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Systematic review and meta-analysis of risk of gestational diabetes in women with preconception mental disorders

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ABSTRACT

There is a well-established bidirectional association between Type 2 diabetes and mental disorder and emerging evidence for an increased risk of perinatal mental disorder in women with gestational diabetes (GDM). However, the relation between mental disorder prior to pregnancy and subsequent risk of GDM remains relatively unexplored. This is a systematic review and meta-analysis of the risk of GDM in women with a range of preconception mental disorders. Peer-reviewed literature measuring odds of GDM and preconception mood, anxiety, psychotic and eating disorders was systematically reviewed. Risk of bias was assessed using a checklist. Two independent reviewers were involved. 22 observational studies met inclusion criteria; most were retrospective cohorts from English speaking, high income countries. 14 studies were at high risk of bias. There was evidence for an increased risk of GDM in women with schizophrenia (pooled OR 2.44; 95% CI 1.17,5.1; 5 studies) and a reduced risk of GDM in women with anorexia nervosa (pooled OR 0.63; 95% CI 0.49,0.80; 5 studies). There was some limited evidence of an increased risk in women with bipolar disorder. There was no evidence for an association with preconception depression or bulimia nervosa on meta-analysis. There were insufficient studies on anxiety disorders for meta-analysis. This review indicates that there is not a significant risk of GDM associated with many preconception mental disorders but women with psychotic disorders represent a group uniquely vulnerable to GDM. Early detection and management of GDM could improve physical and mental health outcomes for these women and their children.

1. Introduction

A range of mental disorders affect women of reproductive age, including common mental disorders such as depression and anxiety and psychotic disorders such as schizophrenia and bipolar disorder. There is increasing awareness of the physical-mental health interface, including evidence supporting a relation between Type 2 diabetes and depression. A range of mechanisms have been postulated, including inflammation and shared socioenvironmental risk factors such as obesity and deprivation (Moulton et al., 2015). An association has also been observed between Type 2 diabetes and psychotic disorders. This may be driven in part by the effects of antipsychotic medication (Bhuvaneswar et al., 2009), although there is now evidence to suggest that impaired glucose tolerance may be evident from the first episode of psychosis even in the psychotropic-naïve (Pillinger et al., 2017).

The physical-mental health interface has been relatively less explored in pregnancy. However, we and others have identified an association between gestational diabetes (GDM: diabetes diagnosed for the first time during pregnancy) and a possible increased risk of depressive symptoms in the perinatal period (during pregnancy and up to one year postpartum) (Arafa and Dong, 2019b; Azami et al., 2019; Wilson et al., 2020a). Both GDM and maternal mental disorders are significant contributors to maternal and child morbidity and mortality and both are associated with longer-term adverse outcomes in offspring so

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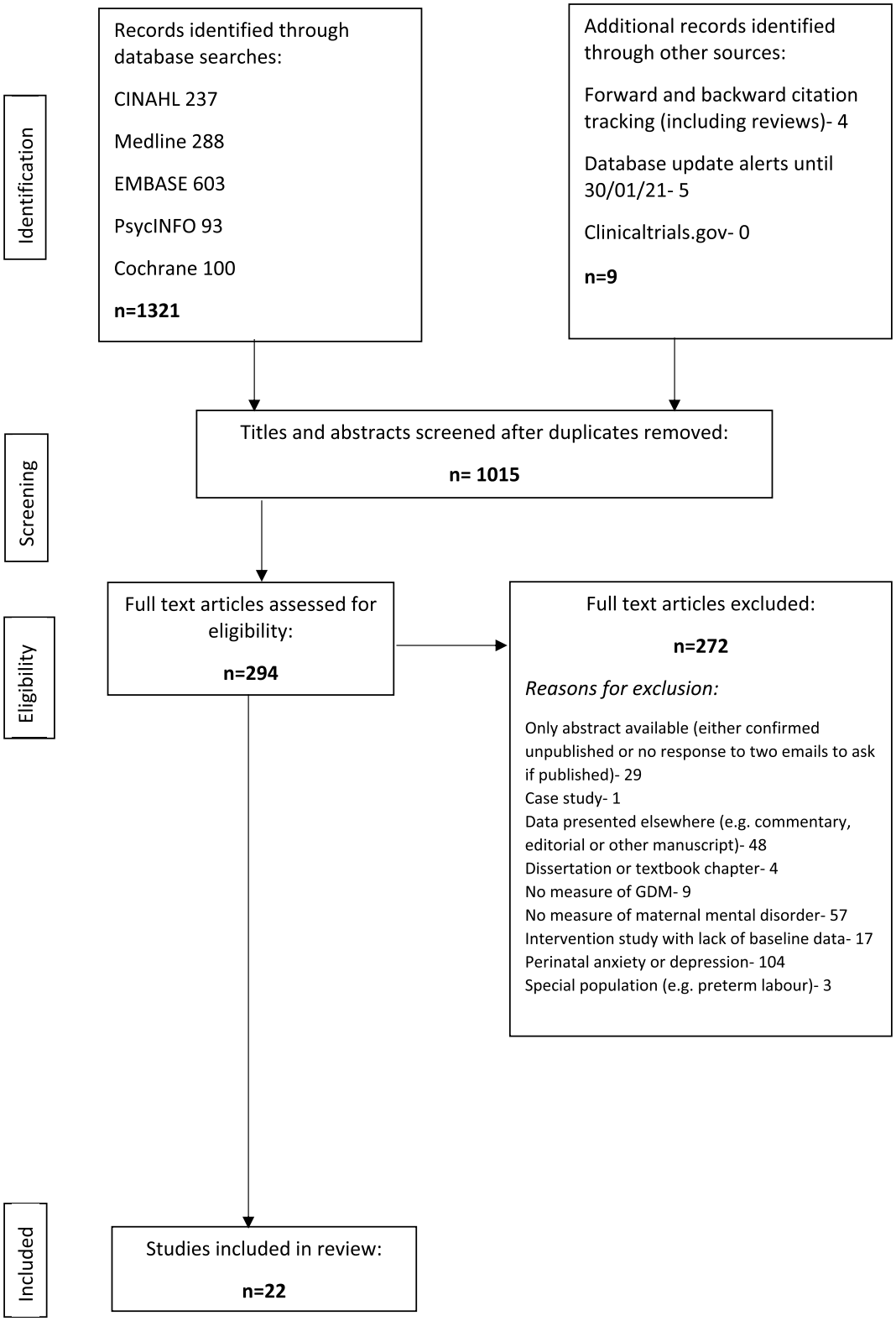
understanding their relation is important in supporting women and children across clinical practice and public health policy (Howard et al., 2014; Kampmann et al., 2015; Stein et al., 2014).

Yet despite this potential increased risk of perinatal depressive symptoms in women with GDM, the risk of GDM in women with mental disorders in the preconception period (prior to pregnancy) is less well understood. Moreover, though research supports a bidirectional relation between Type 2 diabetes and depression, there is some evidence that the direction of association from depression to Type 2 diabetes is stronger than for Type 2 diabetes leading to depression (Mezuk et al., 2008).

