

REVIEW

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The effect of folic acid, protein energy and multiple micronutrient supplements in pregnancy on stillbirths

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Abstract

Background: Pregnancy is a state of increased requirement of macro- and micronutrients, and malnourishment or inadequate dietary intake before and during pregnancy, can lead to adverse perinatal outcomes including stillbirths. Many nutritional interventions have been proposed during pregnancy according to the nutritional status of the mother and baseline risk factors for different gestational disorders. In this paper, we have reviewed three nutritional interventions including peri-conceptual folic acid supplementation, balanced protein energy supplementation and multiple micronutrients supplementation during pregnancy. This paper is a part of a series to estimate the effect of interventions on stillbirths for input to Live Saved Tool (LiST) model.

Methods: We systematically reviewed all published literature to identify studies evaluating effectiveness of peri-conceptual folic acid supplementation in reducing neural tube defects (NTD), related stillbirths and balanced protein energy and multiple micronutrients supplementation during pregnancy in reducing all-cause stillbirths. The primary outcome was stillbirths. Meta-analyses were generated where data were available from more than one study. Recommendations were made for the Lives Saved Tool (LiST) model based on rules developed by the Child Health Epidemiology Reference Group (CHERG).

Results: There were 18 studies that addressed peri-conceptual folic acid supplementation for prevention of neural tube defects (NTDs). Out of these, 7 studies addressed folic acid supplementation while 11 studies evaluated effect of folic acid fortification. Pooled results from 11 fortification studies showed that it reduces primary incidence of NTDs by 41% [Relative risk (RR) 0.59; 95% confidence interval (CI) 0.52-0.68]. This estimate has been recommended for inclusion in the LiST as proxy for reduction in stillbirths. Pooled results from three studies considered to be of low quality and suggest that balanced protein energy supplementation during pregnancy could lead to a reduction of 45% in stillbirths [RR 0.55, 95% CI 0.31-0.97]. While promising, the intervention needs more effectiveness studies before inclusion in any programs. Pooled results from 13 studies evaluating role of multiple micronutrients supplementation during pregnancy showed no significant effect in reducing stillbirths [RR = 0.98; 95% CI: 0.88 – 1.10] or perinatal mortality [RR = 1.07; 95% CI: 0.92 – 1.25; random model]. No recommendations have been made for this intervention for inclusion in the LiST model.

Conclusions: Peri-conceptual folic acid supplementation reduces stillbirths due to NTDs by approximately 41%, a point estimate recommended for inclusion in LiST.

Background

The nutritional status of a woman before and during pregnancy is important for a healthy pregnancy outcome [1]. Pregnancy is a state of increased requirement of macro and micronutrients, and malnourishment or

inadequate dietary intake before and during pregnancy, can lead to adverse perinatal outcomes [2,3].

Stillbirth is an important adverse outcome of pregnancy. Global estimates suggest that at least 3.2 million stillbirths occur annually [4], with 98% of these occurring in the developing world [5]. The risk factors for stillbirths in the low-/middle-income countries are myriad, and a systematic review by Di Mario et al. concluded that poor

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maternal nutritional status is one of the five factors significantly associated with stillbirths [6].

Many nutritional interventions have been proposed for pregnant mothers. These include multiple micronutrients (MMN), iron/folate, balanced protein energy, calcium, zinc and folic acid supplementation [7-11]. Some of these interventions are recommended universally for all women while some are proposed in the context of the nutritional status of mothers which may vary in different populations [3,12]. For example calcium is given during pregnancy for prevention of gestational hypertensive disorders but is effective only in populations with low baseline calcium intake [8,13]. Similarly iodine supplementation is effective in populations with iodine deficiency only.

In this review, our intention is to assess the evidence of the impact of three different nutritional interventions during pregnancy on stillbirths. We have reviewed the effect of peri-conceptual folic acid supplementation, balanced protein energy supplementation and multiple micronutrient supplements during pregnancy. This selection was based on an existing review of nutritional interventions for the prevention of stillbirths [14], and only those interventions have been selected that have a proven benefit for reducing stillbirths or have a strong biological plausibility and now we review them in more depth. Calcium supplementation during pregnancy has been reviewed in another paper for this supplement [15]. This paper is a part of a series of papers to estimate effectiveness of an intervention for input into the Lives Saved Tool (LiST) [16]. The process of generating recommendations for an intervention involve qualitative evaluation of available evidence according to Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria [17] and quantitative evaluation according to Child Health Epidemiology Reference Group (CHERG) rules [16]. For more details of the review methods, the adapted GRADE approach or the LiST model, see the CHERG method's paper [16]. The following are the objectives of this review.

1. To estimate the effectiveness of peri-conceptual folic acid supplementation in reducing neural tube defects (NTDs) related stillbirths.

2. To estimate the effectiveness of balanced protein energy supplementation during pregnancy in reducing all-cause stillbirths.

3. To estimate the effectiveness of multiple micronutrient supplementation during pregnancy in reducing all-cause stillbirths.

Methods

Search

We systematically reviewed all published literature to identify studies addressing peri-conceptual folic acid

supplementation, balanced protein energy and multiple micronutrient supplements during pregnancy. The search strategies used for the above mentioned nutritional interventions on PubMed are given as appendices 1, 2 and 3 respectively in Additional File 1. The last date of the search was 3rd March 2010. Initial search identified titles and abstracts relevant to the interventions of interest. Full texts were then retrieved for selected studies for final inclusion and for data abstraction. We also reviewed the reference lists of identified articles, existing reviews and meta-analyses to identify studies that were not picked up in the main search. Authors were contacted for any additional data, if required.

