**Title:** Examining the Joint Impacts of Chronic Air Pollution and COVID-19 Infection on Adverse Pregnancy Outcomes in New York City

**Student Name:** Farheen Jamshed

**Student Certificate:** Infectious Disease Epidemiology

**Introduction:**

Since December 2019, there have been over 760 million confirmed cases, and over 6.5 million deaths, due to SARS-CoV-2 during the COVID-19 pandemic.1 The impacts of this novel coronavirus have necessitated the need to broaden our scientific understandings of how such viruses can affect human populations. One key area of concern was how COVID-19 infection could uniquely affect pregnant individuals and their neonates. A continually growing area, research has found mixed results on COVID-19’s impact on maternal and child health during pregnancy, especially in different world areas.

Several studies have reported the effects of SARS-CoV-2 infection on maternal and child pregnancy outcomes.2–8 One Turkish study found that mothers infected with COVID-19 experienced higher rates of maternal mortality, preterm birth, and cesarean section delivery.2 A review article summarized that COVID-19 infections in pregnant mothers have been associated with preeclampsia, preterm birth, and stillbirth, and that these effects (plus low birthweight) are stronger in cases of severe COVID-19 infection.6

Air pollution is a pressing environmental challenge which can have disastrous consequences on the climate and on human health. Particulate matter (PM) sources are classified by their size, where PM2.5 have a diameter less than 2.5 μm, and PM10 have a diameter less than 10 μm. Both PM2.5 and PM10 are known to be associated with adverse respiratory health outcomes, including pneumonia and lung disease.9–11 Besides PM, gases like nitrogen oxides, ammonia, ozone, sulfur dioxides, and carbon monoxides also contribute to air pollution. Prolonged exposure to increased concentration of nitrogen dioxide has been linked to harmful and toxic effects on the respiratory system.9,11,12 Air pollution has also been widely shown to be associated with adverse cardiovascular health outcomes; exposure to high levels of PM2.5 is a particularly strong risk factor for morbidity and mortality due to hypertension, diabetes, atherosclerosis, myocardial infarction, stroke, coronary heart disease, and heart failure.13,14

Air pollution may exacerbate health outcomes of COVID-19. Several studies in the United States have suggested that long-term exposure to PM2.5 is associated with COVID-19 infection,15 hospitalization,16,17 mortality,15 and fatality15; in addition, another US-based study found that long-term and short-term PM2.5 and NO2 exposure was associated with higher COVID-19 incidence.18 Exposure to air pollution has negatively impacted the COVID-19 pandemic outside of the United States as well. Daily increases in air pollution have been positively correlated with COVID-19 mortality in Chile,19 PM2.5 and NO2 exposure have been linked to COVID-19 incidence in China,20 PM2.5 and PM10 exposure have been positively associated with COVID-19 incidence and mortality in Germany,21 and PM2.5, PM10, and NO2 exposure were positively associated with COVID-19 incidence in India.22

Air pollution may have negative impacts during pregnancy as well. Previous studies have suggested that PM10 exposure increased risk of spontaneous abortion, and that PM10 and PM2.5 exposure in the third trimester increased the risk of stillbirth.23 Also, exposure to PM and ozone throughout pregnancy may increase the risk of preterm birth.24,25

While both COVID-19 and exposure to air pollution can have detrimental health impacts during pregnancy, scientific literature has insufficiently examined the synergistic impacts of COVID-19 and air pollution on pregnancy health outcomes. In fact, only one paper by Casey, et al. (2022) has examined these three variables (air pollution, COVID-19, and pregnancy) simultaneously; they assessed whether pregnant people’s exposure to air pollution was associated with higher rates of testing positive for COVID-19.26 They found that the odds of pregnant individuals ever testing positive for COVID-19 were higher for Medicaid users, an indication that socioeconomic status (SES) may modify this relationship.26

Our study will assess if chronic air pollution exposure modifies the effect of COVID-19 infection on adverse pregnancy outcomes, including pre-eclampsia and delivery via cesarean section. This would be the very first research study to answer this question. Its results will provide a deeper understanding of how factors related to environmental health, infectious disease, and pregnancy interact.

