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Depression and risk of gestational diabetes: A meta-analysis of cohort studies

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ABSTRACT

Aims: To systematically assess the association between depression and risk of gestational diabetes by a meta-analysis of cohort studies.

Methods: We searched multiple electronic databases for cohort studies investigating depression and risk of gestational diabetes before December 31th, 2018. Pooled odds ratios (ORs) and confidence intervals (CIs) of the included articles were calculated using a fixed- or random-effect model. Publication bias was detected using the Egger's and Begg's tests.

Results: We obtained 5 cohort studies with a total number of 122,197 women. Women with a history of depression compared with those without it had a significantly increased risk of gestational diabetes (pooled OR = 1.20, 95% CI: 1.09, 1.33) but borderline significant evidence of heterogeneity was observed (I^2 = 45.1%, P for heterogeneity = 0.12). Subgroup analysis by study design showed a stronger association in prospective cohort studies than that in retrospective cohort studies (pooled OR: 1.61 [1.17, 2.21] vs. 1.16 [1.05, 1.29]), though the difference was not statistically significant (P for interaction = 0.26). We observed some evidence of publication bias; however, correction for such bias using "trim-and-fill" analysis yielded similar results.

Conclusion: Women with a history of depression may be at an increased risk of gestational diabetes. Future prospective studies of high quality are needed to confirm our findings.

1. Introduction

The prevalence of gestational diabetes has been increasing over the past decades [1]. Several genetic, social, lifestyle and psychological risk factors can contribute to the development of gestational diabetes which leaves mothers and their children with many physical and psychological complications [2,3]. For instance, gestational diabetes is associated with increased risk of macrosomia and cesarean section at delivery [4,5], and in the long term it also increases the risk of type 2 diabetes and cardiovascular diseases in the mother [6,7] and the risk of insulin insensitivity and obesity in the child [8,9].

On the other hand, depression is among the most frequent psychiatric disorders, and women are disproportionately affected more than men [10]. With a remarkable increase in lifetime prevalence, depression has become a public health burden worldwide [11]. It is known that depression coexists with a state of chronic inflammation, and the associations

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between depression and metabolic syndrome appear to be bidirectional [12]. Also, gestational diabetes has been shown to be associated with a higher risk of postpartum depressive symptoms [13]. However, findings from previous studies examining the association between depression and gestational diabetes were inconsistent, with some but not all showing an association [14–18]. Although the association between depression and type 2 diabetes has been examined in a previous meta-analysis [19], there has been no meta-analysis published assessing the association between depression and gestational diabetes. Detection of risk factor of gestational diabetes can help to target women at high risk of the disease and offer them health care that may prevent adverse pregnancy outcomes such as macrosomia and cesarean section. We, therefore, aimed to investigate the association between depression and risk of gestational diabetes by conducting a meta-analysis of cohort studies.

2. Methods

2.1. *Literature search*

The present meta-analysis was reported according to the checklist of Meta-analysis of Observational Studies in Epidemiology [20]. Two investigators independently searched electronic databases including PubMed, Web of Science, and Cochrane Library for potential studies published before December 31th, 2018. We used the following search terms: "depression", "depressive disorder", "depressive symptom", "gestational diabetes", "gestational diabetes mellitus", and "pregnancy diabetes". Only published full-text articles were searched, and no effort was made to identify unpublished studies.

2.2. *Eligibility criteria*

Studies were selected for analysis if they met the following criteria: the study design was prospective or retrospective cohort study, a temporal analysis between depression and subsequent risk of gestational diabetes was performed, and risk estimates (either relative risks [RRs] or odds ratios [ORs]) with corresponding 95% confidence intervals (CIs) were provided. Studies were excluded if they included diabetes other than gestational diabetes. We also excluded studies with cross-sectional or case-control designs to ensure a temporal relationship and reduce selection and recall biases.

