Vitamins & Minerals

Review Article | **Open Access**

Multivitamin Supplementation Supports Immune Function and Ameliorates Conditions Triggered By Reduced Air Quality

Budi Haryanto[1], Tina Suksmasari[2], Eva Wintergerst[3] and Silvia Maggini[3*]

[1]Department of Environmental Health, Jakarta, Indonesia
[2]Bayer Consumer Care Ltd, Jakarta, Indonesia
[3]Bayer Consumer Care Ltd, Basel, Switzerland

Abstract

Our bodies are normally well protected against continual attack from pathogens and noxious insult by a complex and integrated immune system. However, daily bombardment from indoor and outdoor air pollutants can compromise immune function and ultimately lead to infection (e.g. acute respiratory tract infections, diarrhoea) and conditions such as sick building syndrome (with mucosal, skin and general symptoms). All of us may be affected by reduced air quality, although certain factors increase the risk of impaired immunity (e.g. young or advancing age, exposure to tobacco smoke, close proximity to areas of high air pollution, office work, commuting). A major exogenous factor modulating immune function is nutrition; even subclinical deficiencies in various nutrients can have adverse effects on the immune system, which may be exacerbated by environmental threats. In particular, the oxidant-antioxidant balance (vital for communication within the immune system) may be affected. Dietary supplementation can help to restore immune function to the normal range, and an antioxidant-containing multivitamin supplement has been shown to ameliorate the symptoms of sick building syndrome, acute respiratory tract infections and diarrhoea. This review looks at the impact of reduced air quality on the oxidant-antioxidant balance and the role of selected micronutrients (vitamins A, D, E, C, B6, B12, folate and the trace elements copper, iron, selenium and zinc) and multivitamin supplementation.

Keywords: Acute respiratory tract function; Air quality; Diarrhea; Immune function; Micronutrients; Multivitamin supplementation; Nutrition; Sick building syndrome

Introduction

From the moment we are born and throughout every day of our lives, our bodies are under attack from pathogens and noxious insults. Fortunately, our immune systems are usually well equipped to fend off most assaults and can recognize, repel and eradicate pathogens and other foreign molecules to combat infection and protect against damage [1-3]. From birth, the physical barriers of the innate (non-specific) immune system (e.g. skin, mucus secretions, stomach acidity) help to protect against invasion from infectious agents. If any pathogens manage to bypass these defences, or if cells are damaged by noxious insults, innate immunity triggers the process of inflammation. Invading pathogens are differentiated from host cells by non-cellular components with recognition molecules (i.e. C-reactive protein, serum amyloid protein, mannose-binding protein, complement). Chemical mediators (e.g. histamine, prostaglandins, bradykinin) are released to initiate vasodilation and increase blood flow, which manifests as redness and increased heat. Some inflammatory mediators (e.g. prostaglandins, bradykinin) increase sensitivity to pain. The permeability of the blood vessels increases to allow exudation of plasma fluid and proteins into damaged tissue, where it collects and causes swelling. Leukotrienes and cytokines (e.g. interleukins (IL), tumour-necrosis factor (TNF)) attract phagocytic innate immune cells (i.e. monocytes, macrophages, neutrophils, dendritic cells) to the site of infection or injury, where they phagocytize the pathogens or dead or damaged cells and control infection. Phagocytosis stimulates various cellular processes including the 'respiratory burst', in which an increase in oxygen uptake is initiated (resulting in the production of potent oxidant bactericidal agents hypochlorous acid and hydroxyl radical), and reactive oxygen or nitrogen species (ROS or RNS) (i.e. free radicals such as superoxide anion, hydrogen peroxide, nitric oxide) are rapidly released [4-6]. ROS are also generated during chemotactic locomotion and microbicidal activity as part of the physiological function of cells involved in host defence [3].

