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Iron, iodine and vitamin D deficiencies during pregnancy: epidemiology, risk factors and developmental impacts

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Micronutrient deficiency persists throughout the world, and although the burden is higher in low-resource settings, it is also prevalent in wealthy countries, a phenomenon termed 'hidden hunger'. Due to their high requirements for vitamins and minerals relative to their energy intake, young women and children are particularly vulnerable to hidden hunger. As they share several risk factors and impact on overlapping outcomes, we consider how deficiency of iron, iodine and vitamin D can have profound impacts on perinatal health and infant development. We review the epidemiology of these micronutrient deficiencies during pregnancy, including social, environmental and dietary risk factors. We identify the main challenges in defining nutritional status of these nutrients using validated diagnostic criteria linked with meaningful clinical outcomes. Public health strategies are urgently required to improve the overall health and nutritional status of women of reproductive age. Obesity prevention and early detection of malnutrition with standardised screening methods would detect pregnant women at increased risk of iron deficiency. Development of sensitive, individual biomarkers of iodine status is required to protect maternal health and fetal/infant brain development. Risk assessments of vitamin D requirements during pregnancy need to be revisited from the perspective of fetal and neonatal requirements. International consensus on standardised approaches to micronutrient assessment, analysis and reporting as well as sensitive, clinically validated infant and child neuro-behavioural outcomes will enable progression of useful observational and intervention studies.

Iron: Iodine: Vitamin D: Pregnancy: Malnutrition: Deficiency: Hidden hunger

Globally, it is estimated that one in four people (~2 billion) lack the essential micronutrients to grow, develop and maintain health and function[1]. Micronutrients have fundamental roles in fetal weight gain, brain development, immune regulation and musculoskeletal growth and are central modulators of multi-system and organ development[2]. Although micronutrient deficiencies are widespread in low-middle income countries, they are also prevalent in high-resource settings; a phenomenon termed 'hidden hunger'[3]. Due to their high requirements for vitamins and minerals, young women and children are particularly vulnerable to micronutrient malnutrition[1]. Awareness of the importance of a woman's health and nutritional status prior to pregnancy

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; UI/Creat, iodine:creatinine ratio; UIC, urinary iodine concentration.
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Table 1. Dietary reference values for iron, iodine and vitamin D in pregnant and non-pregnant, non-lactating women

	SACN	EFSA	IOM	WHO
Iron				
Pregnant women	14·8 mg	16 mg	27 mg	–
Non-pregnant, non-lactating women	14·8 mg	16 mg	18 mg	19·6 mg
Iodine				
Pregnant women	140 μg	200 μg*	220 μg	250 μg
Non-pregnant, non-lactating women	140 μg	150 μg*	150 μg	150 μg
Vitamin D				
Pregnant women	10 μg	15 μg*	15 μg	5 μg
Non-pregnant, non-lactating women	10 μg	15 μg*	15 μg	5 μg

Dietary reference values presented are RDA/RNI/PRI values.
Scientific Advisory Committee for Nutrition (SACN)[17,152,162]; European Food Safety Authority (EFSA)[18,154,163]; Institutes of Medicine (IOM) [21,153]; World Health Organisation (WHO)[164–166].
*Adequate intake.

is low and there is considerable scope to improve preconception health at a population level[4]. However, progress in resolving the burden of micronutrient malnutrition is slow, and as nutrient deficiencies are underlying factors in the development of both acute and chronic illnesses, failure to address vitamin and mineral deficiencies obstructs achievement of global development goals for health, education and social equity[5].

The present paper focuses on three nutrients that have been identified as concerning during pregnancy: iron, iodine and vitamin D. As they share several risk factors and impact in different ways on overlapping outcomes, particularly neurological development, it is appropriate to consider how deficiency of these nutrients can have profound impacts on pregnancy outcome and fetal and infant development, health and life chances. Often discussed, micronutrient deficiency among young women prior to and during pregnancy is essentially neglected in terms of programmatic research support, policy development and implementation of measures to prevent low intakes and status.

The aim of the present paper, arising from a presentation by the first author at the Nutrition Society Winter Meeting of 2020, is to review evidence for malnutrition during pregnancy of iron, iodine and vitamin D, including non-nutritional and nutritional risk factors and health outcomes associated with deficiency. Emerging data on neurological development and challenges in defining nutritional status, linked to validated health outcomes, are discussed. The present paper is not a systematic review, but an evaluation of available evidence for the purposes of public health nutrition and clinical practice and to identify knowledge gaps.

Iron

Iron deficiency is the most common micronutrient deficiency in the world and pregnant women are vulnerable[6]. Almost 1000 mg of iron must be acquired during pregnancy to support an increased maternal plasma and blood volume, the increased oxygen and iron demands of the fetus and the iron requirements of the placenta itself[7]. Worldwide, up to 38 % of pregnant women have anaemia, with an even higher prevalence in low-resource settings[8]. In Europe, iron deficiency is reported in 28–85 % of pregnancies, particularly in unsupplemented women, and up to a third have iron deficiency anaemia[9].

Risk factors for iron deficiency during pregnancy

Dietary risk factors. To avoid iron deficiency while pregnant, women must enter pregnancy with sufficiently large iron stores and consume a diet abundant in bioavailable iron[10]. Unfortunately, this is not always achievable. In Europe, median serum ferritin concentrations of women of reproductive age range from 26 to 38 μg/l, suggesting that 40–50 % have depleted iron stores (indicated by ferritin ≤30 μg/l, below which no stainable bone marrow haemosiderin iron is observed) before becoming pregnant[9]. To further compound this, inadequate iron intakes and poor compliance with dietary guidelines are widely reported amongst pregnant women worldwide[11–13]; recent European data suggest that 60–100 % of women during pregnancy had iron intakes below the recommended intake[14]. Pregnant women with poorly managed vegetarian and vegan diets[15] and pregnant adolescents[16] are at particular risk.

The dietary reference values for pregnant and non-pregnant, non-lactating women are presented in Table 1, with significant variability between agencies. Recommended intakes are the same for pregnant women as for non-pregnant, non-lactating women from the UK's Scientific Advisory Committee on Nutrition[17] and European Food Safety Authority[18], based on evidence that iron absorption, particularly of non-haem iron, becomes more efficient during pregnancy[19,20]. In contrast, the US Institute of Medicine recommend higher intakes of 27 mg/d, to be met in part by supplementation, on the basis that the increased requirements of pregnancy cannot be met by diet or the body iron stores of the mother[21].

Non-dietary risk factors. Several common pregnancy-related conditions and maternal lifestyle factors can affect maternal-fetal iron supply *in utero*, resulting in an increased risk of iron deficiency in the mother, her fetus or most likely both, even if dietary supply is

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adequate. Relative to first-time and singleton pregnancies, women who have had several pregnancies or expecting more than one baby are at increased risk of iron deficiency during pregnancy[22,23]. Iron deficiency can also occur in the mother and fetus as a result of conditions that decrease fetal iron delivery and/or increase fetal iron demand beyond the transport capacity of the placenta[24]. Gestational diabetes mellitus, hypertension and maternal smoking all induce intrauterine fetal hypoxia, limiting the oxygen supply to the fetus, resulting in increased erythropoiesis, exceeding the system's capacity and increasing the risk of iron deficiency[25–27]. Worryingly, these conditions, particularly gestational diabetes mellitus, have been shown to have lasting consequences for the newborn infant and their development[28,29].

Obesity in women who enter pregnancy is associated with adverse health consequences for both mother and infant[30]. However, until recently, the impact of maternal obesity on maternal and fetal iron status has been widely unacknowledged. Poorer iron status and an increased risk of iron deficiency have been reported in pregnant women who were obese prior to or during pregnancy[31–34]. Although obese women are likely to have different dietary profiles to non-obese women, maternal obesity is thought to result in iron deficiency in both the mother and her infant primarily through the action of the iron regulatory hormone, hepcidin. Hepcidin controls the levels of circulating iron in the body through its influence on intestinal iron absorption and iron sequestration[7]. In healthy pregnancies, hepcidin concentrations are reduced in the second and third trimesters to increase the supply of iron into circulation to meet requirements. In pregnancies complicated by obesity, hepcidin may be overexpressed as a downstream effect of the low-grade, chronic inflammation associated with obesity, inhibiting intestinal iron absorption and the release of iron from body stores[35]. Elevated hepcidin and inflammatory marker concentrations have been observed in a number of studies in pregnant women[31,32,35,36], although further consideration is required on the potential influence of hepcidin on iron requirements during pregnancy, particularly in complicated pregnancies[37].