2.3. *Study selection*

We reviewed the full manuscript of all articles extracted by the primary search. A manual search of the reference lists of the obtained studies was performed to identify additional studies. Then, we subjected these articles to the previously-mentioned eligibility criteria to create a final list of studies for the meta-analysis. Our primary literature retrieved 1058 citations from multiple electronic databases (Fig. 1). After

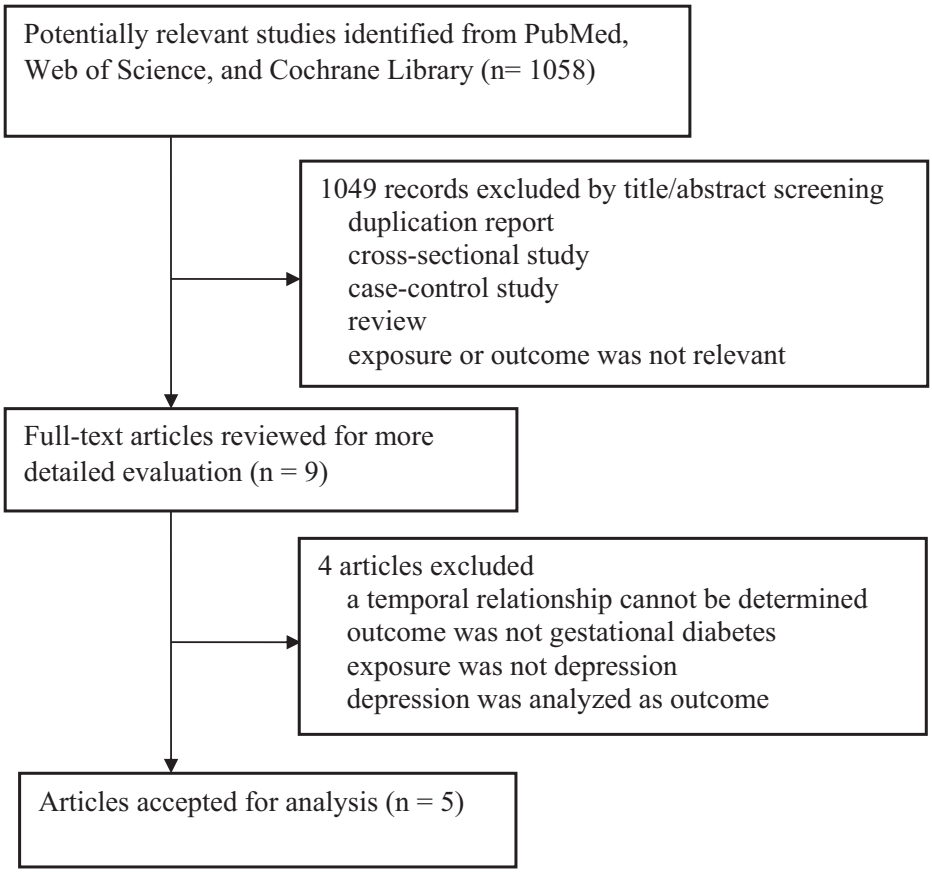

Fig. 1 – Flow chart of the study selection process.

the initial screening of title and abstract, the majority of the citations were excluded mainly because they were duplication reports, cross-sectional studies, case-control studies, review, exposure or outcome was not relevant. Four studies were further excluded due to the following reasons: the outcome was abnormal or impaired glucose tolerance [23], depression was analyzed as the outcome [24], a temporal relationship could not be determined [25], or exposure of interest was mental health status [26]. Finally, we obtained five studies eligible for this meta-analysis.

The following data were extracted from every study: the last name of the first author, year of publication, study area, sample size, study design, measures of depression and gestational diabetes, time of depression diagnosis, confounding variables, and adjusted risk estimates with corresponding 95% CIs. When a given study presented different models that adjusted for several potential confounders, we included the model that adjusted for the largest number of confounders to reduce the risk of confounding bias. In one study that assessed both first- and second-trimester depression in relation to gestational diabetes [16], we used the results for first-trimester depression. In another study, we considered the results only when depression was detected before the incidence of gestational diabetes [14]. The quality of the individual studies was determined using the Newcastle–Ottawa Scale and studies were classified as poor, fair, and good quality based on selection, comparability, and outcome. Two investigators individually extracted the data and assessed the study quality, with differences resolved by discussion.

