risk was higher in women with than without subsequent diabetes development. However, GDM history only impacted risk estimates in women without subsequent diabetes. Subsequent diabetes mediated 35-42% of the associations between GDM and psychiatric morbidity.

*Conclusions*

GDM was associated with increased psychiatric morbidity risk. Subsequent diabetes development played a significant role in the future psychiatric morbidity risk after GDM, although it only partly explained the association.

**Article highlights**

a) Gestational diabetes mellitus (GDM) potentially increases the risk of developing psychiatric morbidity later in life, and the role of subsequent diabetes mellitus development is unknown.
b) We investigated the risks of psychiatric morbidity outcomes according to GDM history and explored whether the risks were affected by subsequent diabetes.
c) GDM was associated with an increased risk of some, but not all, psychiatric morbidity outcomes; subsequent diabetes development played a significant role in the association.
d) Special attention is warranted for the long-term mental health of women with previous GDM.

**(Introduction)**

Gestational diabetes mellitus (GDM), a common pregnancy complication, is characterized by hyperglycemia due to a combination of physiological pregnancy-induced insulin resistance and insufficient insulin response. GDM risk factors include advanced maternal age, overweight/obesity, polycystic ovary syndrome (PCOS), specific ethnicities, higher parity, and previous GDM (1). GDM is associated with an increased risk of complications related to pregnancy, delivery, and the immediate postpartum period (1-3). The risk increases with increasing blood glucose levels (4); therefore, additional perinatal care and examinations are recommended for women diagnosed with GDM, including counseling on diet and exercise, and introduction of insulin treatment, if needed (1, 3). After delivery, glucose metabolism generally normalizes (1), but women with GDM have an increased long-term risk of developing manifest diabetes mellitus (mainly type 2 diabetes) (5), as well as metabolic morbidity (6, 7) and cardiovascular disease (7, 8) compared with women without previous GDM.

In addition to physical morbidity, women with previous GDM may have an increased risk of developing psychiatric morbidity later in life; however, the existing evidence is limited. Two recent meta-analyses found an increased risk of postpartum depression in women with previous GDM (9, 10), whereas evidence regarding incident anxiety disorders is scarce and provides conflicting results (11). Only two studies have examined the risk of depression beyond the 1-year postpartum period (12, 13); moreover, psychiatric disorders beyond depression and anxiety have only been investigated in one other study using a composite score of psychiatric morbidity (12). Thus, population-based data on the long-term risk of overall and subcategorized psychiatric morbidity in women with previous GDM are lacking and will provide novel insight. The development of subsequent diabetes is more common in women with than without GDM; in addition, diabetes is a well-established risk factor of depression (14). Hence, GDM and incident psychiatric morbidity

may be linked through subsequent diabetes development; however, the role of subsequent diabetes in the association between GDM and psychiatric morbidity is unknown. Finally, psychiatric disorders are associated with diabetes development (15), and diabetes complications (16) and can adversely affect the mother-child bond and child development (17); therefore, it is important to clarify the risk of psychiatric disorders after GDM while additionally considering subsequent diabetes development.

The overall aim of this study was to examine the long-term psychiatric morbidity in women with previous GDM based on data from national registers on the complete population of delivering women in Denmark in 1997–2018. The research objectives were (1) to compare the risk of incident psychiatric morbidity in women with and without previous GDM; (2) to investigate the role of subsequent diabetes development in the association between previous GDM and incident psychiatric morbidity; and (3) to quantify the potential mediating effect of subsequent diabetes in the abovementioned association.

## Research design and methods

### *Study design and data sources*

This nationwide, register-based cohort study included data from registers provided by Statistics Denmark and The Danish Health Data Authority. In Denmark, data on a large range of sociodemographic, economic, and health care variables, including redemptions of prescribed medications, are prospectively collected and stored in national registers from which these data can be linked at individual level (18-20). Data were extracted from the Danish Medical Birth Register, which contains data on all pregnancies and deliveries in Denmark (21). The cohort was enriched with data on inpatient, outpatient, and emergency department contacts at psychiatric and non-

psychiatric hospitals from the Danish National Patient Registry (22, 23). The Danish National Prescription Register provided data on redemptions of prescribed psychopharmacological medications (24) and demographic and socioeconomic data were extracted from relevant registers (25-27).

*Study population*

The inclusion criterion was delivery during the study period from 1/1/2017 to 31/12/2018. Women were considered as the study unit, and the index date was defined as date of conception in the index pregnancy, i.e., the first pregnancy during the study period. Women with preexisting diabetes and/or preexisting psychiatric morbidity at or up to 2 years prior to the index date were excluded. The 2-year time frame was adopted to ensure identical criteria for all women (study data were available from 1995 and onwards; study period commenced in 1997). Descriptions of diagnosis codes and medications are listed in Supplemental Table S1. Women with missing data on the *a priori* defined demographic/socioeconomic covariates included in the main adjusted analyses were excluded.

*Exposure*

GDM exposure, based on diagnosis code, was defined as ≥1 pregnancies with GDM during the study period. To address potential change in exposure status in case of women with additional pregnancies during the study period, GDM was considered as a time-varying exposure; hence, a correct classification of each pregnancy was possible. In Denmark, screening for GDM is based on an individual risk factor assessment (28).

*Outcomes*

Psychiatric morbidity was based on selected psychiatric diagnosis codes and/or ≥2 redemptions of prescribed psychopharmacological medications from 6 weeks after delivery (Supplemental Table S1). The primary outcome was 'depression' (composite of diagnosis codes of depressive disorders and/or ≥2 redemptions of antidepressants). Secondary outcomes were 'any psychiatric diagnosis' (composite of diagnosis codes of depressive disorders, anxiety disorders, bipolar disorders, psychotic disorders, and/or postpartum psychiatric disease) and the use of 'any psychopharmacological medication' (composite of ≥2 redemptions within each group of psychopharmacological medications [antidepressants, antipsychotics, and anxiolytics]). Additionally, to address each of the subcategories in the outcome composites, data on the subcategories were analyzed separately. Over time, women may receive several different psychiatric diagnoses/medications, and each woman may therefore be represented in more than one outcome category.

