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NUTRIENT SUPPLEMENTATION FOR PREVENTION OF VIRAL RESPIRATORY TRACT INFECTIONS IN HEALTHY SUBJECTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Short title: Nutrient supplementation for primary prevention of RTIs

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Abstract

It remains uncertain as to whether nutrient supplementation for the general population considered healthy could be useful in the prevention of RTIs, such as COVID-19. In this systematic review and meta-analysis the evidence was evaluated for primary prevention of any viral respiratory tract infection (RTI) such as SARS-CoV-2, through supplementation of nutrients with a recognized role in immune function: multiple micronutrients, vitamin A, folic acid, vitamin B12, C, D, E, beta-carotene, zinc, iron and long chain polyunsaturated fatty acids.

The search produced 15,163 records of which 93 papers (based on 115 studies) met the inclusion criteria, resulting in 199,055 subjects (191,636 children and 7,419 adults) from 37 countries. Sixty-three studies were included in the meta-analyses, which was performed for children and adults separately. By stratifying the meta-analysis by world regions, only studies performed in Asia showed a significant, but heterogeneous protective effect of zinc supplementation on RTIs (RR 0.86, 95%CI 0.7-0.96, I2=79.1%, p=0.000). Vitamin D supplementation in adults significantly decreased the incidence of RTI (RR 0.89, 95%CI 0.79-0.99, p=0.272), particularly in North America (RR 0.82 95%CI 0.68-0.97), but not in Europe or Oceania.

Supplementation of nutrients in the general population has either no, or at most a very limited effect on prevention of RTIs. Zinc supplementation appears protective for children in Asia, while vitamin D may protect adults in the USA and Canada.

In 10/115 (8.7%) studies post-hoc analyses based on stratification for nutritional status was performed. In only one study zinc supplementation was found to be more effective in children with low zinc serum as compared to children with normal zinc serum levels.

Key words: supplementation, nutrients, acute respiratory tract infection, COVID-19

INTRODUCTION

The processes that ensure effective immune reactivity to infectious agents, such as respiratory viruses, are complex and still not fully understood. The coordination of rapid innate immune responses and development of acquired adaptive responses, with appropriate regulatory responses to prevent tissue injury, are influenced by a wide range of lifestyle and environmental factors.(1) Particularly, dietary factors are thought to play a significant role in supporting effective immune function.(2)

Viral respiratory tract infections (RTI's) can occur in epidemics and spread rapidly within communities across the word. (3). Lower respiratory tract infection and pneumonia are two of the leading causes of death, accounting for more than 4 million fatalities annually. It is a particularly important cause of death in low- and middle-income countries (3). Severe acute respiratory syndrome coronavirus (SARS-CoV-2) is currently responsible for millions of deaths.(4) The clinical presentation ranges from asymptomatic or mild disease to severe pneumonia, in which the most severe cases deteriorate with acute respiratory distress syndrome (ARDS), requiring prolonged mechanical ventilation, or even extracorporeal membrane oxygenation (ECMO).(5) The immune system plays a critical role in determining who develops mild disease and who may suffer multi-organ dysfunction and death.(6, 7) Although vaccine development and approvals are proceeding at an unprecedented pace with over 2 billion of vaccines given , there is a significant need to identify and better understand the modifiable factors, such as diet, that might be able to enhance the immune response to improve resistance to RTIs, such as COVID-19, in the general population.

It is well accepted that specific micronutrients can enhance the immune response to improve resistance to RTI's. The European Food Safety Authority (EFSA) evaluated several vitamins (e.g. D, A, C, folate, B6, B12) and minerals (zinc, iron, copper and selenium) and considers them to be essential for the normal growth and functioning of the immune system.(8) Impaired nutritional status or deficiencies of these elements is associated with increased risk and severity of many different types of infections. (9)

A healthy balanced diet that meets recommended daily values should contain all necessary nutrients. It is not quite clear if supplementation of individuals who comply with the recommended daily intake and are expected not to be deficient will lead to any improvement in their immune response to pathogens. In addition, many individuals without any health-related issues do not meet the recommendations for nutrient intake due to unhealthy or unbalanced consumption patterns or due to increased needs. (10) Therefore, there remains uncertainty as to whether nutrient supplementation for the general population considered healthy could be useful in the prevention of RTIs, such as COVID-19. To the best of our knowledge, no systematic review and meta-analysis on the prevention of RTIs by supplementation of a large number of nutrients restricted to otherwise healthy individuals, i.e. the general population, has been published.

Currently there is overwhelming and sometimes misleading information in social media, lay publications and in the scientific literature, about the beneficial effects of nutrient supplementation to prevent SARS-CoV-2. Importantly, there is some evidence of potential harm from taking high doses of certain supplements, e.g. beta-carotene, vitamin A (retinol) and E in the prevention of disease. (11) There is a compelling need for evidence-based information gained from systematic synthesis of studies on supplementation of multiple micronutrients for the primary prevention of RTIs in otherwise healthy individuals.(12) This information can then be used to design trials with selected nutrients for prevention of SARS-CoV-2 infection.

The primary objective of this systematic review was to evaluate the evidence for prevention of any RTI in the general population considered healthy through supplementation with nutrients that already have a recognized role in immune function.

METHODS

Eligibility criteria

Aimed to generate the highest evidence, we included only clinical trials (randomised controlled trials [RCTs], quasi-RCTs, controlled-clinical trials, and controlled before-and-after studies). We selected nutrients of which the impact on the immune system and consequent immune enhancing effects may be biologically plausible.(8) The roles that e.g. vitamins C and D play in immunity are particularly well elucidated. For example, vitamin C affects several aspects of immunity, including supporting epithelial barrier function, growth and function of both innate and adaptive immune cells, white blood cell migration to sites of infection, phagocytosis and microbial killing, and antibody production. (13). Furthermore, nutritional deficiencies in certain essential fatty acids can result in delayed or suboptimal resolution of inflammation.(14) Nutritional interventions involving the administration of vitamin A (retinol) (including alpha and beta carotenes), folic acid, vitamin B2, vitamin B6, vitamin B12, vitamin C, vitamin D, vitamin E (including alpha and beta tocopherols), iron, selenium, zinc, either singly or as a multiple nutrient supplement, and long chain polyunsaturated fatty acids, were eligible. Our primary outcome was the incidence of RTIs, including lower respiratory tract infections (ARLIs) and upper respiratory tract infections (URTIs) with (potential) viral origins in subjects without increased risk of RTIs. Participants of all ages and from any region of the world were eligible. For the meta-analysis, we excluded studies on secondary outcomes of RTIs, such as severity and duration of the infection.

