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ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

"Η επίδραση της διατροφής σε νοσήματα του αναπνευστικού συστήματος."

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"The effect of diet on respiratory system diseases."

Table of Contents

Abstract

Nutrition may be an important aspect of lung health. Antioxidants, vitamin D, fatty acids, minerals, phytochemicals, probiotics and prebiotics, and dietary patterns have been associated with the pathophysiology of various lung diseases. Asthma has been related with reduced antioxidant intake and omega-3 consumption, while vitamin C has consistently been related to improved pulmonary function. Vitamin E supplementation has been associated with lung cancer and should be used with caution in smokers. Vitamin D deficiency is common in tuberculosis patients with uncertain benefits as an adjunct treatment. The Mediterranean diet and a "healthy" diet pattern are associated with reduced lung cancer incidence. Data on phytochemicals and probiotics are encouraging, however, high quality studies are generally lacking.

Keywords: Asthma, Chronic obstructive lung disease, Lung cancer, Cystic fibrosis, Interstitial lung disease, Pulmonary function, Lung development, Antioxidants, Vitamins, Minerals, Probiotics, Prebiotics, Phytochemicals, Plants, Dietary patterns, Mediterranean diet

Introduction

Hippocrates quote “let food be thy medicine” and thousands of years later we have proofs that nutrition is an important aspect of everyday life and a contributor of lung health. Dietary factors may be implicated in the pathogenesis, clinical presentation and treatment of various lung diseases, mainly by manipulating oxidative stress and lung inflammation.

Obstructive lung diseases, mainly asthma and chronic obstructive pulmonary disease (COPD), are characterized by chronic airway inflammation, and thus diet has increasingly been recognized as a potential contributing factor for their presentation. Interestingly, nutrition seems to affect pulmonary function and the development of lung diseases in early (or even later) life. Lung cancer is believed to result from interplay between genetic and environmental factors, like diet. Unfortunately, data on interstitial lung diseases (ILDs) are sparse.

Although changes in body weight may complicate lung diseases, like asthma or COPD, this chapter will focus on the effects of dietary nutrients or dietary patterns in the most common respiratory diseases. For more data in that field the reader is referred to comprehensive reviews (Zammit et al. 2010).

ASTHMA

Asthma is a heterogeneous chronic disease characterized by airway inflammation and airway hyperresponsiveness to direct or indirect stimuli. Patients with asthma exhibit variable expiratory airflow limitation associated with episodic flare-ups (exacerbations) that may be life-threatening. In the same context, asthma symptoms, including wheeze, shortness of breath, chest tightness and cough, typically vary over time and in intensity. The pathogenesis at asthma is complex and involves airway inflammation and enhanced Th-2 responses. In an oversimplified model, *(airway inflammation)* results in the two central components at asthma, i.e. airway hyperresponsiveness and airway obstruction. Asthma prevalence has increased in the recent years, mainly in industrialized countries, possibly due to environmental and lifestyle changes, including diet (Malli et al. 2014). Airway inflammation associated with asthma may be partially triggered by aggravated oxidative stress and pro-inflammatory properties associated with western diet.

Dietary habits

Epidemiological research on the association between diet and asthma is fluent. Different components found in foods have antioxidant, anti-allergic and anti-inflammatory properties, which may protect against asthma development. The majority of epidemiological studies suggest that greater adherence to western dietary patterns (i.e. high consumption of alcohol, meat, dairy products and processed food) and reduced consumption of fruits, vegetables, whole grain cereals, and fish may result in greater asthma risk.

Association of asthma with dietary habits has found support in various studies suggesting that higher intake of soft drinks, energy drinks, sugar added drinks (i.e. tonic, ice tea), and fast food and butter are associated with increased asthma risk. Experimental evidence suggest that dietary habits may enhance inflammatory responses and alter the Th1/Th2 balance, thus underlying the association with asthma (Zhang et al. 2016).

The association of dietary patterns with asthma control and acute exacerbations of the disease are well studied and the results are straightforward; adherence to western diet has a negative impact on asthma control, while high fresh fruit and vegetables consumption and high fish consumption is associated with fewer exacerbations and better asthma control (Guilleminault et al. 2017; Laerum et al. 2007; Miyamoto et al. 2007). Importantly, current guidelines encourage patients with asthma to consume a diet high in fruit and vegetables. Similar results are obtained in children. High fruit intake, and especially apples, citrus fruit and tomatoes, are negatively associated with wheezing and asthma risk suggesting a possible role for flavonoids (Seyedrezazadeh et al. 2014).

Vitamins

Extensive data have examined the possible association of asthma risk and vitamins' consumption based on the hypothesis that a decline in dietary antioxidants intake may increase asthma susceptibility. Experimental data support the aforementioned hypothesis; Vitamin A deficiency worsens ovalbumin-induced lung inflammation through enhanced Th2 responses (Cui et al. 2016), while vitamin E reduces ROS production and improves antioxidant defense in animal asthma (Muti et al. 2016). In the same context, observational studies have shown reduced levels of antioxidants vitamins in asthmatics. Low vitamin A has been reported in severe asthma and may lead to increased airway hypersensitivity. Similarly, vitamins C and E have been inversely correlated with asthma risk.

Interventional studies examining the effect of vitamin supplementation in asthmatics are inconclusive. While some studies have shown significant improvements in asthma symptoms or pulmonary function following vitamin E supplementation others have shown no important clinical benefit. Interestingly,

multiple nutrient supplementation including vitamin A, C, and E has proven beneficial in asthma patients. Overall the beneficial effect of dietary antioxidants has not been proven yet although the data point to that direction.

Vitamin D is under examination as a probable modulator of the development of respiratory diseases characterized by chronic lung inflammation. Epidemiological studies have proven that vitamin D deficiency is common among asthmatics. Serum vitamin D is inversely correlated with airway hyperresponsiveness to metacholine and exercise-induced bronchoconstriction and vitamin D deficiency has been associated with airway remodeling and asthma severity. Vitamin D supplementation improves asthma symptoms while there seems to be no clinical evidence for the reduction of asthma exacerbation. However the relationship between vitamin D with pulmonary function and control of asthma is not consistent among studies. To summarize, the current data provide strong evidence for a beneficial effect of vitamin D in asthma but the clinical benefit of vitamin D supplementation is uncertain.

Minerals

Little is known concerning the association of minerals with asthma. Folate deficiency is associated with severe asthma exacerbations. Asthma patients present reduced selenium concentrations although selenium supplementation has no clinical benefit in asthmatics.

