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Exposures to airborne particulate matter and adverse perinatal outcomes: a biologically plausible mechanistic framework for exploring potential
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Exposures to airborne particulate matter and adverse perinatal outcomes: a biologically plausible mechanistic framework for exploring potential

Abstract. This article has three objectives: to describe the biologically plausible mechanistic pathways by which exposure to particulate matter (PM) may lead to adverse perinatal outcomes of low birth weight (LBW), intrauterine growth retardation (IUGR), and preterm delivery (PTD); review evidence showing that nutrition affects biologic pathways; and explain mechanisms by which nutrition may modify the impact of PM exposure on perinatal outcomes. We propose an interdisciplinary framework that brings together maternal and infant nutrition, air pollution exposure assessment, and cardiopulmonary and perinatal epidemiology. Five possible biologic mechanisms have been put forth in the emerging environmental sciences literature and provide corollaries for the proposed framework. The literature indicates that the effects of PM on LBW, PTD, and IUGR may manifest through the cardiovascular mechanisms of oxidative stress, inflammation, coagulation, endothelial function, and hemodynamic responses. PM exposure studies relating mechanistic pathways to perinatal outcomes should consider the likelihood that biologic responses and adverse birth outcomes may be derived from both PM and non-PM sources. We present strategies for empirically testing the proposed model and developing future research efforts.

Key words: Air pollution, Biomarkers, Birth outcomes, Cardiovascular disease, Nutrition

Resumo. São três os objetivos deste artigo: descrever rotas mecanísticas biologicamente plausíveis pelas quais a exposição à matéria particulada (MP) pode levar a efeitos perinatais adversos, como baixo peso ao nascer (BPN), retardo do crescimento intra-uterino (RCIU) e nascimentos pré-termo (NPT); fazer uma revisão de evidências mostrando que a nutrição afeta rotas biológicas; explicar os mecanismos através dos quais a nutrição pode modificar o impacto da exposição a MP nos efeitos perinatais adversos. Propomos um referencial interdisciplinar que aproxime nutrição materna e infantil, avaliação de poluição do ar e epidemiologia cardiopulmonar e perinatal. Destacaram-se cinco possíveis mecanismos biológicos. A literatura indica que os efeitos da exposição a MP sobre o BPN, o RCIU e os NPT podem se manifestar através de mecanismos de estresse oxidativo cardiovascular, coagulação, inflamação, função endotelial e respostas hemodinâmicas. Estudos de exposição à MP relatando rotas mecanísticas a efeitos perinatais devem considerar a probabilidade de respostas biológicas e efeitos adversos ao nascer serem derivados da exposição à MP e de outras fontes. Apresentamos estratégias para testes empíricos do modelo proposto e para o desenvolvimento de futuras pesquisas.

Palavras-chave: Poluição do ar, Biomarcadores, Doenças do nascimento, Doença cardiovascular, Nutrição
Low birth weight (LBW) affects 20 million infants worldwide. LBW is comprised of two overlapping etiologies: preterm delivery (PTD) and intrauterine growth retardation (IUGR). LBW, IUGR, and PTD are all significantly associated with infant mortality and an array of infant morbidities that range from pulmonary to neurologic outcomes. These associations form the basis for the "fetal origins" or the "Barker hypothesis" which postulates that "fetal growth retardation consequent to malnutrition has long-term structural and physiologic impacts that predispose an individual to chronic diseases in adulthood."

Perinatal outcomes are influenced by a multitude of factors including nutrition and health, genetics, physiologic stressors, and environmental toxicants such as ambient air pollution. In terms of the human health effects, the airborne particulate matter (PM) component has received the greatest attention, and is therefore the focus for this review.

Current epidemiologic evidence suggests that maternal PM exposure is correlated with several adverse perinatal outcomes. Although these studies have become increasingly sophisticated in their measurement of PM exposures, the biologic roles of host factors that may function as effect modifiers of their relationship with birth outcomes have been less thoroughly examined. In particular, the lack of attention to nutrition factors should be considered. Nutrition can be both confounder and effect modifier of the associations between PM exposure and reproductive effects. Given the modifiable nature of both nutrition and PM exposures, future PM research and biomonitoring programs on young women would benefit greatly from the inclusion of selected nutrition factors. It is likely that women of childbearing age with nutritional risk factors (e.g., inadequate caloric intake, suboptimal protective antioxidant micronutrient status) are more likely to live in higher PM-exposed environments—confounded through their relation to socioeconomic status (SES). Despite the considerable effects of nutrition among women of childbearing age, little is known about the nutrition interactions with SES and physical environment, such as PM exposure.