Search strategy and study selection

We searched EMBASE, AMED, CAB International, MEDLINE, Scopus, and ISI Web of Science for papers published from the inception of these respective databases until 10th of April 2020. Search strategies implemented in each database are provided in the supplementary file (T5 Search Strategy table 13). There was no language restriction. References cited in included studies were screened. Titles and abstracts of retrieved articles and full text copies of potentially relevant studies were screened independently by at least two reviewers. Any discrepancy was resolved by discussion, or arbitration by a third reviewer if no consensus was reached. Reasons for excluding studies at the full text screening stage were noted. The screening process is reported in the PRISMA flowchart (*Figure 1*).

Data extraction

We developed a data extraction form in Excel (version16.47), where reviewers in pairs independently extracted relevant data from included studies. The data extraction form was piloted and refined before full use to extract data from all included papers. Discrepancies in the data extraction were resolved by discussion, or arbitration by a third reviewer if no consensus was reached.

Risk of bias assessment

Risk of bias (ROB) in the included studies was assessed using the Cochrane Risk of Bias Tool. (15) Reviewers in pairs independently performed the risk of bias assessment. Discrepancies were resolved by discussion, or arbitration by a third reviewer if no consensus was reached. The Cochrane Risk of Bias Tool provides assessment across six main domains, including selection, performance, detection, attrition, reporting, and other biases. Evaluation was made across these domains and the emanating data was entered into Revman 5.3 to derive the figures for summary risk of bias.

Data analysis

We used descriptive tables to summarise the characteristics of included studies. Effect estimates from studies that were assessed to be reasonably homogenous with regards to their clinical, methodological, and statistical aspects were combined using random-effects meta-analyses. Studies were combined separately for individual nutrients and also for children and adults where there were available data. We subdivided the results into world regions as influencing factors such as genetic differences, different types of infections, nutritional status and sun exposure may differ. Where meta-analysis was not possible, we undertook narrative synthesis of the underlying evidence. The risk ratio (RR) was used as the outcome measure in all meta-analyses. Data from studies presenting effect measures as odds ratio (OR), incidence rate ratio (IRR), or hazard ratio (HR) were first converted to estimates of RR before combining with other studies, using the following formulas as recently recommended by VanderWeele et al (16):

(a) RR ≈ IRR;

(b) RR ≈ HR or OR (if outcome is < 15% by the end of follow-up);

(c) RR ≈ $\sqrt{OR}$ or $\frac{1 - 0.5^{\sqrt{HR}}}{1 - 0.5^{\sqrt{\frac{1}{HR}}}}$ (if outcome is ≥ 15% by the end of follow-up)

We quantified heterogeneity between studies using the I^2 test. Where possible, we stratified the analyses by world regions where the study was undertaken. Due to small number of studies contributing to the meta-analysis for each specific nutrient, we could not evaluate the potential influence of publication bias and small study effects. Meta-analysis was undertaken using Stata 14 statistical software (StataCorp).

Stratification by nutritional status

The effect of micronutrient supplements on the incidence of RTIs in subgroups stratified for malnutrition or deficiencies at baseline was examined if data were provided in the studies. Malnutrition was defined as height-for-age < –2 SD or Weight-for-age < –2 SD). Deficiencies were defined as serum levels below reference values for the nutrient under investigation.

RESULTS

Study selection

In total, 15,163 records were obtained from the search of the databases, of which 93 papers (based on 115 studies) met the criteria to be included in the review. Of the 115 studies, 63 were included in at least one meta-analysis (*Figure 1*). These studies included 199,055 study participants (191,636 children and 7,419 adults) in 37 countries around the world (*Supplementary Tables 1-10*). Of the included studies, meta-analyses were possible in fifteen studies on the effect of micronutrients (nine on multiple micronutrients [MM] supplementation in children and six in adults); eighteen on zinc supplementation in children; six on Vitamin D supplementation in children and seven in adults; nine on vitamin A (retinol) supplementation in children with repeated dose and three in children with single dose supplementation; two on vitamin E supplementation in adults, and three on iron in children.

Risk of bias results

ROB was assessed for all studies included in the systematic review (*Supplementary Figures S1 and S2* risk of bias). The overall ROB across all studies was moderate.

Study characteristics

A full description of the characteristics of the studies is given in *supplementary files (T1 Supplementary tables 1-10, T2 Supplementary table 11, T3 Supplementary table 12).*

Recommended Daily Values

For reference an overview of the Recommended Daily Values (RDV's) per nutrient and for the different age groups included in our data analyses according to the World Health Organisation is presented in *Supplementary table 4 (T4 Recommended daily nutrient intake based on EFSA and WHO reference values).*

Multiple Micronutrients *(Supplementary table 1)*

There were 22 studies (17-33) on MM supplementation, in various combinations, of which thirteen were conducted in children and nine in adults. In the nine studies in children, (intervention group [IG]: N=2088; control group [CG]: N=1995) included in meta-analysis, we observed a small but non-statistically significant effect of MM supplementation on the incidence of RTI (RR 0.99, 95%CI 0.87-1.10, I^2=77.1%, p =0.000) (*Figure 2*). Meta-analysis of the six studies in adults (IG: N=1257; CG: N=1239) showed a small but borderline significant decreased risk of RTI (RR 0.93, 95%CI 0.86-1.00, I^2= 0.0 %, p = 0.549) (*Figure 3*).

Zinc *(Supplementary table 2)*

There were 26 studies (18, 23, 26, 28, 30, 34-52) on zinc supplementation, of which 24 were conducted in children (age: 0.45-10 years). In the majority of studies no significant impact was seen, however Bhandari et al. 2002 (35) and Brooks et al. 2006 (36) showed a positive impact on episodes of pneumonia with zinc supplementation and the studies by Kurugöl et al, 2006 (38), Sanchez et al, 2014, (47) also had a positive impact on the number of common colds and RTIs respectively. Overall, the eighteen studies in children, (IG: N= 51290, CG: N=51344) included in the meta-analysis showed a non-significant decreased risk of incidence of RTI (RR 0.91, 95%CI 0.82-1.01, I^2= 83.70% p =0.000) (*Figure 4*). By stratifying the meta-analysis by regions of the world where the studies were performed, only studies performed in Asia showed a significant (RR 0.86, 95%CI 0.75-0.96, I^2=79.1%, p=0.000) protective effect of zinc supplementation on RTI (*Figure 4*). However, the results for zinc were based on highly heterogeneous effect sizes and thus contradictory outcomes.