Fatty Acids

Epidemiologic studies have shown that populations with increased omega-6 polyunsaturated fatty acids (PUFAs) consumption have greater asthma predominance in contrast to those consuming increased omega-3 fatty acids. One possible explanation is that omega-3 fatty acids produce eicosanoids that are less pro-inflammatory (prostaglandin E3, leukotriene B5) than those derived from omega-6 fatty acids and because metabolites of omega-3 fatty acids have the capability to dissolve inflammation. A 20-years follow-up longitudinal study revealed that consumption of long-chain omega-3 PUFAs was significantly related to a low rate of incidents of asthma (Li et al. 2013), while high omega-3/omega-6 ratio has been associated with reduced airway hyperresponsiveness (as suggested by reduced metacholine-induced provocative dose) and leukotriene 4-excretion. However, the beneficial effects of PUFAs are not consistent among studies and a meta-analysis has suggested that omega-3 may reduce the risk asthma in children with no effects in adults. Although experimental data suggest a beneficial role of omega-3 in asthma, their benefits in real life remain to be clarified. In the same context, PUFAs supplementation studies have inconsistent results possibly due to methodological discrepancies.

Probiotics-Prebiotics

Probiotics such as lactobacilli and bifidobacteria may reduce asthmatic symptoms by enhancing T regulatory cells development and rebalancing Th1/Th2 responses toward a Th1-dominant state. Experimental evidence demonstrated that higher intake of the probiotic lactobacillus paracasei L9 prevents particulate matter 2.5 (PM2.5)-induced enhancement lung inflammatory response (Wang et al. 2017), whilst in a murine house dust mite-induced asthma model dietary prebiotics prevented and reduced symptoms of asthmatic disease (Verheijden et al. 2015). Two meta-analyses referred that probiotics may not be efficient at decreasing the risk of asthma and wheezing (Cabana et al. 2014; Forno et al. 2013). However, a double-blind controlled randomized study (RCT) showed synbiotic may decrease episodes of viral respiratory infection in asthmatic children (Ahanchian et al. 2016). Further research with long-term clinical trials needs to be conducted to assess the effectiveness of specific strains of probiotics and prebiotics in asthma.

Phytochemicals

Phytochemicals are defined as bioactive non nutrient plant compounds in fruits, vegetables, grains, and other plant foods that have been linked to reducing the risk of major chronic diseases and have been studied mainly in animal models of asthma with encouraging results. For example, kaempferol is efficacious in improving epithelial thickening and airway smooth muscle hypertrophy (Shin et al.2015). Curcuma longa extract and its component curcumin has antioxidant and anti-inflammatory properties suggesting a therapeutic prospective. Propolis extracts containing flavonoids and phenolics exert anti-inflammatory properties by free radical scavenging in mouse covalbumin-induced asthma model (El-Aidy et al. 2014). Similarly aerolised honey reduces airway inflammation. Ginger suspends lung inflammation by suppressing Th2-mediated immune responses and airway eosinophilia (Ahui et al. 2008).

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

COPD is currently the fourth leading cause of death and a major cause of chronic morbidity. The disease is characterized by persistent respiratory symptoms and airway obstruction due to airway abnormalities usually caused by exposure to noxious particles or gases. The main risk factor is smoking and the disease results from a complex interaction between genetic and environmental factors.

Nutritional support is indicated for malnourished patients since low BMI is associated with worse outcomes in COPD and poor diet contributes to skeletal muscle dysfunctions. Current guidelines suggest that all COPD patients should have general advice on healthy living including diet (GOLD 2017). For more information concerning nutritional support in COPD the reader is referred to published review (Collins et al. 2013). Here, we will address the possible effects of the most important nutrients or nutrient groups in COPD.

Dietary habits

Epidemiologic (both retrospective or not retrospective) studies have proven that dietary patterns with increased consumption of fruit, vegetables, fish, and whole grains are associated with decreased development of COPD in smokers and nonsmokers, better pulmonary function and decreased long-term COPD mortality, while a decrease in fresh fruit intake is associated with a greater fall in FEV1 (Carey et al. 1998). Mediterranean diet has been related to a 50% reduction in the risk of COPD (Varraso et al. 2007). Alike, a randomised intervention study of COPD patients showed that an increase of fruit and vegetables consumption over a period of 3 years resulted in preseved pulmonary function (Keranis et al. 2010).

Vitamins-Antioxidants

The systemic inflammation related to COPD may be triggered by the impaired oxidative stress that is prevalent in the disease. The level of airway inflammation in COPD correlates with disease severity and is involved in disease pathogenesis. Thus, reduction of oxidative stress through diet may protect against the development of COPD. Epidemiological studies have almost unequivocally suggested that vitamin C is related to better lung function regardless of smoking history (for more details see the section on pulmonary function). Serum vitamin A is negatively related to the presence of COPD. Antioxidant supplementation of vitamins A, C and alpha-lipoic acid reduces oxidative stress in COPD. Low α-tocopherol concentrations in lung tissue are related to more severe cases of COPD (Agler et al. 2013). However, few interventional studies exist. Vitamin E supplementation in almost 39.000 females demonstrated a reduction in the diagnosis of COPD (Agler et al. 2011), while others have challenged this finding (Heart Protection Study Collaborative Group 2002). Taken the above into account, it seems that the role of antioxidant supplementation in COPD is not fully explored. Exploration of their role should be

examined with caution due to the safety concerns associated with increased lung cancer prevalence (Albanes et al. 1996).

Interestingly, vitamin D deficiency accelerated emphysema in animal models through increased protease/anti-protease ratio (Crane-Godreau et al. 2013). Vitamin D deficiency has been consistently reported in the COPD population and has been associated with recurrent exacerbations and hospitalization. Vitamin D supplementation has no effect on spirometry parameters or exacerbations frequency or time to first exacerbation except in patients with dramatically low vitamin D levels. However, vitamin D intake has been associated with improvement in inspiratory muscle strength and oxygen uptake (Hornikx et al. 2012).

Phytochemical-plants

A link has been suggested between phytochemicals and COPD. Delphinidin and cyaniding decrease the production of IL-8 in cells after cigarette smoke extract treatment (Flores et al. 2012). Lycopene, proanthocyanidin and quercetin reduces inflammatory mediators and oxidative stress indicators in THP-1 macrophages exposed to cigarette smoke (Günay et al. 2016; Palozza et al. 2012). Green tea limits oxidative stress and protease/anti-protease imbalance in the airways after exposure to cigarette smoke (Chan et al. 2012). Spirulina consumption decreases oxidative markers and increases antioxidants in COPD patients (Ismail et al. 2014). Sulforaphane stimulates nuclear factor erythroid-2 related factor 2 (Nrf2) activity in vitro and in vivo thereby possibly decreasing oxidative stress and ameliorating bacterial clearance in lung macrophages (Harvey et al. 2011).

The literature on dietary intervention with plants as a treatment on COPD has also grown but the level of evidence is low and most of the studies are not encouraging. For example, pomegranate juice supplementation adds no benefit to the current standard therapy of patients with COPD. However, treatment with pingchuan guben decoction reduces symptoms, improves pulmonary function and reduces exacerbations of COPD and sulforaphane does not affect antioxidants levels or inflammatory markers in COPD. Clearly much are yet to be discovered concerning implication of phytochemicals in COPD.

