Review Article

The role of diet and nutritional supplementation in perinatal depression: a systematic review

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Abstract

This article presents a systematic literature review on whether dietary intake influences the risk for perinatal depression, i.e. depression during pregnancy or post-partum. Such a link has been hypothesized given that certain nutrients are important in the neurotransmission system and pregnancy depletes essential nutrients. PubMed, EMBASE and CINAHL databases were searched for relevant articles until 30 May 2015. We included peer-reviewed studies of any design that evaluated whether perinatal depression is related to dietary intake, which was defined as adherence to certain diets, food-derived intake of essential nutrients or supplements. We identified 4808 studies, of which 35 fulfilled inclusion criteria: six randomized controlled trials, 12 cohort, one case-control and 16 cross-sectional studies, representing 88 051 distinct subjects. Studies were grouped into four main categories based on the analysis of dietary intake: adherence to dietary patterns (nine studies); full panel of essential nutrients (six studies); specific nutrients (including B vitamins, Vitamin D, calcium and zinc; eight studies); and intake of fish or polyunsaturated fatty acids (PUFAs; 12 studies). While 13 studies, including three PUFA supplementation trials, found no evidence of an association, 22 studies showed protective effects from healthy dietary patterns, multivitamin supplementation, fish and PUFA intake, calcium, Vitamin D, zinc and possibly selenium. Given the methodological limitations of existing studies and inconsistencies in findings across studies, the evidence on whether nutritional factors influence the risk of perinatal depression is still inconclusive. Further longitudinal studies are needed, with robust and consistent measurement of dietary intake and depressive symptoms, ideally starting before pregnancy.

Keywords: nutrition, diet, maternal health, perinatal depression.

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Introduction

Perinatal depression, also referred to as maternal depression, is defined as depression during pregnancy and up to 1 year post-partum. It is a common morbidity during pregnancy and lactation and can have severe and long-term consequences for women and their children. A systematic review on the prevalence of perinatal depression reported that the pooled point prevalence for minor depression alone was 11% during pregnancy and 13% post-partum (Gavin *et al.* 2005). In low-income and middle-income countries (LMICs), perinatal depression is thought to be more common because of concomitant stress, anxiety, familial and political instability and poverty (Shidhaye *et al.* 2013). Fisher *et al.* (2012) reported a prevalence of

15.6% of women having depressive symptoms during the antenatal period (from 13 studies) and 19.8% during the post-partum period (from 34 studies) in LMICs.

There is growing concern about the consequences of perinatal depression (Howard *et al.* 2014b), with evidence accumulating of its negative effects on women's health and child development (Walker *et al.* 2007; Stein *et al.* 2014; Patel *et al.* 2004). Studies show that maternal depression is associated with poor self-care and care-giving, poor child growth and cognitive development, child malnutrition and increased incidence of child illness (Stewart 2007; Bennett *et al.* 2004; Rahman *et al.* 2004; Stein *et al.* 2008). Although the detrimental effects of maternal depression are increasingly recognized and studied, the focus has been on treatment

and intervention rather than on risk factors and prevention (Rahman *et al.* 2013).

It has been hypothesized that nutrition could play a biological role in depression (Kaplan *et al.* 2007). Various nutrients are needed for synthesis and modulation in the neurotransmission system and may therefore be involved in mood regulation (Rechenberg & Humphries 2013; Bodnar & Wisner 2005). The biochemistry of each nutrient and its role in mood regulation are discussed elsewhere (Kaplan *et al.* 2007; Rechenberg & Humphries 2013; Leung & Kaplan 2009). During pregnancy and lactation, nutritional demands increase, and deficiencies thus arise more easily. It is also possible that hormonal and life changes post-partum increase the risk for depression (Burt & Stein 2002). Nonetheless, women may experience heightened risks from both nutritional deficiencies and hormonal shifts during the perinatal period.

Previous reviews on certain nutrients and their link to depression concentrate on one nutrient or class of nutrients, such as polyunsaturated fatty acids (PUFAs) (Freeman *et al.* 2006). Most considered depression in general and few had a focus on perinatal depression (Jans *et al.* 2010; Leung & Kaplan 2009; Makrides 2008). Reviews also often mix studies of prevention of depression (supplementation in non-depressed subjects) and treatment of already depressed subjects with certain nutrients.

This review aims to synthesize the evidence on whether dietary intake influences the risk of depression in the perinatal period. Dietary intake is defined as adherence to certain diets, food-derived intake of essential nutrients or supplementation, which encompasses complex

interactions between different ingested nutrients and compounds. Given that intake of foods and supplements is not always indicative of bioavailability, blood levels of certain nutrients will be the focus of a separate review.

Methods

Search strategy

We ran a sensitive and comprehensive search strategy using both MeSH terms and free text keywords in two separate searches that was designed to identify all relevant studies. The first search combined nutrition terms with maternal depression terms, while the second combined nutrition terms with depression terms and maternity terms separately (Fig. 1). PubMed, EMBASE and CINAHL databases were searched for English-language publications from 1966 to 30 May 2015. Two independent reviewers screened all titles and abstracts identified by the search and then reviewed the full text of potentially eligible articles for inclusion.

Eligibility

Articles were eligible for inclusion if they were peer-reviewed and presented measures of association between dietary intake before, during or after pregnancy and depression during pregnancy or up to 1 year post-partum. Analytical studies of any design were eligible for inclusion.

We included studies that evaluated distinct dietary patterns and adherence to those diets or intake of specific nutrients through food or supplementation

Key messages

- Depression in pregnancy and post-partum is common and can have adverse consequences for mother and child.
- During pregnancy and lactation, nutritional demand increases. Lack of key nutrients may negatively impact neurotransmission and increase the risk of perinatal depression.
- We conducted a systematic literature review and present a synthesis of the evidence on whether dietary intake influences perinatal depression.
- The evidence is still inconclusive, because of both mixed results of studies and a lack of high-quality investigations.
- Further research is needed using robust, longitudinal measurement of nutritional exposures and depression outcomes, including in low-income settings.

Figure 1: Search strategy

Databases: PubMed, EMBASE and CINAHL

SEARCH 1:

Nutrition terms: diet (MeSH¹, ti/ab²), nutrition (MeSH), nutri* (ti/ab), food (MeSH, ti/ab), vitamin (MeSH, ti/ab), mineral (MeSH, ti/ab), dietary supplement (MeSH), supplement* (ti/ab), micronutrients (MeSH, ti/ab)

AND

Maternal depression terms: postpartum depression (MeSH, ti/ab), antenatal depression (ti/ab), perinatal depression (ti/ab), maternal depression (ti/ab), maternal mental health (ti/ab)

SEARCH 2:

Nutrition terms as above

AND

General depression terms: depression (MeSH), depress* (ti/ab), affective disorder (MeSH, ti/ab), affective symptoms (ti/ab), mood disorders (MeSH, ti/ab), depressive disorder (MeSH)

AND

Maternity terms: pregnancy (MeSH), pregnan* (ti/ab), mothers (MeSH), matern* (ti/ab), antenatal* (ti/ab), prenatal* (ti/ab), puerper* (ti/ab), postnatal* (MeSH, ti/ab), peripartum (MeSH, ti/ab), postpartum (MeSH, ti/ab), childbirth (ti/ab), maternal health services (MeSH, ti/ab)

¹ MeSH: Medical Subject Headings;

² ti/ab: title or abstract

Fig. 1. Search strategy.

if they used validated food frequency questionnaires (FFQs) or supplement history questionnaires. We excluded studies using non-specific intake questions to measure health behaviours, such as whether or not a woman took supplements but without a measure of specific amount or type. Studies using other measures such as food insecurity, body composition (e.g. body mass index), hormone levels or one-item food questions to assess health behaviours were also excluded from this review.

Studies in women already diagnosed with depressive symptoms or women with underlying health conditions (HIV positive, for example) were excluded. Perinatal depression was required to be assessed through a validated depression screening tool¹ or through clinical diagnosis from a trained interviewer. Studies using prescription of

antidepressants as a proxy for a clinical diagnosis were also included. The Center for Epidemiological Studies Depression Scale (CES-D) and Beck's Depression Inventory (BDI) are frequently used for depression screening, also in pregnancy and post-partum, as they do not emphasize somatic symptoms such as appetite changes and sleep disturbance and have been found to be highly accurate in screening for both minor and major depression (Tandon *et al.* 2012). However, the only screening tools that totally exclude these symptoms and are technically validated for the antenatal (pregnancy) period and post-partum period are the Edinburgh Post-partum Depression Scale (EPDS) and the Post-partum Depression Screening Scale (PDSS), which have been shown to have higher sensitivity than other tools (Gaynes *et al.* 2005; Beck & Gable 2001). Thus, we assigned a lower risk of bias to studies using these tools.

Risk of bias assessment

The methodological quality of the included studies was assessed using the Quality in Prognostic Studies tool (Hayden *et al.* 2013) for observational studies and the

¹EPDS, Edinburgh Post-partum Depression Scale; CES-D, Center for Epidemiologic Studies Depression Scale; BDI, Beck's Depression Inventory; MINI, Mini International Neuropsychiatric Interview; SRQ-20, 20-item Self-reporting Questionnaire; K10, 10-item Kessler Psychological Distress Scale; Goldberg's Depression Scale; SCL-90-R, Symptom Checklist-90-R or Kitgum Maternal Mood Scale; PDSS, Post-partum Depression Screening Scale.

Cochrane Collaboration tool for assessing risk of bias in randomized control trials (RCTs) (Higgins *et al.* 2011). Although the Quality in Prognostic Studies tool was designed for prognostic studies, ‘prognoses’ are similar to ‘risks’ in epidemiology. The tool evaluates risk of bias in studies and comprises six domains: study participation, study attrition (which we replaced by response in cross-sectional studies and by selection of controls in the one case–control study), prognostic factor (in this case exposure) measurement, outcome measurement, confounding, and statistical analysis and reporting.

The confounding domain was assessed based on potential confounders being controlled for and the method by which they were controlled. Several socioeconomic and psychosocial variables have shown relationships to both depression and self-care or eating habits (and thus dietary intake), specifically, a history of depression, social support, poor general health, income and employment (Bennett *et al.* 2004). Studies that did not control for any of these confounders were given a high risk of bias, studies including some confounders, a medium risk of bias and studies that accounted for several of these confounders, including history of depression, a low risk of bias. For Vitamin D studies, measuring a proxy of sunlight exposure, a main source of Vitamin D, was required to be ranked as having low risk of bias. In most studies, confounding was considered in stepwise models, where a univariable analysis was conducted first to identify potential confounders. If important potential confounders were included in a crude model but not associated with the outcome, and the authors therefore did not include them in the final adjusted model, this was still considered sufficient control for confounding in the risk of bias analysis.

For statistical analysis and reporting, if studies used stepwise models including important potential confounders and found no association between the exposure(s) of interest and the outcome and therefore did not proceed to a fully adjusted multivariable model, then they were still given a low risk of bias in this category. However, if an adjusted model was not attempted despite significant associations in a crude model or the analysis strategy was not clear, then studies were ranked as having moderate or high risk of bias for statistical analysis and reporting.

The Cochrane tool for risk of bias in RCTs uses the following domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias) and selective reporting (reporting bias).

Two reviewers independently ranked each study as having high, medium or low risk of bias in each domain. The reviewers compared scores, disagreements were discussed and a consensus reached.

Data extraction

Study characteristics and overall results were extracted from all included studies using a standard data form and are presented in Table 1. The type of analysis performed and detailed results were also extracted and are shown in Appendices 1–4. As studies varied widely in their choice of nutritional exposures and timing of dietary intake assessment and depression assessment, performing a meta-analysis of associations between dietary exposure and perinatal depression was not possible. Therefore, a descriptive summary of all included studies is presented.

Results

Study selection

The process of study selection is shown in Fig. 2. After removing duplicates, 4808 articles were identified from the three databases. Following the screening of all titles and abstracts, 165 full-text articles were retrieved and checked against eligibility criteria. Twenty-three articles that used biomarkers instead of diet or intake measures were excluded and will be separately reviewed. We finally included 35 articles in this review, representing 88 051 distinct subjects (seven study populations were not counted because the analysis came from the same cohorts as other included studies).

