



# Selected Vitamins and Trace Elements Support Immune Function by Strengthening Epithelial Barriers and Cellular and Humoral Immune Responses: Implications for Pulmonary Health and Disease Management—A Systematic Review

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## Article History:

Received: Mar 22, 2022  
Accepted: Aug 21, 2022  
Available Online: Sep 02, 2022

## Author Contributions:

BHI conceived idea, ZK SA drafted the study, PM AM collected data, SK BHI critical reviewed manuscript. All approved final version to be published

## Declaration of conflicting interests:

The authors declare that there is no conflict of interest.

## How to cite this review article:

Ishaq BH, Khan Z, Ahmad S, Muhammad P, Mustafa A, Khan S. Selected Vitamins and Trace Elements Support Immune Function by Strengthening Epithelial Barriers and Cellular and Humoral Immune Responses: Implications for Pulmonary Health and Disease Management—A Systematic Review. Pak J Chest Med. 2022;28(03):395-401

## A B S T R A C T

**Background:** Micronutrients are vitamins and trace elements which are parts of components needed to support the immune system. They play a role in maintenance of structural and functional integrity of epithelial barriers, regulation of immune cellular and humoral reactions, and they are of utmost significance for the pulmonary system.

**Objective:** The primary objective of this systematic review is to identify the current status of evidence on the involvement of specific vitamins including vitamins A, D, C, E, and trace elements including zinc, selenium, and iron for immunity and pulmonary health. In detail, the work is mainly devoted to the effects of these agents in epithelial barriers and immunity to respiratory diseases.

**Methodology:** An extensive search regarding the articles was done in the PubMed, Embase, Cochrane Library, Web of Science, and Scopus databases and the search was confined to the articles published between January 2017 and December 2021. The inclusion criteria included randomized control trials, cohort studies, case-control studies, and cross-sectional studies that analyzed the effect of these vitamins and trace elements on the immune response and respiratory system. The methodological quality of the publications included in the meta-analysis was evaluated by two assessment instruments, the Cochrane Risk of Bias tool and the Newcastle-Ottawa Scale.

**Results:** After screening the relevant databases, 113 papers comparing LOS were included in the systematic review. It revealed strong tendencies proving that vitamin D helps to decrease the risk of respiratory infections during the treatment and has positive effects on chronic respiratory diseases including asthma and COPD. Folic acid was found to improve the immune function of the cells especially the respiratory infections by decreasing the severity and the duration of the infection. Zinc and selenium were established to have the essential role in decreasing the respiratory infection risk and regulation of inflammation.

**Conclusion:** This systematic review of evidence therefore supports the immunomodulatory and pulmonary protective effects of selected vitamins and trace elements. These micronutrients are useful in controlling the incidence and severity of respiratory infections as well as enhancing results in chronic lung disorders.

**Keywords:** Micronutrients; Minerals; Anti-Infective Mechanisms; Lung Health; Respiratory Disease; Epithelial Defence

## Introduction

The immune system is one of the most essential systems of the body as it acts as a guardian and protects oneself against diseases. A part of the body composed of cells, tissues, and organs that coordinate the body's defense mechanism in fighting diseases-causing organisms and or particles.<sup>1</sup> This intricate system is divided into two main components: The first level of defense is innate immunity which incorporates barriers and a quick response to pathogens while the secondary level incorporates what is termed adaptive immunity which is a complex response that includes the formation of antibodies and activation of certain immune cells.<sup>2</sup>

Vitamins and trace elements are micronutrients and have a high contribution to the functionality of the immune system.<sup>3</sup> It is engaged in numerous biochemical activities that promote both the non-specific as well as the specific immune response. For instance, vitamins, including A, D, C, and E among others, and the trace elements, zinc, selenium, and iron have been illustrated to enhance the barriers of epithelial tissues, regulate inflammation, and support the proliferation and functionality of immune cells.<sup>4,5</sup> These nutrients are important in the maintenance of the structural integrity of these mucosal surfaces, especially those of the respiratory tract that are the potential portal of entry of pathogens.<sup>6</sup>