Inclusion/exclusion criteria

All randomized and quasi-randomized controlled trials assessing impact of peri-conceptual folic acid, balanced protein energy and multiple micronutrients supplements during pregnancy outcomes, were eligible for inclusion. Studies were included irrespective of language or publication status. We also reviewed observational studies for peri-conceptual folic acid supplementation as very few trials were conducted after huge protective effects of supplementation as shown in MRC trial [18]. Balanced protein energy supplementation was defined as nutritional supplementation during pregnancy in which proteins provided less than 25% of the total energy content [9]. Those studies were excluded in which the main intervention was simply dietary advice to pregnant women to increase protein intake, high protein supplementation (i.e. supplementation in which protein provided at least 25% or more of total energy content), isocaloric protein supplementation (where protein replaces an equal quantity of non-protein energy content), or low energy diets for pregnant women. Multiple micronutrients were defined as supplementation with at least five micronutrients and were compared with iron folic acid supplementation alone [7].

Data abstraction and validity assessment

Every study that met the eligibility criteria was reviewed in detail and its characteristics abstracted into a standardized form [16]. The main variables extracted were country of the study, quality of allocation concealment, blinding status, characteristics of participants, sample size, description of intervention that included parameters like dose, frequency and duration of the supplements, and the follow-up period. All the studies were then graded according to the CHERG adaptation of the GRADE technique [16,17]. Each study was allocated a quality score of 'high' 'moderate' 'low' or 'very low'. This assessment was based on the methodological quality of the study and consistency of results compared to that of

other selected studies [16]. Any study getting a final score of 'very low' was excluded from the review [16,17]. The detailed data extraction with the limitation of studies is shown in Additional File 2.

Quantitative data synthesis

We generated meta-analyses where data were available from more than one study. Dichotomous data were combined to get a pooled relative risk. In case where data from all the studies were not available in dichotomous form and risk ratios were available, meta-analysis was performed by generic inverse variance (GIV) method. This method is advantageous in these scenarios as it requires standard error (SE) and natural 'log' of effect size and data can be pooled without numerators and denominators [19]. For cluster randomized trials, we used the stated cluster adjusted relative risk and 95% confidence interval, irrespective of the method used. In case cluster adjustment was not done in the study, it was done by either adjusting the original sample size or inflating the SE times square of design effect [19]. Heterogeneity of the meta-analysis was assessed by visual inspection i.e. the overlap of the confidence intervals among the studies, and by the Chi square (P-value) of heterogeneity in the meta-analyses and I^2 value. A low P value (less than 0.10) or a large chi-squared statistic relative to its degree of freedom ($I^2 > 50\%$) was considered as providing evidence of significant heterogeneity. In situations of substantial or high heterogeneity being present, causes were explored by sensitivity analysis. Fixed models were used for primary analysis and random models were used in case of significant heterogeneity in the pooled estimate. Results are presented as Mantel-Haenszel risk ratios (RR) and corresponding 95% confidence intervals (CI). All meta-analyses were conducted using software Review Manager Version 5 [20].

For recommendations to the LiST model, we summarized the evidence for each outcome including qualitative assessment of 'overall' evidence according to GRADE criteria and quantitative measures according to standard guidelines of the Child Health Epidemiological Review Group (CHERG) [16]. The qualitative evaluation of the overall (pooled) evidence was based on the volume and consistency of the evidence across studies, the size of pooled relative risk and the strength of the statistical evidence for an association between the intervention and the health outcome as reflected in the p-value [16].

Results

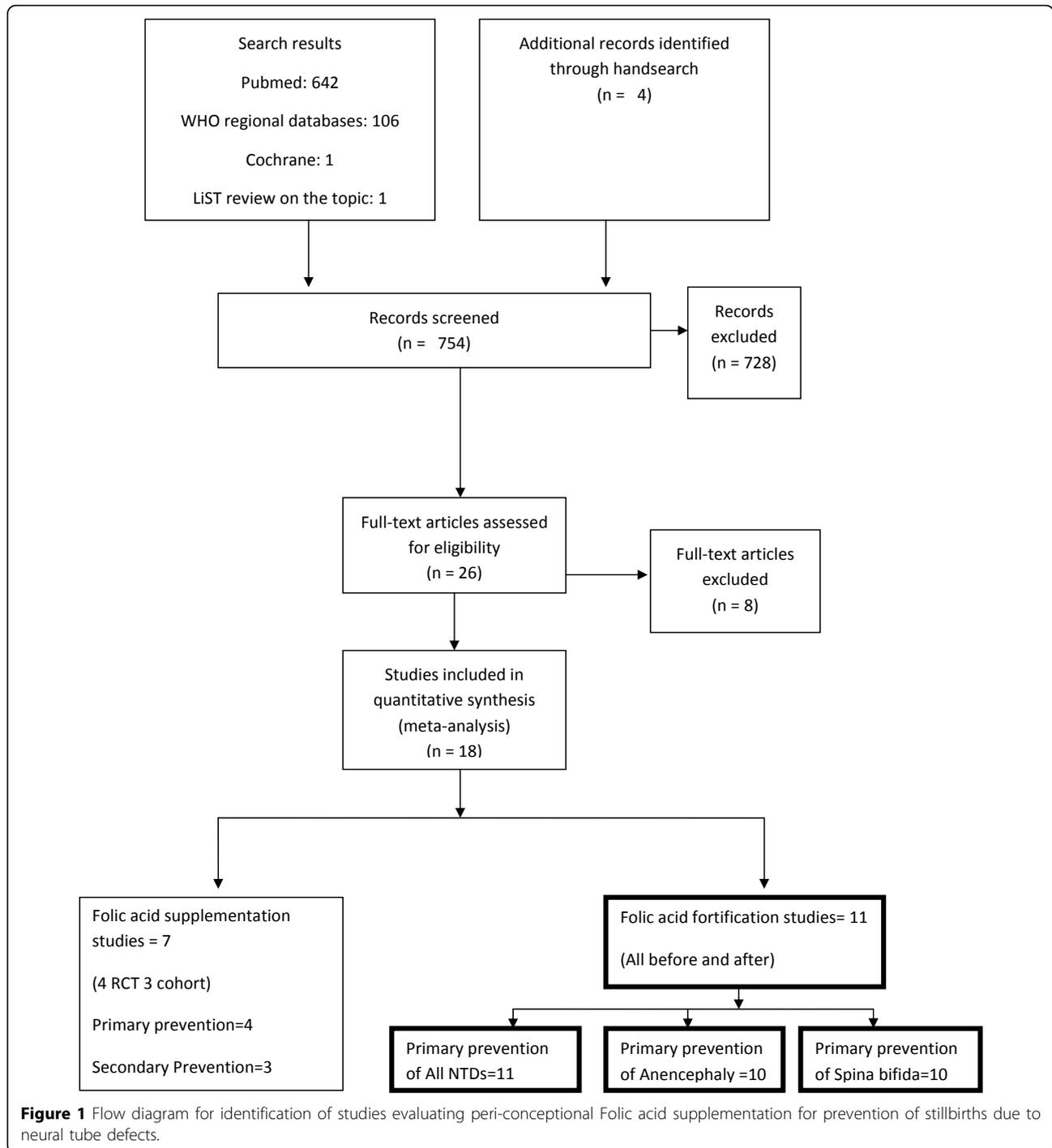
Peri-conceptual folic acid supplementation

