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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-conceptional 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-conceptional 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.

Me hods

Search

We systematically reviewed all published literature to identify studies addressing peri-conceptional 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 3

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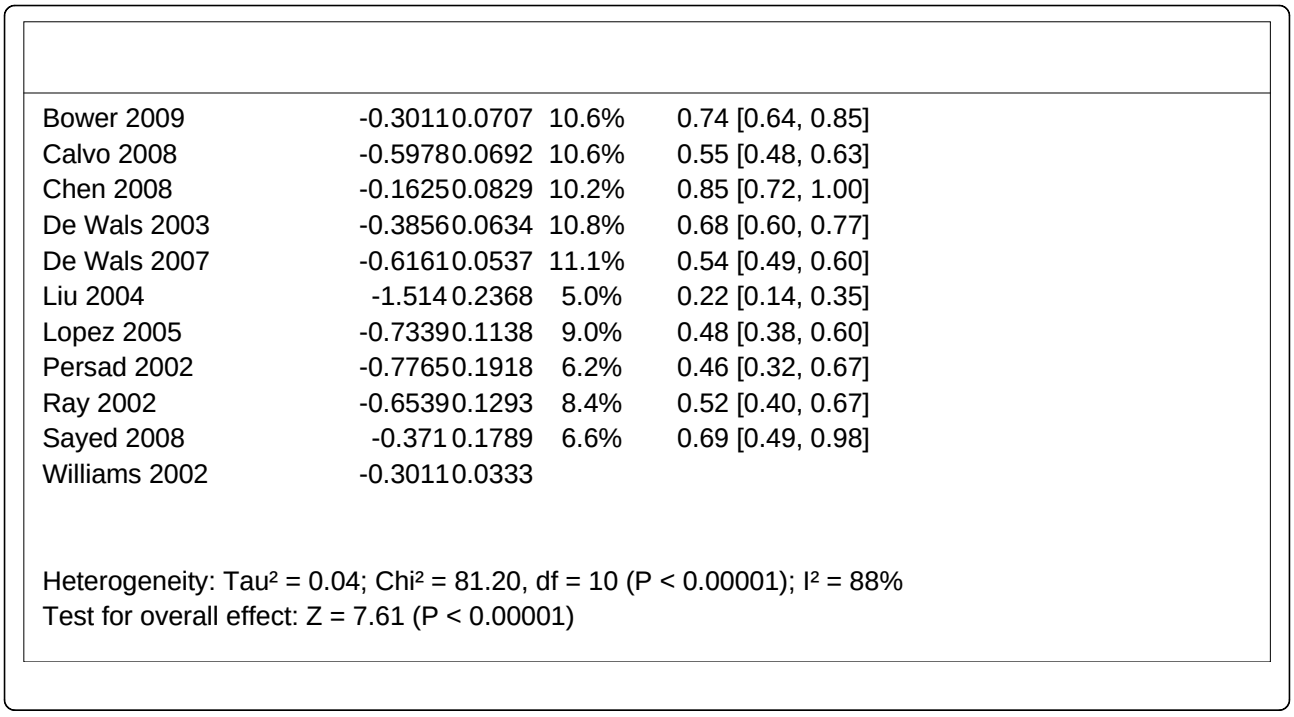
other selected studies [16]. Any study getting a final score of 'very low' was excluded from the review [16,17]. The detailed data extraction with the limitation of studies is shown in Additional File 2.

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



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).

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

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-conceptional 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

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 defi-

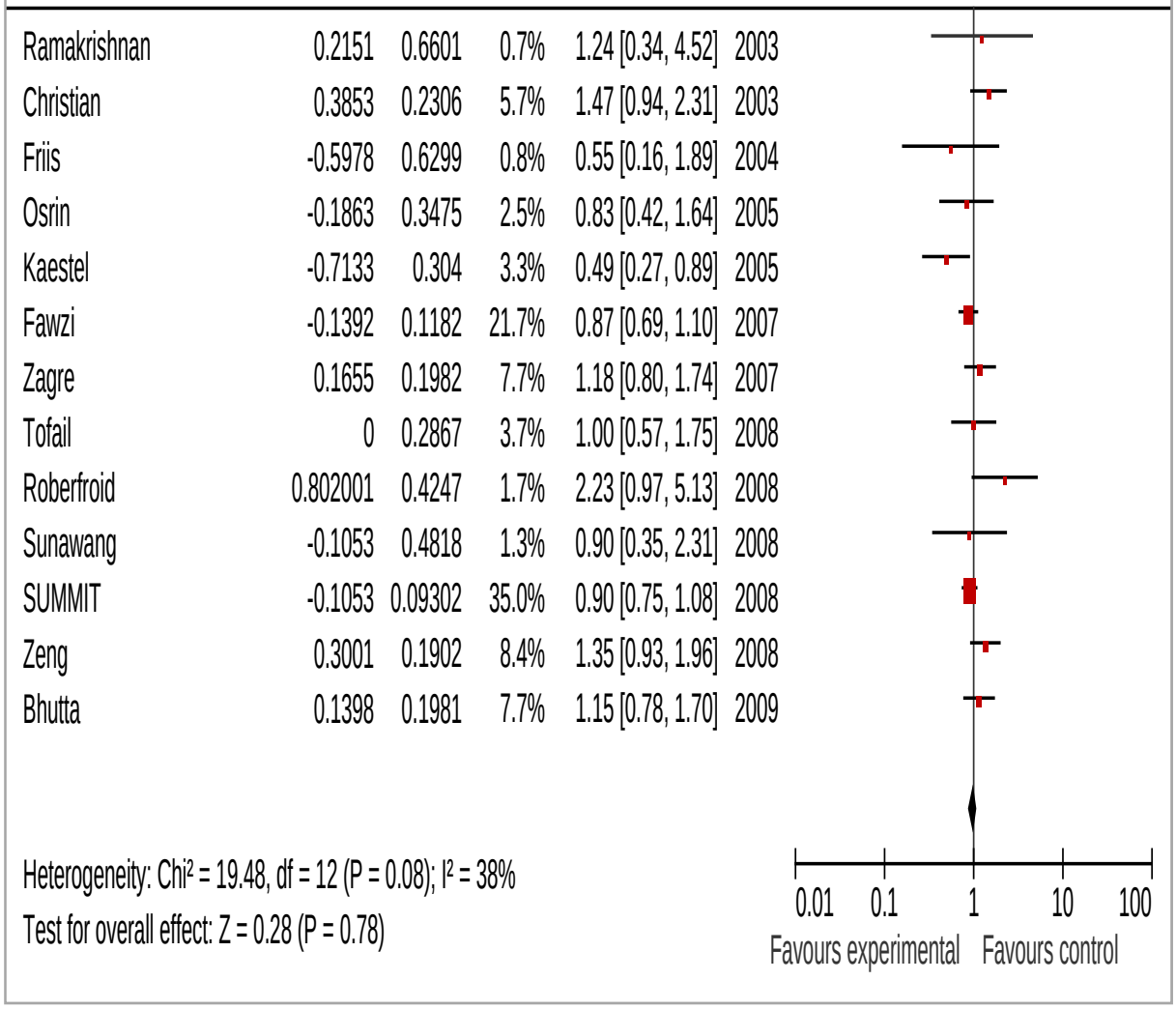


Figure 6 Impact of multiple micronutrients supplementation in pregnancy on stillbirths.

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

significant statistical hete

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