Zinc is an essential trace element involved in different physiological functions. During pregnancy, it plays a crucial role in healthy embryogenesis. This umbrella review, therefore, aimed to summarize the existing literature of meta-analyses evaluating the effect of maternal zinc supplementation or zinc status on maternal and neonatal outcomes. Two databases, PubMed and Scopus, were selected to search the available literature without any temporal restriction. The literature search was performed during October 2020 and a total of 192 records were identified through the literature search. After screening the titles and applying the inclusion/exclusion criteria, finally, 15 articles were included in this umbrella review. This umbrella review showed that maternal zinc supplements reduce the risk of preterm birth. Although no substantial effect of zinc supplements was found for other feto-maternal outcomes. Also, we found a significant relationship between low maternal zinc status and risk of pregnancy complications. Zinc supplements reduce the risk of preterm birth. Long-term interventions and cohort studies are needed for future research directions. Further studies and a thorough investigation will help to decide the recommended zinc dose or intake during pregnancy.
supplements on fetal and maternal complications [15]. Yet, the literature of conflicting studies reflects uncertainty in the evidence linking maternal zinc status and pregnancy complications [16]. However, due to an increase of available studies, systematic reviews, and meta-analyses, conducting an umbrella review is a novel and preferred approach to providing comprehensive, systematic, diverse, and reliable research evidence available for a specific research topic [17]. Therefore, this umbrella review of meta-analyses aimed to summarize the existing meta-analyses regarding the effect of maternal zinc supplementation on maternal and neonatal outcomes. Furthermore, we summarized the available data of meta-analytical studies showing the association between zinc status during pregnancy and perinatal outcomes.

2. Methods

2.1. Data sources and search criteria

A bibliographic search was carried out in October (27/10/20 to 29/10/20) using PubMed and Scopus databases. Two reviewers independently searched the literature by entering the search term (“zinc” or “Zn”) and (“pregnant” or “gestation” or “maternal” or “perinatal” or “neonatal” or “preterm” or “birthweight” or “miscarriage” or “preeclampsia”) and (“metaanalysis” or “meta-analysis”) with no temporal restriction. A database-specific search syntax file regarding complete search terms and strategies for each database are provided (Supp. file 1).

Given that, a total of 192 records were identified through search. At the first screening step, 129 irrelevant titles were excluded not meeting the study objective, leaving 63 articles to scan for abstracts (Figure 1). After reviewing the abstracts, further 29 articles were excluded providing a total of 34 articles for full-text perusal. Finally, 15 meta-analytical articles were included in this umbrella review according to inclusion/exclusion criteria to evaluate the association of maternal zinc supplements or status and its effects on feto-maternal outcomes.

2.2. Inclusion/exclusion criteria

In this umbrella review, the study design i.e. meta-analysis of randomized controlled trials (RCTs) and quasi-randomized trials, interventional studies, or cohort studies, were included to assess the primary outcomes. Focusing on perinatal outcomes, the effects of zinc supplementation on preterm birth, small for gestational age (SGA), low birth weight (LBW), preeclampsia, head circumference, premature rupture of membrane, stillbirth child mental and psycho-motor development index, 5-minute APGAR (appearance, pulse, grimace, activity, and respiration) score and childhood wheeze were taken as primary outcomes. While, meta-analyses evaluating the association of maternal zinc status and its effects on pregnancy complication were considered as secondary outcomes and included the previous meta-analyses comprising case-control, cross-sectional and observational studies.

The availability of odds ratios (OR), β-coefficients, risk ratios (RR), effect size (ES), mean difference, and confidence intervals, was considered as a prerequisite for all included meta-analyses of randomized controlled and interventional trials. Furthermore, the studies excluded on the basis of (a) duplicate, (b) no meta-analysis conducted, and (c) meta-analysis which combined zinc supplements with other micronutrients including trace elements and minerals to analyze the main effect of zinc supplements.