*Follow-up and risk time*

Follow-up and risk time contribution commenced 6 weeks after delivery (marking the end of the immediate postpartum period) and continued until outcome occurrence, death, emigration, or 31/12/2018, whichever occurred first. The risk time spent during any subsequent pregnancy was extracted from the total follow-up period. As GDM was a time-varying exposure, the categorization of subsequent risk time as either 'exposed' or 'unexposed' was subject to potential change. However, once GDM occurred, all subsequent risk time was considered 'exposed'.

*Covariates*

Based on existing literature, covariates from the index pregnancy were *a priori* identified as potential confounders or intermediate factors. Table 1 and Supplemental Table S1 present details on categorizations and definitions. The potential confounders were selected demographic/socioeconomic covariates: maternal age, parity, preexisting comorbidity (29), ethnicity, marital status, income level, education level, occupation, and calendar year of delivery. The potential intermediate covariates of the association between GDM and incident psychiatric morbidity were selected pregnancy complications: preeclampsia, gestational hypertension, preterm delivery, induced labor, cesarean section, stillbirth, and offspring malformations.

*Statistical analyses*

Comparisons of baseline characteristics between women with and without GDM were performed using the Wilcoxon rank-sum test and $chi^2$-test. Cox regression models were used to estimate crude and adjusted hazard ratios (aHR), including 95% confidence intervals (CI) using women without GDM as reference. As each woman could contribute with more than one pregnancy during the study period, repeated measurements from the same woman were taken into account by clustering on each woman in the model specification. The assumption of proportional hazards was tested, and interaction terms were included in the final adjusted model in case of non-proportional hazards, preceded by a likelihood ratio test for model fit.

Missing data regarding pregestational BMI and smoking were expected, as these data were not registered until late 2003 and 1997, respectively. Therefore, these variables were not included in the main analyses but handled in separate sensitivity analyses. For missing data regarding gestational age (<2%), imputation was performed using the mean value.

Subsequent diabetes development was defined as diabetes diagnosis code and/or ≥2 redemptions of antidiabetic agents after delivery and prior to psychiatric morbidity outcome occurrence (Supplemental Table S1). To address the role of subsequent diabetes in the future psychiatric morbidity risk according to GDM history, 'previous GDM' and 'subsequent diabetes development' were included as interaction terms in an additional analysis of the Cox regression models, including a likelihood ratio test for model fit. Therefore, risk estimates were produced for the study population when stratified into four mutually exclusive groups: (1) women without previous GDM and no subsequent diabetes (*no GDM and no diabetes*), (2) women with previous GDM and no subsequent diabetes (*GDM and no diabetes*), (3) women without previous GDM who subsequently developed diabetes (*no GDM and then diabetes*), and (4) women with previous GDM who subsequently developed diabetes (*GDM and then diabetes*).

Additionally, mediation analyses were performed to quantify the potential mediating effect of subsequent diabetes development after pregnancy and prior to outcome occurrence in the association between GDM and psychiatric morbidity. These analyses were based on a counterfactual framework (30), according to which the total effect of an exposure (i.e., GDM) on the outcome incidence (i.e., psychiatric morbidity) can be decomposed into components, one of which resembles the mediated effect by the mediator included within the model (i.e., subsequent diabetes). The aHRs were computed by first *not including* 'subsequent diabetes', and then *including* 'subsequent diabetes' in the Cox regression models. Thereafter, the quantification of the proportion mediated effect was estimated for the outcomes resulting in significant associations in the analyses both excluding and including 'subsequent diabetes'. The proportion mediated effect was reported as proportions with corresponding 95% CIs obtained using bootstrapping with 100 replicates.

All statistical analyses were performed using STATA 17 software (StataCorp, College Station, TX). P-values <0.05 were considered statistically significant.

*Sensitivity analyses*

A series of sensitivity analyses were conducted. In order to minimize the risk of misclassifying GDM exposure, we restricted the study population to women with 1) no previous deliveries before study entry and 2) GDM diagnosis code after gestational week 20 and no diagnosis code for diabetes registered during the same pregnancy. To investigate whether potential bias was introduced due to imputation for missing data on gestational age at delivery, women with missing data on this covariate were excluded. Furthermore, women with missing data on the selected confounders were included in the study population, using missing-categories for the missing data. Subsequently, confounder adjustment was expanded by individually including covariates from the index pregnancy in the model: pregestational BMI, smoking, multiple pregnancy, preexisting PCOS, and preexisting metformin treatment. Finally, women with selected pregnancy complications during the index pregnancy were excluded.

*Ethical approval*

No ethical approval was required (assessment by The Regional Committees on Health Research Ethics for Southern Denmark, 20192000-27). However, the study was approved by the Danish Data Protection Agency (19/11440).

*Data and resource availability*

The dataset is not publicly available due to Danish legislation concerning personalized data. Access to the dataset has been authorized restrictively to the authors by the Danish National Health Data Authority; other researchers are eligible to apply for access.

## Results

*Study population*

In total, 758,978 women delivered from 1997 to 2018. Women with preexisting diabetes (n=3,323), preexisting psychiatric morbidity (n=50,207), and missing data on the selected covariates (n=45,431) were excluded. The resulting study population consisted of 660,017 women (Supplemental Figure S2). Of these, 20,663 (3.1%) were registered with GDM in ≥1 delivery during the study period. Follow-up periods ranged from 0 to 21.9 years, with medians differing from 9.5 (interquartile range [IQR] 4.0–16.4) to 12.4 years (IQR 5.6–18.0) depending on outcome category. Subsequent diabetes development occurred in 17.3% and 1.4% of women with and without GDM, respectively. Women were censored from the Cox regression analyses, if psychiatric morbidity occurred during the time period from the index date to the beginning of follow-up (i.e., 6 weeks postpartum) as they were then not considered as being at risk during the follow-up period. This reduced the total number of women eligible for these analyses to 656,783.

*Baseline data*

Clinical, demographic, and obstetric characteristics in the index pregnancy for women with and without GDM are shown in Table 1. The two groups differed significantly in terms of almost all parameters. Compared to women without GDM, a greater proportion of women with GDM were

aged above 30 years, overweight/obese, primiparous, of non-Danish ethnicity, non-smokers, from the low- and high-income tertiles, and at lower educational levels; moreover, they were more often in the "under education" or "early retirement" categories. Pregnancy and labor complications were more prevalent in women with GDM.