Studies were grouped according to four categories of dietary intake: (1) dietary patterns, such as ‘healthy’ or ‘processed’ (nine studies); (2) food intake separated into a full panel of essential nutrients (six studies); (3)

Table 1. Summary of studies evaluating associations between dietary intake and perinatal depression

Author (year)	Study characteristics			Exposure			Outcome		Results		
	Country	n	Study design	Depression prevalence	Nutrients/diet	Tool; recall/ intervention period	Time assessed	Tool; cut- point	Time assessed	Adj. model	Protective associations (unless noted; final models reported)
DIETARY PATTERNS											
Chatzi <i>et al.</i> (2011)	Greece ⁿ	519	Cohort	14%	PCA grouped into 'Health conscious' and 'Western'	FFQ; pregnancy	Mid- pregnancy	EPDS; 13	PP: 8–10 weeks	Y	High (vs. low) adherence to health conscious diet
Murakami <i>et al.</i> (2008)	Japan [*]	865	Cohort	14%	GI and GL index	FFQ; 1 month recall	Pregnancy	EPDS; 9	PP: 2–9 months	Y	Third quartile (vs. first) of GI score
Okubo <i>et al.</i> (2011)	Japan [*]	865	Cohort	14%	Factor analysis grouped into 'Healthy', 'Western' and 'Japanese'	FFQ; 1 month recall	Pregnancy	EPDS; 9	PP: 2–9 months	Y	Second quartile (vs. first) of adherence to Western pattern
Pina-Camacho <i>et al.</i> (2015)	UK [†]	7814	Cohort	Not reported	Factor analysis to determine level of unhealthy diet	FFQ; 1 week recall	Third trimester	EPDS; linear	Second, Third trimester	Y	None
Vilela <i>et al.</i> (2014)	Brazil	246	Cohort	Not reported	PCA grouped into 'Common Brazilian', 'Healthy' and 'Processed'	FFQ; 6 months prior to pregnancy	First trimester	EPDS; linear	Each trimester	Y	High (vs. low) adherence to healthy dietary pattern before and during pregnancy
Fowles <i>et al.</i> (2011)	United States	50	Cross-section	Not reported	Frequency of eating fast food	DOI-P; 3 × 24 h recall	First trimester	EPDS; 10 or mean difference	First trimester	N	Low (vs. high) frequency of fast food consumption
Fowles <i>et al.</i> (2012)	United States	71	Cross-section	Not reported	Dietary Quality Index during pregnancy score, high vs. low	DOI-P; 3 × 24 h recall	First trimester	EPDS; mean difference	First trimester	N	High (vs. low) DOI-P score
George <i>et al.</i> (2005)	United States	146	Cross-section	Not reported	Compliance with US dietary guidelines	FFQ; 6 months recall	1 year PP	CES-D; mean difference	PP: 1 year	N	Highest (vs. lowest) tertile of dietary compliance

(Continues)

Table 1. (Continued)

Study characteristics				Exposure		Outcome		Results			
Author (year)	Country	n	Study design	Depression prevalence	Nutrients/diet	Tool; recall/ intervention period	Time assessed	Tool; cut- point	Time assessed	Adj. model	Results
Miyake <i>et al.</i> (2015b)	Japan [†]	1745	Cross-section	19%	Intake of seaweed	FFQ; 1 month recall	Pregnancy	CES-D; 16	Pregnancy	Y	High (vs. low) seaweed consumption
TOTAL NUTRIENT INTAKES											
Paoletti <i>et al.</i> (2013)	Italy	552	RCT	14%	Group A: Vit A, B1, B2, B6, B12, B7, B9, C, D3, E, Ca, Fe, Mg, Mn, Cu, P and Zn Group B: calcium and Vit D3	Randomized; pregnancy	N/A	EPDS; 12	PP: 3, 15 and 30 days	N	Full multivitamin supplementation (group A) vs. calcium and Vit D3 (group B)
Leung <i>et al.</i> (2013)	Canada [‡]	475	Cohort	12%	Intake of Vit B1, B3, B6, B9, B12, D, iodine, Fe, Mg, Se, Zn and n-3 PUFA	Supplement Questionnaire; pregnancy	Each trimester	EPDS; 10	Each trimester PP: 12 weeks	Y	High (vs. low) intake of selenium
Bae <i>et al.</i> (2010)	Korea	114	Cross-section	43%	Intake of kcal, protein, fat, carbohydrate, fibre, Ca, P, Fe, Na, K, Vit A, B1, B2, B3, B6, B9, C, E, cholesterol, PUFA, MUFA, SFA, PM/S ratio	FFQ; 24 h recall	Pregnancy	BDI; 10	Pregnancy	N	High (vs. low) intake of total calcium, plant calcium, plant iron, potassium, total folate and dietary folate
Fowles <i>et al.</i> (2011)	United States	18	Cross-section	94%	Intake of grains, fruit, vegetables, kcal, % kcal from fat, Ca, Vit B9, Fe	FFQ+DQI-P; 3 × 24 h recall	First trimester	CES-D; 16	First trimester	N	Low (vs. high) intake of calcium-rich foods
Lukose <i>et al.</i> (2014)	India	365	Cross-section	33%	Intake of kcal, protein, fat, Vit C, B9, B12, Ca, P, Fe, Cu, Mn, Zn	FFQ; 3 months recall	First trimester	K-10; 6	First trimester	Y	None

(Continues)

Table 1. (Continued)

Author (year)	Study characteristics			Exposure		Outcome		Results	
	Country	n	Study design	Depression prevalence	Nutrients/diet	Tool; recall/ intervention period	Time assessed	Tool; cut-point	Time assessed
Watanabe <i>et al.</i> (2010)	Japan	86	Cross-section	62%	Intake of total energy, % energy from protein, fat, carbohydrate, Ca, Fe, Zn, Vit B9, B6, B12, C	BDHQ; 1 month recall	First trimester	CES-D; 16	First trimester
B VITAMINS									
Blunden <i>et al.</i> (2012)	UK ^e	2856	Cohort	32%	Intake of folate (B9), Vit B6 and B12	FFQ; 3 months recall	First and third trimester	EPDS; 13	PP: 6 months, 1 year
Lewis <i>et al.</i> (2012)	UK [†]	6809	Cohort	Preg.: 14% PP: 9%	Folic acid supplementation during pregnancy	Supplement Questionnaire; pregnancy	Second and third trimester	EPDS; linear/12	Second, Third trimester
Miyake <i>et al.</i> (2006a)	Japan [*]	865	Cohort	14%	Intake of folate (B9), Vit B2, B6 and B12	FFQ; 1 month recall	Pregnancy	EPDS; 9	PP: 8 and 21 months
Cho <i>et al.</i> (2008)	Korea	1277	Cross-section	8%	Folic acid supplementation during pregnancy	Folic acid supplementation questionnaire; pregnancy	Pregnancy	Goldberg's depression scale; 22	PP: 2-9 months
CALCIUM									
Harrison-Hohner <i>et al.</i> (2001)	United States	293	RCT	14% (OR) 22% (NM)	Group A: calcium supplement Group B: placebo	Randomized; pregnancy	Second trimester	EPDS; 14	PP: 6 and 12 weeks
Miyake <i>et al.</i> (2015a)	Japan [†]	1745	Cross-section	19%	Intake of dairy and calcium (milk products and calcium-rich foods)	FFQ; 1 month recall	Pregnancy	CES-D; 16	Pregnancy
VITAMIN D									
Miyake <i>et al.</i> (2015b)	Japan [†]	1745	Cross-section	19%	Dietary intake of Vitamin D	FFQ; 1 month recall	Pregnancy	CES-D; 16	Pregnancy
ZINC									
Roy <i>et al.</i> (2010)	Canada	2030	Cross-section	Not reported	Intake of zinc	FFQ, supplements; 1 month recall	First or second trimester	CES-D; 16	First or second trimester

(Continues)

Table 1. (Continued)

Study characteristics				Exposure		Outcome		Results			
Author (year)	Country	n	Study design	Depression prevalence	Nutrients/diet	Tool; recall/ intervention period	Time assessed	Tool; cut-point	Time assessed	Adj. model	Protective associations (unless noted; final models reported)
FISH FAT AND PUFAS											
Doombos <i>et al.</i> (2009)	Netherlands	119	RCT	6%	Group A: DHA+AA Group B: DHA Group C: placebo	Randomized; First trimester – 3 months PP	N/A	EPDS; 12	First and second trimester PP: 6 weeks PP: 2-6 weeks	N/A	None
Judge <i>et al.</i> (2014)	United States	42	RCT	10% (PDSS ≥80)	Group A: DHA Group B: placebo	Randomized; Second to third trimester	Third trimester	PDSS: mean difference		N/A	DHA supplementation (vs. placebo)
Llorente <i>et al.</i> (2003)	United States	138	RCT	7% (BDI >20)	Group A: DHA Group B: placebo	Randomized; 0-4 months PP	N/A	BDI; linear EPDS, SCID-CV	Third trimester PP: 3 weeks and 2 and 4 months PP: 6 months	N/A	None
Makrides <i>et al.</i> (2010)	Australia	2399	RCT	10% vs. 11%	Group A: DHA+ EPA Group B: placebo	Randomized; pregnancy	N/A	EPDS; 12		N/A	None
Da Rocha and Kac (2012)	Brazil	106	Cohort	26%	Intake of PUFA ratio: n-6/n-3	FFQ; First trimester recall	First trimester	EPDS; 11	PP: ≥30 days	Y	n-6/n-3 PUFA ratio <9:1 (vs. >9:1)
Miyake <i>et al.</i> (2006b)	Japan*	865	Cohort	14%	Intake of fish, meat, eggs, dairy, total fat, SFA, MUFA, n-3 PUFA, n-6 PUFA, LA, ALA, AA, EPA, DHA, ratio of n-3 to n-6 PUFA	FFQ; 1 month recall	Pregnancy	EPDS; 9	PP: 2-9 months	Y	None
Strom <i>et al.</i> (2009)	Denmark	54 202	Cohort	PPD admit: 0.3% PPD Rx: 1.6%	Intake of fish and n-3 PUFA	FFQ; 1 month recall	Mid-pregnancy	PPD admit PPD Rx (%)	PP: within 1 year	Y	High (vs. low) fish intake group for PPD prescription
Browne <i>et al.</i> (2006)	New Zealand	80	Case-control	BDI: 17% SCID-CV: 9%	Intake of PUFA	FFQ; recall NR	Pregnancy	BDI; SCID-CV; EPDS	PP: 6 months	N	None
Cosatto <i>et al.</i> (2010)	Australia	94	Cross-section	Not reported	Intake of n-3 PUFA	FFQ; 3 months recall	First trimester	EPDS; 10	First trimester	N	None
Golding <i>et al.</i> (2009)	UK†	9960	Cross-section	14%	Intake of n-3 PUFA	FFQ; pregnancy recall	Third trimester	EPDS; 13	Third trimester	Y	High (vs. low) intake of omega-3 from seafood
<i>(Continues)</i>											

(Continues)

Table 1. (Continued)

Author (year)	Study characteristics			Depression prevalence	Exposure		Outcome		Results		
	Country	n	Study design		Nutrients/diet	Tool; recall/ intervention period	Time assessed	Tool; cut- point		Time assessed	
Miyake <i>et al.</i> (2013)	Japan	1745	Cross-section	19%	Intake of fish, meat, total fat, SFA, MUFA, n-3 PUFA, n-6 PUFA, LA, ALA, AA, EPA, DHA, ratio of n-3 to n-6 PUFA	FFQ; 1 month recall	Pregnancy	CES-D; 16	Pregnancy	Y	High (vs. low) intake of fish, EPA and DHA
Sontrop <i>et al.</i> (2008)	Canada ⁶	2394	Cross-section	19%	Intake of fish and EPA+DHA	FFQ; 1 month recall	First and second trimester	CES-D; 16	Second or third trimester	Y	None