The specific objectives of this review are three-fold: to describe the biologically plausible mechanistic pathways by which PM exposure may lead to adverse perinatal outcomes (LBW, IUGR, and PTD); review the evidence showing that nutrition affects the biologic pathways; and describe biologic markers that mediate the impact of nutrition and thereby explain the mechanisms by which nutrition may serve as effect modifiers of the association between PM exposure and perinatal outcomes.

Responses to PM exposures: biologically plausible mechanisms

The specific biologic mechanisms whereby PM influences perinatal outcomes remain to be fully elucidated. However, epidemiologic, clinical, and experimental evidence correlates current levels of PM with both respiratory and cardiovascular effects, and provide corollaries around which we have developed biologically plausible hypotheses linking PM exposures and birth outcomes. Figure 1 illustrates both chronic and acute PM effects together. Five possible albeit not exclusive biologic mechanisms have been put forth in the literature to explain these effects. In the following text, we describe these mechanisms. Although an increasing number of studies support the notion that PM is associated with cardiovascular effects, these studies at present provide only a fragmentary and somewhat inconclusive picture of the complex biologic pathways involved.

Oxidative stress. PM exposure may contribute to systemic oxidative stress (Figure 1). Direct effects from oxidative activities of combustion-derived particles or by transition-metal constituents (e.g., iron, copper, chromium, and vanadium) may adversely affect the embryo in its earliest phase of growth. In addition, oxidative stressors resulting from PM exposure may arise from organic compounds and from activation of inflammatory cells capable of generating reactive oxygen species (ROS) and reactive nitrogen species (RNS). F2a (8-iso-PGF2a) isoprostane is one of the most promising biomarkers for assessing oxidative injury and has been studied the most extensively for PM exposures.

Oxidative stress-induced DNA damage appears to be a particularly important mechanism of action of urban particulate air pollution. As theorized by Hartwig et al., metals such as nickel in PM may inhibit DNA repair enzymes. We hypothesize that transplacental exposures to transition metals contained in PM could result in
oxidative stress that may lead to DNA damage, disrupting DNA transcription which in turn may increase the number of placental DNA adducts. This hypothesis is partially supported by observations from the Czech Teplice study that found that maternal blood and placental DNA adducts are more common in areas with higher levels of air pollution\textsuperscript{24}. One mechanism postulated to mediate the effects is that PM absorbs and transports polycyclic aromatic hydrocarbons (PAHs), exposure to which may lead to increased DNA adducts\textsuperscript{25}, thus resulting in LBW\textsuperscript{25,26} and IUGR\textsuperscript{8}. Researchers suggest that DNA damage measured by oxidized DNA bases purines and pyrimidines and protein and lipid peroxidation indicated by plasma malondialdehyde may be more sensitive than bulky DNA adducts as markers of exposure to PM\textsuperscript{26}. PAHs in PM can induce biotransformation by cytochrome\textsubscript{P450}, epoxide hydrolase, and dihydrodiol dehydrogenase\textsuperscript{28} in addition to the direct action of coal combustion toxics on antioxidants/enzymes (e.g., superoxide dismutase, catalase) that may adversely affect the embryo in its earliest phase of growth\textsuperscript{19}. Alternatively, PM may also bind receptors for placental growth factors, resulting in decreased fetal-placental exchange of oxygen and nutrients\textsuperscript{8}. Nutrient and oxygen supply during gestation are key factors regulating fetal growth\textsuperscript{29}.

Pulmonary and placental inflammation. PM exposure is associated with systemic inflammation\textsuperscript{30,31,32,33,34} (Figure 1). We hypothesize that inhalation of particles during pregnancy can induce acute placental\textsuperscript{8} and pulmonary inflammation. In contrast to the PM composition-induced effects on oxidative stress that have been extensively studied, specific components in particles that elicit inflammation are less thoroughly investigated, although recent research points to the contribution of compositional trace elements\textsuperscript{35} and bioavailable transition metals to cardiopulmonary injury in healthy and compromised animal models\textsuperscript{36}. Based on cell culture methodologies, the up-regulation of pro-inflammatory mediators in response to transition metals chromium, aluminum, silicon, titanium, iron, and copper within PM were found to contribute to pulmonary inflammation\textsuperscript{30}.