Vitamin D *(Supplementary table 3)*

There were 19 studies (53-70) on vitamin D, of which ten were among children (dosages 1000 – 2000 IU/day on average), all but one of which were performed in Asia (Aglipay et al 2017 (53) North America). Of the seven studies among adults (dosages 1000 – 4000 IU/day on average), most were performed in North America (N=4) and Europe (N=2) and one in New Zealand. Meta-analysis of the six studies in children, (IG: N=3400; CG: N=3443) showed a non-significant decreased incidence of RTI with vitamin D supplementation (RR 0.88, 95%CI 0.66-1.11, I^2=80.4%, p=0.000) (*Figure 5*). Meta-analysis of the seven studies among adults (IG: N= 2028, CG: N= 1966) showed a significant decreased incidence of RTI (RR 0.89, 95%CI 0.79-0.99, I^2=20.7%), p=0.272). However, when subdivided by world regions, studies performed in North America showed a significant effect (RR 0.82 95%CI 0.68-0.97), but not those from Europe (RR 1.02, 95%CI 0.60-1.44) or Oceania (RR 0.97, (95%CI 0.84-1.10) (*Figure 6*). The heterogeneity of the results for vitamin D in adults in the USA and Canada was low to moderate, based on uniform beneficial effects of vitamin D supplementation.

Vitamin C *(Supplementary table 4)*

There were 13 studies (71-80) on vitamin C, of which twelve were in adults. One study comparing doses of 0.25, 1 or 2 g/daily, (Anderson et al 1973 (81)) found no effect. Another study on symptoms associated with rhinovirus infection (Schwartz et al 1973 (82)) found no effect of vitamin C supplementation. In contrast, one study found a lower number of participants with a cold (RR = 0.55, 95% CI 0.33-0.94) in the vitamin C group (2 g/daily) (Johnston et al 2014 (75)). Another found a reduction (between 14% and 21%)

in symptoms associated with common colds, in subjects taking 80 mg/daily of vitamin C (Baird et al 1979 (83)). Also van Straten et al (84)) found that the vitamin C group (daily dose of 1 gram vitamin C) had significantly lower number of cold episodes (37 vs 50, P<.05) in their study. Due to heterogeneity between the studies in terms of population composition, definition of the intervention, and definition and measurement of the outcome, no meta-analysis was undertaken for the studies on vitamin C.

Vitamin A (retinol) ***(Supplementary table 5)***

There were 16 studies (26, 85-99) on vitamin A (retinol) supplementation, of which fifteen were conducted in children. Three studies performed in children (IG: N=23005, CG: N=23023) with one single high dose supplementation (50.000 – 200.000 IU) of vitamin A (retinol) were included in the meta-analyses, which showed a small but non-significant increased risk of development of RTI (RR 1.07, 95%CI 0.96-1.18, I^2=0.0%, p =0.857) (*Figure 7*). Meta-analysis of nine studies on children (IG: N= 16625, CG: N= 15504) receiving multiple high dose supplementation (10.000 – 206.000 IU) showed a small but non-significant decreased incidence of RTI (RR 0.95, 95%CI 0.73-1.16 I^2=97.4%, p =0.00 (*Figure 8)*.

Beta-carotene ***(Supplementary table 6)***

There were three studies (100-102) on beta-carotene supplementation and none were included in a meta-analysis due to observed heterogeneity between the studies. No significant effect on beta- carotene supplementation was found on incidence of RTI across the studies.

Vitamin E ***(Supplementary table 7)***

There were four studies (21, 101, 103, 104) on vitamin E supplementation. Two studies (IG: N=470, CG: N=459) were included in a meta-analyses, which showed no effect of vitamin E supplementation on the incidence of RTI (RR: 0.99, 95%CI 0.80-1.18 I^2= 43.7 %, p = 0.182) (*Figure 9*).

Folic Acid and Vitamin B12 ***(Supplementary table 8)***

There were only two studies (33) on folic acid and vitamin B12 supplementation. No significant difference was found between treatment groups and placebo with folic acid or B12 supplementation on incidence of RTI across the studies.

Iron ***(Supplementary table 9)***

There were five studies (18, 27, 30, 105, 106)on iron supplementation and none were included in a meta-analysis. Three studies found no significant effect of iron supplementation on the incidence of RTI, while two studies found an adverse, increased risk.

Fatty acids *(Supplementary table 10)*

There were five studies (27, 107-110)(3 in children and 2 in adults) on fatty acids, especially on long chain polyunsaturated fatty acids (LCPUFAS), but none were included in the meta-analysis. One study in new-borns showed that infants fed with DHA (Docosahexaenoic acid) and ARA (arachidonic acid) supplemented formula in the first year of life developed less URTI compared to placebo (OR 0.22, 95% CI 0.08-0.58, p=0.006) (Birch et al, 2010 (107)). Also, two other studies found reduced incidence of RTI in children by ALA (alpha-linoleic acid)/LA (linoleic acid) (110)) and EPA (Eicosapentaenoic acid)/DHA (27)).

Vitamin B2, B6 and Selenium

No eligible studies were found for vit B2, vit B6 and selenium.

Stratification for nutritional status *(Supplementary table 11)*

In nine studies (17, 23, 26, 42, 54, 63, 88, 89, 93, 96) subgroup analyses were performed based on stratification for nutritional status, i.e. malnutrition (Height-for-age < –2 SD or Weight-for-age < –2 SD) or deficient for the nutrient under investigation *(Supplementary table 11).* Two analyses were performed on studies in adults and 8 in children. Two analyses were performed for multi micronutrients, two for zinc, two for vitamin D and four for repeated high doses vitamin A (retinol). All studies were performed in developing countries, except one study in the UK and one in the USA. Only 1 study, for zinc, Osendarp et al, 2001 ((42)) found a reduced incidence of acute lower respiratory tract infections (ALRI) in zinc deficient children after zinc supplementation (<9.18 mcmol/L) as compared to normal (≥9.18 mcmol/L) zinc serum concentration, RR (95% CI): 0.30 (0.10-0.92). All other studies found no effect. For repeated high doses of vitamin A (retinol), two studies found an adverse, increased effect on RTIs in not stunted *vs* stunted children (88) or normal weight *vs* underweight children (96) while one study (93) found increased incidence of ARI in children who remained deficient after vitamin A (retinol) supplementation.

DISCUSSION

Based on the review of the 115 included studies (including 9 nutrients, multiple nutrients and fatty acids), our findings suggest that overall, the supplementation of nutrients has either no effect, or at most a very limited effect, on the prevention of RTI. However, there was some evidence that zinc supplementation might potentially confer protection among children from Asia, but not in other world regions. Furthermore, supplementation of vitamin D appeared to also confer some protection in adults from the USA and Canada, but not in other world regions. We did not find any evidence favouring an effect of supplementation with vitamins A, C, E, iron and other nutrients investigated on the incidence of RTI, in either children and adults, although the effect of multi nutrient supplementation had a borderline significant preventive effect. The overall quality of the included studies was only moderate.

The disparity of results for different world regions may be explained by genetic variance, different types of infections, nutritional status and sun exposure. Children in Asia may have a lower nutritional status as children in the Western World, which may explain the beneficial effects of zinc supplementation in these children. Most of the studies on zinc supplementation in children were performed in low income countries. Indeed, in one study the efficacy of zinc supplementation in children in Bangladesh with low zinc serum levels was confirmed (40).

