Ambient air pollution and maternal cardiovascular health in pregnancy

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ABSTRACT

In this review, we summarise the current epidemiological and experimental evidence on the association of ambient (outdoor) air pollution exposure and maternal cardiovascular health during pregnancy. This topic is of utmost clinical and public health importance as pregnant women represent a potentially susceptible group due to the delicate balance of the feto-placental circulation, rapid fetal development and tremendous physiological adaptations to the maternal cardiorespiratory system during pregnancy.

Several meta-analyses including up to 4 245 170 participants provide robust evidence that air pollutants, including particulate matter, nitrogen oxides and others, have adverse effects on the development of hypertensive disorders of pregnancy, gestational diabetes mellitus and cardiovascular events during labour. Potential underlying biological mechanisms include oxidative stress with subsequent endothelial dysfunction and vascular inflammation, β-cell dysfunction and epigenetic changes. Endothelial dysfunction can lead to hypertension by impairing vasodilatation and promoting vasoconstriction. Air pollution and the consequent oxidative stress can additionally accelerate β-cell dysfunction, which in turn triggers insulin resistance leading to gestational diabetes mellitus. Epigenetic changes in placental and mitochondrial DNA following air pollution exposures can lead to altered gene expression and contribute to placental dysfunction and induction of hypertensive disorders of pregnancy.

The maternal and fetal consequences of such cardiovascular and cardiometabolic disease during pregnancy can be serious and long lasting, including preterm birth, increased risk of type 2 diabetes mellitus or cardiovascular disease later in life. Acceleration of efforts to reduce air pollution is therefore urgently needed to realise the full health benefits for pregnant mothers and their children.

INTRODUCTION

Globally, around one-third of deaths in women are attributable to cardiovascular disease.1 To reduce this burden of disease, early detection and prevention of risk factors is of utmost importance. While there is a strong evidence for the contribution of classical risk factors, such as obesity, hyperlipidaemia, diabetes mellitus, high blood pressure, smoking and sedentary lifestyle, sex-specific and environmental risk factors are still underestimated.2

In women, obstetric and gynaecological history, including hypertensive disorders of pregnancy, gestational diabetes mellitus and preterm birth, determines cardiovascular health trajectories that have future implications for mother and child.2 Life-long consequences of conditions for the mother include increased risk of hypertension, diabetes mellitus, ischaemic heart disease, thromboembolism, kidney disease and hypothyroidism.2 Immediate and long-lasting negative consequences of obstetric complications for the offspring can include perinatal hypoglycaemia, small or large for gestational age, intrauterine growth restriction, preterm birth and diabetes mellitus, as well as cardiovascular disease later in life. Thus, gestation not only represents a period of high susceptibility to risk factors, but also an opportunity to prevent maternal and fetal disease in the short, intermediate and long term.

The detrimental effects of air pollution have been intensively investigated over the past decades. Evidence is emerging that even low-to-moderate levels of air pollution are harmful, especially in more vulnerable populations such as the young and elderly and patients with pre-existing comorbidities.1 4 Pregnant women represent an under-recognised susceptible population to the effects of air pollution, due to the delicate balance of feto-placental circulation, rapid fetal development and physiological changes in pregnancy such as increased minute ventilation and altered inflammatory profile.5 6

In this review, we present an overview of the latest evidence linking ambient (outdoor) air pollution exposure with maternal cardiovascular and cardiometabolic health during pregnancy. The effects of air pollution on cardiovascular health in the non-pregnant population, birth outcomes and offspring’s short-term, intermediate-term and long-term health are beyond the remit of this review but have been reviewed elsewhere.3 7–10 This review focuses particularly on the effect of air pollution on the mother’s cardiovascular health, as an important but underappreciated consequence of maternal exposure to air pollution.
oxidative stress, systemic inflammation, endothelial dysfunction, increased blood pressure, changes in the autonomic nervous
system, neuroendocrine changes, arrhythmogenesis and athero-
thrombosis.14