*Incidence of psychiatric morbidity*

Table 2 shows associations between previous GDM and incident psychiatric morbidity. Previous GDM was associated with a significantly increased risk of depression, any psychiatric diagnosis and the use of any psychopharmacological medication, with aHRs ranging from 1.20 [95% CI 1.13–1.27] to 1.22 [95% CI 1.18–1.27]. The findings were similar for the subcategory outcomes depressive disorders, anxiety disorders, antidepressant medication use, and antipsychotic medication use, with aHRs ranging from 1.14 [95% CI 1.05–1.25] to 1.32 [95% CI 1.22–1.42]. Risks of incident diagnosis of psychotic disorder, bipolar disorder, substance use disorder, postpartum psychiatric disease, and anxiolytic medication use were similar in women with and without previous GDM.

Generally, the sensitivity analyses produced risk estimates equaling those of the main analyses (data not shown). Minor differences were found when women with previous deliveries prior to the study period were excluded. When pregestational BMI was included in the adjusted analyses (n=342,572), the risk estimates were lower, although the differences remained statistically significant (Supplemental Table S3). After excluding women with selected pregnancy complications, risk estimates remained relatively unchanged; however, the risk of antipsychotic medication use lost significance.

*Role of subsequent development of diabetes*

Figure 1 depicts the risk of incident psychiatric morbidity according to previous GDM, considering subsequent diabetes development. Overall, risk of psychiatric morbidity was higher in women who subsequently developed diabetes compared with women without subsequent diabetes. Specifically in women without subsequent diabetes, GDM was associated with a significantly increased risk of psychiatric morbidity, with aHRs ranging from 1.15 [95% CI 1.08–1.23] to 1.18 [95% CI 1.13–1.23]. This pattern of increased risk related to GDM history was not similarly seen in women who subsequently developed diabetes; however, the risk estimates were higher in women with than without subsequent diabetes.

*Quantification of mediation by subsequent diabetes*

Results of the mediation analyses are presented in Table 3. Subsequent diabetes development significantly mediated the association between previous GDM and incident depression by 35.7% [95% CI 27.3–44.2%]. Similarly, diabetes was found to have a mediating effect on the incidences of all other psychiatric outcome categories that were significantly associated with previous GDM; the mediation analyses produced estimated proportions of mediation ranging from 35.0% [95% CI 11.1–59.0] to 42.2% [95% CI 27.5–57.0].

## Conclusions

This large nationwide cohort study provides novel insight as it is the first study to examine the risk of a variety of psychiatric disorders after GDM beyond the 1-year postpartum period. Overall, significant associations between previous GDM and incident psychiatric morbidity were observed.

Subsequent diabetes development played a significant role in the future psychiatric morbidity risk, although it only partly explained the associations between GDM and psychiatric morbidity.

*Incidence of psychiatric morbidity*

Our study showed that GDM was associated with an increased risk of incident depression. This is in line with the findings of studies focusing on the risk of depression after GDM up to 1 year postpartum (9). However, our results contrast with a study from the United States (n=18,109), which reported a similar, confounder-adjusted risk of depression in women with and without GDM after approximately 4 years of follow-up (12). This difference may be explained by the longer follow-up period and the larger study population in our study.

Our study also demonstrated a clear and not previously reported increased risk of developing anxiety disorders in women with previous GDM compared with women without a GDM history. This finding differed from those of previous studies (12, 31, 32), probably due to the use of self-reported anxiety symptoms (31, 32), shorter follow-up periods, and smaller study populations in the previous studies (12, 31, 32).

To our knowledge, only one other large-scale study has examined risk of psychiatric disorders other than depression and anxiety after GDM; the study investigated a composite score of mental health disorders, excluding depression and anxiety. They found a similar psychiatric morbidity risk among women with and without previous GDM (12). In our study, we reported data on type-specific subcategories of psychiatric morbidity outcomes and found that the risks of being diagnosed with bipolar disorders, psychotic disorders, substance use disorders, and postpartum psychiatric disease were comparable in women with and without previous GDM. The difference in the risk of requiring anxiolytic medication according to previous GDM was also insignificant. Thus, our study showed

that the increased psychiatric morbidity after GDM was constituted by diagnoses of depressive and anxiety disorders as well as the use of antidepressant and antipsychotic medications, whereas the other investigated psychiatric outcomes appeared to be unrelated to GDM history.

*Role of subsequent development of diabetes*

This study provides unprecedented results regarding the role of subsequent diabetes development on the psychiatric morbidity risk in relation to GDM history. We found that whether or not a woman developed diabetes subsequently, constituted a significant role in the association between previous GDM and the future risk of psychiatric morbidity. In women without subsequent diabetes, previous GDM was associated with a modestly increased risk of psychiatric morbidity. Women with subsequent diabetes had a much higher risk of developing psychiatric disorders compared with women without subsequent diabetes; however, a history of GDM did not seem to substantially affect the future risk of psychiatric morbidity in the women with subsequent diabetes as the risk estimates were relatively similar regardless of previous GDM. These findings need further exploration.

*Quantification of mediation by subsequent diabetes*

Our mediation analyses showed that subsequent diabetes development contributed substantially to the risk of incident psychiatric morbidity. The associations between GDM and psychiatric morbidity were mediated by subsequent diabetes by approximately 40%, implying that the associations were only partly mediated by subsequent diabetes; thus, a direct association between GDM and incident psychiatric morbidity remained. This pattern of mediation was observed

consistently for all outcomes that were significantly associated with previous GDM. In studies among people with type 2 diabetes, both shared and causal physiological and psychological mechanisms have been proposed to explain the link between diabetes and depression (33). Next to incident diabetes, mechanisms linking GDM to psychiatric disorders could be negative self-perceptions in connection with a GDM diagnosis (34), awareness of increased diabetes risk, and increased parenting stress due to more adverse outcomes observed among offspring of women with GDM (35, 36). More research is warranted to clarify the link between GDM and incident psychiatric disorders. To our knowledge, the mediating role of diabetes has not previously been quantified with regard to incident psychiatric morbidity after GDM; however, a study found that type 2 diabetes mediated the association between GDM and incident cardiovascular disease by 23% (37). Thus, subsequent diabetes seems to play a profound mediating role in the future morbidity after GDM, yet does not exclusively account for it. The prevention of subsequent diabetes after GDM can potentially reduce not only diabetes but also the risk of other morbidity types.

