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Review Article

Effect of micronutrient supplements on low-risk pregnancies in high-income countries: a systematic quantitative literature review

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Abstract

Objective: To assess the quantity and focus of recent empirical research regarding the effect of micronutrient supplementation on live birth outcomes in low-risk pregnancies from high-income countries.
Design: A systematic quantitative literature review.
Setting: Low-risk pregnancies in World Bank-classified high-income countries, 2019.
Results: Using carefully selected search criteria, a total of 2475 publications were identified, of which seventeen papers met the inclusion criteria for this review. Data contributing to nine of the studies were sourced from four cohorts; research originated from ten countries. These cohorts exhibited a large number of participants, stable data and a low probability of bias. The most recent empirical data offered by these studies was 2011; the most historical was 1980. In total, fifty-five categorical outcome/supplement combinations were examined; 67·3 % reported no evidence of micronutrient supplementation influencing selected outcomes.
Conclusions: A coordinated, cohesive and uniform empirical approach to future studies is required to determine what constitutes appropriate, effective and safe micronutrient supplementation in contemporary cohorts from high-income countries, and how this might influence pregnancy outcomes.

Keywords
Birth outcomes
High income
Pregnancy
Micronutrients
Supplements

Evidence regarding the effect of malnutrition on pregnancy outcomes has been extensively documented[1–4], with micronutrient supplement interventions traditionally focused on low- and middle-income countries[5]. This is in part due to the disproportionate rate of poor perinatal outcomes attributable to malnutrition compared to high-income regions[6,7]. However, suboptimal nutrition also represents a significant public health concern in high-income countries as a result of undernourishment, over-nourishment or micronutrient deficiency[8]. Despite this knowledge, women from high-income countries represent an under-researched population[2].

Over recent years, the Cochrane Database of Systematic Reviews has thoroughly examined published research regarding the effect of multiple micronutrient supplements (MuMS)[3], folic acid[9], iron[10], zinc[11], calcium[12], iodine[13] and vitamin D[14] on pregnancy outcomes. However, the majority of studies exhibited vast heterogeneity in data, cohorts, context and examined outcomes, with many reporting low or no evidence of significant benefits of supplements in low-risk women and high-income countries. Further, each Cochrane review cautiously highlights the need for further randomised controlled trials in view of perceived pregnancy risks and ethical considerations[3,9–13]. Despite these limitations, systematic reviews remain the foundation of clinical practice recommendations[15–17].

This is potentially problematic in that the effects of supplementation in the absence of identified deficiency,

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low-risk pregnancies and high-income countries are largely unknown. This review and synthesis of contemporary empirical research aimed to determine how, where and when empirical research was conducted, the cohorts studied, and who the major publishers are in this field. In addition, this review identifies what has been most commonly studied in terms of demographics, outcomes, supplements and their timing over the last decade, and synthesises a consensus of findings relating to the effect of micronutrient supplements on the birth outcomes of low-risk pregnancies in high-income countries. Identified research deficits and implications for policy and practice are subsequently discussed.

Methods

The systematic quantitative literature review

Systematic literature reviews are commonly used in the health sector and are an important component of evidence-based health care, assisting in the development and maintenance of guidelines and policies, institutional and personal practice[18]. However, while systematic reviews aid in the identification of knowledge gaps, they do not necessarily highlight research deficits[19]. The systematic quantitative literature review is emerging in a range of scientific disciplines as an appropriate methodology in heterogeneous research contexts. The quantitative approach facilitates an analysis of varying approaches in discipline, design, context, intent and methodology[19]. This review is systematic in that a structured framework has been used to establish project parameters, assess the literature and construct a database of literature for review according to PRISMA guidelines[20].