Diagnostic criteria for iron deficiency during pregnancy

Various biomarkers are available to characterise the different stages of iron status, moving from iron depletion to deficiency to iron deficiency anaemia. Hb is the most frequently used of these, due in part to the wide availability of point-of-care tests. However, Hb only assesses anaemia, the last stage of iron depletion. This is a concern, as all organs of the body become iron deficient before erythrocyte indicators are altered[28]. Iron supply to the liver, heart, skeletal muscle and perhaps most crucially, the brain, is compromised prior to a reduction in Hb concentrations. Ideally, assessment of iron status amongst pregnant women should be based on a battery of biomarkers that assess iron storage, transport and functional markers. At the very least, assessment of iron status should incorporate both serum ferritin and Hb[38]. Although much debate exists as to the appropriate thresholds to apply to these biomarkers in pregnant women[39,40], the WHO currently recommends a threshold of <110 g/l for Hb and <15 μg/l for ferritin (accounting for inflammation as ferritin is an acute phase reactant). Although further research is needed to ensure that these thresholds are related to meaningful clinical outcomes, beyond haematological outcomes[41], application of these thresholds for both markers consistently across regions would be a start to defining the scope of the problem.

Health impacts of iron deficiency during pregnancy

Maternal and pregnancy-related. Once the oxygen carrying capacity of the blood becomes diminished, pregnant women may experience the common anaemia symptoms of paleness, weakness, fatigue and general lethargy[10]. However, the consequences of iron deficiency, particularly its end stage of anaemia, can be much more severe, resulting in adverse pregnancy and birth outcomes. Low Hb in the first trimester has been associated with an increased risk of preterm birth and low birth weight[42–44]. Such associations appear to be much weaker in the second or third trimester[44], but a threshold effect exists; moderate to severe, but not mild anaemia, was associated with an increased risk of small-for-gestational age in a meta-analysis by Kozuki and colleagues[45]. Far fewer studies have explored associations with indices of iron deficiency, with conflicting evidence to date from those that have, particularly given the confounding impact of inflammation on ferritin[46,47]. Moreover, the U-shaped curve of risk associated with iron status during pregnancy must also be considered, as elevated iron status indices, including ferritin and Hb, particularly in the third trimester, have been associated with an increased risk of some adverse birth outcomes[42,44,48]. Excess iron intakes or elevated iron status during pregnancy is thought to increase blood viscosity, impair placental blood flow and contribute to oxidative stress, further emphasising the caution required when prescribing iron supplementation to pregnant women[44].

Fetal and infant development. Iron deficiency during pregnancy presents a triple threat for fetal development, but most critically, for fetal brain development. Iron is essential for the developing brain, due to its key role in the fundamental neuronal processes of neurotransmitter and energy metabolism and myelination, summarised in Table 2[10,49]. An inadequate supply of iron, particularly during sensitive periods of critical brain development, can therefore disrupt these fundamental processes, with lasting consequences.

Low maternal iron intake and status during pregnancy can present an immediate threat to fetal brain development. Low maternal iron intake during the third trimester resulted in altered neonatal brain structure, most notably in cortical grey matter[50] and Schmidt and colleagues reported an inverse association between maternal intake and risk of autism spectrum disorders in early

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Table 2. Iron and fundamental neuronal processes in the developing brain

Neurotransmitter metabolism	Main direct effect of iron is on the synthesis of the monoamine neurotransmitters: dopamine, serotonin and norepinephrine. Monoamine synthesis begins in mid-gestation, until about 3 years of age. Altered monoamine metabolism results in disturbed sleep cycles, motor control, memory and social-emotional development.
Energy metabolism	Iron deficiency affects neuronal energy metabolic balance, especially in the hippocampus, the region responsible for recognition memory processing and other cognitive functions. Disrupted energy metabolism results in abnormal branching of dendrites and synapse formation, leading to long-lasting morphological changes.
Myelination	Iron deficiency, particularly in the late fetal and early childhood period, results in hypomyelination, a decrease in the production and quality of myelin, the fatty acid sheath surrounding neurons. Hypomyelination impacts all brain regions, but disturbances in the auditory and visual systems of infants have been most closely linked to impaired myelination.

Modified from McCarthy and Kiely[67].

childhood[51]. In a recent systematic review, Janbek *et al.* concluded that there was some evidence that maternal iron status during pregnancy may be associated with offspring behaviour, cognition and academic achievement, but not motor development[52]. However, this research field has significant limitations due to huge variability in study design, neurological assessments performed and the timing of both the exposure and outcome assessments. The most crucial limitation is the reliance of most studies on Hb to assess maternal iron status. A large Spanish birth cohort recently reported higher scores in working memory and executive function at 7 years in children whose mothers had serum ferritin concentrations >12 µg/l in the first trimester[53].

Fetal iron accretion is compromised in mothers with moderate to severe iron deficiency. Maternal ferritin concentrations of 12–13·6 µg/l were identified as important thresholds below which fetal iron accretion is significantly reduced[54,55]. Maternal iron deficiency, in addition to pregnancy complications including fetal growth restriction and prematurity, delivery by Caesarean section and the maternal and pregnancy-related factors we have already discussed, all increase the risk of neonatal iron deficiency[24,56]. Neonatal iron deficiency itself is associated with abnormalities in the newborn auditory system[57,58], poorer recognition memory at ~15 d old[29] and poorer language ability, fine mother skills and tractability at 5 years of age[59]. More recently, in our generally healthy, low-risk maternal–infant cohort in Ireland, we identified lasting behavioural consequences of neonatal iron deficiency in children born to mothers with obesity or delivered by Caesarean section[60]. This is especially concerning as early cognitive and social-emotional development are strong determinants of future educational attainment, mental health, career and earning potential and overall quality of life[61,62]. As a final threat, infants born iron deficient or with reduced iron stores are also at increased risk of continued iron deficiency, as low iron stores at birth track through infancy and early childhood[63,64]. Particularly during the period of critical brain development from 6 to 24 months of age, iron deficiency is associated with irreversible consequences for cognition, motor development and behaviour[65].

Conclusion: iron

Inadequate iron supply *in utero*, due to iron malnutrition, inflammation, obesity or an underlying metabolic disease, presents a massive threat of long-term neurological consequences and represents a real cost and burden to individuals and society. Public health strategies are urgently required to improve the overall health and nutritional status of women of reproductive age, with the rising prevalence of overweight and obesity a major concern amongst this population group. Iron sufficiency during pregnancy is essential to ensure the health of the mother, improve pregnancy outcomes and protect fetal and infant brain development[66]. A dual approach encompassing strategies targeting prevention and early detection is required[67]. An enhanced focus on the most effective supplementation strategies in pregnant women is also needed, with further consideration of dosing, forms of iron used and side effects. Finally, the development of screening strategies to enable early detection of pregnant women at increased risk of iron deficiency should be prioritised, with the dual purpose of protecting the health of the mother and fetal/infant brain development.

Iodine

Iodine is an essential trace element required for thyroid hormone synthesis. Critical to the regulation of BMR and macronutrient metabolism, thyroid hormones are also fundamental to normal development of the central nervous system via their regulation of cell migration, differentiation and myelination[68]. Iodine deficiency disrupts the metabolism of thyroid hormones; therefore, adequate iodine status prior to and during pregnancy is critical. During pregnancy, the requirement for iodine increases by 50 %[69]. This is to enable increased maternal thyroxine production to ensure adequate fetal supply until the fetal thyroid can concentrate iodine and produce thyroid hormones, and to supply the placental transfer of iodine to support fetal thyroid hormone production. In addition, the increased rate of glomerular filtration during pregnancy increases renal clearance of iodine.

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Determinants of iodine status

Diet and fortification. Recognition of country-specific habitual food consumption and iodised salt coverage is essential in considering dietary risk factors for low iodine status. Consumption of iodised salt is the most influential dietary determinant of iodine intake and status. Recent global estimates from UNICEF show that 88 % of households consume iodised salt[70]. The highest coverage was reported for East Asia and the Pacific and South Asia (92 and 89 %, respectively) whereas in Western and Central Africa, 76 % of individuals had access to iodised salt. Although coverage has increased significantly from 70 % reported in 2012[71], it is estimated that 29 % of countries with data on household penetration met the international goal of at least 90 % of households consuming adequately iodised salt, whereas 30 % of countries had coverage rates of <50 %. In Europe, 27 % of households have iodised salt[72], but coverage can be as low as 5 %[73].

In many countries, particularly in those without a salt iodisation policy, milk and dairy products make significant contributions to iodine intake and status in women of childbearing age[74–76] and in pregnant women[76–80]. However, a shift in consumption patterns away from dairy towards plant-based milks, many of which are not fortified with iodine, may reduce iodine intake and increase the risk of iodine deficiency[81]. Consumption of fish and shellfish has been associated with iodine status in UK and Spanish pregnant populations[78], but consumption of seafood is typically low among women of childbearing age.