With regards to differences for vitamin D supplementation in adults, we do not have an explanation for the fact that an effect was demonstrated in USA and Canada, but not in Europe, but this could be explained by the low number of European studies included in the meta-analysis.

We implemented a comprehensive search of the literature by including the major databases in the field. The screening of literature, data extraction, and quality appraisal of included studies were all performed in pairs, ensuring that potential biases in these processes were minimized and during the whole process we followed recommended steps for undertaking a high-quality evidence synthesis. (15, 16) We had no language restrictions and translated papers written in languages other than English. Although we had no protocol registered prior to undertaking this review, we ensured that the review process followed recommended processes to avoid post-hoc decisions.

A strength of our study is that, consistent with our selection criteria, a large number of studies were included in the systematic review and in the meta-analysis (115 and 63 studies respectively).

Another strength of our study is that, since only healthy populations without increased susceptibility to RTIs were included, therefore has the benefit that the results are applicable to those subjects within the general population without any predisposing conditions, even for COVID 19. Although micronutrient supplementation in healthy subjects with an adequate diet can hardly be expected to have a beneficial effect, at the same time there is less to no information on this subject and the general public tends to have the illusion that using supplements protects against all kind of infections. However, as it is known that by far not all consumers comply with the recommended daily intakes, it could be worthwhile to perform studies on the benefits of nutrient supplementation in subgroups of the general population at risk for a poor nutritional status, such as the elderly, consumers with poor dietary habits, people with obesity and multiple comorbidities, pregnant women and low exposure to sun light.

Because nutritional status may independently increase susceptibility to RTIs, we analysed the studies in which post-hoc analyses were performed based on nutritional status, i.e. underweight, overweight or low serum levels, for the nutrient under study. Only In 10/115 (8.7%) studies stratification based on nutritional status was reported. In only one study zinc supplementation was found to be more effective in children with low zinc serum as compared to children with normal zinc serum levels (42) and therefore did not affect the primary outcomes of this review. In 2/10 studies adverse effects (increased risk of RTIs) were found for repeated high doses (100.000 – 200.000 IU every 4 months or 10.000 IU per week of vitamin A (retinol) of in normally growing children (88, 96) or stunted but not wasted children. Therefore, we conclude that low serum levels may not be an indication for nutrient supplementation to prevent RTIs, although this conclusion is based on a low number of studies.

An important practical aspect to be considered in low income countries regarding nutrient supplementation advice on a regular base in large groups of children or adults, are the high costs and lack of feasibility.

A limitation of our study is that in the meta-analysis studies on secondary prevention of RTIs such as severity and duration of the infection, as well as effects of treatment, were excluded. Based on our results we therefore cannot comment on the preventive effect of nutrient supplementation on duration and severity of RTIs.

Out of all the nutrients included, vitamin D has gained the most attention during the COVID-19 pandemic for its putative protective effects. Over the years, several systematic reviews and meta-analyses have been published on vitamin D in the prevention of RTIs, of which the most recent and extensive study was by Joliffe et al 2020. (111) This meta-analysis included 42 RCTs, of which 15 in patients with a known disease, increased risk for RTI (13 studies) or preterm infants (2 studies). Overall, a modest statistically significant protective effect of vitamin D supplementation, as compared with placebo (OR 0.91, 95%CI 0.84-0.99) was found. In contrast to our meta-analysis, the included study populations were much more heterogeneous and were not limited to individuals without increased risk for RTIs as in our study. In contrast to findings of a previous meta-analysis (Martineau et al, 2017) (112) and in agreement to our findings, the authors did not observe enhanced protection in those with the lowest 25(OH)D levels at baseline.

Zinc is a trace element whose role in the support of immune response against viral infections has been extensively studied, particularly in children. Mayo-Wilson et al. (113) performed a systematic review and meta-analysis on the preventative effect of zinc supplementation in children in 2014. This study included 80 randomised controlled trials and 205.401 participants and found no impact on both incidence and prevalence of respiratory illness, but a positive impact on diarrhoea. Current guidelines by the World Health Organization, only support zinc supplementation for diarrhoea and not for respiratory illness (WHO guidelines on zinc supplementation).(114) In spite of many published studies on zinc supplementation for the prevention of viral respiratory illness, our data only shows a mild impact in children, which warrants further research. (115)

In terms of biologic plausibility, vitamin C is known to be an antioxidant and a variety of studies have suggested its potential on the prevention of RTIs by modulation of the immune system (13). However, based on the current findings, vitamin C supplementation cannot be recommended to prevent RTI's incidence either in adult or a paediatric population. Only one study that complied with our inclusion criteria was performed in children with no effect. Among the trials conducted on adults, most studies were negative and high heterogeneity was observed. In addition, the majority of the trials were under-powered. The supplementation period, vitamin C dosage and the age of patients were different between studies.

Taken together, based on the lack of major preventive effects of supplementation of on RTIs, supplementation of vitamins and minerals on a large scale for the general population does not or at most very limited seem to be effective in the prevention of RTI. Stratification for malnutrition did not change our results, although available data were limited. Supplementation of vitamin D in adults in the prevention of COVID-19 can be a matter of debate, but studies should always adjust for individual inflammatory status, due to the changes of vitamin D as acute phase reactant (116) and other confounders (117, 118). As far as therapeutic interventions (a further point out of the scope of present systematic review), recent evidence has not shown effects of vitamin D and vitamin C together with zinc in the treatment of moderate-severe and mild COVID-19 cases, respectively. (119)

Significant marketing in the lay-press has occurred in regards to nutrient supplementation to prevent SARS-CoV-2. However, the main message based on our study is that enhancement of the immune function to prevent COVID-19 is unlikely to be obtained through specific micronutrient supplementation. In contrast, data from the current pandemic have shown that metabolic and anthropometric conditions associated with an unhealthy and pro-inflammatory lifestyle (including diet) may increase the risk for

COVID-19 even at relatively younger ages (120). It is important that the message of a healthy anti-inflammatory lifestyle, including improved diet quality, should be disseminated by all health care workers, including physicians, dieticians, nutritionists and policy makers. Ideally patients at risk should be reviewed by a physician and dietitian or nutritionist and targeted nutritional blood sampling could be performed as a result. It is also important to communicate that within lifestyle components that may be favourably changed, the total diet composition matters, rather than just single nutrients or foods.