If the innate immune system is unable to clear the infection in a short time, adaptive (specific or acquired) immunity takes over. Extravasated plasma fluid is funnelled by lymphatics to the regional lymph nodes, flushing pathogens along to start the recognition and attack phase; T- and B-cells work together to recognize and form antibodies against antigens on the invading pathogen that identify it as a foreign body. The activities of T-helper cells in particular are considered to be of utmost importance and guarantee an adequate and efficient immune response [7]. There are two types of T-helper cells, type 1 (TH1) and type 2 (TH2), both of which contain the protein marker CD4+ on their surface. This enables them to send signals to surface protein markers on other immune cells, such as CD8+ on cytotoxic T-cells, natural killer (NK) cells or dendritic (antigen-presenting) cells. Following elimination of the pathogen, many of the T- and B-cells die through apoptosis, but some remain as memory cells to help the immune system activate much faster following a second exposure to the same antigen or after immunization.

The complex network of specialized tissues, organs, cells and chemicals that make up the immune system relies on communication to function effectively. Communication within adaptive immunity, and between the innate and adaptive systems, is dependent on direct cell-to-cell interactions (e.g. T- and B-cells) as well as on the production of chemical messengers (e.g. TNF and cytokines such as IL and interferon (IFN)). The oxidant-antioxidant balance is an important factor in cell communication [8]. For example, ROS are essential for activation of several signalling pathways, modulate gene expression and are released into the cytoplasm in response to ligand-receptor interactions on the

membranes of immune cells to regulate the biosynthesis of antibodies or cytokines [6,9]. At high concentrations, however, ROS can mediate damage to cell structures by attacking and denaturing structural and functional molecules (e.g. lipids (particularly polyunsaturated fatty acids), proteins, carbohydrates, nucleic acids, nitric oxide, etc.) and by modulating the activities of redox-sensitive signal transduction pathways, for example [10,11]. Therefore, endogenous antioxidants (with input from co-factors) and ingestion of exogenous antioxidants are necessary to decrease the concentration of ROS by donating an electron to the ROS and generating a more stable species [10,12]. This helps to restore cell signalling to a steady state8 and to protect the cells against damage [10,13]. If the presence of ROS exceeds the protective effects of the body's antioxidant defence system (e.g. because of a decrease in antioxidant status or an increase in the concentration of ROS), 'oxidative stress' occurs where the excess oxidants are free to attack other cell components [14,15].

Immune cells are particularly sensitive to changes in the oxidant-antioxidant balance as they contain a high percentage of polyunsaturated fatty acids in their plasma membranes, which are more susceptible to lipid peroxidation by ROS and generate more ROS in the process [9]. Oxidative damage can compromise the integrity of immune cell membranes, altering membrane fluidity and altering the transmission of signals both within and between different immune cells [16]. Thus, the production of ROS by phagocytic immune cells can damage the cells themselves if they are not sufficiently protected by antioxidants, and oxidative damage can result in alterations in the transmission of signals both within and between different immune cells [17]. Interference with the signalling system is deleterious and results in an impaired immune response [3]. Therefore, adequate amounts of neutralizing antioxidants are required to prevent damage to the immune cells and maintain normal immunity [17].

Immune function is influenced by a variety of different factors including age, nutrition, and genetic as well as environmental factors [18]. Many environmental or lifestyle-related factors can temporarily or permanently move specific immune function(s) outside the normal range, thus failing to support optimal health [18]. If this is sustained or becomes more extreme, it may contribute to pathogenic processes and modify disease risk [18]. Air pollution is a major problem, particularly in developing countries, and contributes towards 7 million premature deaths each year [19]. Air pollution can increase the risk of acute respiratory tract infection (ARTI), [20,21] and 14% of air pollution-related deaths are due to lung or respiratory diseases [21]. Contamination of water sources via pollution can lead to diarrhoea [20,22]. An underlying feature of the toxic effects of air pollutants is oxidative stress [11,14,23-30]. Oxidative stress is also associated with indoor air pollution and sick building syndrome (SBS) [31-36]. SBS consists of a group of mucosal, skin, and general symptoms that are temporally related to working in particular buildings [37]. Indoor air pollution can also cause building-related illness, which includes infectious diseases spread from the building services, such as Legionnaires' disease, and diseases spread from worker to worker within a building, such as viral infections [37,38]. It also includes any toxic reactions to chemicals used within the building, or derived from fungi growing within a building [37,38].

The purpose of this review is to look at factors that negatively affect immune function, with a particular focus on reduced air quality and its impact on health, as well as the immune mechanisms that may be affected. The role of nutrition in immunity will also be examined, with specific reference to the mechanisms affected by air pollution, as well as the benefits of micronutrient supplementation in general and in

ameliorating any adverse effects that may arise as a result of reduced air quality.