Limited research to date provides some evidence for an increased risk of GDM in women with depression, with a recent review reporting a



pooled odds ratio on meta-analysis of five studies of 1.20 (95% confidence interval 1.09,1.33) for GDM in women with depression versus those without (Arafa and Dong, 2019a). However, this review included depression measured both prior to and in early pregnancy and did not examine other mental disorders. Thus the aim of this study was to systematically review the evidence for risk of GDM in women with a range of preconception mental disorders.

2. Material and methods

The review followed 'Meta-Analyses and Systematic Reviews of Observational Studies' (MOOSE) (Stroup et al., 2000) and 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) guidelines (Moher et al., 2009). It was registered with PROSPERO (CRD42020173283).

2.1. Data sources

Medline, PsycINFO, EMBASE, CINAHL and Cochrane Library were searched separately from inception until 17/07/2020. Search terms were adapted from previous systematic reviews in the area (Molyneaux et al., 2014; Trevillion et al., 2012) and Cochrane specialised registers (Cochrane Common Mental Disorders Group, 2021; Cochrane Pregnancy and Childbirth Group, 2021) (supplementary material 1). Forward and backward citation tracking was also undertaken.

2.2. Study selection

Inclusion criteria were published, peer-reviewed studies in any language, measuring both GDM and mental disorder occurring any time prior to the woman's first ever pregnancy or prior to the index pregnancy affected by GDM. Mental disorders included mood, anxiety, psychotic or eating disorders, as there were plausible mechanisms for an association between these disorders and GDM. Mental disorder was measured either by medical records, self-report or diagnostic and screening measures.

Exclusion criteria were studies classifying mental disorder based solely on medication status due to the risk of misclassification bias when psychotropic prescriptions alone are used to identify mental disorder (Thielen et al., 2009). The mechanisms underlying the relation with GDM may differ between mental disorders. Therefore, studies were also ineligible if they did not define what mental disorders were measured or aggregated different disorders into one measure; for example studies reporting only on 'psychiatric illness'. For the more transient common mental disorders of depression and anxiety, studies that grouped together common mental disorders occurring both prior to and during pregnancy were ineligible as the mechanisms underlying the relation between GDM and preconception common mental disorders and indeed the clinical implications of such a relation, may differ from that of disorders occurring during pregnancy (Batt et al., 2020; Brummelte and Galea, 2010).

Following de-duplication, titles and abstracts were screened, followed by full text screening by two independent reviewers (CAW and JN). 22 studies met the study's inclusion criteria.

2.3. Data extraction

Data extraction was conducted by two independent reviewers (CAW and NS) and included study characteristics such as study design and measurement of GDM and mental disorder. Study characteristics were summarised according to 1) sample size (i) <1,000, ii) 1000–100,000, iii) >100,000), 2) study design (i) cross-sectional, ii) case-control study, iii) prospective cohort, iv) retrospective cohort) and 3) location (i) Africa, ii) Asia, iii) Australasia, iv) Europe, v) North America, vi) South America). Odds ratios (ORs) were extracted as this was the most common measure of risk reported in the included studies. For studies in which preconception mental disorder and GDM had been measured but ORs could not be calculated from the data presented in the paper, study authors were contacted to request this information.

2.4. Risk of bias assessment

A component approach to assessment of risk of bias was employed, as per current PRISMA guidelines (Moher et al., 2009). A modified Newcastle Ottawa Scale (Wells et al.,)(piloted prior to use) was used (supplementary material 2) by two independent reviewers (CAW and NS). Of most interest were measurement and selection biases as most of the studies were anticipated to be of observational design and these sources of bias are most likely to impact on the results of an observational study. Each item was assigned a score from zero (high risk of bias) to two (low risk of bias). Selection bias was scored via an assessment of: 1) sample representativeness and 2) participation rates. Measurement bias was scored via an assessment of: 1) measure of GDM and 2) measure of mental disorder. A study with a score of zero in any of these four elements was deemed at high risk of bias. Otherwise studies were deemed at low to moderate risk.

2.5. Data synthesis

Studies were grouped by mental disorder. If ORs for at least three studies were available for each disorder, meta-analysis was undertaken (Deeks et al.,)

Data were analysed using Stata 15 (StataCorp LP, 2007). Metan and metaprop commands were used to produce pooled unadjusted ORs and 95% confidence intervals (CIs) displayed as forest plots. Unadjusted ORs were used as studies adjusted for different covariates. DerSimonian-Laird random effects meta-analysis (DerSimonian and Laird, 1986) was used as there was expected to be a degree of heterogeneity between studies (Higgins et al., 2009; Schmidt et al., 2009). Heterogeneity was assessed using I^2: proportion of total variation in study estimates that is due to heterogeneity (Higgins and Thompson, 2002). It was decided a-priori that I^2 >90% would preclude meta-analysis as this represents substantial heterogeneity (Higgins et al., 2003). Sensitivity analyses on effect of risk of bias were conducted when sufficient studies were available (high or low to moderate risk excluded depending on which allowed at least three studies for meta-analysis). For the common mental disorders of depression and anxiety, additional sensitivity analyses were undertaken to examine the effect of different measures of mental disorder, for example self-report and screening tools versus diagnostic codes. Publication bias was not assessed as the requirement for at least ten studies in the meta-analysis was not met (Sterne et al., 2011).

The investigation was carried out in accordance with the latest version of the Declaration of Helsinki.

3. Results

3.1. Study characteristics

An overview of characteristics for all 22 included studies is provided in Table 1.

Most of the studies (N = 15) were from English speaking countries and all studies were written in English, with none from low- or middle-income countries. Most studies were retrospective cohorts (Table 1). However, types of studies and measures utilised differed according to type of mental disorder under study, with corresponding differences in the sources of bias. Studies on women with psychotic disorders were large, population-level cohorts using diagnostic codes for GDM and mental disorder from linked data such as hospital records, likely necessitated by the relatively lower population prevalence of these more severe mental illnesses compared to the common mental disorders of depression and anxiety, the studies of which tended to be in slightly

Table 1
Characteristics of included studies.

Disorder	Depression	Anxiety	Psychotic	Eating
Total N (NB one study measures both depression and psychotic disorders)	7	1	8	7
Sample size				
<1000	3	0	1	2
1000–100,000	1	1	4	4
>100,000	3	0	3	1
Study design				
Cross-sectional	0	0	0	0
Case-control study	1	0	0	1
Prospective cohort	1	0	0	2
Retrospective cohort	5	1	7	4
Location				
Africa	0	0	0	0
Asia	0	0	1	0
Australasia	1	0	4	0
Europe	1	0	1	6
North America	5	1	2	1
South America	0	0	0	0

smaller samples utilising a broader range of mental disorder measures. These included self-report and screening tools. Studies pertaining to eating disorders often used diagnostic interview as a measure of mental disorder, with a few of these studies being prospective. Thus the sources of bias in the studies of common mental disorders tended to be related to concerns about sampling, whereas many of the studies from the larger, population-level cohorts using linked data did not provide diagnostic criteria or a data extraction algorithm for GDM, which introduced the possibility of measurement bias, particularly in the studies of eating disorders; this is considered further in the discussion below.

3.2. Depression

Seven studies met inclusion criteria and measured diagnoses or symptoms of depression prior to pregnancy and subsequent risk of GDM. Their characteristics, including the effect estimates used to obtain a pooled unadjusted OR are displayed in Table 2.