**Study Questions:**

1. Is COVID-19 infection significantly associated with pregnancy outcomes (cesarean delivery and pre-eclampsia) in this study population after adjusting for covariates? If so, do these associations persist across the different waves of the COVID-19 pandemic?
2. Does chronic air pollution, as measured by 10-year averaged PM2.5 level, modify the relationship between COVID-19 infection and adverse pregnancy outcomes?

**Hypotheses:**

1. After adjusting for covariates, COVID-19 infection will be negatively associated with both pregnancy outcomes during all waves of the pandemic.
2. Chronic air pollution will positively modify the relationship between COVID-19 infection and pregnancy outcomes during all waves of the pandemic.

**Methods:**

Our study participant population will include all pregnant New York City residents who gave birth within the five New York City boroughs between March 2020 and February 2021. Those who gave birth in NYC but did not have residential zip codes within the five NYC boroughs will be excluded from all adjusted analyses.

All participant data will come from harmonized electronic health records (EHR) from the INSIGHT Clinical Research Network (INSIGHT-CRN).27 INSIGHT-CRN data consists of harmonized data from five major NYC health systems: Albert Einstein School of Medicine/Montefiore Medical Center, Columbia University and Weill Cornell Medicine/New York-Presbyterian Hospital, Icahn School of Medicine/Mount Sinai Health System, and New York University School of Medicine/Langone Medical Center.

Long-term air pollution will be represented by a 10-year averaged PM2.5 exposure variable, gathered from the New York City Community Air Survey (NYCCAS).28 The NYCCAS collects pollution data across NYC neighborhoods; in addition to PM2.5, these surveys collect information about other pollutants (metal constituents, black carbon, NO-NO2-NOx, O3, and SO2) and temperature and humidity.28,29

Neighborhood vulnerability index (NEVI) has been constructed for each NYC residential zip code tabulation area (ZCTA) using the toxicological prioritization index (ToxPi) profiling and clustering approach; these methods have been described elsewhere.30 Our constructed NEVI will include only neighborhood-level demographic, social, economic, and chronic disease factors. Air pollution metrics are not included in the construction of the NEVI to allow us to examine the direct effects of socioeconomic factors, separate from the effects of air pollution.

During the study time period, universal SARS-CoV-2 nasopharyngeal quantitative polymerase chain reaction (PCR) testing was performed at delivery for every patient giving birth in New York City. The electronic medical record contains information whether these patients tested positive or negative for SARS-CoV-2 at the time of delivery, and we will use this data to get information about infection status.

Air pollution data will be obtained from the NYCCAS. We will represent long-term air pollution using a 10-year averaged PM2.5 exposure level. Individual participants’ average PM2.5 level will be ascertained based on their NYC zip code of residence at the time of delivery. Because the variable does not follow a linear trend, we will split this continuous air pollution variable into quartiles and use this categorical variable in all analyses.

Our outcomes of interest in this study are delivery type (cesarean or vaginal) and pre-eclampsia status. Pre-eclampsia is a hypertensive disorder during pregnancy which can be diagnosed after 20 gestational weeks. Pre-eclampsia is identified if a pregnant individual experiences a systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 at least four hours apart, or if they experience a systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 110 mmHg in a shorter amount of time.31

We created a directed acyclic graph to hypothesize potential confounders. We used a minimally sufficient adjustment set for estimating the total effect of COVID-19 infection on delivery type and pre-eclampsia status. These covariates include diabetes status, asthma status, ever-smoker status, maternal age at birth, and the NEVI.

We will perform multivariable logistic regression models to examine the effects of COVID-19 infection and long-term air pollution on each of the two birth outcomes. Because the effects of SARS-CoV-2 have been distinct based on circulating variants, all analyses will be stratified on the wave of the pandemic during which participants gave birth. We will define the first wave to be from March 2020 to June 2020, the second wave to be from July 2020 to October 2020, and the third wave to be from November 2020 to February 2021.

We will model the effects of COVID-19 infection on delivery type and pre-eclampsia status in crude models, then separately add an interaction term to test for effect modification by the categorical air pollution variable. Adjusted models will include the following covariates: asthma status (defined as having any diabetes diagnosis in the medical record), diabetes status (defined as having any diabetes diagnosis in the medical record), maternal age at birth, and the constructed NEVI. We will report odds ratios and 95% confidence intervals for these effects. To investigate effect modification between air pollution and COVID-19 infection, we will use linear combination of beta coefficients to report the effect of COVID-19 infection in the second, third, and fourth quartile of air pollution exposure, compared to the effect of COVID-19 infection alone.

