Exposure to air pollution and risk of gestational diabetes mellitus (GDM)

By: Haweya Farah*, Marium Nawaz* & Roa Sabra*
* Interdisciplinary School of Health Sciences, University of Ottawa

uOttawa

ABSTRACT

Background: Air pollution is known to have many grave impacts on the health of individuals; over 80% of people living in urban areas are exposed to levels of air pollutants that exceed the limits set by the World Health Organization (WHO, 2016). Past studies have examined the association between air pollution exposure and development of gestational diabetes mellitus, but there is limited evidence of this association.
Objectives: To review the literature, in order to explore existing studies that look at the association between exposure to $PM_{2.5}$ or ozone and the development of gestational diabetes mellitus (GDM).
Methods: A structured literature review was conducted in the PubMed (Medline) database to investigate the research question. The keywords searched in the final strategy were "(Particulate matter OR ozone) AND gestational diabetes". Quantitative studies were included in the search, while studies with a focus on type 2 diabetes mellitus or smoking were excluded.
Results: The initial search strategy returned 18 results, with the final number of articles being narrowed down to 5. Only one study was able to confirm a positive association between the two variables under study. Three other studies showed an association between exposure to ozone or $PM_{2.5}$ and GDM, but only under very specific conditions. The remaining study did not show an association between the variables under study.
Conclusions: The literature does not show robust evidence of an association between ozone or $PM_{2.5}$ and the development of GDM. Further research is needed in order to be able to draw more accurate conclusions.

INTRODUCTION

Background:
- Air pollution is one of the major environmental concerns today, because of its many negative impacts on ecosystems.
- The United Nations has considered this problem in the Millennium Development Goals to the Sustainable development goals[1].
- Apart from impact on environment, air pollution also has adverse effects on health and well-being of humans and animals.
- According to the World Health Organization, over 80% of people living in urban areas are exposed to air pollution levels that exceed the limits set by this organization[2].
- Among many other health risks, exposure to air pollution is known to cause frequent asthma attacks, lung cancer, wheezing and coughing, shortness of breath, cardiovascular damage, and susceptibility to infections[3].
- Exposure to pollutants poses more severe health risks to vulnerable populations (ex. Young children, elderly individuals, pregnant women, etc.) than to healthy individuals; thus it is important to consider the health impacts of this sort of exposure on such individuals.
- According to recent studies, pregnant women and their future children are at risk of adverse effects to their health due to air pollution[4].
- An example of a very common condition that can occur during pregnancy, and that is currently on the rise, is gestational diabetes mellitus (GDM)[5].
- Although it does not always lead to further complications, GDM can be very detrimental to the health of the mother and the child; in the child, it can lead to birth injuries and other perinatal complications, while in the mother, it has been associated with future development of type 2 diabetes mellitus and metabolic syndrome[6].
- The rise of GDM is associated with urbanization, among many other factors[5].

Rationale:
- It is known that urbanization entails increase in air pollution, thus implying that there might be an association between air pollution and GDM.
- Because of the very adverse risks that it poses, it is very important to explore the possible risk factors associated with this condition, in order to be able to eventually decrease its prevalence. Since there is some research indicating that air pollution could possibly be a risk factor for GDM, this structured review has been conducted to examine the existing literature pertaining to the research question below.

Research question:
- Is exposure to particulate matter 2.5 or ozone associated with development of gestational diabetes mellitus?

METHODS

Study design:
- Structured review of literature, using the PubMed (Medline) database

Search stragegy:
- First step was to search up the terms "(Particulate matter OR ozone) AND gestational diabetes AND Canada" (to restrict study to Canadian women).
- No results corresponding to the association that was being studied, thus restriction of location was removed; final overall search strategy: **"(Particulate matter OR ozone) AND gestational diabetes"**.

Inclusion criteria:
- Included scientific quantitative studies in which data collected was mainly about the glycemic analyses of pregnant women who were exposed to air pollution.
- Only scientific articles that were primary sources, presenting a revised research protocol, were included in this structured literature review, so existing review articles were not included in this study.

Exclusion criteria:
- Excluded articles that studied the association between GDM and first- or second-hand smoking (since focus of study was exposure to $PM_{2.5}$ or ozone through air pollution) and search results on type 2 diabetes mellitus (since study was limited to gestational diabetes mellitus)
- Results only contained one review article: a systematic review that synthesized the results of association between exposure to air pollution and T2DM. However, because it contained the exclusion criteria of T2DM, it was automatically disregarded in this study.
- After application of inclusion/exclusion criteria, retained articles were read by 3 raters.