Minerals

A number of experimental studies suggest a possible link of minerals with COPD, but the quality of evidence is low. Experimental studies demonstrate that copper deficiency results in emphysematous destruction of the lungs and an increase of the mean alveolar airspace areas and mean linear intercept (Mizuno et al. 2012). Mg deficient patients with COPD report notable worse COPD-related Quality of life although Mg levels are not associated with spirometry values. Beetroot juice, which is rich in nitrate ($NO3^-$) reduces oxygen consumption during exercise in COPD patients. COPD patients present lower calcium, phosphorus and iron intake while an inverse association exists between dietary calcium intake and COPD risk.

Fatty acids

PUFAs intake may protect against COPD development through reduction in COPD related inflammation. Varraso et al. (2015) reported no significant relationship between PUFAs consumption and risk of COPD in two cohort studies. However, high dietary intake of omega-3 is inversely associated with COPD risk in a dose-dependent manner. The associations between PUFAs and COPD are inconsistent. PUFAs supplementation improves exercise capacity in COPD and may reduce the rate of lung function deterioration. Based on limited proof there is a weak support for the role of omega-3 PUFAs in COPD with some evidence for the improvement of functional ability.

Probiotics-fibre

Probiotics may act as immunomodulatory agents and may regulate immune responses responsible for COPD. The aforementioned hypothesis has little literature confirmation. Mortaz et al. (2013) suggested that probiotic Lactobacillus casei strains shirota (LcS) may be useful in COPD patients, especially those with recurrent viral infections, since daily consumption of LcS increases natural killer cell activity in smokers and thus may be implicated in COPD exacerbations (Morimoto et al. 2005; Naruszewicz et al. 2002). Increase in dietary fibre consumption has been associated with reduced COPD risk, improvement in pulmonary function and decreased respiratory symptoms.

LOWER RESPIRATORY TRACT INFECTIONS (LRTIs)

Lower respiratory infections (LRTIs) are a leading cause of morbidity and mortality affecting both adults and children worldwide. Although not uniformly defined, the term LRTIs usually refers to infections of the airway such as acute bronchitis and acute bronchiolitis, as well as infection of the lung alveoli (pneumonia). Community acquired pneumonia (CAP) is one of the most common infectious diseases worldwide and is defined as pneumonia in patients that do not reside in a long-term care facility or pneumonia that occurs within 48 hours after hospital admission. Pneumonia that was not incubating at the time of hospital admission and that occurs more than 2 days after hospitalization is termed hospital-acquired pneumonia. Health-care associated pneumonia mainly affects patients that were hospitalized for more than 2 days in the last 90 days or residents of long-term care facilities.

The increase in the incidence of acute lower respiratory infections (mainly pneumonia), as well as their severity and mortality, may be associated with malnutrition, and impaired immune response may be one of the underlying mechanisms. Several nutrients have immunomodulatory roles and studies have suggested that they may be implicated in the development as well as the outcome of LRTIs.

Vitamins-Antioxidants

Several vitamins may be involved in the development and outcome of respiratory infections. Nutrients with antioxidant properties may enhance immune response and natural defenses and therefore one may speculate that they may protect against LRTIs. However, data in the literature are not straightforward concerning this hypothesis. Besides their antioxidant capacity, vitamins may exert direct roles in the immune system. For example, vitamin C enhances the function of phagocytes and the proliferation of lymphocytes. In a population based study vitamin C relieved oxidative stress and proinflammatory mediators associated with pneumonia (Chen et al. 2014).

Vitamins A and C deficiency may be related to a higher burden of respiratory infections, possibly thorough the negative impact on immune function. However, others have failed to demonstrate an association of vitamins C and E and beta carotene with milder forms of respiratory infections, such as common cold (Hemila et al. 2002; Takkouche et al. 2002). On the contrary, low levels of vitamins A and D are related to severe outcomes of LRTIs such as admission to ICU or need of mechanical ventilation. Interestingly, in a Cochrane meta-analysis, vitamin A did not confer a significant benefit in preventing LRTIs (Chen et al. 2008). In the same context, studies have examined the possible benefit of antioxidant vitamins supplementation in LRTIs with conflicting results. Vitamin A supplementation does not affect the clinical course or reduce severity of CAP. On the contrary, vitamin C intake reduces the duration of mechanical ventilation in patients with pneumonia and decreases the pneumonia risk in patients with vitamin C shortage. A study showed reduced hospitalization duration for pneumonia in patients with vitamin C supplementation (Yaqub et al. 2015).

Vitamin E intake may reduce the incidence of pneumonia in elderly. However, vitamin E and β-carotene addition does not affect the risk of severe hospital-treated pneumonia, eventhough some have stated that vitamin E might augment the risk of pneumonia in patients with increased vitamin C intake. Interestingly, dietary supplementation which contained vitamins (A, B1, B2, B3, B5, B6, B7, B12, C, E), and minerals (selenium, zinc, copper, manganese) decreases the incidence of clinically diagnosed acute respiratory infections, which include common cold, flu, pharyngitis, sinusitis, laryngitis, bronchitis and pneumonia (Bernal-Orozco et al. 2015). The conflicting results may be due to the heterogeneity of studies population since some have speculated that the beneficial effects of vitamin supplementation depend on the prevalence of vitamins deficiency in the patients.

Vitamin D has attracted a lot of attention recently since it possesses significant immunomodulatory properties. Vitamin D suppresses T-helper cell (Th-1) and enhances Th-2 immune responses and induces the production of antimicrobial peptides such as cathelicidin. Observational studies have linked vitamin D deficiency with increased risk of LRTIs in both adults and children. Vitamin D deficiency has been associated with both increased risk and severity of LRTIs in children. Similar results have been obtained in adults where vitamin D deficiency has been inversely associated with CAP severity. The role of vitamin D supplementation in LRTIs prevention and treatment has been studied as well. Data from RCT suggest that vitamin D may have a protective role against influenza infection (Urashima et al 2010), although not associated with the duration of the resolution of pneumonia or the incidence of LRTIs (Robertsen et al. 2013). Interestingly, a recently published meta-analysis suggested that vitamin D supplementation may prevent LRTIs (Martineau et al. 2017). Although data suggest that vitamin D has important implications in LRTIs, the beneficial effect of vitamin D supplementation remains unclear.

Probiotics-Prebiotics

Data support the use of probiotics for the prevention and treatment of gastroenteritis. The possible role of probiotics and prebiotics in respiratory infections has attracted attention as well. For example, probiotics like lactic acid bacteria have proven effects in innate and humoral immune response against streptococcus pneumoniae associated LRTIs. Meta-analyses support that the use of probiotics is related to a statistically notable decrease in the prevalence of hospital induced pneumonia (Liu et al. 2012). Similarly, consumption of probiotics is associated with lower occurrence of VAP. Probiotic introduction in the diet reduces cases of LRTIs as well as RTIs in the elderly. Bernard et al. (2015) demonstrated that prebiotics, such as pectin-derived acidic oligosaccharides taken out from citrus, improved the outcomes of pseudomonas aeruginosa lung infection in mice by regulating the intestinal microbiota and the inflammatory and immune responses. As there was a decrease in bacterial load, pectin-derived acidic oligosaccharides could be suggested as an adjuvant therapy to antibiotics. A systematic review and network meta-analysis demonstrated that synbiotic therapy (combination of probiotics and prebiotics) was the best regulated course in decreasing pneumonia in adult surgical patients in comparison with probiotics and prebiotics alone (Kasatpibal et al. 2017). Although the aforementioned data are encouraging, further studies are warranted, before any definite suggestions are made concerning probiotics and prebiotics role in LRTIs.