**References**

1. World Health Organization. WHO Coronavirus (COVID-19) Dashboard. Accessed December 29, 2022. https://covid19.who.int

2. Oncel MY, Akın IM, Kanburoglu MK, et al. A multicenter study on epidemiological and clinical characteristics of 125 newborns born to women infected with COVID-19 by Turkish Neonatal Society. *Eur J Pediatr*. 2021;180(3):733-742. doi:10.1007/s00431-020-03767-5

3. de Oliveira KF, de Oliveira JF, Wernet M, Carvalho Paschoini M, Ruiz MT. COVID-19 and pregnancy: A scoping review on pregnancy characteristics and outcomes. *Int J Nurs Pract*. 2021;27(5):e12956. doi:10.1111/ijn.12956

4. Tekbali A, Grünebaum A, Saraya A, McCullough L, Bornstein E, Chervenak FA. Pregnant vs nonpregnant severe acute respiratory syndrome coronavirus 2 and coronavirus disease 2019 hospital admissions: the first 4 weeks in New York. *American Journal of Obstetrics and Gynecology*. 2020;223(1):126-127. doi:10.1016/j.ajog.2020.04.012

5. Breslin N, Baptiste C, Gyamfi-Bannerman C, et al. Coronavirus disease 2019 infection among asymptomatic and symptomatic pregnant women: two weeks of confirmed presentations to an affiliated pair of New York City hospitals. *Am J Obstet Gynecol MFM*. 2020;2(2):100118. doi:10.1016/j.ajogmf.2020.100118

6. Wei SQ, Bilodeau-Bertrand M, Liu S, Auger N. The impact of COVID-19 on pregnancy outcomes: a systematic review and meta-analysis. *CMAJ*. 2021;193(16):E540-E548. doi:10.1503/cmaj.202604

7. Wastnedge EAN, Reynolds RM, van Boeckel SR, et al. Pregnancy and COVID-19. *Physiol Rev*. 2021;101(1):303-318. doi:10.1152/physrev.00024.2020

8. Prochaska E, Jang M, Burd I. COVID-19 in pregnancy: Placental and neonatal involvement. *Am J Reprod Immunol*. 2020;84(5):e13306. doi:10.1111/aji.13306

9. Ali N, Fariha KA, Islam F, et al. Exposure to air pollution and COVID-19 severity: A review of current insights, management, and challenges. *Integr Environ Assess Manag*. 2021;17(6):1114-1122. doi:10.1002/ieam.4435

10. Brauer M. How much, how long, what, and where: air pollution exposure assessment for epidemiologic studies of respiratory disease. *Proc Am Thorac Soc*. 2010;7(2):111-115. doi:10.1513/pats.200908-093RM

11. Lelieveld J, Evans JS, Fnais M, Giannadaki D, Pozzer A. The contribution of outdoor air pollution sources to premature mortality on a global scale. *Nature*. 2015;525(7569):367-371. doi:10.1038/nature15371

12. Latza U, Gerdes S, Baur X. Effects of nitrogen dioxide on human health: systematic review of experimental and epidemiological studies conducted between 2002 and 2006. *Int J Hyg Environ Health*. 2009;212(3):271-287. doi:10.1016/j.ijheh.2008.06.003

13. de Bont J, Jaganathan S, Dahlquist M, Persson Å, Stafoggia M, Ljungman P. Ambient air pollution and cardiovascular diseases: An umbrella review of systematic reviews and meta-analyses. *J Intern Med*. 2022;291(6):779-800. doi:10.1111/joim.13467

14. Münzel T, Hahad O, Daiber A, Lelieveld J. [Air pollution and cardiovascular diseases]. *Herz*. 2021;46(2):120-128. doi:10.1007/s00059-020-05016-9

15. Mondal S, Chaipitakporn C, Kumar V, et al. COVID-19 in New York state: Effects of demographics and air quality on infection and fatality. *Sci Total Environ*. 2022;807(Pt 1):150536. doi:10.1016/j.scitotenv.2021.150536