2.4. Statistical analysis

The ORs and their CIs were used as measures of the association, and RR used in one study [16] was treated as OR. The incident rate of gestational diabetes was low in that study (<5%), and therefore RR would be similar to OR. We calculated the I^2 to examine statistical heterogeneity across studies. I^2 is the proportion of the observed variations attributed to heterogeneity among studies rather than chance [21]. A fixed-effects model, or in the presence of heterogeneity a random-effects model, was used to compute the summary ORs [22]. Heterogeneity of the results from individual studies was tested by Q statistic at $P < 0.10$ level of significance. We also performed subgroup analysis by study design (prospective cohort vs. retrospective cohort) to explore the possible source of heterogeneity and effects of modification. Meta-regression analysis was used for the interaction test. A sensitivity analysis was conducted to examine the influence of one single study on the overall OR by omitting one study and combining the remainders in each turn. Potential publication bias was assessed by Egger's test and Begg's test [23]. Both tests are formalized statistical tests for assessing funnel plot asymmetry and considered as a standard procedure of meta-analysis [23]. In the presence of such bias, the "trim-and-off" analysis was used for correction. All analyses were performed using STATA version 12.0 (StataCorp, College Station, TX).

3. Results

3.1. Characteristics of selected studies

The five included studies had a total population of 122,197. Characteristics of these studies are shown in Table 1. The individual studies were published between 2013 and 2016; four of them were conducted in the USA and one in Australia. Two cohort studies used a prospective design, while the other three studies used a retrospective design.

The Edinburgh Postnatal Depression Scale (EDPS) was used to assess depression in two studies, the International Classification of Diseases (ICD) in one study, Center for Epidemiologic Studies Depression Scale in one study, and self-report in one study. Depression assessment was conducted one year before pregnancy in one study and during early pregnancy before the diagnosis of gestational diabetes in the other four studies. As for the diagnosis of gestational diabetes, one study used oral glucose tolerance test, one used the ICD-10, and the others used self-report data or did not report such information. The most adjusted covariates included age, ethnicity, parity, body mass index (BMI), education, income, smoking, and marital status.

3.2. Meta-analysis

Although the five studies reported an increased risk of gestational diabetes, not all reached statistical significance (Fig. 2). Combined, women with depression before or during early pregnancy were at a higher risk for developing gestational diabetes compared to those without depression

Table 1 – Characteristics of the included cohort studies.

Author, publication year	Country	Sample size	Design	GD Diagnosis	Depression Diagnosis	Depression diagnosis time	Covariates	Quality*
Bowers, 2013 [14]	USA	111,952	RC	ICD-9	ICD-9	Prior to GD	1,2,3,4	Good
Dahlen, 2015 [15]	Australia	3092	RC	NA	EPDS $\geq$ 13	Prior to GD	1,2,3,4,7	Fair
Wilson, 2015 [18]	USA	3655	RC	Self-report	Self-report	Before pregnancy	1,2,4,6,7	Fair
Hinkle, 2016 [16]	USA	2477	PC	OGTT	EPDS $\geq$ 10	1st trimester	1,2,4,5,8	Good
Morrison, 2016 [17]	USA	1021	PC	NA	CES-D $\geq$ 10	1st trimester	1,4,5,6,8	Fair

CES-D: Centre for Epidemiologic Studies Depression Scale, EPDS: Edinburgh Postnatal Depression Scale, GD: gestational diabetes, ICD: International Classification of Diseases, NA: not available, OGTT: oral glucose tolerance test, PC: prospective cohort, RC: retrospective cohort, SR: self-report.

Covariates: 1: age, 2: race/ethnicity, 3: parity, 4: body mass index, 5: education, 6: income, 7: smoking, 8: marital status.

* According to the Newcastle–Ottawa Scale.