The Pickering and Byrne[19] approach utilises a unique fifteen-step process that encourages researchers to develop a categorisation framework based on an iterative and inductive process to develop, implement and present their review – a process consistent with but more detailed than traditional systematic reviews[21,22]. A significant benefit of this quantitative methodology is that the examination technique expands rather than refines the depth of the review[19]; research gaps are easily identified under these systematic conditions in addition to research 'hotspots'. This differs from traditional systematic reviews in which the examination commences with a broad foundation, and content is deductively reduced, limiting the scope of the review to collation of current knowledge and relying on deductive reasoning to identify research deficits[19]. As such, this approach is appropriate for areas of research with a diversity of scope[19], a feature demonstrated by the literature regarding supplementation during pregnancy, the range of micronutrients, outcomes, settings and demographic groups studied, and the methodologies employed to do so.

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations[20] and conforms to the systematic quantitative literature review approach described by Pickering and Byrne[19]. The PRISMA flowchart (Fig. 1) details the review process; methods and results are detailed according to PRISMA reporting criteria.

Search strategy

To identify papers examining the effects of micronutrient supplementation on the birth outcomes of low-risk pregnancies in high-income countries, a systematic search was conducted using the electronic databases CINAHL, EMBASE, MEDLINE, PubMed and Google Scholar from 1 March 2009 to 1 March 2019, a timeframe determined by the recent systematic reviews[3,9–13]. A literature search was conducted using a combination of the following keywords: (supplement* OR vitamin* OR mineral OR micronutrient OR 'micro nutrient' OR micro-nutrient) AND ('high income' OR developed OR industrial* OR 'first world') AND ((birth OR pregnanc*) AND outcomes). Studies were considered eligible if original, peer-reviewed, detailing empirical data pertaining to supplementation in low-risk pregnancies (including the periconception period), examining live birth outcomes in relation to supplementation in either primary or secondary capacity, undertaken on women living in high-income countries according to 2019 indexes[23], and published in English language within the last 10 years.

Selection criteria

All papers were screened by the first author by title and/or abstract for suitability; discussion papers, papers examining supplementation in non-pregnant populations or low- and middle-income regions, or in the presence of known pregnancy risks, or reporting haematological values alone were excluded. Similarly, errant results with no reference to pregnancy outcomes and micronutrient supplementation were excluded. References cited by each study and meeting stage one eligibility were reviewed to identify additional potential studies; systematic reviews were excluded. Full-text versions of all studies passing this initial screening were reviewed in detail. A second screening was employed whereby a study was excluded if it did not meet the established parameters. Included and excluded papers were recorded at each screening stage according to the PRISMA statement. Risk of bias was assessed at a study level; each addressed the potential for bias within the individual research protocol or discussion. Two included papers were known to the authors and included as additional resources. Both papers met the selection criteria and, as such, selection bias was considered minimal. The analysis of reviewed articles is reported in terms of bibliographic details and research design, examined variables and key findings.