Fatty Acids

PUFAs have great immunomodulatory and inflammatory effects. Experimental evidence suggest that PUFAs promote phagocytosis of pseudomonas aeruginosa (Adolph et al. 2012) as well as the survival of mice following infections of pseudomonas aeruginosa and klebsiella pneumoniae (Caron et al. 2015). Similarly, omega-3 PUFAs amplifies phagocytic ability of mice alveolar macrophages and reduces alveolar macrophage apoptosis by streptococcus pneumoniae (Saini et al. 2013). High consumption of

ALA and linoleic acid is related to reduced pneumonia risk. On the contrary, DHA and EPA have been associated with increased CAP risk while oleic acid is inversely associated with pneumonia prevalence.

Dietary supplementation with DHA and arachidonic acid decreases viral infections and therefore LRTIs. Omega 3 intake is beneficial in ARDS patients. However a meta-analysis suggests that there are no benefits at omega 3 supplementation in patients with ARDS (Li et al. 2015). The data concerning the role of PUFAs in RTIs are inconsistent.

Phytochemicals

Current data suggest that phytochemicals may have preventive and therapeutic role in RTIs however the quality of evidence is low. Green tea consumption is related to a lower risk of death from pneumonia. Pleuran decreases the number of pneumonia and bronchitis in children. Manuka honey has antimicrobial activities against pseudomonas aeruginosa. Extract from North American ginseng (panax quinquefolius) suspends pseudomonas aeruginosa development. Interestingly, combination therapy of curcumin with antibiotics in mice models reduces inflammation, and bacterial proliferation and lung tissue injury.

Minerals

Data suggest clinical benefit for mineral supplements like zinc in LRTIs. A meta-analysis concluded that zinc supplementation for more of 3 months decreases the risk of LRIs (Roth et al. 2010). Zinc supplementation may reduce pneumonia mortality in children and may serve as an adjuvant therapy (Shah et al. 2017). Zinc reduces the incidence of severe pneumonia. In the same context, selenium reduces VAP prevalence. Selenium, zinc and copper administration is linked to reduced incidence of nosocomial pneumonia.

TUBERCULOSIS (TB)

Tuberculosis (TB) represents an infectious disease usually caused by Mycobacterium tuberculosis (Mtb). One third of the world population is infected with Mtb, while TB was responsible for 1.3 million deaths in 2016. About 90% of patients do not present symptoms and suffer from latent TB, while active cases present with cough, hemoptysis, fever, night sweats and weight loss. TB can affect any part of the body although most commonly affects the lungs. The disease pathogenesis commonly involves the formation of caseous granulomas in infiltrated tissues involving macrophages, T-lymphocytes, B-lymphocytes and fibroblasts. Treatment of TB involves the combination of antituberculosis drugs for long periods of time.

Dietary patterns

Several factors make people more susceptible to TB. Malnutrition among others has long been recognized as a risk factor for pulmonary TB. Data on the role of dietary patterns in TB are sparse. Poor fruit and vegetable intake is related to an increased susceptibility to infection with Mtb but not active TB. In an animal experiment it was found out that alcohol consumption dulled the development of the adaptive immune response to BCG vaccination (Porretta et al. 2012).

Vitamins-antioxidants

Although studies have shown deficiency of several antioxidant vitamins in TB, the available data cannot confirm causality. Experimental data suggest that vitamins like vitamin C and E have bactericidal activity against Mtb and thus may exert potential benefits to anti-tuberculosis treatment. TB patients present low levels of vitamin A, considering it as a risk factor of TB infection and clinical severity. Similar results have been reported for vitamins E, A and C. Taken the above into consideration, nutritional supplements could help people recover from TB due to their effects on the immune system. However, there are no

clear data that routine supplemention provides clinically important benefits. Although vitamins and micronutrients supplementation may help the treatment of these patients in terms of earlier sputum smear conversion or reduced hepatotoxicity, no definite conclusions can be drawn yet.

The strong association of vitamin D deficiency and TB may be due to the production of cathelicidin which is implicated in the innate immune response to Mtb infection (Liu et al. 2006). Observational studies have shown a positive association between low levels of vitamin D and TB prevalence. Additionally, vitamin D hypovitaminosis is a risk factor for worse treatment outcomes like delayed sputum conversion.Vitamin D deficiency has been widely accepted as a risk factor for active TB. However, the effect of vitamin D supplementation in TB remains controversial. Adjunct therapy with vitamin D has some beneficial effects towards clinical recovery. However, the results are inconsistent among the studies. At this point the beneficial effect of vitamin D supplementation remains unclear and high-quality studies are necessary to establish the role of vitamin D manipulation in TB.

Minerals

Patients with TB present low serum concentrations of zinc and selenium, high levels of copper and cobalt. Low plasma selenium levels is a risk factor related to anemia in these patients (Van Lettow et al. 2005). High copper is related to worse outcomes and low zinc is associated with clinical severity. Experimental evidence suggest that copper is essential for the control of Mtb infection (Wolschendorf et al. 2011). Further studies in this field are clearly needed.

Fatty acids

The impact of PUFAs on TB is not well known. Omega-3 PUFAs supplementation might have a harmful effect on immunity against Mtb. Experimental data have linked omega-3 PUFAs with reduced skin test positivity and reduced inflammatory response to Mtb. Although observational data suggest that omega-3 and omega-6 consumption may be related to reduced risk of active TB, overall the available data suggest that PUFAs may increase susceptibility to Mtb infection. Clearly well-designed studies are warranted in order to elucidate PUFAs role in TB in vivo.

Phytochemicals-plants

Many studies have been conducted on the potential effect of medicinal plants as alternatives and adjunctives therapies for the treatment of TB. It has been reported that ursolic acid and hydroquinone may have chemotherapeutic potency against Mtb and immunoregulatory properties against TB in mice. Curcuma longa provides defense against Mtb infection in alveolar macrophages, via repression of nuclear factor-kappa B (NFκB) activation (Bai et al. 2016). In addition, aristolochia brevipes, garlic and garlic derived fatty acids, and ambrosia confertiflora have antibacterial activity against Mtb. Excoecaria agollacha may protect against multi-drug resistant TB (Amudha et al. 2014). Pomegranate fruit inhibits Mtb and manuka honey may be efficient as a hepatoprotective agent. Although the aforementioned data are encouraging, the lack of well-designed clinical trials limits their importance.

Probiotics

Strains of lactic acid bacteria, as l. rhammosus GG and bifidobacterium bifidum MF 20/5 increase the autophagic capacity of mononuclear phagocytes in response to Mtb antigen in a vivo study (Ghadimi et al. 2010). Unfortunately, there are no studies about the impact of probiotics on TB.