Factors Influencing Immune Function

Nutritional status is one of the major exogenous factors modulating different aspects of immune function, and essential micronutrients work in synergy to serve as cofactors in the development, maintenance and expression of the immune response [16,18,39-42]. Undernutrition (including deficiencies in specific micronutrients) can suppress immune functions that are fundamental to protect the host from infectious agents (e.g. bacteria, viruses, fungi, parasites) and other noxious insults (e.g. from chemical pollutants) that exist in the environment [39,43,44]. Table 1 [3,16] summarizes the most important roles of selected micronutrients in immune function.

Throughout life, the immune system is influenced by age [45-47]. At birth, the newborn relies on its own innate immune system and on passive protection (i.e. maternal colostrum and milk, maternal antibodies) [48,49]. The immunologic competence of the newborn progresses rapidly and the acquired immune system gains antigenic experience, which is essential to drive maturation and expansion of cells throughout the whole of the immune system. Microbial antigens play a vital role in the education of the immune system and represent an important factor in predisposition to allergic, inflammatory and autoimmune diseases in later life [48-51]. In healthy adults with a mature immune system, the main determinants of immune competence are lifestyle-related factors such as diet, stress, sleeping habits, sedentary lifestyle, excessive exercise, frequent travelling, pollution, smoking and alcohol abuse [39]. In the elderly, immune dysregulation begins to occur such that cell-mediated immune responses decrease while antibody responses remain relatively preserved. As a result, there is a greater risk of infection in aged individuals, who are 2–10 times more likely to die of infection than their younger counterparts [16]. Innate immunity appears to be less affected by the ageing process, but there is a longer inflammatory process in the elderly [52-54].

The immune system is normally regulated within boundaries specific to each person, but this can be disrupted by external factors [18]. Unfortunately, in today's society we are regularly exposed to environmental and lifestyle factors that can move specific immune functions outside the normal range, thus failing to support optimal health (Figure 1) [18]. If this is sustained or becomes more extreme, it may contribute to an increased risk of disease [18]. For instance, one of the most widespread environmental threats is from reduced air quality as a result of indoor or outdoor air pollution, [20,21] resulting in exposure to higher concentrations of ROS which cannot be managed by the antioxidant defence mechanisms [55]. The subsequent increase in oxidative stress can impair the immune response and, for example, give rise to inflammatory [11,23,24] and respiratory symptoms and decreased resistance to respiratory infections [56,57]. There may also be an increased risk of infection if there is a greater exposure to pathogens, such as in those who spend a prolonged amount of time in close proximity to other people (e.g. frequent travellers, [58-60] office workers [61, 62]), particularly if immune function is suboptimal because of an inadequate diet [39,40,43,44,63].

Pollution, Immune Function and Health

The quality of the air that we breathe and the water that we drink influences our health in many ways through exposure to various physical, chemical and biological risk factors that can directly initiate, facilitate or exacerbate the pathological immune process [11,14,27,29,64-67]. Reductions in air and water quality are major risk factors for disease