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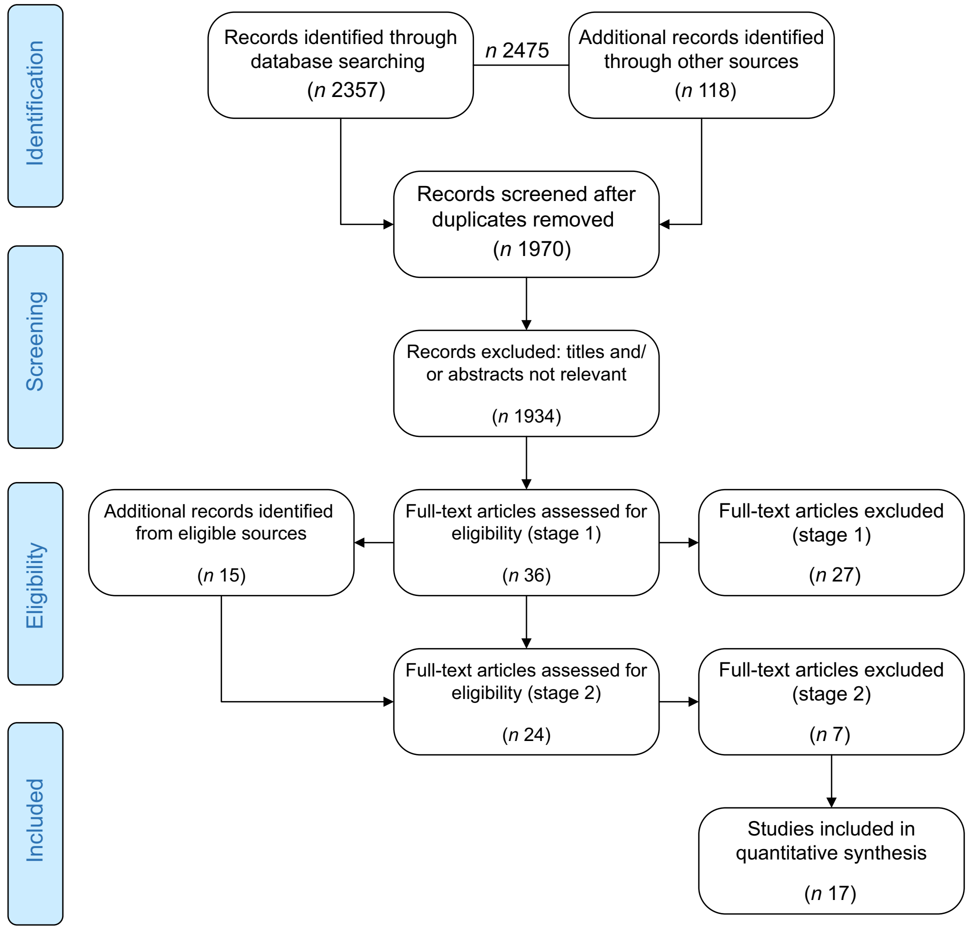

Fig. 1 (colour online) PRISMA flow diagram[41]

Categories

Characteristics regarding the nature and scope of research surrounding the effects of micronutrient supplementation on the outcomes of low-risk pregnancies in high-income countries were measured across a range of emergent categories[19].

The final categories comprised bibliographic details (authors, year, title, journal, genre), settings and methods (country (state, region), study/cohort, year of collection, funding source, number of participants, method (observational/experimental – single/double-blinded randomised controlled trial, single/multisite), descriptive groups (ethnicity, age group, parity, BMI, smoker, education, socioeconomic status), trimester (periconception, trimester 1, 2, 3, 1 & 2, 2 & 3 and 1, 2 & 3), supplementation (MuMS, folic acid, vitamin C/vitamin E, vitamin D, zinc, iron, calcium, DHA, supplement combinations) and birth outcomes (pre-eclampsia, gestational diabetes, induction of labour, birth < 37 weeks, birth > 41 weeks, gestation at birth, low birthweight/small for gestational age, birthweight). Subcategories were created on an emergent basis; all affirmative categories were recorded in a spreadsheet with value 1 and totalled at the end of analysis. The frequency of examined variables was documented along with reference numbers (online supplementary material).

Results

A total of 2475 potentially relevant studies were identified. Of the fifty-one full-text articles meeting stage one and two criteria, seventeen were retained for quantitative analyses in this systematic review[24–40] (Fig. 1, Table 1). Of the thirty-four papers excluded, sixteen were systematic reviews[3,9–11,42–53], four were systematic reviews with meta-analyses[2,54–56] and two presented meta-analyses alone[57,58]. A further six were discussion papers[12,59–63], four included women with an identified risk[64] or diagnosis of pregnancy-related morbidities (pre-eclampsia[65,66] and gestational diabetes[14]), one study was ceased due to adverse outcomes[13] and one examined a particular micronutrient administered in a MuMS formulation[67] (online supplementary material).

