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Racial disparities in preterm birth: an overview of the potential role of nutrient deficiencies

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Abstract

Objective—To give an overview of the literature for evidence of nutrient deficiencies as contributors to the disparity in preterm birth (PTB) between African-American and Caucasian women.

Design—Structured literature survey.

Methods—We searched MEDLINE to identify observational and experimental studies that evaluated the relation between nutrient intake and/or supplementation and PTB. For nutrients for which studies supported an association, we searched MEDLINE for studies of the prevalence of deficiency in the USA by race.

Main Outcome Measures—Summarized findings on nutrients for which there is both evidence of a role in PTB and variability in the prevalence of deficiency by race.

Results—Nutrient deficiencies for which there are varying levels of evidence for an association with PTB and a greater burden among African-American compared with Caucasian women include deficiencies of iron, folic acid, zinc, vitamin D, calcium and magnesium, and imbalance of ω-3 and ω-6 polyunsaturated fatty acids. There are inadequate high-quality studies that investigate the role of nutrient deficiencies in PTB, their potential interaction with other risks, the proportion of excess risk for which they account, and whether supplementation can reduce the risk of, and racial disparities in, PTB in US populations.

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Conflict of interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

Conclusion—Deficiencies of several nutrients have varying levels of evidence of association with PTB and are of greater burden among African-American compared with Caucasian women. Although further research is needed, strategies that improve the nutritional status of African-American women may be a means of addressing a portion of the racial disparity in PTB.

Keywords

African-American; health disparity; micronutrients; nutritional deficiency; pregnancy outcome; preterm birth; women's health

Introduction

In the USA, preterm birth (PTB; defined as birth <37weeks' gestation) is the leading cause of mortality for African-American infants and the second leading cause for Caucasian infants. The mortality rate for African-American infants is approximately 2.3 times that for Caucasians (1), and approximately 80% of this disparity is attributable to differences in rates of PTB (2). Racial disparities in PTB cannot be explained by differences in traditional measures of socioeconomic status, such as income or level of education, or by differences in maternal health behaviors, such as substance use (3,4).

A substantial proportion of cases of PTB are attributed to activation of the inflammatory pathway (5), which is the effector pathway theorized to primarily account for African-Americans' increased rate of PTB relative to Caucasians (6,7). Activation of the inflammatory pathway to PTB is likely to represent interaction among socioenvironmental exposures, individual behaviors, responses to exposures (including allostatic load) and genetics (including immunoreactivity) (8). Socioenvironmental factors hypothesized to contribute to activation of the inflammatory pathway to PTB, and thereby potentially to contribute to racial disparities in PTB, include nutritional factors, reproductive tract infections, pregnancy intendedness and spacing and psychosocial stressors (8). The potential role of reproductive tract infections, pregnancy intendedness and spacing and psychosocial stressors in racial disparities in PTB are discussed in this issue (9–11). The purpose of this paper is to review the literature for evidence of nutrient deficiencies as contributors to the disparity in PTB between African-American and Caucasian women in the USA.

Methods

We reviewed the literature to identify experimental and observational studies that evaluated the relation between nutrient intake and/or nutrient supplementation and the outcome of PTB. We performed our search in MEDLINE using the following medical subject headings, limited to human studies that were published between January 1970 and January 2010: 'Premature birth' or 'Premature obstetrical labor' or 'Preterm delivery' combined with 'Nutritional status' or 'Micronutrients' or 'Nutrition disorders' or 'Malnutrition' or 'Deficiency diseases' or 'Avitaminosis'. This strategy yielded 279 discrete articles. As our purpose was to better understand the potential role of nutrient deficiencies in racial disparities in PTB in the USA, we included only those articles that were set in higher resource countries. We included systematic reviews if they included studies from such country settings. We excluded retrieved articles that described research studies conducted

solely in low-resource settings or that examined nutritional factors other than nutrient deficiencies or imbalances (such as obesity, underweight, poor pregnancy weight gain, diabetes, gestational diabetes, insulin resistance or eating disorders) or contaminants in food (such as mercury in fish) or that focused on the growth and development of preterm infants rather than the outcome of PTB, or were restricted to special populations (such as HIV-infected women only). The references of retrieved articles were reviewed to identify potentially relevant studies missed in the MEDLINE search.