Six studies were included in meta-analysis (Bowers et al., 2013; Byrn and Penckofer, 2015; Clark et al., 2019; Mei-Dan et al., 2015; Schoenaker et al., 2019; Singh et al., 2004). Schoenaker et al. (2019) provided estimates for depression measured on both a screening tool (CESD-10) and as self-report diagnosis. Using the estimate from CESD-10 alongside the ORs from the other four studies produced pooled OR of 1.09 (95% CI 0.79,1.50) (N = 576,914). Heterogeneity as I^2 was 88.6% (Fig. 1). Using Schoenaker et al.'s (2019) estimate from self-report diagnosis instead of CESD-10, changed this to 1.10 (95% CI 0.80,1.52); I^2 = 89.2%.

Sensitivity analysis in which the two studies at high risk of bias were removed brought the I^2 above 90% (91.6%), precluding meta-analysis. Likewise a further sensitivity analysis in which only studies using International Classification of Diseases (ICD) diagnostic codes for depression were included in meta-analysis (Bowers et al., 2013; Clark et al., 2019; Mei-Dan et al., 2015) resulted in I^2 = 92.4%.

Two of the studies included in meta-analysis which provided evidence of an increased risk of GDM in women with preconception depression adjusted for relevant confounders; there was not significant attenuation of estimates with adjustment. Bowers et al. (2013) estimate was only slightly attenuated after controlling for age, race, study site, insurance, parity, pre-pregnancy body mass index (BMI) and gestational weight gain (adjusted OR 1.17; 95% CI 1.03,1.33). Byrn and Penckofer (2015)'s estimate was also robust to adjustment for age, income, marital status, BMI and gravidity (adjusted OR 3.79; 95% CI 1.07,13.45).

Raisanen et al. reported an increased proportion of women with a history of depression prior to pregnancy developing GDM (versus women without a history of depression). However, an effect estimate as an OR was unavailable for inclusion in meta-analysis (Raisanen et al., 2014).

3.3. Anxiety disorders

Regarding anxiety disorders, only one study met inclusion criteria which examined the risk of GDM in women with ICD-9 diagnoses of post-traumatic stress disorder (PTSD) (Shaw et al., 2017). In this retrospective US cohort of military veterans with 15,986 singleton deliveries, rated at low to moderate risk of bias, there was no evidence that a history of PTSD prior to pregnancy predicted GDM development. 5.3% of those with a history of PTSD developed GDM versus 4.6% with no PTSD (difference reported as non-significant).

3.4. Psychotic disorders

There were eight studies reporting risk of GDM in women with psychotic disorders; their characteristics are presented in Table 3.

Five studies provided unadjusted ORs for risk of GDM in women with schizophrenia (Frayne et al., 2019; Judd et al., 2014; Kitai et al., 2014; Nguyen et al., 2012; Vigod et al., 2014). Pooled OR was 2.44 (95% CI 1.17,5.11) (N = 518,002). Heterogeneity (I^2) was 86.4% (Fig. 2). Sensitivity analysis in which the one study at low to moderate risk of bias was removed increased the pooled OR to 3.46 (95% CI 2.22,5.41); I^2 26.3%.

Five studies measured GDM risk in bipolar disorder (Bodén et al., 2012; Frayne et al., 2019; Judd et al., 2014; Mei-Dan et al., 2015; Nguyen et al., 2012). Pooled OR was 1.34 (95% CI 0.90,2.00); N = 849, 655; I^2 = 66.9% (Fig. 3). Sensitivity analysis removing the two studies at low to moderate risk of bias also slightly increased the OR to 1.83; 95% CI 1.20,2.79; I^2 14.6%.

While one study measured GDM in women with psychotic disorders, data were unavailable as an OR for meta-analysis (Galbally et al., 2020). This study reported the prevalence of GDM in women with psychotic disorders to be 20.9%: almost triple the prevalence in the Australian general population where the study was set.

3.5. Eating disorders

There were seven studies reporting risk of GDM in women with eating disorders; their characteristics are presented in Table 4.

Five studies provided unadjusted ORs for risk of GDM in women with anorexia nervosa (AN) (Ante et al., 2020; Bulik et al., 2009; Kouba et al., 2005; Linna et al., 2014; Micali et al., 2012). Pooled OR was 0.63 (95% CI 0.49,0.80) (N = 2,179,380 pregnancies). Heterogeneity as I^2 was 0% (Fig. 4).

Four studies measured risk for GDM in women with bulimia nervosa (BN) (Bulik et al., 2009; Kouba et al., 2005; Linna et al., 2014; Micali et al., 2012). Pooled OR was 0.97; 95% CI 0.66,1.43; N = 45,202 pregnancies; I^2 = 0% (Fig. 5).

One study also reported prevalence of GDM in a cohort of women with a history of treatment for BN prior to pregnancy (Morgan et al., 2006); 12 of 73 women with active BN during pregnancy developed GDM versus 2 women in the group of 60 with quiescent BN. Another study only reported GDM prevalence in a group experiencing both AN and BN (2/82; 2.4%) and it was significantly higher than a control group with no psychiatric disorder (48/10636; 0.5%; p = 0.01) (Micali et al., 2007).

Two of the included studies also examined risk for GDM in women with binge eating disorder (BED) and found no evidence for an increased risk compared to those unexposed to an eating disorder; unadjusted relative risk 1.1 (95% CI 0.83,1.6) in 1812 women with BED and 33,742 unexposed (Bulik et al., 2009) and unadjusted OR 0.94 (95% CI 0.24, 3.75) in 52 women with BED and 6319 unexposed (Linna et al., 2014).

Table 2
Summary of data provided by each study and effect estimates used in meta-analysis for depressive symptoms and diagnoses.