Adj. model, statistical analysis adjusted for potential confounding factors; RCT, randomized control trial; PCA, principle component analysis; EPDS, Edinburgh Post-partum Depression Scale; CES-D, Center for Epidemiological Studies Depression Scale; BDI, Beck's Depression Inventory; SCID-CV, Structured Clinical Interview; K-10, Kessler Depression Scale; PDSS, Post-partum Depression Screening Scale; Rx, prescription for antidepressants; admit, hospital admission for depression; NR, not reported; PPD, post-partum depression; Preg, pregnancy; PP, post-partum; FFQ, food frequency questionnaire; DQI-P, Dietary Quality Index in Pregnancy; BDHQ, Brief Diet History Questionnaire; RDA, Recommended Daily Allowance; Vit, Vitamin/s; Ca, calcium; Fe, iron; Mg, magnesium; Mn, manganese; Cu, copper; P, phosphorus; Se, selenium; Zn, zinc; B1, thiamin; B2, riboflavin; B3, niacin; B6, pyridoxine; B7, biotin; B9, folic acid; B12, cobalamin; PUFA, polyunsaturated fatty acid; MUFA, monounsaturated fatty acid; SFA, saturated fatty acid; n-3 PUFA, omega-3 polyunsaturated fatty acids; n-6 PUFA, omega-6 polyunsaturated fatty acids; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; ALA, alpha-linolenic acid; LA, linolenic acid; AA, arachidonic acid; OR, Oregon study site; NM, New Mexico study site; GI, glycemic index; GL, glycemic load; 'KOMCHS, Kyushu Okinawa Maternal and Child Health Study; *OMCHS, Osaka Maternal and Child Health Study; 'APRON, Alberta Pregnancy Outcomes and Nutrition study; 'ALSPAC, Avon Longitudinal Study of Parents and Children; ⁶Prenatal Health Project.

food intake used to identify a certain class of nutrients, including intake of B vitamins (four studies), calcium (two studies), Vitamin D (one study) and zinc (one study); and (4) fish and PUFAs (12 studies). The study populations were population-based prospective cohorts ($n = 14$), recruited from hospitals or clinics ($n = 15$), a baseline assessment of an RCT (Lukose *et al.* 2014), RCTs recruiting from health facilities ($n = 5$) and one RCT that did not report the source population (Doornbos *et al.* 2009).

The studies measured depression using a structured clinical interview, such as the Structured Clinical Interview for DSM-IV Diagnoses, or a screening tool for depressive symptoms, such as the EPDS or CES-D. The prevalence of perinatal depression reported in the general population was between 10% and 15% (Blunden *et al.* 2012; Chatzi *et al.* 2011; Da Rocha & Kac 2012; Leung *et al.* 2013). Several of the cross-sectional studies reported a very high prevalence of depressive symptoms, ranging from over 40% to 94% (Bae *et al.* 2010; Fowles *et al.* 2011a; Watanabe *et al.* 2010). In the cohort studies, prevalence of perinatal depression ranged from 12% (Leung *et al.* 2013) to 31.7% (Blunden *et al.* 2012).

Risk of bias assessment

There were several common sources of bias of the included studies, presented in Figures 3–5. Because risk of bias in certain domains (such as study attrition) was different for cross-sectional and cohort studies, these studies are presented separately. One case–control study is presented with the cohort studies (Browne *et al.* 2006). The RCTs were assessed by a different tool and are also presented separately.

All of the cross-sectional studies had some risk of bias in one or more domains, often because study characteristics were not adequately reported. In the study participation domain, only four studies achieved low risk of bias, while 75% (12/16) had medium or high risk of bias. Only 6/16 (38%) studies had low risk of bias concerning participation rates and potential differences between participants and non-participants. Overall, cross-sectional studies described appropriate exposure measurement, with only three out of 16 studies having high or medium risk of bias. Nine studies had high or

medium risk of bias in the outcome measurement domain, which often resulted from using a depression screening tool not validated for pregnancy (i.e. not the EPDS or the PDSS) and from inconsistent timing of outcome measurement. Another weak domain was the presentation of statistical analysis, in which only 44% (7/16) had low risk of bias.

Out of 12 cohort studies and one case–control study, only two studies had low risk of bias across all domains. Studies performed best on measurement of exposure and outcome and statistical analysis with nearly all studies ranked as low risk of bias on these domains. Half of the studies suffered from high or unreported study attrition. Not accounting sufficiently for potential confounding was a weakness in many observational studies. Only 8/16 (50%) cross-sectional studies and 8/12 (67%) cohort studies had a low risk of bias in this domain.

Only one RCT, Makrides *et al.* (2010) in Australia, had low risk of bias across all domains. Five out of six RCTs had incomplete outcome data causing possible attrition bias. Doornbos *et al.* (2009), Harrison-Hohner *et al.* (2001) and Paoletti *et al.* (2013) failed to report on at least some of the methods for allocation concealment or blinding of participants and outcome assessors.

Results from studies

Eleven studies showed clear protective effects from dietary intake: four cohort studies, three RCTs and four cross-sectional studies (Chatzi *et al.* 2011; Vilela *et al.* 2014; Paoletti *et al.* 2013; Miyake *et al.* 2015a; Da Rocha & Kac 2012; Miyake *et al.* 2013; Strom *et al.* 2009; Miyake *et al.* 2014; Miyake *et al.* 2015b; Harrison-Hohner *et al.* 2001; Judge *et al.* 2014). Eleven studies (seven cross-sectional and four cohort studies) detected associations that could have been spurious, as they were only observed within one or two strata (i.e. quartiles or quintiles) but not as a trend. Some of these studies observed only one or two associations from many tests of different nutrients or dietary components but not in an overall pattern or group. Thirteen of 35 studies reported weak or no associations at a threshold significance level of 0.05 (five cross-sectional studies, five cohort studies and three RCTs). All studies are described by group of exposure.

Fig. 2. Flowchart of study selection.

(1) Dietary patterns (Appendix 1)

Four cross-sectional studies and five cohort studies examined the relationship between dietary patterns and perinatal depression. Chatzi *et al.* (2011) used principle component analysis (PCA) and factor loading to identify two different dietary patterns, termed ‘healthy’ and ‘Western’, in pregnant women in Greece. They were ranked as having low risk of bias in all domains except study attrition and found that the ‘healthy’ pattern was protective against depressive symptoms 8–10 weeks post-partum in both the second and third tertiles [second tertile: risk ratio (RR)=0.52, 95% confidence interval (CI) 0.30–0.92, $P=0.03$; third tertile: RR=0.51, 95% CI 0.25–1.05, $P=0.07$; P -value for trend=0.04] compared with the least ‘healthy’ tertile, after adjusting for potential confounders. Similar results were observed when analysing the depression score as a continuous variable. There was no evidence that the degree of adherence to the Western dietary pattern was associated with depression.

Vilela *et al.* (2014) conducted a cohort study in Brazil and also found a healthy dietary pattern to be protective against antenatal depression. Using PCA, they

identified a ‘healthy’ pattern, a ‘common Brazilian’ pattern and a ‘processed’ pattern. They were ranked as having a low risk of bias in 5/6 domains and showed evidence for an association between adherence to a healthy dietary pattern and a lower EPDS score (β -coefficient = -0.72 , 95% CI -1.28 to -0.17 , $P=0.01$), while there was no evidence for any effect of the other dietary patterns tested.

Two cohort studies from Osaka, Japan, analysed dietary patterns identified with factor analysis (‘Healthy’, ‘Western’ and ‘Japanese’) as well as glycemic index and glycemic load, both of which suffered from risk of bias in several domains. One found evidence that a ‘Western pattern’ was associated with less perinatal depression but only in the second quartile of dietary compliance compared with the first [adjusted odds ratio (OR)=0.52, 95% CI 0.30–0.93] (Okubo *et al.* 2011). The other study found that glycemic load was not associated with perinatal depression but that the third highest quartile (vs. lowest) of glycemic index score was associated with less depressive symptoms (adjusted OR=0.56, 95% CI 0.32–0.995) (Murakami *et al.* 2008). Pina-Camacho *et al.* (2015) used a large birth cohort from England and found no association

Risk of bias: High Unclear Low

	Study participation	Study attrition	Exposure measurement	Outcome measurement	Study confounding	Statistical analysis and reporting
Bae 2010	High	Unclear	Unclear	Unclear	Unclear	High
Cho 2008	Unclear	Unclear	High	High	Unclear	Unclear
Cosatto 2010	Unclear	High	Low	Low	High	High
Fowles 2011a	Unclear	Low	Low	Low	High	High
Fowles 2011b	Unclear	Low	Low	Unclear	High	High
Fowles 2012	Unclear	Low	Low	Low	Low	High
George 2005	Unclear	Low	Low	Unclear	Low	High
Golding 2009	Low	Unclear	Low	Low	Low	Low
Lukose 2014	Low	Unclear	Low	Unclear	Low	Unclear
Miyake 2013	Unclear	Unclear	Low	Low	Low	Low
Miyake 2014	Unclear	Low	Low	Low	Low	Low
Miyake 2014a	Unclear	Unclear	Low	Unclear	Low	Low
Miyake 2015	Unclear	Unclear	High	Unclear	Unclear	Low
Roy 2010	Low	Unclear	Low	Unclear	Low	Low
Sontrop 2008	Low	Unclear	Low	Unclear	Unclear	Low
Watanabe 2010	Unclear	Low	Low	Unclear	Unclear	Unclear

Fig. 3. Risk of bias assessment for cross-sectional studies.

between unhealthy diet, determined using PCA, and post-partum depression, although their primary outcome of interest was not perinatal depression.

Three cross-sectional studies from the United States found some protective associations with depression, for instance, with low (vs. high) frequency of fast food consumption, high (vs. low) Dietary Quality Index in Pregnancy and high (vs. low) adherence to US national dietary guidelines (Fowles *et al.* 2011b, Fowles *et al.* 2012; George *et al.* 2005), despite very small sample sizes (51, 70 and 146, respectively). The authors did

	Study participation	Study attrition	Exposure measurement	Outcome measurement	Study confounding	Statistical analysis and reporting
Blunden 2012	Low	Unclear	Low	Low	Low	Low
Browne 2006	Low	Low	Unclear	Low	Unclear	Unclear
Chatzi 2011	Low	Unclear	Low	Low	Low	Low
da Rocha 2012	Low	High	Low	Low	Low	Low
Leung 2013	Low	Low	Low	Low	Low	Low
Lewis 2012	Low	Low	Low	Low	Low	Low
Miyake 2006a	Unclear	Unclear	Low	Low	Low	Low
Miyake 2006b	Low	Unclear	Low	Low	Low	Low
Murakami 2008	Unclear	Unclear	Low	Low	Unclear	Low
Okubo 2011	Low	Unclear	Low	Low	Unclear	Low
Pina-Camacho 2015	High	Unclear	Low	Unclear	Unclear	Unclear
Strom 2009	Low	Low	Low	Unclear	Low	Low
Vilela 2014	Low	Low	Low	Low	Unclear	Low

Fig. 4. Risk of bias assessment for cohort and case-control studies.

not present an analysis adjusted for confounding factors. Miyake *et al.* (2014) examined cross-sectional associations between seaweed intake and antenatal depression and found in an adjusted model that those in the highest quartile of seaweed consumption were less likely to be depressed than those in the lowest, observing a linear trend between quartiles (highest quartile OR 0.68 (CI 0.47–0.96), P for trend = 0.03), but this study was ranked as having unclear or medium risk of bias in 3/6 domains.