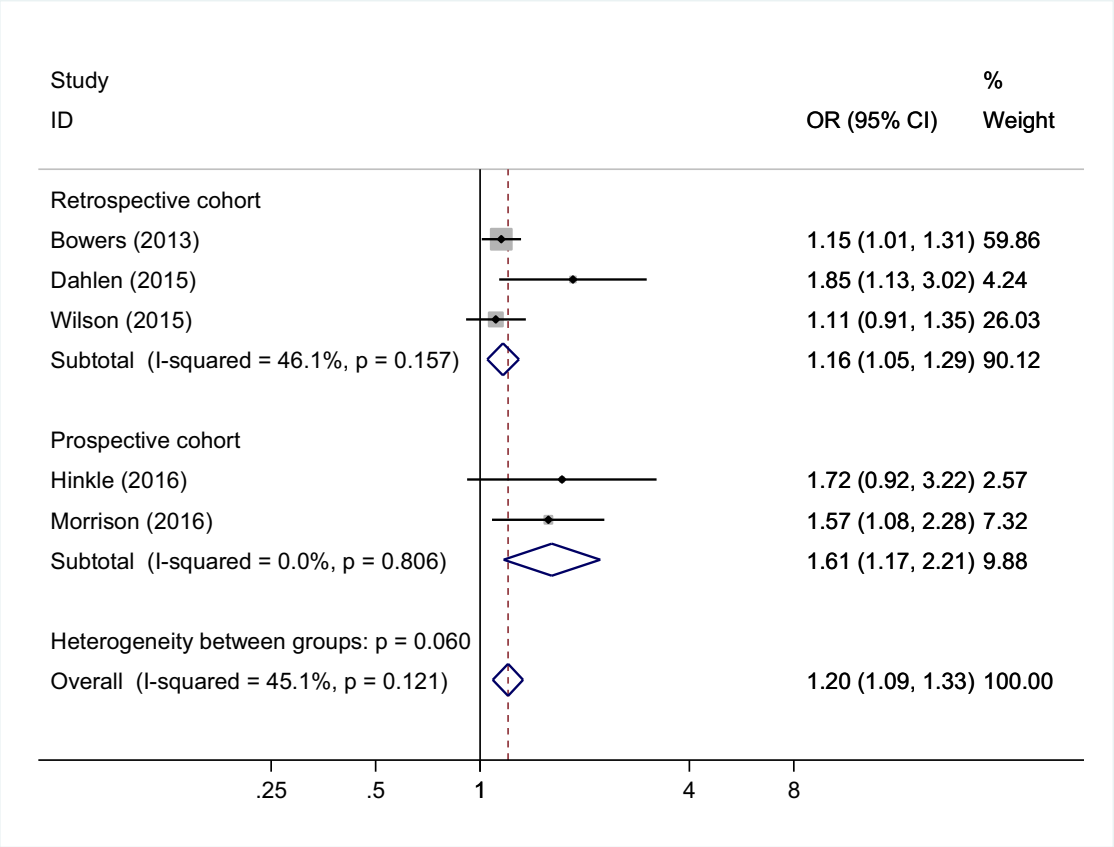

Fig. 2 – Meta-analysis of cohort studies examining the association between depression and risk of gestational diabetes.

(pooled OR = 1.20, 95% CI: 1.09, 1.33). Borderline significant evidence of heterogeneity was observed (I^2 = 45.1%, P for heterogeneity = 0.12). Subgroup analysis by study design showed a stronger association in prospective cohort studies than that in retrospective cohort studies (pooled OR: 1.61 [1.17, 2.21] vs 1.16 [1.05, 1.29]), though the difference was not significant (P for interaction = 0.26). Results of sensitivity analysis yielded a range of ORs between 1.18 (1.06, 1.31) and 1.28 (1.09, 1.50), indicating that no single study had a substantial impact on the overall result. Test for the small-study effect showed some evidence of publication bias in Egger's test (P = 0.03) but not Begg's test (P = 0.12). Correction for this bias using the "trim-and-fill" analysis yielded a pooled OR of 1.17 (95% CI: 1.05, 1.29) and 1.20 (95% CI: 1.00, 1.43) using the fixed- and random-effects model, respectively.

4. Discussion

Findings of the present meta-analysis indicated that depression before or during early pregnancy was associated with an increased risk of gestational diabetes. Besides, the association appeared to be stronger in prospective cohort studies than retrospective cohort studies. Of note, we only included cohort studies with a longitudinal design to ensure a temporal relationship between depression and subsequent risk of gestational diabetes.

4.1. *Interpretations and related studies*

The relationship between depression and risk of type 2 diabetes has been summarized in a previous meta-analysis conducted on 424,557 participants from 23 longitudinal studies. The authors concluded that depressed people had an increased risk of developing type 2 diabetes (pooled relative risk = 1.38, 95% CI: 1.23, 1.55) [19]. Apart from diabetes, a body of evidence has shown that depression is associated with several non-communicable diseases, including obesity [24], stroke [25], coronary heart disease [26], and cancers [27]. Of interest, the relationship between depression and gestational diabetes seems to be bidirectional. Several prospective cohort studies have reported that gestational diabetes was associated with a higher risk of postpartum depression [16,28–30], although others found a null association [31].