This strategy yielded 31 articles or systematic reviews that described observational or experimental studies examining nutrient deficiencies or supplementation and PTB in higher-resource country settings. We reviewed these articles to determine whether there was evidence of an association between the nutrient deficiency or supplementation and PTB. For nutrients for which published research supported an association with PTB, we searched MEDLINE for studies that described the prevalence of deficiency of that nutrient in the USA by race as well as potential mechanisms for the association with PTB. In this overview, we have summarized findings for those nutrients for which there is observational or experimental evidence of a role in PTB as well as variability in the prevalence of the deficiency in the USA by race/ethnicity.

Results

Specific nutrients for which observational and/or experimental studies demonstrated an association with PTB in developed country settings and for which deficiencies are more prevalent among African-American compared with Caucasian women are summarized in Table 1. For each of these nutrients, a more detailed explanation of the studies, exploring the association with PTB, potential mechanisms for the association and variation in nutrient status by race, is given below.

Iron

Observational studies have supported a relation between iron-deficiency anemia, especially early in pregnancy, and PTB, as well as other adverse pregnancy outcomes and perinatal mortality (12). Specifically, a prospective study based in the USA showed that women with iron-deficiency anemia early in pregnancy had a significantly greater rate of PTB compared with women who were iron replete early in pregnancy, controlling for other known risk factors, with an adjusted odds ratio (OR) of 2.7 [95% confidence interval (CI) 1.2–6.2] (13).

Iron supplementation during pregnancy is the standard of care in the USA (14); thus, randomized controlled trials (RCTs) of iron supplementation during pregnancy are not feasible there. A recent systematic review (15) that included an analysis of eight trials of iron or iron plus folic acid during pregnancy and the outcome of spontaneous PTB found a non-significant reduction in the risk of PTB among the iron-treated group, but the difference was not significant [relative risk (RR) 0.8, 95% CI 0.7–1.1]. The systematic review suggested that future research into the role of iron supplementation in the prevention of adverse pregnancy outcomes should focus on populations in which iron deficiency is highly prevalent and should initiate supplementation early in pregnancy because interpretation of

existing data is limited by significant heterogeneity in enrolled populations, the timing of initiation of supplementation and the dosage of supplementation (15).

Three potential mechanisms by which maternal iron-deficiency anemia may contribute to PTB have been described: hypoxia, oxidative stress and infection (16). Chronic hypoxia from anemia could initiate a stress response that culminates in early delivery. Increased oxidative stress in iron-deficient women could result in inflammation that damages the fetoplacental unit and leads to PTB. Also, as iron deficiency has well-established links with reduced immune function and increased risk of infection, there could be an increased risk of infection and inflammation culminating in PTB (16).

According to 1999–2000 National Health and Nutrition Examination Survey (NHANES) data, the prevalence of iron deficiency for African-American women is approximately double that for Caucasian women (19–22 vs. 10%) (17). Data from the US National Collaborative Perinatal Project, involving 58 960 pregnant women, reveal that African-American women are substantially more likely than Caucasian women to be anemic during pregnancy (23 vs. 7%) (18). A survey of iron status among pregnant African-American adolescents estimated that 25% are iron deficient in the first trimester of pregnancy (19). In the USA, iron-deficiency anemia is particularly common among low-income pregnant women (20).

Folic acid

Two high-quality prospective, longitudinal observational studies conducted with women from New Jersey and North Carolina have shown that a low dietary intake of folate (21) and a low concentration of serum folate during the second trimester (22) are associated with a greater risk of PTB, controlling for other known risks. Specifically, compared with women who had a folate intake >400μg/day, those with intermediate folate intake (241–400μg/day) and low folate intake (≤240μg/day) had a progressively increased risk of PTB (RR 3.4, 95% CI 1.9–6.1 and RR 1.9, 95% CI 1.0–3.6, respectively) (28). Those with low serum folate levels in the second trimester had a nearly twofold increased risk of PTB (RR 1.8, 95% CI 1.3–2.5) (22).

