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OCCUPATIONAL ALLERGIES (JA POOLE, SECTION EDITOR)

Nutritional Factors in Occupational Lung Disease

Mia Isaak[1] · Arzu Ulu[2] · Abigail Osunde[2] · Tara M. Nordgren[2] · Corrine Hanson[1]

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Abstract

Purpose of Review Lung diseases such as asthma and COPD are major public health issues and related to occupational exposures. While therapies to limit the development and progression of these diseases are limited, nutrition interventions could offer potential alternatives to mediate the inflammation associated with these diseases. This is a narrative review of the current state of relevant nutrients on inflammation and respiratory outcomes associated with occupational exposures.

Recent Findings Relevant nutrients that have been investigated in recent years include omega-3 polyunsaturated fatty acids, zinc, vitamin D, dairy products, and antioxidants. These nutrients have demonstrated the potential to prevent or modify the adverse outcomes associated with occupational exposures, primarily in preclinical studies.

Summary Current therapies for respiratory consequences associated with occupational exposures are limited; therefore, addressing strategies for reducing inflammation is important in improving quality of life and limiting health care costs. More human studies are warranted to determine the effectiveness of nutrition as an intervention.

Keywords Occupational lung disease · COPD · Asthma · Omega-3 fatty acid · Zinc · Vitamin D

Introduction

Environmental and occupational exposures contribute to the inflammation that is part of the etiology and progression of lung diseases such as non-allergic asthma, chronic bronchitis, and chronic obstructive pulmonary disease (COPD) [1, 2]. These diseases are significant public health concerns and result in economic and social burdens that are substantial and increasing. In addition, occupational lung disease is particularly devastating due to its financial and psychological impact on workers and their families when the only option is removal from the work site to reduce exposure. Patients with asthma and COPD suffer from decreased quality of life, increased depression and anxiety, and increased health care utilization. COPD is the third leading cause of death in the USA and the fifth leading cause of death worldwide [3–5]. In 2010, the total economic burden of COPD was estimated to be $32.1 billion with a projected increase to $49 billion by 2020 in the USA alone [5]. In the USA, one in 12 individuals in the USA have a diagnosis of asthma, and direct and indirect costs total $56 billion annually, compared to 1 in 24 and $6 billion in 1990 [6–9]. Both asthma and COPD are characterized by both pulmonary and systemic inflammation that influence the severity of the disease and the quality of life in those with the disease. The degree of inflammation is associated with decline in lung function, increased frequency of exacerbations, anxiety and depression, and decreased functional and health status [9].

Studies support the concept that dietary manipulations could represent an important tool to impact respiratory disease. Evidence has revealed that diet and nutrition are associated with lung function and could potentially be important in shaping an individual's disease risk [10]. Studies have repeatedly demonstrated that increased intake of certain nutrients, especially those with antioxidant and anti-inflammatory properties, is positively associated with pulmonary function [10]. Regarding occupational exposures, certain nutrients such as omega (n)-3 polyunsaturated fatty acids (PUFA), vitamin D, zinc, milk consumption, and phytonutrients with antioxidants have shown potential in the protection against the adverse respiratory effects. The possible role of these nutrients in relation to their protective effects on lung health is presented in Table 1 and will be discussed in more detail in the following review.

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✉ Corrine Hanson
ckhanson@unmc.edu

[1] Division of Medical Nutrition Education, College of Allied Health Profession, University of Nebraska Medical Center, 4045 Nebraska Medicine, Omaha, NE 68198-4045, USA

[2] Division of Biomedical Sciences, School of Medicine, University of California-Riverside, Riverside, CA, USA

Table 1 Selected micronutrients of relevance in lung health and occupational exposures