Maternal factors. Data on the relationship between maternal BMI and iodine status are mixed and subject to confounding. In a sample of Thai pregnant women, no differences in urinary iodine concentration (UIC) were observed between normal weight and overweight women; however, in this group, a BMI ≥23 kg/m^2 resulted in 3·6-fold higher odds of low maternal-free thyroxine in the first trimester[82], which may be reflective of the relationship between adiposity and hypothyroxinaemia, but not necessarily to iodine-related thyroid dysfunction. In an analysis of three European cohorts, BMI was negatively associated with a urinary iodine:creatinine ratio (UI/Creat), but not with UIC[78], which warrants further analysis as BMI is often but not always associated with adiposity. The setting is also an important factor to consider in interpreting the relationship between body weight and iodine status. In a study of Iranian women by Gargari *et al.*[83], the odds of UIC <150 µg/l decreased by 13 % for every 1 kg increase in weight during pregnancy, which the authors posit was a proxy indicator of dietary quality.

Maternal age and social factors. UIC was negatively associated with age in a sample of non-pregnant women in the National Health and Nutrition Examination Survey (NHANES (2001/2006)); however, no association of UIC with age was observed for pregnant women in the same study[76]. Dineva *et al.*[78] reported that there was a positive association of maternal age with UI/Creat; however, the relationship may be confounded by the association of maternal age with dietary patterns and iodine-supplement use. In the study by Gargari *et al.*[83], other factors such as whether the pregnancy was planned, the time since the most recent pregnancy, maternal education level and maternal iodine supplement use prior-to and during pregnancy were associated with better iodine status.

Assessment of iodine intake and status

Dietary reference values for iodine intake are presented in Table 1. As with all dietary assessments, the reliability of an estimate of nutrient intake is largely dependent on the quality of the food composition data[84]. Iodine food data represent a challenge due to incomplete data and natural variability in iodine content of food, which varies with season and as a result of agricultural practices. Furthermore, the iodine content of soil varies considerably across regions[85] due to geological factors[86]. Currently, food composition datasets do not provide any information on the variability of iodine content within foods. Utilisation of a probabilistic modelling approach to account for variability in iodine food composition may overcome this challenge and improve the validity and reliability of iodine intake assessments.

UIC directly reflects dietary iodine intake and is the most common indicator used worldwide to assess population iodine status. The population median UIC is assessed against the reference range for adequacy for pregnant women of 150–249 µg/l[87]. However, one of the major challenges of the iodine field is the absence of an individual biomarker of iodine status. Although it is useful at a population level, UIC is heavily influenced by day-to-day variation in water and protein intakes, making it inappropriate for assessing individual iodine status[86]. To identify mild-to-moderate iodine deficiency, biomarkers of individual iodine status are urgently required. In recent years, thyroid hormones have been proposed as functional markers of iodine status. However, although triiodothyronine, thyroxine and thyroid-stimulating hormone are thyroid functional measures, tight homoeostatic regulation makes them unsuitable as markers of iodine status, as values can remain in the normal reference range in individuals with low iodine intake[88,89]. Thyroglobulin, a thyroid-derived protein that reflects thyroid volume in both iodine-deficient and iodine-sufficient population groups, has shown promise as a functional biomarker of iodine status[90] and further assessment of its usefulness is ongoing.

Epidemiology of iodine deficiency

Iodine deficiency disorders have been described as the leading cause of preventable impaired mental function worldwide[91], estimated to affect 1·88 billion people[92]. In a global analysis of UIC in 2011, one in three school-aged children and 28·5 % of the general population had inadequate iodine intakes[93]. Significant regional differences in prevalence estimates were reported, indicating that iodine deficiency is primarily an issue of geography

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because of variability in iodine content of soil and water as well as country- and region-specific iodisation policies and dietary patterns. Inadequate iodine intakes were estimated in 44 % of the WHO Europe region population, where iodised salt penetration is low[93]. In 2017, pregnant women in thirty-nine of seventy-two countries with UIC data had suboptimal iodine intake where median UIC was <150 µg/l[94]. Of the forty countries with UIC data in both school-aged children and pregnant women, twenty-nine countries reported deficiency in the women and sufficiency in the children, highlighting the limitation of using school-aged children UIC as a proxy of iodine status in other population groups, particularly in settings where child dairy intakes are high[95].

Health and developmental impacts of maternal iodine deficiency

Maternal iodine deficiency can have important clinical consequences for the mother and her offspring, the severity of which are influenced by the timing and extent of the deficiency[96]. Prior to conception, severe iodine deficiency has been associated with reduced fecundity in women of childbearing age[97]. During pregnancy, severe iodine deficiency may result in an increased risk of miscarriage and stillbirth[98]. Neonatal consequences of severe maternal iodine deficiency are profound and most severely can manifest as cretinism, characterised by severe mental impairment with squint, deaf mutism and motor defects. Severe maternal iodine deficiency can also result in neonatal hypothyroidism, impaired growth, goitre and infant mortality[99].

The adverse effects of mild-to-moderate iodine deficiency are less clear. Maternal iodine status has been associated with child neurological outcomes in some[100–105], but not all observational studies[106–108]. Levie and colleagues[109] conducted a recent meta-analysis of individual participant data in three large European birth cohorts (*n* 6180)[110–112]. They reported a curvilinear relationship of UI/Creat with lower verbal but not non-verbal IQ scores. Gestational age at urine sampling was identified as a significant effect modifier of the association of UI/Creat with verbal IQ scores. In stratified analyses, UI/Creat in the first 12 weeks of pregnancy was associated with an overall effect of 5 IQ points; between 12–14 weeks of gestation, UI/Creat showed a linear association with verbal IQ, with an overall effect of 3 IQ points and no association was observed after 14 weeks of gestation. Taken together, these data signpost a critical period for iodine-related (thyroid hormone-mediated) neurological development early in the first trimester. However, a recent systematic literature review and meta-analysis of the effects of iodine supplementation on thyroid function and child outcomes has shown that there is insufficient good-quality evidence to support recommendations for iodine supplementation in pregnancy in the areas of mild-to-moderate deficiency[113]. The authors suggest that the inconsistencies in the evidence may be attributable to maternal iodine status prior to pregnancy or on study entry, the dose and form of iodine supplement, the timing of supplementation and the sensitivity of the developmental tests used.

Conclusion: iodine

There is mounting evidence that low to zero consumption of iodised salt, coupled with a shift away from dairy consumption as well as low seafood intakes among young women is contributing to low intakes of iodine. However, the nature and extent of the impact of this deficit on perinatal and child outcomes is unclear. If we are to clarify the nature of the relationship between maternal iodine status and offspring development and develop point-of-care screening to support timely intervention, we must prioritise the development of valid biomarkers of individual iodine status. Investment in food composition data and global co-operation to develop standardised approaches to using composition data with variability inherent in the estimates of nutrient exposure are also required. Well-designed and well-timed observational studies and intervention studies accounting for maternal iodine status in early gestation, or prior to pregnancy, with sensitive, clinically validated infant and child neuro-behavioural outcomes are urgently required.

Vitamin D

The classical role of vitamin D in maintaining bone health is well-described and much attention in the vitamin D field has shifted towards understanding its role in non-skeletal health outcomes, particularly in relation to immune function, non-communicable diseases and fetal and infant development[114]. During early pregnancy, vitamin D metabolism changes; vitamin D binding protein concentrations increase and increases in 1-α-hydroxylase activity in the maternal kidney, placenta and decidua[115] lead to circulating 1,25-dihydroxyvitamin D concentrations that are –two to three times higher than usual by 12 weeks of gestation, with relatively stable serum 25-hydroxyvitamin D (25(OH)D)[116]. These metabolic shifts appear to be unrelated to calcium metabolism and are not maintained during lactation. There are compelling data to support the possibility that 1,25-dihydroxyvitamin D, a potent immune modulator, is necessary for successful pregnancy implantation by adapting the immune response, creating an anti-inflammatory milieu and enabling fetal growth[116,117]. There is plenty of evidence that 25(OH)D crosses the placenta and infants are born with circulating 25(OH)D concentrations reflective of maternal status, at about 60–80 % of maternal values collected at delivery[118,119].