The literature search identified 754 titles (Figure 1). After initial screenings of titles or abstracts and after duplicates were removed, we reviewed 26 studies. Eight studies were further excluded after review of full texts.

Finally, data for eighteen studies were abstracted. One Cochrane [10] and one LiST review [21] were also available on the topic.

Out of eighteen selected studies, seven studies evaluated the effect of peri-conceptual folic acid supplementation [18,22-27] and eleven studies assessed fortification of food with folic acid [28-38]. All the fortification studies were before and after studies. Of the seven supplementation studies, there were four randomized controlled trials [18,23,24,26] and three cohort studies [22,25,27]. Four of the supplementation studies addressed primary prevention of neural tube defects [22,23,25,27] and three that of secondary preventions [18,24,26]. Meta-analysis of four studies (1 RCT and 3 cohort studies) for primary prevention of NTDs showed a reduction of 62 % in the incidence of NTDs [relative risk (RR) 0.38; 95 % confidence interval (CI) 0.29-0.51, $I^2 = 27.9\%$, fixed model] (data not shown). The overall quality grade for this consistent pooled estimate with 1 RCT [23] and 3 cohort studies [22,25,27] was that of 'moderate' level. Disaggregated data for stillbirth due to NTDs were not available from any of these studies. Pooled results of three RCTs for prevention of recurrent NTDs showed a reduction of 70 % in recurrence of NTDs [RR 0.30; 95 % CI 0.14-0.65, $I^2 = 0\%$, fixed model] (data not shown). As the evidence came from RCTs and the pooled estimate was consistent, the overall quality grade for this estimate was that of 'high' level. In these studies, disaggregated data for stillbirths due to NTDs were available from one study [24] with one stillbirth in the control group and no stillbirth in the intervention group, giving a relative risk of 0.17 (95 % CI 0.01-0.46).

There were eleven before and after studies that addressed primary prevention of NTDs using folic acid fortification. Pooled results from these studies showed a reduction of 41 % in primary occurrence of NTDs [RR 0.59; 95 % CI 0.52-0.68, $I^2 = 88\%$, random model] (Figure 2). As there was a significant heterogeneity in the pooled estimate, random models were used. Ten of the included studies showed a clear benefit. The reason for significant heterogeneity was the difference in magnitude of 'effect size' of the included studies which ranged from a reduction of 26 % [33] to 78 % [38]. Although this evidence came from 'low' quality before and after studies, the overall quality grade for this estimate was that of 'moderate' level due to prominent protective effect in the same direction in most of the included studies. The disaggregated data for stillbirths due to NTDs was available from one study [31] with 5 stillbirths in intervention group and 29 in the control group giving a relative risk of 0.41 (95 % CI 0.16-1.07). This study from Canada found that before fortification (1992-1997), there were 29 stillbirths related to neural tube defects, out of a total of 531268 births, a cause-specific stillbirth rate of 5.5 per



100000 births. The corresponding figure after fortification (1998-2000) was 5 stillbirths out of 221 253, a rate of 2.3 per 100000.

Table 1 shows the summary of findings and qualitative assessment of evidence on folic acid supplementation/fortification in prevention of NTDs and related stillbirths. Keeping in mind the inadequacy of direct data on NTDs related stillbirth, we recommend an approximate

reduction of 41% in NTD related stillbirths with an overall quality grade of “moderate”.