Figure 1. Proposed biologic framework for exploring possible effect modification of PM–birth outcomes by maternal nutrition.
The most widely studied biomarkers of inflammation are high-sensitive C-reactive protein, oxidized low-density lipoproteins, proinflammatory cytokines interleukin (IL)-1, IL-6, and tumor necrosis factor-a, serum amyloid A, the acute phase marker fibrinogen, neutrophil count, and blood platelet count, red blood cells and white blood cells, and albumin. With cell culture methods, PM exposure-induced trace elemental markers of inflammatory response were recently identified by Becker et al., who showed that PM constituent iron and silicon correlated with the release of IL-6, whereas chromium correlated with IL-8.

Inflammation could be associated with inadequate placental perfusion, which can mediate placental inflammatory responses and its biologic sequelae, resulting in impaired transplacental nutrient exchange (Figure 1). We hypothesize that inadequate placental perfusion may cause growth restriction in utero due to interference with some process or processes such as affecting nutrition of the fetus, reduced oxygenation of maternal blood, or both. For example, a rapid decline in the placental delivery of essential fatty acids arachidonic acid and docosahexanoic acid is expected.

Independent of the cascade of events characterized above, the biologic mechanisms that trigger adverse perinatal outcomes may include maternal infections, especially during the last trimester of pregnancy, and may initiate premature contractions and/or rupture of membranes. Although air pollution does not directly cause maternal infections, exposure to specific pollutants may enhance allergic inflammation and increase the maternal risk for adverse birth outcomes.

Coagulation. Systemic alterations in rheologic factors, including blood coagulability and whole blood viscosity as a result of exposure to PM, represent other potential mechanisms of PM toxicity. In response to PM exposure, increase in any of the proteins of the clotting cascade present a possibility for coagulation. Based on a cross-sectional study conducted in London, Pekkanen et al. found ambivalent results for the association between PM 10 (PM < 10 μm in aerodynamic diameter) and plasma fibrinogen - this association was significant only for the warm season. Other measurable biomarkers include factors VII, IX, fibrinD-dimer, and von Willebrand factor. PM exposures may also lead to changes in hemoglobin, platelets, and white blood cells, which may potentially contribute to the association between PM and adverse fetal growth.

Endothelial function. Exposure to PM may influence endothelial functions and could be considered as an intervening pathway in subsequent impact on fetal growth (Figure 1). Although this pathway has been less extensively studied, the impact of PM on vascular function has been the subject of recent investigations. Inhalation of environmental tobacco smoke (ETS) [similar in characteristics to PM 2.5 (PM < 2.5 μm in aerodynamic diameter)] causes rapid vasoconstriction, increases plasma endothelin levels, and triggers endothelial dysfunction. Although the specific chemical components of ETS responsible for the observed effect of vasoconstriction have not been adequately characterized, it is likely that the PM in ETS is primarily responsible, as summarized by Brook et al.

A recent animal-based study found that PM 2.5 exposure increased plasma concentrations of asymmetric dimethyl arginine that is associated with impaired vascular function and increased risk of cardiovascular events. Circulating concentrations of soluble adhesion molecules E-selectin, intracellular adhesion molecule (sICAM-1), and vascular cellular adhesion molecule (VCAM-1) are overexpressed when the endothelium encounters inflammatory stimuli. The inhalation of high urban levels of concentrated ambient particles and ozone for 2 hr caused conduit arterial vasoconstriction in healthy adults. As summarized by Brook et al., it is possible that acute systemic inflammation and oxidative stress following PM exposure are responsible for triggering endothelial dysfunction leading to vasoconstriction. Endothelial dysfunction can also be secondary to other cardiovascular disease (CVD) risk factors (e.g., metabolic syndrome). These pathophysiologic reactions in response to PM exposure may result in impaired fetal growth.

