



Ambient Air Pollution Exposure Assessments in Fertility Studies: a Systematic Review and Guide for Reproductive Epidemiologists

Johanna R. Jahnke¹ · Kyle P. Messier² · Melissa Lowe² · Anne Marie Jukic¹

Accepted: 9 March 2022 / Published online: 13 May 2022

This is a U.S. Government work and not under copyright protection in the US; foreign copyright protection may apply 2022

Abstract

Purpose of Review We reviewed the exposure assessments of ambient air pollution used in studies of fertility, fecundability, and pregnancy loss.

Recent Findings Comprehensive literature searches were performed in the PUBMED, Web of Science, and Scopus databases. Of 168 total studies, 45 met the eligibility criteria and were included in the review. We find that 69% of fertility and pregnancy loss studies have used one-dimensional proximity models or surface monitor data, while only 35% have used the improved models, such as land-use regression models (4%), dispersion/chemical transport models (11%), or fusion models (20%). No published studies have used personal air monitors.

Summary While air pollution exposure models have vastly improved over the past decade from a simple, one-dimensional distance or air monitor data to models that incorporate physiochemical properties leading to better predictive accuracy, precision, and increased spatiotemporal variability and resolution, the fertility literature has yet to fully incorporate these new methods. We provide descriptions of each of these air pollution exposure models and assess the strengths and limitations of each model, while summarizing the findings of the literature on ambient air pollution and fertility that apply each method.

Keywords Air pollution exposure · Fertility · Fecundability · Pregnancy loss

Introduction

Recent reviews of the literature regarding the associations of ambient air pollution with fertility and pregnancy loss have addressed important issues for epidemiology, including the synthesis of key results in human [1–3] and animal studies [4–6], the comparison of fertility in the general population, and those attempting to conceive through assisted reproductive technology (ART) [1, 2, 5, 6], considerations of biological mechanisms [4, 6], and the assessment of the relevant timing of exposure for these outcomes [3, 4]. These reviews

highlight the associations that have been found between the criteria air pollutants identified by the U.S. Environmental Protection Agency (EPA), including ground-level ozone (O₃), particulate matter (PM), carbon monoxide (CO), sulfur dioxide (SO₂), nitrogen oxides (NO_x), and lead (Pb) [7], and fertility and pregnancy loss. However, none of these reviews assesses or compares the air pollution exposure assessment methods used in each study, which may account for some of the variability in findings. As a result, findings in the field are difficult to contextualize, and comparisons across studies are limited. Further, the majority of studies use proximity models or surface monitor data to assess air pollution exposure, while the use of newer and more sophisticated exposure assessment methods is rare.

In this systematic review, we aim to summarize and compare the results from studies on criteria air pollutants and spontaneous fertility and pregnancy loss in humans within and across distinct exposure assessment techniques and recommend air pollution exposure assessment methods for future research in this subject area. Here, we consider eight commonly used approaches to air pollution exposure assessment: (1) proximity models, (2) surface monitor data,

This article is part of the Topical Collection on *Reproductive and Perinatal Epidemiology*

✉ Johanna R. Jahnke
hannahrjahnke@gmail.com

¹ Fertility and Reproductive Health Group, Epidemiology Branch, National Institute of Environmental Health Sciences, Durham, NC, USA

² Spatiotemporal Health Analytics Group, Predictive Toxicology Branch, National Institute of Environmental Health Sciences, Durham, NC, USA

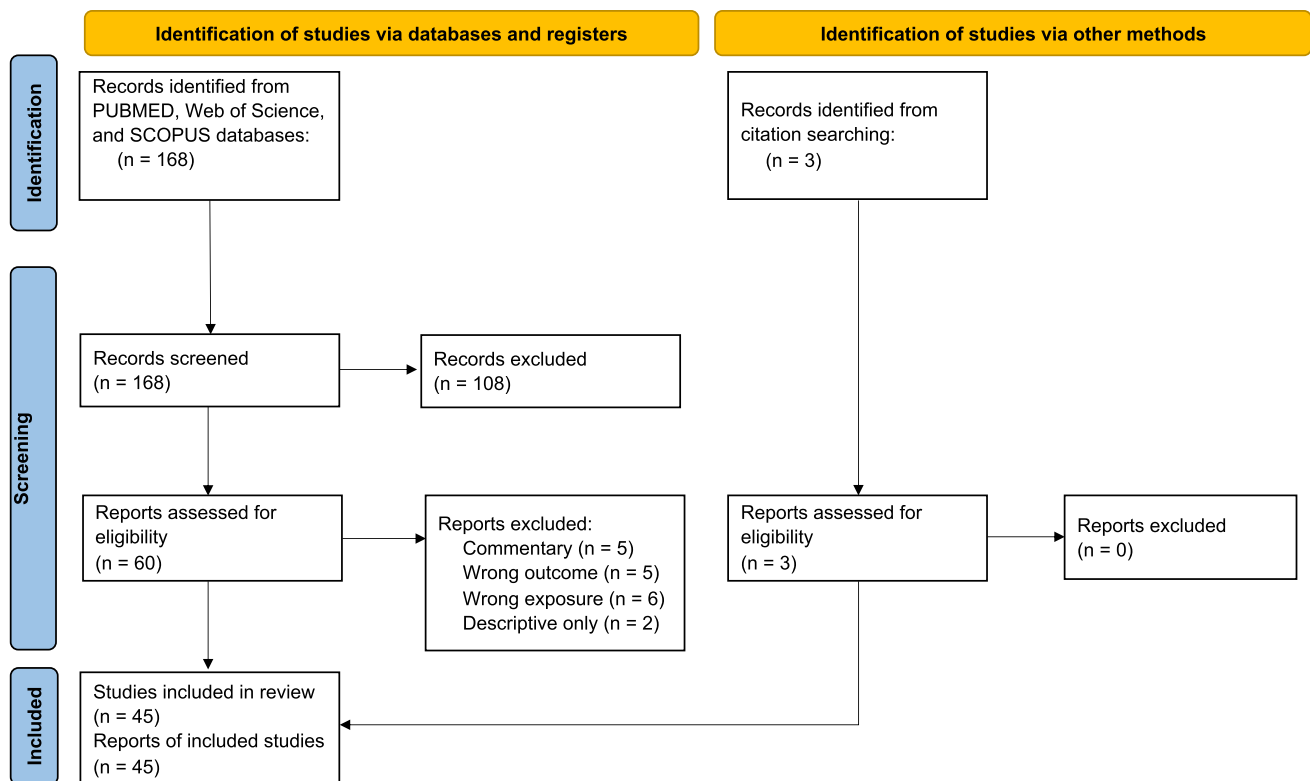


Fig. 1 Flowchart displaying the results from the literature search and screening

(3) kriging and other pure geostatistical methods, (4) land-use regression models, (5) dispersion and chemical transport models, (6) satellite monitor data, (7) fusion models (a combination of any of 2–6), and (8) personal monitor data.

Methods

Comprehensive literature searches were performed in the PUBMED, Web of Science, and Scopus databases. We searched for original research articles that assessed a US EPA ambient criteria air pollutant or a proximity to roadway model and human fertility, fecundability, and pregnancy loss (including both miscarriages and stillbirths). Synonyms for these keywords (i.e., spontaneous abortion, fetal death, and others) were also included in the search. Studies that assessed male fertility, assisted reproductive technology, indoor air pollution, occupational exposures, and proximity to industrial facilities were excluded. Only English-language primary studies of human health were eligible.

Abstracts were screened and excluded if they were not original research articles or if they assessed a different exposure (e.g., indoor air pollution, arsenic) or outcome (e.g., menstrual cycle function, birth weight, gestational age). Full-text articles were screened based on the same criteria. We supplemented database searches with studies identified

through manual searching. Figure 1 shows the study search flowchart. Of 168 total studies, 45 studies that met the inclusion criteria are included in this review. For each eligible article, we recorded the study design and location, air pollution model type, exposures assessed, outcomes assessed, and primary findings.

Results

Air Pollution Modeling in the Fertility Literature

Overall, we found that the majority of studies on air pollution and fertility have not yet incorporated new methods of exposure assessment for ambient air pollution, which offer improved predictive accuracy and precision, increased spatiotemporal variability and resolution, and incorporation of physiochemical properties. These methods have been applied to outcomes such as mortality [8] and lung cancer [9], resulting in important contributions to our understanding of air pollution health effects. However, the majority of fertility literature has yet to fully incorporate these methods. From the most simple to most computationally or logistically intensive, models used to assess air pollution exposure in fertility studies include (1) proximity models (9% of studies reviewed), (2) surface monitor data (60%), (3) land-use

Table 1 Exposure assessment used in air pollution and fertility/pregnancy loss studies

Model type ^a	<i>N</i>	%
Proximity model	4	9%
Surface monitor data	27	60%
Land-use regression model	2	4%
Dispersion/chemical transport model	5	11%
Fusion model	9	20%

^a45 studies are included in the review, and two studies use two types of models

regression models (LUR models; 4%), (4) dispersion and chemical transport models (D/CTMs; 11%), and (5) fusion models (20%) (Table 1). We are not aware of any fertility studies that use kriging and other pure geospatial methods, pure satellite models, or personal monitors to assess air pollution exposure, which all have advantages that we discuss below. Individual study exposures, study design, and findings organized by the outcome and exposure assessment method are presented in Table 2.

Proximity Models

Proximity models are the simplest method for estimating air pollution exposure in epidemiologic studies and are used as the air pollution exposure assessment in 9% of fertility studies. Proximity models estimate pollution exposures as the distance from a pollution source to a fixed participant location, allowing the estimation of individual-level exposures at that location [55, 56]. While proximity models are often inexpensive to implement as they do not require the monitoring or estimation of pollutants, they have several limitations. First, these models are a proxy but do not measure pollutants and do not typically account for pollution dispersion, chemical transformation of pollutants, meteorologic effects on pollutants, land-use, and topography. Second, while these models may offer insight into a recommended distance needed from roadways to communities to mitigate health consequences for city planning purposes, proximity models are non-specific and do not provide data on individual pollutants and disease etiology [55]. The use of proximity models is most appropriate when monitoring data are sparse and the study domain size is small (i.e., neighborhoods or small cities), such that the spatial resolution of available models does not allow for enough variability in exposure estimates.