Epidemiology of vitamin D deficiency

The problem of endemic low vitamin D status in many parts of the world is multifactorial. Low sunshine availability due to latitude, weather, air pollution, skin exposure or clothing practices, or a reduced ability to synthesise cholecalciferol from UVB due to skin colour, age or genetics[120], mean that large sectors of the global population rely on vitamin D in the food supply to

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maintain adequate vitamin D status. Naturally occurring sources of vitamin D, such as oily fish, are consumed irregularly and in low quantities, and global food fortification policies vary[121], contributing to low habitual vitamin D intakes among many populations[122]. Supplementation recommendations rely on individual compliance for their effectiveness and uptake is highly variable, particularly in low- and middle-income settings[123]. Low vitamin D status, denoted in the present paper by a circulating 25(OH)D concentration below 50 nmol/l and vitamin D deficiency, designated as 25 (OH)D <25/30 nmol/l, can also arise as a consequence of underlying health issues, frailty, inflammation, adiposity or smoking[120].

Vitamin D deficiency and low vitamin D status among pregnant women. In a recent systematic review, Mogire *et al.*[124] reported the prevalence of serum 25(OH)D <75, 50 and 30 nmol/l across Africa. Among 133 studies including 21 591 participants from twenty-three African countries, the prevalence of 25(OH)D <50 nmol/l was 34·4 and 18·5 % were <30 nmol/l. Countries in the north of Africa and urban South Africans were most at risk, particularly women and newborn infants. Three studies of pregnant women (in Ethiopia, South Africa and Tunisia) with a total sample of 408 reported that 53 % had a serum 25(OH)D <30 nmol/l and among ten studies with 975 participants, 44 % were below 50 nmol/l. This high prevalence of deficiency and low vitamin D status among many women in Africa is concerning, particularly considering the low calcium intakes in many regions across the continent[125,126], which places children at high risk of nutritional rickets[127].

The first internationally standardised European 25(OH)D dataset, directly comparable to data from the USA and Canada, was reported in 2016[128]. The overall prevalence of 25(OH)D <30 nmol/l was 13 %, about twice that of the USA (5·9 %)[129] and Canada (7·4 %)[130], but persons of ethnic minority were at much higher risk than their white counterparts (36–60 % of Black Asian and Minority Ethnic individuals in the UK and 65 % of South Asian participants in Norway). Among eighty-three low- and middle-income countries, only twenty-nine had population-based assessments of 25(OH)D[131]. Afghanistan, Pakistan, India, Tunisia, Syria, the West Bank and Gaza and Mongolia were classified as 'hot spots' for very low vitamin D status (<25–30 nmol/l) among women, pregnant women or infants on the basis of having a prevalence >20 %. Largely attributed to clothing practices, it has been noted that women and girls in low income and middle eastern countries in particular have lower 25(OH)D than their male counterparts[132,133]. Conclusions and strategies to address the problem are limited by the quality of the available evidence in many countries and the under-representation of minority groups in clinical research undertaken in high-income settings[134].

Palacios and Gonzalez[135] described a high prevalence (>20 %) of 25(OH)D <30 nmol/l among pregnant women and infants in many countries, including South Asia and the Middle East. Up to 60 % of women in India and 86 % of infants in Iran had 25(OH)D <30 nmol/l. Saraf and colleagues[136] estimated the global prevalence of 25(OH)D concentrations <50 nmol/l at 54 % among pregnant women and 75 % among newborn infants, with almost one in five pregnant women and one in three newborns below 25 nmol/l. Studies among pregnant women from ethnic minorities in Wales[137], the Netherlands[138,139] and Sweden[140] as well as white women in the Netherlands[139], Scotland[141] and Sweden[140] consistently report a high prevalence of vitamin D deficiency. Using gold standard 25(OH)D analysis of almost 1800 pregnant women in Ireland, with data comparable to non-pregnant individuals[128–130], we reported a prevalence of 17 % with 25(OH)D <30 nmol/l at 15 weeks of gestation; this was 49 % among women of ethnic minority[142]. Among the infants of this cohort, 46 % of umbilical cord sera had a 25(OH)D <30 nmol/l; this was 73 % among infants born to women of ethnic minority[143]. Overall, these prevalence estimates elevate vitamin D deficiency among mothers and babies to the status of a serious public health problem that requires urgent action.

Implications for perinatal outcomes and fetal/infant development

Increasing mechanistic evidence that vitamin D has a role in the progression of a healthy pregnancy supports a biologically plausible hypothesis that vitamin D deficiency may, in part, contribute to adverse perinatal outcomes resulting from growth restriction, hypertension or pre-eclampsia[118,144]. Neurological development is a potential consequence of vitamin D deficiency in early life. Eyles and colleagues have mapped the presence of the vitamin D receptor and 1-α-hydroxylases throughout brain tissues and have developed *in vitro* and animal models that describe the many ways in which maternal and offspring vitamin D deficiency exerts detrimental effects on behaviour[145]. Vitamin D metabolites have also been shown to cross the blood–brain barrier[146] and it is also worth noting that growth restriction itself, also associated with vitamin D deficiency[142] adversely impacts neurological development, particularly in small and thin for gestational age babies[147].

We did not find any association with maternal or cord 25(OH)D and cognitive or behavioural outcomes at 5 years in a well-characterised low-risk prospective mother–infant cohort[148]. Our analysis of the existing literature at the time showed conflicting signals, with significant heterogeneity in study design, including the timing and methods for exposure and outcome assessments, statistical approaches, variable adjustment for known confounders and cut-offs for 25(OH)D concentrations[148]. Mutua and colleagues'[149] systematic review of vitamin D and neuro-behavioural outcomes in children reached a similar conclusion; following analysis of thirty-two studies among >31 000 participants, the authors recommended standardised cut-offs for assessing vitamin D deficiency, as well as well-validated methods of assessing neuro-behavioural outcomes to allow international harmonisation and comparison of data as well as progression of the field into large well-controlled intervention studies.

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Vitamin D requirements and dietary recommendations

Several systematic reviews of the role of vitamin D supplementation during pregnancy have been published lately[150,151] but there is no consensus as to whether vitamin D requirements are greater during pregnancy than in non-pregnant women and whether supplementation should be recommended. Current dietary requirements for vitamin D were established on the basis of skeletal health outcomes, and most agencies have proposed the same adequacy thresholds for 25(OH)D and dietary recommendations for vitamin D for pregnant and lactating women as non-pregnant adults[152–154], summarised in Kiely *et al.*[155] (Table 1).

The question remains therefore: on what basis should vitamin D requirements and dietary recommendations during pregnancy be targeted? Fetal and neonatal circulating 25(OH)D concentrations are dependent on maternal vitamin D status but dietary recommendations do not consider the vitamin D requirement of the developing fetus or newborn infant and assume immediate availability of an adequate vitamin D supply from early life to redress deficiency. We proposed prevention of neonatal vitamin D status <25−30 nmol/l, indicated by umbilical cord 25(OH)D, as a potential target for defining maternal vitamin D requirements during pregnancy, consistent with prevention of nutritional rickets[127,156]. The vitamin D_3 intake required to maintain maternal 25(OH)D >50 nmol/l in almost all mothers, which ensured that cord sera were all >25 nmol/l, was 30 µg/d (1200 IU)[156]. This was consistent with other dose–response studies from Canada[157] and New Zealand[158]. Further similar dose–response studies are required in different racial and ethnic groups and in various settings to generate an inclusive estimate of maternal vitamin D requirements for the prevention of neonatal deficiency, with adequate consideration of calcium intake[159]. The design and protocol for such studies are available and would be a cost-effective approach to ensure safe evidence-based antenatal prevention of vitamin D deficiency among mothers and newborn infants.

Widespread maternal and neonatal vitamin D deficiency is a present danger requiring immediate public health action. Whether there is a role for *additional* vitamin D over and above current dietary recommendations, to support healthy pregnancy and promote optimal perinatal outcomes and infant development, is a separate question, which requires further investigation in well-designed placebo-controlled randomised trials, discussed separately[160]. These issues are often conflated in the literature, leading to confusion and a narrow discussion of the core question. For example, the most recent WHO statement on vitamin D supplements during pregnancy did not address the most important issue of vitamin D deficiency prevention and the grave risk of nutritional rickets in many regions[161]; by issuing a report on the Cochrane reviews of supplementation only, this statement missed an opportunity to address the most critical concerns. Public health measures, such as food fortification with vitamin D, would benefit the population as a whole, including women prior to and during pregnancy, by increasing vitamin D in the food supply, raising vitamin D intakes and status and providing a better chance of avoiding deficiency[160].

Conclusions

Deficiencies of iron, iodine and vitamin D are common, have multifactorial dietary and non-nutritional risk factors and overlap in their contribution to adverse clinical outcomes, including neurological development in children, which impacts life chances. The adverse effects of poor-quality diets, with limited availability of micronutrients, are compounded by increasing rates of obesity among young women, with consequent inflammatory and metabolic disorders, all implicated in iron and vitamin D deficiencies and interlinked in the pathways for suboptimal neural development.