LUNG CANCER

Lung cancer (LC) is the leading cause of cancer death in the United States. The vast majority of cases are caused by smoking with the remaining often due to a combination of genetic factors and exposure to radon or asbestos. Most patients are not curable, thus avoidance of risk factors, mainly smoking, is of special importance in order to prevent the disease. An issue of ongoing research is the effect of diet on lung cancer development and its therapeutic potential.

Dietary patterns

Emerging data have indicated that dietary habits play a crucial role in lung cancer development and as a result they have attracted increased attention. Processed meat and meat mutagen (found in fried, barbecued, and processed meat), red meat, white bread, fat and high dietary glycaemic index foods, polycyclic aromatic hydrocarbons (found in charcoal-broiled, fried, and smoked meat) and coffee consumption have all been associated with increased lung cancer risk mainly among smokers. On the contrary, fish consumption, fruits and vegetables and a healthy dietary pattern have been consistently associated with lower lung cancer risk. Of great importance seems to be the adherence to the mediterranean diet that has strong evidence in favor of a reduced lung cancer risk.

Vitamins-Antioxidants

Oxidative stress has been implicated in lung cancer development and thus one may speculate that dietary antioxidants may prevent carcinogenesis. Several epidemiological studies have associated antioxidant intake with lower lung cancer risk. Intake of vitamins A, C, and E may provide protection against lung cancer development but with a possible modification of this effect by smoking habit. Similar data have been reported for riboflavin (B2) and folate (vitamin B9). However, interventional studies have not replicated these results, while the use of antioxidants supplements may be harmful. In a double blind RCT which involved almost 30.000 male smokers, there was an association of beta-carotene supplementation with higher incidence of LC as early as 18 months after the initation of the study (Albanes et al. 1996). Similarly, a study involving 18.000 men and women at high risk for LC supplemented with beta carotene and vitamin A was stopped early due to higher death rate in the antioxidant groups (Omenn et al. 1996). On the contrary, they seem to be harmful. Surely, the available data do not provide any evidence of any preventive effect. The mechanism underlying the potential increase in lung cancer incidence is not known but studies have suggested that antioxidants may promote tumor growth and metastasis.

The effect of antioxidant supplements during lung cancer treatment is not well studied. Some have shown that vitamin addition combined with chemo therapy may inhibit cell proliferation in cell lines (Lee et al. 2017). However, studies have shown inconsistent results and some have reported worse outcomes. Therefore, antioxidant supplements should be used with caution by lung cancer patients.

Vitamin D may exhibit anti-carcinogenic effects via the inhibition of cell proliferation and angiogenesis, as well as the enhancement of apoptosis and cell differentiation. Experiments have shown that vitamin D intake might provide protection against lung cancer development and metastatic ability via giving off of E-cadherin and catenin, which help the adherence of cancer cells and decrease the possibility of metastasis (Zhou et al. 2005). In the same context, high levels of 25-hydroxyvitamin D [25(OH)D] may be related to a decreased risk of LC, particularly in people with vitamin D deficiency. Some have reported that the protective nature of vitamin D against LC is limited to women and non-smokers. Data have connected positively vitamin D with LC mortality. Unfortunately, literature lacks data from well-designed studies and the causal direction of these results cannot be established.

Minerals

Dietary mineral intake may influence lung cancer development but the direction of the association depends on the type of the mineral. A prospective cohort study among 482.875 participants suggested that total calcium consumption was protective for smokers and individuals with adenocarcinoma, while total magnesium intake increased risk in men and smokers and total iron consumption was inversely related to risk in women. Mineral intake from supplements did not influence LC risk (Mahabir et al. 2010). A diet rich in zinc and iron may be related to reduced risk but no relationship was found between selenium, calcium, magnesium and copper consumption (Muka et al. 2017). Others have associated low selenium with high risk of LC (Jaworska et al. 2013), while selenium supplementation is not benefit in terms of prevention of second primary tumors in patients with resected NSCLC.

Fatty acids

Fatty acids, especially omega-3 PUFAs, have been associated with a lower predominance of various types of cancer. Experimental studies support the protective role of PUFAs in LC possibly through increased oxidative stress and apoptosis of cancer cells and modulation of cyclooxygenase activity and cell surface receptors (Kim et al. 2015).The aforementioned data are consistent with observational data suggesting that high fish consumption, which is rich in n-3 PUFAs is related to a reduction of LC risk even after adjustment for smoking status. Supplementation of eicosapentaenoic acid (EPA) increased lean body mass, energy and protein intake and reduced fatigue and neuropathy in non-small cell lung cancer (NSCLC) patients undergoing chemotherapy (Sánchez-Lara et al. 2014). Adjunctive omega-3 supplementation in LC therapy may prevent cachexia, and improve performance status and physical activity in LC patients (Finocchiaro et al. 2012). Due to the limited available data that are generally based on small cohorts, no definitive conclusions can be drawn.

Phytochemicals-plants

Many phytochemicals have been studied in the context of LC due to their possible role in LC cells apoptosis, chromatin remodeling, and DNA methylation among other pathways. Quercetin-rich food is inversely associated with LC risk, whilst quercetin enhances the activity of anti-cancer drugs. (6)-shogaol suppresses the growth of NSCLC cells and enhances apoptosis in cancer cells. Silibinin in combination with epigenetic drugs (HDAC or DNMT inhibitor) inhibits both aggression and migration of NSCLC cells and could be a potent treatment to more advanced stages of NSCLC, whilst combination of indole-3-carbinol and silibinin intake may protect against LC. Both green and black tea consumption are related to lower risk for LC. Triptolide which has been studied for its anti-rheumatic effects, shows anticancer properties against NSCLC. Chlorella sorokiniana causes mitochondrial-mediated apoptosis in NSCLC cells, whilst chlorella vulgaris inhibits LC cells growth and migration.

Many studies have assessed the inhibitory activity of **curcumin** on lung cancer cell line growth and metastasis in vitro and in vivo as well as its reinforcement of anti-cancer drugs. A few studies proved the inhibitory effect of panax ginseng on tumor growth and lung metastasis in vitro and in animals. Unfortunately, RCTs are lacking and the aforementioned findings are mostly based on experimental studies.

CYSTIC FIBROSIS

Cystic fibrosis (CF) is a genetic disorder caused by mutations of the gene for the cystic fibrosis transmembrane conductance regulator (CFTR) protein. CFTR is involved in sweat, digestive fluid and mucus production and when affected it results in thicker secretions. The disease affects the lungs due to

mucus clogging of the airways resulting in inflammation and infection. The thick mucus blocks the digestive system causing meconium ileus and in later life the thickened secretions of the pancreas blocks the exocrine part of the organ and result in irreversible damage. Due to malabsorption, patients with CF are often malnourished and have poor growth. Replacement of digestive enzymes is indicated in CF, while they present malabsorption of fat-soluble vitamins (A, D, E, and K). Also, they exhibit signs of oxidative stress, due to the inflammation and malabsorption of vitamins A and E. CF patients should consume 120% to 150% of the recommended daily allowance (RDA) for energy expenditure, with 40% coming from fat. Nutritional supplementation may include omega-3 PUFAs, vitamins A, D, E, K, proteins ≥120% of RDA.