A single prospective observational study conducted in the USA showed that supplementation with folic acid for one year prior to conception was associated with a nearly 70% reduction in the risk of spontaneous PTB <28weeks (RR 0.3, 95% CI 0.1–0.9) and an approximately 47% reduction in the risk of spontaneous PTB 28–32weeks (RR 0.5, 95% CI 0.3–0.9) (23). This study noted a biological gradient, with a significant trend of decreased risk of spontaneous PTB across the seven categories of duration of folic acid supplementation (23). There has been compulsory folic acid fortification of flour in the USA since 1998. While the prevalence of singleton PTB has declined as folic acid intake has increased following flour fortification (24), the decline in occurrence of PTB (and also neural tube defects) is substantially less than was expected from clinical studies (24), which is attributed to the insufficient amount of supplementation provided by flour fortification.

Results of experimental trials of folic acid supplementation during pregnancy are inconclusive. One RCT conducted in France showed lower serum folate levels among

women with PTB and longer duration of gestation among women with higher folate levels and those treated with iron plus folic acid rather than iron alone (25). Another RCT, also conducted in France, showed no differences in rates of PTB, but an increase of nearly one week in mean gestational age (40.7 vs 39.9weeks) among women supplemented with folic acid during the third trimester (26). In contrast, three other early trials showed no association between prenatal supplementation with folic acid and length of gestation (27–29); however, interpretation of these studies is hampered by lack of information about randomization, compliance, gestational age upon initiation of supplementation, other potential confounding variables and substantial loss to follow up.

Folate may mediate intrauterine inflammation because it serves as a methyl donor, and methylation is known to impact epigenetic mechanisms and to be crucial in the development and function of T-cells (30). Low plasma folate is associated with impaired T-cell and neutrophil function and increased prevalence of bacteriuria in pregnancy (31,32). Folate intake is also linked to the presence of bacterial vaginosis (33), with a significant inverse association between the severity of bacterial vaginosis and the intake of folate (RR 0.4, 95% CI 0.2–0.8). Bacterial vaginosis is a documented risk factor for PTB, particularly recurrent PTB among African-American women (34).

According to 2001–2002 NHANES data, African-American women have lower folate intake (from both food and supplement sources). While approximately 40% of Caucasian women consume 400μg of folic daily, only 5% of African-American achieve 400μg of folic acid daily from fortified foods and supplements. The prefortification mean red blood cell folate was lower for African-Americans compared with Caucasians, and fortification produced a smaller shift in mean red blood cell folate for African-Americans compared with Caucasians (35).

There is also some evidence for racial variation of the effect of folic acid. One study showed a race-specific interaction between dietary folate intake and PTB, whereby African-American women with a genetic variant in serine hydroxymethyltransferase 1 (*SHMT1*), a gene in the folate pathway, who were in the lowest quartile of dietary folate intake, had an elevated risk of PTB (36).

Zinc

Among a cohort of low-income urban girls and women in the USA, low intake of dietary zinc early in pregnancy has been associated with a greater than threefold increased risk of PTB preceded by premature rupture of membranes, controlling for other known risks (OR 3.5, 95% CI 1.0–11.5). If iron-deficiency anemia was also present at the time of entry into prenatal care, the OR for PTB <33weeks of gestation increased (OR 5.4, 95% CI 1.6–18.8) (37).

Several trials have examined the potential benefit of prenatal zinc supplementation on birth outcomes. A systematic review that included 13 RCTs (6 854 women) found that prenatal zinc supplementation resulted in a significant reduction in PTB (RR 0.8, 95% CI 0.7–0.9) (38). One included RCT (39) that examined daily zinc supplementation beginning at 19weeks' gestation in low-income African-American women with low plasma zinc

concentrations in early pregnancy found a non-significant reduction in PTB among women randomized to the zinc supplement group vs. placebo (10.2 vs. 13.3%, p=0.25) as well as a non-significant reduction in PTB <34weeks (3.4 vs. 6.3%, p=0.10), with the differences being more pronounced for those in the supplement vs. placebo group with a body mass index less than 26kg/m^2 (3.0 vs. 6.8%, p=0.15) (39). A strength of this study was its selection of women with low plasma zinc concentrations early in pregnancy, while a limitation was its relatively late initiation of supplementation (19weeks).