The mechanisms underlying the relationship between depression and gestational diabetes are uncertain. Biologically, the immune dysfunction related to depression activates the hypothalamus–pituitary–adrenal axis and the sympathetic nervous system, which increases the production of inflammatory cytokines and stress hormones. Both inflammatory cytokines and stress hormones can interact with the pancreatic β-cells to induce insulin resistance [32,33]. Moreover, depression is linked to many lifestyle choices that increase the risk of diabetes such as physical inactivity, poor diet, and other behavioral problems [34].

However, it should be mentioned that we observed borderline significant evidence of heterogeneity across studies, which was unsurprising given the different study designs, the variant measures for depression and gestational diabetes assessment, and the dissimilarities in the socio-demographic characteristics of the participants. Study design may be one source of heterogeneity across studies. We detected a stronger association in prospective cohort studies than that in retrospective cohort studies, though the difference did not reach statistical significance. The reason why there were such differences between prospective and retrospective studies is that in prospective cohort studies, the cohort and the exposure are selected before the outcome occurs, while in retrospective cohort studies, health records of the cohort are reviewed and their experience is reconstructed as if it had been prospectively followed up [35]. Further, compared with prospective cohort studies, retrospective cohort studies suffer more shortcomings attributed to the questionable quality of data, the absence of data on potential confounders, the difficulty in determining a temporal association, and the vulnerability to selection, recall, and misclassification biases [35].

Also, it is known that obesity is a shared risk factor of depression [24] and gestational diabetes [36]. When Hinkle et al. stratified the analysis by pre-pregnancy obesity, a significant association between depression and incident gestational diabetes in non-obese women was detected but a null association was observed in obese women [16]. The null association in obese women may be explained by the elevated baseline risk of gestational diabetes in this group that has masked the variation in increased depressive symptoms [16]. Unfortunately, no other included studies performed subgroup analysis by pre-pregnancy BMI and further studies are needed to clarify whether BMI could modify the association between depression and gestational diabetes. One strength of this meta-analysis is that all included studies have adjusted their results for BMI, indicating that depression was associated with an increased risk of gestational diabetes independent of BMI.

Based on our findings, depression treatment was therefore expected to decrease the risk of gestational diabetes. Unfortunately, we found little evidence from intervention studies examining the effect of depression treatment on risk of gestational diabetes. Of note, a previous meta-analysis of five longitudinal studies showed that antidepressant drug use was associated with an increased risk of type 2 diabetes (pooled relative risk = 1.68 [1.17, 2.40]) [19]. However, antidepressant drug use may serve as an indication of depression severity and the observed increased diabetes risk may be due to severe depressive symptoms rather than the use of antidepressant drugs. Nevertheless, findings from our study support a significant association between depression and risk of gestational diabetes. Targeting women with depression may help detect gestational diabetes and offering them health care may help prevent gestational diabetes and adverse pregnancy outcomes

4.2. *Limitations*

It should be noted that this meta-analysis had some limitations. First, the assessment tools of depression and gestational diabetes varied across studies. Some studies did not clarify how gestational diabetes was diagnosed, and even the cut-offs adopted in depression scales differed across studies. For example, the EPDS was used in two studies with cut-off points at 10 and 13. Second, the included studies differed regarding the adjusted covariates which could under- or over-estimate the pooled risk estimate. For example, several studies did not adjust their results for education. Thirdly, less than half of the included studies were of good quality, which might encompass several limitations that could not be solved by this meta-analysis. Fourthly, we observed some evidence of publication bias but correction for this bias yielded similar results.

5. Conclusion

In summary, the present meta-analysis suggested that women with a history of depression may be at an increased risk of developing gestational diabetes. Future prospective studies of high quality are needed to confirm our results.

Author contributions

A.A. collected the data, analyzed the data, and wrote the manuscript. J-Y. D. designed the study, collected the data, analyzed the data, conducted the technique review and reviewed and edited the manuscript. J-Y. D. is the guarantor of this work and, as such, 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.

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Role of the funder

The funder had no role in the conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript findings.

Declaration of Competing Interest

None.

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