RESULTS

Records generated through PubMed database, using search strategy "(particulate matter OR ozone) AND gestational diabetes"

↓

Articles identified and selected by database based on primary subject (n=18)

Sorted by three independent evaluators, based on titles and summaries; eliminated articles (n=10)

↓

Articles retained (n=8)

No articles have been eliminated due to duplicates because only one database was used (n=0)

↓

Articles retained (n=8)

Sorted by three independent evaluators, based on inclusion and exclusion criteria and quick overview of the complete texts; eliminated articles (n=3)

↓

Articles retained (n=5)

Further analysis and full reading of the articles by three independent evaluators; Eliminated articles (n=0)

↓

Articles retained (n=5)

Figure 1: Flow chart of extracted and excluded studies from the PubMed database.

Table 1: Summary of charted data and results obtained for the search strategy "(particulate matter OR ozone) AND gestational diabetes" in the PubMed database.
[a] Quality assessment was done using the US National Institutes of Health's "Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies".

Authors (year); location	Sample information	Research design	Purpose of study	Major findings	Quality assessment[a]
Fleisch et al. (2014); Boston, Massachusetts, United States[7]	N = 2,093; women in the Boston-area with gestational age of ≤ 22 weeks and a singleton pregnancy	Method; design: quantitative; prospective cohort study Collection: daily measure of $PM_{2.5}$ and black carbon at Harvard University Countway Library; estimates of $PM_{2.5}$ and black carbon concentrations at residential address of participants (using spatiotemporal land use regression model); serum glucose levels (routine clinical screening for GDM); interviews and questionnaires (socioeconomic information and maternal characteristics)	To determine whether or not there is an association between second-trimester exposure to fine particulate matter ($PM_{2.5}$) and hyperglycemia in pregnancy	Exposure to $PM_{2.5}$ and other traffic-related pollutants is associated with impairments in glucose tolerance, but not with GDM	Good; response &/or recall bias possible for covariate information
Fleisch et al. (2016); Massachusetts, United States[8]	N = 159,373; nulliparous women in Massachusetts, pregnant between 2003 and 2008 (inclusively), with no history of diabetes, and delivering at 28 weeks of gestation	Method; design: quantitative; retrospective cohort study Collection: $PM_{2.5}$ exposure estimated at womens' residential addresses using a hybrid spatiotemporal model; information about maternal GDM designation and other maternal characteristics (ex. age, education, health status, etc.) obtained from birth records	To investigate the association between a woman's first- and second-trimester residential exposure to $PM_{2.5}$ and neighbourhood traffic density, and the development of GDM	Overall, there does not seem to be an association between exposure to air pollution and GDM; however, increased exposure to $PM_{2.5}$ during the second trimester, in the youngest group of women (i.e. less than 20 years old), is associated with higher risk of GDM	Fair; misclassification bias possible in exposure and outcome measures
Hu et al. (2015); Florida, United States[9]	N = 410,267; women having given singleton birth in Florida in 2004 or 2005, with gestational age between 24 and 42 weeks	Method; design: quantitative; retrospective cohort study Collection: blood glucose levels obtained in oral glucose challenge test (OGCT), between weeks 24 and 28 of pregnancy; air pollution exposure data provided by US Environmental Protection Agency (EPA) using hierarchical Bayesian space-time statistical model (HBM), for $PM_{2.5}$ and O_3	To assess the association of prenatal exposure to $PM_{2.5}$ and ozone during different gestational periods (ex. trimesters vs full pregnancy) with the development of GDM	Exposure to ozone and to $PM_{2.5}$ (during each trimester of a pregnancy and also during the full pregnancy) is associated with higher risk of GDM	Fair; misclassification bias possible in measuring both variables
Lu et al. (2016); Chiayi City, Taiwan[10]	N = 3589; women who underwent a two-step approach to detect GDM, and who delivered their babies at the Department of Obstetrics and Gynecology of DMF-CYCH in Taiwan, between March 2006 and December 2014	Method; design: quantitative; retrospective cohort study Collection: plasma glucose levels obtained through non-fasting 50-gram glucose challenge test (GCT), done at 24-28 weeks of gestation; measurement of venous plasma glucose levels done through the hexokinase-G6PDH method, using a Hitachi 7170 automatic analyzer; air pollutant concentrations (for PM, O_3, CO, NO_X, and SO_2) obtained from the Chiayi station, a single fixed-site monitoring station run by Taiwan's Environmental Protection Agency (with temporal distribution to correct for variations)	To examine the association between exposure to fine particulate matter ($PM_{2.5}$) and indicators of glucose homeostasis during pregnancy (using fasting, 1h, 2h and 3h glucose levels in Oral Glucose Tolerance Test)	Exposure to $PM_{2.5}$ seems to be positively associated with indicators of glucose homeostasis ,and thus not associated with GDM	Fair; misclassification bias possible in exposure measures
Robledo et al. (2014); United States[11]	N = 219,952; women with singleton pregnancies	Method; design: quantitative; retrospective cohort study Collection: clinical and demographic date (ex. age, marital status, etc.) obtained from obstetric electronic medical record (EMR); presence/absence of GDM also obtained from EMR; average maternal exposures to air pollutant levels ($PM_{2.5}$, NO_X, CO, O_3, SO_2) obtained for delivery hospital referral region	To study the association between criteria air pollutants regulated by the US Environmental Protection Agency (i.e. NO_X, SO_2, & O_3) and development of GDM	Mothers who are exposed to NO_X and SO_2 before conception and in the first few weeks of pregnancy have higher risk of GDM. Exposure to O_3 is only associated with higher GDM risk starting in mid-pregnancy	Fair; misclassification bias possible in measuring both variables