2.3. Quality assessment

Both reviewers assessed the methodological quality of each included meta-analyses. In this regard, reviewers followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18]. Also, the process for selecting studies including screening, determining eligibility, citation details, study aim and objective of the included meta-analysis, participant details, setting and context, number of databases sourced and searched, number and type of studies, and reported result outcomes were assessed by using the Aromataris and colleagues study guidelines [17]. While the tools for assessing quality and susceptibility to bias in observational studies were assessed by using the study protocols as described in proposed by [19].

2.4. Maternal and child outcomes

Maternal and child outcomes such as preterm birth, low birth weight, change in birth weight, small for gestational age, head circumference, psycho-motor Development Index (PDI), Mental Development Index (MDI), Stillbirth or neonatal death, low 5-minute APGAR score (<5), childhood wheeze, premature rupture of membrane and preeclampsia were categorized as primary result outcomes to evaluate the effects of maternal zinc supplementation on pregnancy complications and perinatal outcomes. All discrepancies regarding exclusion/exclusion criteria, a full-text perusal of studies, and selection of included studies were resolved through discussion and consensus of both reviewers.

2.5. Data extraction

A qualitative methodological approach used for organizing and reporting the findings. In this regard, we extracted data and reviewed each meta-analysis according to (1) availability of odds ratio (OR), relative risk (RR), mean difference (MD), effect size (ES), or β coefficient, (2) test for heterogeneity (p-value), (3) I² value (%), and (4), and whether fixed or random-effects models were used in the pooling of results. The number of trials, type of the included studies, zinc interventions and dose, and information about the number of interventional and control group participants were extracted from the selected meta-analyses.
Finally, the concluding remarks from the paper were included to better understand the result outcomes.

In addition, we summarized the previous meta-analyses showing the association of maternal zinc status and perinatal outcomes. On the same lines, we extracted the available information regarding study reference, year, outcomes, study aim, number of trials, analysis model, test for heterogeneity (p-value), I² value, and extraction of MD or RR, and concluding study remarks.

3. Results

3.1. Effect of zinc supplementation on pregnancy outcomes

As a result of the given search and selection criteria, total 10 papers were found eligible to evaluate the effect of zinc supplementation on maternal and neonatal outcomes [20, 21, 22, 23, 24, 25, 26, 27, 28, 29]. The studies included RCTs (n = 6), RCTS and quasi-randomized trials (n = 2), interventional studies (n = 1) and cohort studies (n = 1).

The available number of participants treated with zinc supplements were inclusive of 35,115 pregnant women in the zinc supplemented group and 34,482 in the control group. However, the participants' detailed descriptions of both groups were not provided in the remaining 8 study trials (Table 1). The number of trials in the selected meta-analyses varied from 1 up to 24 and the provided dose of zinc supplements during pregnancy was 1mg/day to 62 mg/day. Almost all studies used a test for heterogeneity (p-value) and I² (%) to validate the pooled estimates. The I² value in the selected studies ranged from 0% to 96%, whereas the p-value varied from <0.00001 to 0.97. Most of the study trials used the fixed-effect model (n = 20) compared to the random effect model (n = 9).

3.2. Preterm birth

In total, 12 feto-maternal outcomes, i.e., preterm birth, small for gestational age, low birth weight, change in birth weight, preeclampsia, head circumference, psychomotor development, mental development, stillbirth, premature rupture of membrane, low APGAR score (<5) and childhood wheezing were identified from the selected papers.

Given that, five studies conducted meta-analyses to determine the effects of zinc supplements on preterm birth [20, 21, 22, 23, 24]. Most of the studies indicated that zinc supplements reduce the risk of preterm birth. Likewise, Mahomed and colleagues [24] found that zinc supplementation resulted in a small but significant reduction in preterm birth [RR: 0.86 (0.76–0.98)]. Correspondingly, the meta-analyses of Ota et al [22] and Chaffee and King [23] included the studies of pregnant women treated with zinc supplements ranging from 5-50 mg/day and found that maternal zinc supplementation lowering the risk of preterm birth respectively [RR: 0.86 (0.76–0.97)] and [RR: 0.86 (0.75–0.99)]. While meta-analysis of Lassi and allies [21] included the studies with a lower range of zinc supplements (14–20 mg/day) and reported that pregnant adolescent women supplemented with even smaller zinc dose can reduce the risk of preterm births. However, only the study of Oh and colleagues did not observe any significant positive effect of zinc supplementation on preterm birth [20].