Balanced protein energy supplementation during pregnancy

We identified 4160 titles from searches conducted in all databases (Figure 3). After screening the titles and abstracts, 22 studies were identified that addressed

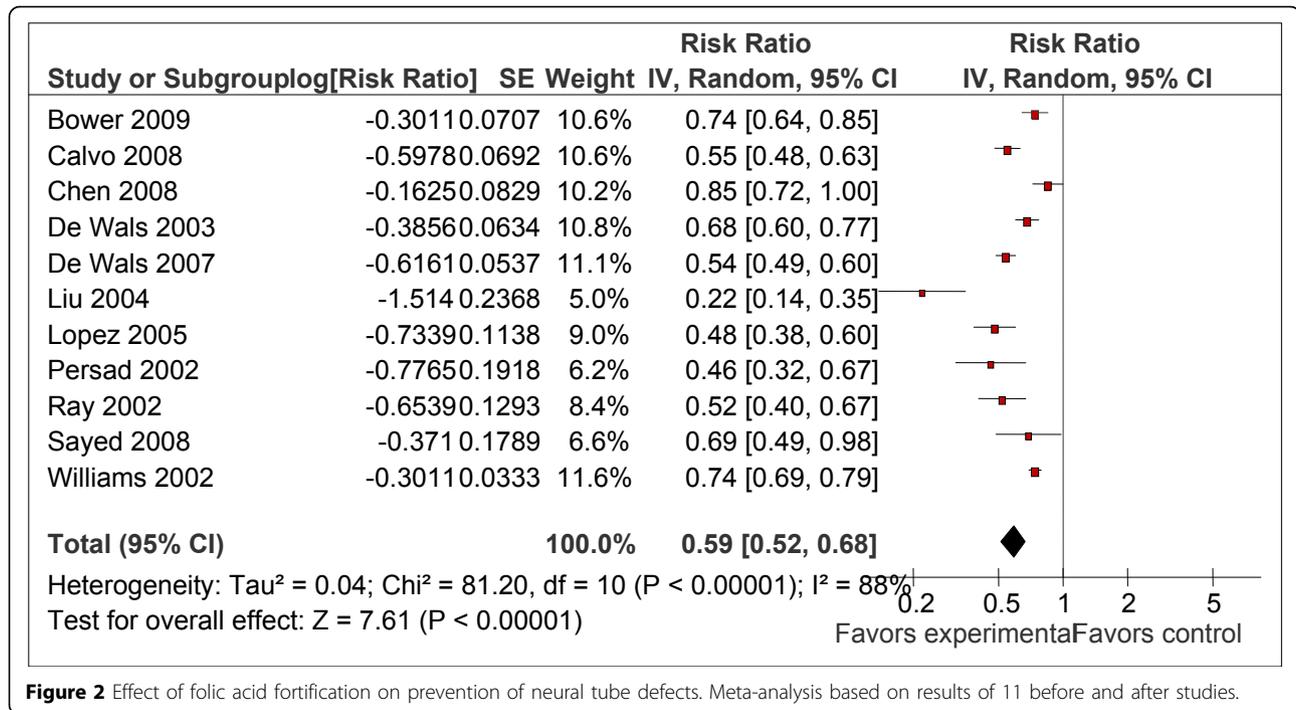


Figure 2 Effect of folic acid fortification on prevention of neural tube defects. Meta-analysis based on results of 11 before and after studies.

protein/energy supplementation during pregnancy. Eight of these studies were excluded because the intervention in these studies was either dietary advice about increase in protein/energy content, supplementation with isocaloric or high protein food [39-46]. Fourteen studies addressed balanced protein/energy supplementation during pregnancy [47-60]. Two of these studies were excluded because both the groups received food supplementation (high versus low energy) [53,54]. Another study was excluded because of 'very low' quality [60]. Eight studies were excluded because data for outcome of interest was not available [47-49,51,52,56,58,59].

Finally three studies were included in the review [50,55,57]. A Cochrane review was also available on the topic [9]. Two of the included studies were from developing countries [50,55] and one from a developed country [57]. The participants in all three studies were malnourished (as defined by authors). Pooled results from these three studies included a total of 2186 pregnancies and 49 stillbirths, showed that balanced protein energy supplementation during pregnancy leads to a significant reduction of 45% in all-cause stillbirths [RR 0.55, 95 % CI 0.31-0.97] (Figure 4). The overall grade quality of pooled data was that of 'Low' level (Table 2).

Table 1 Quality assessment of studies of peri-conceptual folic acid supplementation (by fortification) to prevent stillbirths from neural tube defects

No. of studies (Ref)	Design	Quality Assessment		Directness		Summary of findings		
		Limitations	Consistency	Generalizability to Population of Interest	Generalizability to intervention of Interest	Events in intervention group	Events in control group	Relative Risk (95 % CI)
NTDs related stillbirths: Low outcome specific quality								
1	Before and after study	Only one study. Total event < 50 so cannot be considered for inclusion in the LIST	Only one study	Study from Canada	Folic acid fortification study	5	29	0.41 (0.16-1.07) ^a
NTD incidence: Moderate outcome specific quality								
11	Before and after	Low quality population based studies	Significant heterogeneity (I ² = 88%)	All studies from high-middle income countries	Folic acid fortification studies			0.59 (0.52-0.68) ^b

a: directly calculated from study data, b: pooled estimate calculated by generic inverse variance.