Zinc is crucial for the normal development and functioning of cells involved in innate and adaptive immunity and is a cofactor for the activity of over 300 enzymes involved in synthesis of DNA, RNA and protein and in cell division and activation (40). Zinc also plays a role in cellular apoptosis, functions as an antioxidant and stabilizes cell membranes (40).

Mean plasma zinc levels are lower for African-American compared with Caucasian women, multiparous compared with nulliparous women, and those with body weight >69.9 vs. ≤69.9kg. Black maternal race and low socioeconomic status are among the strongest predictors of plasma zinc concentrations among pregnant women (41).

Vitamin D

There are limited human data relating vitamin D status to PTB. However, a recently presented abstract reported findings from an RCT of a high-dose (4 000IU/day) vitamin D supplementation trial vs. 400IU/day from 12weeks' gestation on a composite outcome of co-morbidities of pregnancy that included pre-eclampsia, gestational diabetes, infection and PTB. This trial found a 50% reduction in the risk of the composite outcome of co-morbidities among those supplemented with 4 000IU/day, controlling for race (RR 0.5, 95% CI 0.3–0.9) (42). Measured serum concentrations of 25-hydroxy-vitamin D (25-OH-D) levels were significantly higher among the group supplemented with 4 000 vs. 400IU/day (39.0 vs. 33.4ng/mL, p<0.008). Details regarding the research design, methods and results of this RCT are not yet available in the published literature.

The active form of vitamin D (1,25-dihydroxyvitamin D_3) is a key modulator of the immune response, and vitamin D is known to be a potent regulator of placental immunity, stimulating antimicrobial responses while suppressing inflammation (43). The placenta expresses vitamin D receptor and CYP26b1 (vitamin D_3 1α-hydroxylase) in the maternal decidua and fetal trophoblast (44). It is theorized that vitamin D can protect against infection-associated PTB by activating antimicrobial responses and suppressing inflammation within the fetal–maternal unit, and conversely that vitamin D insufficiency may increase susceptibility to infection and inflammation and thereby increase the risk of PTB. There is a dose–response association described between 25-OH-D and the prevalence of bacterial vaginosis in a case–control study; compared with a serum 25-OH-D concentration of 75nmol/L, there were 1.7-fold (95% CI 1.0–2.7) and 1.2-fold (95% CI 1.0–1.6) increases in the prevalence of bacterial vaginosis associated with a serum 25-OH-D concentration of 20 and 50nmol/L, respectively, after adjustment for race and sexually transmitted diseases (45). It is also hypothesized that vitamin D may mitigate activation of the stress pathway to PTB (43,44). Vitamin D increases the rate-limiting enzyme in the catecholamine biosynthetic pathway (by

upregulating the tyrosine hydroxylase gene, *CYP26b1*), which is a mechanism by which it may control the adaptation to stress (46).

Circulating levels of 25-OH-D are a direct reflection of total body vitamin D status, which depends upon access to vitamin D either through exposure to sunlight or by dietary intake. Vitamin D status varies significantly in populations depending on geographical and socioeconomic factors. The NHANES data from 1988–1994 revealed that 42% of African-American women of childbearing age had 25-OH-D levels lower than 37.5nM, half the current optimal target level, compared with only 4% of white women (47). Vitamin D insufficiency, defined by 25-OH-D<75nM, is common among pregnant women, being more prevalent among African-American compared with Caucasian women (74–95 vs. 46–62%) (45).

Calcium

A cross-sectional study in Poland showed decreased serum concentrations of total calcium (2.15±0.07 vs. 2.25±0.11mmol/L, $p<0.001$) among women with preterm labor between 23 and 28weeks' gestation and women without preterm labor at the same gestational age (48). In this study, 15.1% of women with preterm labor who had low serum concentrations of calcium, phosphorous and magnesium experienced PTB, in contrast to 7% among those with adequate concentrations of these nutrients ($p=0.34$).