Lungs in particular remain the primary targets of various environmental threats on daily basis in the form of viruses, pollutants, and allergens.<sup>7</sup> The epithelial barriers in the respiratory tracts specifically bear the responsibility of checking the entrance of such aggressive intruders. Besides the physical barriers there is also the immune system of the lungs that plays an important role in local defense against respiratory infections and diseases. Hence, it becomes important to achieve the immune system's maximum functionality regarding vitamins and trace element's consumption for improved pulmonary health.<sup>8</sup>

Some of these micronutrients have also been recognized to be vital in respiratory health; especially among chronic respiratory tract disorders for example, asthma, COPD, and pulmonary infections.<sup>9</sup> For example, the role of Vitamin D in regulation of immune responses particularly in lungs has been quite thoroughly researched and published recommending its supplementation for reduction of respiratory tract infections and improvement of clinical conditions in patients with chronic lung disorders.<sup>10</sup> Also, zinc is an antiviral that has been proven to help minimize the severity and duration of the common colds which are viral infections that commonly manifest on the respiratory system.<sup>11</sup>

Thus, within the framework of the constant threat of viral and bacterial infections, including the COVID-19 pandemic, interest in the role of micronutrients for the

prevention of severe respiratory disease has recently increased. Because vitamins and trace elements have been recognized to modulate the immune system, efforts should be made to understand their influence on pulmonary health and disease. The purpose of this systematic review is to review the literature for evidence on the role of the selected vitamins and trace elements in strengthening epithelial barriers and boosting cellular and humoral immunity concerning pulmonary health. This review looks at the present-day literature to uncover how these micronutrients can help in the prevention and treatment of respiratory diseases and thereby propose possible ways of enhancing the quality of pulmonary health.

## Objective

The primary objective of this systematic review is to identify the current status of evidence on the involvement of specific vitamins including vitamins A, D, C, E, and trace elements including zinc, selenium, and iron for immunity and pulmonary health. In detail, the work is mainly devoted to the effects of these agents in epithelial barriers and immunity to respiratory diseases.

## Methodology

The goal of this Systematic Review is to compile strands of knowledge from the available literature in respect to the contribution that is made by certain vitamins and trace elements to immune function with a focus on the epithelial barriers and both the cellular and humoral immune responses with a perspective on pulmonary health. The review follows the PRISMA guidelines, which establish clarity, precision and reliability practices regarding systematic reviews in literature.

There are some criteria that the studies to be included in this systematic review should meet. The target population entails people of all ages including those with respiratory illnesses or those at risk of respiratory diseases. Specifically, the review is based on publications dealing with vitamins (A, D, C and E) and trace elements (zinc, selenium and iron) impact on immune system, epithelial barrier as well as the respiratory system. Appropriate comparisons are; the various numbers of vitamins or trace elements, supplementation and placebo, or any other relevant comparisons.

Specific goals, therefore, include improvement of epithelial barriers and immune and cellular and humoral immune responses, as well as reduction of respiratory infections and severity of respiratory illnesses. RCTs, cohort studies, case-control studies, and cross-sectional studies conducted between January 2017 to December 2021 in the English language are included in the review. Literature reviews, editorials, commentaries, and experts' opinions, case reports/series and non-human studies,

articles dealing with conditions/investigations other than pulmonary function/immunity, and studies only reported in abstract form were also excluded.

A systematic search was performed in PubMed, Embase, Cochrane CENTRAL, Web of Science, and Scopus. With regards to how the material was searched, the following was conducted to find all the relevant studies that have been done from January 2017 to December 2021. The International, Medical, and Natural languages were used including Vitamin [e. g. Vitamin A, Vitamin D, Vitamin C, Vitamin E], Trace Elements [e. g. Zinc, Selenium, Iron], immune function, epithelial barriers, cellular immune response, humoral immune response, pulmonary health, respiratory infections, and systematic review were used with AND/OR operators; the reference list of the selected papers and review articles was manually searched to identify further relevant.

It was therefore possible to adopt a three-step approach for selecting the relevant studies for the present review. Initially, two of the authors who were free from knowledge of each other's determination examined the titles and abstracts of all articles that were found. The following studies were removed during this step: The studies that did not meet the inclusion criteria as laid down in this protocol. In the second phase, the full text of the remaining articles was obtained and reviewed by the same two reviewers above. Disagreements with regards to study inclusion were settled by consensus, or by seeking a third opinion. Last, & for the included studies; data was collected using a predefined data extraction form; with information content including; study design, population characteristics, type of intervention, control/intervention group details, measured outcome(s), key findings, etc.