To underpin the association between health outcomes and diet, scientists should continuously search for more evidence for the prevention of RTIs, including COVID-19, through anti-inflammatory foods and dietary patterns. This will only be possible if sufficient funding by national and international funding bodies will be made available. So far, during this COVID-19 pandemic, the focus of prevention has been on short-term measures, whilst the long-term prevention due to improved immune function through increased diet quality has been underexposed. Yet, the latter approach is promising, also in light of an increased efficacy of worldwide vaccination programs, and it is important to remain open-minded to emerging results from rigorously conducted studies.(121)

Conclusions

Based on this systematic review and meta-analysis, there is little evidence that the supplementation of nutrients in the general population considered healthy will prevent respiratory infections, such as COVID-19. However, there is evidence that zinc supplementation may be beneficial in children in Asia, and 1000 – 4000 IU vitamin D/day supplementation appears to offer some protection in adults in the USA or Canada.

More benefit is expected from preventing metabolic and pro-inflammatory derangements associated with the worst evolution of the COVID-19 pandemics, even in younger subjects. The present systematic review could help in the establishment of more rigorously conducted studies able to supply further data on the role of nutrition in preventing and modulating these worldwide devastating diseases.

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Conflicts of Interest

BVB reports personal fees from Marfo Food Group, Lelystad, The Netherlands, personal fees from Abbott, grants from Nutricia Research, outside the submitted work;

RM reports other from Nestle, grants and personal fees from Nutricia/Danone, personal fees from Mead Johnson, personal fees and other from Abbott, outside the submitted work; Antonella Muraro reports speaker's fees from Mylan, Nestlè Health Institute , Aimmune, DVB Technologies, Nestlè Purina, Nutricia , outside the submitted work; Ilena Solokowska reports grants from Swiss National Science Foundation, grants from GSK, outside the submitted work;

IS reports grants from Swiss National Science Foundation, grants from GSK, outside the submitted work; L O'M reports personal fees from PrecisionBiotics, outside the submitted work;

Dr. Venter reports grants from Reckitt Benckiser and Abbott, personal fees from Danone, NNI, Before Brands, FARE and National Peanut Board during the conduct of the study; personal fees from Danone, NNI, MJN, Abbott, outside the submitted work;

NdJ, CA, VDC, KG, GPM, HOE, IPS, CR, MR, IS, KG, MvS, EU and BN have nothing to disclose.

Figure 1. PRISMA flowchart describing study selection to the systematic review

Figure 2. Multiple nutrient supplementation and risk of any viral infection in children

Figure 3. Multiple nutrient supplementation and risk of any viral infection in adults

Figure 4. Zinc supplementation and risk of any viral infection in children

Figure 5. Vitamin D supplementation and risk of any viral infection in children

Figure 6. Vitamin D supplementation and risk of any viral infection in adults

Figure 7. Supplementation with single high dose vitamin A and risk of any viral infection in children

Figure 8. Repeated high dose vitamin A supplementation and risk of any viral infection in children