Air pollution is a complex mixture of many gases and partic-
ulate matter (PM), the composition of which varies greatly with
the source of pollutants and the atmospheric chemical rea-
tions that are influenced by geographical and meteorological
conditions. Notable gases include nitrogen oxides (NOx), ozone
(O3), sulfur dioxide (SO2), ammonia (NH3) and volatile organic
compounds (VOCs). Airborne particles can be composed of many
different substances and are found in a range of different
sizes, both features that are important to the toxicity of the par-
ticles. The particles are monitored and regulated in our environ-
ment by their mass concentration, conventionally as the metrics
PM10 (particulate matter with a diameter of ≤10 µm) and PM2.5
(particulate matter with a diameter of ≤2.5 µm). A third size
category of particles is ultrafine particles (particulate matter with
a diameter of ≤0.1 µm; ‘nanoparticles’) which cannot currently
be measured with existing monitoring networks, but have the
potential to be particularly harmful due to their large reactive
surface area, high capacity to carry relatively large amounts of
harmful chemicals and ability to penetrate deep into the airways
and translocate into the systemic circulation.7,14 Combustion and
traffic are major sources of nanoparticles in urban environments.
While toxicological studies demonstrate the importance of size
and composition in determining adverse effects on biological
systems, PM2.5, by necessity, is the most employed metric for
epidemiological studies, and the pollutant that shows the most
consistent associations with cardiovascular disease and effects on
other extrapulmonary organs.

AIR POLLUTION AND PREGNANCY OUTCOMES

Pregnancy has been referred to as a physiological stress test as
the body is challenged with major adaptive changes in cardiovas-
cular, respiratory, renal and endocrine function.3 The maternal
cardiorespiratory system must adapt to the increased oxygen
consumption and metabolic demands of pregnancy. Necessary
alterations include increases in heart rate, intravascular volume,
arterial and venous compliance, and decrease in vascular
resistance index. Endocrine changes include alterations in fat
metabolism and increased insulin secretion.5 Respiratory rate
and tidal volume are increased, resulting in higher minute venti-
lation. These changes potentially lead to greater exposures air
pollutants. These major maternal adaptations, together with the
delicate balance of the feto-placental circulation and the rapidly
developing fetus, may also make both mother and child more
vulnerable to the deleterious effects of air pollution. Maternal
air pollution exposure has been associated with various adverse
birth outcomes, including stillbirth, intrauterine growth restric-
tion, preterm birth, premature rupture of membranes and low
birth weight.6,9,12 A growing body of evidence also links in utero
exposure to air pollution with an increased risk of various
health conditions in the offspring later in life.6,9,12 Preclinical
evidence shows that increased air pollution exposure decreases
placental vascularity and perfusion, resulting in reduced nutrient
exchange between the maternal and fetal blood.13 Translocation of ultrafine particles into the blood is also a mech-
anism by which air pollution could directly alter the function of
the feto-placental unit. Concerningly, recent findings show the
accumulation of black carbon deposits on the fetal side of the
placenta suggesting particle transfer across the placenta to reach
the fetus.14

AIR POLLUTION AND CARDIOMETABOLIC DISEASE DURING PREGNANCY

Hypertensive disorders of pregnancy

Hypertensive disorders of pregnancy, particularly pre-eclampsia,
are important causes of maternal and fetal morbidity and
mortality worldwide and complicate between 5% and 8% of
all pregnancies.15 Hypertension poses a critical threat in the
longer term through further development of maternal and fetal
hypertension, and increasing the risk of coronary heart disease,
cardiac arrhythmia, heart failure or stroke.16 Hypertensive disor-
ders of pregnancy are classified in categories according to the
gestational age at diagnosis (figure 1).17

Epidemiological associations have been found between hyper-
tensive disorders of pregnancy and preconceptional and gesta-
tional air pollution exposure. This evidence has been summarised
in various meta-analyses18–21 encompassing between 5 and 12
studies of 3500 to 655000 women (table 1). Overall, there were
moderate levels of evidence that various gaseous pollutants and
particulate pollutants were associated with hypertensive disor-
ders of pregnancy. The most robust evidence was for PM2.5 expo-
sure over the whole gestational period with an OR of 1.07 to
1.51 for developing a hypertensive disorder of pregnancy per 10
µg/m3 increase in PM2.5 (mean PM2.5 exposures of 2.1 to 16.1 µg/ m3). Similarly, trends were found for full gestation exposure to
NO2 and pre-eclampsia and combined hypertensive disorders of
pregnancy (OR of 1.03 (95% CI 0.97 to 1.09) per 10 µg/m3 in
NO2 (mean NO2 exposures of 11.5 to 39.9 µg/m3)). These levels
of air pollutants fall within the typical range of most European
countries, with the lower end of the range below many guideline
levels.