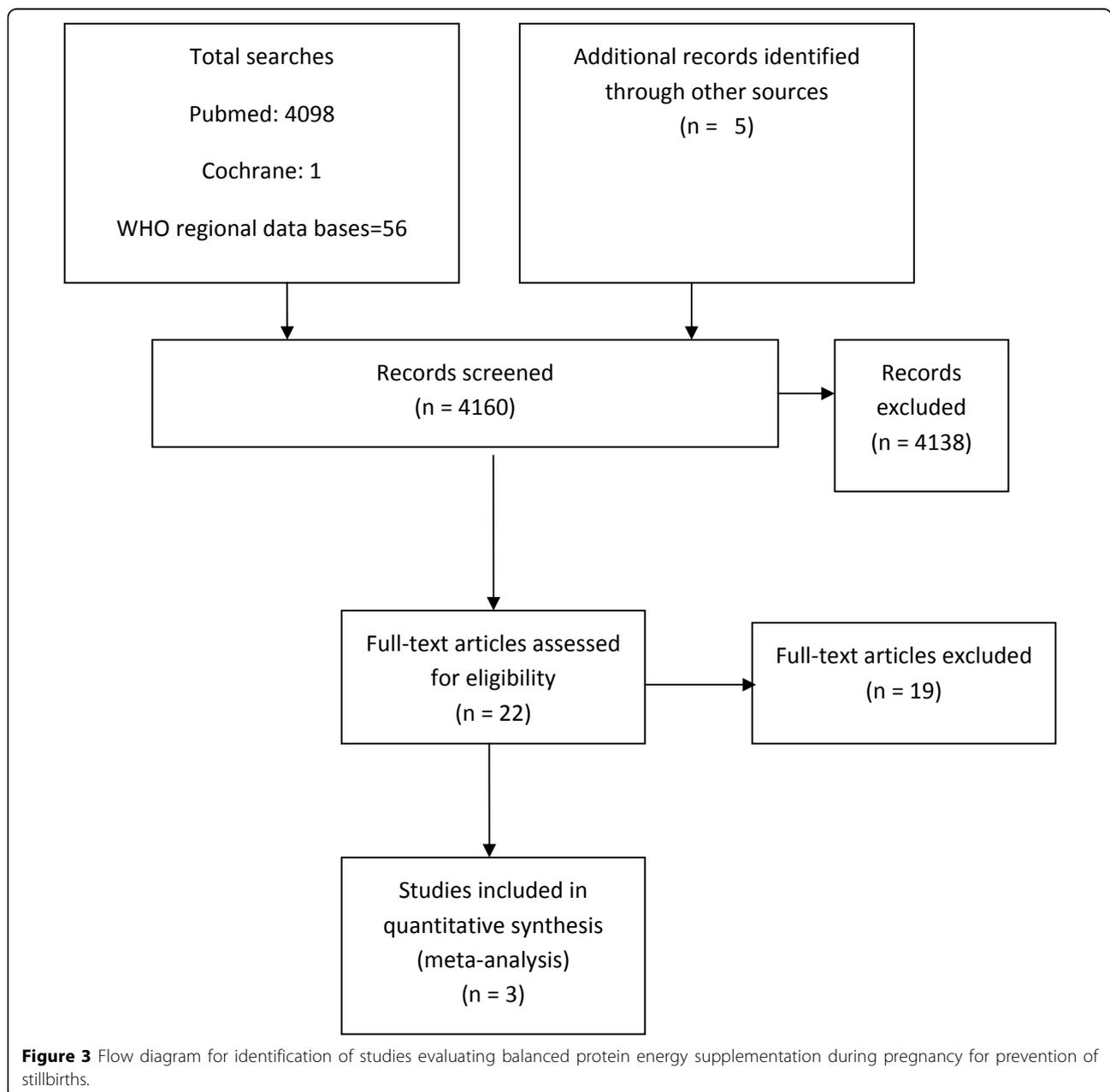
Multiple micronutrient supplements during pregnancy

A total of 4478 titles were identified from our search strategy (Figure 5). After screening the titles and abstracts, 13 studies were selected for inclusion in this paper [61-73]. Six of these 13 studies were cluster randomized trials [67-69,71,73,74]. Supplementation with multiple micronutrients failed to show a significant reduction in stillbirths when compared to iron folate supplementation (RR = 0.98; 95% CI: 0.88 – 1.10) (Figure 6). The impact on perinatal mortality was similar [RR 1.07, 95 % CI 0.92 –1.25] (Data not shown). As there was no significant effect of multiple micronutrient

supplementation in reducing stillbirth or perinatal mortality, no recommendations have been made for LiST for this intervention (Table 3).

Discussion

Evidence from a Cochrane review by Lumley et al. 2001 showed that peri-conceptional folic acid supplementation has a significant protective effect on occurrence of neural tube defects [RR 0.28, 95% CI 0.13–0.58], particularly in women who had a previous pregnancy affected by it (recurrent neural tube defects) [RR 0.31, 95% CI 0.14–0.66] [10]. A review by Blencowe et al. for Lives Saved



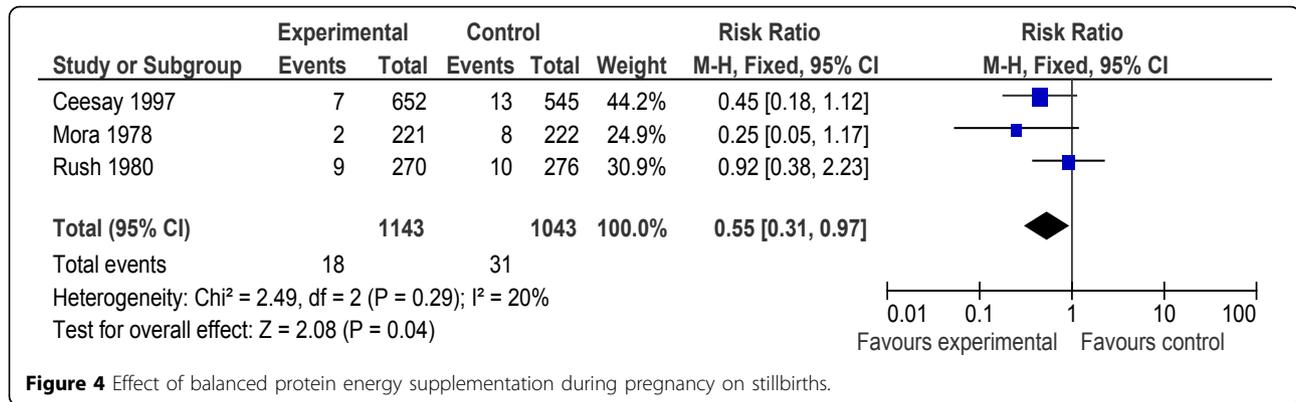


Figure 4 Effect of balanced protein energy supplementation during pregnancy on stillbirths.