Trace elements			
Micronutrient	Roles in immune function	Effects of deficiency	Effects of supplementation
Vitamins			
A	• Important for innate, cell-mediated immunity and antibody response, supporting Th2 anti-inflammatory response • Crucial in development and differentiation of Th1 and Th2 cells • Normal differentiation of epithelial tissue and gene expression • Retinoic acid is essential to imprint T-cells and B-cells with gut-homing specificity, and thus to array T-cells and IgA+ cells into intestinal tissues	• Impairs innate immunity, induces inflammation, potentiates existing inflammatory conditions, impairs defences against pathogens • Evokes an excessive proinflammatory response with impaired ability to defend against extracellular pathogens (increased susceptibility to infection due to impaired regeneration of epithelial mucosal barriers) • Associated with a diminished phagocytic and respiratory burst of macrophages, and a reduced NK cell activity, increased production of IL-12 and TNFα, and a decrease in antigen-specific response (DTH, antibody production, Th1 response)	• Reduces the morbidity and mortality from infectious diseases (especially in children in developing countries) and improves antibody response to vaccinations • Down-regulates IFNγ, TNFα, enhances IL-4, IL-5, IL-I0 secretion, and improves antibody titre response to vaccines (Th2 response) • Excessive intakes suppress T-cell functions (down-regulation of nuclear receptors for vitamin A, decrease in transcription and expression of cytokines, antigen-specific antibody production) with increased susceptibility to infectious pathogens
D	• Potent immunomodulator in the form of 1,25(OH)2D3 • Most cells of the immune system except B-cells express vitamin D receptors • Involved in cell proliferation • Enhances innate immunity by increasing the differentiation of monocytes to macrophages	• Correlates with higher susceptibility to infections due to an impaired localized innate immunity and defects in antigen-specific cellular immune response (diminished DTH) • Correlates with an increased risk of autoimmune diseases • $1,25(OH)_2D_3$ inhibits maturation of dendritic cells (down-regulation of IL-12, up-regulation of IL-10, inhibition of antigen-presenting capacity), reducing capacity to induce T-cell proliferation and cytokine production, supporting a Th2 response	• In those with autoimmune disorders, supplementation with $1,25(OH)_2D_3$ together with a high calcium diet exerts an inhibitory effect on the progression of the disease (suppression of Th1 response, promoting Th2 response)
E	• Most important fat-soluble antioxidant • Potent chain-breaking antioxidant, protecting cell membranes from oxidative damage • Enhances T-cell-mediated functions, lymphocyte proliferation, IL-2 production and NK cell cytotoxic activity • Decreases production of the immunosuppressive factor PGE2 • Optimizes and enhances Th1 and suppresses a Th2 response	• In rare cases of vitamin E deficiency in humans, impaired T-cell function and DTH test were reported	• In healthy adults, significantly increased T-cell proliferation, improved the CD4+/CD8+ ratio, and decreased parameters of oxidative stress • Results in increased resistance to infection • In elderly individuals, improved overall immune function by altering the age-associated anti-inflammatory Th2 response (impaired IL-2; DTH, T-cell proliferation; increased IL-4 and IL-6) to a proinflammatory Th1 response (increased IL-2, decreased expression of IL-4, shift to greater proportion of antigen-experienced memory T-cells)
C	• Effective antioxidant contributing to the maintenance of the redox integrity of cells and protection against ROS generated during respiratory burst and inflammatory response • Regenerates other antioxidants (e.g. vitamin E) • Stimulates leukocyte functions (movement of neutrophils, monocytes) • Role in antimicrobial and NK cell activities, lymphocyte proliferation, chemotaxis and delayed-type hypersensitivity response • Supports integrity of epithelial barrier by promoting collagen synthesis	• Deficiency is associated with decreased of resistance to disease • Impaired leukocyte functions, decreased overall NK cell activity and lymphocyte proliferation • Rapid decline in plasma and leukocytes during stress and infection • Low vitamin C concentrations in elderly predictive of all-cause and cardiovascular disease mortality	• High supplemental intakes stimulate phagocytic and T-cell activity • Improves antimicrobial and NK cell activity, chemotaxis, lymphocyte proliferation, and DTH response (Th1 response) • Decreases duration/severity of common cold • Reduces incidence of common cold and pneumonia in subjects engaged in strenuous exercise or who live in crowded situations
B6	• Interferes with immune function through involvement in nucleic acid and protein biosynthesis together with vitamin B12 and folate • Adequate intake maintains a Th1 immune response	• Deficiency in humans is accompanied by a suppression of a Th1 response and promotion of a Th2 response (decreased lymphocyte growth and proliferation, decreased NK cell activity, decrease in antibody response (DTH), and decrease in proinflammatory cytokines IL-1β IL-2, IL-2 receptor)	• Reverses the immune response (Th1 response); required intakes to obtain optimal lymphocyte proliferation may be higher than the current recommended daily allowance • High intravenous doses of pyridoxal phosphate may be beneficial in the treatment of patients with autoimmunity and HIV
B12	• Interferes with immune function through involvement in nucleic acid and protein biosynthesis together with vitamin B6 and B12 • May act as an immunomodulator for cellular immunity, especially with effects on cytotoxic cells (NK; CD8+ T-cells)	• Suppresses NK cell activity, decreases number of lymphocytes and CD8+ cells and proportion of CD4+ cells leading to an abnormally high CD4+/CD8+ ratio	• Effects of deficiency could be restored by injection of methyl vitamin B12
Folate	• Interferes with immune function through involvement in nucleic acid and protein biosynthesis together with vitamin B12 and folate • Maintains innate immunity (NK cell activity)	• Causes an impaired immune response and resistance to infections (reduction in circulating lymphocytes. decreased proliferation; increased CD4+/CD8+ ratio, decreased DTH, and NK cell activity) (impaired Th1 response) • The reduction in CD8+ cell proliferation may be related to the finding of an increased carcinogenesis due to reduced cytotoxic activity	• Supplementation of elderly individuals improves overall immune function by altering the age-associated decrease in NK cell activity (impaired killing of virus-infected cells and tumour cells) supporting a Th1 response providing protection against infections • Very large intakes of folic acid have been shown to possibly impair NK cell cytotoxicity