Nutrient	Role in lung health	Correlations among intake, serum concentrations, and beneficial effects
Omega-3 fatty acids	Serve as substrates for the biosynthesis of specialized pro-resolving lipid mediators (SPM) that promote the endogenous resolution of inflammation.	There is a wide variation in n-3 blood levels achieved between individuals in response to a given dose of an n-3 supplement. This variability may be due, in part, to genetic variations on n-3 metabolism.
Zinc	Zinc is essential for proper immune function and has been shown to be a key ingredient for cellular activation through a variety of signaling pathways.	Zinc absorption and endogenous excretion fall dramatically when zinc intakes are insufficient, but those adjustments do not prevent a decline in plasma zinc concentrations because zinc is sequestered in slow metabolizing tissues, such as bone and muscle.
Vitamin D	May regulate the expression of genes in bronchial smooth muscle cells; deficiency may increase levels of matrix metalloproteinases, which aggravate inflammatory injury and contribute to changes in lung structure.	Serum levels of 25(OH)D have been established as the marker of vitamin D intake, in the form of diet or sun exposure.
Dairy products	May regulate developing immune system in children, consumption leads to increased interferon gamma release.	Association between raw milk consumption especially before the age of 6 correlates with increased pulmonary function among farmers in Agricultural Lung Health Study.
Antioxidants/phytonutrients	Sorrel extract and N-acetyl cysteine reduce oxidant formation in vitro in NHBE.	Sorrel extract and NAC prevent formation of oxidants including peroxynitrite, hydroxyl radicals, and 8-isoprostane in organic dust-exposed NHBE.

Omega (n)-3 Polyunsaturated Fatty Acids

The health benefits of diets high in n-3 fatty acids are documented in several disease states [11, 12, 13••, 14, 15]. With regard to respiratory outcomes and environmental exposures, a recent study by Brigham et al. reported the relationship between n-3 and n-6 fatty acid intake and pediatric asthma morbidity, and the association between fatty acid intake and strength of indoor, PM-related asthma symptoms, albuterol use, and systemic inflammation [13••]. Their analyses included 135 children with asthma and evaluated the week-long average home indoor concentration of $PM_{2.5}$ and PM_{10}, dietary intake of n-3 and n-6 fatty acids, daily symptoms, and peripheral blood leukocyte at baseline, 3, and 6 months. In adjusted models, their results showed that higher n-6 intake associated with increased odds of increased asthma severity (p=0.02), and lower FEV1 (forced expiratory volume at the first second)/FVC (forced vital capacity) ratio (p=0.01), while higher omega-3 intake associated with reduced effect of indoor PM2.5 on symptoms (p<0.01). This investigation may represent the first evidence of a protective association between n-3 fatty acids and detrimental association between n-6 fatty acids and PM-induced asthma symptoms and systemic inflammation among school-age children with asthma. Similarly, a systematic review also suggested asthmatic children are more sensitive to the effects of n-3 fatty acids than adults [16]. Beneficial effects of n-3 fatty acids have been explored in response to $PM_{2.5}$ exposure in mice. Using both wild-type and *fat-1* transgenic mice, which have the ability to convert n-6 to n-3 PUFAs, Li et al. showed that elevated tissue n-3 levels are protective against $PM_{2.5}$-induced lung inflammation in mice both in a prophylactic and therapeutic manner [17••].

The mechanisms underlying these benefits are less clear. Recently, n-3 PUFAs have been found to serve as substrates for the biosynthesis of specialized pro-resolving lipid mediators (SPM) that promote the endogenous resolution of inflammation [18–21]. SPM are primarily derived from the omega (n)-3 fatty acids docosahexaenoic acid (DHA; producing the resolvin D [RvD]-, maresin-, and protectin-series SPM) and eicosapentaenoic acid (EPA, producing the resolvin E [RvE]-series SPM) [22–24]. Preclinical investigations reveal these SPM potently limit inflammatory processes and promote tissue restitution while having immune-stimulatory and protective effects against infection.