3.3. Small for gestational age

Furthermore, four studies evaluating the effect of zinc intake during pregnancy on small for gestational age (SGA) infants found no association between maternal zinc supplementation and SGA [20, 22, 23, 24]. Such as a study by Oh and colleagues [20] found little or no effect of zinc supplements on reducing the risk of SGA infants [RR: 1.05 (0.97–1.13)]. Similarly, meta-analyses of Chaffee and King [23] in 2012 and Ota and colleagues [22] in 2015 did not find any effect of zinc supplementation on SGA infants [RR: 1.03 (0.91–1.17)] and [RR: 1.02 (0.94–1.11)] respectively. Likewise, a previous Cochrane Database Systematic Review determined the effects of zinc supplements vs no zinc (with or without placebo) in 2007 and did not report any significant effects on SGA [24].

3.4. Low birth weight

Regarding low birth weight (LBW), eight meta-analyses including RCTs and quasi-randomized trials were conducted from 2007 to 2020. Only the study of Lassi and colleagues [21] reported that zinc supplements reduce the risk of LBW [RR: 0.39 (0.15–0.98)], while the other seven meta-analyses found no effect of prenatal zinc supplementation on infant birth weight [20, 22, 23, 24, 25, 26, 27]. For instance, the meta-analysis of Oh [20] and Mahomed [24] with their colleagues determined the effects of zinc supplementation versus placebo and found no impact of zinc supplements on the risk of LBW [RR:1.08 (0.94–1.25) and [RR: 1.03 (0.94–1.13)] respectively. Similarly, Petry and colleagues [26] included the studies of pregnant women treated with <21 mg/day zinc and also found no effects of maternal zinc supplementation on LBW [RR: 0.96 (0.67–1.37)]. On the same lines, the study of Ota and colleagues [22], Chaffee and King [23], and Liu and colleagues [25] included studies of zinc supplementation ranging from 5-50 mg/day and reported no effects on LBW. Considerably, Gebreselassie and Gashe [27], in their meta-analysis included RCTs with even higher zinc doses (ranged from 15-62 mg/day) and found no significant association between prenatal zinc supplementation and infant birth weight [ES: 0.0268 [0.0764 – (-0.0229)].

3.5. Mental and psychomotor development index

To evaluate the effects of mental and psychomotor development index, we found only two meta-analyses. The study of Ota and colleagues [22] found that zinc supplemented group (ranged from 5-44 mg/day) had significantly low psychomotor development index (PDI) and mental development index (MDI) scores respectively as compared to no-zinc group [PDI = Mean difference: -7.00 (-11.92 to -2.08) [MDI = Mean difference: -3.30 (-6.51 to -0.09)]. In contrast, the study from Nissensohn et al. [28] in 2013 found no association between zinc intake and MDI and PDI scores in infants.

3.6. Other outcomes

Also, no positive effect of zinc intake was identified on other outcomes such as infant head circumference [22, 23, 24], 5-minute APGAR score [22], stillbirth, or neonatal death [22], preeclampsia [20, 22], and premature rupture of the membrane [22]. Though, Beckhaus and colleagues [29] in their cohort study, showed the protective effect of maternal zinc intake against childhood wheezing.

3.7. Maternal zinc status and its relation to pregnancy complications or child outcomes

In total, five meta-analyses evaluated the association between maternal zinc status and pregnancy complications and child outcomes [30, 31, 32, 33, 34]. For all outcomes, the meta-analyses included 4 to 29 number of trials and used the random-effect model (Table 2). A high heterogeneity with I² values reported between 62.34% and 96%—the mean difference for different outcomes varied from -0.59 to -15.91.