Author and year	Country	Study design and sample size	Mental disorder measure	GDM measure	Ethnicity, race or country of birth	Socioeconomic status	Risk of bias	Unadjusted OR (95% CI)
Bowers et al. (2013)	USA	Retrospective cohort study 121,260 women with 128,295 pregnancies	ICD-9 codes for depression prior to index pregnancy	ICD-9 codes Diagnostic criteria not reported	Race: Black: 17.3% Hispanic: 19% White: 54.1% Asian/Pacific Islander: 3.6% Multicultural/ other/ unknown:6%	Not reported	Low to moderate	[a]1·26 (1.12,1.42) N = 128,295 pregnancies
Byrn and Penckofer (2015)	USA	Retrospective cohort study 135 women with 135 pregnancies	Self-report 'Have you ever been diagnosed with depression?'	'Medical data to verify GDM status' Diagnostic criteria not reported	Race: White: 32·6% Black: 23% Hispanic: 32·6% Other: 11·9%	Less than $5000: 17% $5000–9999: 3% $10,000–19,999: 11.9% $20,000–29,999: 17% $30,000–39,999: 14.1% $40,000–49,999: 7.4% $50,000–59,999: 6.7% $60,000–69,999: 6.7% >$70,000: 11.1%	High	[b]3.20 (1.16,8.84) N = 135 pregnancies
Clark et al. (2019)	USA	Case-control study 694 women with 694 pregnancies	ICD-9 codes for at least one depressive episode 'prior to pregnancy'	1 h OGTT, 75 g load: >7.8 mmol/l OR 1 h OGTT, 100 g load: >10 mmol/l OR 2 h OGTT,100 g load: >8.45 mmol/l OR Fasting glucose: >5.1 mmol/l	Race: Caucasian: 53.9% Hispanic: 19.7% African American: 5.3% Asian: 14.6% Native American: 1.3% Unknown: 5.2%	$30–40,000: 0.3% $40–50,000: 3% $50–60,000: 8.1% $60–70,000: 6.9% $70–80,000: 9.1% $80–90,000: 17.4% $90–100,000: 14.4% $100–110,000: 8.2% >$110,000: 32.6%	Low to moderate	[b]1·23 (0.79,1.91) N = 694 pregnancies
Mei-Dan et al. (2015)	Canada	Retrospective cohort study 437,941 women with 437,941 pregnancies	ICD–9 or ICD-10 codes for major depressive disorder from hospital records within 5 years preceding the index pregnancy	Validated ICD-10 codes or Canadian Classification of Health Interventions procedure codes Diagnostic criteria not reported	Not reported	Income quintile Q1 (lowest): 23.7% Q2: 20.7% Q3: 20% Q4: 19.5% Q5 (highest): 15.7%	Low to moderate	[b]0.72 (0.60,0.86) N = 436,082 pregnancies (excluding bipolar disorder)
Raisanen et al. (2014)	Finland	Retrospective cohort study 511,938 women with 511,938 pregnancies	ICD-10 codes for depression 'prior to pregnancy' from Hospital Discharge Register for outpatient visits to specialised healthcare since 1998 and inpatient visits to specialised healthcare since 1996	ICD-10 GDM diagnoses from Hospital Discharge Register (O24.4) Diagnostic criteria not reported	Not reported	Upper white-collar worker 3.7–8.6% Lower white-collar worker 25.5–34.5% Blue-collar worker 14.2–16% Others 25.7–31.9% Missing 17.2–25.3%	Low to moderate	Not reported
Schoenaker et al. (2019)	Australia	Prospective cohort study 6317 women with 11,556 pregnancies	CESD-10 ≥ 10 prior to first ever pregnancy OR Self-report of doctor-diagnosed depression three years prior to first ever pregnancy	Self-report 'Were you diagnosed or treated for gestational diabetes?' Diagnostic criteria at the time of the study was 0 h OGTT, 75 g load: ≥5.5 mmol/l OR ≥5.1 OR 2 h OGTT, 75g load: ≥8 mmol/l OR ≥8.5 mmol/l	Not reported	Highest qualification completed: Up to year 12: 21.4% Trade, certificate or diploma: 21.5% (Higher) university degree: 57.1%	Low to moderate	Screening tool: [c]1.42 (1.16,1.67) Self-report of doctor diagnosis:[c]1.47 (1.21,1.72) N = 11,556 pregnancies
Singh et al. (2004)	USA	Retrospective cohort study	Medical chart review and self-report		Non-White race: 40.1%	Not reported	High	

(continued on next page)

Table 2 (*continued*)

Author and year	Country	Study design and sample size	Mental disorder measure	GDM measure	Ethnicity, race or country of birth	Socioeconomic status	Risk of bias	Unadjusted OR (95% CI)
		152 women with 152 pregnancies	questionnaire for history of depression prior to pregnancy	Medical charts Diagnostic criteria not reported				[b]0.43 (0.20,0.91) N = 152 pregnancies

GDM: gestational diabetes; OR: odds ratio; OGTT: oral glucose tolerance test.
[a] Estimate given in paper.
[b] Derived from data in paper.
[c] Data provided by study author.

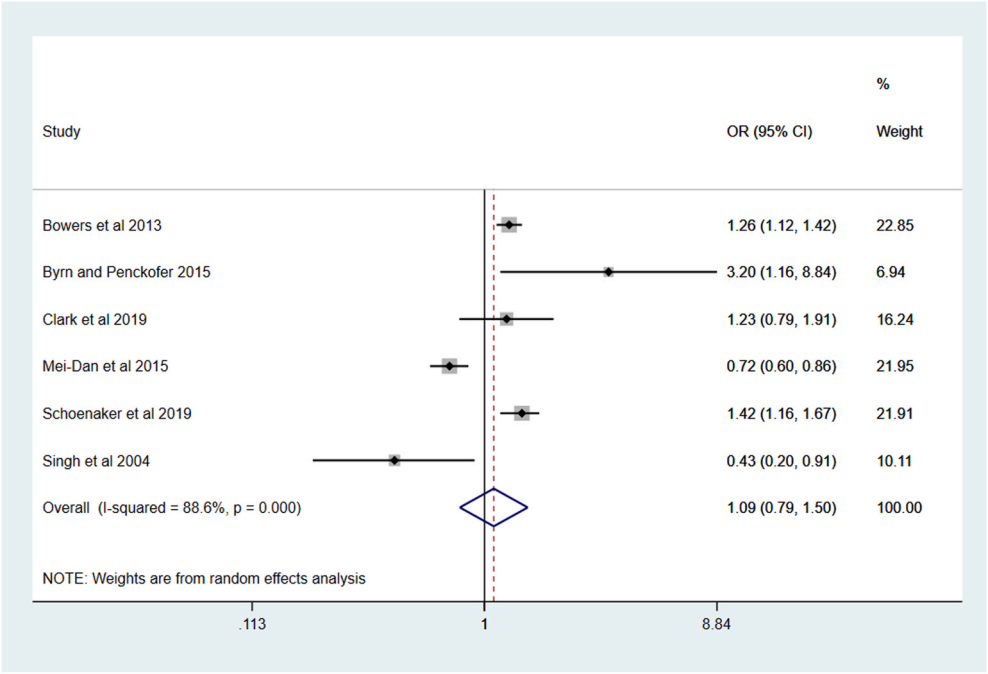


Fig. 1. Forest plot showing pooled odds ratios for GDM in women with versus without preconception depressive symptoms and diagnoses.

4. Discussion

4.1. Main findings and comparison with previous studies

This is the first systematic review and meta-analysis of data from studies measuring risk of GDM in women with a range of preconception mental disorders. There was no evidence for an effect of preconception depression on risk of GDM, although there was a dearth of studies examining anxiety disorders. One of the largest studies to date, not meeting our inclusion criteria as it grouped both anxiety and depression into one exposed group, found an increased risk of GDM in women exposed to both of these common mental disorders (Beka et al., 2017), yet our own study in a UK cohort found no such increased risk in those exposed to preconception depression and/or anxiety (Wilson et al., 2020b). The findings of this meta-analysis differ from that of another recent meta-analysis which reported an increased risk of GDM in women with depression but this is perhaps unsurprising given that the other review also included studies of depression in early pregnancy (Arafa and Dong, 2019a). Such studies were excluded from our review as the pathophysiology and epidemiology of perinatal depression may differ from depression at other times; with distinct vulnerabilities associated with the neuroendocrine fluxes and psychosocial stressors characteristic of the perinatal period (Batt et al., 2020; Brummelte and Galea, 2010).

There was evidence for an increased risk of GDM in women with schizophrenia but less evidence for bipolar disorder. However, pooled estimates were lower when studies with low to moderate risk of bias were included then when they were excluded in sensitivity analyses, suggesting that bias in some of the included studies may have in part influenced the estimates. Regarding eating disorders, while there was evidence for a reduced risk of GDM in women with AN, there was no evidence for a reduced, or indeed increased, risk with other eating disorders (BN or BED).