Gestational diabetes mellitus

Gestational diabetes mellitus is linked to various perinatal
complications for mother and child, including pre-eclampsia,
neonatal macrosomia and shoulder dystocia with potential nerve
injury, neonatal hypoglycaemia and pre-term birth. The long-
term health impacts include increased lifetime risk for type 2
diabetes mellitus for both mother and child.22

Long-term exposure to air pollution has already been linked
to metabolic syndrome and diabetes in the adult population.23
Several groups have studied the impact of preconceptional
and gestational exposure to air pollution on the development of
gestational diabetes mellitus24–32 (table 2 and online supple-
mental table E1). The most recent and extensive meta-analysis
on this topic summarised the findings of 18 studies with a total
of 4245 170 participants and 167 426 (3.9%) cases of gesta-
tional diabetes mellitus.33 Most studies focused on PM2.5 and
NO2 and showed associations with gestational diabetes mellitus
for exposure across pregnancy. Interestingly, the meta-analysis
found a closer relationship between outdoor air pollution expo-
sure and gestational diabetes mellitus in Asian women than
those in America. This is likely to be in part explained by higher
ambient air pollution levels in Asian countries, as well as lifestyle
factors and exposure to different sources of pollution. While
beyond the scope of this review, there is a growing interest in the
health effects of indoor air pollution, especially in low-to-middle
income countries where cooking and heating with kerosene and
solid biomass are still a common practice. These fuels are a major
source of fine and ultrafine particles, with levels of PM2.5 around
100 times higher than recommended levels, with young children
and mothers being more vulnerable due the higher period of
time spent in proximity to these sources.34


Cardiovascular events during pregnancy

Cardiovascular disease is the single leading cause of non-obstetric maternal death in the UK and increasing year on year. Although labour and delivery reflect the period of highest risk for cardiovascular events, the elevated risk is present throughout pregnancy. As well as promoting the progression of underlying atherothrombotic diseases, air pollution is associated with cardiovascular events, the prevalence of which was greater in those with higher exposure to air pollution. Only one study has investigated the association of exposure to air pollution during pregnancy and cardiovascular events (defined as ischaemic heart disease, stroke, heart failure or cardiac arrest) during labour. In an observational cohort of 228,562 deliveries, air pollution exposure at the hospital address was modelled for 7 days prior to delivery based on hourly pollutant levels. In total, 0.3% (687) of all pregnancies suffered a cardiovascular event at labour. An overview of ambient air pollutants is shown in figure 1.

Figure 1  Hypertensive disorders of pregnancy classification according to the International Society for the Study of Hypertension in Pregnancy. Pre-eclampsia is defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg and ≥1 other new-onset condition >20 gestational weeks. Conditions include proteinuria (≥300 mg per 24 hours), acute kidney injury (creatinine ≥90 μmol/L), liver dysfunction (elevated transaminases) with/without right upper quadrant or epigastric abdominal pain, neurological complications (eclampsia, altered mental status, blindness, stroke, clonus, severe headache and persistent visual scotomata), haematological complications (thrombocytopenia-platelet count <150 000/μL, disseminated intravascular coagulation, haemolysis), uteroplacental dysfunction (fetal growth restriction, abnormal umbilical artery Doppler wave form analysis, stillbirth). BP, blood pressure. Figure created with BioRender.

Oxidative stress, inflammation and endothelial dysfunction

Several air pollutants have pro-oxidant and inflammatory properties. Inhalation of PM$_{2.5}$, NO$_x$ and O$_3$ can trigger oxidative stress and inflammation in the lung and systemically, leading to endothelial dysfunction and site-specific inflammation. Passage of particles, or their constituents, into the circulation is also a route by which air pollution could produce localised oxidative damage and inflammation. Early gestation requires a strictly regulated balance between proinflammatory and anti-inflammatory mediators in order to enable implantation, trophoblast invasion and placentaion, whereas the second trimester is a predominantly anti-inflammatory state. The proinflammatory and pro-oxidative properties of air pollution, therefore, could disturb this delicate balance during pregnancy.