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Table 1 List of papers included in this review

Ref no.	Authors	Year	Title	Journal	Country	Cohort/year
(24)	Alwan N, Greenwood D, Simpson N, McArdle H, Cade J.	2010	The relationship between dietary supplement use in late pregnancy and birth outcomes: A cohort study in British women	*BJOG: An International Journal of Obstetrics and Gynaecology*	UK	2003–6
(25)	Brough L, Rees GA, Crawford MA, Morton RH, Dorman EK	2010	Effect of multiple-micronutrient supplementation on maternal nutrient status, infant birth weight and gestational age at birth in a low-income, multi-ethnic population	*British Journal of Nutrition*	UK	2002–4
(26)	Carlson SE, Colombo J, Gajewski BJ, Gustafson KM, Mundy D, Yeast J, *et al.*	2013	DHA supplementation and pregnancy outcomes	*The American Journal of Clinical Nutrition*	USA	2006–11
(27)	Catov JM, Bodnar LM, Olsen J, Olsen S, Nohr EA	2011	Periconceptional multivitamin use and risk of preterm or small-for-gestational-age births in the Danish National Birth Cohort 1–4	*The American Journal of Clinical Nutrition*	Denmark	DNBC,1997–2003
(28)	Catov JM, Nohr EA, Bodnar LM, Knudson VK, Olsen SF, Olsen J	2009	Association of periconceptional multivitamin use with reduced risk of preeclampsia among normal-weight women in the Danish National Birth Cohort	*American Journal of Epidemiology*	Denmark	DNBC, 1997–2003
(29)	Chan KKL, Chan BCP, Lam KF, Tam S, Lao TT	2009	Iron supplement in pregnancy and development of gestational diabetes – a randomised placebo-controlled trial	*BJOG: An International Journal of Obstetrics and Gynaecology*	Hong Kong	2005–7
(30)	Czeizel AE, Puhó EH, Langmar Z, Ács N, Bánhidy F	2009	Possible association of folic acid supplementation during pregnancy with reduction of preterm birth: a population-based study	*European Journal of Obstetrics & Gynecology and Reproductive Biology*	Hungary	1980–96
(31)	Haugen M, Brantsæter AL, Trogstad L, Alexander J, Roth C, Magnus P, *et al.*	2009	Vitamin D supplementation and reduced risk of preeclampsia in nulliparous women	*Epidemiology*	Norway	MoBA, 2002–9
(32)	Hauth JC, Clifton RG, Roberts JM, Spong CY, Myatt L, Leveno KJ, *et al.*	2010	Vitamin C and E supplementation to prevent spontaneous preterm birth: a randomised controlled trial	*Obstetrics and Gynecology*	USA	Eunice Kennedy Shiver cohort, 2003–8
(33)	Martinussen MP, Bracken MB, Triche EW, Jacobsen GW, Risnes KR	2015	Folic acid supplementation in early pregnancy and the risk of preeclampsia, small for gestational age offspring and preterm delivery	*European Journal of Obstetrics & Gynecology and Reproductive Biology*	USA	Eunice Kennedy Shiver cohort, 1996–2000