Tool has shown that folic acid supplementation can reduce the primary incidence of NTDs by 62 % [RR 0.38; 95 % CI 0.29-0.51] and recurrence of NTDs by 70 %. [RR 0.30; 0.14-0.65] [21]. They also pooled data for fortification studies and showed a reduction of 46 % in primary incidence of NTDs. Our pooled estimates for primary prevention of neural tube defects by folic acid supplementation/fortification are similar to these reviews. The pooled estimate for folic acid fortification showed a reduction of 41 % (95 % CI 32 % to 48 %) in the occurrence NTDs. The small difference in effect size compared to previous LiST review was because we added three more studies to the previous met-analysis [28,30,32].

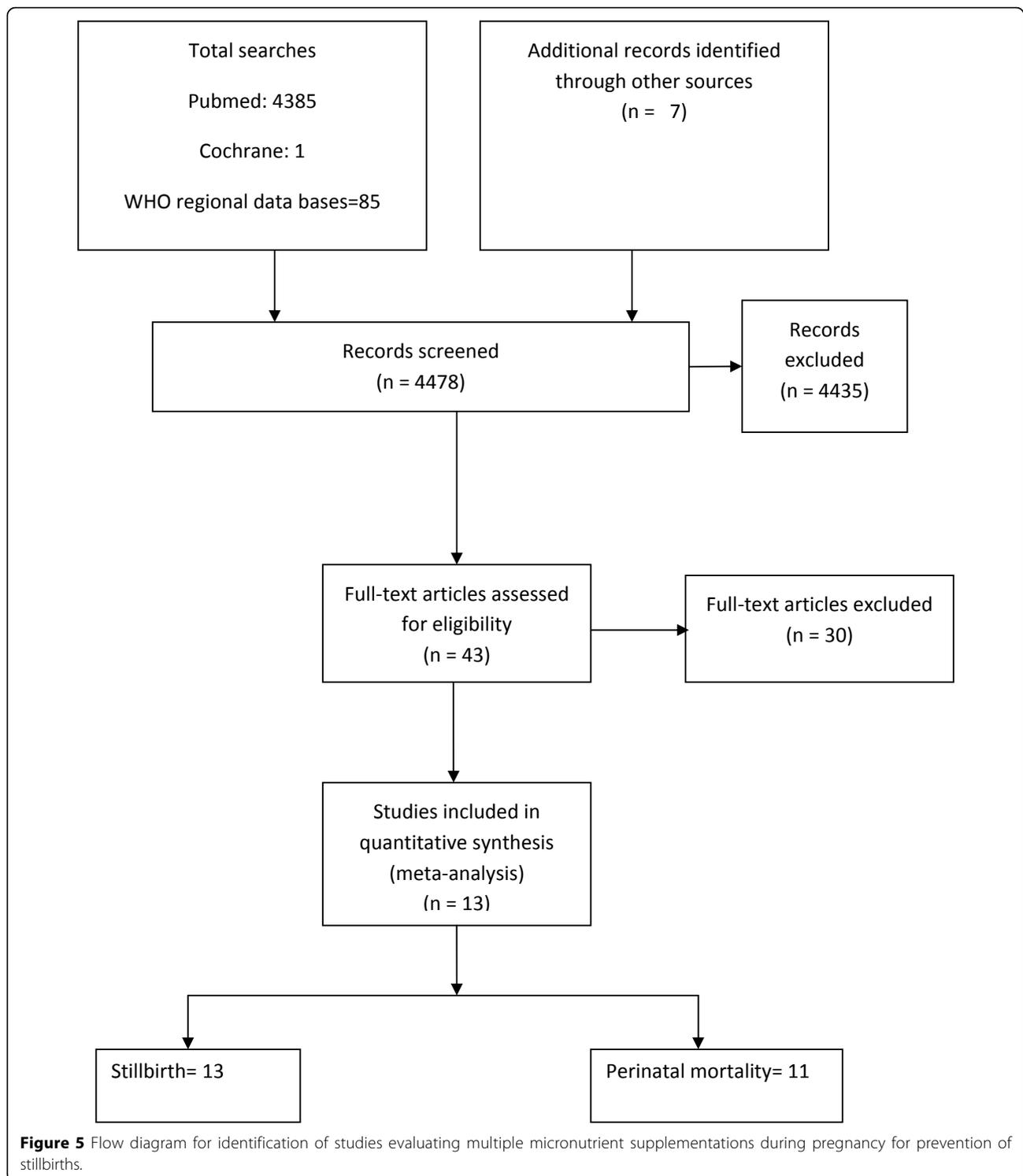
There was no convincing evidence from the current published literature in favor or against of peri-conceptual folic acid supplementation/fortification for prevention of stillbirths due to NTDs. Although it can be argued that a reduction in NTDs should be associated with a reduction in stillbirths, most of the studies did not report disaggregated data on proportion of stillbirths due to NTDs. Only one supplementation study [24] and one fortification study [31] reported direct data on NTD related stillbirths. We know from the previous literature that a major proportion of anencephalic babies and those with spina bifida cystica result in stillbirths

[75-77]. Given the strong biological plausibility in favor of the intervention based on results of supplementation and fortification studies, we assumed that reduction in NTD incidence would be equal to reduction in NTDs related stillbirths with equal rates of incidence and fatalities of Anencephaly and Spina Bifida. It is important to mention that this estimate is applied to NTD related stillbirths only and the absolute effect of folic acid fortification for all-cause stillbirths will depend on the coverage of intervention and baseline incidence of NTDs in any given population.