4.2. Potential mechanisms

Differing risks between preconception mental disorders provide potential insights into mechanisms underlying the associations (or lack of) with GDM. While many of the studies included in the review offered hypotheses for the mechanisms underlying the possible risk of GDM in women with preconception mental disorders, few studies tested these. Potential mechanisms are similar to that proposed for Type 2 diabetes. Activation of the body's stress response controlled by the hypothalamic-pituitary-adrenal (HPA) axis, as has been observed in those with mental disorder, involves release of cortisol, which opposes the action of insulin, leading to insulin resistance (Champaneri et al., 2010). Insulin resistance has been observed in those with both common mental disorders (Kan et al., 2013) and psychotic disorders (Pillinger et al., 2017). Such a mechanism may be illuminated by observing a dose response relation of increasing risk alongside increasing levels of insulin resistance. Exploration of this was limited as many of the included studies did not report diagnostic criteria used for GDM, which differs substantially between studies (see tables). Yet there is some evidence for a relation

Table 3
Summary of data provided by each study and effect estimates used in meta-analysis for psychotic disorders.

Author and year	Country	Study design and sample size	Mental disorder measure	GDM measure	Ethnicity, race or country of birth	Socioeconomic status	Risk of bias	Unadjusted OR (95% CI) for schizophrenia	Unadjusted OR (95% CI) for bipolar disorder
Bodén et al. (2012)	Sweden	Retrospective cohort study 332,137 women with 332,137 pregnancies	At least two recorded ICD-10 codes from national health registers (F30-31)	ICD-10 code O24 from national health registers Diagnostic criteria not reported	Maternal country of birth: Sweden: 78.5% Other Nordic countries: 19.9% Non-Nordic countries: 1.6%	Not reported	Low to moderate	Not reported	[b]1.10 (0.67,1.80) Using both treated and untreated BPAD as exposure N = 332,137 pregnancies
Frayne et al. (2019)	Australia	Retrospective cohort study 33,867 women with 34,348 deliveries	ICD-10 codes (F20, F25, F28, F31)	Medical records Diagnostic criteria not reported	Country of birth: Australia- 67.9–89.5% Asia: 5.6–14.3% African/ Middle East: 3.2–6.3% New Zealand/ Pacific: 1.2–4.8% Americas: 0.5–1.6% Aboriginal or Torres Strait descent: 5.1–8.5%	Low SES (lowest 2 quintiles): 19–35%	High	[a]3.59 (2.18,5.91) N = 33,548 women (excluding women with other mental disorders)	[b]1.50 (0.93,2.42) N = 33,636 women (excluding women with other mental disorders)
Galbally et al. (2020)	Australia	Retrospective cohort study 539 women with 539 pregnancies	Clinical interview Psychotic disorders (including schizophrenia, schizoaffective and related psychotic disorders) and bipolar disorder	OGTT 75g load: 2 h- ≥8 mmol/l OR ≥8.5 OR 1 h- ≥10 OR Fasting glucose: ≥5.1 OR ≥5.5	Not reported	Not reported	Low to moderate	Not reported	Not reported
Judd et al. (2014)	Australia	Retrospective cohort study 19,867 women with 19,867 pregnancies	Clinical interview using DSM-IV criteria for schizophrenia and bipolar disorder	Hospital electronic birth records Diagnostic criteria not reported	Not reported	Not reported	High	[c]2.44 (1.20,4.95) N = 19,818 pregnancies (excluding women with bipolar disorder)	[c]1.66 (0.66,4.20) N = 19,804 pregnancies (excluding women with schizophrenia)
Kitai et al. (2014)	Japan	Retrospective cohort study 1166 women with 1166 pregnancies	ICD-10 codes from hospital records (F2)	From hospital records Diagnostic criteria not reported	Not reported	Recipients of public assistance: 10%	High	[b]0.56 (0.03,9.45) Using Haldane-Anscombe correction for zero cases of GDM in exposed N = 1038 pregnancies in schizophrenia and no mental disorder groups	Not reported
Mei-Dan et al. (2015)	Canada	Retrospective cohort study 437,941 women with 437,941 pregnancies	ICD–9 or ICD-10 codes from hospital records	Validated ICD-10 codes or Canadian Classification of Health Interventions procedure codes Diagnostic criteria not reported	Not reported	Income quintile Q1 (lowest): 23.7% Q2: 20.7% Q3: 20% Q4: 19.5% Q5 (highest): 15.7%	Low to moderate	Not reported	[b]0.89 (0.71,1.12) N = 434,217 pregnancies (excluding major depressive disorder)
	Australia	Retrospective cohort study		From hospital records	Not reported	Not reported	High	[b]5.54 (2.66,11.55)	[b]3.08 (1.39,6.81)

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Table 3 (*continued*)

Author and year	Country	Study design and sample size	Mental disorder measure	GDM measure	Ethnicity, race or country of birth	Socioeconomic status	Risk of bias	Unadjusted OR (95% CI) for schizophrenia	Unadjusted OR (95% CI) for bipolar disorder
Nguyen et al. (2012)		29,943 pregnancies	Clinical diagnosis using ICD-10 criteria	Diagnostic criteria not reported				N = 29,849 pregnancies (excluding bipolar disorder and non-psychotic SMI)	N = 29,861 pregnancies (excluding schizophrenia and non-psychotic SMI)
Vigod et al. (2014)	Canada	Retrospective cohort study 433,749 women with 555,468 deliveries	Inpatient diagnosis or two or more outpatient physician service claims for schizophrenia: ICD–9 or ICD-10 codes	Validated ICD-10 codes or Canadian Classification of Health Interventions procedure codes captured during index delivery hospitalisation Diagnostic criteria not reported	Not reported	Income quintile Q1 (lowest): 23.6% Q2: 20.6% Q3: 20% Q4: 19.6% Q5 (highest): 15.7%	Low to moderate	[a]1.19 (0.95,1.50) N = 433,749 women	Not reported

GDM: gestational diabetes; OR: odds ratio; OGTT: oral glucose tolerance test.
[a] Estimate given in paper.
[b] Derived from data in paper.
[c] Data provided by study author.