Table 1 *Continued*

Ref no.	Authors	Year	Title	Journal	Country	Cohort/year
(34)	McAlpine JM, Scott R, Scuffham PA, Perkins AV, Vanderlelie JJ	2015	The association between third trimester multivitamin/mineral supplements and gestational length in uncomplicated pregnancies	*Women and Birth*	Australia	EFHL, 2006–11
(35)	Nilsen RM, Vollset SE, Monsen ALB, Ulvik A, Haugen M, Meltzer HM, *et al.*	2010	Infant birth size is not associated with maternal intake and status of folate during the second trimester in Norwegian pregnant women	*Journal of Nutrition*	Norway	MoBA, 2002–3
(36)	Papadopoulou E, Stratakis N, Roumeliotaki T, Sarri K, Merlo D, Kogevinas M, *et al.*	2013	The effect of high doses of folic acid and iron supplementation in early-to-mid pregnancy on prematurity and fetal growth retardation: the mother–child cohort study in Crete, Greece (RHEA study)	*European Journal of Nutrition*	Greece	RHEA, 2007–8
(37)	Pastor-Valero M, Navarrete-Muñoz EM, Rebagliato M, Iñiguez C, Murcia M, Marco A, *et al.*	2011	Periconceptional folic acid supplementation and anthropometric measures at birth in a cohort of pregnant women in Valencia, Spain	*British Journal of Nutrition*	Spain	Infancia y Medio Ambiente, 2004–5
(38)	Roberts JM, Myatt L, Spong CY, Thom EA, Hauth JC, Leveno KJ, *et al.*	2010	Vitamins C and E to prevent complications of pregnancy-associated hypertension	*The New England Journal of Medicine*	USA	Eunice Kennedy Shiver cohort, 2003–8
(39)	Timmermans S, Jaddoe VWV, Hofman A, Steegers-Theunissen RPM, Steegers EAP	2009	Periconception folic acid supplementation, fetal growth and the risks of low birth weight and preterm birth: the Generation R Study	*British Journal of Nutrition*	Netherlands	Generation R, 2002–6
(40)	Vanderlelie J, Scott R, Shibl R, Lewkowicz J, Perkins A, Scuffham PA	2016	First trimester multivitamin/mineral use is associated with reduced risk of pre-eclampsia among overweight and obese women	*Maternal & Child Nutrition*	Australia	EFHL, 2006–11

Bibliographic details and design

Authors and data pools

A total of 103 authors were credited with authorship across the eligible papers. Sixteen authors were responsible for first authorship of the seventeen; one author was responsible for first authorship of two papers[27,28]. Large birth cohorts were responsible for generating the majority of data: the Danish National Birth Cohort (DNBC 1997–2003, *n* 2)[27,28], Norwegian Mother and Baby cohort (MoBA 2002–9, *n* 2)[31,35], Environments for Healthy Living cohort (EFHL 2006–11, *n* 2)[34,40] and the New England, USA dataset (collected with support from the Eunice Kennedy Shriver National Institute of Child Health and Human Development's (NICHD) Maternal-Fetal Medicine Units Network 1996–2008, *n* 3)[32,33,38], which all accounted for the bulk of eligible papers (Table 1). Additionally, RHEA (2007–8)[36], Generation R (2002–6)[39] and Infancia y Medio Ambiente[37] cohorts (2004–5) contributed to the final data pool (*n* 147 323 women).

Five countries each contributed one unique cohort and one subsequent publication to the field of research (Table 1); Australia[34,40], Denmark[27,28] and Norway[31,35] each contributed one cohort from their respective countries; each of these cohorts contributed data to two unique papers. The United Kingdom added a further two studies on independent cohorts to the research[24,25]. The United States was responsible for three studies originating from one cohort of women[33], two of which reported the same intervention on different outcomes[32,38]. The United States contributed an additional unique cohort and intervention to the pool of research[26] (Table 1).

Year of publication and research methodologies

The quantity of empirical studies has declined over the past decade. While 2009 and 2010 both returned five qualifying studies each, the years 2011–16 produced seven empirical studies in total. No research meeting these parameters was found after 2016 (Table 1). The majority were observational studies (*n* 12); of these, nine were conducted in multicentre collaborations (75·0 %). Multicentre research also accounted for two out of the five experimental studies[32,38] (40 %), with the remainder being conducted with a single-centre approach[25,26,29]. All experimental studies were randomised controlled trials; four of these used double-blinded methodologies (Table 1) with the remaining ones being blinded to participants but not researchers[29].