(2) Full panel of nutrients (Appendix 2)

Four cross-sectional studies, one cohort study and one RCT used FFQs to quantify a whole range of

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Doornbos 2009	?	?	?	?	●	?
Harrison-Hohner 2001	●	●	?	?	●	●
Judge 2014	?	●	●	●	●	●
Llorente 2003	●	●	●	●	●	●
Makrides 2010	●	●	●	●	●	●
Paoletti 2013	●	?	?	?	●	●

Fig. 5. Risk of bias assessment for randomized control trials.

essential nutrient intake. Paoletti *et al.* (2013) conducted an RCT in Italy, comparing Vitamin D and calcium supplementation with a full multivitamin supplement, measuring EPDS scores at 3 and 30 days post-partum. They found that at 1 month post-partum, the mean EPDS score was significantly ($P < 0.01$) lower in the full multivitamin supplementation group (3.2, SD 2.8, $n = 274$) than in the Vitamin D and calcium group (4.5, SD 3.8, $n = 278$). They reported that the difference was greater in the subgroup of women who screened positive for depression at entry into the study (EPDS score ≥ 12) but did not provide an interaction test. Their study had high or medium risk of bias in 4/6 domains. Leung *et al.* (2013) in their cohort study in Canada quantified the mean, range and percent of Recommended Daily Allowance in intake of various B vitamins, Vitamin D, omega-3 PUFAs, iodine, iron, zinc and selenium. Of these nutrients, only selenium

supplementation seemed protective against depression at 12 weeks post-partum (adjusted OR = 0.76, 95% CI 0.74–0.78, $P = 0.02$). This study had low risk of bias across all domains.

Four cross-sectional studies examined a range of nutrients and their possible associations with depression in pregnancy, three of which were carried out in the first trimester. These studies had medium and high risk of bias in several domains. Bae *et al.* (2010) in Korea found that intake of total calcium, plant calcium, plant iron, potassium, dietary folate and total folate (including supplements) was associated with depression but did not present an adjusted model. Fowles *et al.* (2011a) in the United States included 18 women in their sample, 17 of whom screened positive for depression, and found that higher calcium intake was associated with more depressive symptoms. Lukose *et al.* (2014) in India and Watanabe *et al.* (2010) in Japan found no evidence for protective associations from any of numerous vitamins and minerals tested.

(3) Specific nutrients (Appendix 3)

B vitamins. None of the studies evaluating B vitamins showed clear evidence of protective effects against perinatal depression. Cho *et al.* (2008) in a cross-sectional study in Korea, ranked as having high and medium risk of bias in all domains, found no evidence that supplementation with folic acid (Vitamin B9) was protective against depressive symptoms during pregnancy. Blunden *et al.* (2012) measured intake of B vitamins 6, 9 (folate) and 12, finding no relationship with depressive symptoms at either 6 months or 1 year post-partum in a study with low risk of bias in 5/6 domains. Lewis *et al.* (2012) did not find any evidence for an effect of folic acid supplements during pregnancy on risk of depression at 8 months post-partum, although there was a protective effect at 21 months post-partum in those with the MTHFR C677T genotype. Only one of four studies evaluating B vitamins found weak evidence of a protective association, but only in the third highest, and not in the highest quartile of riboflavin intake (Miyake *et al.* 2006a).

Calcium, Vitamin D and zinc. Harrison-Hohner *et al.* (2001) supplemented pregnant women with calcium

or a placebo and then measured post-partum depression in two different study sites. Results reported for one study site showed 6% of the supplementation group and 15% of the placebo group screened positive for major depressive disorder. This study had high or medium risk of bias in blinding of participants and assessors, incomplete outcome data and selective reporting.

Miyake *et al.* (2015a) in a cross-sectional study in Japan found a protective linear association between overall calcium and yoghurt intake (in quartiles) and depressive symptoms during pregnancy (CES-D score; ≥ 16 vs. < 16): highest vs. lowest quartile of calcium intake: OR 0.59, 95% CI 0.40–0.88, $P = 0.01$; highest vs. lowest quartile of yoghurt intake: OR 0.69, 95% CI 0.48–0.99, $P = 0.03$. The authors adjusted for many different potential confounders and found little difference between adjusted and unadjusted results.

Miyake *et al.* (2015b) used the same cross-sectional data to examine Vitamin D intake and antenatal depression. The study had a high or medium risk of bias in several domains and did not incorporate proxy measures of sunlight exposure. They detected a protective effect of intake when comparing the highest with lowest quartile (adjusted OR 0.52 CI 0.30–0.89, P for trend = 0.02).

Roy *et al.* (2010) measured zinc intake in over 2000 women in Canada and found that women in the lowest quintile of zinc consumption had a higher risk of antenatal depression between 10 and 22 weeks of gestation (lowest quintile $\beta = 1.0$, standard error 0.5, $P = 0.03$).

(4) Fish and PUFA intake (Appendix 4)

Only one of the four RCTs on supplementation with PUFAs, comprising docosahexaenoic acid (DHA), arachidonic acid and/or eicosapentaenoic acid (EPA), found an effect on perinatal depression. Judge *et al.* (2014) randomized 42 participants to receive either DHA in fish oil or a placebo during pregnancy and found that post-partum depression was lower in the DHA supplementation group (repeated measures least square mean: 46.03 (2.17) vs. 52.11 (2.4), $P = 0.02$). Doornbos *et al.* (2009) in the Netherlands supplemented 119 women with DHA and arachidonic acid, only DHA or placebo from the first trimester until 3

months post-partum and found no evidence of an effect on depressive symptoms using the EPDS at 6 weeks post-partum. This study suffered from high or medium risk of bias across all domains. Llorente *et al.* (2003) in a trial with 138 women in the United States also found no evidence that women supplemented with DHA for the first 4 months post-partum scored differently than those on placebo on the BDI. Makrides *et al.* (2010) ran a large trial ($n = 2399$) in Australia, supplementing women for the entire pregnancy with DHA and EPA or placebo and measuring their depressive symptoms at 6 months post-partum using the EPDS. They also found no strong evidence of a protective effect against depressive symptoms (adjusted RR 0.85, CI 0.70–1.02, $P = 0.09$) and also had a low risk of bias across all domains.

Two of four cohort studies on fish and essential fatty acid intake showed a clear protective effect. Da Rocha & Kac (2012) found that pregnant women in Brazil who ate a high ratio of n-6 to n-3 PUFAs had a 2.5 times higher prevalence of depressive symptoms (95% CI 1.21–5.14, $P = 0.01$) compared with women with a lower ratio, but they had high risk of bias from high study attrition. Strom *et al.* (2009) used an innovative approach linking fish and n-3 PUFA intake data from the Danish National Birth Cohort to registries containing information on hospital admission for depression and prescriptions for antidepressants within 1 year of giving birth. They found no associations with hospital admission for post-partum depression, but women who were in the lowest group of fish intake (vs. the highest) had 1.46 times the odds of having filled a prescription for anti-depressants (95% CI 1.12–1.90, $P = 0.04$). Browne *et al.* (2006) in a case-control study and Miyake *et al.* (2006b) in a cohort study found no evidence of associations between PUFA intake and post-partum depression.

Two out of four cross-sectional studies on fish and PUFA intake found evidence of protective effects on depressive symptoms during pregnancy. Golding *et al.* (2009) in the UK found a protective effect of eating fish (none vs. any fish intake (three groups combined): OR 1.54, 95% CI 1.25–1.89, test for trend over four groups: $P < 0.01$). Miyake *et al.* (2013) in Japan found evidence of protective effects from overall fish intake, DHA and

EPA intake (highest vs. lowest quartiles of fish intake: OR 0.61, 95% CI 0.42–0.87, $P=0.01$; EPA: OR 0.66, 95% CI 0.46–0.95, $P=0.02$; and DHA: OR 0.64, 95% CI 0.44–0.93, $P=0.007$). They also found evidence that higher intakes of total fat and saturated fat were risk factors for depressive symptoms (highest vs. lowest quartiles of total fat: OR 1.42, 95% CI 1.00–2.03, $P=0.06$; saturated fat: OR 1.74, 95% CI 1.22–2.49, $P=0.001$). Cosatto *et al.* (2010) and Sontrop *et al.* (2008) found no evidence for protective effects against depressive symptoms of eating fish or consuming PUFAs during pregnancy.

Discussion

Overall, there is limited evidence that dietary intake influences the risk of perinatal depression. While 13 studies, including three PUFA supplementation trials, found no evidence of an association, 22 studies showed some protective effects from healthy dietary patterns, multivitamin supplementation, fish and PUFA intake, calcium, zinc and possibly selenium. However, given the methodological limitations of studies on this topic, the lack of evidence does not necessarily imply the absence of true associations. In order to clearly answer the question whether certain diets and nutrients influence the risk of perinatal depression, the issues discussed below warrant consideration in future study designs.

Exposure measurement

Most dietary intake assessments rely on FFQs, which are the best available option for ascertaining dietary and nutrient intake but are still imprecise measures and can suffer from reporting bias (Ioannidis 2013). In the case of Vitamin D, measuring dietary intake alone is insufficient because a main source of bioavailable Vitamin D is sunlight exposure (Millen & Bodnar 2008). Blood analysis can verify what is processed and made available by the body, and four of the reviewed studies evaluated both dietary intake and nutrient blood levels (Bae *et al.* 2010; Fowles *et al.* 2011a; Lukose *et al.* 2014; Watanabe *et al.* 2010). However, blood analysis is costly, often limited to a few nutrients and does not capture unknown food

compounds and food synergies. For these reasons, it is difficult to detect robust associations between nutrition and health outcomes.

Often, nutrition is only measured at one point during pregnancy, while long-term dietary habits may be more relevant, and pregravid nutritional status and intake is an important baseline for nutrient changes (primarily losses) during pregnancy and lactation. Dietary intake prior to pregnancy was not measured in any included study, although some studies had a recall period covering pre-pregnancy, and four of the Japanese studies included a question about whether there were significant changes in the diet in the previous month (Miyake *et al.* 2006a, 2006b; Okubo *et al.* 2011; Murakami *et al.* 2008). Da Rocha & Kac (2012), Strom *et al.* (2009) and Miyake *et al.* (2015a, 2015b) included pre-pregnancy BMI. Only 6/35 studies (17%) measured dietary intake more than once (Blunden *et al.* 2012; Lewis *et al.* 2012; Roy *et al.* 2010; Sontrop *et al.* 2008; Vilela *et al.* 2014; Leung *et al.* 2013), and the timing of measurements was highly variable between subjects enrolled. Because dietary intake and nutritional needs can fluctuate heavily during the perinatal period, the timing of exposure measurement should be considered in any multivariable model of nutrition and depression but was included in only 10/35 studies (29%). Ideally, dietary intake should be measured at baseline or prior to pregnancy and again at several follow-up time points to offset the imprecision of a FFQ with a long recall period. Such successive intake measurements were performed by only five studies included in this review (Leung *et al.* 2013; Blunden *et al.* 2012; Lewis *et al.* 2012; Roy *et al.* 2010; Sontrop *et al.* 2008).

Outcome measurement

Clinical diagnosis of perinatal depression is the gold standard but requires a trained interviewer and an evaluation that often takes over an hour and thus is usually not feasible for epidemiological purposes (Bennett *et al.* 2004). Depression screening tools are commonly used instead, and the EPDS and PDSS are particularly designed and validated for the perinatal period. Because symptoms can change rapidly and dramatically, especially during the perinatal period, a standard and well-timed measurement is particularly

important (Noble 2005). While screening tools for perinatal depression are not a substitute for a clinical diagnosis of depression, they can have good sensitivity and specificity, depending on the cut-off point and population (Gibson *et al.* 2009; Hewitt *et al.* 2009). The EPDS has been validated for many cultural contexts (Gibson *et al.* 2009) and for use during pregnancy. A cut-off point of ≥ 13 for the EPDS (used by Chatzi *et al.*, Blunden *et al.* and Golding *et al.*) has been shown to have a sensitivity of 0.91 (95% CI 0.84–0.99) and a specificity of 0.91 (95% CI 0.88–0.94) for post-partum depression (Hewitt *et al.* 2009). Nineteen of the 35 studies used the EPDS or PDSS or a clinical diagnosis of depression, while the others used screening tools that may not produce valid results in the perinatal period.