Public health strategies are urgently required to improve the overall health and nutritional status of women of reproductive age. Strategies encompassing obesity prevention and early detection of malnutrition are required. Standardised screening including clinical risk factors and indices of iron status would detect pregnant women at increased risk of iron deficiency. Development of sensitive, individual biomarkers of iodine status is needed for inclusion of iodine to screening strategies, with the dual purpose of protecting the health of the mother and fetal/infant brain development. Risk assessments of vitamin D requirements during pregnancy need to be revisited from the perspective of fetal and neonatal requirements. International consensus on standardised approaches to micronutrient assessment, analysis and reporting as well as sensitive, clinically validated infant and child neuro-behavioural outcomes are required to enable useful observational and intervention studies to proceed.

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Conflict of Interest

None.

Authorship

The authors had sole responsibility for all aspects of preparation of this paper.

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References

1. International Food Policy Research Institute (2014) *Global Hunger Index: The Challenge of Hidden Hunger*. Bonn/Washington D.C./Dublin: IFPRI.
2. Interagency Committee on Human Nutrition Research (2016) *National Nutrition Research Roadmap 2016–2021: Advancing Nutrition Research to Improve and Sustain Health*. Washington, DC: Interagency Committee on Human Nutrition Research.
3. World Health Organization (2013) *Vienna Declaration on Nutrition and Noncommunicable Diseases in the Context of Health 2020*. Denmark: World Health Organization.
4. Stephenson J, Heslehurst N, Hall J *et al.* (2018) Before the beginning: nutrition and lifestyle in the preconception period and its importance for future health. *Lancet* **391**, 1830–1841.
5. Högler W, Aguiar M, Kiely M *et al.* (2016) Consensus recommendations for prevention of nutritional rickets: food fortification and micronutrient supplements for global health. *AIMS Public Health* **3**,40–48.
6. McLean E, Cogswell M, Egli I *et al.* (2009) Worldwide prevalence of anaemia, WHO Vitamin and Mineral Nutrition Information System, 1993–2005. *Public Health Nutr* **12**, 444–454.
7. Fisher AL & Nemeth E (2017) Iron homeostasis during pregnancy. *Am J Clin Nutr* **106**, 1567s–1574s.
8. World Health Organization (2015) *The Global Prevalence of Anemia 2011*. Geneva: World Health Organization.
9. Milman N, Taylor CL, Merkel J *et al.* (2017) Iron status in pregnant women and women of reproductive age in Europe. *Am J Clin Nutr* **106**, 1655s–1662s.
10. Lynch S, Pfeiffer CM, Georgieff MK *et al.* (2018) Biomarkers of nutrition for development (BOND)–iron review. *J Nutr* **148**, 1001s–1067s.
11. Livock M, Anderson PJ, Lewis S *et al.* (2017) Maternal micronutrient consumption periconceptionally and during pregnancy: a prospective cohort study. *Public Health Nutr* **20**, 294–304.
12. Harika R, Faber M, Samuel F *et al.* (2017) Micronutrient status and dietary intake of iron, vitamin A, iodine, folate and zinc in women of reproductive age and pregnant women in Ethiopia, Kenya, Nigeria and South Africa: a systematic review of data from 2005 to 2015. *Nutrients* **9**, 1096.
13. Caut C, Leach M & Steel A (2020) Dietary guideline adherence during preconception and pregnancy: a systematic review. *Matern Child Nutr* **16**, e12916.
14. Milman NT (2020) Dietary iron intake in pregnant women in Europe: a review of 24 studies from 14 countries in the period 1991–2014. *J Nutr Metab* **2020**, 7102190.
15. Piccoli GB, Clari R, Vigotti FN *et al.* (2015) Vegan-vegetarian diets in pregnancy: danger or panacea? A systematic narrative review. *BJOG* **122**, 623–633.
16. Marvin-Dowle K, Burley VJ & Soltani H (2016) Nutrient intakes and nutritional biomarkers in pregnant adolescents: a systematic review of studies in developed countries. *BMC Pregnancy Childbirth* **16**, 268.
17. Scientific Advisory Committee on Nutrition (2010) *Iron and Health*. London: The Stationary Office.
18. EFSA NDA Panel (2015) Scientific opinion on dietary reference values for iron. *EFSA J* **13**, 4254.
19. Barrett JF, Whittaker PG, Williams JG *et al.* (1994) Absorption of non-haem iron from food during normal pregnancy. *Br Med J* **309**, 79–82.
20. Whittaker PG, Lind T & Williams JG (1991) Iron absorption during normal human pregnancy: a study using stable isotopes. *Br J Nutr* **65**, 457–463.
21. Institute of Medicine (2001) *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*. Washington, DC: The National Academies Press.
22. Farooq A, Rauf S, Hassan U *et al.* (2011) Impact of multiparity on iron content in multiparous women. *J Ayub Med Coll Abbottabad* **23**, 32–35.
23. Ru Y, Pressman EK, Cooper EM *et al.* (2016) Iron deficiency and anemia are prevalent in women with multiple gestations. *Am J Clin Nutr* **104**, 1052–1060.
24. Rao R & Georgieff MK (2007) Iron in fetal and neonatal nutrition. *Semin Fetal Neonatal Med* **12**, 54–63.
25. Sweet DG, Savage G, Tubman TR *et al.* (2001) Study of maternal influences on fetal iron status at term using cord blood transferrin receptors. *Arch Dis Child Fetal Neonatal Ed* **84**, F40–43.
26. Georgieff MK, Mills MM, Gordon K *et al.* (1995) Reduced neonatal liver iron concentrations after uteroplacental insufficiency. *J Pediatr* **127**, 308–304.
27. Chełchowska M, Ambroszkiewicz J, Gajewska J *et al.* (2016) Hepcidin and iron metabolism in pregnancy: correlation with smoking and birth weight and length. *Biol Trace Elem Res* **173**, 14–20.
28. Petry CD, Eaton MA, Wobken JD *et al.* (1992) Iron deficiency of liver, heart, and brain in newborn infants of diabetic mothers. *J Pediatr* **121**, 109–114.
29. Siddappa AM, Georgieff MK, Wewerka S *et al.* (2004) Iron deficiency alters auditory recognition memory in newborn infants of diabetic mothers. *Pediatr Res* **55**, 1034–1041.
30. Poston L, Caleyachetty R, Cnattingius S *et al.* (2016) Preconceptional and maternal obesity: epidemiology and health consequences. *Lancet Diabetes Endocrinol* **4**, 1025–1036.
31. Jones AD, Zhao G, Jiang YP *et al.* (2016) Maternal obesity during pregnancy is negatively associated with maternal and neonatal iron status. *Eur J Clin Nutr* **70**, 918–924.
32. Garcia-Valdes L, Campoy C, Hayes H *et al.* (2015) The impact of maternal obesity on iron status, placental transferrin receptor expression and hepcidin expression in human pregnancy. *Int J Obes* **39**, 571–578.
33. Flores-Quijano ME, Montalvo-Velarde I, Vital-Reyes VS *et al.* (2016) Longitudinal analysis of the interaction between obesity and pregnancy on iron homeostasis: role of hepcidin. *Arch Med Res* **47**, 550–556.
34. Cao C, Pressman EK, Cooper EM *et al.* (2016) Prepregnancy body mass index and gestational weight gain have no negative impact on maternal or neonatal iron status. *Reprod Sci* **23**, 613–622.
35. Dao MC, Sen S, Iyer C *et al.* (2013) Obesity during pregnancy and fetal iron status: is hepcidin the link? *J Perinatol* **33**, 177–181.
36. Flynn AC, Begum S, White SL *et al.* (2018) Relationships between maternal obesity and maternal and neonatal iron status. *Nutrients* **10**, 1000.
37. Koenig MD, Tussing-Humphreys L, Day J *et al.* (2014) Hepcidin and iron homeostasis during pregnancy. *Nutrients* **6**, 3062–3083.
38. World Health Organization/Centers for Disease Control and Prevention (2004) *Assessing the Iron Status of Populations*. Geneva: WHO.
39. Daru J, Allotey J, Peña-Rosas JP *et al.* (2017) Serum ferritin thresholds for the diagnosis of iron deficiency in pregnancy: a systematic review. *Transfus Med* **27**, 167–174.
40. Pasricha SR, Colman K, Centeno-Tablante E *et al.* (2018) Revisiting WHO haemoglobin thresholds to define