Figure 9. Vitamin E supplementation and risk of any viral infection in adults

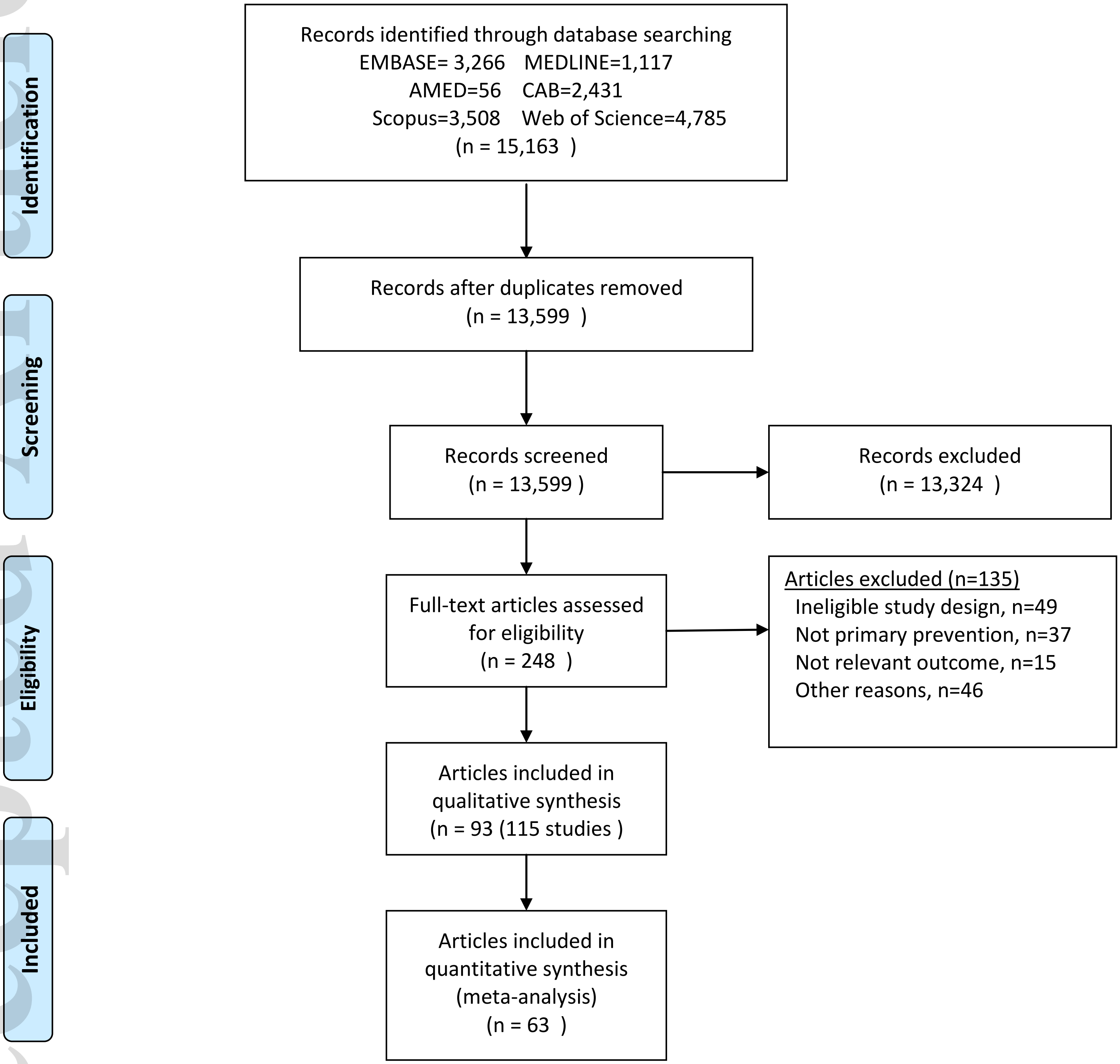


Figure 1. PRISMA flowchart describing study selection to the systematic review

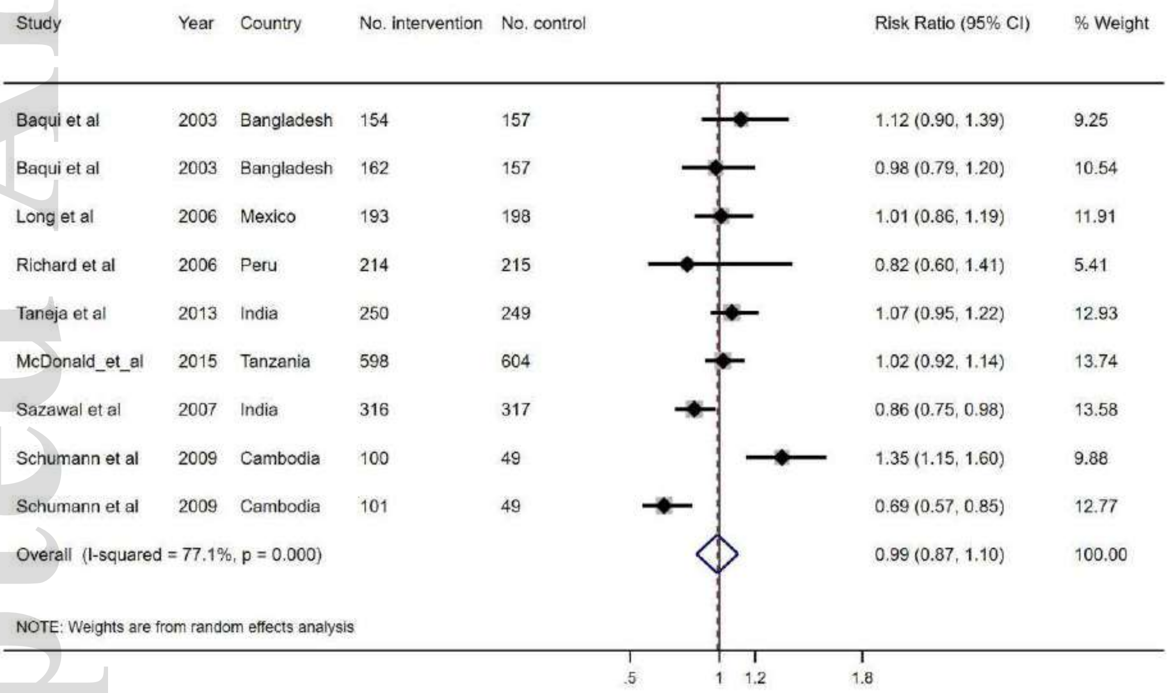
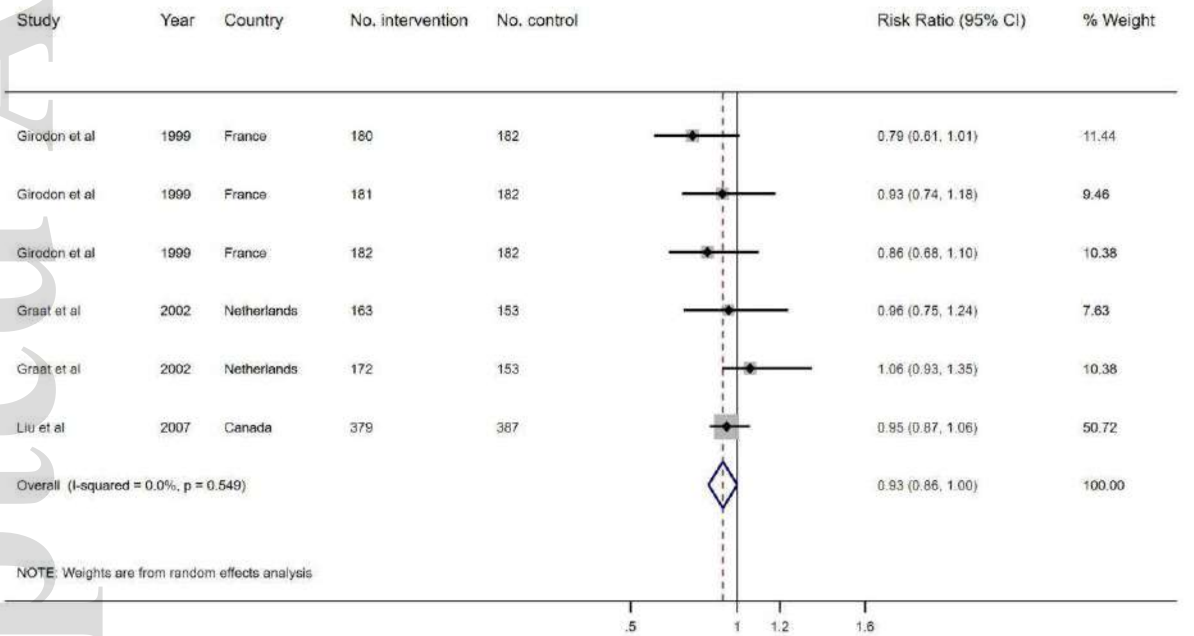


Figure_2 Vlieg-Boerstra et al



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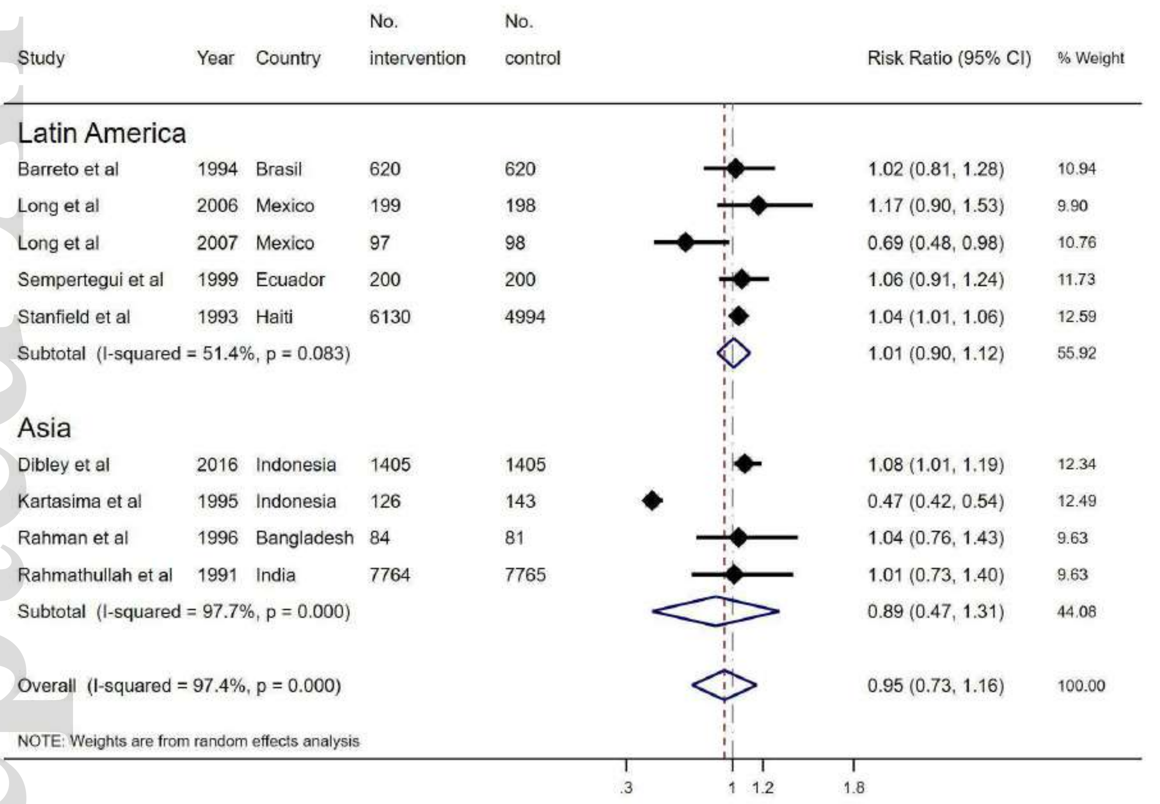