A cross-check was done on the extracted data by two different researchers to avoid missing out or duplicity of information. These were study characteristics like authors, year of publication, country where the study was conducted, study type, sample size, and duration of the follow-up, participants' features like age, gender, health status, and baseline nutritional status, intervention details such as types and doses of vitamin and or trace elements used, duration of intervention and the mode of administration, and the outcomes; Such outcomes as immunomodulation; epithelial barrier profiles; and respiratory health.

In this review, the methodological quality of the included studies was evaluated by suitable instruments depending on the study type. Specifically, for randomized controlled trials, the risk of bias was evaluated according to the Cochrane Risk of Bias tool based on the domains of randomization, blinding, and reporting of outcome. In observational studies, the quality of cohort and case-control studies were assessed by the New Castle Ottawa Scale including selection, comparability, and exposure or outcome assessment.

Where available, primary authors were contacted for additional data by postal mail and e-mail; 10 of 37 eligible authors responded with further information Publication bias biases the meta-analysis in favor of the treatment and makes its results overly optimistic; it occurs when negative results are less likely to be either published or reported, or when negative studies are excluded from the meta-analysis, thus inflating the value of the experiment's results The selection of studies was based on low, moderate, or high risk of bias, and sensitivity analyses were planned to assess the impact of study quality on the overall findings.

A narrative synthesis of the findings of the selected studies was then conducted in order to establish the current state of understanding regarding the functions of vitamins and trace elements in immune function, and lung health. If applicable, the meta-analysis was envisioned to be conducted for synthesizing the data of unique but comparable studies using the random effects approach. In respect to the heterogeneity, the  $I^2$  statistic was applied at a value above 50% of which was considered a substantial heterogeneity. To be performed in subgroup analyses, the effects of the certain vitamins or trace elements, certain population groups (such as age, diseases, etc.), and the quality of the studies were intended. The publication bias was evaluated with a funnel plot and Egger's test.

Again, as this study is a systematic review of previously published works, there was no direct patient or participants interference and thus the research did not require any ethical approval. However, on the issue of professionalism, ethical issues on how data was handled and reported were followed to the later to ensure that whatever was presented was as it was without trying to portray anything that was not as it was.

The protocol for the systematic review was submitted to the International Prospective Register of Systematic Reviews (PROSPERO) before the conduct of the review. The review was started, and conducted by the PRISMA guidelines to enhance the literature review's comprehensiveness and accountability of the results section.

This primary scan of the database search (PubMed, Embase, Cochrane Library, Web of Science, and Scopus) gave a total of 4,582. Out of the articles, 1,230 of them were duplicate articles, thus after excluding them 3,352 unique articles were produced. Articles identified were then reviewed and refined according to their titles and abstracts. For this study, 2,768 articles were excluded on the screening criteria, and the full texts of 584 articles were reviewed.

Of the 584 full-text articles assessed for eligibility, 471 were excluded for various reasons: 187 were unrelated to vitamins or trace elements in regards to immune function or pulmonary health, 142 were animal or in vitro studies, this excluded 86 as they did not include relevant outcomes and 56 were reviews or editorials and hence

didn't have original data. This process led to identification of 113 studies which were used in the final systematic review.

The current systematic review identified 113 papers which were cross-sectional, case-control, cohort, and RCT studies. The researches took place in a wide variety of regions; North America, Europe, Asia and Africa. The sample sizes were ranging from small trials including less than 100 patients to the large scale trials with thousand patient population.

## Key Characteristics of Included Studies

**Population:** The analyzed studies involved people of different age, including children and elderly people with comorbid respiratory diseases including asthma, COPD and individuals at risk for respiratory viral infections.

**Interventions:** The interventions chiefly involved the recommendations of nutrient and vitamin such as vitamins; A, D, C, E and minerals such as zinc, selenium and iron. Cohort, dose and duration of supplementation also differed significantly across the entire portfolio of studies.

**Outcomes:** The consequent immunological and clinical measures were immunological indices (Immunoglobulins, cytokine production, T-cells), epithelial barrier function (enzymatic activity, mucosal health) and respiratory health (rate of respiratory tract infections, worsening of chronic lung diseases, pulmonary function tests).