A recent meta-analysis of 12 trials (15 528 women) of prenatal calcium supplementation found a significant reduction in the risk of high blood pressure, pre-eclampsia and maternal death compared with placebo. There was a 19% reduction in the risk of PTB overall, but this was not significant (10 trials; RR 0.8, 95% CI 0.6–1.0), but a significant reduction in PTB for women at high risk of pre-eclampsia recruited from four small RCTs ($n=578$; RR 0.5, 95% CI 0.2–0.8) showed a possible difference for that condition (49). A high-quality RCT involving high-risk adolescent pregnancies in the USA showed that supplemental prenatal calcium (2g/day) could reduce spontaneous PTB in relation to placebo (6.4 vs. 17.9%, $p=0.01$) (50).

Calcium plays an important role in fetal growth and development, as well as in altering membrane permeability and smooth muscle excitability and contractility, which in turn can affect blood pressure, as well as uterine contractions (51). The finding that women <20years of age seem to benefit more from calcium supplementation during pregnancy may be related to an increased demand for calcium mediated by their own growth and development (51).

The median calcium intake of black women <25years of age is only slightly lower than that of white women. More marked racial differences in calcium intakes are notable for women ≥25years old, with the median intake of African-American women being approximately 70–80% of that for Caucasian women (52). The median intake of calcium for both black and white women <25years of age is well below the recommended daily intake (52). Nationally representative data for 1994–1996 demonstrate that for low-income women of childbearing age, the mean calcium intake for African-American women was 49.2% of the recommended intake, whereas the mean intake for Caucasians was 63.2% (53).

Magnesium

A cross-sectional Polish study showed decreased serum concentrations of magnesium (0.63±0.05 vs. 0.71±0.22mmol/L, $p<0.01$) among women with preterm labor between 23 and 28weeks' gestation and women without preterm labor at the same gestational age (48). In a pregnant Danish cohort of good socioeconomic status, dietary intake and serum levels of magnesium at 30weeks' gestation was not associated with PTB (54).

A systematic review of five trials involving 2 275 women conducted in developed countries (USA, Hungary and Austria) found that magnesium supplementation before 25weeks gestation is associated with a 27% reduction in the rate of PTB (RR 0.7, 95% CI 0.6–0.9) in comparison with placebo (55). However, there is the possibility of bias in these results because the exclusion of a large cluster randomized trial from Hungary that contributed 985 women rendered the relation between magnesium supplementation and mean gestational age non-significant.

Magnesium is a required cofactor for over 300 enzyme systems and is involved in energy metabolism, maintaining an adequate supply of nucleotides for nucleic acid synthesis and maintaining intracellular potassium to control membrane gradients. Magnesium also serves as a calcium channel blocker and is involved in muscle contractility (56).

The NHANES data from 1999–2000 demonstrated that dietary magnesium intake is substantially lower for African-American women compared with Caucasian women (median 177 vs. 237mg/day, $p<0.01$), and that magnesium intake was poor for the US population overall (57). Dietary magnesium intake is also noted to be lower for those of lower socioeconomic status (55).

Polyunsaturated fatty acids

A Danish cohort study showed an association between low fish consumption during pregnancy and risk of PTB (OR 3.6, 95% CI 1.2–11.2) (58), while another demonstrated an association between no fish consumption during the first and second trimester and PTB (OR 2.4, 95% CI 1.2–4.6) (59). A cohort study in Brittany, France, found that each additional monthly meal that included fish during pregnancy significantly increased gestational length by 0.02week (95% CI 0.002–0.035); however, no effect on the overall risk of PTB was observed (60). Yet another Danish cohort study found no association between the overall prenatal intake of ω-3 polyunsaturated fatty acid from fish and other sources and gestational age, birthweight or birth length (61).

