Title:

The use of antipsychotic agents during pregnancy and the risk of gestational diabetes mellitus: A systematic review and meta-analysis

Short title: Antipsychotics in pregnancy and the risk of GDM

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Abstract (234/250 words):

Background: Previous studies have found contradicting results with regard to the use of antipsychotics during pregnancy and the risk of gestational diabetes mellitus (GDM). We aimed to evaluate the association between antipsychotic use in pregnancy and GDM.

Methods: A systematic literature search was conducted in PubMed, EMBASE, PsycINFO and Cochrane Library databases up to March 2019, for data from observational studies assessing the association between gestational antipsychotic use and GDM. Non-English studies, animal studies, case reports, conference abstracts, book chapters, reviews and summaries were excluded. The primary outcome was GDM. Estimates were pooled using a random effect model, with the I^2 statistic used to estimate heterogeneity of results. Our study protocol was registered with PROSPERO number: CRD42018095014.

Results: 10 cohort studies met the inclusion criteria in our systematic review with 6,642 exposed and 1,860,290 unexposed pregnancies. Six studies were included in the meta-analysis with a pooled adjusted relative risk (RR) of 1.24 overall (95% Confidence Interval [CI]: 1.09-1.42). The I^2 result suggested low heterogeneity between studies (I^2=6.7%, p=0.373).

Conclusion: We found that the use of antipsychotic medications during pregnancy is associated with increased risk of GDM in mothers. However, the evidence is still insufficient, especially for specific drug classes. We recommend more studies to investigate this association for specific drug classes, dosages and comorbidities to help clinicians to manage the risk of GDM if initiation or continuation of antipsychotic prescriptions during pregnancy is needed.

Key words: Pregnancy; Antipsychotics; Gestational diabetes

Introduction

Antipsychotics including first generation antipsychotics (FGAs) and second generation antipsychotics (SGAs) are commonly utilized as pharmacological treatment for schizophrenia, psychotic disorders and bipolar disorder (Barbui et al., 2013; Buchanan et al., 2009; Gentile, 2008). Women with pre-existing severe mental illness (SMI) sometimes require antipsychotics therapy during pregnancy to reduce symptoms and to prevent relapse. Furthermore, pregnancy can cause physiological, hormonal, and psychological changes (Andersson et al., 2003; Howard, 2005; Jones, Chandra, Dazzan, & Howard, 2014; Vesga-Lopez et al., 2008) that may increase the risk of psychiatric disorders, such as postpartum mood disorders (O'Hara, Schlechte, Lewis, & Varner, 1991; Yonkers, Vigod, & Ross, 2012). The benefits and the potential risks of the use of antipsychotic drugs during pregnancy should both be considered as well as any potential risks associated with stopping on-going antipsychotic therapy. Discontinuance may raise maternal anxiety levels, and also influence fetoplacental integrity and foetal central nervous system development (Cohen & Rosenbaum, 1998). In the past two decades, the use of antipsychotics in pregnant women, especially SGAs, has increased (Lao et al., 2017; Mitchell et al., 2011; Toh et al., 2013). Studies are vital to explore the comparative safety and effectiveness of these drugs with respect to other therapeutic choices in pregnancy.

Gestational diabetes mellitus (GDM) is considered as a common adverse obstetric outcome in mothers with an estimated global prevalence of 4% to 16%, with differences between ethnicities and geographic regions (Brand et al., 2018; Guariguata, Linnenkamp, Beagley, Whiting, & Cho, 2014; Scholl, Sowers, Chen, & Lenders, 2001). Any woman can develop GDM during pregnancy, but the risk is especially high in women with a higher BMI, a previous overweight baby, a previous GDM history, and parents or siblings with diabetes (NHS, 2018). Women with GDM are at higher risk for developing type 2 diabetes after pregnancy and more likely to have delivery complications including intrauterine foetal death, neonatal jaundice, preterm delivery, and infant macrosomia (Association, 2004; DeSisto, Kim, & Sharma, 2014; Vesco et al., 2012).