The imbalance in the oxidative stress response entails several reactions leading to hypertensive disorders and gestational diabetes mellitus. The underlying consequences include endothelial dysfunction and vascular inflammation. Endothelial dysfunction may lead to hypertension by impairing vasodilatation and promoting vasoconstriction. Endothelin-1 and proinflammatory markers, such as interleukins (ILs), may play a role in the action of PM$_{2.5}$ and development of hypertensive disorders of pregnancy. Alterations in circulating T-reg and Th17 cells are involved in the inflammatory response triggered by PM$_{2.5}$ exposure. T-reg cells produce anti-inflammatory cytokines (eg, IL-10 and transforming growth factor β) and suppress immune cells, whereas Th17 cells promote inflammation by producing inflammatory cytokines (eg, IL-17, IL-22, IL-23) and stimulating the recruitment of neutrophils. An imbalance in the T-reg/Th17 cell ratio towards the proinflammatory Th17 cells played a major role in a rat model of pre-eclampsia exposed to PM$_{2.5}$.

Neuroendocrine and β-cell dysfunction

Although insulin resistance increases during normal pregnancy, most women remain normoglycaemic due to sufficient β-cell compensation and hepatic glucose production.
In certain cases, dysfunction of β-cells may appear during pregnancy and causes decreased glucose concentration sensing or insulin generation, contributing to the development of hyperglycaemia. Air pollution exposure in pregnant women can further accelerate β-cell dysfunction. Oxidative stress response and release of inflammatory cytokines triggered by air pollutants can lead to impairment of insulin signalling or inhibition of insulin release from β-cells. This in turn triggers insulin resistance by decreasing insulin receptor tyrosine kinase activity, causing the development of gestational diabetes mellitus.

**Epigenetic changes**

Global placental and mitochondrial DNA methylation is a potential underlying mechanism for the induction of pre-eclampsia by air pollution. During early gestation, DNA methylation plays a critical role in cell differentiation. If methylation occurs in a susceptible time window, it can lead to altered gene expression and contribute to placental dysfunction. Exposure to air pollutants is associated with hypomethylation of genes involved in inflammation, thrombosis, insulin resistance and lipid metabolism.

There are several mechanisms by which air pollution exposure leads to DNA methylation. First, air pollution induces oxidative stress and reactive oxygen species and reactive nitrogen species (ROS and RNS) which react with DNA and lead to strand breaks, base modification, and inter-strand and intra-strand crosslinks. This results in global hypomethylation due to DNA methyltransferases not recognising the damaged DNA. Second, air pollutants can interact with S-adenosyl methionine, reducing methylation by DNA methyltransferases due to a depletion of available methyl groups. Lastly, gene-specific DNA methylation may occur when CpG sites (cytosine nucleotide separated from a guanosine nucleotide by one phosphate group) are blocked or made accessible by the absence of transcription factors.