All studies showed that low maternal zinc status increases the risk of pregnancy complications. For example, a recent meta-analysis from Akdas and Yazhihan [30] found low maternal zinc status and low cord blood zinc levels in pregnant women with complications than healthy controls. Similarly, two meta-analytical studies [31, 32] stated that women with preeclampsia had a lower zinc status than healthy control pregnant women. Likewise, He and colleagues [33] reported a high incidence of Pregnancy-induced hypertension in pregnant women with low serum zinc status [MD: -1.14 [-1.69 – (-0.59)]. Moreover, Molina-Solana and collaborators [34] found an association between a
| Study outcome                  | Reference/year | Studies included                                      | No. of trials | No. of participants | Analysis model        | Zinc interventions or dose | Risk estimates (RR/OR/ES/MD/ß (95%CI)) | I² value (%) | Test for heterogeneity (p value) | Conclusion                                                                 |
|-------------------------------|----------------|-------------------------------------------------------|---------------|---------------------|------------------------|----------------------------|----------------------------------------|--------------|----------------------------------|---------------------------------------------------------------------------|
| Preterm birth                 | Oh et al [20] 2020 | Randomized controlled trials (RCTs) and quasi-randomized trials | 11            | Total (n) = 5017 zinc group/controls (2524/2493) | Random effect model   | Zinc supplementation versus placebo | RR: 0.97 (0.80–1.17)                  | 22%          | p = 0.73                         | The results showed no significant effect of zinc supplements on reducing the risk of preterm birth. |
|                               | Lassi et al [21] 2017 | Interventional trials (zinc supplementation versus placebo) | 2             | N/A                 | Random effect model   | 14–20 mg/day             | RR: 0.57 (0.46–0.69)                  | 0%           | p = <0.00001                     | The studies on pregnant adolescents reported that zinc supplements reduce the risk of preterm births. |
|                               | Ota et al [22] 2015 | RCTs                                                   | 16            | Total (n) = 7637 zinc group/controls (3851/3786) | Fixed effect model   | 5–44 mg/day              | RR: 0.86 (0.76–0.97)                  | 17%          | p = 0.012                        | Zinc supplementation helps to reduce the risk of preterm birth.          |
|                               | Chaffee and King [23] 2012 | RCTs                                                 | 16            | Total (n) = 7818    | Fixed effect model   | 5–50 mg/day             | RR: 0.86 (0.75–0.99)                  | 26%          | p = 0.162                        | The study results found that maternal zinc supplementation lowers the risk of preterm birth, however, no evidence of zinc supplements on other fetal outcomes was reported. |
|                               | Mahomed et al [24] 2007 | RCTs                                                  | 13            | Total (n) = 6854 zinc group/controls 3421/3433 | Fixed effect model   | Zinc supplements vs no zinc (with or without placebo) | RR: 0.86 (0.76–0.98)                  | 22%          | p = 0.021                        | Zinc supplementation resulted in a small but significant reduction in preterm birth. |
| Small for Gestational Age (SGA) | Oh et al [20] 2020 | RCTs and quasi-randomized trials                      | 3             | Total (n) = 2174 zinc group/controls (1094/1080) | Random effect model   | Zinc supplementation versus placebo | RR: 1.05 (0.97–1.13)                  | 0%           | p = 0.24                         | The study found little or no effect of zinc supplements on reducing the risk of SGA infants. |
|                               | Ota et al [22] 2015 | RCTs                                                   | 8             | Total = 4252 zinc group/controls (2161/2091) | Fixed effect model   | 5–44 mg/day              | RR: 1.02 (0.94–1.11)                  | 28%          | p = 0.58                         | No effect of zinc supplementation was seen on SGA infants.                 |
|                               | Chaffee and King [23] 2012 | RCT                                                   | 5             | Total (n) = 3441    | Fixed effect model   | 25–45 mg/day             | RR: 1.03 (0.91–1.17)                  | 59%          | p = 0.04                         | No effect of zinc supplements was reported on SGA.                       |
|                               | Mahomed et al [24] 2007 | RCTs                                                  | 5             | Total = 3469 zinc group/controls (1731/1738) | Fixed effect model   | Zinc supplements vs no zinc (with or without placebo) | RR: 1.04 (0.96–1.13)                  | 22%          | p = 0.30                         | No significant effect of zinc supplements was observed on SGA infants.     |