Bench studies of DHA as a modulator of lung repair following dust-induced injury have shown positive results. In 2014, Nordgren et al. investigated whether nutritional supplementation of DHA could reduce the airway inflammatory consequences of exposures to organic dust [25••]. Agricultural workers living in areas near a farm site develop respiratory disease due to exposure to a variety of contaminants including organic dust, pesticides, and zoonotic pathogens [26]. Aqueous extracts of organic dusts from swine confinement facilities (hog dust extract or HDE) were utilized. In DHA-pretreated human bronchial epithelial cells (BECs), lung fibroblasts, monocyte cell cultures, and precision-cut murine lung slices, they found that DHA pretreatment dose-dependently decreased HDE-induced inflammatory cytokine production. To determine the in vivo significance of DHA,

C57BL/6 mice were orally administered DHA for 7 days prior to treatment with intranasal HDE or saline inhalations. Animals treated with 2 mg DHA demonstrated significant reductions in HDE-induced bronchial alveolar lavage fluid (BALF) neutrophil influx and pro-inflammatory cytokine/chemokine production compared to mice exposed to HDE alone.

This same group in 2018 explored how DHA, along with epidermal growth factor receptor (EGFR) and amphiregulin (AREG, an EGFR ligand), modulate lung repair processes following dust-induced injury. Primary BEC and BEAS-2B cells were treated with HDE in the presence of DHA and AREG or EGFR inhibitors. Mice were exposed to HDE intranasally with or without EGFR inhibition and DHA. Using a decellularized lung scaffolding tissue repair model, BEC recolonization of human lung scaffolds was analyzed in the context of HDE, DHA, and AREG treatments. In vitro, HDE-induced AREG release from BEC, and DHA treatment following HDE exposure, enhanced this release. Both DHA and AREG also enhanced BEC repair capacities and rescued HDE-induced recellularization deficits. In vivo, DHA treatment enhanced AREG production following HDE exposure, whereas EGFR inhibitor-treated mice exhibited reduced AREG in their lung homogenates [27••]. Taken together, these data indicate a role for n-3 PUFAs in the process of tissue repair after inflammatory lung injury caused by environmental dust exposure and implicate a role for DHA in regulating AREG-mediated repair and signaling mechanisms during lung inflammation. Similar results have been shown in other animal models with respiratory issues related to dust exposure; racehorses with recurrent airway obstruction and inflammatory airway disease that were fed n-3 supplemented diets showed clinical improvement in their symptoms compared to placebo. The group that received n-3 PUFA had greater improvement in clinical signs (cough score improved 60%), lung function (respiratory effort decreased 48%), and BALF (neutrophils decreased from 23 to 9%) when compared to placebo (cough score improved 33%, respiratory effort decreased 27%, BALF neutrophils increased from 11 to 17%; $p < .05$) [28••].

Recently, Nordgren et al. also evaluated the effects of a 4-week dietary DHA consumption on lung inflammation as a result of acute exposure to agricultural dust in mice [29••]. Dietary supplementation of DHA decreased the infiltrating neutrophils, and BALF AREG and MPO. Concurrently, DHA supplementation also resulted in elevated levels of Resolvin-D1, a DHA-derived SPM involved in resolution of acute inflammation [21, 30]. In this acute exposure model, long-term DHA supplementation upregulated genes encoding macrophage surface markers (*ITGAX* gene encoding Cd11c), macrophage polarization (*MARCO*, a scavenger receptor involved in pattern recognition), and airway hyperresponsiveness (*BCL3, CFB*). Another DHA-derived SPM maresin-1 (MaR1) has also been shown to lower airway inflammation induced by exposure to organic dust. Nordgren et al. have investigated whether MaR1 is effective at limiting lung inflammation following acute and repetitive exposures to organic dust. In 2013, they used BEC cell line (BEAS-2B) to determine if treatment with MaR1 reduced inflammation. Cells were pretreated for 1 h with 0–200 nM MaR1, followed by 1–24-h treatment with 5% HDE. They found that MaR1 dose dependently reduced IL-6 and IL-8 production following HDE exposure of BECs. MaR1 also reduced HDE-stimulated cytokine release including TNF-α in a mouse lung slice model when given before or following HDE treatment [31••].