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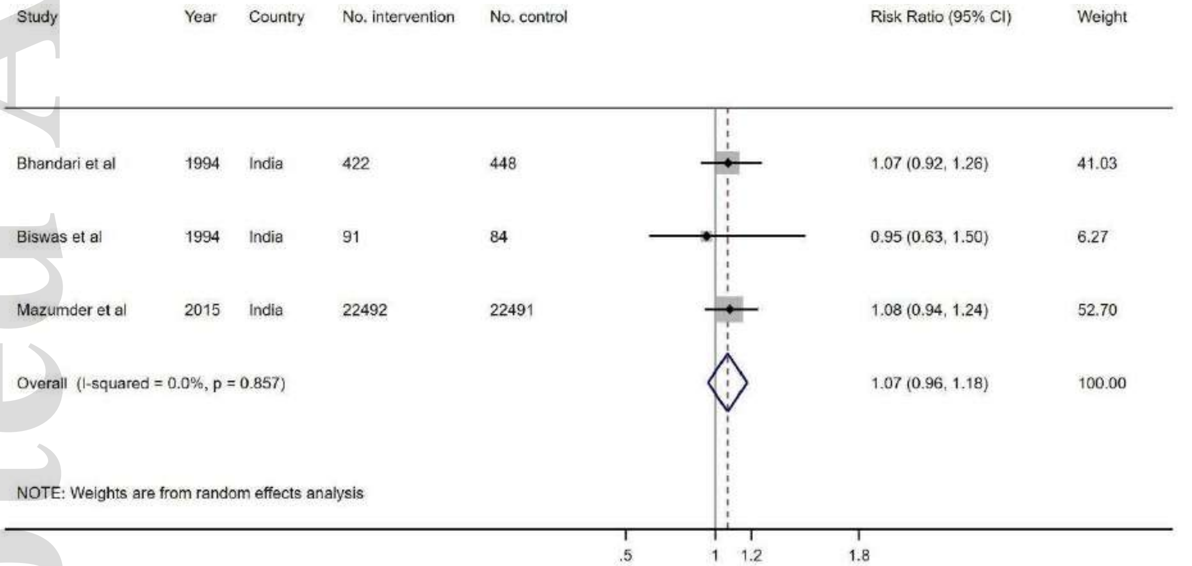

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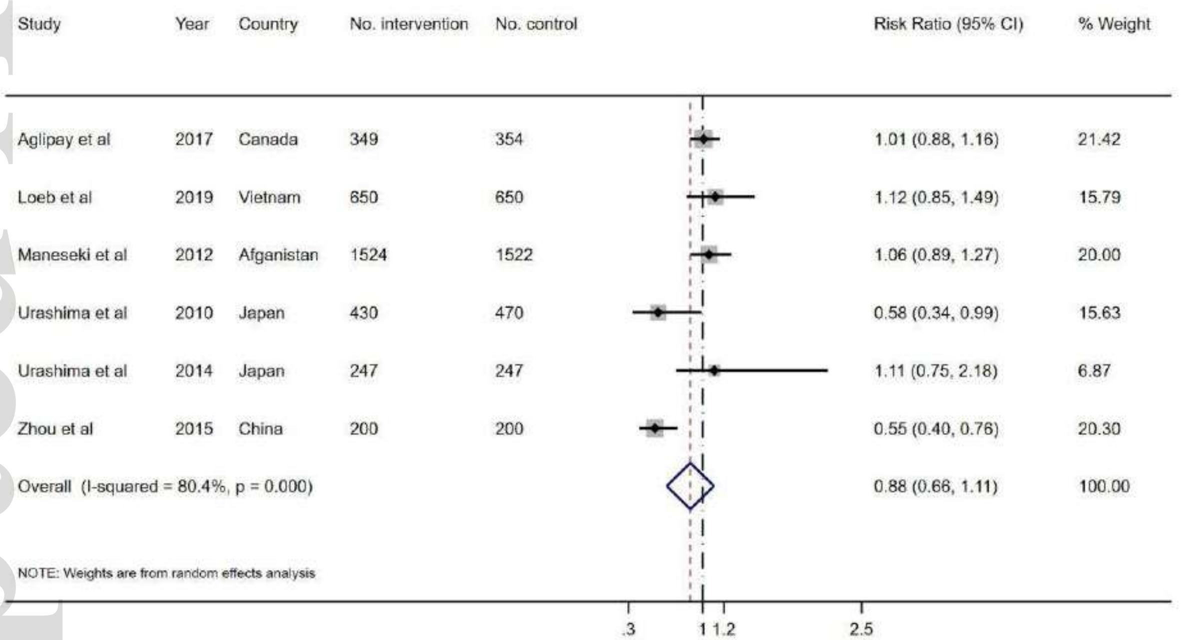