In the fertility literature, four studies have used proximity models to estimate exposure to pollutants generated by vehicle exhaust [10, 11, 19, 35] (Table 1). Three of these studies defined the exposure as the distance from participant residences to any Class A roadway, defined by class codes on the U.S. Census [10, 11, 35]. Class A roadways include

three categories: Class A1 (primary roads, typically interstate highways, with limited access, the division between the opposing directions of traffic, and defined exits), Class A2 (primary major, non-interstate highways, and major roads without access restrictions), and Class A3 (smaller, secondary roads, usually with more than two lanes) [10]. In one study, the distance to the roadway was calculated from participants' residential addresses to the nearest Class A road segment, and results showed that living closer to a Class A roadway was associated with increased risk of infertility, defined as failure to conceive with at least 12 months of unprotected intercourse [10]. In another study, Mendola et al. (2017) estimated exposure as the distance from the participants' residences to the nearest Class A major roadway, finding that the likelihood of conceiving rose by 3% for every 200 m further between the couples' residence and the major roadway [11]. A third study that also classified the exposure as the distance from the participants' homes to the nearest Class A roadway found that women living within 100 m of a Class A roadway have a moderately higher risk 1.75 (95% CI 0.82–3.76) of stillbirth than those living over 200 m away from a Class A roadway [35].

More complex proximity models can distinguish analyses by road subtype (Class A1, A2, A3, and others) or incorporate traffic flow and land use [55]. The third study using proximity models incorporated traffic flow by assigning the annual average daily traffic (AADT) counts (according to the California Department of Transportation) to principal arterial interstates, principal arterial freeways and highways, minor arterials, and major and minor collectors [19]. The authors then estimated residential traffic exposure for participants based on the traffic counts for all road segments within a 300-m radius of each woman's residence [19]. In the full sample, these traffic measures were not associated with increased risk for spontaneous abortion, but in subgroup analyses limited to African-American women and non-smokers, these measures were associated with increased risk for spontaneous abortion [19].

Surface Monitor Data

Surface monitor data are used to define air pollution exposure in 60% of fertility studies (Table 1). These data are often the product of national regulatory networks, like the Air Quality System from the United States Environmental Protection Agency (U.S. EPA) [57]. Estimating exposures through monitor data has many benefits: they are readily accessible to researchers, use consistent monitoring methods, include refined temporal measures (often hourly), and offer long-term historical data [58]. For example, the U.S. EPA's Air Quality System offers monitoring data for some pollutants since 1980 [57]. Consequently, surface monitor

Table 2 Results from studies on ambient air pollution and fertility, miscarriage, and stillbirth

Model type	Exposure	Study design, location, cohort	Windows of exposure	Primary findings	Reference
Fertility & fecundability Proximity model	Distance from Class A roadway	Prospective cohort USA Nurses' Health Study II	–	Living closer to a major road is associated with a higher HR of infertility (primary, secondary, and overall)	[10]
	Distance from Class A roadway	Prospective cohort USA Longitudinal Investigation of Fertility and Environment (LIFE) Study	–	Living further from a major road is associated with a higher FOR	[11]
Surface monitor data	NO ₂ , O ₃ , SO ₂ , PM _{2.5}	Retrospective cohort Teplice, Czech Republic	Average exposure: • 60-day window before the end of the first month of unprotected intercourse	Higher NO ₂ and PM _{2.5} exposures are associated with a lower AFR	[12]
	SO ₂	Retrospective cohort Teplice, Czech Republic	Average exposure: • During each of the four months prior to conception	Higher SO ₂ exposure in the second month before conception is associated with a lower aOR of fecundability	[13]
	NO ₂ , NO _X , PM ₁₀ , PM _{10-2.5} , PM _{2.5}	Cross-sectional Barcelona, Spain	Annual average concentration	Higher PM _{10-2.5} exposure is associated with significantly reduced IRR of fertility rate Higher PM ₁₀ and PM _{2.5} exposures are associated with reduced IRR of fertility rate, not statistically significant	[14]
Fusion model	NO _X , CO, O ₃ , SO ₂ , PM ₁₀ , PM _{2.5}	Prospective cohort USA Longitudinal Investigation of Fertility and Environment (LIFE) Study	Average exposure (from daily averages): • During the cycle prior to the observed cycle • During the proliferative phase (days 1–10) of the observed cycle During sensitive windows of hormonal variability of each observed cycle (range: 5 days before to 10 days following ovulation)	Higher NO _X exposure is associated with a lower FOR at 8 days post ovulation Higher O ₃ exposure is associated with a lower FOR the day before ovulation Higher PM ₁₀ exposure is associated with a <i>greater</i> FOR 6 days post ovulation	[15]
	PM _{2.5}	Retrospective cohort China	Average annual exposure in 2009 and 2010	Higher PM _{2.5} exposure is associated with reduced FR	[16]
	PM _{2.5}	Retrospective cohort China	Average exposure in the current and previous year in each county	Higher PM _{2.5} exposure is associated with reduced FR	[17]

Table 2 (continued)

Model type	Exposure	Study design, location, cohort	Windows of exposure	Primary findings	Reference
Miscarriage Proximity model	PM _{2.5}	Retrospective cohort USA	Average exposure (from monthly averages): • 0–8 months before birth to approximate pregnancy • 9–11 months before birth • During the 12 months before birth	Higher PM _{2.5} exposure during pregnancy but not in the pre-gestation window is associated with reduced FR	[18]
	PM ₁₀ , PM _{10-2.5} , PM _{2.5}	Prospective cohort USA Nurses' Health Study II	Average exposure (from daily averages): • During the 2 prior calendar years • During the 4 prior calendar years Cumulative average exposure: • From 1989 to the current time period	Higher PM ₁₀ , PM _{10-2.5} , PM _{2.5} exposures are associated with a higher HR for infertility (primary, secondary, and overall)	[10]
	Distance from Class A roadway	Prospective cohort California, USA	Annual average daily traffic (AADT) • Adjusted for average NO ₂ monitor levels during: 1) Periconceptual period (0–29 days post-LMP) 2) Second month of pregnancy (30–59 days post LMP)	In the full sample, living closer to a road with AADT is not associated with higher odds of SAB In sub-samples limited to African Americans and non-smokers, living closer to a road with AADT is associated with higher odds of SAB	[19]
Surface monitor data	NO, NO ₂ , CO, O ₃ , SO ₂ , PM ₁₀ , PM _{2.5}	Time series Khuzestan province, Iran	Average exposure (from daily averages): • Lag days 0–6 after exposure to pollutants	Higher SO ₂ on lags 0, 1, 3, 4, and 6 and higher PM ₁₀ on lag 0 were associated with a greater RR of SAB	[20]
	NO ₂ , CO	Case-control Shanghai, China	Average exposure (from daily averages): • First day of LMP to the date of abortion • 30 days before the first day of the LMP • 60 days before the first day of the LMP • 90 days before the first day of the LMP	Higher NO ₂ exposure during pregnancy is associated with a higher OR of SAB	[21]

Table 2 (continued)

Model type	Exposure	Study design, location, cohort	Windows of exposure	Primary findings	Reference
	NO ₂	Time series Boston, USA (surface monitor data) Tel Aviv, Israel (D/CTM)	Average exposure (from daily averages): • LMP week (lag 0) to gestational week 40 (lag 40)	Higher NO ₂ exposure during the 15th gestational week is associated with a lower RR of live birth in Boston (surface monitor data) Higher NO ₂ exposure during the 16th gestational week is associated with a lower RR of live birth in Tel Aviv (D/CTM)	[22]
	CO, O ₃ , SO ₂ , PM _{2.5}	Retrospective cohort Beijing, China	Average exposure (from daily averages): • Tested 7 windows: 0, 30, 60, 90, 120, 150, or 180 days before the first day of the LMP to the last exposure time (LET=LMP+gestational age) • From 90 days before the LMP to the LET had strongest association with MAFT, so these data were used for the analyses	Higher CO, O ₃ , SO ₂ , and PM _{2.5} exposures are associated with a higher aOR of MAFT	[23]
	NO, NO ₂ , CO, O ₃ , SO ₂ , PM ₁₀	Time series Khuzestan province, Iran	Average exposure: • On days 0–14 before SAB	Higher SO ₂ exposure on lag 0 and 9 days is associated with a higher RR of SAB	[24]
	NO ₂ , O ₃ , PM ₁₀	Retrospective cohort Apulia, Italy	Average monthly exposure was linked to monthly number of SABs in the same geographic area	Higher monthly O ₃ and PM ₁₀ exposures are associated with a higher monthly SAB rate	[25]
	NO ₂ , CO, SO ₂ , PM ₁₀ , PM _{2.5}	Retrospective cohort Ulaanbaatar, Mongolia	Monthly averages of pollutants	Dose response correlation coefficients between higher monthly NO ₂ , CO, SO ₂ , PM ₁₀ , and PM _{2.5} and monthly fetal deaths	[26]
	NO ₂ , SO ₂ , PM ₁₀ , total suspended particles (TSP)	Case-control Tianjin, China	Average exposure (from daily averages): • 3 months pre-conception to conception • 2 months pre-conception to conception • 1 month pre-conception to conception • During the month of conception • Conception to 1 month post-conception	Higher exposure to SO ₂ during the month of conception and in the first month of pregnancy were associated with a higher aOR fetal loss Higher exposure to NO ₂ during 2- and 1-month pre-conception and during pregnancy were associated with a higher aOR fetal loss	[27]

Table 2 (continued)

Model type	Exposure	Study design, location, cohort	Windows of exposure	Primary findings	Reference
Surface monitor data with IDW	NO ₂ , CO, O ₃ , SO ₂ , PM ₁₀	Case-control Tehran, Iran	Average exposure: • Cases: LMP to date of SAB • Controls: LMP to 14 weeks gestation	Higher exposure to NO ₂ , CO, O ₃ , and PM ₁₀ are associated with a higher OR of SAB, with the strongest effects for CO SO ₂ was not associated with SAB	[28]
	NO ₂ , O ₃ , PM _{2.5}	Time-stratified case-crossover Utah, USA	Used the average daily exposures of the day of the spontaneous pregnancy loss and the preceding 2 days to calculate: • 3-day averages for the case/ referent date and 2 days prior (i.e., lag0, lag1, and lag2) • 7-day averages for the case/referent date and 6 days prior (i.e., lag0, lag1–lag6) • 3-day maximum value • 7-day maximum value	Higher 7-day average NO ₂ exposure during is associated with a higher OR of SAB Higher 3-day and 7-day average PM _{2.5} exposures were associated with a higher OR of SAB, but not statistically significant O ₃ was not associated with SAB	[29]
LUR model	PM _{2.5}	Case-control Tianjin, China	Average over 10 windows of exposure (from daily averages): • Preconception: 4 weeks, 2 weeks, and 1 week before conception • Post-conception: first, second, third, and fourth single week, the first and second 2-week periods, and the entire 1-month period after conception	Higher PM _{2.5} exposure in the 2nd week and 1-month period post-conception is associated with a higher OR of CREPL	[30]
D/CTM	NO ₂	Time series Boston, USA (surface monitor data) Tel Aviv, Israel (D/CTM)	Average exposure (from daily averages): • LMP week (lag 0) to gestational week 40 (lag 40)	Higher NO ₂ exposure during the 15th gestational week is associated with a lower RR of live birth in Boston (surface monitor data) Higher NO ₂ exposure during the 16th gestational week is associated with a lower RR of live birth in Tel Aviv (D/CTM)	[22]
	NO _x , PM ₁₀	Retrospective cohort Northern Italy	Average exposure (from monthly averages): • During the first 3 months of pregnancy	Higher PM ₁₀ exposure was associated with a greater aOR of miscarriage only for participants without prior miscarriages	[31]