Genres and journals

Covering four genres, nutrition[25–27,35–37,39,40] (*n* 8, 47·1 %), medicine[24,29,30,32,33,38] (*n* 6, 35·3 %), epidemiology[28,31] (*n* 2, 11·8 %) and midwifery[34] (*n* 1, 5·9 %) journals produced all eligible articles. The *British*[25,37,39] (*n* 3) and *American*[26,27] *Journals of Nutrition* (*n* 2) published eligible research most frequently, along with the *European Journal of Obstetrics & Gynecology and Reproductive Biology*[30,33] (*n* 2) and the *British Journal of Obstetrics and Gynaecology*[24,29] (*n* 2). A further eight journals published one study each[28,31,32,34–36,38,40]. These journals were produced by a range of publishers.

Variables examined

Supplements

In total, nine micronutrients – either alone or in combination – were examined with empirical research methodology in the specified timeframe (Table 1). Folic acid was the most frequently examined supplement (*n* 10). Of these ten studies, three examined the use of folic acid in combination with either a multivitamin (*n* 2)[30,34] or iron[36] (*n* 1). MuMS were examined independently in five studies, iron in two[29,34]; vitamins C and E in combination accounted for two studies[32,38] and one study examined zinc and calcium both independently and in combination with all previously mentioned micronutrients[34]. Studies evaluating the roles of DHA[26] (*n* 1) and vitamin D[31] (*n* 1) in pregnancy outcomes were performed in the absence of other supplements.

Outcomes

Reporting of birth outcomes was limited to gestation at birth (continuous, *n* 8; categorical, <37 weeks, *n* 10, >41 weeks, *n* 1), birthweight (continuous, *n* 8; low birthweight (<2500 g/small for gestational age <10th centile), *n* 12), onset of labour (*n* 2) and the development of hypertensive disorders during pregnancy (including pre-eclampsia, *n* 6; gestational diabetes, *n* 2; Table 1).

Timing of supplementation

Supplement use was examined across all three trimesters of pregnancy in six of the studies (Table 1). A further five examined supplement use in the periconception period only, that is, 3 months before conception through until 3 months after conception. Examination exclusively by trimester was performed by the minority (Table 1).

Demographic groups

Maternal age was recorded by all papers and reported as mean and standard deviation of a continuous variable in nine of the seventeen studies (Table 1). Categorisation by maternal age groups was difficult given the lack of consistency in age group categories between the remaining studies. A total of twenty-seven age group categories were reported among the eight studies, citing the division of maternal age into categorical variables for ages <18 to ≥40 years. The age groups ranged from two- to nine-year spans, preventing category reduction through combination and descriptive reporting of age group representation in the cohort as a whole.

Ethnicity was poorly reported in these studies, with seven of the eligible papers not declaring ethnicity (Table 1); a further two recorded the country of birth rather than ethnic background[24,39]. For those that recorded ethnic identity, 44 % (*n* 12 154) of the combined cohort recorded

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ethnicity as 'other'. Hispanic was the most frequently recorded ethnic origin (*n* 4), followed by Caucasian (*n* 2), African American (*n* 2) and the generic category 'Black' (*n* 2). Nine individual ethnicities were recorded in these studies (Table 1).

Parity was well reported, with all papers reporting it as a descriptive variable. While 88 % (*n* 15) of these did not report associations with outcomes (Table 1), two did – one exclusively examined supplementation in nulliparous women[31], the other reported differences between women in first and subsequent pregnancies[34]. The majority of research was undertaken in nulliparous women (*n* 78 520, 62 %). Smoking status was reported by 76 % of the papers (*n* 13); four papers did not provide such details[25,29,30,35]. Smokers comprised 15 % (*n* 18 730) of the total cohort that reported smoking habits (*n* 122 967).

Reporting of education level and socioeconomic status (SES) was inconsistent. Education level was unrecorded or reported as years completed (±SD) in all but two studies[34,37]. SES was more frequently recorded, with low- (*n* 4), middle- (*n* 2) and high-income categories (*n* 2) examined to some extent (Table 1).