(continued on next page)
| Study outcome                  | Reference/year | Studies included                  | No. of trials | No. of participants | Analysis model | Zinc interventions or dose | Risk estimates [RR/OR/MD/95%CI] | I² value (%) | Test for heterogeneity (p value) | Conclusion                                                                 |
|-------------------------------|----------------|-----------------------------------|---------------|---------------------|----------------|--------------------------|----------------------------------|--------------|----------------------------------|---------------------------------------------------------------------------|
| Low Birth Weight (LBW)        | Oh et al [20]  | RCTs and quasi-randomized trials  | 10            | Total (n) = 4633    | Random effect model | zinc supplementation versus placebo* | RR: 1.08 (0.94–1.25) | 14%          | p = 0.26                        | The results found no impact of zinc supplements on the risk of LBW.        |
|                               | Liu et al [25] | RCTs                              | 24            | Total (n) = 13,167  | N/A             | 10–50 mg/day            | RR: 0.76 (0.52–1.11) | 91.1%        | p = 0.000                        | Maternal zinc supplementation has no effects on LBW                      |
|                               | Lassi et al [21]| RCTs                              | 6             | Total (n) = 507     | Fixed effect model | 14–20 mg/day           | RR: 0.39 (0.15–0.98) | N/A          | p = 0.04                         | The studies on pregnant adolescent reported that zinc supplements reduce the risk of low birth weight |
|                               | Petry et al [26]| RCTs and quasi-randomized trials  | 7             | Total (n) = 6,2518  | Random effect model | ≤21 mg/day             | RR: 0.96 (0.67–1.37) | 0%           | p = 0.83                         | The results found that 21 mg/day of zinc during pregnancy has no significant effect on the prevalence of LBW |
|                               | Ota et al [22] | RCTs                              | 14            | Total (n) = 5643    | Random effect model | 5–44 mg/day            | RR: 0.93 (0.78–1.12) | 38%          | p = 0.46                         | No clear differences were seen between the zinc and no zinc groups for the reduction of LBW |
|                               | Chaffee and King [23] | RCT                          | 11            | Total (n) = 5614    | Fixed effect model   | 5–50 mg/day            | RR: 1.06 (0.91–1.23) | 37.5%        | p = 0.100                        | No effect of zinc supplements was reported on LBW.                      |
|                               | Mahomed et al [24]| RCTs                              | 11            | Total (n) = 4860    | Fixed effect model   | Zinc supplements vs no zinc (with or without placebo) | RR: 1.03 (0.94–1.13) | 17%          | p = 0.51                         | The results showed no effect of zinc supplements on LBW infants           |
|                               | Gebreselassie and Gashe [27] | RCTs                              | 17            | Total (n) = 6209    | Fixed effect model   | 15–62 mg/day            | ES: 0.0268 (0.0764 – (-0.0229)) | N/A          | p = 0.09                         | The results found no association between prenatal zinc supplementation and infant birth weight |
| Pre-eclampsia                 | Oh et al [20]  | RCTs and quasi-randomized trials  | 3             | Total (n) = 1226    | Random effect model   | zinc supplementation versus placebo* | RR: 1.01 (0.53–1.93) | 0%           | p = 0.97                         | The results showed no effect of zinc supplements on reducing the risk of preeclampsia/eclampsia. |
|                               | Ota et al [22] | RCTs                              | 7             | Total (n) = 2975    | Fixed effect model   | 5–44 mg/day            | RR: 0.83 (0.64–1.08) | 26%          | p = 0.17                         | The study reported no effect of zinc intake on pre eclampsia.             |
| Head circumference(cm)        | Ota et al [22] | RCTs                              | 7             | Total (n) = 3991    | Fixed effect model   | 5–44 mg/day            | Mean difference: -0.03 (0.17 – 0.11) | 45%          | p = 0.67                         | The study reported no effect of zinc intake on infant head circumference |
|                               | Chaffee and King [23] | RCT                          | 11            | Total births (n) = 5065 | Fixed effect model   | 5–50 mg/day            | Mean difference: 0.3 (-0.3 – 0.9) | 52.3%        | p = 0.021                        | There was no evidence to support a meaningful zinc supplementation effect on change in head circumference |
|                               | Mahomed et al [24]| RCTs                              | 7             | Total (n) = 3991    | Fixed effect model   | Zinc supplements vs no zinc (with or without placebo) | Mean difference: -0.06 (-0.15 – 0.04) | 45%          | p = 0.24                         | The study reported no effect of zinc intake on infant head circumference |