https://doi.org/10.1017/S0029665121001944

anaemia in clinical medicine and public health. *Lancet Haematol* **5**, e60–e62.
41. Brannon PM, Stover PJ & Taylor CL (2017) Integrating themes, evidence gaps, and research needs identified by workshop on iron screening and supplementation in iron-replete pregnant women and young children. *Am J Clin Nutr* **106**, 1703s–1712s.
42. Scanlon KS, Yip R, Schieve LA *et al.* (2000) High and low hemoglobin levels during pregnancy: differential risks for preterm birth and small for gestational age. *Obstet Gynecol* **96**, 741–748.
43. Haider BA, Olofin I, Wang M *et al.* (2013) Anaemia, prenatal iron use, and risk of adverse pregnancy outcomes: systematic review and meta-analysis. *Br Med J* **346**, f3443.
44. Dewey KG & Oaks BM (2017) U-shaped curve for risk associated with maternal hemoglobin, iron status, or iron supplementation. *Am J Clin Nutr* **106**, 1694s–1702s.
45. Kozuki N, Lee AC & Katz J (2012) Moderate to severe, but not mild, maternal anemia is associated with increased risk of small-for-gestational-age outcomes. *J Nutr* **142**, 358–362.
46. Alwan NA, Cade JE, McArdle HJ *et al.* (2015) Maternal iron status in early pregnancy and birth outcomes: insights from the baby's vascular health and iron in pregnancy study. *Br J Nutr* **113**, 1985–1992.
47. Khambalia AZ, Collins CE, Roberts CL *et al.* (2016) Iron deficiency in early pregnancy using serum ferritin and soluble transferrin receptor concentrations are associated with pregnancy and birth outcomes. *Eur J Clin Nutr* **70**, 358–363.
48. Rahman SM, Siraj MS, Islam MR *et al.* (2021) Association between maternal plasma ferritin level and infants' size at birth: a prospective cohort study in rural Bangladesh. *Glob Health Action* **14**, 1870421.
49. Lozoff B & Georgieff MK (2006) Iron deficiency and brain development. *Semin Pediatr Neurol* **13**, 158–165.
50. Monk C, Georgieff MK, Xu D *et al.* (2016) Maternal prenatal iron status and tissue organization in the neonatal brain. *Pediatr Res* **79**, 482–488.
51. Schmidt RJ, Tancredi DJ, Krakowiak P *et al.* (2014) Maternal intake of supplemental iron and risk of autism spectrum disorder. *Am J Epidemiol* **180**, 890–900.
52. Janbek J, Sarki M, Specht IO *et al.* (2019) A systematic literature review of the relation between iron status/anemia in pregnancy and offspring neurodevelopment. *Eur J Clin Nutr* **73**, 1561–1578.
53. Arija V, Hernández-Martínez C, Tous M *et al.* (2019) Association of iron status and intake during pregnancy with neuropsychological outcomes in children aged 7 years: the prospective birth Cohort Infancia y Medio Ambiente (INMA) Study. *Nutrients* **11**, 2999.
54. Shao J, Lou J, Rao R *et al.* (2012) Maternal serum ferritin concentration is positively associated with newborn iron stores in women with low ferritin status in late pregnancy. *J Nutr* **142**, 2004–2009.
55. Jaime-Perez JC, Herrera-Garza JL & Gomez-Almaguer D (2005) Sub-optimal fetal iron acquisition under a maternal environment. *Arch Med Res* **36**, 598–602.
56. McCarthy EK, Kenny LC, Hourihane JO *et al.* (2017) Impact of maternal, antenatal and birth-associated factors on iron stores at birth: data from a prospective maternal-infant birth cohort. *Eur J Clin Nutr* **71**, 782–784.
57. Amin SB, Orlando M & Wang H (2013) Latent iron deficiency *in utero* is associated with abnormal auditory neural myelination in ≥35 weeks gestational age infants. *J Pediatr* **163**, 1267–1271.
58. Choudhury V, Amin SB, Agarwal A *et al.* (2015) Latent iron deficiency at birth influences auditory neural maturation in late preterm and term infants. *Am J Clin Nutr* **102**, 1030–1034.
59. Tamura T, Goldenberg RL, Hou J *et al.* (2002) Cord serum ferritin concentrations and mental and psychomotor development of children at five years of age. *J Pediatr* **140**, 165–170.
60. McCarthy EK, Murray DM, Hourihane JOB *et al.* (2021) Behavioral consequences at 5 y of neonatal iron deficiency in a low-risk maternal-infant cohort. *Am J Clin Nutr*. doi: 10.1093/ajcn/nqaa367.
61. Georgieff MK (2017) Iron assessment to protect the developing brain. *Am J Clin Nutr* **106**, 1588s–1593s.
62. Grantham-McGregor S, Cheung YB, Cueto S *et al.* (2007) Developmental potential in the first 5 years for children in developing countries. *Lancet* **369**, 60–70.
63. Hay G, Refsum H, Whitelaw A *et al.* (2007) Predictors of serum ferritin and serum soluble transferrin receptor in newborns and their associations with iron status during the first 2 y of life. *Am J Clin Nutr* **86**, 64–73.
64. Georgieff MK, Wewerka SW, Nelson CA *et al.* (2002) Iron status at 9 months of infants with low iron stores at birth. *J Pediatr* **141**, 405–409.
65. Lozoff B, Smith JB, Kaciroti N *et al.* (2013) Functional significance of early-life iron deficiency: outcomes at 25 years. *J Pediatr* **163**, 1260–1266.
66. Georgieff MK (2020) Iron deficiency in pregnancy. *Am J Obstet Gynecol* **223**, 516–524.
67. McCarthy EK & Kiely ME (2019) The neonatal period: A missed opportunity for the prevention of iron deficiency and its associated neurological consequences? *Nutr Bull* **44**, 309–319.
68. Bougma K, Aboud FE, Harding KB *et al.* (2013) Iodine and mental development of children 5 years old and under: a systematic review and meta-analysis. *Nutrients* **5**, 1384–1416.
69. Pearce EN (2012) Effects of iodine deficiency in pregnancy. *J Trace Elem Med Biol* **26**, 131–133.
70. UNICEF. Global database, 2019, based on Multiple Indicator Cluster Surveys (MICS), Demographic and Health Surveys (DHS) and other nationally representative household surveys, 2013–2018 (accessed February 2021).
71. Zimmermann MB & Andersson M (2012) Update on iodine status worldwide. *Curr Opin Endocrinol Diabetes Obes* **19**, 382–387.
72. World Health Organization (2007) *Iodine Deficiency in Europe: A Continuing Public Health Problem*. No. 9241593962. Geneva: World Health Organization.
73. Lazarus JH & Smyth PPA (2008) Iodine deficiency in the UK and Ireland. *Lancet* **372**, 888.
74. McNulty BA, Nugent AP, Walton J *et al.* (2017) Iodine intakes and status in Irish adults: is there cause for concern? *Br J Nutr* **117**, 422–431.
75. Brantsæter AL, Knutsen HK, Johansen NC *et al.* (2018) Inadequate iodine intake in population groups defined by age, life stage and vegetarian dietary practice in a Norwegian convenience sample. *Nutrients* **10**, 230.
76. Perrine CG, Herrick K, Serdula MK *et al.* (2010) Some subgroups of reproductive age women in the United States may be at risk for iodine deficiency. *J Nutr* **140**, 1489–1494.
77. Brantsæter AL, Abel MH, Haugen M *et al.* (2013) Risk of suboptimal iodine intake in pregnant Norwegian women. *Nutrients* **5**, 424–440.
78. Dineva M, Rayman MP, Levie D *et al.* (2020) Similarities and differences of dietary and other determinants of iodine status in pregnant women from three European birth cohorts. *Eur J Nutr* **59**, 371–387.