Key findings

In total, fifty-five categorical outcome/supplement combinations were examined across these seventeen publications. Of these, 67·3 % (*n* 37) found no evidence of increasing or decreasing risk of the selected outcomes due to micronutrient supplementation. A decrease in the risk of suboptimal outcomes was detected in 25·5 % (*n* 14), while the risk was found to have increased in 7·3 % (*n* 4) of combinations (Table 2). Two studies reported a reduction in the risk of low birthweight with the use of folic acid in the periconception period[27,39] and iron supplementation in trimesters 2 and 3[29].

A reduction in risk was found in a majority of studies examining hypertensive disorders of pregnancy and preterm birth. Four of the included studies contributed to this consensus, three of which examined the use of MuMS and/or folic acid[28,33,40]. The remaining study reported a reduced risk of pre-eclampsia by vitamin D supplementation in the context of nulliparous pregnancy[31]. MuMS were found to reduce the risk of preterm birth and pre-eclampsia in the two separate Danish cohort studies; this did not extend to folic acid supplementation[27,28].

However, one study examining MuMS across the whole gestation reported an increased risk of preterm birth[24]; another reported an increased risk of small-for-gestational-age infants in women using iron supplements in the first and second trimesters[36]. An increased risk for birth beyond 41 completed weeks in women using supplement combinations in the third trimester was reported by one of the two related papers[34]; induction of labour was reported to be higher in this study. No evidence of benefit or harm was reported with regard to micronutrient supplementation and the development of gestational diabetes.

Discussion

This review aimed to quantify and characterise recently published empirical studies that examined the effects of micronutrient supplementation on birth outcomes in high-income countries. A systematic quantitative literature review methodology[19] facilitated the identification of a number of challenges faced by research in this field. These include data pool limitations, diversity of methodologies and lack of research in supplement use beyond the first trimester.

Data informing this research originated from about ten countries; however, these ten countries represent only 12 % of the high-income countries based on the World Bank ranking[23]. Further, four cohorts provided data for nine of these studies. These cohorts reported data pertaining to a large number of participants, thereby reducing the potential of recruitment bias[68–71]. However, the low number of unique data pools is problematic, in that data typifies its specific population[72]. This resulted in homogeneity within each data extraction irrespective of the intended investigation and prevented a comparison of the efficacy of interventions between different descriptive groups. Further, heterogeneity was present within the methodology of each study, with a lack of consistency contributing to a lack of cohesion between reported findings.

Table 2 Number of studies and effects by outcomes

			Decreased risk		No effect		Increased risk	
	Total studied	Total outcomes	*n*	%	*n*	%	*n*	%
Pre-eclampsia	6	8	5	62·5	3	37·5	0	0
Gestational diabetes	2	2	0	0	2	100·0	0	0
Induction of labour	2	7	0	0	6	85·7	1	14·3
Birth < 37 weeks	10	15	6	40·0	8	53·3	1	6·7
Birth > 41 weeks	1	6	0	0	5	83·3	1	16·7
Low birthweight/SGA	12	17	3	17·6	13	76·5	1	5·9
Total	33	55	14	25·5	37	67·3	4	7·3

SGA, small for gestational age.

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Another problem faced by researchers in this field is the currency of data available for examination. The most recent empirical data offered by these studies pertained to 2011; some data was collected nearly four decades ago, although getting published in 2009[30]. These datasets and their demographic foci are representative of known health risk groups at the time of data collection. However, baseline maternal health and diets have changed substantially in this timeframe[73]. Physical determinants such as obesity and poor nutrition are driving factors for non-communicable diseases such as essential hypertension, heart disease and diabetes in high-income countries[74]. These historically rare concerns represent significant risks during pregnancy and are increasingly affecting birth outcomes[73]. Determining the effects of dietary supplementation in women who might experience these comorbidities is vital if improvements are to be made in associated perinatal morbidities.