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Table 1 (continued)

| Study outcome                  | Reference/year | Studies included | No. of trials | No. of participants | Analysis model     | Zinc interventions or dose | Risk estimates [RR/OR/ES/MD/ß (95%CI)] | I² value (%) | Test for heterogeneity (p value) | Conclusion                                                                                           |
|--------------------------------|----------------|------------------|---------------|---------------------|--------------------|---------------------------|----------------------------------------|--------------|---------------------------------|------------------------------------------------------------------------------------------------------|
| Psycho- motor Development Index (PDI) | Ota et al [22] 2015 | RCTs 1           | 83/85         | Fixed effect model  | 5–44 mg/day        | Mean difference: -7.00 (-11.92 – -2.08) | N/A                     | p = 0.0053     | The zinc group had significantly worse psychomotor development index scores than the no-zinc group. |
| Mental Development Index (MDI) | Nissensohn et al [28] 2013 | RCTs 11          | Total (n) = 1775 Intervention/control group (917/858) | Random effect model | 1–10 mg/day | β: 0.00 (-0.03 – -0.02) | 96%                     | p = 0.83     | The study found no association between zinc intake and PDI scores in infants.                     |
| Stillbirth or neonatal death   | Ota et al [22] 2015 | RCTs 8           | Total (n) = 5100 zinc group/controls (2646/2454) | Fixed effect model  | 5–44 mg/day        | RR: 1.12 (0.86 – 1.46)           | 0.0%                     | p = 0.38     | No effect of zinc supplementation was seen on stillbirth or neonatal deaths.                     |
| Premature rupture of membrane  | Ota et al [22] 2015 | RCTs 2           | Total (n) = 1691 zinc group/controls (827/864) | Fixed effect model  | 5–44 mg/day        | RR: 0.93 (0.78 – 1.11)           | 0%                      | p = 0.43     | The study reported no effect of zinc intake on the premature rupture of the membrane.            |
| 5-minute APGAR score (<5)      | Ota et al [22] 2015 | RCTs 2           | Total (n) = 1691 zinc group/controls (827/864) | Fixed effect model  | 5–44 mg/day        | RR: 1.02 (0.26 – 4.03)           | 0%                      | p = 0.96     | Zinc intake has no effect on APGAR score                                                       |
| Childhood wheeze               | Beckhaus et al [29] 2015 | Cohort studies 3 | Total (n) = 3315 | Fixed effect model  | N/A                | OR: 0.57 (0.40 – 0.81)          | 0%                      | p = 0.002    | Maternal zinc intake has a protective effect against childhood wheeze.                           |

* Dose of zinc supplementation is not available.
* N/A = not available or applicable.
Table 2. Maternal zinc status and pregnancy complications or child outcomes: A summary of meta-analyses.

| Study aim | No. of trials | Studies included | Analysis model | MD or RR (95%CI) | I² value (%) | Test for heterogeneity p-value |
|-----------|--------------|-----------------|----------------|----------------|-------------|-------------------------------|
| Cord blood zinc level vs pregnancy outcomes | 29 | Random effect model | Cord blood zinc level vs all studies | MD: -7.9 [-12.48 to -3.31] | 98% | p = 0.0008 |
| Maternal blood zinc level vs pregnancy outcomes | 18 | Random effect model | Maternal blood zinc level vs all studies | MD: -0.61 [-0.74 to -0.48] | 88.5% | p = 0.000 |
| Maternal zinc status vs perinatal outcomes | 13 | Random effect model | Maternal zinc status vs all studies | MD: -0.59 [-0.96 to -0.21] | 88.4% | p = <0.0001 |
| Maternal zinc status vs prematurity | 8 | Random effect model | Maternal zinc status vs prematurity | RR: 1.82 (0.88–3.79) | 62.34% | p = 0.001 |
| Maternal zinc status vs preeclampsia | 8 | Random effect model | Maternal zinc status vs preeclampsia | RR: 1.92 (0.85–4.29) | 63.34% | p = 0.074 |