https://doi.org/10.1017/S0029665121001944

79. McMullan P, Hamill L, Doolan K *et al.* (2019) Iodine deficiency among pregnant women living in Northern Ireland. *Clin Endocrinol* **91**, 639–645.
80. Bath SC, Walter A, Taylor A *et al.* (2014) Iodine deficiency in pregnant women living in the South East of the UK: the influence of diet and nutritional supplements on iodine status. *Br J Nutr* **111**, 1622–1631.
81. Dineva M, Rayman MP & Bath SC (2020) Iodine status of consumers of milk-alternative drinks v. cows' milk: data from the UK National Diet and Nutrition Survey. *Br J Nutr* 1–9.
82. Gowachirapant S, Melse-Boonstra A, Winichagoon P *et al.* (2014) Overweight increases risk of first trimester hypothyroxinaemia in iodine-deficient pregnant women. *Matern Child Nutr* **10**, 61–71.
83. Gargari SS, Fateh R, Bakhshali-bakhtiari M *et al.* (2020) Maternal and neonatal outcomes and determinants of iodine deficiency in third trimester of pregnancy in an iodine sufficient area. *BMC Pregnancy Childbirth* **20**, 174.
84. Elmadfa I & Meyer AL (2010) Importance of food composition data to nutrition and public health. *Eur J Clin Nutr* **64**, S4–S7.
85. Andersson M, Takkouche B, Egli I *et al.* (2005) Current global iodine status and progress over the last decade towards the elimination of iodine deficiency. *Bull World Health Organ* **83**, 518–525.
86. Rohner F, Zimmermann M, Jooste P *et al.* (2014) Biomarkers of nutrition for development – iodine review. *J Nutr* **144**, 1322S–1342S.
87. World Health Organization (2007) *Assessment of Iodine Deficiency Disorders and Monitoring Their Elimination: A Guide for Programme Managers*. 3rd ed. Geneva: World Health Organization.
88. Scientific Advisory Committee on Nutrition (2014) *SACN Statement on Iodine and Health*. London: Public Health England.
89. Ma ZF & Skeaff SA (2014) Thyroglobulin as a biomarker of iodine deficiency: a review. *Thyroid* **24**, 1195–1209.
90. Bath SC, Pop VJM, Furmidge-Owen VL *et al.* (2017) Thyroglobulin as a functional biomarker of iodine status in a cohort study of pregnant women in the United Kingdom. *Thyroid* **27**, 426–433.
91. Zimmermann MB, Jooste PL & Pandav CS (2008) Iodine-deficiency disorders. *Lancet* **372**, 1251–1262.
92. Darnton-Hill I (2019) Public health aspects in the prevention and control of vitamin deficiencies. *Curr Dev Nutr* **3**.
93. Andersson M, Karumbunathan V & Zimmermann MB (2012) Global iodine status in 2011 and trends over the past decade. *J Nutr* **142**, 744–750.
94. Gizak M, Rogers L, Gorstein J *et al.* (2018) Global iodine status in school-age children, women of reproductive age, and pregnant women in 2017. American Society for Nutrition (ASN) Nutrition Conference 2018.
95. Hennessy A, ní Chaoimh C, McCarthy EK *et al.* (2017) Variation in iodine food composition data has a major impact on estimates of iodine intake in young children. *Eur J Clin Nutr* **72**, 410–419.
96. Cao XY, Jiang XM, Dou ZH *et al.* (1994) Timing of vulnerability of the brain to iodine deficiency in endemic cretinism. *N Engl J Med* **331**, 1739–1744.
97. Mills JL, Buck Louis GM, Kannan K *et al.* (2018) Delayed conception in women with low-urinary iodine concentrations: a population-based prospective cohort study. *Hum Reprod* **33**, 426–433.
98. Dillon JC & Milliez J (2000) Reproductive failure in women living in iodine deficient areas of West Africa. *BJOG* **107**, 631–636.
99. Zimmermann MB (2009) Iodine deficiency. *Endocr Rev* **30**, 376–408.
100. Abel MH, Caspersen IH, Meltzer HM *et al.* (2017) Suboptimal maternal iodine intake is associated with impaired child neurodevelopment at 3 years of age in the Norwegian Mother and Child Cohort Study. *J Nutr* **147**, 1314–1324.
101. Bath SC, Steer CD, Golding J *et al.* (2013) Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC). *Lancet* **382**, 331–337.
102. Hynes KL, Otahal P, Hay I *et al.* (2013) Mild iodine deficiency during pregnancy is associated with reduced educational outcomes in the offspring: 9-year follow-up of the gestational iodine cohort. *J Clin Endocrinol Metab* **98**, 1954–1962.
103. Markhus MW, Dahl L, Moe V *et al.* (2018) Maternal iodine status is associated with offspring language skills in infancy and toddlerhood. *Nutrients* **10**, 1270.
104. van Mil NH, Tiemeier H, Bongers-Schokking JJ *et al.* (2012) Low urinary iodine excretion during early pregnancy is associated with alterations in executive functioning in children. *J Nutr* **142**, 2167–2174.
105. Murcia M, Espada M, Julvez J *et al.* (2018) Iodine intake from supplements and diet during pregnancy and child cognitive and motor development: the INMA Mother and Child Cohort Study. *J Epidemiol Community Health* **72**, 216–222.
106. Murcia M, Rebagliato M, Iniguez C *et al.* (2011) Effect of iodine supplementation during pregnancy on infant neurodevelopment at 1 year of age. *Am J Epidemiol* **173**, 804–812.
107. Rebagliato M, Murcia M, Alvarez-Pedrerol M *et al.* (2013) Iodine supplementation during pregnancy and infant neuropsychological development. INMA Mother and Child Cohort Study. *Am J Epidemiol* **177**, 944–953.
108. Ghassabian A, Steenweg-de Graaff J, Peeters RP *et al.* (2014) Maternal urinary iodine concentration in pregnancy and children's cognition: results from a population-based birth cohort in an iodine-sufficient area. *BMJ Open* **4**, e005520.
109. Levie D, Korevaar T, Bath SC *et al.* (2019) Association of maternal iodine status with child IQ: a meta-analysis of individual participant data. *J Clin Endocrinol Metab* **104**, 5957–5967.
110. Guxens M, Ballester F, Espada M *et al.* (2012) Cohort profile: the INMA–INfancia y Medio Ambiente–(Environment and Childhood) Project. *Int J Epidemiol* **41**, 930–940.
111. Kooijman MN, Kruithof CJ, van Duijn CM *et al.* (2016) The generation R study: design and cohort update 2017. *Eur J Epidemiol* **31**, 1243–1264.
112. Boyd A, Golding J, Macleod J *et al.* (2013) Cohort profile: the 'children of the 90s' – the index offspring of the Avon Longitudinal Study of Parents and Children. *Int J Epidemiol* **42**, 111–127.
113. Dineva M, Fishpool H, Rayman MP *et al.* (2020) Systematic review and meta-analysis of the effects of iodine supplementation on thyroid function and child neurodevelopment in mildly-to-moderately iodine-deficient pregnant women. *Am J Clin Nutr* **112**, 389–412.
114. Brannon PM & Picciano MF (2011) Vitamin D in pregnancy and lactation in humans. *Annu Rev Nutr* **31**: 89–115.
115. Zehnder D, Evans KN, Kilby MD *et al.* (2002) The ontogeny of 25-Hydroxyvitamin D(3) 1alpha-hydroxylase