Depression prior to pregnancy is a known risk factor for perinatal depression, and antenatal depression may predict post-partum depression; therefore, it is critical to include pre-pregnancy or antenatal screening measurements. However, only eight studies took repeated measurements of depression (Vilela *et al.* 2014; Leung *et al.* 2013; Paoletti *et al.* 2013; Blunden *et al.* 2012; Lewis *et al.* 2012; Judge *et al.* 2014; Harrison-Hohner *et al.* 2001; Pina-Camacho *et al.* 2015), and only 10 studies included a history of depression in their analysis (Chatzi *et al.* 2011; Leung *et al.* 2013; Blunden *et al.* 2012; Miyake *et al.* 2013, 2015a; Strom *et al.* 2009; Miyake *et al.* 2014, 2015b; Harrison-Hohner *et al.* 2001; Judge *et al.* 2014).

Other sources of bias

Many of the included studies suffered from design issues. Ten studies had sample sizes less than 200, limiting the power to detect differences between depressed and non-depressed women. Sixteen of the 35 studies were cross-sectional, and associations in these studies could be due to reverse causality: depression may cause changes in self-care and eating habits, which may change dietary intake. In order to assess whether nutritional factors cause depression, intake has to be measured prior to ascertaining depression with an appropriate lag time. However, of the 11 reviewed studies that reported clear protective effects, eight were cohort studies or RCTs, and therefore, only four were

limited by potential reverse causation (Miyake *et al.* 2013, 2015a, 2014, 2015b). Thirteen of the studies were nested in large cohorts and therefore benefitted from larger sample sizes, lag time between exposure and outcome measurement, and longer follow-up periods. In some studies, there was high variability in the timing of both exposure and outcome measurements, which limited comparability between subjects. The enrollment and inclusion criteria of study participants were often not described in detail, with the exception of those within research cohorts. Many studies did not adjust for potential confounders, meaning that associations observed could have been due to other factors related to both dietary intake and perinatal depression.

Prevalence of nutritional deficiency

Most studies included in this review were undertaken in high-income settings where dietary intake is generally sufficient and the prevalence of nutrient deficiencies is often very low. In order to create an evidence base that is generalizable and relevant for vulnerable populations, studies must also be carried out in LMICs where prevalence rates of perinatal depression, as well as insufficient nutrition, are higher (Fisher *et al.* 2012; Patel *et al.* 2004). Only one of the 35 studies was from a lower-middle-income country, India, and two from a higher-middle-income country, Brazil. If we assume that there is a nutritional ‘threshold’, i.e. a critical point below which deficiencies will lead to symptoms of depression, and the studies included few or no women below the threshold, this could explain the lack of associations. In other words, there may have been insufficient power to detect effects because of the low number of participants in the included studies eating a diet that places them in the most deficient range. Conversely, a Canadian study in a socio-demographically homogenous clinic population in London, Ontario, found that women in the lowest quintile of zinc intake (around or below the recommended daily intake) had a one point higher depression score on average than women in the highest quintile, a difference that the authors did not consider ‘clinically meaningful’ but which reached statistical significance because of a large sample size of 2030 women (Roy *et al.* 2010). Another

explanation for the absence of associations in many studies could be a lack of variation in dietary intake in the sample. For example, Blunden *et al.* (2012) report null results for folate (Vitamin B9), Vitamin B6 and Vitamin B12, but 96% of the women in that study reported taking folic acid supplements during pregnancy, and the prevalence of folate deficiency in the study sample was below 5%.

Practical implications

The study of single nutrients or foods may not capture how ingested foods interact in complex biochemical systems to influence mood regulation and outcomes such as depression. Considering diets and dietary patterns, however, better reflects the synergies that result from cumulative food consumption, nutrient interactions, food quality, unknown substances or unknown effects of substances in food. More holistic approaches to exposure measurement may therefore be a promising approach in epidemiological studies of the effects of nutrition on disease outcomes (Jacobs & Steffen 2003). Two studies included in this review suggest that there may be a protective effect against perinatal depression from eating a healthy diet (Chatzi *et al.* 2011; Vilela *et al.* 2014), a finding that may encourage further investigation. Other studies have examined the role of specific dietary patterns on depression outside of the perinatal period (Akbaraly *et al.* 2009; Jacka *et al.* 2010; Sanchez-Villegas *et al.* 2006), and one found that a 'healthy' diet was protective against depression in Australian women (Jacka *et al.* 2010).

The current interest in the relationship between dietary intake and perinatal depression focuses mostly on treatment of depression with non-pharmacological interventions, such as PUFAs (Ellsworth-Bowers & Corwin 2012). Existing interventions for perinatal depression are often inaccessible or ineffective for women who are exposed to numerous risk factors, so a shift of focus to prevention is warranted.

A series of articles published in *The Lancet* in 2014 highlighted risk factors for perinatal depression such as low socioeconomic status, trauma, domestic violence, lack of support, migration status, history of psychopathology, and chronic illness and medical

problems (Howard *et al.* 2014a). Several reviews highlight non-nutritional treatment options for perinatal depression in LMICs that focus on social support and complex interventions (Rahman *et al.* 2013; Howard *et al.* 2014a). Some of the complex interventions suggested comprise health and economic components that are also designed to improve nutrition. Better understanding the root causes of perinatal depression may allow a shift from treatment to prevention, and targeting these root causes might simultaneously alleviate other adverse health outcomes.

Strengths and limitations

We opted for broad inclusion criteria and a sensitive search strategy, which meant that the studies reviewed were heterogeneous and covered a wide range of dietary intake measurements, including whole diets. We included both antenatal and post-partum depression in our review, which have previously often been separated (O'Hara & Wisner 2014; Howard *et al.* 2014b). Recent epidemiological studies suggest that antenatal depression is both common unto itself and a risk factor for post-partum depression (Patel *et al.* 2002; Liabsuetrakul *et al.* 2007; Husain *et al.* 2006), and therefore, we decided that these should be considered together. The heterogeneity of studies excluded the possibility of a meta-analysis, but this review is the most current synthesis of the evidence available on this topic.

Only English-language papers were included, which limits our ability to incorporate evidence presented in other languages that might be relevant. Additionally, this review only included published study results, which may have introduced bias as studies that found no associations between dietary intake and perinatal depression are less likely to be published.

A main limitation of this review is that few studies were from settings where severe or widespread nutrient deficiencies exist, and nutrient intake levels may therefore have been too high and their range too narrow to detect any association with depression. It should also be noted that several studies came from the same groups of researchers, one group from Japan contributed eight studies and another group from the United States contributed three. Because they provided

distinct analyses of different nutrients, all of these were included, but the populations and study designs in these groups were the same or very similar, and thus, they do not represent independent pieces of evidence.

Conclusions

This review shows that there is inconclusive evidence that individual nutrients or dietary patterns contribute to the development of perinatal depression. Further studies in populations that have a wider variation in nutrient intake and compromised nutrition are needed to better elucidate this relationship. Also, future studies should incorporate baseline levels of nutrition and depression, as well as measuring dietary intake and depression at several time points throughout the perinatal period. High-quality longitudinal studies could also overcome the problem of reverse causality between dietary intake and perinatal depression.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Contributions

TS proposed the concept and compiled the search. SG and NH advised on conceptual issues. NH, RN and TS screened titles, abstracts and full text articles for

inclusion, and completed the risk of bias assessment. TS led the review process and the writing. SG led the editing process, and all authors read, edited and approved the final manuscript.

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Appendix Table 1. Results of studies evaluating associations between dietary patterns and perinatal depression

Author (year)	<i>n</i>	Nutrients/diet (components of analysis)	Analysis	Unit of exposure	Unit of outcome	Unadjusted associations significant at $p < 0.10$ (effect size, 95% CI, <i>P</i> -value)	Adjusted associations significant at $p < 0.10$ (effect size, 95% CI, <i>P</i> -value)	Potential confounders considered	Limitations
Chatzi <i>et al.</i> (2011)	519	FFQ into principle component analysis; factor loading. • 'Healthy pattern' = high vegetables, fruit, pulses, olive oil, fish/seafood, milk and nuts. • 'Western pattern' = high meat/meat products, potatoes/starches, sugar/sweets, cereals, fats except olive oil, eggs, alcoholic and non-alcoholic drinks, snacks and sauces	Multivariable log-binomial regression	Tertiles of dietary compliance (T1: lowest/ reference, T2: middle, T3: highest)	EPDS score; ≥ 13 vs. < 10	Healthy: T1: ref. • T2: RR = 0.54 (CI 0.31–0.95); $P = 0.03$ • T3: RR = 0.56 (CI 0.28–1.12); $P = 0.10$ • <i>P</i> for trend = 0.07 • Western: tertiles NS, <i>P</i> for trend: NS	Healthy: T1: ref. • T2: RR = 0.52 (CI 0.30–0.92); $P = 0.03$ • T3: RR = 0.51 (CI 0.25–1.05); $P = 0.07$ • <i>P</i> for trend = 0.04 • Western: tertiles NS, <i>P</i> for trend: NS	Age, education, parity, house tenure, depression in previous pregnancies and total energy intake during pregnancy.	• Low participation rate (57%), but analysis shows no significant differences between participants and non-participants
Murakami <i>et al.</i> (2008)	865	FFQ to quantify high GI and GL in diet. • GI = consumed foods * weighted GI value.	Multivariable logistic regression	Quartiles of dietary indices (Q1: lowest/ reference,	EPDS score; ≥ 9 vs. < 9	Healthy: T1: ref. • T2: $\beta = -0.80$ (CI -1.86–0.25); $P = 0.14$ • T3: $\beta = -0.63$ (CI -1.69 to -0.43); $P = 0.04$ • <i>P</i> for trend = 0.24 Western: T1: ref. • T2: $\beta = -0.91$ (CI -0.14–1.96); $P = 0.09$ • T3: $\beta = 1.27$ (CI 0.21–2.32); $P = 0.02$ • <i>P</i> for trend = 0.02	Healthy: T1: ref. • T2: $\beta = -1.13$ (CI 2.25–0.0); $P = 0.05$ • T3: $\beta = -1.75$ (CI -3.22 to -0.28); $P = 0.02$ • <i>P</i> for trend = 0.02 Western: T1: ref. • T2: $\beta = 0.96$ (CI -0.17–2.00); $P = 0.10$ • T3: $\beta = 1.32$ (CI -0.19–2.76); $P = 0.07$ • <i>P</i> for trend = 0.07 GI diet compliance: Q1: ref. • Q2: OR 0.68 (CI 0.39–1.17)	Age, gestation, parity, smoking, family structure, occupation, family income, education, changes	• Assessment timing not standard for all participants

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Appendix Table I. (Continued)

Author (year)	<i>n</i>	Nutrients/diet (components of analysis)	Analysis	Unit of exposure	Unit of outcome	associations significant at $p < 0.10$ (effect size, 95% CI, <i>P</i> -value)	associations significant at $p < 0.10$ (effect size, 95% CI, <i>P</i> -value)	Potential confounders considered	Limitations
Miyake <i>et al.</i> (2014)	1745	FFQ to quantify seaweed consumption (g / d)	Multivariable logistic regression	Quartiles of intake (Q1: reference, Q2, Q3, Q4: highest)	CES-D score; ≥ 16 vs. < 16	Seaweed intake: Q1: ref. • Q2: OR 0.70 (CI 0.51–0.97) • Q3: OR 0.62 (CI 0.45–0.86) • Q4: OR 0.60 (CI 0.43–0.83) • <i>P</i> for trend = 0.002	Seaweed intake: Q1: ref. • Q2: OR 0.72 (CI 0.51–1.004) • Q3: OR 0.71 (CI 0.50–1.01) • Q4: OR 0.68 (CI 0.47–0.96) • <i>P</i> for trend = 0.03	Age, gestation, residence, parity; family structure, history of depression, family history of depression, smoking, secondhand smoke exposure, job type, household income, education, BMI and intake of fish and yoghurt	- Primary study outcome not depression - Assessment timing not standard for all participants - Participation rate and characteristics not available

ANOVA, Analysis of Variance; BMI, body mass index; CES-D, Center for Epidemiological Studies Depression Scale; CI, confidence interval; d, day; DIETSYS, Dietary Analysis Systems software; DQI-P, Dietary Quality Index in Pregnancy; EPDS, Edinburgh Post-partum Depression Scale; GI, glycemic index; GL, glycemic load; kcal, kilocalories; NS, not significant; OR, odds ratio; g, grams.