In summary, we described the summary of 15 meta-analyses meeting our selection criteria to determine the effect of maternal zinc supplements and zinc status during pregnancy. Most of the studies discovered the effects of zinc supplementation on feto-maternal outcomes. Yet, very few meta-analyses were available, showing the association between maternal zinc status and perinatal outcomes.

The findings of this umbrella review suggested that zinc supplements during pregnancy significantly reduce the risk of preterm infants, though weak or no substantial evidence was found for other maternal and neonatal outcomes. A reduced risk of preterm births has been found previously in the zinc supplemented pregnant group [35]. Villar and colleagues suggested that zinc supplements might help decline neonatal mortality and preterm births [36]. Similarly, another study found that low maternal serum zinc concentration is associated with a high risk of preterm births [37].

Hypertensive disorders, hemorrhage, and intrauterine growth restriction are few common diagnoses associated with preterm births. Moreover, cigarette smoking, short cervix, history of previous preterm birth, and low serum levels of micronutrients, including zinc, have been suggested to increase the risk of preterm births [38]. In the period of early fetal development, zinc deficiency might have adverse effects on embryogenesis and the duration of pregnancy due to a reduced amount of hepatic stores [39]. Different physiological changes during pregnancy, such as alterations in tissue zinc distribution, an increase of zinc absorption, reduced endogenous zinc losses, and changes in the exchangeable zinc pools kinetics, appear to influence the maternal zinc status [40]. Also, the percentage of total serum zinc bound to albumin, and the affinity of zinc for serum albumin, are found lower during pregnancy, which might decrease the total circulating zinc concentrations during pregnancy [40].

Regarding SGA, this umbrella review of previous meta-analyses showed no association between maternal zinc supplementation and SGA. However, the impact of zinc in inflammatory processes on fetal outcomes is well-reviewed [41, 42]. Previously, an association between placental inflammation and the incidence of SGA infants was found during pregnancy due to activation of placental NF-κB signaling and elevation of serum inflammatory cytokines [43].

Furthermore, most of the included meta-analyses did not find any effect of zinc supplements during pregnancy to reduce the risks of LBW. The bioavailability of zinc supplement might be the major reason suggested in previous studies to explain the insignificant zinc supplements effect on birth weight [35, 44].

Additionally, in agreement with previous studies [35, 45], we found a weak or no clear benefit of maternal zinc supplements on different other perinatal outcomes, including head circumference, and stillbirth or neonatal death. The study on pregnant women in Iran found no effect of zinc supplements on prematurity, preeclampsia, premature rupture of membrane, stillbirth, small for gestational age, and head circumference [46]. Yet, our results identified that zinc supplements negatively affect PDI and MDI scores. In contrast, a previous study by Caulfield and colleagues found no effect of prenatal zinc supplementation on children’s cognitive, social, or behavioral development [47]. Nonetheless, the availability of very few studies, the difference in population groups, high heterogeneity, small effect magnitude, publication bias, and duration of intervention necessitated further research in this regard.

Moreover, our results showed that low maternal zinc status increases the risk of different perinatal and child complications. Simultaneously, few previous studies found no association between maternal zinc status and feto-maternal outcomes [16, 48]. A positive association between low maternal zinc status and etiology of preeclampsia and pregnancy-induced hypertension has been found in pregnant women due to a decline in low maternal zinc level and risk of cleft lip and/or palate in children [RR: 1.82 (0.88–3.79)].

4. Discussion
antioxidant activities [49, 50, 51]. Moreover, the beneficial effects of zinc to improve the immune system, cellular functions, signal transduction, and its anti-inflammatory activities are well known during the gestational period [40, 42].