https://doi.org/10.1017/S0029665121001944

expression in human placenta and decidua. *Am J Pathol* **161**, 105–114.
116. Hollis BW & Wagner CL (2018) Vitamin D in pregnancy and lactation: moving into the future. In: *Vitamin D*, 4th ed. vol. **2**, pp. 1159–1176 [D Feldman, editor]. Academic Press.
117. Tamblyn JA, Hewison M, Wagner CL *et al.* (2015) Immunological role of vitamin D at the maternal-fetal interface. *J. Endocrinol* **224**, R107–121.
118. Hollis BW & Pittard WB 3rd (1984) Evaluation of the total fetomaternal vitamin D relationships at term: evidence for racial differences. *J Clin Endocrinol Metab* **59**, 652–657.
119. Viö Streym S, Kristine Moller U, Rejnmark L *et al.* (2013) Maternal and infant vitamin D status during the first 9 months of infant life – a cohort study. *Eur J Clin Nutr* **67**, 1022–1028.
120. Giovannucci E (2018) Methods of evaluating population studies of vitamin D: strengths and weaknesses. In: *Vitamin D*, 4th ed. vol. **2**, pp. 3–14 [D Feldman, editor]. Academic Press.
121. Calvo MS, Whiting SJ & Barton CN (2004) Vitamin D fortification in the United States and Canada: current status and data needs. *Am J Clin Nutr* **80**(Suppl. 6), 1710S-6S.
122. Kiely M & Black LJ (2012) Dietary strategies to maintain adequacy of circulating 25-hydroxyvitamin D concentrations. *Scand J Clin Lab Invest Suppl* **243**, 14–23.
123. Gomes F, King SE, Dallmann D *et al.* (2021) Interventions to increase adherence to micronutrient supplementation during pregnancy: a systematic review. *Ann N Y Acad Sci.* doi: 10.1111/nyas.14545 Epub ahead of print.
124. Mogire RM, Mutua A, Kimita A *et al.* (2020) Prevalence of vitamin D deficiency in Africa: a systematic review and meta-analysis. *Lancet Glob Health* **8**, e134–42.
125. Pettifor JM (2004) Nutritional rickets: deficiency of vitamin D, calcium, or both? *Am J Clin Nutr* **80**(Suppl), 1725S–9S.
126. Prentice A, Schoenmakers I, Jones KS *et al.* (2009) Vitamin D deficiency and its health consequences in Africa. *Clin Rev Bone Miner Metab* **7**, 94–106.
127. Munns CF, Shaw N, Kiely M *et al.* (2016) Global consensus recommendations on prevention and management of nutritional rickets. *J Clin Endocrinol Metab* **101**, 394–415.
128. Cashman KD, Dowling KG, Škrabáková Z *et al.* (2016) Vitamin D deficiency in Europe: pandemic? *Am J Clin Nutr* **103**, 1033–44.
129. Schleicher RL, Sternberg MR, Looker AC *et al.* (2016) National estimates of serum total 25-hydroxyvitamin D and metabolite concentrations measured by liquid chromatography-tandem mass spectrometry in the US Population during 2007–2010. *J Nutr* **146**, 1051–61.
130. Sarafin K, Durazo-Arvizu R, Tian L *et al.* (2015) Standardizing 25-hydroxyvitamin D values from the Canadian Health Measures Survey. *Am J Clin Nutr* **102**, 1044–50.
131. Cashman KD, Sheehy T & O'Neill CM (2019) Is vitamin D deficiency a public health concern for low middle income countries? A systematic literature review. *Eur J Nutr* **58**, 433–453.
132. Roth DE, Abrams SA, Aloia J *et al.* (2018) Global prevalence and disease burden of vitamin D deficiency: a roadmap for action in low- and middle-income countries. *Ann N Y Acad Sci* **1430**, 44–79.
133. Lips P, Cashman KD, Lamberg-Allardt C *et al.* (2019) Current vitamin D status in European and Middle East countries and strategies to prevent vitamin D deficiency; a position statement of the European Calcified Tissue Society. *Eur J Endocrinol* **180**, P23–P54.
134. O'Callaghan KM & Kiely ME (2018) Ethnic disparities in the dietary requirement for vitamin D during pregnancy: considerations for nutrition policy and research. *Proc Nutr Soc* **77**, 164–173.
135. Palacios C & Gonzalez L (2014) Is vitamin D deficiency a major global public health problem? *J Steroid Biochem Mol Biol* **144**(Pt A), 138–45.
136. Saraf R, Morton SM, Camargo CA Jr *et al.* (2016) Global summary of maternal and newborn vitamin D status – a systematic review. *Matern Child Nutr* **12**, 647–68.
137. Datta S, Alfaham M, Davies DP *et al.* (2002) Vitamin D deficiency in pregnant women from a non-European ethnic minority population – an interventional study. *BJOG* **109**, 905–908.
138. Van Der Meer IM, Karamali NS, Boeke AJ *et al.* (2006) High prevalence of vitamin D deficiency in pregnant non-western women in the Hague, Netherlands. *Am J Clin Nutr* **84**, 350–353.
139. Leffelaar ER, Vrijkotte TG & Van Eijsden M (2010) Maternal early pregnancy vitamin D status in relation to fetal and neonatal growth: results of the multi-ethnic Amsterdam born children and their development cohort. *Br J Nutr* **104**, 108–117.
140. Bärebring L, Schoenmakers I, Glantz A *et al.* (2016) Vitamin D status during pregnancy in a multi-ethnic population-representative Swedish Cohort. *Nutrients* **8**, 655.
141. Haggarty P, Campbell DM, Knox S *et al.* (2013) Vitamin D in pregnancy at high latitude in Scotland. *Br J Nutr* **109**, 898–905.
142. Kiely ME, Zhang JY, Kinsella M *et al.* (2016) Vitamin D status is associated with uteroplacental dysfunction indicated by pre-eclampsia and small-for-gestational-age birth in a large prospective pregnancy cohort in Ireland with low vitamin D status. *Am J Clin Nutr* **104**, 354–61.
143. Kiely M, O'Donovan SM, Kenny LC *et al.* (2017a) Vitamin D metabolite concentrations in umbilical cord blood serum and associations with clinical characteristics in a large prospective mother–infant cohort in Ireland. *J Steroid Biochem Mol Biol* **167**, 162–168.
144. O'Callaghan KM & Kiely M (2018) Systematic review of vitamin D and hypertensive disorders of pregnancy. *Nutrients* **10**, 294.
145. Eyles DW (2020) Vitamin D: brain and behavior. *JBMR Plus* 18;**5**, e10419.
146. Eyles DW, Smith S, Kinobe R *et al.* (2005) Distribution of the vitamin D receptor and 1 alpha-hydroxylase in human brain. *J Chem Neuroanat* **29**, 21–30.
147. O'Neill SM, Hannon G, Khashan AS *et al.* (2017) Thin-for-gestational age infants are at increased risk of neurodevelopmental delay at 2 years. *Arch Dis Child Fetal Neonatal Ed.* **102**, F197–F202.
148. McCarthy EK, Murray DM, Malvisi L *et al.* (2018) Antenatal vitamin D status is not associated with standard neurodevelopmental assessments at age 5 years in a well-characterized prospective maternal-infant cohort. *J Nutr* **148**, 1580–1586.
149. Mutua AM, Mogire RM, Elliott AM *et al.* (2020) Effects of vitamin D deficiency on neurobehavioural outcomes in children: a systematic review. *Wellcome Open Res* **5**, 28.
150. Roth DE, Qamar H, Watterworth J *et al.* (2017) Vitamin D supplementation during pregnancy: state of the evidence from a systematic review of randomised trials. *Br Med J* **359**, j5237.

https://doi.org/10.1017/S0029665121001944

151. Palacios C, Kostiuk LK & Peña-Rosas JP (2019) Vitamin D supplementation for women during pregnancy. *Cochrane Database Syst Rev* 26:**7**, CD008873.
152. Scientific Advisory Committee on Nutrition (2016) *Vitamin D and Health*. London: The Stationary Office.
153. Institute of Medicine (2011) *Dietary Reference Intakes for Calcium and Vitamin D*. Washington, DC: National Academies Press.
154. EFSA Panel on Dietetic Products, Nutrition and Allergies (2016) Scientific opinion on dietary reference values for vitamin D. *EFSA J* **14**, 4547.
155. Kiely M, Hemmingway A & O'Callaghan KM (2017) Vitamin D in pregnancy: current perspectives and future directions. *Ther Adv Musculoskelet Dis* **9**, 145–154.
156. O'Callaghan KM, Hennessy Á, Hull GL *et al*. (2018) Estimation of the maternal vitamin D intake that maintains circulating 25-hydroxyvitamin D in late gestation at a concentration sufficient to keep umbilical cord sera ≥25–30 nmol/L: a dose–response, double-blind, randomized placebo-controlled trial in pregnant women at northern latitude. *Am J Clin Nutr* **108**, 77–91.
157. March KM, Chen NN, Karakochuk CD *et al*. (2015) Maternal vitamin D(3) supplementation at 50 Mug/D protects against low serum 25-hydroxyvitamin D in infants at 8 Wk of age: a randomized controlled trial of 3 doses of vitamin D beginning in gestation and continued in lactation. *Am J Clin Nutr* **102**, 402–410.
158. Grant CC, Stewart AW, Scragg R *et al*. (2014) Vitamin D during pregnancy and infancy and infant serum 25-hydroxyvitamin D concentration. *Pediatrics* **133**, e143–153.
159. Hemmingway A, Kenny LC, Malvisi L *et al*. (2018) Exploring the concept of functional vitamin D deficiency in pregnancy: impact of the interaction between 25-hydroxyvitamin D and parathyroid hormone on perinatal outcomes. *Am J Clin Nutr* **108**, 821–829.
160. Kiely ME, Wagner CL & Roth DE (2020) Vitamin D in pregnancy: where we are and where we should go. *J Steroid Biochem Mol Biol* **201**, 105669.
161. WHO antenatal care recommendations for a positive pregnancy experience (2020) *Nutritional Interventions Update: Vitamin D Supplements During Pregnancy*. Geneva: World Health Organization.
162. Scientific Advisory Committee on Nutrition (2014) *SACN Statement on Iodine and Health*. London: Public Health England.
163. EFSA Panel on Dietetic Products, Nutrition and Allergies (2014) Scientific opinion on dietary reference values for iodine. *EFSA J* **12**, 3660.
164. WHO/FAO (2004) Vitamin and mineral requirements in human nutrition: report of a Joint FAO/WHO Expert Consultation. Bangkok, Thailand, 21–30 September 1998. 341 pp.
165. WHO, UNICEF & ICCIDD (2007) *Assessment of Iodine Deficiency Disorders and Monitoring their Elimination*. Geneva: World Health Organization.
166. WHO (2016) *WHO Recommendations on Antenatal Care for a Positive Pregnancy Experience*. Geneva: World Health Organization.

https://doi.org/10.1017/S0029665121001944