Hemodynamic responses. Biologic measures that assess hemodynamic changes in response to PM exposure have typically included systolic blood pressure (SBP) and diastolic blood pressure (DBP). Panel studies conducted of adults with preexisting CVD found an increase in SBP associated with elevated particulate exposures. In contrast, based on population exposures, an increase of a 5-day average of ultrafine particles was associated with a small decrease in SBP and DBP. Specific biologic mechanisms for the observed PM-associated effects on blood pressure (BP) have been suggested to include an increase in sympathetic tone and/or the modulation of basal systemic vascular tone.
Another potential mechanism whereby pollut-
ant components can increase BP is superoxide-
mediated inhibition of the actions of nitrous ox-
ide in inducing vasodilatation.

If PM exposure is also associated with BP ele-
vations in pregnant women, this could increase
the risk of adverse perinatal outcomes as a conse-
quence of preexisting hypertension or pregnan-
cy-induced hypertension. Elevation of BP to lev-
els that is defined as pregnancy-induced hyper-
tension has been associated with IUGR (Misra
1996) and PTD. Severely impaired fetal growth
is preceded by maternal hemodynamic maladapt-
ation. These changes may force the fetus to
adapt, down-regulate growth, and prioritize the
development of essential tissues. Hypertension
can also be secondary to oxidative stress and vas-
cular inflammation or other risk factors, for low
maternal body weight, for example, thus enhanc-
ing the susceptibility to adverse birth outcomes.

Exploring effect modification by nutrition

Although the specific underlying mechanisms
that contribute to normal or adverse birth out-
comes are not yet fully understood, an adequate
periconceptional nutrition status is considered a
key determinant. Given that both dietary com-
position and CVD risk are strongly socially pat-
tered, this suggests one way to approach the
possible interaction between air pollution and SES
(in affecting birth outcomes). As is described in
more detail below and illustrated in Figure 1, di-
etary composition has been demonstrated to re-
late to those same biologic mechanisms hypoth-
esized to explain the possible effects of PM expo-
sure on birth outcomes.

The nutrition aspects of the framework shown
in Figure 1 are not intended to include every pos-
sible parameter worthy of consideration. Explor-
ations about what to add to various layers of
the framework could be one of its most useful
applications in future work on this topic. Al-
though no previous studies of the perinatal ef-
fects of PM exposure have examined effect mod-
ification by nutrition, theoretical and empirical
evidence is growing. Investigators studying air
pollution and birth outcomes have suggested that
nutrition status may play a role in protecting the
fetus or magnifying the effects. Other investig-
ators have cited the potential importance of
nutrition as a buffering or synergistic factor with
regard to PM-induced cardiovascular respons-
es. Using data from the Third National
Health and Nutrition Examination Survey (NHANES III), Schwartz considered the role of
nutrition in the association between PM expo-
sures and incident ischemic events. Considering
a limited set of dietary factors (saturated fat, fi-
ber, alcohol, caffeine, fish and shellfish), Swift
reported that the selected factors did not modify the association. Furthermore, the biomarkers were limited to fibrinogen, platelet
and white blood cell count, SBP, total cholesterol,
and high-density lipoprotein cholesterol. On the
other hand, we propose that researchers should
explore the potential effect-modifying roles us-
ing a more comprehensive list of dietary vari-
ables and biomarkers.

Consideration of a hypothesis
of nutritional susceptibility

The Institute of Medicine describes combina-
tions of environmental exposures and greater
susceptibility as a form of “double jeopardy.”
Maternal nutrition stressors such as micronu-
trient deprivation are likely to occur around the
world in subpopulations that experience dispar-
ate air pollution profiles. Considerable research
evidence supports the important role played by
nutrition, particularly micronutrients, in deter-
mining positive pregnancy outcomes. In addi-
tion, gestational energy stress, a phenomenon
characterized by lower plasma volume expan-
sion, protein-energy malnutrition, and preg-
nancy complications, may also co-occur. As de-
picted in Figure 1, we propose that maternal nu-
trition could be exacerbating or buffering in the
association between PM and birth outcomes for
a subgroup of women of childbearing age. In the
following section, we contextualize these biologic
pathways for nutrition: first based on intakes of
nutrients, next based on the consumption of
foods or of groups of foods, and finally based
on indices and dietary patterns that combine both
approaches.