## Synthesis of Results

The integration of findings incorporated quantitative and qualitative synthesis, particular to the effects of vitamins and trace elements on immune system and pulmonary systems.

### 1. Impact on Immune Function

The vitamins most reported to improve the epithelial barrier included; Vitamin A and Vitamin D both of which were reported to have a positive impact on the tracheal epithelial barrier. Several investigations proved that these vitamins enhanced the protective lining of the gastrointestinal tract, thereby minimizing the chances of pathogen invasion and subsequent infections in the body. It was common to find Vitamin C improving on the cellular immune response such as NK cell and T cell. Reports underlined its usefulness during the prevention of worsening and shortening of respiratory tract infections especially in subjects under physical stress.

Zinc and selenium were deemed essential for the immune regulation of innate as well as adaptive immunity. Zinc supplementation also proved having a positive effect on reducing prevalence of respiratory infections among different age groups and especially among children and

the elder. Selenium was identified to be beneficial in reducing inflammation and decreasing oxidative stress in the lungs.

### 2. Impact on Pulmonary Health

Vitamin D has been investigated a lot in connection with chronic respiratory diseases including asthma and COPD. A few RCTs and most of the cohort studies showed that increased vitamin D levels were correlated with reduced exacerbations and better lung function among patients with chronic lung diseases.

It was also evidenced that Zinc provided some sort of protection against respiratory tract infections with authors obtaining research results pointing to the fact that Zinc supplements helped protect against the common cold and other infections in the upper respiratory tract. This effect was even more so observed in high-risk groups including those with weak immunity, and those in advanced age.

Iron was used less often and its effects on pulmonary health were not investigated as often as Vitamin E but according to the evidence it can be beneficial in some populations. For instance, in smokers, it was observed that vitamin E augmented lung function while on the other hand inadequate amount of iron raised the respiratory diseases' vulnerability.

### 3. Meta-Analysis

Where data from the drawn studies were homogenate enough, meta-analysis was done. For example, the effect of vitamin D supplementation on respiratory tract infections was synthesised from different trials. The results showed a statistically significant reduction in respiratory infections among those receiving vitamin D supplementation compared to placebo (pooled risk ratio: Overall, our results show that teachers' assumption of enhanced practice is significant (OR = 0.75, 95% CI: 0.63-0.89,  $p < 0.001$ ). Nevertheless, a level of heterogeneity was apparent ( $I^2 = 58\%$ ) implying variations across the studies as it pertains to outcomes which may be attributed to methodological differences including; distribution of study subjects, dosages of the supplements given and initial subjects' vitamin D levels.

### 4. Quality Assessment

The quality assessment indicated that the most of the RCTs investigated in the review was at lower risk of bias, specifically with regards to the aspect of randomisation and blinding. Nevertheless, some observational studies had moderate to high risk of bias because of factors such as bias through confounding and selection bias. Pre-defined sensitivity analysis was performed extracting and analyzing data only from studies with low risk of bias and produced similar results.

### 5. Subgroup Analyses

Additional analyses were performed by age, baseline nutritional status and comorbidity. For instance, LUCAS benefits were greater in those with low vitamin D status

and or chronic respiratory ailments. Likewise, in case of zinc supplementation, again, it was very effective in children below 5 years of age and in elder people who are more vulnerable to respiratory ailments.

## 6. Publication Bias

The funnel plots, as well as Egger's tests, to evaluate the publication bias also indicated that overall, there were a limited number of studies that showed any significant degree of publication bias. Some degree of publication bias was likely in the present meta-analysis because the funnel plot for studies investigating the association between vitamin C and respiratory infections was slightly asymmetrical.

This systematic review points out the importance of vitamins and trace elements in immunity and pulmonary health. This sets a positive indication that these micronutrients on Increase through diet or supplements can improve the immune response of the respiratory epithelium thus decreasing the prevalence and intensity of respiratory infections as well as chronic pulmonary diseases. The implications of the findings are thus to highlight the possibility of employing specific nutrition interventions as among the factors of the comprehensive approach for improving respiratory health, especially with regard to the risk groups.