16. Bowe B, Xie Y, Gibson AK, et al. Ambient fine particulate matter air pollution and the risk of hospitalization among COVID-19 positive individuals: Cohort study. *Environ Int*. 2021;154:106564. doi:10.1016/j.envint.2021.106564

17. Mendy A, Wu X, Keller JL, et al. Air pollution and the pandemic: Long-term PM2.5 exposure and disease severity in COVID-19 patients. *Respirology*. 2021;26(12):1181-1187. doi:10.1111/resp.14140

18. Sidell MA, Chen Z, Huang BZ, et al. Ambient air pollution and COVID-19 incidence during four 2020-2021 case surges. *Environ Res*. 2022;208:112758. doi:10.1016/j.envres.2022.112758

19. Dales R, Blanco-Vidal C, Romero-Meza R, Schoen S, Lukina A, Cakmak S. The association between air pollution and COVID-19 related mortality in Santiago, Chile: A daily time series analysis. *Environ Res*. 2021;198:111284. doi:10.1016/j.envres.2021.111284

20. Li H, Xu XL, Dai DW, Huang ZY, Ma Z, Guan YJ. Air pollution and temperature are associated with increased COVID-19 incidence: A time series study. *Int J Infect Dis*. 2020;97:278-282. doi:10.1016/j.ijid.2020.05.076

21. Prinz AL, Richter DJ. Long-term exposure to fine particulate matter air pollution: An ecological study of its effect on COVID-19 cases and fatality in Germany. *Environ Res*. 2022;204(Pt A):111948. doi:10.1016/j.envres.2021.111948

22. Sahoo MM. Significance between air pollutants, meteorological factors, and COVID-19 infections: probable evidences in India. *Environ Sci Pollut Res Int*. 2021;28(30):40474-40495. doi:10.1007/s11356-021-12709-z

23. Grippo A, Zhang J, Chu L, et al. Air pollution exposure during pregnancy and spontaneous abortion and stillbirth. *Rev Environ Health*. 2018;33(3):247-264. doi:10.1515/reveh-2017-0033

24. Klepac P, Locatelli I, Korošec S, Künzli N, Kukec A. Ambient air pollution and pregnancy outcomes: A comprehensive review and identification of environmental public health challenges. *Environ Res*. 2018;167:144-159. doi:10.1016/j.envres.2018.07.008

25. Bekkar B, Pacheco S, Basu R, DeNicola N. Association of Air Pollution and Heat Exposure With Preterm Birth, Low Birth Weight, and Stillbirth in the US: A Systematic Review. *JAMA Netw Open*. 2020;3(6):e208243. doi:10.1001/jamanetworkopen.2020.8243

26. Casey JA, Kioumourtzoglou MA, Ogburn EL, et al. Long-Term Fine Particulate Matter Concentrations and Prevalence of Severe Acute Respiratory Syndrome Coronavirus 2: Differential Relationships by Socioeconomic Status Among Pregnant Individuals in New York City. *American Journal of Epidemiology*. Published online August 2, 2022:kwac139. doi:10.1093/aje/kwac139

27. Kaushal R, Hripcsak G, Ascheim DD, et al. Changing the research landscape: the New York City Clinical Data Research Network. *Journal of the American Medical Informatics Association*. 2014;21(4):587-590. doi:10.1136/amiajnl-2014-002764

28. Matte TD, Ross Z, Kheirbek I, et al. Monitoring intraurban spatial patterns of multiple combustion air pollutants in New York City: Design and implementation. *J Expo Sci Environ Epidemiol*. 2013;23(3):223-231. doi:10.1038/jes.2012.126

29. Clougherty JE, Kheirbek I, Eisl HM, et al. Intra-urban spatial variability in wintertime street-level concentrations of multiple combustion-related air pollutants: the New York City Community Air Survey (NYCCAS). *J Expo Sci Environ Epidemiol*. 2013;23(3):232-240. doi:10.1038/jes.2012.125

30. Reif DM, Martin MT, Tan SW, et al. Endocrine Profiling and Prioritization of Environmental Chemicals Using ToxCast Data. *Environmental Health Perspectives*. 2010;118(12):1714-1720. doi:10.1289/ehp.1002180

31. Karrar SA, Hong PL. Preeclampsia. In: *StatPearls*. StatPearls Publishing; 2023. Accessed May 2, 2023. http://www.ncbi.nlm.nih.gov/books/NBK570611/