Nutrients potentially contributing to bio-
logic pathways. In the past two decades, under-
standing of cardioprotective nutrients and foods
has grown substantially owing to studies of the
molecular mechanisms and the metabolic effects.
Investigators typically estimate nutrient intakes
using food frequency questionnaires, food records, and/or 24-hr dietary recalls. Nutrient
values may be derived using existing databases
supplemented with information from manufac-
turers and biochemical analyses.
Oxidative stress. Ingestion of particular micronutrients causes a shift in oxidative status. The micronutrients most relevant to the pathways shown in Figure 1 include the fat-soluble carotenoids and vitamin E, water-soluble vitamin C, and methyl nutrients including the B vitamins pyridoxine (B6), cyanocobalamin (B12), and folic acid. Carotenoids may protect against oxidant damage. Dietary micronutrient trace minerals such as zinc and manganese may display indirect antioxidant activity as constituents of enzymes including superoxide dismutase.

Micronutrients may extend the gestational period to full term or counteract the damage caused to lipids and DNA triggered by PM exposures. Methyl nutrients are involved in DNA methylation, and the resulting methyl nutrient status may modify PM-induced alterations in oxidative stress through its impact on DNA stability, repair, and the different gene expression processes. Suboptimal methyl nutrient status may also increase the risk for PTD associated with preclampsia and LBW.

Inflammation. Dietary macronutrient intakes may produce inflammatory responses. Unlike micronutrients, some macronutrients may show opposite effects. Reducing trans- and saturated fatty acids and increasing omega-3 fatty acids are also associated with a reduced inflammatory status. Food sources rich in n-6 polyunsaturated fatty acids are shown to enhance IL-1 production; n-3 fatty acids on the other hand have been demonstrated to have the opposite effect.

Coagulation. A deficiency in any one of the methyl nutrients could result in elevated homocysteine. Homocysteine thiolactone can subsequently influence vascular coagulation. In addition, high total dietary fat may lead to fibrin deposits and thrombus formation through activation of coagulation.

Endothelial function. Micronutrient antioxidants representing β-carotene subfractions derived from vegetables and fruits are inversely related to E-selectin. Polyphenols have been found to inhibit expression of endothelial adhesion by regulating gene transcription. Micronutrient intakes such as arginine and folic acid have been shown to improve endothelial function. Unlike the possible cardioprotective effects of micronutrients and polyphenols, macronutrients may be beneficial or detrimental. Based on the Nurses Health Study, Lopez-Garcia et al. reported a positive relationship between trans-fats and endothelial dysfunction, whereas n-3 fatty acids were inversely associated with sICAM-1, sVCAM-1, and E-selectin.

Hemodynamic responses. The favorable effects of fruits and vegetables, low-fat dairy products, and reduced sodium suggested by Dietary Approaches to Stop Hypertension (DASH) indicate the possible role for micronutrients in reducing the risk for prepregnancy hypertension. Several mechanisms of polyphenols have been researched, including their antioxidant functions.

Contributions of foods/food groups to biologic pathways. There is a growing list of foods and food groups consumption of which is associated with the various biologic pathways depicted in the present framework (Figure 1). Fruits and vegetables contain myriad of different components of varying antioxidant capacity, thus offering a range of possibilities for altering PM-induced oxidative effects. Based on the NHANES III findings, grain consumption is inversely associated with an elevated CRP concentration. Similarly, fresh fruit, olive oil, mushrooms, cruciferous vegetables, and nuts are associated with a favorable homocysteine profile. Adding vegetables may reverse the increases in ICAM-1 and VCAM-1, whereas high intakes of refined grains, and processed meat and low consumption of cruciferous and yellow vegetables may exacerbate the inflammatory processes.

Dietary patterns are contributors to the biologic pathways. Dietary pattern analysis serves as a complementary approach to the nutrient-focused and food-group analysis described above. Dietary patterns are food intake patterns over a referent period and consider the overall dietary matrix. However, most of these studies did not focus on the dietary patterns among women of childbearing age.

Dietary patterns cannot be measured directly, and one must rely on statistical methods that employ dimension-reduction techniques such as factor analysis and cluster analysis. The advantage of novel statistical approaches such as the reduced rank regression is that the derived pattern incorporates the biologic pathways presented in the current framework and thus is hypothesis driven.

Gene–nutrient interactions and impact on biologic pathways. Nutrigenomic researchers have provided evidence for interactions among dietary factors, genetic variants, and biochemical markers of CVD. Genetic background can interact with habitual total dietary fat and fatty acid composition, thereby affecting predisposition to the woman's responsiveness to PM exposure.
sures. Similarly, genetic susceptibility related to functional polymorphisms in genes coding for antioxidant and DNA repair enzymes may be expected to modify the levels of oxidative DNA damage caused by exposure to PM. In addition, there is significant evidence that genes are involved in determining enzymes, receptors, cofactors, and structural components involved in regulation of BP and inflammatory and coagulation factors.