Table 2 (continued)

Model type	Exposure	Study design, location, cohort	Windows of exposure	Primary findings	Reference
Fusion model	PM ₁₀ , PM _{10-2.5} , PM _{2.5}	Prospective cohort USA Nurses' Health Study II	Average exposure (from monthly averages): • 1-year prior to first pregnancy • 2-years prior to first pregnancy • Cumulative of 1 year and 2 years prior to first pregnancy	In the main analysis, greater exposure to PM ₁₀ , PM _{10-2.5} , or PM _{2.5} during 1 year or 2 years prior to pregnancy were not associated with an increase in SAB In the case-crossover analysis, exposure to PM ₁₀ , PM _{10-2.5} , and PM _{2.5} in the year prior to pregnancy were associated with higher odds of SAB	[32]
	PM _{2.5}	Self-compared case-control Multiple locations, Africa	Average exposure (from monthly averages): • Cases: exposure during the full gestation period • Controls: exposure on the basis of gestational length of the matched case, regardless of the control's gestational length	Higher PM _{2.5} exposure was associated with higher odds of SAB	[33]
	NO ₂ , NO _x , CO, O ₃ , SO ₂ , PM ₁₀ , PM _{2.5}	Prospective cohort USA Longitudinal Investigation of Fertility and Environment (LIFE) Study	Average exposure: • 2 weeks before ovulation in the pregnancy cycle • The last 2 weeks of pregnancy • The whole pregnancy (ovulation to loss or birth)	Higher O ₃ and PM _{2.5} exposure over the whole pregnancy are associated with a higher HR for pregnancy loss	[34]
Stillbirth					
Proximity model	Distance from Class A roadway	Retrospective cohort Massachusetts, USA	–	Found some evidence that living closer to a major roadway is associated with a higher RR of stillbirth	[35]
Surface monitor data	NO, NO ₂ , CO, O ₃ , SO ₂ , PM ₁₀ , PM _{2.5} NO ₂ , CO, O ₃ , SO ₂ , PM _{2.5}	Time series Khuzestan province, Iran Time series Tehran, Iran	Daily averages on lag days 0–6 after exposure to pollutants Daily averages on lag days 0–6 after exposure to pollutants	None of the pollutants were significantly associated with stillbirth Higher SO ₂ exposure at lag 0 was associated with a higher RR of stillbirth	[20] [36]

Table 2 (continued)

Model type	Exposure	Study design, location, cohort	Windows of exposure	Primary findings	Reference
	NO ₂ , CO, O ₃ , SO ₂ , PM ₁₀ , PM _{2.5}	Prospective cohort Yancheng, China	Average exposure (from daily averages): • First trimester • Second trimester • Third trimester • Entire pregnancy (LMP to delivery)	Higher O ₃ exposure in the first and third trimester were associated with higher stillbirth rate Higher PM _{2.5} exposure in each trimester and over the entire pregnancy was associated with higher stillbirth rate Higher PM ₁₀ exposure the first trimester was associated with higher stillbirth rate	[37]
	PM _{2.5}	Nested case–control California, USA	Average exposure (from daily averages): • Cases: exposure during the full gestation period • Controls: exposure on the basis of gestational length of the matched case, regardless of the control's gestational length	Higher PM _{2.5} exposure was associated with higher stillbirth rate	[38]
	NO ₂ , CO, SO ₂ , PM ₁₀ , PM _{2.5}	Prospective cohort Wuhan, China	Average exposure (from daily averages): • Gestational months 1 • Gestational month 2 • Gestational month 3 • First trimester • Second trimester • Third trimester • Entire pregnancy (LMP + 14 days to delivery)	Higher PM _{2.5} in each window of exposure was associated with higher aOR of stillbirth Higher CO exposure in the third trimester and over the entire pregnancy were associated with higher aOR of stillbirth Higher SO ₂ , NO ₂ , and PM ₁₀ exposure in the third trimester was associated with higher aOR of stillbirth	[39]
	PM _{2.5}	Retrospective cohort Ohio, USA	Average exposure (based on monthly averages calculated from daily averages): • First trimester • Second trimester • Third trimester	Higher PM _{2.5} in the third trimester only was associated with higher aOR of stillbirth	[40]
	NO ₂ , CO, SO ₂ , O ₃ , PM _{2.5}	Retrospective cohort California, USA	Average exposure (from weekly averages): • First trimester • Second trimester • Third trimester • Entire pregnancy (LMP + 2 weeks to delivery)	Higher PM _{2.5} and NO ₂ during the entire pregnancy were associated with higher aOR of stillbirth Higher O ₃ during the third trimester was associated with higher aOR of stillbirth	[41]

Table 2 (continued)

Model type	Exposure	Study design, location, cohort	Windows of exposure	Primary findings	Reference
	NO ₂ , CO, SO ₂ , PM _{2.5}	Time-stratified case-crossover New Jersey, USA	Average exposure (from daily averages): <ul style="list-style-type: none"> • Case period: lag day 2 (i.e., 2 days preceding the day of stillbirth) • Control period: (3–4 per case) were selected by matching on weekday within the same calendar month • Additional analysis: OR of stillbirth 2–6 days before delivery 	Higher NO ₂ , CO, SO ₂ , and PM _{2.5} exposure 2 days before delivery was associated with higher aOR of stillbirth Higher CO, SO ₂ , and PM _{2.5} exposure 2 through 6 days before delivery was associated with higher aOR of stillbirth	[42]
	NO ₂ , CO, SO ₂ , PM _{2.5}	Retrospective cohort New Jersey, USA	Average exposure (from hourly averages, except PM _{2.5} which was every third day): <ul style="list-style-type: none"> • First trimester • Second trimester • Third trimester • Entire pregnancy 	Higher NO ₂ exposure in the first trimester was associated with higher aOR of stillbirth Higher CO exposure in the second and third trimester were associated with higher aOR of stillbirth Higher SO ₂ exposure in the first and third trimester were associated with higher aOR of stillbirth	[43]
	PM ₁₀	Prospective cohort Korea	Average exposure (from hourly averages): <ul style="list-style-type: none"> • First trimester • Second trimester • Third trimester • Each month of pregnancy • 6 weeks before delivery to delivery 	Higher PM ₁₀ exposure in the third trimester was associated with higher aOR of stillbirth	[44]
	NO ₂ , SO ₂	Ecological Czech Republic	Annual average (from daily readings)	Stillbirth rate was not associated with any pollution measure	[45]
	NO ₂ , CO, O ₃ , SO ₂ , PM ₁₀	Time series São Paulo, Brazil	Average exposure (from daily averages): <ul style="list-style-type: none"> • Lags from 2–14 days from exposure (different lags and moving averages for each pollutant) • NO₂: 5-day moving average • CO: 3-day moving average • SO₂: mean of concurrent day • O₃, PM₁₀: unspecified Annual average	Higher NO ₂ exposure was associated with higher aOR of intrauterine mortality	[46]
	NO ₂ , NO, SO ₂	Retrospective cohort Tokyo Bay, Japan	Annual average	Higher annual NO ₂ and SO ₂ exposure are correlated with the fetal death rate	[47]

Table 2 (continued)

Model type	Exposure	Study design, location, cohort	Windows of exposure	Primary findings	Reference
Surface monitor data with IDW	NO ₂ , CO, SO ₂ , O ₃ , PM _{10-2.5} , PM _{2.5}	Time-stratified case-crossover California, USA	Average exposure (from daily averages): • Single day and/or cumulative average days (up to a 6-day lag) of exposure	Higher SO ₂ and O ₃ exposure at lag 4 days were associated with higher OR of stillbirth Higher PM _{10-2.5} exposure at lag 2 days was associated with higher OR of stillbirth	[48]
	NO ₂ , O ₃ , PM _{2.5}	Retrospective cohort Texas, USA	Average exposure (from weekly averages): • Conception to 20th week • Conception to 21st week, etc., through last week gestation	Higher O ₃ exposure at was associated with a higher OR of stillbirth, effects were stronger among pregnancies less than 37 weeks	[49]
	NO ₂ , CO, SO ₂ , O ₃ , PM ₁₀	Case-control Taiwan	Average exposure (from monthly averages): • Each month of pregnancy • First trimester • Second trimester • Third trimester • Entire pregnancy	Higher SO ₂ exposure in the first trimester was associated with a higher aOR of stillbirth, particularly among preterm births Higher PM ₁₀ exposure in the first and second month of pregnancy was associated with a higher aOR of stillbirth, particularly among preterm births	[50]
D/CTM	NO ₂ , NO _x , O ₃ , PM ₁₀ , PM _{2.5}	Retrospective cohort UK	Average exposure (from monthly averages): • First trimester • Second trimester • Last 3 months of pregnancy	Higher O ₃ exposure in the first and second trimester was associated with a higher OR of all-cause stillbirth	[51]
	PM ₁₀	Retrospective cohort, case-control UK	Average exposure (from daily averages): • Entire pregnancy	Higher PM ₁₀ exposure was not associated with increased risk of stillbirth	[52]
	NO, SO ₂	Retrospective cohort Sweden	Unspecified	Stillbirth rate was not associated with any pollution measure	[53]
Fusion model	PM _{2.5}	Self-compared case-control Multiple locations, Africa	Average exposure (from monthly averages): • Cases: exposure during the full gestation period • Controls: exposure on the basis of gestational length of the matched case, regardless of the control's gestational length	Higher PM _{2.5} exposure was associated with higher odds of stillbirth	[33]

Table 2 (continued)

Model type	Exposure	Study design, location, cohort	Windows of exposure	Primary findings	Reference
	NO _x , CO, SO ₂ , O ₃ , PM ₁₀ , PM _{2.5}	Retrospective cohort USA Consortium on Safe Labor	Average exposure (from daily averages): • First trimester • Entire pregnancy • Day of delivery and each of the 7 days prior to delivery	Higher O ₃ exposure during the first trimester, the entire pregnancy, and on days 2, 3, and 5–7 prior to delivery were associated with a greater ARR of stillbirth	[54]

APR adjusted fecundability ratio, aOR adjusted odds ratio, ARR adjusted risk ratio, CI confidence interval, CREPL clinically recognized early pregnancy loss, FOR fecundability odds ratio, HR hazard ratio, IQR interquartile range, IRR incidence rate ratio, MAFT missed abortion in the first trimester, OR odds ratio, RR relative risk, SAB spontaneous abortion

data are particularly useful for examining changes over time and thus could be in projects with a case-crossover design.