A study comparing red blood cell long-chain ω-3 fatty acid to ω-6 polyunsaturated fatty acid (PUFA) ratios for Faroese (high fish intake) and Danish (comparatively low fish intake) women suggested that a 20% increase in the ω-3/ω-6 ratio was associated with a significant increase in pregnancy duration of 5.7days (95% CI 1.4–10.1days) among Danish women that was not seen for Faroese women (+0.7days, 95% CI-2.0–3.3days) (62). A case–control study in the USA involving 37 women with PTB (mean 34weeks) and 34 term control women found that the maternal percentage of total arachidonic acid (20:4-ω-6) in red blood cells and plasma was increased at the time of delivery in PTB vs. control women (3.8- and 1.6-fold, respectively, $p<0.05$) and both eicosapentaenoic acid (20:5-ω-3) and the ω-3/ω-6

fatty acid ratio were lower in PTB vs. control women (1.98±0.15 vs. 4.64±0.32, p<0.0001, and 0. 58±0.22, p<0.009, respectively) (63). Docosapentaenoic acid, a marker of ω-3 fatty acid deficiency, was also significantly higher in preterm maternal red blood cells (1.26±0.18 vs. 0.12± 0.07, p<0.0001) and amnion (1.27±0.19 vs. 0.58±0.13, p<0.001) compared with term control women (63).

A systematic review of marine oil and other prostaglandin precursor supplementation during pregnancy that included six RCTs involving 2 783 women (mostly of northern European descent) of varying degrees of risk found insufficient evidence to support the routine use of marine oil or other prostaglandin precursor supplementation during pregnancy. While this systematic review did not find a significant difference in PTB before 37weeks, women in the marine oil group did have a mean gestation that was 2.6days longer than women in the placebo group and a significantly reduced risk of PTB <34weeks (RR 0.7, 95% CI 0.5–0.9) (64). A separate systematic review restricted to four RCTs of long-chain PUFA supplementation involving women with high-risk pregnancies (defined variably in each study to include women with a prior or current pregnancy complicated by PTB, intrauterine growth restriction or pregnancy-induced hypertension), also found no overall reduction in PTB <37weeks, but a significant reduction in risk of PTB <34weeks (two RCTs, n=291, RR 0.4, 95% CI 0.2–0.8) (65). Another systematic review involving six RCTs of healthy (low-risk) pregnant women supplemented with ω-3 long-chain polyunsaturated fatty acids found no difference in the prevalence of PTB overall, yet a small but significant increase in length of gestation (+1.5days, 95% CI 0.4–2.8days) (66).

The proportions of different PUFAs in tissues of the reproductive tract reflect dietary consumption. In addition to contributing to the membrane phospholipid pool, PUFAs are related to cellular level inflammation; they have inflammatory actions in their own right and also regulate the production of inflammatory mediators, including pro-inflammatory cytokines and prostaglandins. Polyunsaturated fatty acids may influence the timing of delivery through alterations to prostaglandins or adrenal steroid synthesis (67).

Western diets are generally deficient in ω-3 PUFAs (found in fish, flax, sunflower and safflower oils, as well as in eggs and walnuts) and have excessive amounts of ω-6 PUFAs, found in palm and hydrogenated vegetable oils and in processed bakery foods, meat and dairy products. African-American adults have a lower ω-3 PUFA intake and higher ω-6 PUFA intake compared with Caucasians (68). A large cohort of young adults, 18–30years of age, showed that among women the total ω-3 fatty acid dietary intake was significantly lower for African-Americans compared with Caucasians (7.11 vs. 6.28kcal/1 000kcal, p<0.0001), while the total ω-6 fatty acid dietary intake (70.3 vs. 59.7kcal/1 000kcal, p<0.0001) and ratio of ω-6 to ω-3 fatty acid intake (10.3 vs. 9.8, p<0.01) were significantly higher (69).

Discussion

Existing data demonstrate that deficiencies of several nutrients and/or supplementation with particular nutrients affecting known pathophysiological pathways involved in parturition have varying levels of evidence of association with PTB and are of greater burden among

African-American compared with Caucasian women in the USA (Table 1). As PTB is a heterogeneous phenotype resulting from complex and interacting pathophysiological pathways, it is unlikely that any single cause will explain, or that any single ‘magic bullet’ will eliminate, racial disparities in PTB. However, strategies that improve the nutritional status of African-American women may be one means of addressing a portion of the racial disparity in PTB in the USA and elsewhere.