Trace elements			
Micronutrient	**Roles in immune function**	**Effects of deficiency**	**Effects of supplementation**
Selenium	• Key role in redox regulation and antioxidant function through glutathione peroxidases by removing excess of potentially damaging radicals produced during oxidative stress • Essential for optimum immune response: influences both innate and acquired immunity	• Decreases immunoglobulin titres and aspects of cell-mediated immunity • Causes viruses to undergo mutations to more virulent forms	• Counteracts decreases in immunoglobulin titres and cell-mediated immunity • In adults with marginal status: enhanced the cellular immune response (increased IFNγ production, Th1 response), had a more rapid clearance of an orally given poliovirus, lower numbers of mutations • In healthy subjects: augmented T-cell-mediated immune response, enhanced proliferation, increased response to antigen stimulation, increased cytotoxic and NK cell activity, increased IFNγ (Th1 response) • In the elderly: restores the age-related defect in cell proliferation (NK cell and cytotoxic activity), preventing an increased susceptibility to inflammatory and malignant disease • Suppresses progression of HIV-1 viral burden and improves CD4 counts
Zinc	• Required for optimal functioning of both innate and acquired immunity • Is involved in the cytosolic defence against oxidative stress • Essential cofactor for thymulin which modulates cytokine release and induces proliferation • Adequate intake supports a Th1 response • Helps to maintain skin and mucosal membrane integrity • Unbound zinc ions exert a direct antiviral effect on rhinovirus replication	• Causes increased oxidative stress with higher susceptibility to oxidative DNA damage • Impairs phagocytosis of macrophages and neutrophils, NK cell activity, generation of the respiratory burst and complement activity by suppression of Th1 response (decreased IFNγ and IL-2, impaired NK cell activity, reduction in macrophage functions (e.g. phagocytosis, intracellular killing, generation of respiratory burst, chemotaxis), reduction in cytolytic T-cell activity, decreased DTH), with unaffected Th2 response • Leads to increased susceptibility to infections, especially during childhood • Causes thymus involution, depresses lymphocytes proliferation, Th1 cytokines production, DTH skin responses and antibody response	• Increases cellular mediators of innate immunity (e.g. phagocytosis of macrophages and neutrophils, NK cell activity, generation of respiratory burst, DTH activity), antibody response, and increased numbers of cytotoxic CD8+ T cells (Th1 response) • Supplementation of elderly individuals improves impaired immune function by reversing the age-associated decrease in NK cell activity (impaired killing of virus-infected cells and tumour cells) supporting a Th1 response providing protection against infections • Can suppress IFNγ production and T-cell functions, and decrease expression of anti-apoptotic factors, stimulating apoptosis • Reduces the risk and duration of pneumonia in children, and is beneficial in the management of infantile diarrhoea • May help to reduce the incidence of infections (i.e. common cold, cold sores and flu) and pneumonia and associated morbidity in the elderly • Could prevent age-related degenerative diseases in the elderly such as cancer, atherosclerosis, dementia and Alzheimer's disease
Iron	• Essential for cell differentiation and growth, component of enzymes critical for functioning of immune cells (e.g. ribonucleotide reductase involved in DNA synthesis; myeloperoxidase involved in killing bacteria by neutrophils) • Involved in the regulation of cytokine production and action • Involved in the killing process of bacteria by neutrophils through the formation of highly toxic hydroxyl radicals	• Impairs secretion of cytokines (IFNγ, TNFα, IL-2) and reduces NK cell activity, T-cell proliferation, DTH response, impairs bactericidal macrophage activity, causes a reduction in the ratio of CD4+/CD8+ with relative expansion of CD8+ cells, and a small decrease in IL-10, indicating that deficiency affects both innate and cell-mediated immunity (suppression of a Th1 response, limited decline in Th2 response) • Th1 cell subsets are more sensitive to deficiency than Th2 cell subsets due to the lower expression of surface transferrin receptors and a smaller iron pool • Changes in cellular iron homeostasis to deficiency (or overload) have unfavourable functional consequences on the immune system	• There is little evidence that oral iron supplementation to deficient subjects inhibits immune response or increases susceptibility to most infections, possibly with the exception of HIV, malaria-related diseases and pneumonia
Copper	• Part of Cu/Zn-superoxide dismutase, a key enzyme in the defence against ROS • Maintains intracellular antioxidant balance, suggesting an important role in inflammatory response • Important role in the innate immune response (macrophages, neutrophils and monocytes), changes in homeostasis are a crucial component of respiratory burst	• Limited data in humans due to copper's efficient homeostatic regulation and lack of appropriate parameters to determine status • In those with marginally-adequate intake, decrease in T-cell proliferation and increase in circulating B-cells, but little effect on serum IL-2 receptor concentration, on neutrophil phagocytic activity or on NK cell activity • No increase in tshe incidence of infections during low intake	• Adequate intake supports a Th1 response and both deficiency and excessive intake modulate the immune response • Long-term high intake in healthy adults significantly reduced the percentage of circulating neutrophils, serum IL-2 receptor, and antibody titre against the Beijing strain of influenza, and enhanced the average inflammatory response (IL-6); no pro-oxidant effect was observed, and high intake protected red blood cells against in vitro-induced peroxidation