Despite these strengths, monitor data are sparse, as most counties in the USA do not have a regulatory air pollution monitor [56]. Fertility studies that use surface monitor data to estimate exposures have taken a variety of approaches to address this limitation (Fig. 2):

- 1) Generalizing exposure estimates by **averaging monitor data regionally** (not based on individual participant addresses) [12, 13, 20–22, 24–26, 36, 45–47]
- 2) Estimating individual exposure using the **closest monitoring station** within a designated distance to (a) zip code centroids of participant residence [38, 41, 44] and (b) the residence itself [27, 28, 37, 39, 40, 42, 43], the residence, and the workplace [23]
- 3) Estimating individual exposure through **inverse distance weighting** to participant addresses [49], or zip code centroids [29, 48] or postal codes of participant residence [50]

Of the studies using surface monitor data, 12 of the 26 studies (46%) assessing NO_x (including NO and NO₂) found an association between high exposure to NO_x and a poor fertility outcome (including low fertility, low fecundability, and high pregnancy loss) (Fig. 3). Associations for high exposure to pollutants and poor fertility outcomes were also found in 13 of the 20 studies that assessed SO₂ (65%), 6 of the 17 studies that assessed CO (35%), 7 of the 14 studies that assessed ozone (50%), 9 of the 16 studies that assessed PM_{2.5} (56%), 8 of the 12 studies that assessed PM₁₀ (67%), and in the one study that assessed PM_{10-2.5} (100%) (Fig. 3). Nonetheless, these studies varied widely in defining windows of exposure (Table 2), and significant associations were not found in every window of exposure assessed in each study.

By specific outcome, one study found an association between NO₂ exposure and fecundability [12], one study found an association between SO₂ and fecundability [13], and one study found an association between PM_{2.5} and fecundability [12] (Table 2). Greater exposure to NO₂ [21, 22, 26–29], CO [23, 26, 28], O₃ [23, 25, 28], SO₂ [20, 23, 24, 26, 27], PM₁₀ [20, 25, 26, 28, 29], and PM_{2.5} [23, 26] have all been associated with increased risk of miscarriage. Finally, greater exposure to NO₂ [39, 41–43, 46, 47], CO [39, 42, 43], O₃ [37, 41, 48, 49], SO₂ [36, 39, 42, 43, 47, 48, 50], PM₁₀ [37, 39, 44, 50], PM_{10-2.5} [48], and PM_{2.5} [37–42] have been associated with stillbirth.

Land-Use Regression Models

Just 4% of studies assessing the effect of air pollution on fertility use land-use regression (LUR) models as the exposure assessment method. LUR models, which use multivariable

Fig. 2 Methods used to assign exposures with surface monitor data

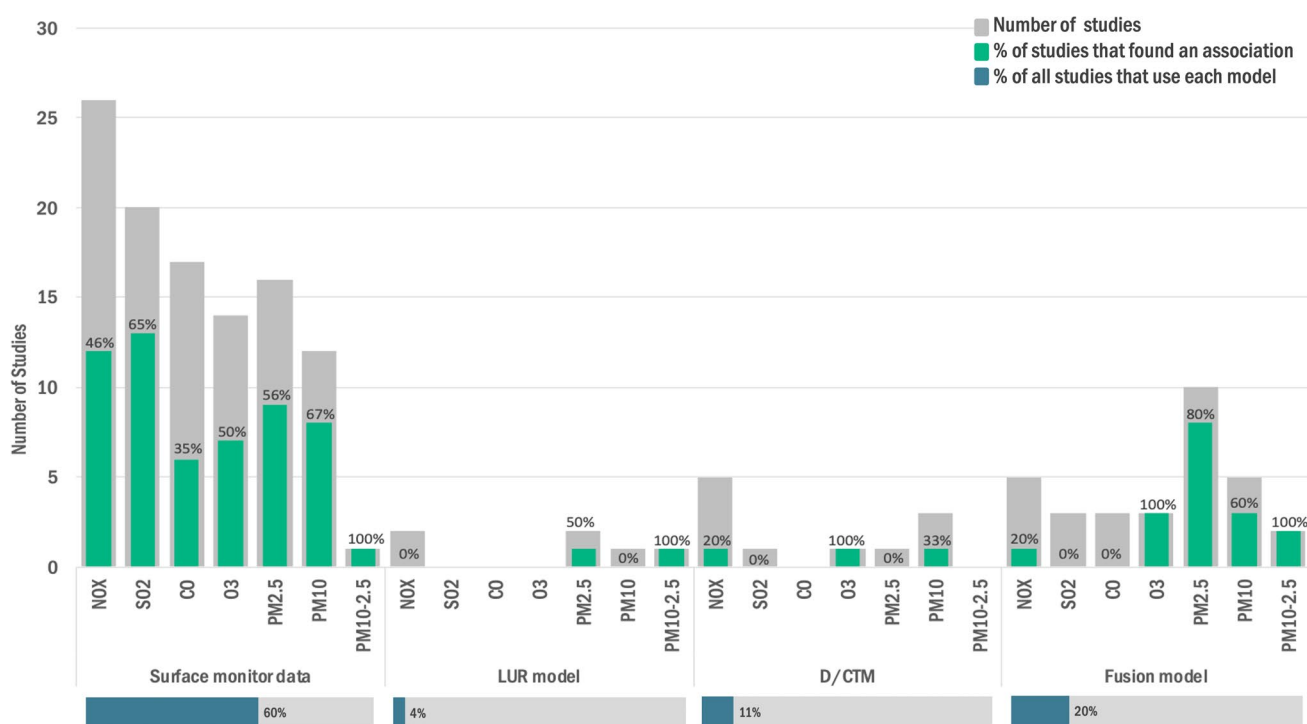
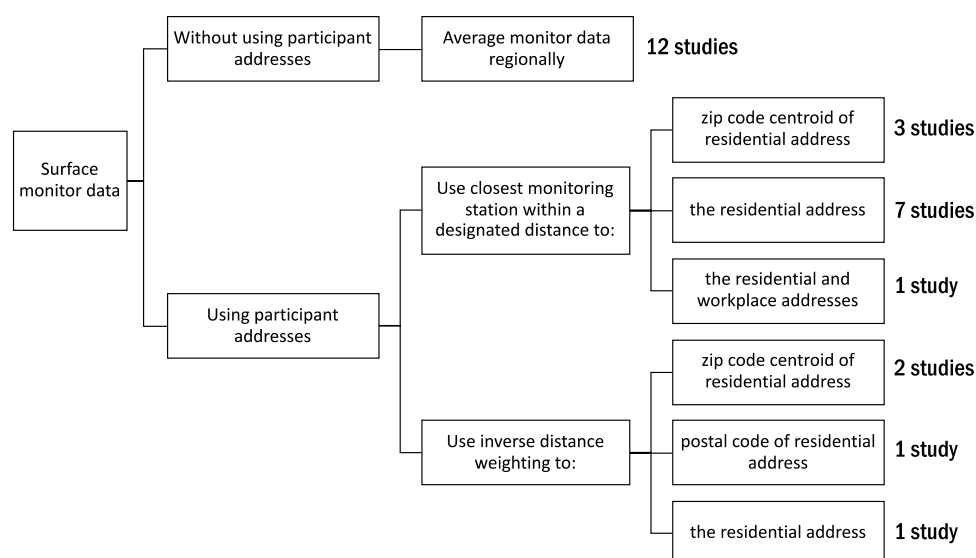


Fig. 3 Proportion of studies that found an association between pollutants and poor fertility outcomes. ^aPoor fertility outcomes are defined as low fertility/fecundability or high pregnancy loss. Blue percentages

do not add to 100% because proximity models are not represented here and two studies use two types of models. See Table 1 for breakdown of the percentage of studies using each model

linear regression models to estimate the spatial distribution of pollutant concentrations [58, 59], were first used for air pollution modeling in 1997 [60]. These models incorporate air monitor data, emissions data, land-use data (traffic, population density, etc.), and meteorological data (altitude, wind speed) to predict pollutant concentrations at point-specific locations where there is not monitor-based data [58, 59, 61,

62]. Monitoring data used for LUR models are usually based on ambient monitoring networks [57], but some city-wide models are developed based on study-specific temporary networks of monitors. The strengths of LUR models include their ability to (1) predict at unmonitored locations at an address or point-level spatial scale, (2) use readily available ambient monitoring data, (3) use readily available GIS

datasets for covariates (4), and deliver a meaningful interpretation of coefficients. Nonetheless, these models have a few key limitations. Primarily, while LUR models can in theory predict at any spatial and temporal resolution, the predicted variability is often underestimated. Mobile monitoring studies have shown significantly more variability in air pollution than LUR models can predict [63, 64]. The ability of LUR models to capture local variability is tied to the availability and quality of local covariates, like construction sites and gas stations, which are not often readily available [63, 64]. Nonetheless, some researchers have attempted to address this limitation with information from Google Place, with mixed results [65].

In the fertility literature, only two studies have used LUR models to estimate ambient air pollution exposures. Nieuwenhuijsen et al. (2014) assessed how the annual average concentration at the census tract level for NO_2 , NO_x , PM_{10} , $\text{PM}_{10-2.5}$, and $\text{PM}_{2.5}$ affected risk estimates for fertility in women and found that only $\text{PM}_{10-2.5}$ is significantly associated with a reduced fertility rate [14]. Zhang et al. (2019) used a LUR model with a spatial resolution of 1 km² grid to assess how exposure to $\text{PM}_{2.5}$ during three pre-conception and seven post-conception windows of exposure influenced the odds of clinically recognized early pregnancy loss (CREPL) [30]. This study found an association between higher $\text{PM}_{2.5}$ exposure and CREPL in two of the windows of exposure: during the second week post-conception and during the entire 1-month period post-conception [30]. Overall, of the studies that have used LUR models, neither of the analyses assessing NO_x (NO_2 and NO_x), nor the one study assessing PM_{10} were associated with poor fertility outcomes (Fig. 3). One of the two studies assessing $\text{PM}_{2.5}$ and the one study assessing $\text{PM}_{10-2.5}$ were associated with poor fertility outcomes. No studies using LUR models have assessed exposure to SO_2 , CO, or ozone and our fertility outcomes of interest.