In a follow-up study in 2015, C57Bl/6 mice were treated with MaR1 or vehicle control and intranasally instilled with HDE once or daily for 3 weeks. Bronchioalveolar lavage fluid was analyzed for total and differential cell counts and proinflammatory cytokine levels, and lung tissues were assessed for histopathology and ICAM-1 expression. In both single and repetitive HDE exposure studies, MaR1 significantly decreased bronchoalveolar lavage neutrophil infiltration, IL-6, TNF-α, and chemokine C-X-C motif ligand 1 levels without altering repetitive HDE-induced bronchioalveolar inflammation or lymphoid aggregate formation. Lung tissue ICAM-1 expression was also reduced in both single and repetitive exposure studies [32••, 33••].

Welding industry workers are exposed to welding fumes (WF), and the damage caused by the exposure varies for everyone depending on their health status, diet, and duration of exposure. In a 24-week study by Antonini et al., rats with different generic backgrounds (Fischer-344, SD, and Brown-Norway) were exposed to WF while maintained on a high-fat diet (HFD, 44.6% fat) or regular diet (RD, 6.2% fat) [33••]. At 6 weeks, animals were started on HFD or RD, and at week-7, during diet maintenance groups of rats from each strain were exposed to WF or filtered air until the week 12. Pulmonary responses were measured at 7 weeks (baseline before WF exposure), 12 weeks (directly after WF exposure), and 24 weeks (after a 12-week recovery from WF exposure). At week 24 besides worsened kidney toxicity, specifically SD strain of rats that were on HFD and exposed to WF had increased LDH activity in BALF. This study cautioned on the importance of strain differences when studying the effects of exposures on the resolution of inflammation and recovery.

Another occupational exposure is respirable crystalline silica, which affects 2.3 million US workers as per Occupational Safety & Health Administration. Recently, Gilley et al. investigated the influence of Western diet and addition or replacement of the Western diet with an n-3 PUFA-rich diet in a murine model of crystalline silica ($cSiO_2$)-triggered lupus [34••]. They found that DHA supplementation is effective in protecting against $cSiO_2$-induced cytokine/chemokine release, autoantibody production, and leukocyte infiltration into the lung. Furthermore, addition of the n-3 PUFA to the

Western diet rather than completely avoiding a Western diet was protective against lupus, which is promising because dietary patterns are difficult to change. The same group also reported that the mechanism of action of DHA in inhibiting cSiO2-triggered inflammation through inhibiting inflammasome activation and IL-1 cytokine release in alveolar macrophages in vitro [35••].

These studies support the notion that diets high in n-3 PUFA may be beneficial in inflammatory lung conditions associated with occupational exposures. However, typical Western diets have relatively low n-3 PUFA content and high n-6 PUFA content; this dietary n-6:n-3 PUFA disequilibrium is thought to contribute to increased risk for a variety of inflammatory conditions. An approximate equal balance between n-6 and n-3 fatty acids is considered important for preventing inflammatory diseases. However, a study of n-3 PUFA intakes in a cohort of veterans with agricultural exposures in Nebraska revealed that intakes were very low compared to the Institute of Medicine recommendations. Omega-3 intakes were very low while omega-6 fatty acid levels were increased, with a mean individual n-6:n-3 ratio of 151:1 [36••]. These data highlight both the potential vulnerability of occupational workers in this measure of dietary insufficiency, and the high potential impact of a dietary intervention in these individuals. Additional nutrients may also enhance the effect of n-3 fatty acids; some studies support for a combination of nutrients including omega-3 PUFA, vitamin C, and Zn to be effective in asthma [37].