*Strengths and limitations*

A major strength of this study was the large study population size and, specifically, that it included the complete population of delivering women in Denmark during a 22-year period minimizing the risk of selection bias.. Furthermore, this approach facilitated an unprecedented, population-based insight into the long-term mental health implications beyond the postpartum period as we addressed previously unexplored conditions.

GDM exposure and psychiatric morbidity outcomes were based on register data that were considered valid and reliable for health research (22, 38). Although prior research has shown that a GDM diagnosis based solely on diagnosis codes is valid, this strategy potentially underestimates the

future health consequences of GDM due to misclassification (38). By considering GDM as a time-varying exposure, we optimized insights into the implications of GDM, as the strategy facilitated full exposure history in each woman during the entire study period. Thus, exposure status was not limited to a selected/random pregnancy. The outcome categories, including depressive and anxiety disorders, were analyzed as distinct conditions although they may co-occur and present similar traits. Both diagnosis codes and medication use were addressed, which constituted a valuable strategy as it also enabled investigation into the proportion of women experiencing psychiatric conditions without assigned hospital diagnosis codes. The latter group received psychopharmacological medication prescribed exclusively from the primary health care sector, which accounts for most cases with mild to moderate mental illness (22). Through this strategy, we obtained a more clinically relevant and extensive insight into the mental health implications of GDM. Requiring at least two redemptions further qualified and validated the use of redemptions as indicative of morbidity. Potential confounding and influence of pregnancy/labor complications were addressed and sensitivity analyses were performed to test the robustness of the findings.

Our study had some limitations. As the scope was to investigate incident psychiatric morbidity, we excluded women with preexisting psychiatric morbidity within 2 years prior to the index date. However, some women may have been diagnosed/medicated prior to the 2-year period and thus not correctly excluded from the study. This would result in a misinterpretation of an incident outcome that was rather a recurrent condition. Psychiatric illness may increase the GDM risk (39). Psychiatric illnesses often co-occur, and depression is known to be recurrent (40); hence, the GDM-related risk on psychiatric morbidity might have been overestimated. Moreover, the use of prescribed psychopharmacological medication only resembled a proxy for psychiatric morbidity as these medications have heterogeneous and also non-psychiatric indications; this is an important limitation. Regarding GDM exposure, this may be underestimated due to the selective rather than

universal screening in Denmark. In addition, GDM exposure may be misclassified, as some women classified as non-GDM may experience GDM pregnancies after the study period. However, this would generate more conservative results. Another important limitation of this study design is the definition of subsequent diabetes, which was defined as incidence of diagnosis code and/or antidiabetic medication. Thus, we were not able to address unknown/undiagnosed diabetes, or to explore whether the mediation by subsequent diabetes reflected biological/physiological and/or psychological mechanisms. Additionally, in the mediation analysis, some women diagnosed with GDM may have had undiagnosed type 2 diabetes instead. Data on potential confounders were derived from the index pregnancy; such data might not be representative in subsequent pregnancies or in later life. Further, some data were self-reported with potential limited validity. As obesity and depression are linked, the inability to adjust for BMI beyond pregestational BMI at the index pregnancy, is a noteworthy limitation. Furthermore, it was beyond the scope of this study to explore the incidence of additional comorbidities developing after GDM, which might influence future psychiatric morbidity risk. Residual confounding also remained a limitation. Other statistical approaches could have been chosen, including a multiple outcome approach hereby addressing correlations between outcomes, which could have further elucidated the interdependence between psychiatric outcomes. However, in a large study population like ours, such an approach would be computationally infeasible and also, the interpretation of results would be too complex. Finally, surveillance bias might be a concern; women with GDM were recommended to be followed up by a general practitioner at an interval of 1-3 years (28). Such women might be more prone to be diagnosed/medicated, which may overestimate the incidence of psychiatric morbidity in women with than without previous GDM. The generalizability of the study findings is potentially restricted. The Danish health care system provides free access to most services, and the Danish population is

relatively homogenous with regard to race/ethnicity. Thus, our findings may not necessarily be applicable to countries with different health care systems and race/ethnicity profiles.

In conclusion, we found that previous GDM was significantly associated with an overall higher risk of incident psychiatric morbidity (especially depression and anxiety), whereas other psychiatric outcomes were not related to GDM history. Subsequent diabetes development played an important role in the association between previous GDM and the future psychiatric morbidity risk; however, it only partly explained the association. The findings highlight the importance of special attention to the long-term mental health of women with previous GDM, irrespective of subsequent diabetes. Further research is needed to address the development of strategies for prevention, detection, and management of psychiatric morbidity in women with previous GDM.

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**Tables**

**Table 1 –** Clinical, demographic, and obstetric characteristics from index pregnancy according to GDM in women delivering in Denmark in 1997-2018