Concerning the lung, in the early stages, inflammation and decreased mucociliary clearance results in copious phlegm production and insufficient coughing. In later life patients develop structural changes in the lungs, mainly bronchiectasis. For malnutrition in CF the reader is refer to a published review paper (Culhane et al. 2013). Here we will report the main findings on the role of dietary compounds in the disease.

Vitamins-Antioxidants

Vitamin C reduces with age in people with CF and supplementation with antioxidant vitamins may retard the deterioration of pulmonary function. Experimental data suggest that vitamin C activates the CFTR channel in the respiratory tract (Fischer et al. 2004). Clinical studies suggest that vitamin C concentration in CF patients is associated with indexes of lung inflammation. High levels of vitamin A are related to improved lung function in CF patients and β-carotene supplementation could benefit CF patients. Vitamin E levels have been reported low in CF. Little is known about vitamin A. High α-tocopherol levels have no beneficial effects on pulmonary function in CF patients. RCTs in the field are lacking.

Vitamin D supplementation has anti-microbial and anti-inflammatory properties in CF patients and is related to reduction in inflammatory cytokines, i.e. IL-6 and TNF-a (Grossmann et al. 2012; Herscovitch et al. 2014). Vitamin D deficiency is associated with pulmonary exacerbations. Similarly, vitamin D consumption may regulate positively inflammation in CF by decreasing serum total IgG levels, serum haptoglobin and erythrocyte sedimentation rate (Pincikova et al. 2011).

Minerals

Serum levels of calcium, copper, and iron in CF patients are reduced during exacerbations of the disease. Zinc deficiency is common in CF patients and low zinc levels are associated with worse pulmonary function. However, zinc supplementation does not improve pulmonary function neither decreases pulmonary infections (Sharma et al. 2016). CF patients have lower levels of selenium. Iron deficiency is usual in adults with CF and associated with disease severity. Iron administration does not reduce respiratory symptoms or change the sputum microbiome in CF patients (Gifford et al. 2014). CF patients have increased lung iron levels that enhance ROS production and encourage bacterial growth (Childers et al. 2007). High iron levels in the airways of CF patients may conduce to the sensibility to chronic bacterial infections that are related to CF. Administration of iron chelators might isolate host iron and prevent approachability of iron to bacteria (Aali et al. 2017).

Fatty Acids

Low-dose supplementation with omega-3 and omega-6 PUFAs improves lung function, respiratory exacerbations, antibiotic consumption, lean body mass, inflammation, and oxidative markers. A RCT also showed that omega-3 PUFAs may decrease leukotriene LTB4/LTB5 ratio, demonstrating anti-inflammatory effects (Panchaud et al. 2006).

Phytochemicals

Curcumin may stimulate CFTR Cl^- channels (Berger et al. 2005). Garlic improves lung function in CF patients having chronic Pseudomonas aeruginosa infection. Rhodiola kirilowii (Regel) maxim and cocoa flavanols have antidiarrheal activity in CF patients by inhibition of CFTR Cl^- channel activity (Schuier et al. 2005). Also, bergamot (citrus bergamia risso) extracts inhibits IL-8 expression in an in vitro study (Borgatti et al. 2011).

Probiotics

A systematic review revealed that the effectiveness of probiotics in children with CF is restricted (Ananthan et al. 2016).

INTERSTITIAL LUNG DISEASES

Interstitial lung diseases (ILDs) are a group of heterogenous diseases of the lung that affect the interstitium. The group includes many different conditions. Here we will emphasize on two of the most common ILDs, Idiopathic Pulmonary Fibrosis (IPF) and sarcoidosis.

The reduced antioxidant defense, causing oxidative stress and inflammation are two key triggers in the pathophysiology of IPF. A diet rich in antioxidants might have an advantageous effect on ILD patients and some argue that it might prevent against the development of IPF. In addition, fruit consumption may prevent the development of IPF. A study found a reduction in the risk of IPF, which is related to high consumption of green tea, vegetables, and higher intake of fish (Iwai et al. 1994). High consumption of vitamin A has been related to decreased rate of progression in asbestos-related lung fibrosis (Chuwers et al. 1997). However, the role of antioxidants is probably of limited importance since the administration of NAC in IPF patients offers no significant benefits (Idiopathic Pulmonary Fibrosis Clinical Research Network 2014).

Vitamin D deficiency is konown in patients with ILD. Sarcoidosis patients should be supplemented with vitamin D, only when diagnosed with vitamin D deficiency due to the high levels of 1-a-hydroxylase in sarcoid granulomas.

Several studies in animals have suggested the potential therapeutic properties of phytochemicals in ILDs. Fenugreek (trigonella foenum graceum) seed extract and berberine exhibits anti-fibrotic results through induction of Nrf2 (an antioxidant balance regulation factor) and inhibits profibrogenic molecules in bleomycin-induced rat models (Chitra et al. 2015). Citrus reticulata (commonly known as mandarin orange) extract inhibits the proliferation of human lung fibroblasts and inflammation (Zhou et al. 2013). Flaxseed oil, which is rich in omega-3 and omega-6 PUFAs, attenuates bleomycin-induced pulmonary fibrosis in rats and reduces pulmonary oxidative stress (Abidi et al. 2016). Intraperitoneal curcumin administration exhibited antifibrotic effects on bleomycin-induced pulmonary fibrosis in mice and curcumin administration prevents against the development of carbon tetrachloride-induced pulmonary fibrosis. Hesperidin reduces the severity of pulmonary fibrosis in rats. Nigella sativa has anti-inflammatory and antifibrotic effects on bleomycin-induced pulmonary fibrosis in rats. Administration of quercetin could benefit IPF patients by reducing inflammation, oxidative stress, and retarding disease progression (Veith et al. 2017). Similarly, Boots et al. (2009; 2011) indicated that quercetin might be useful for sarcoidosis patients by decreasing OS and inflammation.

MATERNAL DIET AND DIET IN EARLY LIFE IN LUNG HEALTH

Maternal diet in pregnancy is considered to be one of the most relevant prenatal and early postnatal risk factors for the development of respiratory diseases. The development of the lungs is almost completed prenatally and, following birth, airway development is mostly restricted to size growth. Thus, fetal or early life exposure may have disproportional effects on the development of respiratory diseases. Research has focused on the obstructive lung diseases such as asthma and COPD.

Dietary patterns

Various dietary patterns may contribute to lung development or disease. Experiments in animals showed that maternal high-fat diet and hypercaloric diet were associated with deteriorated fetal lung development, airway hyperresponsiveness and chronic airway inflammation in the offspring (Griffiths et al. 2016).