It is well-known that treatment with antipsychotics is associated with metabolic side effects, such as weight gain and hyperglycemia (Bak, Fransen, Janssen, van Os, & Drukker, 2014; Regenold, Thapar, Marano, Gavirneni, & Kondapavuluru, 2002). This association has been reported in clinical trials including children and adolescents, but no studies to date have included pregnant women (Bobo et al., 2013; De Hert, Dobbelaere, Sheridan, Cohen, & Correll, 2011). To our knowledge, the latest published systematic review on this topic included articles in PubMed up to 31 March 2018 (Uguz, 2019). This review included not only observational studies but also review studies and concluded that no adequate evidence indicated a causal association between antipsychotics exposure in pregnancy and the risk of GDM. Furthermore, they did not conduct a meta-analysis; hence they were not able to provide an overall quantitative summary of their results. We therefore conducted a systematic review and meta-analysis on this topic including all observational studies published until March 2019 to demonstrate whether prenatal antipsychotics use can lead to a higher risk of GDM.

Methods

Search strategy and selection criteria

A systematic literature search was conducted in PubMed, EMBASE, PsycINFO and Cochrane Library databases up to 14 March 2019 following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines and checklist (Appendix 1). Observational studies that investigated the relationship between antipsychotic use during pregnancy and the risk of GDM were searched using comprehensive search terms (Appendix 2). Articles that met the following criteria were included in this review: 1) cohort or case-control design; 2) reported the association between gestational antipsychotic use and the risk of GDM; and 3) published in English language. Other study types, including animal studies, case reports, conference abstracts, book chapters, reviews and summaries or articles written in other languages were excluded. Our study protocol was registered in the International Prospective Register of Systematic Reviews database (PROSPERO: CRD42018095014).

Data analysis

All searched articles were screened independently by two investigators (ZW and BA) in order to identify the relevant papers based on titles, abstracts as well as full text contents. Discrepancies were resolved through discussion. Information from eligible papers was extracted independently by two authors (ZW and PM) using a standardised data collection form which included the publishing year, study site, study period, data source (categorised with reference to previous methodological study (Wang et al., 2018)), study design, sample size, medication exposure, exposure period and pregnancy definition, exposure as well as outcome ascertainment, selection of study and comparison group, confounding adjustment, and statistical analysis. Outcome metrics such as risk ratio (RR), odds ratio (OR) and the corresponding 95% confidence intervals (CI) were extracted and included in the meta-analysis if appropriate. For the articles that did not provide relevant outcome metrics, the corresponding risk estimates were calculated if sufficient information was reported in the study.

The Newcastle-Ottawa Scale (NOS) was used to assess the methodological quality of observational studies. Separate NOS criteria were used for case-control and cohort studies. The assessment focuses on three major sections: selection (definition of cases/exposed subjects, representativeness of the cases/exposed subjects, selection of control/non-exposed subjects), comparability (controls or adjustment for confounding factors) and outcome/exposure (assessment/ascertainment of outcome/exposure, adequate non-response rate or follow-up time) with the total score ranging from zero to nine (Higgins & Green, 2011; Stang, 2010) and a higher score indicating a better quality. The quality of studies was independently assessed by two investigators (ZW and PM) and the studies that were rated as good (a score of one or above in each section and a total score of six or above) were included in the meta-analysis. Estimates were pooled using a random-effect model with the corresponding 95% CI for each outcome in the meta-analyses (DerSimonian & Laird, 1986). Subgroup analyses were conducted for users of 1) FGAs only, 2) SGAs only, and 3) any antipsychotics. Heterogeneity among

included studies was evaluated using I^2, where a value of 0% is considered as no observed heterogeneity and larger values indicating increasing heterogeneity (Higgins, Thompson, Deeks, & Altman, 2003). A cut-off p-value of 0.1 was considered statistically significant for heterogeneity which indicates a high degree of variance among the included studies. For articles using the same data source or population, the study with the largest sample size was included in the meta-analyses. All analyses were conducted using STATA 15. We conducted several sensitivity analyses in which we removed the study with the largest weight from the meta-analysis.

Results

A total of 1,784 records were identified for screening after removing 254 duplicates on 14 March 2019. Out of 22 full-text articles that were assessed for eligibility, 10 studies met the inclusion criteria for this systematic review with a total of 6,642 exposed pregnant women and 1,860,290 unexposed controls (Bellet et al., 2015; Boden, Lundgren, Brandt, Reutfors, & Kieler, 2012; Frayne et al., 2017; McKenna et al., 2005; Panchaud et al., 2017; Park et al., 2018; Petersen et al., 2016; Reis & Kallen, 2008; Sadowski, Todorow, Yazdani Brojeni, Koren, & Nulman, 2013; Vigod, Gomes, Wilton, Taylor, & Ray, 2015) (Fig. 1).