*Significant ($P < 0.05$) in final model.

Appendix Table 2. Results of studies evaluating associations between nutrient intake and perinatal depression

Author (year)	<i>n</i>	Nutrients/diet (components of analysis)	Analysis	Unit of exposure	Unit of outcome	Unadjusted associations significant at $P < 0.10$ (effect size, 95% CI, P -value)	Adjusted associations significant at $P < 0.10$ (effect size, 95% CI, P -value)	Potential confounders considered	Limitations
Paoletti <i>et al.</i> (2013)	552	Group A: Vit A, 3600 IU; Vit B1, 1.55 mg; Vit B2, 1.8 mg; Vit B6, 2.6 mg; B7, 0.2 mg; Vit B12, 4 mcg; Vit C, 100 mg; Vit D3, 500 IU; Vit E, 15 IU; Vit B9, 800 mcg; Ca, 125 mg; Fe, 60 mg; Mg, 100 mg; Mn; 1 mg; Cu, 1 mg; P, 125 mg; Zn, 7.5 mg Group B: Ca, 500 mg; Vit D3, 400 IU	Mean difference between groups	Group A vs. group B	Mean EPDS score	Mean differences in EPDS score with $P < 0.05$: • All participants: group A 3.2 (SD 2.8) vs. group B 4.5 (SD 3.8) • Basal EPDS <12: group A 2.7 (SD 2.5) vs. group B 3.5 (SD 3.2) • Basal EPDS ≥ 12 : group A 6.8 (SD 3.8) vs. group B 9.9 (SD 3.8)	Not reported	No baseline imbalance for age, BMI, baseline haematological parameters and EPDS score.	• Food intake not measured • Loss to follow-up not analysed for differences in completers and non-completers • No history of depression considered
Leung <i>et al.</i> (2013)	475	Supplement questionnaire to quantify mean, range and percent of RDA through prenatal supplement intake of Vit B1 (mg), B3 (mg), B6 (mg), B9 (mcg), B12 (mcg), D (IU), iodine (mcg), Fe (mg), Mg (mg), Se (mcg), Zn (mg) and n-3 PUFA (mg)	Multivariable logistic regression	Mean nutrient intake	EPDS score <10 vs. ≥ 10	Univariable analysis: • n-3 PUFA supplement intake (for EPDS <10 vs. ≥ 10) 180 vs. 90 mg/day, $P = 0.01$ • Selenium supplement (for EPDS <10 vs. ≥ 10) 25 vs. 19 mcg/day $P = 0.002$ Full model: • Selenium supplement intake OR = 0.97 (CI 0.95–0.99), $P = 0.03$ • Mean nutrient intakes from other supplements higher in women with low EPDS scores but NS.	Final model: • Selenium supplement intake OR = 0.76 (CI 0.74–0.78); $P = 0.02$	Age, parity, marital status, education, income, born outside Canada, ethnicity, BMI, stressors during pregnancy, stressors prior to pregnancy, stressors prior to age 17, social support*, prenatal EPDS scores* and prenatal selenium supplement*	• 90% above RDA, very few women deficient • Multi-collinearity in sets of nutrients commonly combined in supplements • Food intake not measured • No history of depression included
Fowles <i>et al.</i> (2011a)	18	3 × 24 h quantitative food recall including intake of grains (oz/d), fruit (cups/d), vegetables (cups/d), energy (kcal/d), % kcal from fat, calcium (mg/d), folate (mg/d) and iron (mg/d)	Spearman's rho	Mean nutrient intake	CES-D score; linear	Higher depression score associated with higher calcium intake: • Spearman's rho 0.60, $P = 0.02$	Not reported	Not included in univariable or adjusted model	• No adjusted model of the association of interest • No potential confounders included in model
Bae <i>et al.</i> (2010)	114	Energy (kcal/d), protein (g/d), fat (g/d), carbohydrate (g/d), fiber (g/d), total Ca(mg/d), plant Ca (mg/d), animal Ca (mg/d), P (mg/d), total Fe	T-test and chi-squared test	Mean nutrient intake	BDI score; ≥ 10 vs. <10	• Higher intake of energy, protein, fat, in non-depressed group, but NS Significant associations: • Total Ca: 648.33 (SD 252.11)	Not reported	Tested for association with the outcome, but not included in final model: age, pre-pregnancy BMI,	• Cut-point for depression based on mean, not validated cut-point for screening depressed vs. non-depressed

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Appendix Table 2. (Continued)

Author (year)	<i>n</i>	Nutrients/diet (components of analysis)	Analysis	Unit of exposure	Unit of outcome	Unadjusted associations significant at <i>P</i> < 0.10 (effect size, 95% CI, <i>P</i> -value)	Adjusted associations significant at <i>P</i> < 0.10 (effect size, 95% CI, <i>P</i> -value)	Potential confounders considered	Limitations
Lukose <i>et al.</i> (2014)	365	(mg/d), plant Fe (mg/d), animal Fe (mg/d), supplement Fe (mg/d), Na (mg/d), K (mg/d), Vit A (mg/d), B1 (mg/d), B2 (mg/d), B3 (mg/d), B6 (mg/d), Total B9 (mg/d), dietary B9 (mg/d), supplement B9 (mg/d), C (mg/d), E (mg/d), Cholesterol (mg/d), PUFA (g/d), MUFA (g/d), SFA (g/d), PUFA/MUFA/SFA ratio	Chi-squared test; multivariable log binomial regression	Mean nutrient intake	K-10 score; ≥ 6 vs. < 6	vs. 533.08 (SD 251.52); <i>p</i> =0.02 • Plant Ca: 308.50 (SD 118.78) vs. 252.80 (SD 117.39); <i>p</i> =0.01 • Plant iron: 11.43 (SD 8.56) vs. 8.33 (SD 3.02); <i>p</i> =0.01 • K: 3,073.10 (SD 1192.30) vs. 2,430.30 (SD 881.11); <i>p</i> =0.001 • Total folate: 281.15 (SD 113.99) vs. 230.47 (SD 89.16) <i>p</i> =0.04 • Dietary folate: 288.07 (SD 128.93) vs. 229.26 (SD 91.94); <i>p</i> =0.006 Nutrient intakes NS	vs. pregnancy BMI, delivery birth BMI, parity*, education, income, occupation, morning sickness, nutritional supplements	Age, education, occupation, parity, BMI, anaemia*, nausea and vomiting*	• Assessment timing not standard for all participants • No adjusted model of the association of interest • No history of depression considered • Only univariable tests of nutrients, no effect sizes or <i>p</i> -values reported if <i>p</i> > 0.05 and not included in adjusted model • Unrealistically high depression prevalence • BDHQ not a robust FFQ • Depression measured in first trimester • No history of depression considered
Watanabe <i>et al.</i> (2010)	86	Brief self-administered diet history questionnaire (BDHQ) to quantify intake of total energy, % energy from protein, fat, carbohydrate, Ca, Fe, Zn, Vit B9, B6, B12 and C	<i>t</i> -test, chi-squared test and logistic regression	Mean nutrient intake	CES-D score; < 16 vs. ≥ 16	Iron (mg/1000 kcal) • Non-depressed group: 4.3 (SD 0.9) • Depressed group: 3.9 (SD 0.8); <i>P</i> = 0.06 Other nutrient intakes NS but higher intake in non-depressed group	Folate, Vitamins B6, B9 and B12 intake included; NS	Age, height, pre-pregnancy weight, pre-pregnancy BMI, gestational age*, parity* and vomits per day*	• Depression measured in first trimester • No history of depression considered

Admit, hospital admission for depression; B1, thiamin; B2, riboflavin; B3, niacin; B5, pantothenic acid; B6, pyridoxine; B7, biotin; B12, cobalamin; B9, folic acid; BDI, Beck's Depression Inventory; BMI, body mass index; Ca, calcium; CES-D, Center for Epidemiological Studies Depression Scale; CI, confidence interval; Cu, copper; EPDS, Edinburgh Post-partum Depression Scale; Fe, iron; FFQ, Food frequency questionnaire; K-10, Kessler Depression Scale; kcal, kilocalorie; Mg, magnesium; Mn, manganese; n-3 PUFA, omega-3 polyunsaturated fatty acids; n-6 PUFA, omega-6 polyunsaturated fatty acids; NS, not significant; OR, odds ratio; P, phosphorus; PUFA, polyunsaturated fatty acid; RCT, randomized control trial; Rx, prescription for antidepressants; SD, standard deviation; Se, selenium; Vit, Vitamin; Zn, zinc; g, grams; mg, milligrams; oz, ounces.

*Significant ($P < 0.05$) in final model.

Appendix Table 3. Results of studies evaluating associations between intake of specific nutrient groups and perinatal depression

Author (year)	<i>n</i>	Nutrients/diet (components of analysis)	Analysis	Unit of exposure	Unit of outcome	Unadjusted associations significant at $P < 0.10$ (effect size, 95% CI, <i>P</i> -value)	Adjusted associations significant at $P < 0.10$ (effect size, 95% CI, <i>P</i> -value)	Potential confounders considered	Limitations
B VITAMINS									
Blunden <i>et al.</i> (2012)	2856	FFQ to quantify intake of folate (B9), Vit B6 and B12	Multivariable Poisson regression	Strata of intake, per 10 units	EPDS score; ≥ 13 vs. < 13	Nutrient intakes NS at any time point	Not reported	History of mental illness*, education, scoring positive for depression on the GHQ*, smoking, alcohol, social benefits, financial strain, breastfeeding*, folic acid supplements and pregravid and early pregnancy red-cell folate.	• Less than 5% of study population with low/marginal folate • PPD screening done on average at 1 year PP
Lewis <i>et al.</i> (2012)	6809	Self-reported folic acid supplementation during pregnancy	Multivariable linear regression, stratification by genotype	Supplementation vs. no supplementation	EPDS score; linear	Supplementation NS within 1 year post-partum.	Not reported	Age, pre-pregnancy BMI, education and parity, and other confounders tested by MTHFR C677T genotype stratification	• Self-reported supplementation history, no amount or frequency • Women taking multivitamins • Were included in unexposed group • Folate deficiency in population not known • No history of depression considered
Miyake <i>et al.</i> (2006a)	865	FFQ to quantify intake of folate (B9), Vit B2, B6 and B12	Multivariable logistic regression	Quartiles of intake (Q1: lowest/reference, Q2, Q3, Q4: highest)	EPDS score; ≥ 9 vs. < 9	Vitamin B2 intake: Q1: ref. • Q2: ref. OR 0.58 (CI 0.33–0.98) • Q3: OR 0.50 (CI 0.28–0.87) • Q4: OR 0.82 (CI 0.49–1.35) • <i>P</i> for trend = 0.35 Other B vitamins NS in any quartile	Vitamin B2 intake: Q1: ref. • Q2: OR 0.61 (CI 0.34–1.06) • Q3: OR 0.53 (CI 0.29–0.95) • Q4: 0.88 (CI 0.51–1.50) • <i>P</i> for trend = 0.55 Other B vitamins NS in any quartile	Age, gestation, parity, smoking, family structure, occupation, family income, education, changes in diet in previous month, season of baseline data, BMI, time of delivery, problems during pregnancy, baby's sex and baby's birth weight.	• Assessment timing not standard for all participants • Potential confounders not included in model • No history of depression considered
Cho <i>et al.</i> (2008)	1277	Multivitamin and folic acid supplementation (MV/FA) during pregnancy	Chi-squared test	Supplementation vs. no supplementation	Goldberg's Depression Scale score; ≥ 22 vs. < 22	MV/FA intake in preconception period NS: • 10.7% vs. 7.9%, OR	Not reported	Tested for association with the outcome but not included in final model: age, gestational age, pregnancy intended, education, income, family	• Nutrition measure not robust (yes/no for MV/FA supplementation)