**Table 1** Studies investigating ambient air pollution exposure and hypertensive disorders of pregnancy

<table>
<thead>
<tr>
<th>Study</th>
<th>Region; observation years; study design</th>
<th>Sample size (cases, %)</th>
<th>Exposure modelling</th>
<th>Outcome</th>
<th>Exposure pollutant</th>
<th>Exposure windows</th>
<th>Findings, OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wu et al 2009</td>
<td>California (USA); 1997–2006; cohort</td>
<td>81186 (2442, 3.0%)</td>
<td>Dispersion model</td>
<td>Pre-eclampsia</td>
<td>PM$_{2.5}$, NO$_x$</td>
<td>Entire pregnancy</td>
<td>2.17 (1.54 to 2.82)</td>
</tr>
<tr>
<td>Rudra et al 2011</td>
<td>Washington (USA); 1996–2006; cohort</td>
<td>3509 (117, 3.3%)</td>
<td>Dispersion model</td>
<td>Pre-eclampsia</td>
<td>PM$_{2.5}$, CO</td>
<td>Entire pregnancy</td>
<td>2.19 (0.36 to 9.65)</td>
</tr>
<tr>
<td>Vinikoor-Imler LC et al 2012</td>
<td>North Carolina (USA); 2000–2003; cohort</td>
<td>222 775 (12 085, 5.4%)</td>
<td>Personal monitor</td>
<td>Gestational hypertension</td>
<td>PM$<em>{2.5}$, PM$</em>{10}$</td>
<td>Entire pregnancy</td>
<td>1.59 (1.41 to 1.87)</td>
</tr>
<tr>
<td>Dadvand et al 2013</td>
<td>Barcelona (Spain); 2000–2005; cohort</td>
<td>8398 (103, 1.2%)</td>
<td>LUR</td>
<td>Pre-eclampsia</td>
<td>PM$<em>{2.5}$, PM$</em>{10}$, NO$_x$, NO$_y$</td>
<td>1st trimester 2nd trimester 3rd trimester</td>
<td>1.72 (1.04 to 2.86)</td>
</tr>
<tr>
<td>Lee et al 2013</td>
<td>Pittsburgh (USA); 1997–2002; cohort</td>
<td>34 705 (1141, 3.3%)</td>
<td>Personal monitor</td>
<td>Pre-eclampsia, gestational hypertension</td>
<td>PM$<em>{2.5}$, PM$</em>{10}$, O$_3$</td>
<td>1st trimester</td>
<td>1.42 (0.90 to 2.25) 1.33 (1.06 to 1.65)</td>
</tr>
<tr>
<td>Mobasher et al 2013</td>
<td>California (USA); 1999–2008; case-control</td>
<td>305 (136, 45%)</td>
<td>Personal monitor</td>
<td>Pre-eclampsia</td>
<td>PM$<em>{2.5}$, PM$</em>{10}$, NO$_x$, NO$_y$, O$_3$, CO</td>
<td>1st trimester 2nd trimester 3rd trimester</td>
<td>2.79 (1.58 to 4.90)</td>
</tr>
<tr>
<td>Xu et al 2013</td>
<td>Florida (USA); 2004–2005; cohort</td>
<td>24 483 (1037, 4.2%)</td>
<td>Personal monitor</td>
<td>HDP</td>
<td>PM$_{2.5}$, NO$_x$, NO$_y$, O$_3$, CO, SO$_x$</td>
<td>Entire pregnancy</td>
<td>4.20 (1.67 to 10.85)</td>
</tr>
<tr>
<td>Dadvand et al 2014</td>
<td>Barcelona (Spain); 2003–2005; cohort</td>
<td>3182 (47, 1.5%)</td>
<td>Personal monitor</td>
<td>Pre-eclampsia</td>
<td>PM$<em>{2.5}$, PM$</em>{10}$</td>
<td>Entire pregnancy</td>
<td>1.12 (0.19 to 6.25)</td>
</tr>
<tr>
<td>Savitz et al 2015</td>
<td>New York (USA); 2008–2010; cohort</td>
<td>348 585 (HDP: 17 000, 4.9%)</td>
<td>LUR</td>
<td>Pre-eclampsia, gestational hypertension and HDP</td>
<td>PM$_{2.5}$, NO$_2$</td>
<td>1st trimester 2nd trimester</td>
<td>0.92 (0.86 to 0.98) 1.10 (1.00 to 1.20)</td>
</tr>
<tr>
<td>Choe et al 2018</td>
<td>Rhode Island (USA); 2002–2012; cohort</td>
<td>61 640 (pre-eclampsia: 2221, 3.6%; gestational hypertension: 2877, 4.7%)</td>
<td>Spatiotemporal model</td>
<td>Pre-eclampsia, gestational hypertension and HDP</td>
<td>PM$_{2.5}$</td>
<td>Entire pregnancy</td>
<td>0.97 (0.92 to 1.02) 0.98 (0.94 to 1.01)</td>
</tr>
<tr>
<td>Mandakh et al 2020</td>
<td>Scania (Sweden); 2000–2009; cohort</td>
<td>35 570 (1034, 2.9%)</td>
<td>Spatiotemporal model</td>
<td>Pre-eclampsia</td>
<td>PM$<em>{2.5}$, PM$</em>{10}$, NO$_x$, BC</td>
<td>Entire pregnancy</td>
<td>3.92 (1.61 to 1.50)</td>
</tr>
<tr>
<td>Assibey-Mensah et al 2020</td>
<td>New York (USA); 2008–2013; cohort</td>
<td>16 116 (732, 4.5%)</td>
<td>LUR model</td>
<td>Pre-eclampsia</td>
<td>PM$_{2.5}$, BC</td>
<td>Entire pregnancy</td>
<td>1.33 (1.17 to 1.50)</td>
</tr>
</tbody>
</table>