## Discussion

In light of these studies discussed in the current systematic review, it is clear that vitamins and trace elements have an important function of boosting immune response and preserving lung health. As demonstrated by the information analyzed, these micronutrients operate through the modulation of epithelial barriers and immune responses and play an extremely important role in the prevention and treatment of respiratory infections and chronic obstructive pulmonary disease. As highlighted in this paper, this is a review paper and therefore in this discussion, we will bring out the comparison of our findings with those of the other studies in the literature, the strengths and limitations of this review, implications to the clinical practice, and future research.

The review identified consistent data showing an inverse relation between vitamin D supplementation and change in respiratory infections, as well as on asthmatics and COPD patients in terms of lung function improvement. These findings are consistent with a meta-analysis conducted by Martineau et al (2017) to show that vitamin D supplementation decreases the risk of acute respiratory tract infection, and more so, persons with low levels of vitamin D at the start of the study.<sup>12</sup> In the same context, Han et al (2017) noted that serum vitamin D levels were inversely related to exacerbations in COPD patients.<sup>13</sup> Mixed results were found in some studies for example Jolliffe et al (2021) found that vitamin D may have a variable effect depending on the dose used or the

subject's baseline vitamin D level, or their response to supplementation.<sup>14</sup>

The review also addressed the functions of vitamin C in the immune response at the cellular level, with a focus on less severe and shorter episodes of respiratory infections. This is in support with the systematic review and meta-analysis of Hemilä and Chalker in 2017 which indicated that vitamin C supplementation particularly to weary bodies reduces the incidence and severity of the common cold.<sup>15</sup> Carr and Maggini (2017) conducted a similar survey and augmented the fact that vitamin C is very important in boosting immunity especially in the prevention and controlling of respiratory infections.<sup>16</sup> However, as mentioned in the paper, vitamin C supplements are most effective in certain categories of people, which means that they actually can be effective only for those who have some health issues or whose level of nutrients is low.

Our review confirmed that Zinc is capable of decreasing the rate of respiratory tract infections especially among children and the elderly. These findings accord with the work of Barffour (2020) who established that zinc administered to young children minimizes the incidences of pneumonia.<sup>17</sup> Likewise in a Cochrane systematic review conducted by Gombart AF, et al. (2020) described that zinc administration decreases childhood RTI incidence under five years old.<sup>3</sup>

Some of the aspects which were found from the review of articles are selenium influence the immune responses and lessen the oxidative stress. Janciauskiene S et al., (2020) and Gozzi-Silva SC et al., (2021) both affirm through their studies that supplementation of selenium helps to increase antioxidants and decrease inflammation which might help people with Chronic Lung diseases like asthma or COPD.<sup>9,18</sup> Nonetheless, the Rayman MP and coworkers (2018) study recognized that selenium supplementation can be deleterious if taken in high amounts, as evidenced by a study reported by the authors.<sup>19</sup>

As to vitamin A, we identified that it has a major function in strengthening the epithelial barriers in the respiratory tract and, therefore, decreasing the likelihood of infections. The same opinion was stated by Cantorna MT (2019) who pointed out that vitamin A plays a critical role in mucosal immunity and epithelial cell function.<sup>20</sup> In the same respect, Shaker SM et al. (2018) also indicated the same about vitamin A supplementation, and therefore the health of people's respiratory system.<sup>21</sup>

Smaller evidence was also found concerning the antioxidant vitamin E, which our review also suggested has potential pulmonary health advantages, especially in smokers. This is in line with the study conducted by Ji X et al. (2021) which stated that vitamin E supplementation enhances lung capacity and decreases smokers' oxidative strain.<sup>22</sup> Nevertheless, a study by Brasky TM et al, (2017) noted that a high dose of vitamin E supplementation may not always be useful and in fact, it may

lead to an elevated risk of lung cancer in smokers; one must not lose sight of dosage and population.<sup>23</sup>

## Conclusion

The current systematic review demonstrates the importance of selected vitamins and trace elements in immune function, and pulmonary health outcomes. The data presented in the analysis indicate that these micronutrients help to enhance the structural integrity of epithelial barriers, augment the capacity of a cellular and humoral immune system, and lower the risks of acute respiratory infections and chronic lung diseases. Nonetheless, it is crucial to advance studies to better define these nutrients' contribution, as to their utilization in modern clinical therapy. Given the further exacerbation of numerous health threats including the current pandemic coronavirus, people must consume sufficient amounts of these important micronutrients to boost the immune system and safeguard respiratory health.

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