A summary of the characteristics of the included studies can be found in Table 1. All studies were published in English from 2005 onwards: four prospective cohort studies (Bellet et al., 2015; McKenna et al., 2005; Panchaud et al., 2017; Sadowski et al., 2013), and six retrospective cohort studies (Boden et al., 2012; Frayne et al., 2017; Park et al., 2018; Petersen et al., 2016; Reis & Kallen, 2008; Vigod et al., 2015). Four studies recruited subjects in European countries (Bellet et al., 2015; Boden et al., 2012; Petersen et al., 2016; Reis & Kallen, 2008), four in North America (Panchaud et al., 2017; Park et al., 2018; Sadowski et al., 2013; Vigod et al., 2015), one in Australia (Frayne et al., 2017), and one study was conducted by multiple centres including Israel and western countries such as Canada and UK (McKenna et al., 2005).

Five studies were conducted with administrative databases/registries (Boden

et al., 2012; Park et al., 2018; Petersen et al., 2016; Reis & Kallen, 2008; Vigod et al., 2015), four used ad hoc disease registries (Bellet et al., 2015; McKenna et al., 2005; Panchaud et al., 2017; Sadowski et al., 2013), and one used an ad hoc clinical sample (Frayne et al., 2017). Reis and Kallen (2008) identified exposures through interviews performed by midwives during antenatal care visits. All other administrative database/registry studies identified exposures by prescriptions and/or filled prescription records (Boden et al., 2012; Park et al., 2018; Petersen et al., 2016; Vigod et al., 2015). In studies conducted with ad hoc disease registries, exposure was assessed using questionnaire (Bellet et al., 2015; McKenna et al., 2005), interview (Panchaud et al., 2017) or self-report (Sadowski et al., 2013). Exposure in the ad hoc clinical sample was recorded by obstetric and psychiatric medical staff (Frayne et al., 2017). Women were considered exposed if they had one or more antipsychotic prescriptions between their last menstrual period date and delivery date. Vigod et al. (2015) and Park et al. (2018) restricted their study cohort to women with at least two prescriptions during pregnancy and Sadowski et al. (2013) required pregnant women to use a 2nd generation antipsychotic for a minimum of four weeks during pregnancy. Additionally, six studies limited the exposure period specifically for early pregnancy (usually before the end of the first trimester) (Panchaud et al., 2017; Reis & Kallen, 2008), late pregnancy (Frayne et al., 2017) or a critical period for the outcome of interest: Vigod et al. (2015): within the first or second trimester; Petersen et al. (2016): between 31 to 105 days after pregnancy start; Park et al. (2018): first 140 days of pregnancy (Park et al., 2018; Petersen et al., 2016; Vigod et al., 2015) (Table 1).

Five studies evaluated any antipsychotic exposure in mothers (Boden et al., 2012; Frayne et al., 2017; Petersen et al., 2016; Reis & Kallen, 2008; Vigod et al., 2015), while five focused on SGAs only (Bellet et al., 2015; McKenna et al., 2005; Panchaud et al., 2017; Park et al., 2018; Sadowski et al., 2013). None of the SGAs studies provided details on whether the exposed group was co-prescribed FGAs. Three studies reported the risk of GDM relating to a specific drug (Bellet et al., 2015; Boden et al., 2012; Park et al., 2018). Boden et al. (2012) included women with olanzapine or clozapine alone or together with any

other antipsychotics in the study cohort. Two studies investigated the same drug (aripiprazole), but reported opposite results: Bellet et al. (2015) found a 15% increased risk (95% CI: 0.33-4.04) vs Park et al. (2018) who reported a 18% decreased risk (95% CI: 0.50-1.33). No study investigated the risk of GDM in users of FGAs only.

Only Panchaud et al. (2017) and Park et al. (2018) reported the impact of the dosage on the risk of GDM. Both studies reported a positive dose-response association between the use of SGAs and the risk of GDM. In particular, Park et al. (2018) found the risk of GDM increased with increasing accumulated doses of olanzapine until approximately 700 mg and plateaued thereafter.