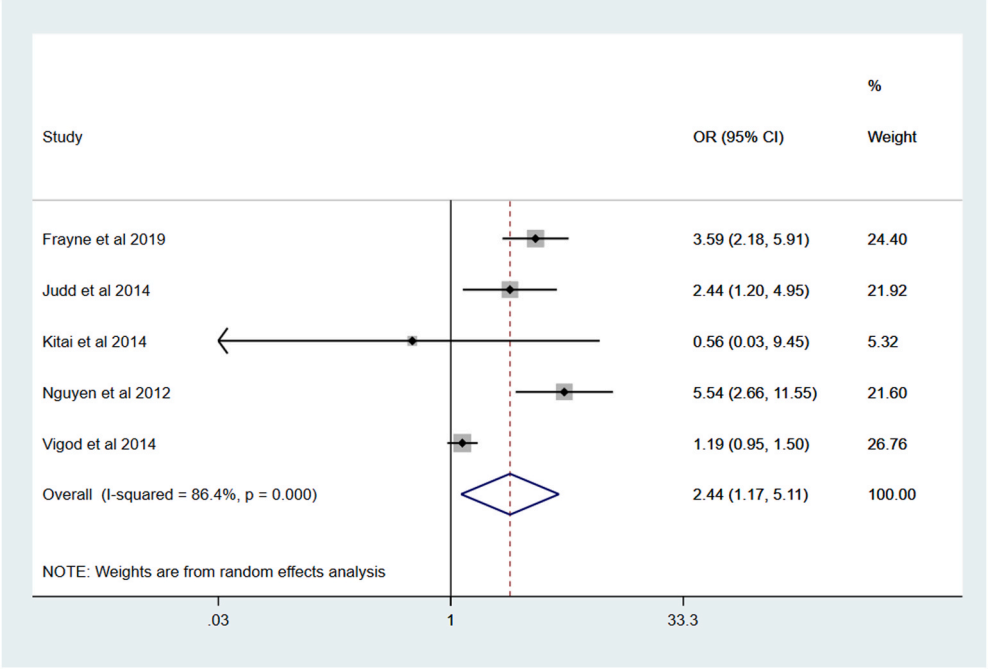

Fig. 2. Forest plot showing pooled odds ratios for GDM in women with versus without schizophrenia.

between blood glucose below diagnostic threshold for GDM and depression and anxiety (Gezginç et al., 2013). Moreover, one of the included studies observed an association between preconception depression and GDM treated with insulin: an association not observed in women whose GDM was managed without insulin (Clark et al., 2019). Management with insulin may indicate a more insulin resistant form of GDM or that women are less able to manage lifestyle changes. In those with schizophrenia, increasing levels of insulin resistance have been correlated with the presence of negative symptoms (Soontornniyomkij et al., 2019).

Insulin resistance may fully or in part be attributable to the use of psychotropic medication, which is an important potential mediator of the association between preconception mental disorder and GDM and may explain the relatively greater risk in schizophrenia. While the evidence base remains equivocal, there is evidence to support an association between GDM and antipsychotics (Wang et al., 2020) but less for mood stabilisers (Bodén et al., 2012) or antidepressants, for which the greatest risk may be for the less commonly prescribed non-SSRI (selective serotonin reuptake inhibitor) classes (Dandjinou et al., 2019; Wen et al., 2006). The dosing and duration of use is also likely to have an impact on GDM risk, certainly for antipsychotics (Schaffer et al., 2019). Perhaps women with schizophrenia are on higher doses of antipsychotics. Indeed one study comparing cardiometabolic risk factors between those with schizophrenia versus bipolar disorder reported less use of psychotropic medication in bipolar disorder (Birkenaes et al., 2007).

While the focus of this review was on the association between mental disorder and GDM, it is often difficult to isolate the effect of disorder from that of medication, although two of the included studies attempted

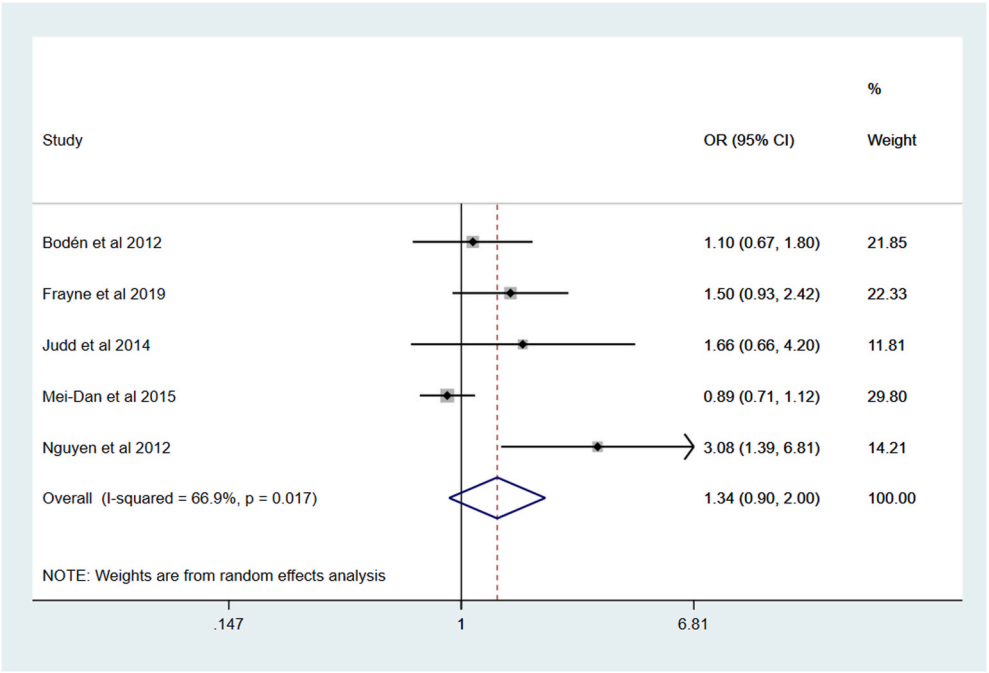

Fig. 3. Forest plot showing pooled odds ratios for GDM in women with versus without bipolar disorder.

to overcome this. One study compared mood stabiliser treated bipolar disorder to untreated and found no difference in GDM risk between the two groups (Bodén et al., 2012) but another study found an increased risk of GDM in women with psychotic disorders treated with antipsychotics versus those untreated (Galbally et al., 2020).

There are also known behavioural manifestations of mental disorder such as smoking, physical inactivity, poor diet and obesity which are risk factors for cardiovascular disease and which may be mediators on the pathway from mental disorder to GDM. Their potential presence on the causal pathway meant that they were not considered important confounders in the review's risk of bias assessment, although it remains possible that the relation between these risk factors and mental disorder may be bidirectional and they may precede the exposure of mental disorder. There is some evidence that BMI may also moderate the impact of preconception depression (Bowers et al., 2013) and psychotic disorders (Freeman et al., 2019) on risk of subsequent GDM. Evidence that these lifestyle factors may be particularly prevalent in those with schizophrenia may help to explain the greater risk observed in this group of women (De Hert et al., 2009). Yet another study found no differences in rates of smoking or obesity between those with schizophrenia versus bipolar disorder (Birkenaes et al., 2007).

The impact of body weight on metabolic risk may also explain the reduced risk of GDM in women with AN. While the process of fasting may increase risk of GDM (Mirghani and Hamud, 2006), women with AN are also more likely to be underweight than those with BN or BED, which may reduce their risk of GDM (Ante et al., 2020).

Finally, two of the studies included in this review found evidence for an association between a childhood trauma history and GDM (Clark et al., 2019; Schoenaker et al., 2019). Indeed adverse childhood experiences (ACEs) may be associated with inflammation and cardiovascular morbidity in adulthood (Danese and McEwen, 2012). Thus preconception mental disorder may be a mediator of the pathway from childhood trauma to GDM. Alternatively, early life adversity such as trauma and abuse, as an antecedent of both mental disorder and GDM, may be a confounder of the mental disorder and GDM relation. Moreover, it is surprising given this association that there was not more evidence in one of the included studies of an increased risk of GDM in women with preconception PTSD (Shaw et al., 2017). Future research may usefully focus on different anxiety disorders, as opposed to studying them as one unified group, in order to better investigate these relations.