DTH: Delayed-Type Hypersensitivity; IL: Interleukin; IFN: Interferon; NK: Natural Killer; PGE2: Prostaglandin E2; ROS: Reactive Oxygen Species; TNFα: Tumour-Necrosis Factor-Alpha.

Table 1: Most important roles of micronutrients in immune function and effects of deficiency and supplementation [3,16].
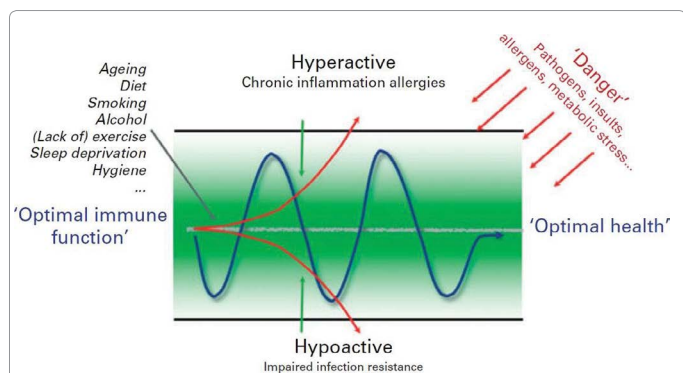
Figure 1: Fluctuations in immune function within the boundaries of a normal range help to maintain optimal health18 [41].
Immune function usually varies between subjects and fluctuate within subjects over time (blue arrow), although apparently within normal limits (green zone) that may be individually defined. Certain factors either alone or in combination can drive immune function to a state of hypo- or hyperactivity (red arrows).

burden and mortality [68]. Around 7 million premature deaths each year (1 in every 8 deaths [69]) can be attributed to the effects of urban outdoor air pollution and indoor air pollution (caused by the burning of solid fuels) [19]. The World Health Organization (WHO) has determined that unsafe water, sanitation and hygiene, indoor smoke from solid fuels and urban outdoor air pollution are among the top 19 risk factors worldwide contributing to disease burden and death [68]. Residents in fast-growing cities of the developing world in particular may be exposed to their combined health hazards [20]. The main perils of air pollution are lung and respiratory infections, which contribute towards 10.7% of the disease burden globally [20] – and more than 50% in the populations of developing countries [21] – and are responsible for 14% of deaths worldwide [21]. Diarrhoea is a disease with the largest environmental contribution (mostly attributed to water, sanitation and hygiene), accounting for an estimated 94% of all cases of diarrhoea worldwide; globally, such diarrhoeal diseases comprise 16.4% of the disease burden and are responsible for 12.8% of deaths [20]. The environmental burden per capita of diarrhoeal diseases and lower respiratory infections is 120- to 150-times greater in certain WHO developing regions (e.g. parts of Africa, China, India, Pakistan) compared to developed regions (e.g. USA, western Europe), mainly as a result of variations in exposure to environmental risks and in access to healthcare [20].