A systematic review of randomized clinical trials (RCTs) indicated that making inferences from RCTs has been challenging due to the heterogeneity of studies reporting different outcomes in asthma, following different doses and frequency, using different sources of fatty acids and supplements versus dietary interventions, and missing data and insufficient information on asthma or COPD medications [38]. This study suggested that large RCTs using high-dose encapsulated n-3 fatty acids and outcomes using standard inflammatory and respiratory measures reflecting asthma pathology are needed to make firm conclusions on the beneficial effects of n-3 fatty acids

Vitamin D

Vitamin D status, as measured by 25 hydroxyvitamin D (25(OH)D) levels, has been associated with measures of lung function both in the general population and in patients with impaired lung function [39, 40]. In addition to an association with pulmonary function measures, vitamin D could potentially augment anti-inflammatory defenses, and vitamin D supplementation has been associated with reduced concentration of markers of systemic inflammation [41].

Only a few studies have examined if vitamin D's role in pulmonary diseases extend to protection from harmful exposures. One such study examined the effect of vitamin D deficiency and smoking on lung function and lung function decline [42••]. In this study, a total of 626 men from the Normative Aging Study had 25-hydroxyvitamin D levels measured at three different times between 1984 and 2003 with concurrent spirometry. Vitamin D deficiency was defined as serum level ≤ 20 ng/ml. While the analysis did not show a significant effect of vitamin D deficiency on lung function or on lung function decline, there was effect modification by vitamin D status on the association between smoking and lung function in both cross-sectional and longitudinal multivariable models. Cross-sectional analysis revealed lower lung function in current smokers with vitamin D deficiency (FEV_1, FVC, and FEV_1/FVC; $p \leq 0.0002$), and longitudinal analysis showed more rapid rates of decline in FEV_1 ($p = 0.023$) per pack-year of smoking in subjects with vitamin D deficiency as compared with subjects who were vitamin D sufficient. This suggests that vitamin D sufficiency may have a protective effect against the damaging effects of smoking on lung function.

To explore vitamin D in the context of work-related exposures, Golden et al. investigated whether vitamin D reduces organic dust–induced inflammatory outcomes in cell culture and animal models [43••]. Organic dust extracts obtained from swine confinement facilities (i.e., HDE) induced neutrophil chemokine production (human IL-8, murine CXCL1/CXCL2). Neutrophil chemokine induction was then reduced in human blood monocytes, human BECs, and murine lung slices pretreated with 1,25-(OH)2D3. Intranasal inhalation of HDE induced neutrophil influx, and CXCL1/CXCL2 release was also decreased in mice fed a relatively high vitamin D diet as compared to mice fed a low vitamin D diet. Vitamin D treatment led to reductions in neutrophil chemoattractant release from ex vivo HDE-stimulated monocytes, epithelial cells, and lung tissues. Furthermore, high dietary intake of vitamin D resulted in reduced neutrophil influx and neutrophil chemoattractant in mice, which was associated with blunted tracheal epithelial cell PKCα and PKCε activity and modulated whole lung TLR2 and TLR4 expression. This study provides evidence that vitamin D may be an important immunomodulator in organic dust–induced airway responses [43••].

Similar to this study, Dusad et al. investigated whether dietary vitamin D supplementation is protective against lung inflammation and associated bone loss following repetitive exposure to organic dust and LPS [44••]. Mice were put on low and high vitamin D diets for 5 weeks, and then exposed to HDE for 3 weeks. They determined a 10-fold difference in serum 25-OH vitamin D levels between the low and high vitamin D groups with the highest degree of lung inflammation in the low vitamin D group, and lowest bone loss parameters in the high vitamin D group. The lung has its own microbiome [45, 46], and dietary vitamin D has been shown to alter the lung microbiome, which also occurs in COPD [47].

Recently how gut microbiota alone might regulate immunity in the lung has been reviewed [48]. Similar to COPD, accumulating evidence suggests an association between reduced gut microbiome in childhood and development of asthma [49, 50]. This is consistent with the "hygiene hypothesis" that supports early-life exposures to microbial environment in developing microbial diversity and thus a stronger immune system. More studies investigating the effects of micronutrients on lung health and immunity through changes in gut microbiome are needed in work-related lung disease.