Dispersion and Chemical Transport Models

Eleven percent of fertility studies use dispersion and chemical transport models to assess air pollution exposure. Dispersion models (DMs) mathematically simulate air pollution concentrations through physical, fluid dynamical processes of the transport, and dispersion of air pollutants in the atmosphere from known or estimated emission inventories [61, 66]. Transport is accounted for by incorporating meteorological data such as wind speed, velocity, and atmospheric boundary layer heights. Chemical transport models (CTMs) are unique from dispersion models in that they simulate processes of chemical transformation, diffusion, and deposition to predict chemical concentrations in the atmosphere [61]. In practice, these models are often combined into dispersion/chemical transport models (D/CTMs) [61], which are

deterministic models that incorporate principles from physics and chemistry and include data on emissions, meteorology, topography, and land-use to simulate how pollutants are distributed into the atmosphere [58, 66]. DMs, CTMs, and D/CTMs can account for a variety of types of emission sources, such as point (waste sites, industrial facilities, etc.), area (also waste sites and industrial facilities), and line sources (roads), increasing their accuracy of prediction [55]. Mathematically, these models are formulated as a series of differential equations on a 4-dimensional space/time grid (e.g., longitude, latitude, elevation, and time).

While these models attempt to improve upon LUR models through the addition of physical and chemical processes, their performance is highly dependent on the quality of the input data [58]. Some comparisons of the performance of LUR models and D/CTMs for NO_2 have found that D/CTMs performed better than LUR models for monitored and modeled concentrations on multiple sites, while other studies have seen moderate to good correlations between LUR models and D/CTMs [61]. Compared to LUR models, D/CTMs often produce models with higher temporal resolution but lower spatial resolution [67] since emission and meteorology predictions are more precise across time than space. Moreover, the computational intensity of D/CTM scales directly with the spatial resolution.

D/CTMs provide the benefit of not requiring a dense network of surface monitors for exposure estimation [62]. Further, D/CTMs incorporate explicit physics and chemistry so that they can better predict the secondary formation of pollutants. Nonetheless, these models have a few important limitations. First, D/CTMs require a larger quantity and variety of input data than simpler models, which can be expensive, time-consuming, and need D/CTM-specific expertise to prepare [55, 58, 62]. D/CTMs are suitable for research questions that require a refined temporal resolution, a large spatial domain (e.g., national or global), and circumstances in which changes in emissions are investigated [67].

In the fertility literature, D/CTMs have been used to estimate exposures with monthly averages at 20 × 20 m grid points [51], with monthly averages at a participant's place of residence [31], with weekly averages for an entire city district [22], at daily averages for postcode centroids [52], and at the municipality level (timing not specified) [53]. Of these studies, one of the five studies assessing NO_x found an association between greater exposure to NO_x and a poor fertility outcome (including low fertility/fecundability and high pregnancy loss) (Fig. 3). More specifically, this study found an association between higher NO_2 exposure during the 16th gestational week and a lower relative risk of live birth [22]. Of the three studies that assessed PM_{10} , only one found an association with a poor fertility outcome, specifically a higher risk of miscarriage among participants without prior miscarriages [31]. Only one study assessed ozone,

finding that high ozone exposure in the first and second trimester was associated with a higher risk of stillbirth [51]. The one study that assessed exposure to SO_2 did not find a significant association with stillbirth [53], and the one study that assessed exposure to $\text{PM}_{2.5}$ did not find an association with stillbirth [51]. No studies that assessed exposure to CO or $\text{PM}_{10-2.5}$ used a D/CTM.

Fusion Models

Fusion models combine any of the above methods and may incorporate monitoring data, emissions, meteorology, land-use, satellite imagery, or model components from LUR models, machine learning, and D/CTMs [55]. For example, a D/CTM may be used as a covariate in a LUR model that incorporates the physical and chemical properties of the D/CTM to the LUR model, but effectively calibrates the D/CTM to ground-based monitoring data. Moreover, LUR models usually benefit from the incorporation of satellite imagery data, particularly in data sparse regions, or from the integration of a LUR model into a kriging model [68]. Generally, LUR models and D/CTMs are improved by incorporating them into a kriging of the Gaussian process model.

In comparison to other air pollution exposure models, fusion models typically reduce prediction variance and bias due to their ability to capitalize on the advantages of their component parts [55, 69]. Nonetheless, fusion models have a few important limitations. First, fusion models may be limited by the same concerns of their constituent model parts; for example, when combining a model with surface monitor data, the fusion model will be limited by the density of the surface monitor network [55]. Second, as models use varying temporal and spatial scales, integration can be both complex and computationally challenging [55].

The fertility literature includes a variety of fusion models to estimate air pollution exposures, including those that integrate surface monitoring data and D/CTMs [10, 15, 18, 32, 34, 54], satellite measures and D/CTMs [33], and surface monitoring data, satellite data, and D/CTMs [16, 17]. Of the studies using fusion models, 1 of the 5 studies (20%) assessing NO_x (including NO and NO_2) found an association between high exposure to NO_x and a poor fertility outcome (including low fertility, low fecundability, and high pregnancy loss) (Fig. 3). Associations for high exposure to pollutants and poor fertility outcomes were also found in: all three studies that assessed ozone (100%), 8 of the 10 studies that assessed $\text{PM}_{2.5}$ (80%), 3 of the 5 studies that assessed PM_{10} (60%), and both of the studies that assessed $\text{PM}_{10-2.5}$ (100%).

Specifically, three studies identified an association between $\text{PM}_{2.5}$ and a reduced fertility rate [16–18], while another found associations between PM_{10} , $\text{PM}_{2.5}$, and particularly $\text{PM}_{10-2.5}$ and higher frequency of infertility [10]

(Table 2). Another study found that NO_2 and O_3 exposures are associated with a lower fecundability odds ratio (FOR), but that PM_{10} is associated with a *greater* FOR [15]. Three studies that use fusion models found associations between $\text{PM}_{2.5}$ and miscarriage [32–34], one found that higher O_3 and $\text{PM}_{2.5}$ exposure over the whole pregnancy are associated with a higher HR for pregnancy loss [34], one found that in a case-crossover analysis exposure to PM_{10} , $\text{PM}_{10-2.5}$, and $\text{PM}_{2.5}$ in the year prior to pregnancy were associated with higher odds of spontaneous abortion (SAB) [32], and one found that $\text{PM}_{2.5}$ exposure was associated with higher odds of SAB. Of the studies that investigated stillbirth, one found that O_3 exposure in various windows of exposure during pregnancy was associated with stillbirth [54], while another found that $\text{PM}_{2.5}$ was associated with higher odds of stillbirth [33].

Other Methods of Exposure Assessment Not Applied in Studies of Fertility

To our knowledge, air pollution exposure estimates based purely on kriging models or satellite data, and estimates based on personal monitor data, have not been used in fertility studies.

Kriging, also known as Gaussian process regression, represents a common and well-established method for geostatistical analysis. Like inverse distance weighting, kriging interpolates values at unmeasured locations based on values from measured locations like a surface monitor. However, unlike inverse distance, Kriging provides a theoretical basis for the weights where interpolation is developed from spatial correlation, the integration of covariates, and by quantifying and incorporating predictive uncertainty [70, 71]. Kriging may be estimated through classical, maximum likelihood, and Bayesian approaches. The simplest approaches, simple and ordinary kriging, assume no spatial patterns for the estimation of the mean and that all spatial variation is a component of the error. However, this limits the inclusion of covariates and is generally less flexible [71]. Kriging approaches incorporating ancillary information through the mean trend, referred to as universal kriging, kriging with an external drift, or land-use regression kriging, offer greater flexibility and more realistic interpolations of values than pure kriging or IDW. An early publication on kriging by Oliver et al. (1992) [72] includes a useful and simple description of the structure of kriging and applies it to estimate the risk of childhood cancer in UK electoral wards. Further descriptions of kriging/Gaussian processes, and their various iterations, are found in many textbooks [71, 73] and are supported in many programs including ArcGIS, QGIS, R, Python, and Matlab. To our knowledge, no fertility studies have assessed air pollution using a pure kriging or other geostatistical method. Nonetheless, kriging alone has been used

in other reproductive health studies, including those assessing the effects of ambient air pollution on preterm birth [74, 75] and on low birth weight [76, 77].

Satellite data are particularly useful in filling gaps in areas with few ground monitors or with poor D/CTM resolution. Though satellite data have not been used independently in fertility studies, they have been incorporated into fusion models [16, 17, 33]. Satellite data are derived from processed spectral imagery of the Earth's surface that is used to detect and classify cloud cover, greenness on the planet's surface, particulate matter, and the occurrence of gases in the atmosphere [78]. Particulate matter is measured by columnar aerosol optical depth (AOD), which is currently derived from the Moderate Resolution Imaging Spectroradiometer (MODIS) and Multiangle Imaging Spectroradiometer (MISR) satellite instruments. An upcoming 2022 mission from the National Aeronautics and Space Administration (NASA), Multi-Angle Imager for Aerosols (MAIA), will specifically focus on producing satellite AOD data for epidemiologic studies to capture the variation of PM_{2.5} and PM₁₀ [79]. More information on AOD measures can be found in Sorek-Hamer et al.'s (2016) review [78]. Other criteria pollutants can be measured by the Tropospheric Monitoring Instrument (TROPOMI) on the Sentinel-5 Precursor satellite [80]. TROPOMI provides measurements for atmospheric pollutants from 2018 to near real-time at 0.01 arc degree resolution for NO₂, O₃, SO₂, CO, methane (CH₄), and formaldehyde (CH₂O) [80]. Despite the advantages of satellite data, interpreting the ground level concentration directly from the satellite images can be confounded by cloud cover, reflectance, and complexities of atmospheric mixing [81]. Further, depending on the satellite orbit, the spatiotemporal coverage of the atmosphere may be geostationary and temporally consistent or cover different swaths of the globe at different time intervals. Numerous algorithms have been developed to interpolate across the missing space and time values in the data. Duncan et al. (2014) provide a thorough overview of satellite data, though some of the available instruments and algorithms have changed since that publication [81].