Although most of the burden of disease from indoor air pollution is related to the use of solid fuels for cooking and heating, [70] health problems can also arise in people spending a lot of time indoors. People in the industrialized world spend about 90% of their life indoors, mostly at home, and the working population spends an average of 20% of the time at work [71]. The indoor environment of modern buildings may be affected by the occupants, their activities, equipment, plants, furnishings, building materials, ventilation systems and outdoor air pollution [38]. Thus, many of us may be exposed to poor indoor air quality that can lead to conditions such as the so-called 'sick building syndrome' (SBS), where inadequate ventilation, for example, may increase exposure to pollutants, or to 'building-related illnesses' (BRI) such as those caused by viral infections, toxic chemicals or fungi within a building [37,72].

Outdoor Air Pollution

Contamination of the outdoor (or indoor) environment by any chemical, physical or biological agent that modifies the natural characteristics of the atmosphere is regarded as air pollution [21]. During the last century, economic and industrial growth led to a massive increase in emissions of air pollutants in a large number of European and North American countries and made air quality an environmental problem of the first order that is now an emerging problem in other developing regions of the world [28]. Air pollution is currently the world's largest single environmental health risk, and 3.7 million premature deaths were attributed to outdoor air pollution in 2012 [19]– the greatest number of which occurred in the WHO Western Pacific and South-East Asia regions [73]. The vast majority of deaths were related to ischaemic heart disease and strokes (80%), but also to chronic obstructive pulmonary disease (COPD), acute lower respiratory infections (14%) or lung cancer (6%) [73]. The impact of outdoor air pollution on health is associated with high economic costs. For example, in Europe, the year 2000 annual health-related external costs caused by air pollution from European emissions were estimated to be €766 billion [74]. In China, where air pollution emissions have increased compared to many parts of the world, the health-related cost of outdoor air pollution in 2005 was thought to be as high as 3.8% of GDP [75] (US $85,789 million). In Jakarta, Indonesia (one of the world's megacities), the health-related cost of air pollution in 1989 was US $220 million [76] – a cost that should be equally applicable today as Jakarta is one of the most polluted cities in the world [77]. Air pollution in Mexico City also continues to represent a severe environmental problem, despite environmental programs over the last 20 years that have improved air quality [78]. In Sao Paulo, Brazil, 4,655 people died in 2011 as a result of air pollution; in that same time period, traffic fatalities accounted for 1,556 deaths [79]. During that year, pollution contributed to over twice as many deaths than both AIDS (874) and breast cancer (1,277) combined. Air pollution particulates in Sao Paulo average 20–25 $\mu g/m^3$ – over twice what is deemed safe by WHO [80]. Across the entire state of Sao Paulo, air pollution has been cited as responsible for the deaths of nearly 100,000 people from 2006 to 2011 from respiratory illness. As more cars are added to the road, and likewise more people move into the dense urban centres, that number is likely to raise – both in Brazil and throughout the world.

One of the major factors contributing to mortality associated with outdoor air pollution is exposure to small particulate matter (PM) of 10 microns or less in diameter (PM_{10}), which can cause respiratory symptoms and adverse cardiovascular effects (Table 2) [73]. Despite a global improvement in PM_{10} levels in recent years, the average urban resident is still exposed to annual concentrations that exceed WHO guidelines [80,81]. Other key air pollutants include ozone (O_3), nitrogen dioxide (NO_2) and sulphur dioxide (SO_2) [73]. The exact combination of these pollutants varies from one microenvironment to another, [14] but all are associated with health effects, particularly respiratory symptoms (Table 2) [82]. In addition, heavy metals (e.g. lead, arsenic, cadmium) from burning of fossil fuels, in pesticides, mining, construction work, tobacco smoke, etc. can be released into the air and into nearby ground water sources, resulting in acute respiratory tract infections (ARTI) if inhaled and diarrhoea if ingested [83]. In the European Union, around 40 million people in the largest cities are exposed to poor air quality with at least one pollutant exceeding WHO guidelines [84].