Zinc

Zinc is the second most abundant trace element, next to iron, in our bodies and is required for proper immune function and defense against pathogens. Zinc has been shown to be a key ingredient for cellular activation through a variety of signaling pathways. In particular, zinc is a potent modulator of monocyte and macrophage function in response to harmful stimuli through regulation of PKA, PKC C/EBP, NFκB, and MAPK signaling pathways, all of which are associated with regulation of innate immune function [51–53].

About one-half of the world's population consumes diets that are insufficient in zinc and it is conservatively estimated that up to 25% are at risk of zinc deficiency [54]. Disadvantaged populations around the world subsist primarily on low zinc-containing diets due to socioeconomic factors and cereal-based diets, which are high in phytate, a compound that binds zinc and reduces its absorption. The third National Health and Nutrition Examination Survey (NHANES) conducted in the USA found that among adults greater than 60 years old, 35–41% of men and 36–45% of women consumed dietary zinc that is inadequate by current standards [55].

One recent study was conducted to evaluate if insufficient zinc intake can result in enhanced lung inflammation because of exposure to agricultural organic dust [56••]. Adult male C57BL/6 mice were randomized to zinc-deficient or matched zinc-sufficient diets for 3 weeks and subsequently treated with intranasal HDE inhalation or saline once or daily for 3 weeks while maintained on specific diets. Bronchoalveolar lavage fluid and lung tissue were collected. Conditions of zinc deficiency were also studied in macrophages exposed to HDE. Single and repetitive HDE inhalation exposure resulted in increased influx of total cells and neutrophils, increased mediator hyperresponsiveness (TNFα, IL-6, CXCL1, and amphiregulin), and enhanced tissue pathology that was more pronounced in zinc-deficient mice compared to normal dietary counterparts. Airway inflammation was most pronounced in zinc-deficient mice treated with repetitive HDE for 3 weeks. Similarly, macrophages maintained in a zinc-deficient environment exhibited increased CXCL1 and IL-23 production as a result of increased NF-κB activation. This study also collected data from forty-one rural Midwestern veterans with proven agricultural dust exposures and COPD. Consistent with national data, of those forty-one samples, the mean zinc intake was 15 mg per day, and 29% of them had insufficient intake of zinc, resulting in a potential association between decreased lung function and a lower intake of zinc. This study can be seen to show evidence that a modification in one's diet to intake more zinc can become a tactic to counter and prevent lung disease due to agricultural organic dust exposure. Supporting these results, one study showed that insufficient Zn intake results in increased lung injury following prolonged cigarette smoke exposure in mice. Furthermore, they showed that not only insufficiency but any imbalance in Zn homeostasis as shown in experiments with increased and decreased zinc transporter protein, ZIP8 leads to irreversible tissue damage after prolonged cigarette smoke exposure [57••].

Dairy Products

Early life exposure to farming has been associated with protection from allergy and asthma in the adult life [58]. A study evaluated associations between childhood exposure to farming environment and improvement in lung function [59••]. This study included 3061 adults from the Agricultural Lung Health Study (ALHS) (https://aghealth.nih.gov/). Participants of this study included both farmers and their spouses, who completed questionnaires and completed spirometry measurements during home visitations, all of which were collected between 2009 and 2013. One of the common experiences for children living on farms is raw milk consumption, which differs from pasteurized milk due to fatty acid composition and microorganisms [60]. Wyss et al. reported that, 73.4% of people consumed raw milk in their study with 84% of individuals starting before 6 years of age. They found an association between childhood raw milk consumption and higher FEV_1 and FVC, which was much more pronounced in people starting raw milk consumption before the age of 6. Furthermore, this link between the improved pulmonary function and childhood raw milk consumption was more apparent in non-asthmatics than asthmatics among the farmer families [60, 61••]. Several studies found elevated levels of pro-inflammatory cytokines such as interferon gamma in children who consume raw milk, which was associated with stronger immunity [62–65]. A recent meta-analysis found a protective effect of raw farm milk consumption (independent of other exposures in farms) on respiratory symptoms including wheezing, hay fever, atopic sensitization, and allergic rhinitis in children with asthma [66]. Consistent with these findings, Nordgren et al. evaluated the effects of extracellular vesicles (EV) derived from bovine milk as an underlying mechanism of agricultural dust induced lung inflammation [61••]. In this study, increased levels of pro-inflammatory BALF cytokines (IL-6, CXCL-1, and AREG) were consistent with the presence of bovine milk extracellular vesicles when

