Maternal glucose levels and future risk of developing cardiovascular disease: a systematic review and meta-analysis protocol

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ABSTRACT

Introduction Hyperglycaemia during pregnancy has been considered as one of the risk factors for cardiovascular diseases (CVDs) among women. Although the evidence regarding the association between gestational diabetes mellitus (GDM) and subsequent CVD has been synthesised, there are no systematic reviews covering the evidence of the association among the non-GDM population. This systematic review and meta-analysis, therefore, aim to fill the gap by summarising existing evidence on the association between maternal glucose levels and the risk of future CVD in pregnant women with or without a diagnosis of GDM.

Methods and analysis This systematic review protocol was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols guidelines. Comprehensive literature searches were performed in the following electronic databases: MEDLINE, EMBASE and CINAHL to identify relevant papers from inception to 31 December 2022. All observational studies (case-control studies, cohort studies and cross-sectional studies) will be included. Two reviewers will perform the abstract and full-text screening based on the eligibility criteria through Covidence. The Newcastle-Ottawa Scale will be used to assess the methodological quality of included studies. Statistical heterogeneity will be assessed by using the I² test and Cochrane’s Q test. If the included studies are found to be homogeneous, pooled estimates will be calculated and meta-analysis will be performed using Review Manager 5 (RevMan) software. Random effects will be used to determine weights for meta-analysis, if needed. Pre-specified subgroup analysis and sensitivity analysis will be performed, if needed. The study results will be presented in the sequence of main outcomes, secondary outcomes and important subgroup analysis for each type of glucose level separately.

Ethics and dissemination Given no original data will be collected, ethics approval is not applicable for this review. The results of this review will be disseminated by publication and conference presentation.

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INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death according to 2017 WHO report. It is estimated that CVD had caused nearly 18 million deaths worldwide in 2019, accounting for 32% of all deaths. An estimated 30% of female deaths are caused by CVDs. Most CVDs can be prevented if individuals at high CVDs risk can be detected and appropriately managed in a timely manner. Thus, targeting women who are at increased risk for developing CVD will be useful for early screening and prevention for CVDs incidence as well as lowering the mortality rate of CVD. A recent review found that women with pregnancy complications, such as preterm birth, preeclampsia, gestational hypertension, stillbirth, gestational diabetes and so on, have a higher risk of developing CVD. Perinatal care might potentially provide the opportunity to identify future risk of CVD for the majority of women given that over 80% of women will experience pregnancy at some point in their lifetime and hence are likely to undergo antepartum glucose screening.

Perinatal glucose screening for gestational diabetes mellitus (GDM) has been part of standard obstetrical care worldwide to identify women at increased risk of short-term and long-term adverse outcomes in the context of hyperglycaemia during pregnancy to ensure treatment is given to reduce these
complications. Universal screening for GDM in asymptomatic pregnant women after 24 weeks of gestation has been recommended since 2013 in the USA.6 7 Meanwhile, the National Institutes of Health and the American College of Obstetricians and Gynaecologists advocate that women with significant risk factors of GDM, such as body mass index >35 kg/m² or maternal age ≥40 years, and previous macrosomia must be screened for unrecognised type 2 diabetes before 24 weeks of gestation.8 9 Glucose screening may be an effective and efficient tool to identify women at risk of developing CVD for prevention if there is an association between glucose levels at screening with subsequent risk of CVD within the general obstetric population.

Previous studies have shown that elevated maternal glycaemia levels were associated with an increased risk of developing CVD. A recent systematic review and meta-analysis covering 5 390 591 women revealed that those with GDM had twice the risk of future CVD, which becomes apparent within the first decade after delivery.16 However, the association between maternal hyperglycaemia and subsequent CVD risk may extend to the non-GDM range based on the finding of a few recent studies.4 11 Although the association of borderline elevated maternal glycaemia level with future risk of developing CVD in pregnant women may not be as strong as GDM, interventional targeting of this group of women may have a greater impact on the overall disease burden in the society as the size of affected women is larger.

Although evidence regarding the association between GDM and subsequent CVD has been synthesised, there are no systematic reviews covering the evidence of the association among the non-GDM population. This systematic review and meta-analysis, therefore, aim to fill the gap by summarising existing evidence on the association between maternal glucose levels and the risk of future CVD in pregnant women with or without a diagnosis of GDM.

METHODS

Eligibility criteria

Population
This review focuses on women who had a delivery history along with glucose levels measured during pregnancy. Studies included in this review were required to report results for either both the GDM and non-GDM population, or non-GDM population only.

Exposure
Most of the diagnosis criteria for GDM or type 2 diabetes in clinical practice include 100g 3 hours oral glucose tolerance test (OGTT) or 75g 2 hours OGTT.12 13 This review will examine maternal glucose level measured by fasting plasma glucose (FPG), post plasma glucose (PPG) measured by the 50g glucose challenge test (50g GCT), the 75g OGTT or the 100g OGTT and the glycated haemoglobin level (HbA1c). No specifications were made regarding the gestational age of the maternal glucose level.