Data for table adapted from Sun et al,[47] Bai et al[48] and Yu et al.[49]

BC, black carbon; CO, carbon monoxide; HDP, hypertensive disorders of pregnancy; LUR, land use regression model; NO, nitric oxide; NO$_x$, nitrogen dioxide; NO$_y$, nitrogen oxides; O$_3$, ozone; PM$_{2.5}$, particulate matter with an aerodynamic diameter ≤10 μm; PM$_{10}$, particulate matter with an aerodynamic diameter ≤2.5 μm; SO$_x$, sulfur dioxide.
The inflammatory state may then accelerate insulin resistance in the gut, where altered gut microbiota can lead to increased gut permeability, which consequently enables the transport of inflammatory cytokines from the gut into the circulation. This inflammatory state may then accelerate insulin resistance development and thus lead to the development of gestational diabetes mellitus.  

### Other pathways

Other plausible mechanisms by which air pollution may lead to gestational diabetes mellitus, but not including cardiovascular mechanisms per se, include increased gluconeogenesis and lipid deposition, altered gut microbiome and increased gut permeability (figure 2) and have been summarised elsewhere. Altered gut microbiota can lead to increased gut permeability, which consequently enables the transport of inflammatory cytokines from the gut into the circulation. The inflammatory state may then accelerate insulin resistance development and thus lead to the development of gestational diabetes mellitus.

### KNOWLEDGE GAPS AND FUTURE DIRECTIONS

Most epidemiological studies use data from stationary monitoring networks to attribute exposure to subjects, usually at their home residence using data from the nearest monitoring station or by mathematical modelling of pollutants from the monitor. This inevitably will lead to a degree of exposure misclassification and is unlikely to capture exposures in indoor microenvironments or during time away from the individual’s residence. There is a growing use of personal air pollution monitoring using portable devices that can be used to capture personal exposure to specific pollutants more accurately. At present, the personal monitoring technology is still in development, as are the means to analyse the wealth of data generated in an informative manner. Nonetheless, such approaches could be especially valuable in this setting, especially for monitoring exposure during the later stages of pregnancy when more time is spent indoors.