| | **GDM** ***n* = 20,663** | **No GDM** ***n* = 639,354** | **p-value** |
|---|---|---|---|
| ***Clinical characteristics*** | | | |
| Maternal age (years) | 28 (25–32) | 28 (25–31) | <0.001 |
| <20 | 500 (2.4) | 20,482 (3.2) | <0.001 |
| 20-24 | 3,532 (17.1) | 115,943 (18.1) | <0.001 |
| 25-29 | 7,891 (38.2) | 260,456 (40.7) | <0.001 |
| 30-34 | 5,704 (27.6) | 173,352 (27.1) | 0.118 |
| 35-39 | 2,498 (12.1) | 59,825 (9.4) | <0.001 |
| ≥40 | 538 (2.6) | 9,296 (1.5) | <0.001 |
| Primiparity | 17,332 (83.9) | 494,231 (77.3) | <0.001 |
| Pregestational BMI (kg/m$^2$)* | 27.1 (23.0–31.6) | 22.8 (20.7–25.7) | <0.001 |
| Underweight (BMI<18.5) | 266 (1.9) | 14,686 (4.4) | <0.001 |
| Normal weight (BMI 18.5–24.9) | 4,849 (35.0) | 218,974 (66.0) | <0.001 |
| Overweight (BMI 25–29.9) | 4,217 (30.4) | 65,146 (19.6) | <0.001 |
| Obesity (BMI ≥30) | 4,532 (32.7) | 32,814 (9.9) | <0.001 |
| Smoking during pregnancy† | 2,935 (15.6) | 89,604 (16.3) | 0.017 |
| No comorbidity‡ | 20,399 (98.7) | 633,517 (99.1) | <0.001 |
| ***Demographic characteristics*** | | | |
| Ethnicity | | | |
| Danish | 16,230 (78.5) | 561,818 (87.9) | <0.001 |
| Immigrant, Western | 579 (2.8) | 20,461 (3.2) | 0.001 |
| Immigrant, Non-Western | 3,338 (16.2) | 47,209 (7.4) | <0.001 |
| Descendant§ | 516 (2.5) | 9,866 (1.5) | <0.001 |
| Marital status | | | |
| Single/not living with a partner | 2,268 (11.0) | 73,726 (11.5) | 0.014 |
| Married/living with a partner | 18,395 (89.0) | 565,628 (88.5) | 0.014 |
| Income | | | |
| Low tertile | 6,479 (31.4) | 196,401 (30.7) | 0.051 |
| Middle tertile | 6,538 (31.6) | 219,893 (34.4) | <0.001 |
| High tertile | 7,646 (37.0) | 223,060 (34.9) | <0.001 |
| Highest completed education | | | |
| Lower secondary | 4,430 (21.4) | 116,270 (18.2) | <0.001 |
| Upper secondary | 8,768 (42.4) | 270,770 (42.4) | 0.813 |
| Post-secondary | 7,465 (36.1) | 252,314 (39.5) | <0.001 |

| | | | |
|---|---|---|---|
| Occupation | | | |
| Employed | 14,760 (71.4) | 468,408 (73.3) | <0.001 |
| Unemployed or on welfare payment | 2,231 (10.8) | 82,953 (13.0) | <0.001 |
| Under education | 2,301 (11.1) | 58,098 (9.1) | <0.001 |
| Early retirement | 149 (0.7) | 1,885 (0.3) | <0.001 |
| ***Obstetric characteristics*** | | | |
| Previous spontaneous abortion(s) | 3,070 (14.9) | 84,823 (13.3) | <0.001 |
| Multiple pregnancy | 553 (2.7) | 14,417 (2.3) | <0.001 |
| Preeclampsia | 1,413 (6.8) | 22,085 (3.5) | <0.001 |
| Gestational hypertension | 830 (4.0) | 10,269 (1.6) | <0.001 |
| Induction of labor | 7,144 (34.6) | 95,100 (14.9) | <0.001 |
| Cesarean section | 5,853 (28.3) | 121,619 (19.0) | <0.001 |
| Gestational age at delivery (days) | 277 (268–283) | 281 (273–287) | <0.001 |
| Preterm delivery (<GA 37 weeks) | 2,075 (10.0) | 42,240 (6.6) | <0.001 |
| Stillbirth | 173 (0.8) | 2,455 (0.4) | <0.001 |
| Offspring malformation | 1,660 (8.0) | 41,620 (6.5) | <0.001 |

Data presented as median (interquartile range) or number (%)
*$n$ = 345,484
† $n$ = 569,932
‡Charlson Comorbidity Index score of 0
§Person born in Denmark by parents born outside of Denmark and without Danish citizenships
GDM, gestational diabetes mellitus; BMI, body mass index; GA, gestational age

**Table 2 –** Risk of psychiatric morbidity according to previous GDM in women delivering in Denmark in 1997-2018

| | GDM | | | No GDM | | | Hazard ratio (95% CI) | Hazard ratio (95% CI) |
|---|---|---|---|---|---|---|---|---|
| | *n* events | Risk time | IR (95% CI)* | *n* events | Risk time | IR (95% CI)* | Crude | Adjusted† |
| ***Primary outcome*** | | | | | | | | |
| **Depression‡** | 2,982 | 144,440 | 20.6 (19.9–21.4) | 106,932 | 6,555,607 | 16.3 (16.2–16.4) | 1.25 (1.20–1.29) | 1.22 (1.18–1.27) |
| ***Secondary outcomes*** | | | | | | | | |
| **Any psychiatric diagnosis§** | 1,230 | 164,260 | 7.5 (7.1–7.9) | 40,712 | 7,235,517 | 5.6 (5.6–5.7) | 1.32 (1.25–1.40) | 1.20 (1.13–1.27) |
| **Depressive disorders** | 726 | 168,848 | 4.3 (4.0–4.6) | 21,577 | 7,394,986 | 2.9 (2.9–3.0) | 1.46 (1.36–1.57) | 1.32 (1.22–1.42) |
| **Anxiety disorders** | 376 | 171,916 | 2.2 (2.0–2.4) | 11,711 | 7,481,464 | 1.6 (1.5–1.6) | 1.38 (1.25–1.53) | 1.23 (1.11–1.36) |
| **Bipolar disorders** | 60 | 174,705 | 0.3 (0.3–0.4) | 2,413 | 7,560,277 | 0.3 (0.3–0.3) | 1.05 (0.81–1.36) | 1.02 (0.79–1.32) |
| **Psychotic disorders** | 71 | 174,346 | 0.4 (0.3–0.5) | 2,670 | 7,554,021 | 0.4 (0.3–0.4) | 1.15 (0.91–1.45) | 0.95 (0.75–1.21) |
| **Substance use disorders** | 307 | 172,656 | 1.8 (1.6–2.0) | 13,117 | 7,474,855 | 1.8 (1.7–1.8) | 1.00 (0.89–1.12) | 0.96 (0.86–1.07) |
| **Postpartum psychiatric disease** | 8 | 174,841 | 0.0 (0.0–0.1) | 314 | 7,571,260 | 0.0 (0.0–0.0) | 1.23 (0.61–2.47) | 1.14 (0.56–2.31) |
| **Any psychopharmacological medication‖** | 3,112 | 141,900 | 21.9 (21.2–22.7) | 115,169 | 6,446,424 | 17.9 (17.8–18.0) | 1.21 (1.17–1.25) | 1.21 (1.17–1.25) |
| **Antidepressants¶** | 2,892 | 145,337 | 19.9 (19.2–20.6) | 104,452 | 6,579,879 | 15.9 (15.8–16.0) | 1.23 (1.19–1.28) | 1.22 (1.17–1.26) |
| **Antipsychotics¶** | 530 | 170,554 | 3.1 (2.9–3.4) | 17,509 | 7,438,797 | 2.4 (2.3–2.4) | 1.29 (1.19–1.41) | 1.14 (1.05–1.25) |
| **Anxiolytics¶** | 649 | 167,144 | 3.9 (3.6–4.2) | 28,242 | 7,266,608 | 3.9 (3.8–3.9) | 0.99 (0.92–1.07) | 1.08 (1.00–1.17) |