In humans, high consumption of (processed) meat, fast food (i.e. large portions of processed meat, refined carbohydrates, saturated and trans-fatty acids, sodium, sugar, preservatives and colorants), are all associated with wheeze and asthma symptom in children. On the contrary, high maternal intake of peanut, milk, wheat, leafy vegetables, malaceous fruits and chocolate may be related to a decreased likelihood of wheeze and/or asthma but not consistently. Adherence to the mediterranean diet during pregnancy seems to be preventive for wheeze. Subsequently, early import of solid food has been associated with reduced probability of developing asthma. The effect of breastfeeding for 4-6 months or longer is related to reduced risk of developing asthma and LRTIs (Tromp et al. 2017).

Vitamins-Minerals-Antioxidants

Maternal dietary antioxidant intake may contribute to increases in asthma risk. Low maternal vitamin E and zinc intake is associated with increased asthma-like symptoms, whilst vitamin E levels during pregnancy are positively related to post-bronchodilator FEV1 (Devereux et al. 2006). Vitamin E affects positively neonatal airways epithelial cell secretory function (Miller et al. 2015). Increased intake of vitamin C in pregnancy is associated with wheezing. Interestingly, maternal antioxidant intake may decrease the risk of RTIs in the offspring. High maternal selenium and copper levels may prevent wheeze, an effect that is limited to the first years of life (Baiz et al. 2017). The current data support the association of antioxidants with childhood asthma but must be interpreted with caution, since the observational nature of the studies cannot establish causality.

The data concerning vitamin D are rather conflicting. Experimental evidence suggest that prenatal vitamin D is associated with lung development and surfactant synthesis. Low maternal and low neonatal vitamin D levels have been linked to bronchopulmonary dysplasia, asthma and wheeze. Others have challenged these results reporting no relation of maternal levels of vitamin D with asthma and wheeze (Magnus et al. 2013). Low levels of vitamin D in newborns and low vitamin D blood levels have been linked to increased risk of LRTIs and higher airway resistance.

Fatty Acids

PUFAs intake in pregnancy seem to play a role in respiratory symptoms in the offspring. Increased consumption of omega-3 PUFAs in the maternal diet has protective effects against allergic diseases (eczema, rhino-conjunctivitis, asthma) in the offspring. In the same context, fish oil supplementation during pregnancy may prevent asthma, although the relationship may be limited to asthmatics mothers (Salam et al. 2005).

Supplementation with omega-3 PUFAs in infants may influence later respiratory health. Infants who consumed omega-3 PUFAs had reduced odds of wheezing at 18 months, a result that is dulled at 3 and 5

years of age (Marks et al. 2006). Also, early introduction of fish into the diet (at <9 months of age) reduces odds of wheezing (Goksor et al. 2011) and is associated with a reduced risk of all asthma types. In addition, margarines consumption from mothers during lactation was weakly related to an increased risk of asthma (Lumia et al. 2012).

Probiotics

Despite evidence for an effect on immune development, overall the current data do not support an association of probiotic supplementation and childhood asthma. Evidence from two meta-analyses supported that prenatal and/or early life probiotic administration could not protect against asthma or childhood wheeze (Azad et al. 2013; Elazab et al. 2013). More studies are needed to assess the possible mechanisms through which probiotics could prevent respiratory symptoms in the offspring since most of the clinical trials currently available commence supplementation in late pregnancy.

DIET AND PULMONARY FUNCTION

A healthy overall diet, as assessed by the Healthy Eating Index 2005 (HEI-2005) is associated with better lung function as determined by the ratio FEV1/FVC and FEV1%pred. Animal protein and PUFAs consumption show a positive association with pulmonary function, whereas there is a negative association between pulmonary function and total calories and dietary saturated fatty acids. A dietary pattern based on higher-antioxidant food consumption may be associated with improvement in lung function at least in COPD patients (Keranis et al. 2010).

Epidemiological studies have indicated that vitamin C consumption is beneficially related to lung function, regardless of smoking intensity and prevents the development of emphysema in chronic smokers. Vitamin A is necessary for lung development and pulmonary cell differentiation and its deficiency could lead to lung dysfunction due to disordered composition of collagen IV and laminin and reduction on matrix metalloproteinase concentrations (Esteban-Pretel et al. 2013). B-carotene is positively associated with FEV1 and is related to slower decline of FEV1 in an 8-year follow-up study (Grievink et al. 2000). In accordance to these findings, serum carotenoids concentrations are inversely associated with a decline in lung function (Thyagarajan et al. 2011).

High vitamin E intake has a positive association with FEV1 and FVC with a dose-dependent response, whilst others have questioned the relationship between vitamin E and lung function. An increase in serum selenium was associated with an increase in FEV1 among smokers (Hu et al. 2000).

According to a nutritional epidemiological study, dietary intake of magnesium, folate (vitamin B9), niacin (vitamin B3), vitamins A and D, long chain unsaturated fatty acids (eicosenoic fatty acid and omega-3 PUFAs), and dietary fiber are associated with better FEV1 in chronic smokers (Leng et al. 2017). It has been also suggested that keeping sufficient vitamin D levels is necessary for optimal lung health and may regulate the lung microbiome in a sex-specific fashion (Roggenbuck et al. 2016). Low fibre intake is related to decreased measures of lung function.

Anthocyanins (flavonoids found in fruits, mainly in berries) intake is associated with slower age-related rates of FEV1 and FVC decline (Mehta et al. 2016).

Challenges in diet and lung health research

Accumulated evidence from observational studies suggest that diet is a potential cofactor in lung health and disease. However, due to the nature of these studies (i.e. lack of control for biases that may influence

outcomes, often retrospective nature), the temporal relation cannot be stablished. Clearly, well designed studies (i.e. RCTs) are needed in order to determine causality and often the clinical importance of dietary interventions. The association of various nutrients with lung diseases needs to be addressed more thoroughly, like the potential implication of probiotics and phytochemicals with COPD or the role of minerals in asthma.