We based our recommendations on folic acid fortification studies rather than of synthetic supplementation. This is based on the observation that widespread adoption of policies of folic acid supplementation in many developed countries have yielded disappointing results at a public health level [81]. The main contributing factors to this could be a relatively high proportion of unplanned pregnancies [82] and lack of easy access to a functioning health system and effective local social marketing interventions [23]. A policy of folic acid supplementation would be even more difficult to implement in low-income countries with high levels of poverty, poor health-care infrastructure and more number of unplanned pregnancies compared to developed

Table 2 Quality assessment of studies of balanced protein energy supplementation during pregnancy to prevent stillbirths

No. of studies (Ref)	Quality Assessment		Directness		Summary of findings			
	Design	Limitations	Consistency	Generalizability to Population of Interest	Generalizability to intervention of Interest	Events in intervention group	Events in control group	Relative Risk (95 % CI)
Stillbirth: Low outcome specific quality								
3	RCT and quasi RCT	Methods of sequence generation and allocation concealment were not adequate in two of the included studies	Heterogeneity in the pooled data was not significant (I ² =20%)	One of the study from developed country (USA); however, the participants in this study were from lower socioeconomic status	Different studies used different composition of formula for delivery of balance protein energy.	18	31	0.55 (0.31-0.97)



countries [23,81,83,84]. Folic acid fortification seems a more suitable option for developing countries but it requires careful considerations including level of folic acid fortification and selection of suitable food vehicle. For example in certain population use of rice may be more common than flour or maize.

It is important to note that the effect of folic acid on incidence of NTDs and related stillbirths will be different in different countries. The amount of protective effect will depend on baseline NTDs incidence rate, folate deficiency in child bearing women, genetic susceptibility and existing system for screening and termination of affected

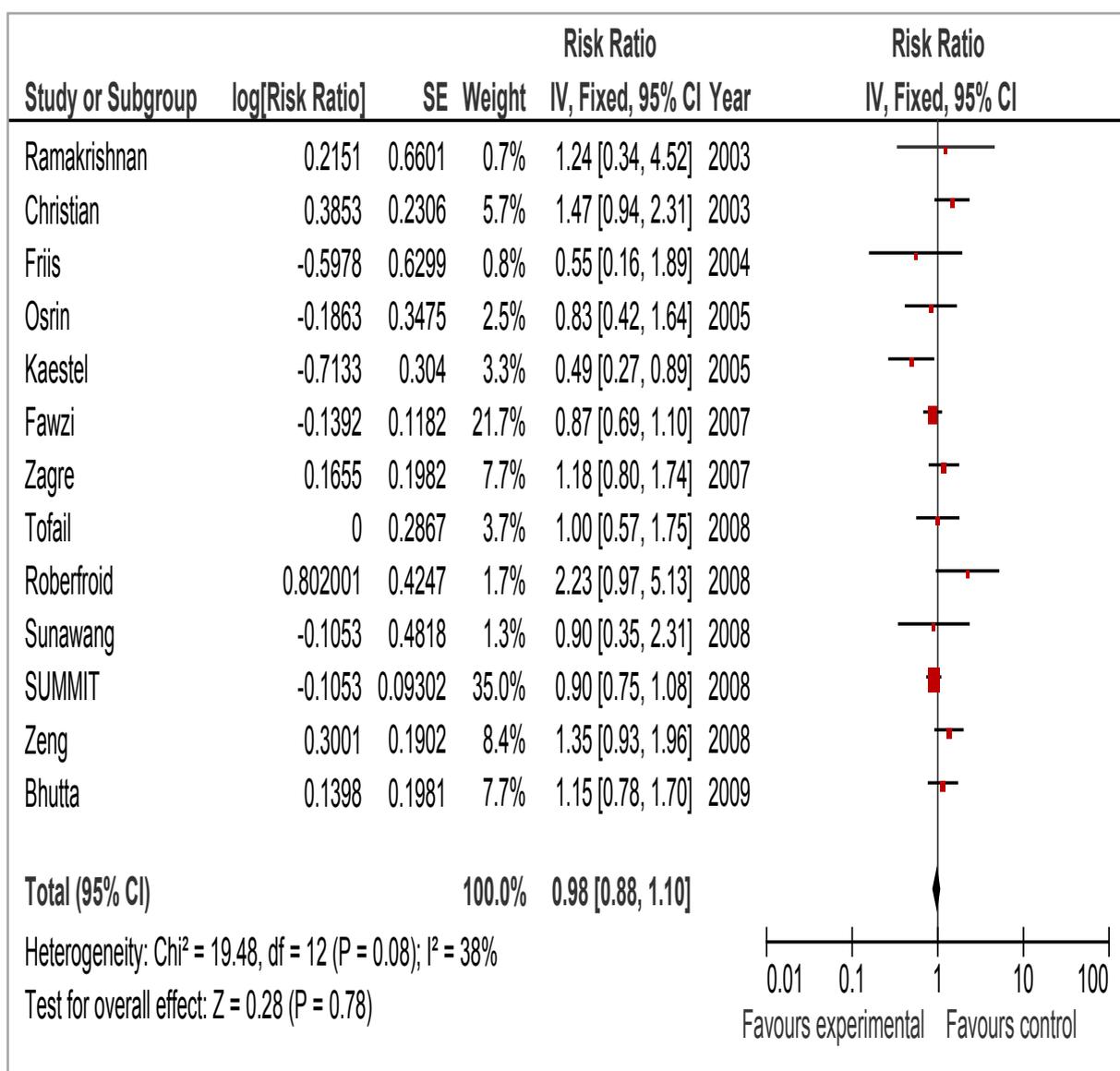


Figure 6 Impact of multiple micronutrients supplementation in pregnancy on stillbirths.