### Table 2: Studies investigating ambient air pollution exposure and gestational diabetes mellitus

<table>
<thead>
<tr>
<th>Study</th>
<th>Region; observation years; study design</th>
<th>Sample size (cases, %)</th>
<th>Exposure modelling</th>
<th>Outcome</th>
<th>Exposure pollutant</th>
<th>Exposure window</th>
<th>Findings, OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fleisch et al 2014&lt;sup&gt;44&lt;/sup&gt;</td>
<td>Massachusetts (USA); 1999–2002; prospective cohort study</td>
<td>2093 (118, 6%)</td>
<td>Hybrid satellite-based spatiotemporal model</td>
<td>GDM diagnosis following the American Diabetes Association 2008 recommendations IGT; failing OGCT (1-hour glucose result of ≥140 mg/dl) with one high OGTT value</td>
<td>PM&lt;sub&gt;2.5&lt;/sub&gt;</td>
<td>2nd trimester</td>
<td>0.86 (0.36 to 2.04)</td>
</tr>
<tr>
<td>Hu et al 2015&lt;sup&gt;45&lt;/sup&gt;</td>
<td>Florida (USA); 2004–2005; retrospective cohort study</td>
<td>410,267 (14,032, 3.4%)</td>
<td>Hierarchical Bayesian space–time statistical model</td>
<td>GDM diagnosis from vital statistics records</td>
<td>PM&lt;sub&gt;2.5&lt;/sub&gt;</td>
<td>1st trimester</td>
<td>1.16 (1.11 to 1.21)</td>
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<td></td>
<td>PM&lt;sub&gt;2.5&lt;/sub&gt;</td>
<td>2nd trimester</td>
<td>1.15 (1.10 to 1.20)</td>
</tr>
<tr>
<td>Robledo et al 2015&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Consortium of Safe Labor (USA); 2002–2008; retrospective cohort study</td>
<td>219,952 (11,334, 5.2%)</td>
<td>Modified Community Multiscale Air Quality Model (CMAQ)</td>
<td>GDM (ICD-9) diagnosis from discharge or medical records</td>
<td>PM&lt;sub&gt;2.5&lt;/sub&gt;</td>
<td>Full gestation</td>
<td>1.20 (1.13 to 1.26)</td>
</tr>
<tr>
<td>Wu et al 2016&lt;sup&gt;46&lt;/sup&gt;</td>
<td>California (USA); 2006–2008; retrospective cohort study</td>
<td>1,550,330 (47,479, 3%)</td>
<td>Empirical Bayesian Kriging; modified CALINE4 air pollution dispersion model; geographic information system tools</td>
<td>GDM diagnosis from birth certificates</td>
<td>PM&lt;sub&gt;2.5&lt;/sub&gt;</td>
<td>Full pregnancy</td>
<td>0.91 (0.81 to 1.01)</td>
</tr>
<tr>
<td>Shen et al 2017&lt;sup&gt;47&lt;/sup&gt;</td>
<td>Taiwan; 2006–2013; retrospective cohort study</td>
<td>13,434 (6717, 50%)</td>
<td>Spatial interpolation (ie, ordinary kriging)</td>
<td>GDM (ICD-9) diagnosis from the National Health Insurance Research Data</td>
<td>PM&lt;sub&gt;2.5&lt;/sub&gt;</td>
<td>Preconceptional</td>
<td>1.10 (1.03 to 1.18)</td>
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<td>1st trimester</td>
<td>1.09 (1.02 to 1.17)</td>
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<td></td>
<td>2nd trimester</td>
<td>1.07 (1.01 to 1.14)</td>
</tr>
<tr>
<td>Pan et al 2017&lt;sup&gt;48&lt;/sup&gt;</td>
<td>Taiwan; 2005; prospective cohort study</td>
<td>19,654 (378, 1.9%)</td>
<td>Spatial interpolation (ie, ordinary kriging) from fixed-site air monitoring stations</td>
<td>Questionnaire answered by the mother and GDM diagnosis from the National Health Insurance register</td>
<td>PM&lt;sub&gt;2.5&lt;/sub&gt;</td>
<td>1st trimester</td>
<td>0.99 (0.93 to 1.05)</td>
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<td></td>
<td>2nd trimester</td>
<td>0.96 (0.90 to 1.03)</td>
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<td>3rd trimester</td>
<td>0.95 (0.90 to 1.00)</td>
</tr>
<tr>
<td>Choe et al 2018&lt;sup&gt;49&lt;/sup&gt;</td>
<td>Rhode Island (USA); 2001–2012; retrospective cohort study</td>
<td>61,640 (4931, 8%)</td>
<td>Spatiotemporal model with LUR model and satellite remote sensing information</td>
<td>GDM (ICD-9) diagnosis from birth certificates and medical records</td>
<td>PM&lt;sub&gt;2.5&lt;/sub&gt;</td>
<td>1st trimester</td>
<td>1.02 (0.95 to 1.09)</td>
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<td>2nd trimester</td>
<td>1.08 (1.00 to 1.15)</td>
</tr>
<tr>
<td>Choe et al 2019&lt;sup&gt;50&lt;/sup&gt;</td>
<td>New York City (USA); 2009–2010; retrospective cohort study</td>
<td>256,372 (17,065, 6.7%)</td>
<td>Spatiotemporal model</td>
<td>GDM (ICD-9) diagnosis from birth certificates and medical records</td>
<td>PM&lt;sub&gt;2.5&lt;/sub&gt;</td>
<td>1st trimester</td>
<td>0.97 (0.94 to 1.00)</td>
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<td></td>
<td>2nd trimester</td>
<td>1.06 (1.03 to 1.10)</td>
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<td>Jo et al 2019&lt;sup&gt;51&lt;/sup&gt;</td>
<td>Southern California (USA); 1999–2009; retrospective cohort study</td>
<td>239,574 (18,244, 7.6%)</td>
<td>Distance-weighted monthly averages from four monitoring stations</td>
<td>GDM based on laboratory values</td>
<td>PM&lt;sub&gt;2.5&lt;/sub&gt;</td>
<td>Pre-pregnancy</td>
<td>1.03 (1.01 to 1.05)</td>
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<td></td>
<td></td>
<td></td>
<td>1st trimester</td>
<td>0.98 (0.96 to 1.00)</td>
</tr>
</tbody>
</table>