Unlike the other exposure assessments discussed, personal monitoring devices offer the opportunity to quantify individual-level exposure to pollutants within specific microenvironments [56, 82]. Personal monitors may be active monitors that use a power source, or a passive sampling technology such as a silicon wristband [83, 84], some of which are able to characterize hundreds of different pollutants [85]. To date, the high cost of personal monitors, measurement accuracy and precision concerns, and the relatively high burden to the participant have limited the use of personal monitors in research [56] and restricted the sample size and duration of exposure assessment in existing studies [85]. Nonetheless, recent advances in personal monitor technology have lowered the costs and made monitors

smaller and more manageable for participants, creating an opportunity for future work [85]. We are not aware of any fertility studies that have used personal monitors to assess air pollution exposures, though the pre-conception period and pregnancy may provide important areas of opportunity for the use of personal monitors in research, particularly since exposure windows may be short and discrete. In other reproductive health research, personal monitors have been used to assess acute air pollution exposure during each trimester in a study assessing the effect of air pollution on fetal growth and birth outcomes [86] and to assess exposure to polycyclic aromatic hydrocarbons in pregnant women [87].

Discussion

The aim of this project was not to review the point estimates in the air pollution and fertility literature, but rather to review the air pollution exposure assessments used in the human fertility field. Figure 3 shows a summary of the results from studies assessing the relationship between ambient air pollution and fertility and pregnancy loss. The differences in exposure/disease definitions and spatial/temporal scales of interest make general comparisons across studies difficult. However, the results from fusion models show larger total exposure variability and better spatial/temporal heterogeneity compared to surface monitor data, which should improve the power to detect effects. There were not enough studies using LUR models or D/CTMs to draw similar comparisons. More studies are needed to make claims about whether more complex models truly offer an improvement upon traditional methods used in epidemiology in assessing these outcomes.

Other Considerations for Exposure Assessment in Fertility Research

Aside from the type of air pollution exposure assessment method used, the heterogeneity in spatial and temporal resolution also makes findings in the fertility literature difficult to compare across studies.

The spatial resolution of air pollution exposure across the studies reviewed varies widely, as do the methods used to assign exposures to participants. Fertility studies that use surface monitor data have estimated pollutant exposure using three methods: (1) (without using individual participant addresses) averaging monitor data regionally or (2) (using participant addresses) using the closest monitoring station [23, 27, 28, 37–44] or (3) inverse weighting [29, 48–50] to more refined geographic areas, including zip codes, postal codes, residential addresses, and places of work (Fig. 2). Most of the studies average monitor data regionally, in regions as broad as a province. In these cases, the heterogeneity in exposure estimates rely more heavily on

temporal differences than geographic differences. For studies that do use individual participant addresses to assign exposures, some assign exposures at the address itself while others assign exposures to the zip or postal code centroids of the addresses. However, assigning exposures based on zip codes can lead to exposure misclassification, as zip codes were developed as mail delivery routes, and thus, they vary widely in size and shape, and they are not tied to potentially meaningful geographic data including municipal boundaries, land-use data, or human-activity patterns [88]. This is important since location-based exposure misclassification can cause a bias toward the null [89], dampening the ability to discern associations between environmental exposures and health outcomes. Moving away from surface monitor data, air pollution output from LUR models, D/CTMs, and fusion models generally take the form of refined exposure estimates at the grid-cell level. In the fertility literature, most LUR models, D/CTMs, and fusion models provide air pollution estimates at 12-km or 20-km grids.

Existing air pollution exposure methods offer data with set geographic resolutions that provide exposure estimates at points (latitude × longitude), grids, census tracts, zip codes, cities, or other areas. While it may be tempting to try to improve the accuracy of individual exposure assessment by using an exposure assessment method that provides data at a point in order to assign exposures at an exact residence or workplace, this strategy may actually increase exposure misclassification. While participants' homes may be where they accumulate most of their pollution exposure, realistically, many people spend hours a day away from their homes at work or school, running errands, commuting, socializing, exercising, etc. Consequently, assigning exposures to the 12- or 20-km grid cell of residence may more appropriately quantify a person's daily exposure. In considering the spatial resolution of exposures for humans, epidemiologists must strike a balance to use an area that is an accurate estimate of a participant's realistic life exposure. For example, the authors of a recent miscarriage study attempted to improve the accuracy of their air pollution assessment by estimating exposures as 1/3 of the woman's exposure at her workplace and 2/3 of her exposure at her residence [23]. While these are important considerations, depending on the research question, the decision as to which exposure assessment method to use may ultimately be derived from other factors, including the pollutants of interest, the temporal resolution of a model, model type, or other characteristics. Last, these considerations are important when using existing air pollution data, but prospective studies that use personal monitors will capture daily exposures at an individual level, thereby mitigating this potential exposure misclassification.

In the studies reviewed here, the temporal resolution of the air pollution exposure ranges from yearly to daily pollutant concentrations that are used to calculate windows

of susceptibility, with many studies assessing similar but slightly different exposure windows. For example, six studies that assessed the effect of pollutants on miscarriage defined different preconception windows of susceptibility [21, 23, 27, 30, 32, 34], ranging from the average concentration over the 2 years prior to pregnancy [32] to the average concentration over the week prior to conception [30]. More detail on each study's windows of exposure is provided in Table 2. For each of these disparate windows of exposure, every study reviewed here averaged pollutants across their selected windows of exposure with the exception of Mahalingaiah et al. (2016) [10], who also added the cumulative average exposure over a time period to the analysis, and the time-series studies [20, 22, 24, 36], which use daily averages. To our knowledge, no studies in the fertility literature have examined differences between the average and the peak (or extended peak) pollutant concentrations within an exposure window. This distinction may be important in order to better understand how extremes in pollutant exposures influence the biological mechanisms underpinning fertility and reproductive health.

Temporal considerations present specific challenges for reproductive health and fertility studies, which often require refined daily exposure data. While chronic exposure to air pollution may contribute to infertility or reproductive health consequences, often research on fertility requires exposure assessment methods with daily temporal data on exposures to define windows of susceptibility for ovulation, conception, gestational trimesters, discrete periods before a pregnancy loss, or other exposure windows of interest. Studies examining acute exposures may require even more refined temporal resolution, at the hourly level, which are available from some chemical transport models including the US EPA's Community Multiscale Air Quality Modeling System (CMAQ) [90]. Further, while surface monitor data have many limitations, they do use consistent monitoring methods, refined temporal measures, and long-term historical data, making them a potentially good choice for studies examining changes over time for limited geographic areas, such as city or county-scale case-crossover study designs [91].

Currently, 69% of fertility studies examining air pollution use proximity models or surface monitor data to assess the air pollution exposure. Future research in this field would benefit from the incorporation of newer and more sophisticated modeling methods with LUR models, D/CTMs, and fusion models. Embracing these new technologies could improve the predictive accuracy, precision, spatiotemporal variability, and resolution of air pollution exposure assessment methods. This shift is particularly important for fertility work and reproductive health epidemiology more broadly, which requires refined exposures to define discrete and biologically meaningful windows of exposure.

Funding This research was supported by the intramural research program of the National Institute of the Environmental Health Sciences under award number Z01ES103333 and by the Division of the National Toxicology Program of the National Institute of Environmental Health Sciences, National Institutes of Health.

Data Availability Not applicable.

Code Availability Not applicable.

Declarations

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Conflict of Interest The authors declare that they have no conflict of interest.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