There are certainly limitations and knowledge gaps concerning existing studies that examined the potential role of nutrients in racial disparities in PTB. Presently, there are inadequate human studies investigating the potential role of specific nutrients, and their potential interactions with one another and with other risks for PTB, as contributors to PTB for African-American and Caucasian women in the USA. Likewise, there are inadequate high-quality trials examining the effect of specific nutrient supplementation on the risk of PTB for African-American and Caucasian women with varying socioeconomic status and prevalence of other known and potential risk factors for PTB.

Most of the existing observational studies exploring the role of particular nutrient deficiencies and interventional trials are limited by a focus upon the pregnancy, typically the middle trimester of pregnancy or later, while growing data suggest that the preconception period may be the more important period for determining and intervening to influence pregnancy outcomes (70). Furthermore, given the role that appropriate nutrition plays in growth and development, an approach that considers nutritional status across the life course (71) may be vital for a full understanding of the role of nutrients in contributing to racial disparities in birth outcomes.

Given current shortcomings in knowledge of the spectrum of risk factors and the prevalence of nutritional and other risks by race/ethnicity in the USA, we cannot accurately estimate the population attributable risk of PTB due to nutrient deficiencies at present. Further research will be important for determining the proportion of racial disparities in PTB that might be explained by nutrient deficiencies, the particular nutrients or nutrient combinations that offer the greatest potential for reducing the risk of PTB and the critical time period for intervention.

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Abbreviations

CI	confidence interval
NHANES	National Health and Nutrition Examination Survey
25-OH-D	25-hydroxy-vitamin D

OR	odds ratio
PTB	preterm birth
PUFA	polyunsaturated fatty acid
RCT	randomized controlled trial
RR	relative risk

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Table 1

Summary of studies of nutrient deficiencies or nutrient supplementation and preterm birth conducted in developed country settings.