DISCUSSION

Key Findings:
- Three of the five articles conclude that there **exists some sort of association between $PM_{2.5}$ or O_3 exposure and GDM risks**, however, conditions for this association vary between studies (ex. trimester of exposure, maternal age, etc.)[8,9,11].
  - One of these studies states that a higher risk for GDM was observed in the youngest age stratum (less than 20 years old), for $PM_{2.5}$ exposures in the second trimester[8].
  - One of the articles states definitively that increased exposure to air pollution during pregnancy is associated with increased risk of GDM and that this association persists even after adjusting for possible confounding variables resulting from maternal characteristics (ex. education, marital status, ethnicity, prenatal care, etc.)[9].
  - The third article does not state conclusions about $PM_{2.5}$, but it says that exposure to O_3 was associated with higher risk of GDM in mid-pregnancy and on[11].
- One of the other two articles does not show a link between $PM_{2.5}$ exposure and GDM, but it does say that there is an **association between such exposure and impaired glucose tolerance (IGT)**[7].
- The last article (in Chiayi City, Taiwan) suggests that there is a positive association between $PM_{2.5}$ and glucose homeostasis during pregnancy, and that having exposure to $PM_{2.5}$ specifically during the second trimester increases this effect[10]. This suggests that there is no association between $PM_{2.5}$ exposure and GDM.
- All the studies are cohort studies due to ethical issues - it would be unethical to purposely expose pregnant women to air pollution at the desired levels to observe its association with GDM.
- Studies that happened in the U.S. showed some sort of correlation (even if limited) between air pollution and decreased glucose tolerance, while the study in Taiwan did not show such a correlation.

Contextualization of results:
- Overall, results are not very surprising since previously done epidemiological studies show a positive association between air pollution exposure and type 2 diabetes mellitus or some degree insulin resistance[8,9,10,11].
- Air pollution during pregnancy can increase risk of oxidative stress, leading to inflammation, insulin resistance, dyslipidemia, and systemic metabolic dysfunction[9].
- Studies done on rodents have shown that $PM_{2.5}$ exposure leads to oxidative stress and adipose inflammation[7].
  - Air pollution exposure causes increased proinflammatory macrophage and insulin signaling abnormalities which could lead to insulin resistance[7]. One would already be at risk of diabetes, but not demonstrate the disease until the body undergoes a physical stress, such as pregnancy.
  - This can explain why "one third of women with GDM will eventually develop type 2 diabetes" [9].
  - Insulin resistance occurs during pregnancy in order to provide fuel for the fetus; this is a part of the normal physiological changes in expecting mothers[7].
  - $PM_{2.5}$ exposure in the second trimester increases insulin resistance, causing a synergistic effect with the body's normal response of insulin resistance during pregnancy, potentially leading to hyperglycemia[10].
- Obesity-induced insulin resistance is thought to occur in a similar way as gestational insulin resistance.
- The only unexpected result is the association of exposure to air pollution with glucose homeostasis[10].
- Non-differential misclassification bias possible in all four retrospective studies, biasing results towards null hypothesis.

Limitations in the study:
- Only used one database (Pubmed (Medline)), and could only use articles that were accessible through the University of Ottawa's subscribed journals
  - This could have caused a selection bias in the study: results of the search could have only included the articles that reject the null hypothesis.
  - If other databases were looked at, and a more in depth search were to be done, it is possible for there to have been a greater amount of articles supporting the null hypothesis, showing that the observation of rejecting the null hypothesis might be flawed
- Didn't look at other types of air pollutants and their effects on GDM; this is important because there are many different types of particles and gases in the air that can affect health, and can act as confounding variables in this relationship, making it seem like there is a greater association between GDM risk and $PM_{2.5}$ than there really is.
- Didn't consider preconception exposure to air pollutants.
- Didn't look at exposure to indoor air pollution; this could have influenced results greatly, since indoor air pollution could act as a confounding variable in this relationship.
  - Women are often surrounded by smoke from cooking; in developing countries, they are exposed to very high levels of air pollution for 3-7 hours a day for many years[2]. This can expose them to different types of particulate matter, and other pollutants, increasing the apparent association between outdoor air pollution exposure and risk of GDM; this would result in the results moving further away from the null hypothesis.