Measurement indices for nutrients, foods, and food groups and dietary patterns

Individual dietary constituents may have small biologic effects that emerge only when the components are integrated into a simple unidimensional score. Appendix 1 lists candidate tools, and we have classified them in three categories as a function of their determination mode, based on a now classical review: (a) indices based on intakes of nutrients (or at least of certain nutrients); (b) indices based on the consumption of foods or of groups of foods; and (c) indices that combine both approaches resulting in dietary patterns. In the following section, we present examples of these measurement indices that add quantitative elements to qualitative aspects, and some are based on thresholds or recommendations. In a few cases, the indices were studied to link to the biologic parameters in the present framework.

Nutrient indices. Oxidative stress has been described as a disturbance in the balance between free radical production and antioxidant capacity. Reflecting this definition, the dietary antioxidant index summarizes the combined intakes of carotenoids, flavonoids, tocopherols, tocotrienols, selenium, and vitamin C. The integrated oxidative balance score reflects antioxidant (e.g., vitamin C) and pro-oxidant (e.g., iron) intakes. The antioxidant scores for commonly consumed fruits, fruit juices, and vegetables are published as oxygen radical absorbance capacity (ORAC) or ferric-reducing antioxidant power. More than 80% of the antioxidant capacity in fruits and veggies may also be attributed to flavonoids that have the ability to chelate metal ions and have particular relevance here.

Foods and food group indices. Dietary variety determined by Recommended Foods score (simple count of consumed food items) and diversity measured as Dietary Diversity Score (count of represented food groups) are both good candidates for measuring overall dietary quality. The Healthy Eating Index based on the Dietary Guidelines for Americans is an additional measure of quality. The Mediterranean pattern now recommended for the secondary prevention of coronary artery disease quantifies adherence to the traditional Mediterranean diet using a 9 point scale. Minor variants to these indices, the alternate Healthy Eating Index and the alternate Mediterranean dietary pattern were found to be associated with markers of inflammation.

Dietary pattern indices. The possibility that dietary patterns may exert an effect on biologic measures was first suggested through the findings of the DASH clinical trial. As shown in Appendix 1, other population studies conducted in the United States indicate two major dietary patterns: "prudent" and "Western." The prudent pattern was found to be inversely associated with homocysteine and positively associated with folate while also showing a beneficial effect on the endothelium. The Western pattern, on the other hand, was positively correlated with homocysteine, high-sensitive C-reactive protein, and impaired endothelial function and negatively associated with folate. Similarly, low-glycemic load-based patterns in biomarkers of exposure/effect and are informed of inflammation. Women of child-bearing age were associated with improved fibrinolysis. Glycemic load may be determined using the updated table that provides glycemic index scores for 1,300 national food entries (Appendix 1).

Recommendations related to the proposed framework

In appendix 2, we recommend strategies for developing future research efforts in three overarching areas. Certainly many factors could function as mediators of the association between PM and birth outcomes. However, few studies are sufficiently comprehensive to understand the multifactorial etiologies and pathways. In particular, the confounding nature of SES and air pollution should be explored in future work, Future studies that include biomarkers of exposure/effect and informed by biologic pathways will help tease out those aspects of SES that explain differences in PM birth effects among population subgroups.

The current framework may be advanced by biomonitoring women with unique circumstances (e.g., genetic polymorphisms). Further research will help identify susceptible population subgroups, such as for the potential for genetic variation in metabolic pathways (e.g., detoxifying such
as cytochrome P450) that could underlie differences in susceptibility toxicities related to PM exposures\textsuperscript{26, 114}. Altered expressions of DNA repair and other defense genes have yet to be studied for up-regulation of the involved PM exposures\textsuperscript{20}. The available data are consistent with the occurrence of PM-related systemic oxidative, inflammatory, and hemodynamic responses, but evidence on endothelial dysfunction and procoagulatory states is limited. In addition to these pathways, other alternate mechanisms (e.g., disruption in iron homeostasis)\textsuperscript{115} should be studied. Although mechanisms underlying the adverse effects of PM on the cardiopulmonary systems remain a primary focus of research, additional hypotheses suggest the involvement of neurogenic processes\textsuperscript{116, 33}. Finally, researchers should also consider the synergistic interactions among the various biologic mechanistic pathways.