Comparator
For this review, the reference group refers to those women whose glucose levels were in the lowest range as defined by each study. The index pregnancy refers to the eligible pregnancy in which the glucose measurements were included.

Outcome
The primary outcome was incident of CVD following the delivery of the index pregnancy, which is a composite of heart failure, coronary heart disease (myocardial infarction, angina, myocardial ischemia, coronary artery disease, acute coronary syndrome, angina), stroke, transient ischaemic attack, intracranial haemorrhage and peripheral vascular disease. Studies that include any of the conditions above were included in this review. The secondary outcome was any CVD diagnosis.

Setting and language
This review will not restrict settings, publication dates and languages.

Study design
All observational studies (case-control studies, cohort studies and cross-sectional studies) will be included.

Exclusion
This review will exclude case reports, case-series, unpublished abstracts, commentaries, editor letters and reviews without original data presented. Studies without a comparison of exact glucose level, but rather with a categorisation of the population by a diagnosis of GDM or non-GDM will be excluded as well. Studies indexed as child only and animal studies will be excluded from this review.

Information sources
Comprehensive literature searches will be performed in the following electronic databases: MEDLINE, EMBASE and CINAHL to identify relevant papers. Since no restrictions were set for the date of publication, the search will be from inception to 31 December 2022. Information sources will be updated prior to submission of this review. To ensure all relevant studies will be covered in this review, the information sources will be further supplemented by scanning the reference list of selected studies and systematic reviews of similar scope.

Search strategy
Our search strategy was created with the aid of a medical librarian based at the University of Ottawa who is experienced in systematic review searches. A combination of Medical Subject Headings and keyword terms relevant to both exposure and outcome of interest was used to develop the search strategy. No restrictions based on date or languages were set to the literature search. Search
strategies for MEDLINE, EMBASE and CINAHL were presented in online supplemental appendices 1, 2 and 3 respectively.

Protocol
This systematic review protocol was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) guidelines. Online supplemental appendix 4 provides the details of the PRISMA-P checklist. The protocol has been registered on the PROSPERO International Prospective Register of Systematic Reviews. The date, rationale and details of changes for each section will be provided if protocol adjustments are required.

Patient and public involvement
None.

Data management
Results from the literature search are to be imported, screened, stored and analysed by professional software-based platforms, including Review Manager 5 (RevMan) and Covidence. Duplicates will be automatically removed by Covidence in addition to manually checking for study similarities (year of publication, author’s name, volume, issue and so on) via authors.

Selection process
Two reviewers (NZ, WW) will perform the abstract and full-text screening based on the eligibility criteria through Covidence. Any disagreements between the two reviewers will be resolved via a third reviewer (SWW). During the phase of full-text screening, a separate category will be created in Excel to include those relevant studies by scanning the reference list of included studies and systematic reviews of the same scope. Meanwhile, the reasons for exclusion will be documented during the full-text screening. A final decision regarding the included studies could be made based on both the results from Covidence and the spreadsheet. PRISMA flow diagrams will be used to present the results from the study selection.

Data collection
A data extraction form will be created as a standardised data collection tool. A pilot test using the form will be conducted among groups, and if necessary, the form will be modified based on the group feedback. Data obtained from included studies will be independently extracted by two reviewers (NZ, WW). A calibration exercise will be undertaken by reviewers to ensure consistent methods of assessment across reviewers. The principal investigator (SWW) will be involved in the event of any discrepancies that arise between reviewers.

Data items
The following data items will be extracted from included studies: (1) study data: title, author name, year of publication, country of study, journal, sample size, study period, study design, follow-up period and limitations; (2) population: characteristics of the participants, for example, mean age, social economic status, race/ethnicities, whether or not there was a diagnosis of GDM, whether or not there was a progression to type 2 diabetes; (3) exposure: maternal glucose level measured using FPG, PPG from 50g-GTT or 75g-OGTT or 100g-OGTT and HbA1c. If the maternal glucose level is categorised, then the cut-off points will be specified; (4) comparison: reference category will be specified if the maternal glucose level is considered to be a categorical variable; (5) outcome: composite of outcome events, start of follow-up period, length of follow-up for outcome variables; (6) effect measures: reported effect measures for the composite outcomes and separate outcomes if available, including p values, SD and CIs and (7) sources of funding.

Outcomes and prioritisation
The composite of CVDs (as defined by each study) will be collected. CVDs include heart failure, coronary heart disease (myocardial infarction, angina, myocardial ischaemia, coronary artery disease, acute coronary syndrome, angina), stroke, transient ischaemic attack, intracranial haemorrhage, peripheral vascular disease as well as relevant procedures (coronary artery bypass grafting, percutaneous coronary intervention or carotid endarterectomy and so on). The composite of the CVDs will be regarded as the main outcome, while each reported CVD will be considered as the secondary outcome.