Six of the included articles dealt with confounding factors either by using multivariable adjustments in the regression model, restriction in control group selection or with propensity score (PS) methods (Boden et al., 2012; Panchaud et al., 2017; Park et al., 2018; Petersen et al., 2016; Reis & Kallen, 2008; Vigod et al., 2015). In addition to comparing the outcome rate between the exposed group and unexposed group, four studies used further control groups in order to address confounding by indication: Petersen et al. (2016) and Park et al. (2018) used ‘discontinuers’ (women who had taken prescriptions before pregnancy but had no prescriptions dispensed for an antipsychotic medication during pregnancy) as a control group; Panchaud et al. (2017) restricted pregnant women who were not exposed to SGAs but with a psychiatric condition as a control group; Boden et al. (2012) included women who had taken any other type of antipsychotics (e.g. less anabolic or other generation antipsychotics) as an active control group. Among the four studies, three addressed maternal psychiatric diagnosis as a confounding factor (Panchaud et al., 2017; Park et al., 2018; Petersen et al., 2016).

Most studies were conducted from 2005 onwards. One study that was included in the meta-analysis (Reis & Kallen, [2008]) used data from 1995 until 2005. As SGAs were not widely used until 1995 (re-introduction of clozapine), their study sample mainly included women exposed to first generation antipsychotics. As well as having a slightly different exposure group, Reis and Kallen (2008) used

multivariable adjustment only to control for possible confounding. All other studies that were included in the meta-analysis used either PS methods or discontinuers as a control group to try to tease out confounding by indication.

All included studies ascertained GDM in either a database, a physician's diagnosis report, or by structured questionnaire and selected adequate follow-up time for their outcome of interest. Two studies did not provide a description of those lost to follow-up (Bellet et al., 2015; McKenna et al., 2005).

Six included studies were considered as of good quality according to NOS assessment (Appendix 3). McKenna et al. (2005), Sadowski et al. (2013), Bellet et al. (2015) and Frayne et al. (2017) were excluded due to the poor quality with a score of zero in the NOS comparability assessment.

A summary of the individual study results can be found in Appendix 4. The results of our meta-analysis, with adjusted estimates for potential confounders, show that antipsychotic use in pregnancy can increase the risk of GDM by 24% (RR=1.24; 95% CI: 1.08-1.42) (Boden et al., 2012; Panchaud et al., 2017; Park et al., 2018; Petersen et al., 2016; Reis & Kallen, 2008; Vigod et al., 2015) (Fig. 2). Within these six studies, four (Boden et al., 2012; Petersen et al., 2016; Reis & Kallen, 2008; Vigod et al., 2015) focused on any antipsychotics exposure with a pooled adjusted RR of 1.30 (95%CI: 1.06-1.60).

Two studies investigated the risk of GDM in users of SGAs only and reported a pooled adjusted RR of 1.12 (95% CI: 0.79-1.60) (Panchaud et al., 2017; Park et al., 2018). No study specifically focused on FGAs. The heterogeneity of the meta-analysis was low (I^2=6.7%, p=0.373).

We conducted a subgroup analysis according to the timing of exposure during pregnancy. Two studies specifically defined the exposure time as first trimester with an adjusted RR of 1.17 (95% CI: 0.64-2.16) (Panchaud et al., 2017; Reis & Kallen, 2008). However, the heterogeneity of the meta-analysis was high (I^2=64.6%, p=0.093). Three studies (Park et al., 2018; Petersen et al., 2016; Vigod et al., 2015) selected patients exposed to antipsychotics in a specific period during pregnancy (Vigod et al. [2015]: within first or second trimester;

Petersen et al. [2016]: between 31 to 105 days after pregnancy start; Park et al. [2018]: first 140 days of pregnancy). An increased risk of GDM was found among these three studies (adjusted RR: 1.19, 95% CI: 1.03-1.37, I^2=0.0%, p=0.632). Only Boden et al. (2012) (Boden et al., 2012) generally presented the exposure time as pregnancy rather than any trimester or specific period during pregnancy.

Discussion

We conducted a systematic review and meta-analysis to investigate whether the use of antipsychotic agents during pregnancy is associated with increased risk of GDM. All included studies were assessed for data quality based on the exposure identification method, adequate follow-up, outcome assessment method, and representativeness of the general population (Wang et al., 2018).