References

- Conforti A, Mascia M, Cioffi G, De Angelis C, Coppola G, De Rosa P, et al. Air pollution and female fertility: a systematic review of the literature. *Reprod Biol Endocrinol* [Internet]. 2018 [cited 2020 Jul 1];16:117. <https://doi.org/10.1186/s12958-018-0433-z>.
- Vizcaíno MAC, Gonz Alez-Comadran M, Jacquemin B. Outdoor air pollution and human infertility: a systematic review. *Fertil Steril* [Internet]. 2016 [cited 2020 Jul 8];106:897–904. <https://doi.org/10.1016/j.fertnstert.2016.07.1110>.
- 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* [Internet]. 2020;3:e208243.
- Grippio A, Zhang J, Chu L, Guo Y, Qiao L, Myneni AA, et al. Air pollution exposure during pregnancy and spontaneous abortion and stillbirth. *Rev Environ Health* [Internet]. De Gruyter; 2018 [cited 2020 Aug 17];33:247–64. <https://doi.org/10.1515/reveh-2017-0033>.
- Frutos V, González-Comadrán M, Solà I, Jacquemin B, Carreras R, Vizcaíno MAC. Impact of air pollution on fertility: a systematic review. *Gynecol Endocrinol Informa Healthcare*. 2015;31:7–13.
- Carré J, Gatimel N, Moreau J, Parinaud J, Léandri R. Does air pollution play a role in infertility?: a systematic review. *Environ Heal*. 2017;16:82.
- US Environmental Protection Agency. Criteria air pollutants [Internet]. 2021 [cited 2021 Jan 20]. Available from: <https://www.epa.gov/criteria-air-pollutants>.
- Di Q, Wang Y, Zanobetti A, Wang Y, Koutrakis P, Choirat C, et al. Air pollution and mortality in the medicare population. *N Engl J Med*. 2017;376:2513–35.
- Raaschou-Nielsen O, Andersen ZJ, Beelen R, Samoli E, Stafoggia M, Weinmayr G, et al. Air pollution and lung cancer incidence in 17 European cohorts: prospective analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE). *Lancet Oncol*. 2013;14:813–22.
- Mahalingaiah S, Hart JE, Laden F, Farland L V, Hewlett MM, Chavarro J, et al. Adult air pollution exposure and risk of infertility in the Nurses' Health Study II. *Hum Reprod* [Internet]. 2016 [cited 2020 Jul 8];31:638–47. Available from: <https://academic.oup.com/humrep/article-abstract/31/3/638/2384689>.
- Mendola P, Sundaram R, Louis GMB, Sun L, Wallace ME, Smarr MM, et al. Proximity to major roadways and prospectively-measured time-to-pregnancy and infertility. *Sci Total Environ* [Internet]. Elsevier B.V.; 2017 [cited 2020 Jul 8];576:172–7. Available from: www.tele-mart.com.
- Slama R, Bottagisi S, Solansky I, Lepeule J, Giorgis-Allemand L, Sram R. Short-term impact of atmospheric pollution on fecundability. *Epidemiology*. 2013;24:871–9.
- Dejmek J, Jelínek R, Solansky I, Beneš I, Srám RJ. Fecundability and parental exposure to ambient sulfur dioxide. *Environ Health Perspect*. 2000;108:647–54.
- Nieuwenhuijsen MJ, Basagaña X, Dadvand P, Martinez D, Cirach M, Beelen R, et al. Air pollution and human fertility rates. *Environ Int Elsevier Ltd*. 2014;70:9–14.
- Nobles CJ, Schisterman EF, Ha S, Louis GMB, Sherman S, Mendola P. Time-varying cycle average and daily variation in ambient air pollution and fecundability. *Hum Reprod* [Internet]. 2018 [cited 2020 Jul 8];33:166–76. Available from: <https://academic.oup.com/humrep/article-abstract/33/1/166/4616531>.
- Xue T, Zhang Q. Associating ambient exposure to fine particles and human fertility rates in China. *Environ Pollut* [Internet]. Elsevier Ltd; 2018 [cited 2020 Nov 9];235:497–504. <https://doi.org/10.1016/j.envpol.2018.01.009>.
- Xue T, Zhu T. Increment of ambient exposure to fine particles and the reduced human fertility rate in China, 2000–2010. *Sci Total Environ* [Internet]. Elsevier B.V.; 2018 [cited 2020 Nov 9];642:497–504. <https://doi.org/10.1016/j.scitotenv.2018.06.075>.
- Xue T, Zhu T. Association between fertility rate reduction and pre-gestational exposure to ambient fine particles in the United States, 2003–2011. *Environ Int* [Internet]. Elsevier Ltd; 2018 [cited 2020 Nov 8];121:955–62. <https://doi.org/10.1016/j.envint.2018.10.013>.
- Green R, Malig B, Windham GC, Fenster L, Ostro B, Swan S. Residential exposure to traffic and spontaneous abortion. *Environ Health Perspect* [Internet]. Environmental Health Perspectives; 2009 [cited 2020 Jul 8];117:1939–44. <https://doi.org/10.1289/ehp.0900943>.
- Dastoorpoor M, Khanjani N, Moradgholi A, Sarizadeh R, Cheraghi M, Estebsari F. Prenatal exposure to ambient air pollution and adverse pregnancy outcomes in Ahvaz, Iran: a generalized additive model. *Int Arch Occup Environ Health*. 2021;94:309–24.
- Wang B, Hong W, Sheng Q, Wu Z, Li L, Li X. Nitrogen dioxide exposure during pregnancy and risk of spontaneous abortion: a case-control study in China. *J Matern Neonatal Med* [Internet]. 2020;1–7. Available from: <https://www.tandfonline.com/doi/full/10.1080/14767058.2020.1837772>.
- Kioumourtoglou M-A, Raz R, Wilson A, Fluss R, Nirel R, Broday DM, et al. Traffic-related air pollution and pregnancy loss. *HHS Public Access* [Internet]. 2019 [cited 2020 Jul 8];30:4–10. Available from: <https://www.epa.gov/aqs>.
- Zhang L, Liu W, Hou K, Lin J, Zhou C, Tong X, et al. Air pollution-induced missed abortion risk for pregnancies. *Nat Sustain Nature Publishing Group*. 2019;2:1011–7.

24. Dastoorpoor M, Idani E, Goudarzi G, Khanjani N. Acute effects of air pollution on spontaneous abortion, premature delivery, and stillbirth in Ahvaz, Iran: a time-series study. *Environ Sci Pollut Res* [Internet]. Springer Verlag; 2018 [cited 2020 Aug 17];25:5447–58. <https://doi.org/10.1007/s11356-017-0692-9>.
25. Di Ciaula A, Bilancia M. Relationships between mild PM10 and ozone urban air levels and spontaneous abortion: clues for primary prevention. *Int J Environ Health Res*. 2015;25:640–55.
26. Enkhmaa D, Warburton N, Javzandulam B, Uyanga J, Khishigsuren Y, Lodoysamba S, et al. Seasonal ambient air pollution correlates strongly with spontaneous abortion in Mongolia. *BMC Pregnancy Childbirth* [Internet]. 2014 [cited 2020 Aug 4];14:146. Available from: <http://www.biomedcentral.com/1471-2393/14/146>.
27. Hou HY, Wang D, Ping Zou X, Hua Yang Z, Li T-C, Qiong CY. Does ambient air pollutants increase the risk of fetal loss? A case-control study *Arch Gynecol Obs*. 2014;289:285–91.
28. Moridi M, Ziaei S, Kazemnejad A. Exposure to ambient air pollutants and spontaneous abortion. *J Obstet Gynaecol Res Blackwell Publishing*. 2014;40:743–8.
29. Leiser CL, Hanson HA, Sawyer K, Steenblik J, Al-Dulaimi R, Madsen T, et al. Acute effects of air pollutants on spontaneous pregnancy loss: a case-crossover study. *Fertil Steril*. 2019;111:341–7.
30. Zhang Y, Wang J, Chen L, Yang H, Zhang B, Wang Q, et al. Ambient PM2.5 and clinically recognized early pregnancy loss: a case-control study with spatiotemporal exposure predictions. *Environ Int* [Internet]. Elsevier Ltd; 2019 [cited 2020 Nov 8];126:422–9. <https://doi.org/10.1016/j.envint.2019.02.062>.
31. Candela S, Bonvicini L, Ranzi A, Baldacchini F, Broccoli S, Cordioli M, et al. Exposure to emissions from municipal solid waste incinerators and miscarriages: a multisite study of the MONITER Project. *Environ Int* [Internet]. Elsevier Ltd; 2015 [cited 2020 Nov 8];78:51–60. <https://doi.org/10.1016/j.envint.2014.12.0080160-4120/>.
32. Gaskins AJ, Hart JE, Chavarro JE, Missmer SA, Rich-Edwards JW, Laden F, et al. Air pollution exposure and risk of spontaneous abortion in the Nurses' Health Study II. *Hum Reprod Oxford University Press*. 2019;34:1809–17.
33. Xue T, Zhu T, Geng G, Zhang Q. Association between pregnancy loss and ambient PM2.5 using survey data in Africa: a longitudinal case-control study, 1998–2016. *Lancet Planet Heal* [Internet]. Elsevier B.V.; 2019 [cited 2020 Aug 17];3:e219-ee225.
34. Ha S, Sundaram R, Buck Louis GM, Nobles C, Seeni I, Sherman S, et al. Ambient air pollution and the risk of pregnancy loss: a prospective cohort study. *Fertil Steril* [Internet]. Elsevier Inc.; 2018 [cited 2020 Jul 10];109:148–53. Available from: [/pmc/articles/PMC5758402/?report=abstract](https://pubmed.ncbi.nlm.nih.gov/30558402/)
35. Wesselink AK, Carwile JL, Fabian MP, Winter MR, Butler LJ, Mahalingaiah S, et al. Residential proximity to roadways and ischemic placental disease in a Cape Cod Family Health Study. *Int J Environ Res Public Health* [Internet]. 2017;14:682. Available from: www.mdpi.com/journal/ijerph.
36. Ranjbaran M, Mohammadi R, Yaseri M, Kamari M, Habibelahi A, Yazdani K. Effect of ambient air pollution and temperature on the risk of stillbirth: a distributed lag nonlinear time series analysis. *J Environ Heal Sci Eng*. 2020;18:1289–99.
37. Zang H, Cheng H, Song W, Yang M, Han P, Chen C, et al. Ambient air pollution and the risk of stillbirth: a population-based prospective birth cohort study in the coastal area of China. *Environ Sci Pollut Res Springer Verlag*. 2019;26:6717–24.
38. Ebisu K, Malig B, Hasheminassab S, Sioutas C, Basu R. Cause-specific stillbirth and exposure to chemical constituents and sources of fine particulate matter. *Environ Res*. 2018;160:358–64.
39. Yang S, Tan Y, Mei H, Wang F, Li N, Zhao J, et al. Ambient air pollution the risk of stillbirth: a prospective birth cohort study in Wuhan, China. *Int J Hyg Environ Health* [Internet]. Elsevier GmbH; 2018 [cited 2020 Jul 8];221:502–9. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/29422441>.
40. DeFranco E, Hall E, Hossain M, Chen A, Haynes EN, Jones D, et al. Air pollution and stillbirth risk: exposure to airborne particulate matter during pregnancy is associated with fetal death. *PLoS One*. Public Library of Science; 2015;10.
41. Green R, Sarovar V, Malig B, Basu R. Association of stillbirth with ambient air pollution in a California cohort study. *Am J Epidemiol* [Internet]. 2015 [cited 2020 Jul 8];181:874–82. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25861815>.
42. Faiz AS, Rhoads GG, Demissie K, Lin Y, Kruse L, Rich DQ. Does ambient air pollution trigger stillbirth? *Epidemiology*. 2013;24:538–44.
43. Faiz AS, Rhoads GG, Demissie K, Kruse L, Lin Y, Rich DQ. Ambient air pollution and the risk of stillbirth. *Am J Epidemiol* [Internet]. 2012 [cited 2020 Jul 8];176:308–16. Available from: <http://aje.oxfordjournals.org/>.
44. Kim O-J, Ha E-H, Kim B-M, Seo J-H, Park H-S, Jung W-J, et al. PM10 and pregnancy outcomes: a hospital-based cohort study of pregnant women in Seoul. *J Occup Environ Med*. 2007;49:1394–402.
45. Bobak M, Leon DA. Pregnancy outcomes and outdoor air pollution: an ecological study in districts of the Czech Republic 1986–8. *Occup Env Med*. 1999;56:539–43.
46. Pereira LA, Loomis D, Concei GM, Braga Sio L, Arcas RM, Kishi HS, et al. Association between air pollution and intrauterine mortality in Sao Paulo, Brazil *Environ Health Perspect*. 1998;106:325–9.
47. Sakai R. Fetal abnormality in a Japanese industrial zone. *Int J Environ Stud*. 1984;23:113–20.
48. Sarovar V, Malig BJ, Basu R. A case-crossover study of short-term air pollution exposure and the risk of stillbirth in California, 1999–2009. *Environ Res*. 2020;191:110103.
49. Rammah A, Whitworth KW, Han I, Chan W, Symanski E. Time-varying exposure to ozone and risk of stillbirth in a nonattainment urban region. *Am J Epidemiol* [Internet]. 2019 [cited 2020 Nov 8];188:1288–95. Available from: <https://academic.oup.com/aje/article/188/7/1288/5492683>.
50. Hwang BF, Lee YL, Jaakkola JJK. Air pollution and stillbirth: a population-based case-control study in Taiwan. *Environ Health Perspect*. 2011;119:1345–9.
51. Smith RB, Beevers SD, Gulliver J, Dajnak D, Fecht D, Blangiardo M, et al. Impacts of air pollution and noise on risk of preterm birth and stillbirth in London. *Environ Int*. 2020;134:105290.
52. Ghosh RE, Freni-Sterrantino A, Douglas P, Parkes B, Fecht D, de Hoogh K, et al. Fetal growth, stillbirth, infant mortality and other birth outcomes near UK municipal waste incinerators; retrospective population based cohort and case-control study. *Environ Int Elsevier Ltd*. 2019;122:151–8.
53. Landgren O. Environmental pollution and delivery outcome in southern Sweden: a study with central registries. *Acta Paediatr*. 1996;85:1361–4.
54. Mendola P, Ha S, Pollack A, Zhu Y, Seeni I, Kim S, et al. Chronic and acute ozone exposure in the week prior to delivery is associated with the risk of stillbirth. *Int J Environ Res Public Health* [Internet]. MDPI AG; 2017 [cited 2020 Jul 10];14:731. Available from: <http://www.mdpi.com/1660-4601/14/7/731>.
55. Zou B, Wilson JG, Zhan FB, Zeng Y. Air pollution exposure assessment methods utilized in epidemiological studies. *J Environ Monit*. 2009;11:475–90.
56. Brokamp C, Brandt EB, Ryan PH. Assessing exposure to outdoor air pollution for epidemiological studies: model-based and personal sampling strategies. *J Allergy Clin Immunol Mosby Inc*. 2019; 143:2002–2006.