Appendix 2. Recommendations for advancing the current framework.

Sampling, measurement, and characterization of PM exposures
- Consider the roles of co-pollutants (e.g., ozone, carbon monoxide, nitrogen dioxide) with PM and use multiple-influence chemical characterization models.
- Incorporate trace elements that are characteristic to their specific source type and emissions through specific source “fingerprints.”
- Integrate personal PM exposures with fixed-site and community-level assessment.
- Consider the geographical and seasonal toxicity profiles for PM and constituents.
- Collect continuous ambient PM exposure over and beyond “daily” PM data.
- Explore the intracellular pathways by which PM and constituent transition metals may modulate the gene expression of biologic responses.
- Assess nutritional status, biologic pathways, and biomarkers of response
  - Explore the possible dietary influences by incorporating a priori approach, which builds on previous knowledge concerning the cardiac and pulmonary effects, and birth outcomes.
  - Assess specific food features, depending on the contexts relevant to PM monitoring area, and construct dietary indices accordingly.
  - Enhance the reliability and validity of self-reported nutrition measures by incorporating relevant biologic measures.
- Clarifying the temporal and spatial vulnerabilities and unique circumstances
  - Expand the proposed framework using the definition of maternal health that fosters linkages with a woman’s health during her reproductive years.
  - Consider all gestational time windows of PM and in utero nutrition exposures.
  - Explore susceptibility resulting possibly from compromised maternal health, in addition to effects exerted directly across the placenta.
  - Clarify the roles of multiple determinants (SES and other stressors) in causing adverse birth outcomes.

Appendix 1. Measurement indices assessing nutrients, foods, food groups, and dietary patterns.

**Dietary intakes of nutrients**
- Dietary Antioxidant Index\textsuperscript{103}: carotenoids, flavonoids, tocopherols, tocotrienols, selenium, and vitamin C
- Oxidative Balance Score\textsuperscript{104}: vitamin C, \(\beta\)-carotene, and iron
- Oxygen Radical Absorbance Capacity (ORAC)\textsuperscript{105, 106}: ORACROO (peroxyl radical), ORAC-OH (hydroxyl radical), and ORAC-Cu (copper)

**Dietary intakes of foods and food groups**
- Dietary Diversity Score\textsuperscript{75}: foods from dairy, meat, grain, fruit, and vegetable groups
- Recommended Foods Score\textsuperscript{75}: weekly consumption of fruits, vegetables, lean poultry and alternates, low-fat dairy, and whole grains

**Combined dietary intakes of nutrients, foods, and food groups**
- Dietary Approaches to Stop Hypertension\textsuperscript{92}: 4–5 servings fruits; 4–5 servings vegetables; 2–3 servings low-fat dairy products; 7–8 servings of grain products; 2 or less servings of meats, poultry, fish/day; 4–5 servings of nuts, seeds, legumes/week
- Alternate Healthy Eating Index\textsuperscript{111}: protein source, trans fat, PFA:SFA, cereal fiber, moderate alcohol, and long-term multivitamin use
- Alternate Mediterranean Diet\textsuperscript{111}: excludes potato products from vegetable group, separates fruit and nuts into two groups, eliminates dairy group, includes “whole grain” products only, only red and processed meats for meat group
- Prudent Pattern\textsuperscript{100}: fruits, vegetable, fish, whole grains, and legumes
- Western Pattern\textsuperscript{100}: red and processed meat, high-fat dairy products, sugar-containing beverages, sweets, and desserts
- Glycemic Load\textsuperscript{113}: glycemic quality and quantity
Conclusion

Several ongoing U.S. population-based research projects funded through the National Institute of Environmental Health Sciences (e.g., the Health Disparities Initiative) provide unique opportunities to apply and evaluate the current framework. The resulting findings would be relevant for PM regulation and primary prevention of CVD and other diseases influenced by the pathways proposed in the current framework and reducing the risks for adverse birth effects. If exposure interactions are found for PM with nutrition, they may also offer geographically relevant nutrition–environment interactions-based intervention opportunities through various federal food and nutrition assistance venues including the Special Supplemental Nutrition Program for Women, Infants, and Children.

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