* IR, incidence rate presented as number of events per 1000 person-years

† Adjusted for age, parity, Charlson Comorbidity Index score, ethnicity, marital status, income, education, occupation, and calendar year of delivery

‡ Diagnoses of depressive disorder and/or ≥2 redeemed prescriptions of antidepressant medication

§ Diagnosis of depressive disorders, anxiety disorders, bipolar disorders, psychotic disorders, substance use disorders, or postpartum psychiatric disease

‖ ≥2 redeemed prescriptions within each of the groups: antidepressants, antipsychotics, or anxiolytics

¶ ≥2 redeemed prescriptions

GDM, gestational diabetes mellitus

**Table 3 –** Mediation by subsequent development of diabetes in the association between previous GDM and psychiatric morbidity

| | **$aHR_{NoDM}$ (95% CI)*** | **$aHR_{DM}$ (95% CI)†** | **Proportion mediated effect‡ % (95% CI)** |
|---|---|---|---|
| **Depression§** | 1.22 (1.18–1.27) | 1.14 (1.10–1.19) | 35.7 (27.3–44.2) |
| **Any psychiatric diagnosis‖** | 1.20 (1.13–1.27) | 1.11 (1.05–1.18) | 42.0 (26.9–56.6) |
| **Depressive disorders** | 1.32 (1.22–1.42) | 1.18 (1.09–1.28) | 42.2 (27.5–57.0) |
| **Anxiety disorders** | 1.23 (1.11–1.36) | 1.15 (1.03–1.28) | 35.0 (11.1–59.0) |
| **Bipolar disorders** | 1.02 (0.79–1.32) | 0.94 (0.72–1.22) | – |
| **Psychotic disorders** | 0.95 (0.75–1.21) | 0.88 (0.69–1.13) | – |
| **Substance use disorders** | 0.96 (0.86–1.07) | 0.92 (0.82–1.04) | – |
| **Postpartum psychiatric disease** | 1.14 (0.56–2.31) | 1.16 (0.57–2.36) | – |
| **Any psychopharmacological medication¶** | 1.21 (1.17–1.25) | 1.13 (1.09–1.17) | 36.9 (27.2–46.6) |
| **Antidepressants#** | 1.22 (1.17–1.26) | 1.14 (1.10–1.18) | 36.2 (26.9–45.5) |
| **Antipsychotics#** | 1.14 (1.05–1.25) | 1.04 (0.95–1.14) | – |
| **Anxiolytics#** | 1.08 (1.00–1.17) | 1.02 (0.94–1.11) | – |

* $aHR_{NoDM}$: Not adjusted for subsequent development of diabetes, but adjusted for age, parity, Charlson Comorbidity Index score, ethnicity, marital status, income, education, occupation, and calendar year of delivery.
† $aHR_{DM}$: Adjusted for subsequent development of diabetes and adjusted for age, parity, Charlson Comorbidity Index score, ethnicity, marital status, income, education, occupation, and calendar year of delivery.
‡ Proportion mediated effect calculated as: $(aHR_{NoDM} - aHR_{DM})/(aHR_{NoDM} - 1)$ with 95% CIs obtained by bootstrapping with 100 replicates. Only reported for outcomes with significant $aHR_{NoDM}$ and $aHR_{DM}$
§ Diagnoses of depressive disorder and/or ≥2 redeemed prescriptions of antidepressant medication
‖ Diagnosis of depressive disorders, anxiety disorders, bipolar disorders, psychotic disorders, substance use disorders, or postpartum psychiatric disease
¶ ≥2 redeemed prescriptions within each of the groups: antidepressants, or antipsychotics or anxiolytics
# ≥2 redeemed prescriptions
GDM, gestational diabetes mellitus; DM, subsequent diabetes mellitus

## Figure legends:

**Figure 1 –** Risk of psychiatric morbidity according to previous GDM and subsequent development of diabetes

White circles = women without subsequent diabetes development preceding psychiatric morbidity
Black circles = women with subsequent diabetes development preceding psychiatric morbidity
*Adjusted for age, parity, Charlson Comorbidity Index score, ethnicity, marital status, income, education, occupation, and calendar year of delivery
GDM, gestational diabetes mellitus; DM, subsequent diabetes mellitus