57. US Environmental Protection Agency. Air quality system data mart [Internet]. 2021 [cited 2021 Jan 20]. Available from: <https://www.epa.gov/airdata>.
58. Hoek G. Methods for assessing long-term exposures to outdoor air pollutants. *Curr Environ Heal Reports* Springer. 2017;4:450–62.
59. Ma R, Ban J, Wang Q, Li T. Statistical spatial-temporal modeling of ambient ozone exposure for environmental epidemiology studies: a review. *Sci Total Environ*. 2020;701:134463.
60. Briggs DJ, Collins S, Elliott P, Fischer P, Kingham S, Lebre E, et al. Mapping urban air pollution using GIS: a regression-based approach. *Int J Geogr Inf Sci* [Internet]. 1997 [cited 2020 Dec 1];11:699–718. Available from: <https://www.tandfonline.com/action/journalInformation?journalCode=tgis20>.
61. Hennig F, Sugiri D, Tzivian L, Fuks K, Moebus S, Jöckel K-H, et al. Comparison of land-use Regression Modeling with dispersion and chemistry transport modeling to assign air pollution concentrations within the Ruhr area. *Atmosphere (Basel)* [Internet]. 2016;7:48. Available from: www.mdpi.com/journal/atmosphere.
62. Xie X, Semanjski I, Gautama S, Tsiligianni E, Deligiannis N, Rajan RT, et al. A review of urban air pollution monitoring and exposure assessment methods. *ISPRS Int J Geo-Information*. MDPI AG; 2017;6.
63. Apte JS, Messier KP, Gani S, Brauer M, Kirchstetter TW, Lunden MM, et al. High-resolution air pollution mapping with Google Street View cars: exploiting big data. *Environ Sci Technol* [Internet]. 2017 [cited 2021 Mar 11];51:6999–7008. Available from: <https://pubs.acs.org/sharingguidelines>.
64. Messier KP, Chambliss SE, Gani S, Alvarez R, Brauer M, Choi JJ, et al. Mapping air pollution with Google Street View cars: efficient approaches with mobile monitoring and land use regression. *Environ Sci Technol* [Internet]. American Chemical Society; 2018 [cited 2021 Mar 11];52:12563–72. Available from: <https://pubs.acs.org/sharingguidelines>.
65. Qi M, Hankey S. Using street view imagery to predict street-level particulate air pollution. *Environ Sci Technol* [Internet]. 2021;55:2695–704. <https://doi.org/10.1021/acs.est.0c05572>.
66. Oliveri Conti G, Heibati B, Kloog I, Fiore M, Ferrante M. A review of AirQ Models and their applications for forecasting the air pollution health outcomes. *Environ Sci Pollut Res Springer Verlag*. 2017;24:6426–45.
67. Tessum CW, Hill JD, Marshall JD. InMAP: a model for air pollution interventions. *PLoS One. Public Library of Science*; 2017;12.
68. Young MT, Bechle MJ, Sampson PD, Szpiro AA, Marshall JD, Sheppard L, et al. Satellite-based NO₂ and model validation in a national prediction model based on universal kriging and land-use regression. *Environ Sci Technol Am Chem Soc*. 2016;50:3686–94.
69. Di Q, Kloog I, Koutrakis P, Lyapustin A, Wang Y, Schwartz J. Assessing PM_{2.5} exposures with high spatiotemporal resolution across the continental United States. *Environ Sci Technol*. 2016;50:4712–21.
70. Kravchenko A, Bullock DG. A comparative study of interpolation methods for mapping soil properties. *Agron J*. 1999;91:393–400.
71. Gelfand AE, Diggle P, Guttorp P, Fuentes M. *Handbook of spatial statistics*. New York: CRC Press; 2010.
72. Oliver MA, Muir KR, Webster R, Parkes SE, Cameron AH, Stevens MCG, et al. A geostatistical approach to the analysis of pattern in rare disease. *J Public Health Med* [Internet]. 1992 [cited 2021 Mar 8];14:280–9. Available from: <https://academic.oup.com/jpubhealth/article/14/3/280/1571501>.
73. Cressie NAC. *Statistics for spatial data (Revised Edition)*. John Wiley & Sons, Inc.; 1993.
74. Sun Y, Sheridan P, Laurent O, Li J, Sacks DA, Fischer H, et al. Associations between green space and preterm birth: windows of susceptibility and interaction with air pollution. *Environ Int*. 2020;142:105804.
75. Lee PC, Roberts JM, Catov JM, Talbott EO, Ritz B. First trimester exposure to ambient air pollution, pregnancy complications and adverse birth outcomes in Allegheny County. *PA Matern Child Health J*. 2013;17:545–55.
76. Laurent O, Benmarhnia T, Milesi C, Hu J, Kleeman MJ, Cockburn M, et al. Relationships between greenness and low birth weight: investigating the interaction and mediation effects of air pollution. *Environ Res*. 2019;175:124–32.
77. Laurent O, Hu J, Li L, Kleeman MJ, Bartell SM, Cockburn M, et al. Low birth weight and air pollution in California: which sources and components drive the risk? *Environ Int* [Internet]. Elsevier Ltd; 2016 [cited 2020 Aug 3];92–93:471–7. <https://doi.org/10.1016/j.envint.2016.04.034>.
78. Sorek-Hamer M, Just AC, Kloog I. The use of satellite remote sensing in epidemiological studies. *Curr Opin Pediatr*. 2016;28:228–34.
79. NASA. Getting to the Heart of the (Particulate) Matter: NASA's MAIA to study how particulate matter air pollution affects our health [Internet]. 2020. Available from: <https://climate.nasa.gov/news/3027/getting-to-the-heart-of-the-particulate-matter/>.
80. Veefkind JP, Aben I, McMullan K, Förster H, de Vries J, Otter G, et al. TROPOMI on the ESA Sentinel-5 Precursor: A GMES mission for global observations of the atmospheric composition for climate, air quality and ozone layer applications. *Remote Sens Environ*. 2012;120:70–83.
81. Duncan BN, Prados AI, Lamsal LN, Liu Y, Streets DG, Gupta P, et al. Satellite data of atmospheric pollution for U. S. air quality applications: examples of applications, summary of data end-user resources, answers to FAQs, and common mistakes to avoid. *Atmos Environ*. 2014;94:647–62.
82. Brauer M. How much, how long, what, and where: air pollution exposure assessment for epidemiologic studies of respiratory disease. *Proc Am Thorac Soc*. 2010;7:111–5.
83. Hammel SC, Hoffman K, Webster TF, Anderson KA, Stapleton HM. Measuring personal exposure to organophosphate flame retardants using silicone wristbands and hand sipes. *Environ Sci Technol Am Chem Soc*. 2016;50:4483–91.
84. Kile ML, Scott RP, O'Connell SG, Lipscomb S, MacDonald M, McClelland M, et al. Using silicone wristbands to evaluate preschool children's exposure to flame retardants. *Environ Res*. 2016;147:365–72.
85. Larkin A, Hystad P. Towards personal exposures: how technology is changing air pollution and health research. *Curr Environ Heal Reports* Springer. 2017;4:463–71.
86. Carvalho MA, Bernardes LS, Hettfleisch K, Pastro LDM, Vieira SE, Saldiva SRDM, et al. Associations of maternal personal exposure to air pollution on fetal weight and fetoplacental Doppler: a prospective cohort study. *Reprod Toxicol*. 2016;62:9–17.
87. Dixon HM, Scott RP, Holmes D, Calero L, Kincl LD, Waters KM, et al. Silicone wristbands compared with traditional polycyclic aromatic hydrocarbon exposure assessment methods. *Anal Bioanal Chem Springer Verlag*. 2018;410:3059–71.
88. Grubestic TH. Zip codes and spatial analysis: problems and prospects. *Socioecon Plann Sci*. 2008;42:129–49.
89. Jones RR, DellaValle CT, Flory AR, Nordan A, Hoppin JA, Hofmann JN, et al. Accuracy of residential geocoding in the Agricultural Health Study. *Int J Health Geogr* [Internet]. 2014;13:37. Available from: <http://www.ij-healthgeographics.com/content/13/1/37>.
90. US Environmental Protection Agency. CMAQ Model Version 5.2 Output Data -- 2014 CONUS 12km [Internet]. 2019. <https://doi.org/10.15139/S3/XYW3HL>.
91. Ensor KB, Raun LH, Persse D. A case-crossover analysis of out-of-hospital cardiac arrest and air pollution. *Circulation*. 2013;127:1192–9.

92. Dadvand P, de Nazelle A, Triguero-Mas M, Schembari A, Cirach M, Amoly E, et al. Surrounding greenness and exposure to air pollution during pregnancy: an analysis of personal monitoring data. *Environ Health Perspect.* 2012;120:1286–90.
93. Schembari A, Triguero-Mas M, de Nazelle A, Dadvand P, Vrijheid M, Cirach M, et al. Personal, indoor and outdoor air pollution levels among pregnant women. *Atmos Environ.* 2013;64:287–95.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.