(Continues)

Appendix Table 3. (Continued)

Author (year)	<i>n</i>	Nutrients/diet (components of analysis)	Analysis	Unit of exposure	Unit of outcome	Unadjusted associations significant at $P < 0.10$ (effect size, 95% CI, <i>P</i> -value)	Adjusted associations significant at $P < 0.10$ (effect size, 95% CI, <i>P</i> -value)	Potential confounders considered	Limitations
CALCIUM Harrison-Hohner <i>et al.</i> (2001)	293	Group A: 2000 mg elemental calcium per day Group B: placebo	Comparison of means	Calcium vs. placebo group	EPDS score: ≥ 14 vs. < 14 ; mean difference	1.4 (CI 0.77–2.54) MV/FA intake at any time in pregnancy NS; • 9.4% vs. 6.9%, OR 0.72 (CI 0.48–1.08) % of calcium vs. placebo group ≥ 14 on EPDS groups: • 6 weeks: Oregon: 11% vs. 18%, $P = 0.07$ New Mexico: 24% vs. 21%, $P > 0.05$ • 12 weeks, Oregon only: 6% vs. 15%, $P = 0.014$ Mean EPDS scores (12 weeks, Oregon only): • 6.4 (SEM 0.38) vs. 7.3 (SEM 0.45), $P > 0.05$	Not reported	history of depression* and history of premenstrual syndrome* Baseline differences in age, education, history of depression, gestation, birth weight of baby, breastfeeding, life stress (Oregon only), serum Vit D, calcitonin and parathyroid hormone tested between groups, NS	• No adjusted model of the association of interest • High loss to follow-up (29% completed in NM, 60% completed in Oregon) • Study not designed/powerd for <i>post hoc</i> analysis of depression • Blinding and selective reporting information not available • Study sites not comparable
Miyake <i>et al.</i> (2015)	1745	FFQ to quantify intake of total energy, total dairy, milk, yoghurt, cheese, calcium, fish, SFAs, EPA+DHA, Vitamin D	Multivariable logistic regression	Quartiles of intake (Q1: reference, Q2, Q3, Q4; highest)	CESD score: ≥ 16 vs. < 16	• Yoghurt: Q1: ref. • Q2: OR 0.81 (CI 0.58–1.11) • Q3: OR 0.66 (CI 0.47–0.92) • Q4: OR 0.68 (CI 0.49–0.95) • P for trend = 0.01 Calcium: Q1: ref. • Q2: OR 0.79 (CI 0.57–1.10) • Q3: OR 0.67 (CI 0.48–0.93) • Q4: OR 0.68	• Yoghurt: Q1: ref. • Q2: OR 0.80 (CI 0.57–1.13) • Q3: OR 0.70 (CI 0.49–0.99) • Q4: OR 0.69 (CI 0.48–0.99) • P for trend = 0.03 Calcium: Q1: ref. • Q2: OR 0.75 (CI 0.53–1.06) • Q3: OR 0.63 (CI 0.44–0.92) • Q4: OR 0.59	Age*, gestational age, residential area, parity*, family structure, personal history of depression, family history of depression, ever smoked*, smoke exposure, job type, household income*, education*, BMI, intake of fish, SFAs, EPA, DHA and Vitamin D	• Assessment timing not standard for all participants • Participation rate and characteristics not available

(Continues)

Appendix Table 3. (Continued)

Author (year)	<i>n</i>	Nutrients/diet (components of analysis)	Analysis	Unit of exposure	Unit of outcome	Unadjusted associations significant at $P < 0.10$ (effect size, 95% CI, P -value)	Adjusted associations significant at $P < 0.10$ (effect size, 95% CI, P -value)	Potential confounders considered	Limitations
VITAMIN D									
Miyake <i>et al.</i> (2015b)	1745	FFQ to quantify intake of Vit D (mcg/d)	Multivariable logistic regression	Quartiles of intake (Q1: reference, Q2, Q3, Q4: highest)	CESD score; ≥ 16 vs. < 16	(CI 0.49–0.95) • P for trend = 0.01 Other nutrient variables NS	(CI 0.40–0.88) • P for trend = 0.006 Other nutrient variables NS	Age, gestation, residence, parity, family structure, history of depression, family history of depression, smoking, second-hand smoke exposure, job type, household income, education, BMI, intake of SFA, and intake of EPA plus DHA	• Assessment timing not standard for all participants • Participation rate and characteristics not available • Seasonal variance and sunlight exposure not measured
ZINC									
Roy <i>et al.</i> (2010)	2030	FFQ and supplement questionnaire to quantify zinc intake (mg/d)	Multivariable linear regression	Quintiles of intake (mg/d): Q1 (lowest): < 11.52 Q2: 11.52–14.82 Q3: 14.83–17.28 Q4: 17.29–19.80 Q5 (highest): reference	EPDS score; linear	Zinc intake: Q5: ref. • Q4: β 0.03 (SE 0.5), $P = 0.95$ • Q3: β -0.02 (SE 0.5), $P = 0.97$ • Q2: β 1.3 (SE 0.5), $P = 0.02$ • Q1: β 1.1 (SE 0.5), $P = 0.04$	Zinc intake: Q5: ref. • Q4: β 0.03 (SE 0.5), $P = 0.94$ • Q3: β 0.4 (SE 0.5), $P = 0.38$ • Q2: β 0.8 (SE 0.5), $P = 0.07$ • Q1: β 1.0 (SE 0.5), $P = 0.03$	Education*, marital status*, parity*, employment*, income, preexisting medical conditions, age, shift work and stress	• 75% took supplements during pregnancy • History of depression not included in model

B1, thiamin; B2, riboflavin; B3, niacin; B6, pyridoxine; B7, biotin; B9, folic acid; B12, cobalamin; BMI, body mass index; CESD, Center for Epidemiological Studies Depression Scale; CI, confidence interval; d, day; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; EPDS, Edinburgh Post-partum Depression Scale; FFQ, Food frequency questionnaire; MV/FA, multivitamin and folic acid supplementation; NS, not significant; OR, odds ratio; SE, standard error; SEM, standard error of the mean; SFA, saturated fatty acids; g, grams; mg, milligrams; mcg, micrograms.

*Significant ($P < 0.05$) in stratum or final model.

Appendix Table 4. Results of studies evaluating associations between intake of fish and fats and perinatal depression

Author (year)	<i>n</i>	Nutrients/diet (components of analysis or intervention)	Analysis	Unit of exposure	Unit of outcome	Unadjusted associations significant at $p < 0.10$ (effect size, 95% CI, <i>P</i> -value)	Adjusted associations significant at $p < 0.10$ (effect size, 95% CI, <i>P</i> -value)	Potential confounders considered	Limitations
Doornbos <i>et al.</i> (2009)	119	Group A: DHA+AA (220 mg) Group B: DHA (220 mg) Group C: placebo	ANOVA and chi-squared tests	DHA+AA vs. DHA vs. placebo group	EPDS score: ≥ 12 vs. < 12	Mean differences between average EPDS scores NS at any time point	Not reported	Baseline differences in fish intake, social and obstetric characteristics tested between groups, NS	• High loss to follow-up (31%) • Only powered for large differences • Low PPD prevalence found • Only 60 women completed PP blues evaluation; 16/60 had PP blues • Low dose of DHA compared with other studies • No history of depression considered
Judge <i>et al.</i> (2014)	42	Group A: DHA (300 mg DHA, fish oil) 5 days/week Group B: placebo	<i>t</i> -test and chi-squared test, repeated measures analysis	DHA group vs. placebo group	CES-D score: mean PDSS score: mean	DHA group vs. placebo group means and standard error of means (SEM): • 2 weeks: 47.65 (12.96) vs. 53.86 (15.25) • 6 weeks: 47.61 (14.31) vs. 47.40 (12.42) • 3 months: 45.28 (12.25) vs. 42.63 (9.52) • 6 months: 45.55 (13.50) vs. 48.42 (17.18)	Not reported	Baseline differences in age, pre-pregnancy weight, number of live births, income, education, ethnicity, household size, history of depression or previous treatment for depression tested between groups, NS	• Low response rate (58%) and high loss to follow-up (42% lost at 6 months)

(Continues)

Appendix Table 4. (Continued)

Author (year)	<i>n</i>	Nutrients/diet (components of analysis or intervention)	Analysis	Unit of exposure	Unit of outcome	Unadjusted associations significant at $p < 0.10$ (effect size, 95% CI, P -value)	Adjusted associations significant at $p < 0.10$ (effect size, 95% CI, P -value)	Potential confounders considered	Limitations
Llorente <i>et al.</i> (2003)	138	Group A: DHA (200 mg/d) Group B: placebo	t -test and chi-squared test, regression analysis	DHA group vs. placebo group	BDI score: ≥ 10 vs. < 10 EPDS score and clinical interview in subsample	NS at any time point, for any measure (BDI, EPDS, SCID-CV)	Not reported	Baseline differences in age, education, parity, gestational age, delivery weight, pre-pregnancy weight, ethnicity, caesarean delivery, baby's sex, Apgar score tested between groups, NS	• High loss to follow-up (27%) • Powered to detect 30% difference in groups • Low PPD prevalence found • Low dose and short duration of intervention • No history of depression considered
Makrides <i>et al.</i> (2010)	2399	Group A: 800 mg/d of DHA, 100 mg/d of EPA Group B: vegetable oil capsules without DHA	Log binomial regression	DHA group vs. placebo group	EPDS score: ≥ 12 vs. < 12	• RR 0.86 (CI 0.71–1.05), $P = 0.15$ (9.67% in supplement group vs. 11.19% in placebo group)	• RR 0.85 (CI 0.70–1.02), $P = 0.09$	Baseline differences in maternity centre, parity, Maternal Social Support Index score, age, history of depression and smoking status tested between groups, NS	• High loss to follow-up • Small sample size in second and third trimesters • No history of depression considered • Assessment timing not standard for all participants • No history of depression considered
Da Rocha and Kac (2012)	106	FFQ to quantify mean n-6/n-3 PUFA intake ratio (mg/d), also tested energy (kcal/d), carbohydrate (g/d), lipids (g/d), protein (g/d), n-3 PUFA intake (g/d) and n-6 PUFA intake (g/d)	Multivariable Poisson regression	n-6/n-3 PUFA ratio $> 9:1$ vs. $< 9:1$	EPDS score: ≥ 11 vs. < 11	• n-6/n-3 PUFA ratio in EPDS score ≥ 11 vs. < 11: $P = 0.002$ • Prevalence ratio: 2.73 (CI 1.44–5.18), $P = 0.002$ • All other nutrient variables NS • Increased intake of several nutrient variables protective but NS • Trends NS	• n-6/n-3 PUFA ratio in EPDS score ≥ 11 vs. < 11: $P = 0.01$ • Prevalence ratio: 2.50 (CI 1.21–5.14), $P = 0.01$ • Increased intake of several nutrient variables protective but NS • Trends NS	Income, age, schooling*, skin colour, marital status, smoking, alcohol, age at menarche, delivery type, LBW, prematurity, marital problems, stress, parity and pre-pregnancy BMI*	• High loss to follow-up • Small sample size in second and third trimesters • No history of depression considered • Assessment timing not standard for all participants • No history of depression considered
Miyake <i>et al.</i> (2006b)	865	FFQ to quantify fish, meat, eggs, dairy, total fat (g/d), SFA, MUFA, n-3 PUFA, n-6 PUFA, LA, ALA, AA, EPA, DHA and ratio of n-3 to n-6 PUFA (mg/d)	Multivariable logistic regression	Quartiles of intake (Q1: lowest/reference, Q2, Q3, Q4: highest)	EPDS score: ≥ 9 vs. < 9	• Increased intake of several nutrient variables protective but NS • Trends NS	• Increased intake of several nutrient variables protective but NS • Trends NS • Similar ORs for unadjusted and adjusted	Age, gestation, parity, smoking, family structure, occupation, family income, education, changes in diet in previous month, season of baseline data, BMI, time of delivery, problems during pregnancy, baby's sex and baby's birth weight	• No history of depression considered