Observational studies – nutrient deficiency and preterm birth	Interventional studies – nutrient supplementation and preterm birth	Prevalence of nutrient deficiency in the USA
Iron		
Iron-deficiency anemia early in pregnancy increased the risk of PTB relative to those who were iron replete (OR 2.7, 95% CI 1.2–6.2) in a US cohort (13).	Systematic review of eight trials of iron supplementation during pregnancy found a non-significant reduction in PTB among the iron-treated group (RR 0.8, 95% CI 0.7–1.1) (15).	The prevalence of iron deficiency is 20 vs. 10% (17) and of anemia during pregnancy 23 vs. 7% (18) for African-American compared with Caucasian women. Approximately 25% of pregnant African-American adolescents are iron deficient in the first trimester (19).
Folic acid		
In comparison with intake >400μg/day, there is an increased risk of PTB for those with low (RR 3.4, 95% CI 1.9–6.1) and intermediate intake of folate (RR 1.9, 95% CI 1.0–3.6), defined as ≤240 and 241–400μg/day, respectively (21). Low serum folate in the second trimester increased the risk of PTB (RR 1.8, 95% CI 1.3–2.5) in a US cohort (22).	Supplementation with folic acid for over one year prior to conception decreased the risk of PTB <28weeks (RR 0.3, 95% CI 0.1–0.9) and PTB 28–32weeks (RR 0.5, 95% CI 0.3–0.9) in a US cohort (23). Two RCTs in France suggest that supplementation lengthens gestation (25,26), whereas earlier RCTs (with limited information about study design) do not (27–29).	Approximately 5% of African-American women achieve 400μg folic acid per day from food and supplement sources compared with 40% of Caucasian women (35).
Zinc		
Low dietary zinc early in pregnancy increased the risk of PTB (OR 3.5, 95% CI 1.04–11.5) among a cohort of low-income urban adolescents, particularly if also iron deficient (OR 5.4, 95% CI 1.6–18.8) (37).	Systematic review of 13 RCTs of prenatal zinc supplementation found a 14% reduction in risk of PTB (RR 0.84, 95% CI 0.76–0.98) (39).	Black maternal race and low socioeconomic status are among the strongest predictors of plasma zinc concentration among pregnant women (41).
Vitamin D		
No studies to date relate vitamin D status to PTB. Vitamin D deficiency increased the odds of bacterial vaginosis (OR 1.7, 95% CI 1.0–2.7) compared with those who were vitamin D replete in a US case–control study (45).	RCT in USA comparing supplementation with 4 000 vs. 400IU/day of vitamin D from 12weeks' gestation found 50% reduction in composite outcome of PTB and infection (RR 0.5, 95% CI 0.3–0.9), controlling for race (42).	Vitamin D insufficiency (25-OH-D<75nM) present among 79–95% of pregnant African-American and 46–62% of Caucasian women (45). For women of reproductive age, 42% of African-Americans and 4% of Caucasians had 25-OH-D<37.5nM (47).
Calcium		
Decreased serum calcium among Polish women with vs. without preterm labor (2.15±0.07 vs. 2.25±0.11mmol/L, p<0.001) between 23 and 28weeks' gestation (48). Women with preterm labor and low serum calcium, phosphorus and magnesium had 15.1% risk of PTB vs. 7% for those with adequate nutrients (p=0.34) (48).	Meta-analysis of 12 trials of prenatal calcium supplementation found a non-significant reduction in risk of PTB overall (10 trials; RR 0.8, 95% CI 0.6–1.03) and a significant reduction for women at high risk of pre-eclampsia (n=578; RR 0.5, 95% CI 0.2–0.8) (49). An RCT among high-risk US adolescents found significant reduction in PTB among those supplemented with 2g/day (6.4 vs. 17.9%, p=0.01) (50).	Median calcium intake for African-American women ≥25years of age is 70–80% of that of Caucasian women, with minimal difference for those <25years of age (52). For low-income women of reproductive age, the mean calcium intake for African-Americans vs. Caucasians is 49 and 63%, respectively, of the recommended intake (53).
Magnesium		
Decreased serum magnesium among Polish women with vs. without preterm labor (0.63±0.05 vs. 0.71±0.22mmol/L, p<0.01) between 23 and 28weeks' gestation (48). No association between dietary and serum magnesium and PTB in a Danish cohort (54).	Systematic review of five trials estimates that prenatal magnesium supplementation before 25weeks' gestation is associated with a 27% reduction in PTB (RR 0.73, 95% CI 0.57–0.94) (55).	Dietary magnesium significantly lower for American-American vs. Caucasian women (median 177 vs. 237mg/day, p<0.01) (57) and substantially lower among those of lower socioeconomic status (55).
Polyunsaturated fatty acids		
Increased risk of PTB among those with low prenatal fish consumption (OR 3.6, 95% CI 1.2–11.2) (58) and who never consumed fish (OR	Systematic review of six RCTs of prenatal marine oil supplementation found a significant reduction in PTB <34weeks (RR 0.7, 95% CI	For women 18–30years, total dietary intake of ω-3 fatty acids was significantly lower for African-

Observational studies – nutrient deficiency and preterm birth	Interventional studies – nutrient supplementation and preterm birth	Prevalence of nutrient deficiency in the USA
2.4, 95% CI 1.2–4.6) in Danish cohorts (59), while another study found no relation between total ω-3 fatty acid intake and PTB (61). Maternal percentages of total red cell and plasma arachidonic acid were increased among women with PTB vs. control women (3.8- and 1.6-fold, respectively, $p<0.05$), whereas eicosapentaenoic acid and ω-3/ω-6 ratios were decreased in a US case–control study (63).	0.5–0.9) and a non-significant reduction of PTB <37weeks (64). A systematic review of high-risk women found a non-significant reduction in risk of PTB <34weeks (RR 0.4, 95% CI 0.2–0.8) (65). A systematic review of low-risk women found a non-significant reduction in risk of PTB but an increase in gestational age (+1.5days, 95% CI 0.4–2.8days) among the supplemented group (66).	Americans vs. Caucasians (7.11 vs. 6.28kcal/1 000kcal, $p<0.0001$), while total intake of ω-6 fatty acids (70.3 vs. 59.7kcal/1 000kcal, $p<0.0001$) and ω-6/ω-3 fatty acids ratio (10.3 vs. 9.8, $p<0.01$) were significantly higher (69).

Abbreviations: CI, confidence interval; 25-OH-D, 25-hydroxy-vitamin D; OR, odds ratio; PTB, preterm birth; RCT, randomized controlled trial; RR, relative risk.