Implications for future research or policy:
- To improve the health of pregnant women and their fetus, there needs to be more attention placed on stronger air pollution controls[9]. Interventions should also be placed to help expecting mothers with controlling and managing their air pollution exposure (ex. possibly spending more time in rural areas during pregnancy, than in urban areas).
- More studies needed to examine the extent to which each individual criteria air pollutant (ex. $PM_{2.5}$, NO_X, SO_2, black carbon, and ozone) and mixtures of pollutants, are associated with GDM risk[8].
- Studies should have more accurate and precise estimates of exposure to air pollution during pregnancy, by factoring in environments other than just the place of residence (ex. workplace, leisure activities, etc.), proportionate to the time spent by mother in each environment. They should also keep records of change of residential address during pregnancy.
- A long-term, prospective cohort study should be done, tracking the mother's displacement on an everyday basis (ex. commuting between work and home, etc.), and proportionately calculating air pollution exposure .
- Prospective cohort studies should also be done to look at the association of mothers' preconception exposure to air pollution with development of GDM.
- If there is an association between $PM_{2.5}$ and GDM, then more strict restrictions should be placed to control air pollution for the sake of future generations.

CONCLUSION

Although some studies show an association between $PM_{2.5}$ or ozone exposure and gestational diabetes mellitus under varying conditions (lower maternal age, exposure during mid-pregnancy or during second trimester, etc.), a correlation between these two variables cannot be concluded, as some studies present opposing results. Further research will be needed to investigate this association.

REFERENCES
1) BOERMA, (2015). *Health in 2015: From MDGS, millennium development goals, to SDGS, sustainable development goals* [Report]. Retrieved from http://www.who.int/gho/publications/mdgs-sdgs/en/
2) World Health Organization. (2016, September). Ambient (outdoor) air quality and health. Retrieved November 19, 2016, from http://www.who.int/mediacentre/factsheets/fs313/en/
3) American Lung Association. (2016). Health Effects of Ozone and Particle Pollution. Retrieved November 19, 2016, from http://www.lung.org/our-initiatives/healthy-air/sota/health-risks/
4) US Environmental Protection Agency. (2010, January). *Promoting good prenatal health: Air pollution and pregnancy*. Retrieved November 18, 2016, from https://www.epa.gov/children/promoting-good-prenatal-health-air-pollution-and-pregnancy-january-2010
5) Hunt, K. J., & Schuller, K.L. (2007). The Increasing Prevalence of Diabetes in Pregnancy. *Obstetrics and Gynecology Clinics of North America., 34*(2), 173-199. doi:10.1016/j.ogc.2007.03.002
6) Kaaja, R., & Rönnemaa, T. (2008). Gestational Diabetes: Pathogenesis and Consequences to Mother and Offspring. *The Review of Diabetic Studies, 5*(4), 194-202. doi:10.1900/rds.2008.5.194
7) Fleisch, A. F., Gold, D. R., Rifas-Shiman, S. L., Koutrakis, P., Schwartz, J. D., Kloog, I., . . . Oken, E. (2014). Air Pollution Exposure and Abnormal Glucose Tolerance during Pregnancy: The Project Viva Cohort. *Environmental Health Perspectives, 122*(4), 378-383. doi:10.1289/ehp.1307065
8) Fleisch, A. F., Kloog, I., Luttmann-Gibson, H., Gold, D. R., Oken, E., & Schwartz, J. D. (2016). Air pollution exposure and gestational diabetes mellitus among pregnant women in Massachusetts: A cohort study. *Environmental Health Environ Health, 15*(1). doi:10.1186/s12940-016-0121-4
9) Hu, H., Hu, S., Henderson, B. H., Warner, T. D., Roth, J., Kan, H., & Xu, X. (2015, September 20). Association of Atmospheric Particulate Matter and Ozone with Gestational Diabetes Mellitus. *Environmental Health Perspectives, 123*(9), 853-859. doi:10.1289/ehp.1408456
10) Lu, M., Wang, P., Cheng, T., Yang, C., & Yan, Y. (2016, October 13). Association of temporal distribution of fine particulate matter with glucose homeostasis during pregnancy in women of Chiayi City, Taiwan. *Environmental Research, 152*, 81-87. doi:10.1016/j.envres.2016.09.023
11) Robledo, C. A., Mendola, P., Yeung, E., Männistö, T., Sundaram, R., Liu, D., . . . Grantz, K. L. (2015, January 17). Preconception and early pregnancy air pollution exposures and risk of gestational diabetes mellitus. *Environmental Research, 137*, 316-322. doi:10.1016/j.envres.2014.12.020