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Appendix Table 4. (Continued)

Author (year)	<i>n</i>	Nutrients/diet (components of analysis or intervention)	Analysis	Unit of exposure	Unit of outcome	Unadjusted associations significant at $p < 0.10$ (effect size, 95% CI, <i>P</i> -value)	Adjusted associations significant at $p < 0.10$ (effect size, 95% CI, <i>P</i> -value)	Potential confounders considered	Limitations
Strom <i>et al.</i> (2009)	54 202	FFQ to quantify fish intake (g/d, quintiles), n-3 PUFA intake (mg/d, deciles)	Multivariable logistic regression	Intake groups (g/day): • G1: 0–3 • G2: >3–10 • G3: >10–20 • G4: >20–30 • G5: >30 Deciles of n-3 PUFA intake (D1, lowest–D10, highest)	PPD admit PPD Rx	• NS for fish or n-3 PUFA Fish intake: • G1: OR 1.61 (CI 1.26–2.06) • G2: OR 1.11 (CI 0.90–1.38) • G3: OR 1.14 (CI 0.94–1.40) • G4: OR 1.01 (CI 0.80–1.28) • G5: reference • <i>P</i> for trend = 0.001 n-3 PUFA intake: • D1: OR 1.41 (CI 1.10–1.81) • D2: OR 1.24 (CI 0.96–1.60) • D3: OR 1.05 (CI 0.80–1.37) • D4: OR 1.31 (CI 1.02–1.68) • D5: OR 1.06 (CI 0.81–1.38) • D6: OR 1.09 (CI 0.83–1.42) • D7: OR 1.02 (CI 0.78–1.34) • D8: OR 0.89 (CI 0.67–1.18) • D9 and D10: reference • <i>P</i> for trend = 0.04	• NS for fish or n-3 PUFA Fish intake: • G1: OR 1.46 (CI 1.12–1.90) • G2: OR 1.10 (CI 0.87–1.38) • G3: OR 1.18 (CI 0.95–1.45) • G4: OR 1.03 (CI 0.81–1.32) • G5: reference • <i>P</i> for trend = 0.04 n-3 PUFA intake: • D1: OR 1.24 (CI 0.96–1.61) • D2: OR 1.17 (CI 0.90–1.53) • D3: OR 0.99 (CI 0.75–1.31) • D4: OR 1.29 (CI 0.99–1.68) • D5: OR 1.09 (CI 0.83–1.44) • D6: OR 1.11 (CI 0.84–1.46) • D7: OR 1.04 (CI 0.79–1.38) • D8: OR 0.89 (CI 0.67–1.20) • D9 and D10: reference • <i>P</i> for trend = 0.33	Age, parity, marital status, smoking, alcohol, pre-pregnant, occupation, education, home ownership, social support and previous depression	• Depression measured in severe clinical manifestation, very specific, not very sensitive

(Continues)

Appendix Table 4. (Continued)

Author (year)	<i>n</i>	Nutrients/diet (components of analysis or intervention)	Analysis	Unit of exposure	Unit of outcome	Unadjusted associations significant at $p < 0.10$ (effect size, 95% CI, P -value)	Adjusted associations significant at $p < 0.10$ (effect size, 95% CI, P -value)	Potential confounders considered	Limitations
Browne <i>et al.</i> (2006)	80	FFQ to quantify mean PUFA intake (mg/d)	Logistic regression, F^2 test and t -test	Some fish (any freq.) vs. none	EPDS score; ≥ 9 vs. < 9	F -test for nutrients in logistic regression NS ($P = 0.29$)	Not reported	Alcohol, breastfeeding*, supplement use, education, ethnicity, fish consumption, household income* and smoking	• No adjusted model of the association of interest • No participants consumed oily fish regularly • No adjustment for confounding factors • No adjusted model of the association of interest
Cosatto <i>et al.</i> (2010)	94	FFQ to quantify intake of EPA, DPA, DHA and total n-3 PUFA (mg/d)	Wilcoxon test	Mean nutrient intake	EPDS score; ≥ 10 vs. < 10	NS for any nutrient	Not reported	None	• No adjustment for confounding factors • No adjusted model of the association of interest
Golding <i>et al.</i> (2009)	9960	FFQ to quantify n-3 PUFA intake from fish (g/week)	Multivariable logistic regression	Groups (g/week): • G1: None • G2: 0.1–0.4 • G3: 0.4–1.5 • G5: > 1.5	EPDS score; ≥ 13 vs. < 13	Groups: • G1: OR 1.97 (CI 1.63–2.38) • G2: OR 1.64 (CI 1.37–1.96) • G3: OR 1.31 (CI 1.13–1.52) • G4: reference • P for trend ≤ 0.01	Groups: • G1: OR 1.54 (CI 1.25–1.89) • G2: OR 1.37 (CI 1.13–1.66) • G3: OR 1.20 (CI 1.03–1.41) • G4: reference • P for trend ≤ 0.01	Age, parity, outcome of immediately preceding pregnancy, education, housing, crowding, events in childhood, recent events, chronic stress, smoking, alcohol, ethnicity and energy intake	• High levels of depressive symptoms were associated with not returning FFQ questionnaire
Miyake <i>et al.</i> (2013)	1745	FFQ to quantify mean total meat, total fish, total fat, SFAs, MUFAs, n-3 PUFA, n-6 PUFA, LA, ALA, AA, EPA, DHA, ratio of n-3 to n-6 PUFA and cholesterol (mg/d)	Multivariable logistic regression	Quartiles of intake (Q1: lowest/ reference, Q2, Q3, Q4: highest)	CES-D score; ≥ 16 vs. < 16	Fish intake: • Q1: ref. • Q2: OR 0.77 (CI 0.56–1.07) • Q3: OR 0.79 (CI 0.57–1.10) • Q4: OR 0.58 (CI 0.41–0.82) • P for trend = 0.003 EPA: • Q1: ref. • Q2: OR 0.91 (CI 0.66–1.26) • Q3: OR 0.77 (CI 0.55–1.06) • Q4: OR 0.60 (CI 0.42–0.84) • P for trend = 0.002	Fish intake: • Q1: ref. • Q2: OR 0.72 (CI 0.51–1.02) • Q3: OR 0.79 (CI 0.56–1.10) • Q4: OR 0.61 (CI 0.42–0.87) • P for trend = 0.01 EPA: • Q1: ref. • Q2: OR 0.93 (CI 0.66–1.30) • Q3: OR 0.79 (CI 0.56–1.12) • Q4: OR 0.66 (CI 0.46–0.95) • P for trend = 0.02	Age, gestational age, residential area, parity, family structure, personal history of depression, ever smoked, second-hand smoke exposure, job type, household income, education and BMI	• Assessment timing not standard for all participants • Participation rate and characteristics not available

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Appendix Table 4. (Continued)

Author (year)	<i>n</i>	Nutrients/diet (components of analysis or intervention)	Analysis	Unit of exposure	Unit of outcome	Unadjusted associations significant at $p < 0.10$ (effect size, 95% CI, <i>P</i> -value)	Adjusted associations significant at $p < 0.10$ (effect size, 95% CI, <i>P</i> -value)	Potential confounders considered	Limitations
						DHA: • Q1: reference • Q2: OR 1.06 (CI 0.77–1.45) • Q3: OR 0.84 (CI 0.60–1.17) • Q4: OR 0.60 (CI 0.42–0.85) • <i>P</i> for trend = 0.001 Total fat: • Q1: reference • Q2: OR 1.17 (CI 0.83–1.66) • Q3: OR 1.14 (CI 0.80–1.61) • Q4: OR 1.46 (CI 1.04–2.04) • <i>P</i> for trend = 0.03 SFA: • Q1: reference • Q2: OR 1.16 (CI 0.81–1.66) • Q3: OR 1.29 (CI 0.91–1.83) • Q4: OR 1.66 (CI 1.19–2.34) • <i>P</i> for trend = 0.002 MFA: • Q1: reference • Q2: OR 1.08 (CI 0.77–1.53) • Q3: OR 0.94 (CI 0.66–1.33) • Q4: OR 1.46 (CI 1.05–2.03) • <i>P</i> for trend = 0.03 ALA: • Q1: reference • Q2: OR 0.90	DHA: • Q1: reference • Q2: OR 1.06 (CI 0.75–1.48) • Q3: OR 0.87 (CI 0.61–1.23) • Q4: OR 0.64 (CI 0.44–0.93) • <i>P</i> for trend = 0.007 Total fat: • Q1: reference • Q2: OR 1.18 (CI 0.82–1.69) • Q3: OR 1.12 (CI 0.78–1.62) • Q4: OR 1.42 (CI 1.00–2.03) • <i>P</i> for trend = 0.06 SFA: • Q1: reference • Q2: OR 1.13 (CI 0.78–1.64) • Q3: OR 1.28 (CI 0.89–1.84) • Q4: OR 1.74 (CI 1.22–2.49) • <i>P</i> for trend = 0.001 MFA: • Q1: reference • Q2: OR 1.02 (CI 0.71–1.45) • Q3: OR 0.91 (CI 0.63–1.31) • Q4: OR 1.38 (CI 0.98–1.96) • <i>P</i> for trend = 0.08 ALA: • Q1: reference • Q2: OR 0.90		

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Appendix Table 4. (Continued)

Author (year)	<i>n</i>	Nutrients/diet (components of analysis or intervention)	Analysis	Unit of exposure	Unit of outcome	Unadjusted associations significant at $p < 0.10$ (effect size, 95% CI, P -value)	Adjusted associations significant at $p < 0.10$ (effect size, 95% CI, P -value)	Potential confounders considered	Limitations
Sontrop <i>et al.</i> (2008)	2394	FFQ to quantify intake of fish	Multivariable linear regression	Intake of fish: <1 vs. ≥ 1 serving per week; EPA+DHA: <85 vs. ≥ 85 mg/d	Mean CES-D score	(CI 0.63–1.27) • Q3: OR 0.87 (CI 0.61–1.23) • Q4: OR 1.38 (CI 1.00–1.92) • P for trend = 0.04 n-3/n-6 PUFA ratio: • Q1: reference • Q2: OR 1.07 (CI 0.78–1.48) • Q3: OR 0.78 (CI 0.55–1.09) • Q4: OR 0.74 (CI 0.52–1.04) • P for trend = 0.03 All other nutrient variables NS	(CI 0.63–1.29) • Q3: OR 0.83 (CI 0.57–1.18) • Q4: OR 1.30 (CI 0.92–1.82) • P for trend = 0.12 n-3/n-6 PUFA ratio: • Q1: reference • Q2: OR 1.12 (CI 0.80–1.57) • Q3: OR 0.83 (CI 0.58–1.18) • Q4: OR 0.83 (CI 0.58–1.19) • P for trend = 0.15 All other nutrient variables NS	Age, marital status*, education*, income*, occupation*, smoking*, physical activity* and meeting Canada Food Guide to Healthy Living guidelines	• Not all potential confounders included in model • No history of depression

AA, arachidonic acid; Admit, hospital admission for depression; ALA, alpha-linolenic acid; BDI, Beck's Depression Inventory; BDHQ, Brief Diet History Questionnaire; BMI, body mass index; CES-D, Center for Epidemiological Studies Depression Scale; CI, confidence interval; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPDS, Edinburgh Post-partum Depression Scale; EPA, eicosapentaenoic acid; FFQ, Food frequency questionnaire; LA, linolenic acid; LS, least square; n-3 PUFA, omega-3 polyunsaturated fatty acids; n-6 PUFA, omega-6 polyunsaturated fatty acids; NS, not significant; OR, odds ratio; PDSS, Post-partum Depression Screening Scale; PPD, post-partum depression; PP, post-partum; Preg, pregnancy; PUFA, polyunsaturated fatty acid; RDA, Recommended Daily Allowance; RR, risk ratio; Rx, filled prescription for antidepressants; SCID-CV, Structured Clinical Interview; SEM, standard error of the mean; g, grams; mg, milligrams; meg, micrograms.

*Significant ($P < 0.05$) in stratum or in final model.