Similarly, cultural factors influencing the nutrition status in high-income countries have changed substantially over time, with increasing immigration and inevitable transference of sociocultural norms across international boundaries[75]. This acculturation has resulted in a diversity in baseline health status and food selection practices of pregnant populations in high-income countries[76–78]. Hence, the nutritional needs of pregnant women in contemporary high-income regions differ considerably from those of the cohorts detailed by existing studies. This highlights a knowledge gap regarding the needs and effects of micronutrient supplementation in women from culturally diverse backgrounds. As such, high-quality contemporary data are necessary to ascertain the implications and effects of micronutrient interventions in the context of high-income countries. Randomised controlled trials incorporating baseline nutrition status, biological sampling, supplementation and birth outcomes in specific demographic groups would be a valuable step towards gathering relevant evidence and improving the birth outcomes of culturally diverse women in today's multicultural societies.

The translation of research into practice in the field of supplementation during pregnancy faces a number of challenges. Global, national and state health organisations rely on data synthesis and systematic reviews to inform clinical recommendations[17]. While systematic reviews are a gold standard for evidence-based practice[18], they rely on existing data and publications. However, with the exception of periconception folic acid, the level of evidence informing supplementation guidelines is universally poor. This has resulted in guidelines – being founded on consensus-based recommendations – advising the use and timing of specific supplements during pregnancy. This challenges a consistent dissemination of information among and between health professionals and the wider community, resulting in advices influenced by opinions, rhetoric, anecdotes and a widespread belief that supplements are harmless[79]. However, emerging evidence suggests that an inappropriate use of supplements may be detrimental to select birth outcomes[34]. Outcomes examined reflect morbidity and mortality associated with pre-eclampsia[80], preterm labour[6] and low birthweight[81] infants. However, gestational length beyond 38 completed weeks has also been found to exhibit a linear increase with poor perinatal outcomes[82]. These include an inherent risk of the aging placenta[83] and an increased risk of medical intervention and related sequelae[84].

Several important supplements were absent from these studies, including those considered beneficial (selenium for the prevention of hypertensive disorders[85]) or much recommended (iodine to meet increased need during pregnancy[15]). Both these micronutrients could be toxic if used in excess[86], so well-regulated studies would be required if cohort-specific interventions were proposed. However, recommending such supplements in the absence of an identified deficiency would incur an inherent risk. Further, while folic acid supplementation is highly beneficial in the prevention of neural tube defects in the periconception period[87], little evidence exists describing its effect in the subsequent trimesters. Trimester-specific interventions with all supplements were highly variable, causing an inability to determine timely windows of opportunity for specific addition or withdrawal of supplementation to optimise outcomes.

The paucity of research surrounding supplementation during pregnancy will prevent making an accurate estimation of the percentage of women using such supplements. However, the demonstrated knowledge gap along with the reliance of clinicians and consumers on unsubstantiated information would contribute to a high predicted growth of the global pregnancy supplement market, which is estimated to reach a value of $674 million by 2025[88]. Since little contemporary empirical research data regarding supplement use during pregnancy is available globally, evidence informing the current policies and recommendations remains questionable. As such, understanding the associations between micronutrient supplements and birth outcomes in high-income countries is a matter of research priority.

Conclusion

Data informing our systematic review pertaining to the effects of micronutrient supplementation on birth outcomes in low-risk women in high-income countries are limited due to a lack of current research, limited data pools, heterogeneity in methodologies and traditional dissemination of research to primary health practitioners. Over two-thirds of reports presented no evidence of benefit or harm to birth outcomes as a result of supplementation in low-risk women in high-income countries. Heterogeneity in methodologies used and lack of specificity regarding demographic grouping confound findings regarding what constitutes appropriate and effective supplementation,

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challenging the application of such findings to practice. A coordinated, cohesive and uniform empirical approach is required to determine what constitutes appropriate, effective and safe micronutrient supplementation during pregnancy in contemporary cohorts from high-income countries.

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Supplementary material

For supplementary materials accompanying this article visit https://doi.org/10.1017/S1368980020000725

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