pregnancies [75,78]. For example in one part of China, incidence of NTDs is much higher than other regions in the country and folic acid supplementation was more effective in reducing NTDs in this area compared to others [25]. The estimate in our meta-analysis of folic acid-fortification effect is based primarily on white populations and the effect may differ in different races. A before and after study from USA reported not only lower background NTD rates amongst black Americans compared to Hispanic or white groups, but also a reduced effect of folic acid fortification in the black American group [38]. This indicates that a policy of folic acid fortification may yield different results in different populations across the developing and developed countries.

The beneficial effects of folic acid may extend beyond NTDs and related stillbirths. A recent review by Blencowe et al. for Live Saved Tool has shown that folic acid fortification can reduce congenital anomalies related neonatal mortality by 13 % [21]. A study from Canada has shown that folic acid fortification reduced incidence of severe congenital heart diseases [79]. Another study has reported that folic acid supplementation can reduce spontaneous preterm delivery [80].

Balance protein energy supplementation has been shown to have a significant reduction on incidence of intrauterine growth restriction [2,9]. The current analysis suggests that it could also reduce occurrence of stillbirths [RR 0.55, 95 % CI 0.31-0.97]. There was no

Table 3 Quality assessment of studies of multiple micronutrients supplementation during pregnancy to prevent stillbirths

Quality Assessment			Directness			Summary of findings
No. of studies (Ref)	Design	Limitations	Consistency	Generalizability to Population of Interest	Generalizability to intervention of Interest	Relative Risk (95 % CI)
Stillbirth: Low outcome specific quality						
13	RCT	Methods of sequence generation and allocation concealment were not explicitly described in few of the studies	Heterogeneity in the pooled data was not significant ($I^2=38\%$)	All included studies from developing countries	Nine studies used UNIMMAP formulation (30 mg iron, 400 µg folic acid, 15 mg zinc, 2 mg copper, 65 µg selenium, 800 µg RE vitamin A, 1.4 mg vitamin B1, 1.4 mg vitamin B2, 18 mg niacin, 1.9 mg vitamin B6, 2.6 µg vitamin B12, 70 mg vitamin C, 5 µg vitamin D, 10 mg vitamin E and 150 µg iodine)	0.98 (0.88-1.10) ^a
Peri-natal mortality: Low outcome specific quality						
11	RCT	Methods of sequence generation and allocation concealment were not explicitly described in few of the studies	Significant heterogeneity ($I^2=56\%$). Random models used	All included studies from developing countries	Nine studies used UNIMMAP formulation (30 mg iron, 400 µg folic acid, 15 mg zinc, 2 mg copper, 65 µg selenium, 800 µg RE vitamin A, 1.4 mg vitamin B1, 1.4 mg vitamin B2, 18 mg niacin, 1.9 mg vitamin B6, 2.6 µg vitamin B12, 70 mg vitamin C, 5 µg vitamin D, 10 mg vitamin E and 150 µg iodine)	1.07 (0.92 – 1.25) ^a

a: generic inverse variance.

significant statistical heterogeneity in the pooled estimate ($I^2=20\%$) (Figure 5). The overall grade quality evidence for the pooled estimate was that of 'low' level due to inadequate method of sequence generation and allocation concealment of the two of the included studies. The total numbers of stillbirths in all the three included studies was less than 50. According to CHERG rules, it is a pre-requisite for an estimate to be considered for inclusion in the LiST model that the total number of events is at least greater than 50 [16]. It should also be noted that all three included studies used different formulas to deliver the intervention. There is no single proven formula to recommend on large scale. Thus the value of protein supplementation is uncertain.

There was no effect of multiple micronutrient supplements on incidence of stillbirths compared to iron-folate supplementation alone. The Cochrane review on the subject by us in 2006 [7], however, did not have any meta-analysis on stillbirths as outcome. Most of the studies in the current analysis were representative of low- or middle-income populations. As the results were not statistically significant, we do not recommend MMN supplementation during pregnancy for inclusion in the LiST for reduction of stillbirths. A recently published review on MMN showed similar results [84].

In conclusion, folic acid fortification reduces incidence of neural tube defects and may also have an effect on stillbirths. This estimate of 41% reduction has been recommended as a proxy for reduction in stillbirths due to NTDs, for inclusion in the LiST model. Based on 3

studies balanced protein energy supplementation during pregnancy may reduce all-cause stillbirths by 45%. While promising, there is need of more operations research before we can recommend this intervention on large scale for reducing stillbirths. There is no evidence of effect of multiple micronutrients supplementation on reducing stillbirths.

Additional material

Additional File 1: The search strategies used for the above mentioned nutritional interventions on PubMed.

Additional File 2: Data extraction sheet for studies included in the review.

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Authors' contributions

Professor Zulfiqar A Bhutta developed the review parameters and secured support. Drs Aamer Imdad and Yawar Yakoob undertook the literature search, data extraction and analysis under the supervision of Professor Bhutta. Dr. Zulfiqar A. Bhutta gave advice in all the aspects of the project and was the overall supervisor.

Competing interests

The authors declare no conflict of interest.

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