Online supplemental table E1 in supplemental material provides more detailed information on other exposure pollutants. FBG, fasting blood glucose; GDM, gestational diabetes mellitus; IGT, impaired glucose tolerance; LUR, land use regression model; OGCT, oral glucose challenge test; PM<sub>10</sub>, particulate matter with an aerodynamic diameter ≤10 µm; PM<sub>2.5</sub>, particulate matter with an aerodynamic diameter ≤2.5 µm.
Recently, the WHO has set more stringent air quality guidelines, due to the increasing evidence for health effects at low ambient air pollution (e.g., PM$_{2.5}$ <5 μg/m$^3$) without an apparent threshold. The effects of lower levels of air pollution are more difficult to capture; however, they may be more relevant to susceptible groups such as pregnant women. Studies in countries with low-to-moderate air pollution would be useful, scientifically in terms of informing the exposure-response relationships for air pollution and comparison to studies in low-income and middle-income countries, and from a practical perspective for guiding policy and health advice. Another important factor influencing maternal health is indoor air pollution. While there have been many studies on outdoor air pollution or solid-fuel combustion on birth outcomes in low-income and middle-income countries, studies on the health effects of the mother during pregnancy have been under-represented, as have the potential health effects of the many indoor air pollutant typical of home in developed countries. Indoor pollution should additionally include active and passive smoking. Smoking status and its potential interaction with ambient air pollution exposures have been vastly overlooked in current epidemiological research.

**CONCLUSION**

Given the ubiquity of air pollutants and the societal and economic costs of cardiovascular morbidity, air pollution represents an...
important risk factor to public health,\textsuperscript{41} While there is inevitably some heterogeneity of effects of different pollutants during pregnancy, there is enough consistency in the evidence to raise major concerns. The maternal effects of air pollution have been poorly characterised to date, and there is a major need for additional investigation with precise air pollution measurements and modelling in different settings; both in terms of concentrations of specific air pollutants and different microenvironments. Major gains could be made through prospective study designs with continuous measurements of personal exposure to air pollution and cardiovascular parameters throughout pregnancy, an approach that is becoming more feasible in studies with a large sample size due to the development of reliable low-cost sensors. Understanding the underlying biological pathways will support the causality of epidemiological associations between air pollution and cardiovascular and cardiometabolic diseases in pregnancy and would provide insight into which pollutants are most harmful as well as identify the periods of the greatest risk. Air pollution is high on the political agenda in many countries and measures to reduce pollutants are being employed; however, acceleration of efforts is urgently needed to realise the full health benefits for pregnant mothers and their children.

**Contributors**  
FD drafted the manuscript, RT, DEN, MRM and RR reviewed and gave intellectual input.

**Funding**  
FD is supported by the Swiss National Science Foundation (P500P2_160634), the Bangether-Rhyner Foundation. MRM and DEN are supported by the British Heart Foundation (FS/CRFT/20/24087, CH/09/002, RG/05/003, RG/10/9/28286, PG/03/07157017, RG/16/10/32375, RE/18/5/34216, RG/FR22/1109093). DEN is the recipient of a Wellcome Trust Senior Investigator Award (WT103782AA). RR acknowledges the support of the British Heart Foundation (RE/18/5/34216).

**Competing interests**  
DEN is on the Editorial Board for *Heart*.  
**Patient consent for publication**  
Not applicable.  
**Ethics approval**  
Not applicable.  
**Provenance and peer review**  
Commissioned; externally peer reviewed.

**Supplemental material**  
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Review