Table 2 Effects of nutrients on occupational exposure-induced lung outcomes

Nutrient	Exposure	Outcomes affected by the nutrients	Reference
DHA DHA (2 mg for 7 days via oral gavage)	Swine barn dust (acute exposure)	In vitro: Reduced cytokines in human BECs, THP-1 monocytes and murine lung slices in vitro and ex vivo In vivo: Reduced infiltrating neutrophils and BALF cytokines	Nordgren et al. [25•]
DHA DHA diet (5.8 mg/kg, 4-week dietary supplementation)	Swine barn dust (acute exposure)	In vitro: Increased pro-repair cytokine AREG in BECs, and improved recellularization in decellularized lung scaffolding tissue repair model after DHA treatment In vivo: Increased pro-repair cytokine AREG in mice fed the DHA diet for 4 weeks	Nordgren et al. [26]
DHA diet (5.8 mg/kg, 4-week dietary supplementation	Swine barn dust (acute exposure)	Reduced BALF neutrophils, cytokines, increased pro-repair cytokine AREG and DHA-derived SPM Resolvin-D1 in vivo Increased upregulation of genes related to macrophage polarization	Dominguez et al. [29••]
DHA-derived SPM, Maresin-1	Swine barn dust (acute and repetitive exposure)	Reduced BALF neutrophils, cytokines in vivo Reduced IL-6, IL-8 in BECs in vitro	Nordgren et al. [32••]
Diet enriched with extracellular vesicles originating from bovine raw milk, 5–7 weeks	Swine barn dust (acute and repetitive exposure)	Identified an important role for EVs derived from raw milk in regulating overall immune response and macrophage polarization to swine barn dust	Nordgren et al. [61••]
DHA (2.5 to 9.1 mg/kg, 8-week supplementation)	Equine dirt lot dust	Improved clinical scores and reduced BALF neutrophils in racehorses with chronic respiratory disease receiving the n3-PUFA supplements as compared to placebo	Nogradi et al. [28••]
High-fat diet, 24 weeks	Stainless steel welding industry fumes	Worsened renal toxicity and pulmonary outcomes, some strain dependency found	Antonini et al. [33••]
Dietary DHA supplementation, either alone or in addition to Western diet	Respirable crystalline silica	Reduced cSiO2 induced lupus outcomes (leukocyte infiltration, cytokine/chemokine release, autoantibody production, silica induced inflammasome activation)	Gilley et al. [34••] Wierenga et al. [35••]
Dietary n3 supplementation or use of *fat1* transgenic mice	Respirable particulate matter ($PM_{2.5}$)	Reduced lung inflammation	Li et al. [17••]
n6/n3	Respirable particulate matter ($PM_{2.5}$)	N6 fatty acid intake associated with increased asthma severity (reduced FEV1/FVC)	Brigham et al. [13••]
Sorrel extract	Swine barn dust	Reduced ROS, RNS, nitric oxide, 8-isoprostane in normal human bronchial epithelial cells (NHBE)	Gerald et al. [72••]
Vitamin D	Cigarette smoke	Worse pulmonary function (reduced FEV1/FVC) in smokers with vit D deficiency in Normative Aging Study	Lange et al. [42••]
High vitamin D diet, 6 weeks	Swine barn dust	Reduced infiltrating neutrophils and BALF chemokines in mice on high vitamin D diet	Golden et al. [43••]
High vitamin D diet, 5 weeks	Swine barn dust (repetitive exposure) and LPS	Reversal of bone loss in mice on high vit D diet	Dusad et al. [44••]
Zinc-sufficient versus deficient diets	Swine barn dust (single and repetitive exposure)	Enhanced infiltrating neutrophils and cytokine release in zinc-deficient diet as compared to zinc-sufficient diet This study also reported an association between zinc deficiency in US Veterans confirmed to be exposed to agricultural dust and COPD	Knoell et al. [56••]
Zinc-sufficient versus deficient diets	Cigarette smoke	Lung injury in mice fed the zinc-deficient diet	Knoell et al. [57••]