**Supplemental figure S2 –** Flowchart of study population

GDM, gestational diabetes mellitus

**Supplemental Table S1 –** Descriptions and definitions of variables

| | **Descriptions and definitions** |
|---|---|
| **Exclusion criteria** | At or 2 years before index date |
| Preexisting diabetes mellitus | ICD-10: E10-E14, O240-O243, O245, O249 *and/or*<br>ATC: A10 (except A10BA02) (≥2 redemptions) |
| Preexisting psychiatric morbidity | ICD-10: F00-F99 *and/or*<br>ATC: N05A, N05B, N06A (≥2 redemptions) |
| **Exposure** | |
| GDM | ICD-10: O244 (entered as a time-varying exposure in the statistical analyses) |
| **Outcomes** | From 6 weeks after date of delivery |
| *Primary outcome* | |
| Depression | ICD-10: F32-F33 *and/or*<br>ATC: N06A (≥2 redemptions) |
| *Secondary outcomes* | |
| *Psychiatric diagnosis codes* | |
| Any psychiatric diagnosis | ICD-10: F10-F19, F20-F29, F30-F31, F32-F33, F40-F41, F53 |
| Depressive disorders | ICD-10: F32-F33 |
| Anxiety disorders | ICD-10: F40-F41 |
| Bipolar disorders | ICD-10: F30-F31 |
| Psychotic disorders | ICD-10: F20-F29 |
| Substance use disorders | ICD-10: F10-F19 |
| Postpartum psychiatric disease | ICD-10: F53 |
| *Psychopharmacological medication* | |
| Any psychopharmacological medication | ATC: N05A, N05B, N06A (≥2 redemptions within each group) |
| Antipsychotics | ATC: N05A (≥2 redemptions) |
| Anxiolytics | ATC: N05B (≥2 redemptions) |
| Antidepressants | ATC: N06A (≥2 redemptions) |
| **Covariates** | Data from index pregnancy unless stated otherwise |
| Maternal age | Age in years at date of delivery |
| Primiparity<br>Parity | Firstborn child in index pregnancy<br>For confounder adjustment, parity was entered as a time-varying confounder in the Cox regression models |
| Pregestational BMI | Based on selfreported data or as measured at first antenatal visit |
| Smoking during pregnancy | Any smoking during pregnancy based on selfreported data |
| No comorbidity | Comorbidity score of 0 according to Charlson Comorbidity Index score |
| *Ethnicity* | Combination of data on ethnicity/immigration status and country of origin and divided into four categories: |
| Danish | Born in Denmark or abroad by parents where at least one parent is born in Denmark and holds Danish citizenship |
| Immigrant, Western | Born in 'Other western countries' by parents born outside of Denmark and without Danish citizenship |
| Immigrant, Non-Western | Born in 'Non-western countries' by parents born outside of Denmark and without Danish citizenship |
| Descendant | Born in Denmark by parents born outside of Denmark and without Danish citizenship |
| *Marital status* | Combination of data on marital status and family type and divided into two categories: |
| Single/not living with a partner | Widow/divorced/unmarried or non-cohabiting |
| Married/living with a partner | Married or cohabiting |

| | |
|---|---|
| Income | In the calendar year prior to delivery based on a format by Statistics Denmark and divided into three categories (low, middle, high) |
| Highest completed education | Based on a format by Statistics Denmark and divided into three categories (lower secondary, upper secondary and post-secondary) |
| Occupation | Based on data on connection to the workforce by Statistics Denmark and divided into four categories (employed, unemployed or on welfare payment, under education, early retirement) |
| Preexisting polycystic ovary syndrome | ICD-10: E282 at or 2 years before index date |
| Preexisting metformin treatment | ATC: A10BA02 (≥2 redemptions) at or 2 years before index date |
| Previous spontaneous abortion(s) | One or more spontaneous abortions prior to index pregnancy |
| Multiple pregnancy | Non-singleton pregnancy |
| Preeclampsia | ICD-10: O11, O14 (diagnosed after gestational week 20) |
| Gestational hypertension | ICD-10: O13, O16 (diagnosed after gestational week 20) |
| Induction of labor | Indicator variable in DMBR |
| Cesarean section | Procedure code in DMBR |
| Gestational age at delivery | Gestational age at delivery in days |
| Preterm delivery | Delivery before gestational week 37 |
| Stillbirth | Indicator variable in DMBR |
| Offspring malformation | Indicator variable in DMBR (ICD-10 Q00-Q99 in offspring diagnosed within 1 year after index delivery) |
| Subsequent diabetes prior to outcome | ICD-10: E10-E14, O24-O243, O245, O249 diagnosed after delivery *and/or*<br>ATC: A10 (≥2 redemptions) after delivery *and*<br>no incident outcome prior to date of subsequent diabetes |

ICD-10, International Classification of Diseases, 10th revision, including subgroups; ATC, Anatomical Therapeutic Chemical groups, including subgroups; GDM, gestational diabetes mellitus; DMBR, Danish Medical Birth Register

**Supplemental Table S3 –** Risk of psychiatric morbidity according to previous GDM in women delivering in Denmark in 1997–2018 (*n*=342,572)

| | GDM | | | No GDM | | | Hazard ratio (95% CI) | | |
|---|---|---|---|---|---|---|---|---|---|
| | *n* events | Risk time | IR (95% CI)* | *n* events | Risk time | IR (95% CI)* | Crude | Model 1† | Model 2‡ |
| *Primary outcome* | | | | | | | | | |
| **Depression**§ | 1,271 | 67,207 | 18.9 (17.9–20.0) | 32,917 | 2,038,902 | 16.1 (16.0–16.3) | 1.19 (1.13–1.26) | 1.21 (1.14–1.28) | 1.12 (1.06–1.19) |
| *Secondary outcomes* | | | | | | | | | |
| **Any psychiatric diagnosis**‖ | 535 | 72,976 | 7.3 (6.7–8.0) | 13,322 | 2,166,687 | 6.2 (6.1–6.3) | 1.19 (1.10–1.30) | 1.21 (1.11–1.32) | 1.17 (1.08–1.28) |
| **Depressive disorders** | 311 | 74,459 | 4.2 (3.7–4.7) | 6,685 | 2,206,872 | 3.0 (3.0–3.1) | 1.38 (1.24–1.55) | 1.39 (1.24–1.56) | 1.29 (1.15–1.45) |
| **Anxiety disorders** | 167 | 75,523 | 2.2 (1.9–2.6) | 3,952 | 2,225,560 | 1.8 (1.7–1.8) | 1.22 (1.04–1.42) | 1.23 (1.06–1.44) | 1.28 (1.10–1.50) |
| **Bipolar disorders** | 30 | 76,420 | 0.4 (0.3 0.6) | 803 | 2,244,278 | 0.4 (0.3 0.4) | 1.05 (0.73 1.51) | 1.13 (0.79 1.63) | 1.11 (0.77 1.61) |
| **Psychotic disorders** | 34 | 76,349 | 0.5 (0.3 0.6) | 780 | 2,243,654 | 0.4 (0.3 0.4) | 1.28 (0.91 1.81) | 1.24 (0.88 1.75) | 1.26 (0.89 1.79) |
| **Substance use disorders** | 117 | 75,784 | 1.5 (1.3–1.9) | 3,840 | 2,224,293 | 1.7 (1.7–1.8) | 0.89 (0.74–1.07) | 0.92 (0.77–1.11) | 0.91 (0.75–1.10) |
| **Postpartum psychiatric disease** | 5 | 76,481 | 0.1 (0.0–0.2) | 183 | 2,245,862 | 0.1 (0.1–0.1) | 0.93 (0.38–2.25) | 0.93 (0.38–2.26) | 0.95 (0.38–2.34) |
| **Any psychopharmacological medication**¶ | 1,300 | 66,908 | 19.4 (18.4–20.5) | 34,277 | 2,030,593 | 16.9 (16.7–17.1) | 1.17 (1.11–1.24) | 1.19 (1.12–1.25) | 1.11 (1.05–1.17) |
| **Antidepressants**# | 1,219 | 67,590 | 18.0 (17.1–19.1) | 31,696 | 2,047,326 | 15.5 (15.3–15.7) | 1.19 (1.12–1.26) | 1.21 (1.14–1.28) | 1.11 (1.05–1.18) |
| **Antipsychotics**# | 197 | 75,352 | 2.6 (2.3–3.0) | 4,535 | 2,224,222 | 2.0 (2.0–2.1) | 1.25 (1.08–1.44) | 1.25 (1.08–1.44) | 1.17 (1.01–1.35) |
| **Anxiolytics**# | 178 | 75,181 | 2.4 (2.0–2.8) | 4,977 | 2,215,837 | 2.3 (2.2–2.3) | 1.06 (0.91–1.23) | 1.02 (0.88–1.19) | 1.07 (0.92–1.25) |