We found that exposure to antipsychotics during pregnancy is associated with an increased risk of GDM which is different from Uguz's study (Uguz, 2019). This may be because Uguz summarised the results based on a narrative review rather than an overall quantitative summary of each study's estimates. Similar results, indicating that antipsychotic use in pregnancy is associated with an increased risk of GDM, were observed in previous review studies which included both population-based studies and case reports (Galbally, Snellen, & Power, 2014; Gentile, 2008; Kulkarni et al., 2015). Nevertheless, there is insufficient evidence to demonstrate the effect of specific drug classes (FGAs or SGAs) or individual antipsychotic drugs. Only two studies focused on a specific drug class (SGAs) with opposite results (Panchaud et al., 2017; Park et al., 2018) and no study particularly focused on FGAs. It is not possible to ascertain whether the effect of SGAs is due to the use of SGAs or perhaps the use of other psychotropic medications. FGAs and SGAs have different mechanisms of action which may result in different effects for pregnant women (Meltzer, 2013). The use of SGAs increased over FGAs through 1989 to 2010 in the UK (Margulis, Kang, & Hammad, 2014) and SGAs became a first-line treatment for schizophrenia (Meltzer, 2013). It has been well documented that the use of SGAs could lead to insulin resistance and therefore cause metabolic

adverse effects such as weight gain, glucose dysregulation and hyperlipidemia (Meltzer, 2013). These metabolic adverse events could contribute to the development of GDM (Kulkarni et al., 2015). Recent studies suggested that certain SGAs, i.e. aripiprazole, might have less metabolic effects than other SGAs. It is therefore necessary to analyse the adverse outcomes in FGAs and SGAs separately, and ideally to examine the risks of specific antipsychotics individually.

According to our review, the risk of GDM was higher among women on higher SGAs doses which is similar to the study conducted by Yood et al. (Yood et al., 2011). Panchuad et al. (2017) explained that the dose effect might be explained by the higher BMI in women receiving higher doses. Moreover, different exposed time periods may lead to distinct results relevant to the pathogenesis, e.g. early pregnancy is a time of insulin sensitivity (Association, 2017; Wang et al., 2018). Further studies should be conducted by stratifying results by specific exposed trimesters and drug dosage, where possible.

In this systematic review, we found some methodological challenges. Firstly, studies using administrative databases/registries may be more representative of the general population, but may not comprehensively cover all potential confounders such as diet, alcohol and tobacco use (Wang et al., 2018). Additionally, antipsychotics are often prescribed by specialist care providers rather than primary care providers, and most administrative databases/registries do not contain specialist information which may cause underestimation of exposure duration or overall exposure episodes. Studies conducted using ad hoc disease registries could potentially have more comprehensive information on subjects and may have longer follow-up periods (Wang et al., 2018). However, major disadvantages of disease registries are selection bias and the lack of an untreated control group which may affect the actual drug effect (Wang et al., 2018).

Moreover, poor antipsychotic adherence among patients with schizophrenia is common (Byerly, Nakonezny, & Lescouflair, 2007; Kane, Kishimoto, & Correll, 2013; Valenstein et al., 2004). Referring to the methods in previous studies

addressing drug misclassification (Park et al., 2018; Sadowski et al., 2013; Vigod et al., 2015), we recommend to only include women who are in receipt of at least two prescriptions or with continuous usage for a set period of time.

Confounders can affect the validity of estimates obtained from data and are the main source of bias in observational studies. In most of our included studies, multivariable adjustments were still the most common method to deal with potential confounders. Maternal age, smoking and alcohol consumption are considered the most relevant factors which can influence pregnancy complications and birth outcomes (Cnattingius & Lambe, 2002; Luke & Brown, 2007; Parker, McFarlane, & Soeken, 1994). However, in our meta-analysis, only Petersen et al. (2016) adjusted all three of these factors. Four studies applied PS methods to minimise the effect of confounding factors (Panchaud et al., 2017; Park et al., 2018; Petersen et al., 2016; Vigod et al., 2015), while three latest studies conducted sensitivity analyses using different control groups (Panchaud et al., 2017; Park et al., 2018; Petersen et al., 2016). Additionally, maternal psychiatric diagnosis should be considered as a necessary confounding factor and, where possible, adjusted for in the main analysis as well as sensitivity analyses to minimise the influence of the disease itself. The results of the meta-analysis for FGAs and SGAs combined were largely driven by the results of the study by Reis and Kallen (2008) (weight: 17.76%). Removing this study from the meta-analysis in a post-hoc sensitivity analysis showed that there was only weak evidence for the association between antipsychotic use and GDM (RR 1.19 (95% CI 0.92-1.55)) (Fig. 3).