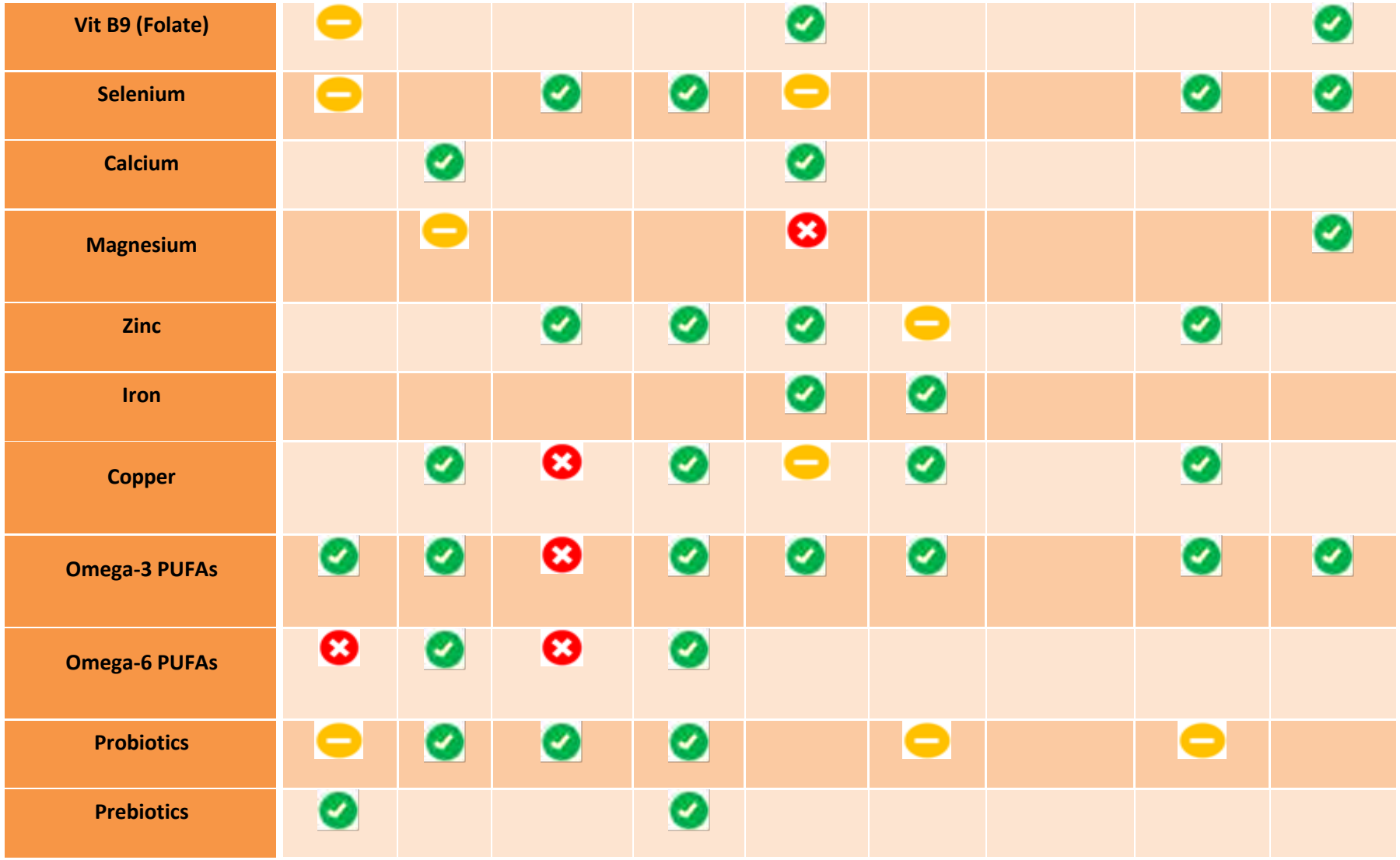
Another important concern that needs to be studied is the potential effect of organic foods in lung health. Currently, products of organic farming are thought to be safer and more nutrient than conventional food, however there are no data examining the relationship with lung health.

Additionally, the data are limited regarding the possible association of the cooking method applied to the foods with the development of lung diseases. For example, processed meat is high in nitrites (thus may contribute to lung inflammation) and benzo(a)pyrene which is mutagenic. Further high quality investigations are needed in order to clarify the possible link.

APPENDIX

Table 1: Nutrients, diet and lung disease. ✓ **Beneficial effect;** ✗ **Negative effect;** − **No effect**

LUNG DISEASE / NUTRIENTS &DIET	ASTHMA	COPD	TUBERCULOSIS	LRTIs	LUNG CANCER	CYSTIC FIBROSIS	INTERSTITIAL LUNG DISEASES	MATERNAL DIET AND DIET IN EARLY LIFE	DIET AND PULMONARY FUNCTION
Vitamin A	✓	−	✓	✓	✗	✓	✓		✓
Vitamin C	✓	✓	✓	✓	✓	✓	✓	✗	✓
Vitamin D	✓	✓	✓	✓	✓	✓		✓	✓
Vitamin E	✓	✓	✓	−	✗	−	✓	✓	✓
Vitamin B12	−	✓							



Fibre		✓							✓
Western dietary patterns	✗				✗			✗	
Mediterranean diet		✓			✓			✓	

Table 2: The role of various nutrients and diet in asthma

ASTHMA

	MAIN FINDINGS	COMMENTS
Vitamin A	Reduced levels in asthmatics, improve asthma symptoms	Interventional studies are inconclusive
Vitamin C	Reduced levels in asthmatics, improve asthma symptoms	Interventional studies are inconclusive
Vitamin D	Reduced levels in asthmatics, improves asthma symptom, is not related to asthma exacerbation	Clinical benefit of vitamin D supplementation is uncertain
Vitamin E	Reduced levels in asthmatics, improve asthma symptoms	Interventional studies are inconclusive
Vit B9 (Folate)	Deficiency is associated with severe asthma exacerbations	Limited data available
Selenium	Reduced concentrations among patients, supplementation has no clinical benefit	Limited data available

Omega-3 PUFAs	Consumption may reduce the asthma risk	Beneficial effects of PUFAs are not consistent
Omega-6 PUFAs	Consumption is associated with increased asthma risk	Limited data available
Probiotics	May reduce asthmatic symptoms	Mainly experimental data available, limited data from clinical trials
Western dietary patterns	Adherence to western dietary patterns is associated with greater asthma risk	Well studied-strong data
Mediterranean diet	High intake of fruits, vegetables and fish are negatively associated with asthma risk, better asthma control and fewer exacerbations	Current guidelines- systematic review and meta-analysis
Curcuma longa	Anti-inflammatory properties, therapeutic prospective	Experimental data
Ginger	Suspends lung inflammation	Experimental data

Table 3: The role of various nutrients and diet in COPD

COPD

	MAIN FINDINGS	COMMENTS
Vitamin A	Is negatively related to the presence of COPD	Cross-sectional study
Vitamin C	Is related to better lung function	Regardless of smoking history

Vitamin D	Vitamin D deficiency has been reported in the COPD population and has been associated with recurrent exacerbations and hospitalization	Retrospective and cohort study
Vitamin E	Low concentrations in lung tissue are related to more severe cases of COPD, supplementation demonstrated a reduction in the diagnosis of COPD	Intervention studies are conflicted
Calcium	Intake inversely associated with COPD risk	case-control study
Magnesium	Levels are not associated with spirometry values	cross-sectional study
Copper	Deficiency results in emphysematous destruction of the lungs	Experimental data
Omega-3 PUFAs	High dietary intake is inversely associated with COPD risk, improves exercise capacity in COPD, may reduce the rate of lung function deterioration	Limited proof
Probiotics	May reduce COPD exacerbations	Little literature confirmation
Fibre	Consumption has been associated with reduced COPD risk, improvement in pulmonary function	Limited proof
Mediterranean diet	Decreased risk of COPD, better pulmonary function, decreased long-term COPD mortality	Mainly consumption of fruit, vegetables, fish, and whole grains
Green tea	Limits oxidative stress	Experimental data

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