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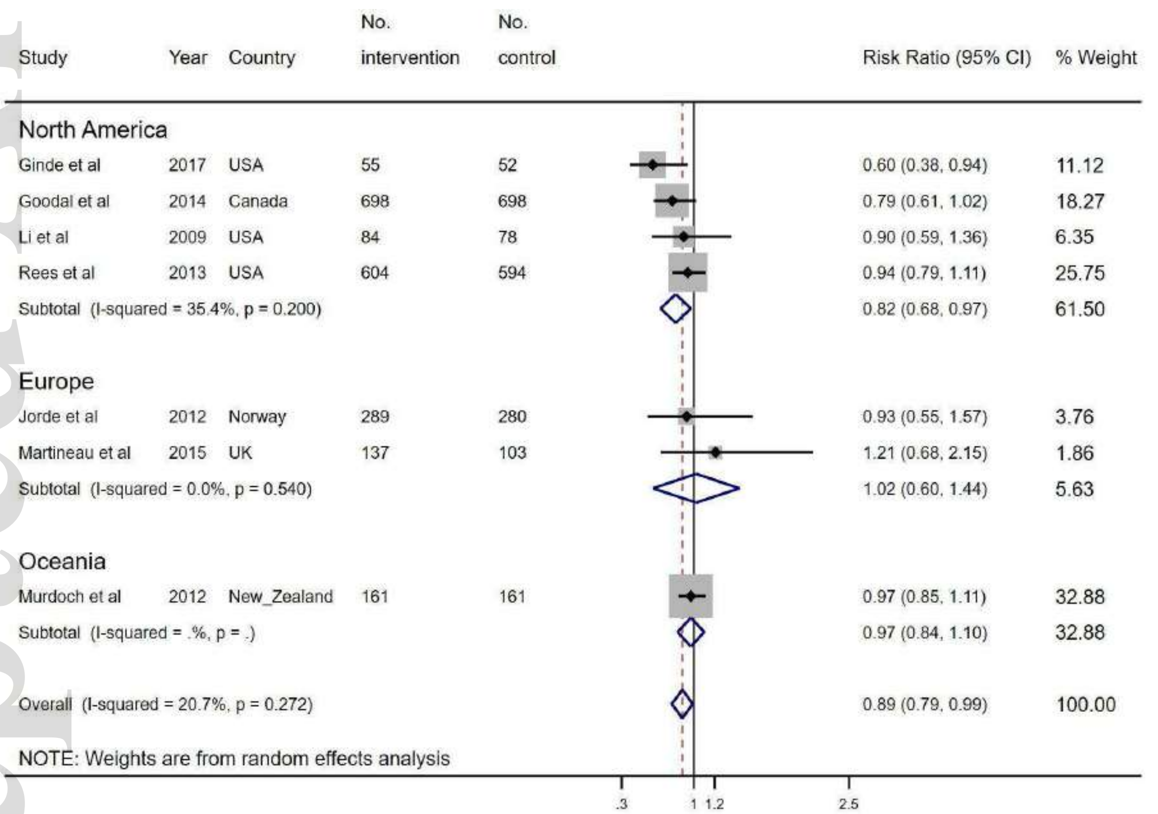

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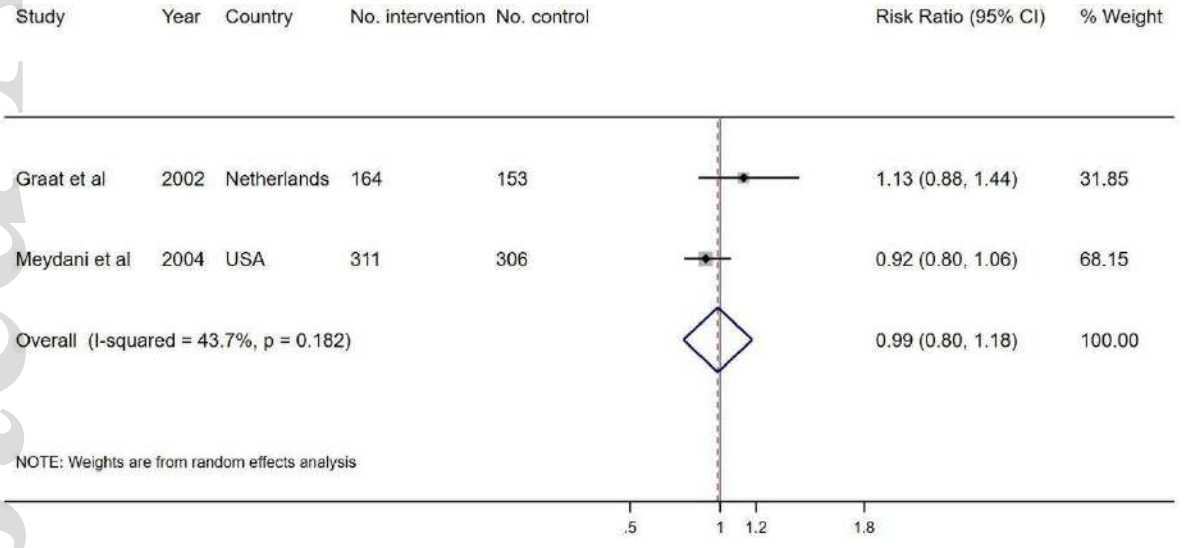

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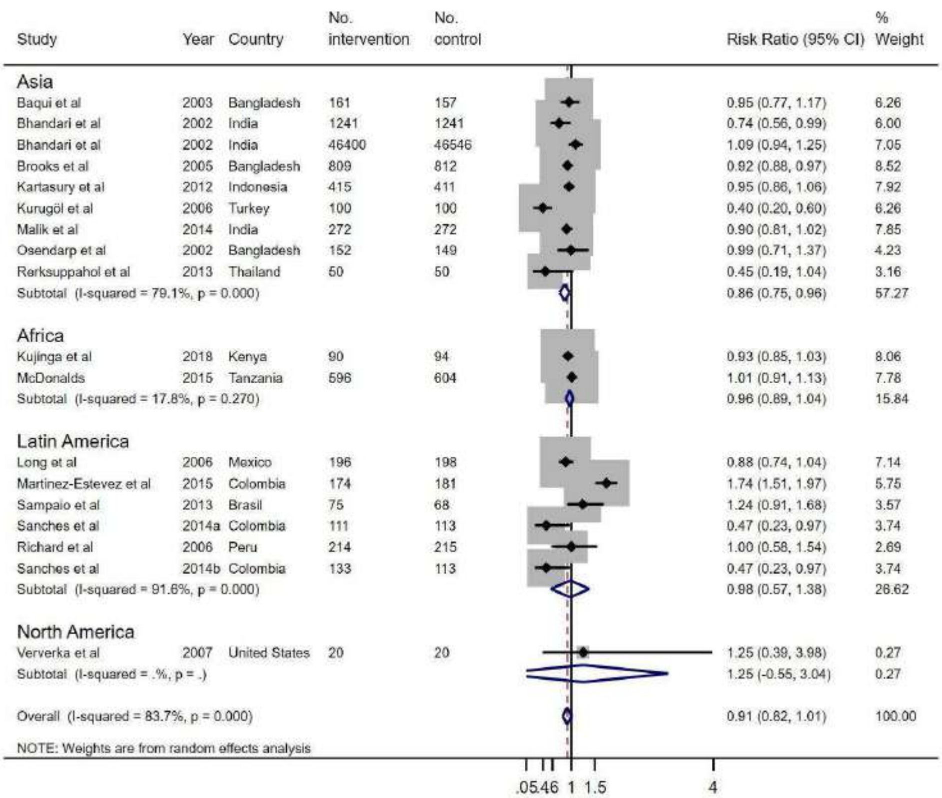

Figure_9 Vlieg-Boerstra et al