The potential consequences of an untreated psychotic episode may be severe and may lead to an increased risk of relapse or exacerbate symptoms, thus, antipsychotics should be prescribed if there is a clinical need (Jones et al., 2014). Clinicians need to weigh the potential adverse outcomes of antenatal exposure to drugs against the potential risk of untreated illness. Our study results indicate that antipsychotic exposure during pregnancy may lead to a higher probability of GDM and emphasize that women using antipsychotic agents in the antenatal period should be referred for GDM testing. NICE guidelines on the clinical management of antenatal and postnatal mental health

recommend that gestational diabetes should be screened in women taking antipsychotic medication – blood glucose and HbA1c monitoring (NICE, 2014). A healthy diet and regular exercise during pregnancy would be of benefit to women to control blood glucose levels. It is also notable that clinicians should not switch treatment e.g. from FGAs to SGAs in the absence of strong evidence that doing so may be of benefit to women. According to NICE guidelines, for women with GDM, in addition to dietary changes and blood glucose monitoring, treatment with antidiabetic agents should be considered to prevent further complications (NICE, 2015).

This study is the first meta-analysis focused on the relationship between prenatal exposure to antipsychotics and the risk of GDM and included all relevant literature to date. Reviewer selection bias was minimised by using a comprehensive search strategy and independent text screening as well as data extraction. All studies included in the meta-analysis were conducted with administrative databases/registries or ad hoc disease registries which provided a relatively large sample size and good generalisability. There has been no published study in Asian populations, and we would recommend future studies to investigate whether the result is different for western and eastern populations. Methodological differences in study designs, the selection of the exposure and control groups, duration of follow-up, exposure and outcome definitions, may influence the accuracy of the risk estimates. Future studies should be conducted using an appropriate exposure period, adequate follow-up time and a larger sample size for more accurate results and a higher validity and representativeness of the general population (Wang et al., 2018). Studies focusing on individual agents, dose effect or comorbidities are also recommended in the future. We observed low heterogeneity in the adjusted pooled estimates which may represent the consistency of the results after adjusting for potential confounding factors. Studies included in our meta-analysis may still have been affected by residual confounding factors. Future studies are therefore necessary to be conducted to address confounding with a more comprehensive approach.

Conclusion

In conclusion, our systematic review and meta-analysis suggest that exposure to antipsychotic agents during pregnancy is associated with a higher risk of GDM. Future studies should focus on specific drug classes: typical or atypical antipsychotics, doses, interaction with comorbidities and/or different trimester exposure in order to help clinicians to manage the risk of GDM if initiation or continuation of antipsychotic prescriptions during pregnancy is needed.

Compliance with Ethical Standards

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Conflict of interest Ian Wong has received grants from The Research Grants Council (Hong Kong), Innovative Medicines Initiative, Shire, Janssen-Cilag, Eli-Lily, Pfizer, and the European Union FP7 pro- gramme, outside the submitted work; was a member of the National Institute for Health and Care Excellence (NICE) ADHD Guideline Group and the British Association for Psychopharmacology ADHD guideline group and acted as an advisor to Shire. Kenneth Man and Ruth Brauer are recipients of the UCL CW Malpethorpe Fellowship. Kenneth Man has received personal fees from IQVIA Ltd, outside the submitted work. Zixuan Wang, Basmah Alfageh and Pajaree Mongkhon have no other competing interests. No other relationships or activities could appear to have influenced the submitted work.

Authors' contributions

Conceptualization: Zixuan Wang, Ian Wong, Ruth Brauer.

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Formal analysis: Zixuan Wang.

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Project administration: Ian Wong, Ruth Brauer.

Supervision: Ian Wong, Ruth Brauer, Kenneth Man.

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Writing-original draft: Zixuan Wang.

Writing-review and editing: Zixuan Wang, Ian Wong, Ruth Brauer, Kenneth Man

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