4.3. Strengths and limitations

This review provides a synthesis of the literature to date on the risk of GDM in women with preconception mental disorders via a thoroughly scoped and comprehensive literature search in July 2020, with updated searches until January 2021. Over half of the studies were judged to be at high risk of bias; all of the eating disorders studies were at high risk. Sensitivity analyses suggested that the results of high risk studies may have inflated the estimates for psychotic disorders. Thus there a number of limitations of the included studies which are important to consider when interpreting the findings.

There were important demographic confounders of the relation between preconception mental disorder and GDM which were not considered in many studies. Both deprivation and non-White race may increase the risk of both mental disorder and GDM (Kampmann et al., 2015; Schwartz and Blankenship, 2014) but information about ethnicity or race and socioeconomic status was often missing from studies (see Tables). Therefore the now well-documented increased diagnostic rates of schizophrenia in those of Black race (Schwartz and Blankenship, 2014), a group also at an increased risk of GDM, suggests that ethnicity could be a confounder of the increased risk of GDM in women with schizophrenia. Likewise, the predominantly White ethnic composition of the eating disorders samples may help to explain the reduced risk of GDM in women with AN. However, it does not explain the divergent risks in AN and BN, given that evidence now suggests that eating disorder prevalence is relatively similar across sociodemographic groups (Mitchison and Hay, 2014), albeit this may have changed since some of the older studies in the review were conducted.

Furthermore, there were high levels of heterogeneity in the studies of depression, although it is unclear why heterogeneity increased when high risk studies were removed from the depression meta-analyses. Both mental disorder and GDM are heterogeneous conditions. Diagnostic criteria for GDM differ widely around the world and are continuously changing (Cundy and Holt, 2017). As previously noted, most of the studies did not report how GDM was defined; despite attempts to gather

Table 4
Summary of data provided by each study and effect estimates used in meta-analysis for eating disorders.

Author and year	Country	Study design and sample size	Mental disorder measure	GDM measure	Ethnicity, race or country of birth	Socioeconomic status	Risk of bias	Unadjusted OR (95% CI) for anorexia nervosa	Unadjusted OR (95% CI) for bulimia nervosa
Ante et al. (2020)	Canada	Retrospective cohort study 2,134,945 pregnancies	ICD-9 and ICD-10 codes for inpatient hospitalisation for anorexia nervosa	Diagnosis recorded in hospital records Diagnostic criteria not reported	Not reported	Composite of education, income and employment Advantaged: 17.7% Moderately advantaged: 18.9% Middle: 19% Moderately disadvantaged: 19% Disadvantaged: 19.7%	High	[b]0.64 (0.50,0.82) N = 2,134,945 pregnancies	Not reported
Bulik et al. (2009)	Norway	Retrospective cohort study 35,929 women with 35,929 pregnancies	Diagnostic interview	From medical notes Diagnostic criteria not reported	Not reported	Not reported	High	[c]0.73 (0.04,11.96) Using Haldane-Anscombe correction for zero cases of GDM in exposed N = 33,777 pregnancies in unexposed and anorexia nervosa groups	[c]1.05 (0.47,2.36) N = 34,046 pregnancies in unexposed and bulimia nervosa groups
Kouba et al. (2005)	Sweden	Case-control study 117 women with 117 pregnancies	Diagnostic interview	Medical records Diagnostic criteria not reported	Not reported	Not reported	High	[b]2.80 (0.05,144.78) Using Haldane-Anscombe correction for zero cases of GDM in exposed and unexposed N = 92 pregnancies (excluding bulimia nervosa and eating disorder NOS)	[b]3.34 (0.06,173.70) Using Haldane-Anscombe correction for zero cases of GDM in exposed and unexposed N = 88 pregnancies (excluding anorexia nervosa and eating disorder NOS)
Linna et al. (2014)	Finland	Retrospective cohort study 4299 women with 7397 pregnancies	ICD-10 codes from hospital records	'Pathologic OGTT' from medical records Diagnostic criteria not reported	Not reported	Not reported	High	[a]0.40 (0.14,1.13) N = 6621 pregnancies (excluding bulimia nervosa and binge eating disorder)	[a]0.91 (0.57,1.46) N = 7043 pregnancies (excluding anorexia nervosa and binge eating disorder)
Micali et al. (2007)	UK	Prospective cohort study 12,254 women with 12,254 pregnancies	Self-report Past history of anorexia nervosa or bulimia nervosa	Not reported	96.2–98.8% White ethnicity	32.8–49.1% in employment or full-time education	High	Not reported	Not reported
Micali et al. (2012)	Netherlands	Prospective cohort study 5256 women with 5256 pregnancies	Self-report Past history of anorexia nervosa or bulimia nervosa	Midwifery and hospital registers Dutch obstetric guidelines: Random glucose: ≥11.1 mmol/l OR Fasting glucose: >7.0 mmol/l	Ethnicity: Caucasian: 63.8–73.6% Non-Caucasian: 25.6–33.1% Missing: 0.8–3.1%	Maternal education None or primary only: 3.3–9% Secondary: 38.6–47.3% Higher: 44.2–52.1% Missing: 1.5–4.4% Net household income (euros/month) <1200: 12.4–15.1% 1200-2000: 19.1–24.9% >2000: 50–61.2% Missing: 4.6–14%	High	[b]0.45 (0.03,7.38) Using Haldane-Anscombe correction for zero cases of GDM in exposed N = 3945 pregnancies in unexposed and anorexia nervosa groups	[b]1.14 (0.27,4.80) N = 4025 pregnancies in unexposed and bulimia nervosa groups
	UK					Not reported	High	Not reported	Not reported

(continued on next page)

Table 4 (*continued*)

Author and year	Country	Study design and sample size	Mental disorder measure	GDM measure	Ethnicity, race or country of birth	Socioeconomic status	Risk of bias	Unadjusted OR (95% CI) for anorexia nervosa	Unadjusted OR (95% CI) for bulimia nervosa
Morgan et al. (2006)		Retrospective cohort study 204 women with 204 pregnancies	Diagnostic interview	Medical records Diagnostic criteria not reported	Ethnicity: 97% Caucasian				

GDM: gestational diabetes; OR: odds ratio; OGTT: oral glucose tolerance test.
[a] Estimate given in paper.
[b] Derived from data in paper.
[c] Data provided by study author.