Different factors including (a) low maternal body stores due to reduced time for placental transfer of zinc, (b) an increase of endogenous zinc losses, and (c) low/marginal zinc intake can increase the risk of zinc-related perinatal complications [39]. Also, an excessive amount of supplemental iron, any gastrointestinal disease could interfere with zinc absorption during pregnancy [44]. High phytate content and cereal-based diets can also have a negative effect on zinc absorption during pregnancy [52]. Moreover, maternal zinc deficiency due to a drug-mineral interaction might induce tissue damage, cytokine release, increased synthesis of metallothionein, sequestration of zinc in the maternal liver, and reduction of feto-maternal zinc concentration [53]. Other factors, such as smoking, alcohol abuse, and acute stress response to infection or trauma, may alter maternal plasma zinc concentrations and its transport to the fetus [4].

Ingestion of zinc supplements up to 40 mg elemental zinc per day in adults is mostly considered safe; however, prolonged exposure more than the tolerable upper intake level may suppress immunity, decrease high-density lipoprotein levels, and may cause hypochromic microcytic, i.e., red cells [54]. During normal conditions, the uptake from the gastrointestinal tract is approximately 20–30% of ingested dose [13]. Under certain deficiency conditions, zinc uptake may increase to more than 90%; however, the uptake may decrease to below 10% under conditions of excess exposure [13].

During pregnancy, zinc as a zinc-binding protein (metallothionein) accumulates in the liver and helps to protect the fetus from zinc deficiency during the immediate postnatal period [8]. Therefore, the requirement for zinc intake has been recommended from 1.1 to 2.0 mg/day in normative pregnant women [6]. Nonetheless, the absorption of at least 3 mg elemental zinc/day is recommended during the last two trimesters of pregnancy, which accounts for a dietary intake of 15 mg zinc/day, assuming a bioavailability of 20% [7].

5. Study limitations

This summary of meta-analyses determines the effect of maternal zinc supplements and zinc status on feto-maternal outcomes. However, our study also has limitations. Due to the varying doses of zinc supplementation, we were unable to determine the ideal dose-response relationship between zinc supplementation and feto-maternal outcomes, however, World Health Organization (WHO) and International Zinc Nutrition Consultative Group provided the gestational zinc requirement of 2.27 (mg/day) and 2.68 (mg/day) respectively [55]. Also, not prior registration on PROSPERO could be taken is another limitation. Our findings are based on available meta-analyses studies and their results. Due to the limited accessibility of databases, we selected PubMed and Scopus databases. These databases were selected because the PubMed database contains multi-disciplinary peer-reviewed literature, while Scopus also contains non-peer-reviewed literature. Whilst, this could be taken as a limitation. Nonetheless, few previous studies included only these 2 databases showing the effects of iron supplementation or iron status on maternal and neonatal outcomes [56]. Further studies for more extensive and more rigorous prospective placebo control trials are needed to confirm the relation between maternal zinc status and perinatal outcomes.

6. Conclusion and recommendations

This summary of meta-analyses showed that maternal zinc supplements could help to reduce preterm birth and low maternal zinc status that is associated with an increased risk of pregnancy complications. However, the effect of perinatal zinc supplements on children’s mental development needs a thorough investigation due to limited available literature.

Several confounders such as duration, dose, and pregnancy stage of the start of the zinc supplementation might be a contributing factor for less consistent results. Moreover, different study designs and various confounders may limit the interpretation of aggregated data. Thus, the need for multisite studies based on a common protocol, minimizing the effects of confounders might help to endorse concrete zinc supplementation effects during pregnancy.

Long-term interventions and cohort studies might help with future research directions. Moreover, by combining the data of available meta-analyses, this umbrella review will provide a better understanding and further insights on maternal zinc supplementation programs to reduce the risk of adverse feto-maternal outcomes. A comprehensive approach and guidelines on zinc and multi-micronutrient supplements are needed to best address the issue.

Declarations

Author contribution statement

Sehar Iqbal and Inayat Ali: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Data included in article/supplementary material/referenced in article.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

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