Risk of bias assessment
The Newcastle-Ottawa Scale (NOS) will be used to assess the methodological quality of included studies. The major three domains (eight items) of bias to be assessed consist of selection, comparability and ascertainment of outcome (cohort or cross-sectional studies) or exposure (case-control studies). Cohort studies and case-control studies will be assessed by NOS for cohort studies and NOS for case-control studies separately. Adapted NOS, which is adjusted based on the NOS for cohort studies, will be used to assess the cross-sectional studies. A maximum of one star could be assigned for the numbered items under the selection as well as ascertainment of outcome or exposure domain. A maximum of two stars could be assigned for the numbered items under the section of comparability. A study with scores from 7 to 9, 4–6 and 0–3 will be considered high quality, high risk and high risk of bias, respectively. Two reviewers (NZ, WW) will be assigned to assess the quality of each study, and a third reviewer (SWW) will be consulted wherever disagreements arise. The results of the risk of bias assessment will be presented in a table.

Data synthesis
Patient characteristics (ie, age, race/ethnicities, social economic status), follow-up periods for outcome and type of test to measure glucose level will be assessed. Statistical heterogeneity will be assessed by using the I²
test and Cochrane’s Q test. Based on the guidelines of Cochrane, heterogeneity will be interpreted as ‘may not be important’, ‘moderate heterogeneity’, ‘substantial heterogeneity’ and ‘considerable heterogeneity’ when the I² is in the range of 0%–40%, 30%–60%, 50%–90% and 75%–100%, respectively. If the included studies are homogeneous, pooled estimates will be calculated and meta-analysis will be performed using Review Manager 5 (RevMan) software. Random effects will be used to determine weights for meta-analysis, if needed. If heterogeneity is at a substantial level (I² ≥50% or p<0.1) or data is not present, a qualitative (narrative) synthesis or summary will be performed instead of meta-analysis. Additionally, if included studies cover both exposures measured continuously and categorically, meta-analysis will be performed separately for these two types of measurement. Meanwhile, if different types of effect measures are used in these included original studies, such as ORs, risk ratios and hazard risks, meta-analysis will be further performed individually for each type of effect measures. The study results will be reported in the sequence of main outcomes, secondary outcomes and important subgroup analysis for each type of glucose measurement separately.

Stratification analysis will be performed to investigate possible causes of between-study variability or to explore the robustness of meta-analysis. Considering that the gestational age of measurement of glucose level greatly impacts the value of maternal glucose level, the study results will be stratified based on gestational age at glucose measurement. Study results will be further stratified based on the study design to determine whether the study design influences the magnitude of association. Additionally, study results will be stratified by maternal age to determine whether age impacts the association between maternal glucose level and future risk of CVD. Given that the length of follow-up periods for CVD might affect the magnitude of the association between the maternal glycemia level and future risk of CVD, subgroup analysis will be conducted by stratifying the duration of follow-up periods for outcomes. Finally, since the race/ethnicity may modify the association of interest, subgroup analysis will be performed based on the race/ethnicity of the majority of the study population. Meta-regression might be considered to deal with potential heterogeneity if more than 10 studies cover the covariates of interest. The following comparisons will be performed by each of the following factors provided that the data are available.

Stratification by gestational age of glucose measurement:
- Gestational age less than 24 weeks.
- Gestational age between 24 and 28 weeks.
- Gestational age more than 28 weeks.
- Anytime during pregnancy.

Stratification by study type:
- Cohort studies.
- Case-control studies.
- Cross-sectional studies.

Stratification by maternal age:
- <35 years old.
- ≥35 years old.

Stratification by length of follow-up periods for outcomes:
- <15 years.
- ≥15 years.

Stratification by race/ethnicity of the majority of the study population:
- Asians.
- Non-Hispanic whites.
- Hispanic whites.
- Black.

Sensitivity analysis will be performed wherever there are small studies, studies with a high to very high risk of bias and industry-funded studies.

**Meta-bias(es)**

Outcome reporting biases will be evaluated by comparing outcomes reported in protocols with outcomes presented in studies. If the protocol of a study is unavailable, outcomes presented in the methods will be compared with the outcomes presented in the results from the published paper. Sensitivity analysis will be performed in order to evaluate the impact of selective reporting on meta-analyses results, if needed. If the number of included studies exceeds 10, funnel plots will be used to explore publication bias, but if it is less than 10, publication bias will not be evaluated given the limited power.

**Confidence in cumulative evidence**

To assess the overall strength of the body of evidence, the Grading of Recommendations Assessment, Development and Evaluation approach will be used. The quality of evidence will be assessed from the following domains: risk of bias, imprecision, indirectness, inconsistency and publication bias. Given that all studies in this review were observational studies, evidence will begin with low ratings, with the potential of upgrading if the magnitude of the effect is sufficiently large, if there is a dose–response relationship or if all plausible biases could decrease the magnitude of an apparent effect.

**Ethics and dissemination**

Given no original data will be collected, ethics approval is not applicable for this review. The results of this review will be disseminated by publication and conference presentation.

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**Contributors** NZ and SWW conceived and designed this study. NZ and WW developed the search strategy. DJC developed the data synthesis section. WL...
drafted the risk of bias assessment section. TK developed the meta-bias section as well as the confidence in cumulative evidence section. WW drafted the information sources and the search strategy sections. NZ drafted the rest part of the protocol. SWW critically revised the protocol. All authors read and approved the final version of the protocol. SWW is the guarantor of the protocol.

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