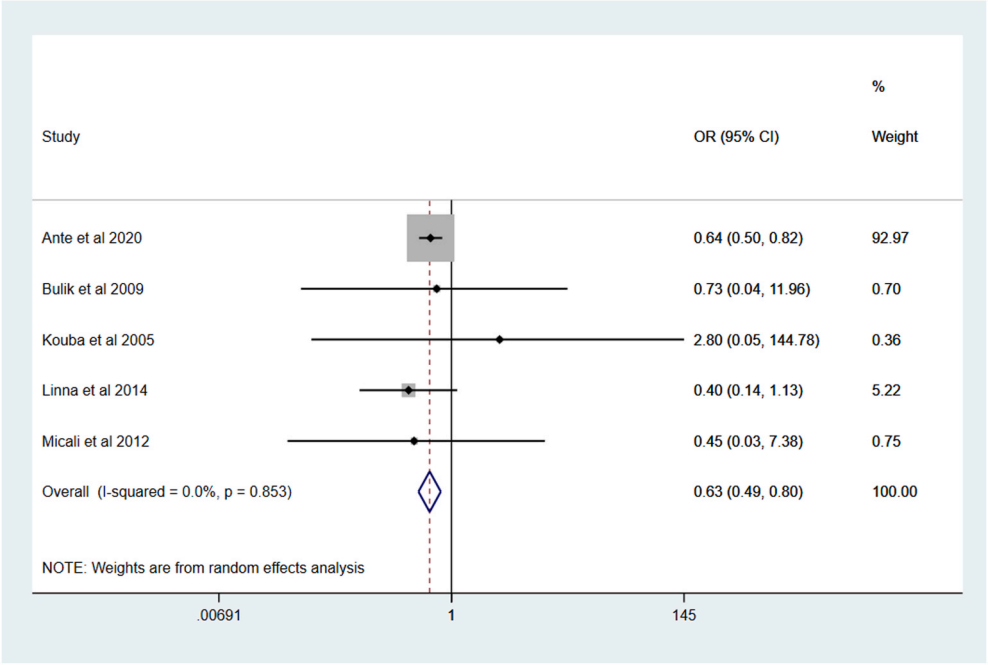

Fig. 4. Forest plot showing pooled odds ratios for GDM in women with versus without anorexia nervosa.

such information when corresponding with study authors, many did not know. Likewise, measures of mental disorder differed between studies, particularly in studies of depression utilising both screening and diagnostic tools with particularly high heterogeneity (I^2) on meta-analysis. However, a sensitivity analysis in which only diagnostic tools were used did not substantially reduce the I^2.

Finally, the term 'preconception' is generally ill defined in the research literature, with few of the included studies being clear about whether or not mental disorder was measured prior to the woman's first ever pregnancy or only prior to the GDM-affected index pregnancy. This is more relevant when considering the common mental disorders of anxiety and depression, which are known to relapse and remit, hence the stricter inclusion criteria for these disorders. Such clarity is important when considering the direction of the relation as the accumulating risk from GDM and/or mental disorder in previous pregnancies could influence risk for GDM in subsequent pregnancies; for example postnatal depression following a woman's first GDM-affected pregnancy may increase the risk for GDM in subsequent pregnancies but may also increase the risk for subsequent mental disorder. Thus timing and chronicity of mental disorder is an important variable, the exploration of which was limited within the included studies. It is also likely that there is a degree of co-morbidity among the different mental disorders in the populations studied.

4.4. Implications

Further research is needed to increase understanding of the relation between preconception mental disorder and GDM; the association between anxiety disorders and GDM remains particularly unexplored and the mechanisms underlying risk pathways poorly understood. Such research has the potential to illuminate targets for intervention to reduce the risk not only of GDM but other metabolic complications of pregnancy such as pre-eclampsia and gestational hypertension which exhibit some similarities to GDM in their pathophysiology and share common risk factors (Carpenter, 2007).

The possible increased risk of GDM in those with schizophrenia, and to a lesser extent bipolar disorder, has implications for this group of women. Early identification and assertive treatment of GDM in women who may be at increased risk is vital in reducing the adverse outcomes associated with GDM, including obstetric complications such as emergency Caesarean delivery and longer-term risks of maternal Type 2 diabetes and adverse neuro-behavioural and metabolic outcomes in offspring (Kampmann et al., 2015). This is facilitated by integrated physical and mental healthcare, such as knowledge of both psychiatric and medical conditions in professionals working across medical and psychiatric settings and access to appropriate referral pathways between specialities. While National Institute for Health and Care Excellence

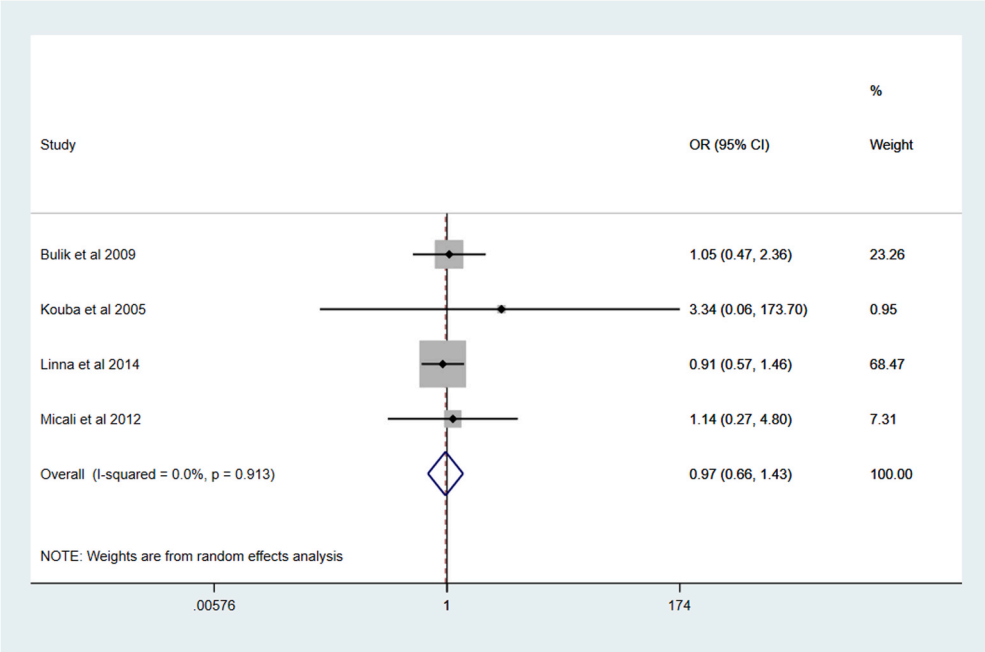

Fig. 5. Forest plot showing pooled odds ratios for GDM in women with versus without bulimia nervosa.

(NICE) guidelines for the management of perinatal mental health recommend that pregnant women taking antipsychotics be screened for GDM (National Institute for Health and Care Excellence,), such a recommendation for this potentially at-risk group could also be included in NICE guidelines for the management of diabetes in pregnancy (NICE, 2020); these guidelines may be read by different professional groups.

There exist a number of integrated models of physical and mental healthcare in the general population (Attoe et al., 2018) but the potential for this to be emulated in the maternity setting is yet to be realised. Yet even in those with common mental disorders, the benefits of effectively treating one condition, such as diabetes are reflected in improved symptoms of mental disorder and vice versa (Moulton et al., 2018; Petrak et al., 2015).

The increased risk of GDM in women with psychotic disorders also underscores the importance of optimising health in the preconception period to reduce the risk of complications during pregnancy such as GDM (Catalao et al., 2020). There is an urgent need for professionals working with women with psychotic disorders of reproductive age to assertively consider the implications of their management for reproductive health and work alongside women to encourage positive behaviour change (Wilson et al., 2018). For example, given that insulin resistance likely begins in the preconception period prior to the diagnosis of GDM during pregnancy, preconception metabolic screening for conditions such as Type 2 diabetes could be particularly valuable. Such a proactive and holistic approach, integrating both physical and mental healthcare could improve short- and long-term outcomes for women and their children.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2022.03.013.

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