compared to EV-derived bovine milk in vivo following both acute and repetitive exposure of mice to agricultural dust. Also, presence of bovine milk-derived EVs was associated with M1 type pro-inflammatory macrophages, all of which supports for an increased inflammatory response to agricultural dust in the presence of bovine milk EVs.

Antioxidants/Phytonutrients

Phytonutrients are a popular alternative approach to prevent inflammation and oxidative stress [67]. A comprehensive review of the beneficial effects of micronutrients and phytochemicals has been performed in COPD and lung cancer [37, 68, 69], which suggested that intervention with nutrients during early life stages would preserve lung function in the later life stages [69]. Similarly, a Polish study found a significant association between the cord blood concentrations of zinc, copper, selenium, vit A, E, and D and prevalence of allergic rhinitis and asthma in children 7–9 years old, which indicated that maternal diet would have a substantial impact on regulating immunity in the children [70]. Another study evaluating seven systematic reviews [71] found an inverse association between wheezing and dietary intake of vit C, E, and D, fruits, and Mediterranean diet.

The positive association between antioxidant intake and respiratory symptoms applies well to HDE exposure, since it leads to increased pro-inflammatory cytokines, increased recruitment of granulocytes and phagocytosis, and oxidative stress [26, 33••, 72••, 73–76]. A recent study investigated the effect of an extract of sorrel (Hibiscus sabdariffa) calyces, which are rich in antioxidants (polyphenols, anthocyanins, and flavonoids), in normal human bronchial epithelial cells (NHBE) exposed to HDE [72••]. This study identified superoxide, nitric oxide, hydrogen peroxide, ROS (reactive oxygen species), and RNS (reactive nitrogen species) oxidant species to be increased after exposure to 5% HDE in NHBE. Sorrel extract as well as NAC (N-acetyl cysteine), a supplement with mucolytic effects, reduced oxidant generation after HDE exposure. In addition, HDE also increased the levels of 8-isoprostane, which is a biomarker for lipid peroxidation, and it is formed by free radicals reacting with arachidonic acid on lipid membranes. This is of significance because 8-isoprostane levels are reported to increase in asthma, COPD, and chronic bronchitis [77, 78]. Both Sorrel extract and NAC also prevented formation of 8-isoprostane, peroxynitrite, and hydroxyl radical formation in HDE-exposed NHBE cells.

As summarized in Table 2, preclinical and clinical studies discussed here give valuable insights on the effects and mechanisms of occupational exposures on lung health, suggesting tremendous potential of micronutrients in the treatment of such exposures.

Conclusion

Given the heterogeneity of measured outcomes associated with diet and respiratory symptoms, interpreting results from epidemiological studies and making predictions and diet recommendations in the treatment of occupational respiratory disease are challenging. Therefore, there is a need to study to protective effects of dietary and supplemental nutrients on environmental and occupational exposures, as current therapies to slow the chronic progressive inflammation associated with chronic respiratory conditions such as asthma and COPD are limited. Taken together, our findings indicate an important biological role for the protective effect of certain nutrients against inflammation associated with occupational exposures.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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