* IR, incidence rate presented as number of events per 1000 person-years

† Model 1: Adjusted for age, parity, Charlson Comorbidity Index score, ethnicity, marital status, income, education, occupation, and calendar year of delivery

‡ Model 2: Adjusted for age, parity, Charlson Comorbidity Index score, ethnicity, marital status, income, education, occupation, calendar year of delivery, and pregestational BMI

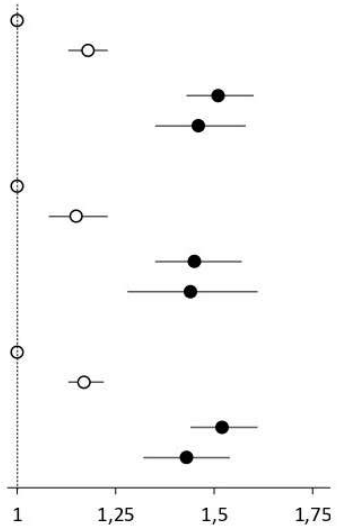
§ Diagnoses of depressive disorder and/or ≥2 redeemed prescriptions of antidepressant medication

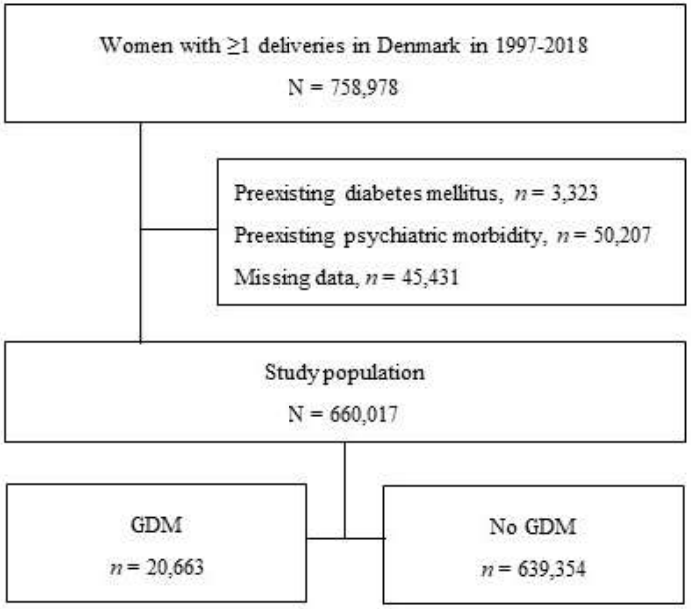
‖ Diagnosis of depressive disorders, anxiety disorders, bipolar disorders, psychotic disorders, substance use disorders, or postpartum psychiatric disease

¶ ≥2 redeemed prescriptions within each of the groups: antidepressants, antipsychotics, or anxiolytics

# ≥2 redeemed prescriptions

| Outcome | N events/N women | Exposure | aHR (95% CI)* | Overall p-value |
|---|---|---|---|---|
| Depression | 105,627/626,675 | No GDM and no DM | 1 (reference) | <0.001 |
| | 2,363/16,942 | GDM and no DM | 1.18 (1.13-1.23) | |
| | 1,305/9,500 | No GDM and then DM | 1.51 (1.43-1.60) | |
| | 619/3,666 | GDM and then DM | 1.46 (1.35-1.58) | |
| Any psychiatric diagnosis | 39,990/624,220 | No GDM and no DM | 1 (reference) | 0.044 |
| | 929/17,110 | GDM and no DM | 1.15 (1.08-1.23) | |
| | 722/11,366 | No GDM and then DM | 1.45 (1.35-1.57) | |
| | 301/4,087 | GDM and then DM | 1.44 (1.28-1.61) | |
| Any psychopharmacological medication | 113,831/626,967 | No GDM and no DM | 1 (reference) | <0.001 |
| | 2,489/16,949 | GDM and no DM | 1.17 (1.13-1.22) | |
| | 1,338/9,267 | No GDM and then DM | 1.52 (1.44-1.61) | |
| | 623/3,600 | GDM and then DM | 1.43 (1.32-1.54) | |




Women with ≥1 deliveries in Denmark in 1997-2018
N = 758,978
Preexisting diabetes mellitus, n = 3,323
Preexisting psychiatric morbidity, n = 50,207
Missing data, n = 45,431
Study population
N = 660,017
GDM
n = 20,663
No GDM
n = 639,354