The main sources of air pollutants in both developed and developing countries include road traffic, small-scale manufacturers and other industries, burning of biomass and coal for cooking and heating, as well as coal-fired power plants [85]. Residential wood and coal burning for heat is also an important contributor to outdoor air pollution, especially during the colder months in rural areas [85]. Air pollutants from vehicles are a particular problem in all global cities with over 100,000

Pollutant	Effects related to short-term exposure	Effects related to long-term exposure
Particulate matter	• Lung inflammatory reactions • Respiratory symptoms • Adverse effects on the cardiovascular system • Increase in medication usage • Increase in hospital admissions • Increase in mortality	• Increase in lower respiratory symptoms • Reduction in lung function in children • Increase in chronic obstructive pulmonary disease • Reduction in lung function in adults • Reduction in life expectancy, owing mainly to cardiopulmonary mortality and probably to lung cancer
Ozone	• Adverse effects on pulmonary function • Lung inflammatory reactions • Adverse effects on respiratory symptoms • Increase in medication usage • Increase in hospital admissions • Increase in mortality	• Reduction in lung function development
Nitrogen dioxide [a]	• Effects on pulmonary function, particularly in asthmatics • Increase in airway allergic inflammatory reactions • Increase in hospital admissions • Increase in mortality	• Reduction in lung function • Increased probability of respiratory symptoms

[a]In outdoor air, nitrogen dioxide serves as an indicator for a complex mixture of mainly traffic-related air pollution

Table 2: Important health effects associated with exposure to air pollutants [82].

inhabitants, and emissions in Mexico, India, China and Indonesia are the highest in the world, more than double in countries such as Australia, USA, Germany and Russia [86]. Over the next few decades to 2050, it has been projected that most of the world's population will be subjected to degradation in air quality (based on the presence of $PM_{2.5}$, NO_2, SO_2, O_3 and carbon monoxide); in India, Bangladesh and China, the degradation of air quality is expected to be almost twice as high as the global increase [87].

One of the major underlying features of the toxic effects of air pollutants is oxidative stress, caused either by an imbalance of pro-oxidant and antioxidant processes linked to increased exposure to the air pollutants, or by the presence of impaired antioxidant defences [11,14,23-30]. Most air pollutants are themselves free radicals (e.g. NO_2, transition metals) or have the ability to initiate the production of free radicals (e.g. O_3, PM) [11,14,24,25,27-29]. They can therefore lead to oxidative stress in the lungs, participate in the induction of inflammation, [88] trigger redox-sensitive signalling pathways [14,64] and impair antigen presentation – making the body more susceptible to both allergic and infectious diseases [55].

An individual's sensitivity to air pollution is related in part to their endogenous pulmonary antioxidant defences against both the primary oxidant challenge and the second wave of oxidative stress [14]. The composition and quantity of antioxidants in the respiratory tract lining fluid (RTLF) may represent an important determinant of individual responsiveness to air pollutants [89]. The susceptibility of the lung to oxidative injury depends largely on its ability to up-regulate protective ROS-scavenging systems, and the speed at which lost antioxidant defences can be replaced is a major determinant [90]. The synergy of endogenous and exogenous antioxidants, which might neutralize free radicals, also plays a key role in the protection against the development of inflammation of the respiratory passage [55].

Indoor Air Pollution

Solid fuels (i.e. wood, charcoal, coal, dung, crop wastes) burnt on open fires or traditional fires are used by around 3 billion people worldwide to cook and heat their homes, often with little ventilation [91]. This method of cooking and heating is inefficient and produces high levels of indoor air pollution [92,93]. The WHO estimated that in poorly ventilated dwellings, smoke in and around the home can exceed acceptable levels for fine particles, for example, 100-fold [91]. In addition to cooking/heating with solid fuels, other sources of indoor pollution that occur worldwide include tobacco combustion, volatile

organic compounds (VOCs) and biological factors (e.g. mould) from furnishings, household products, moist areas, etc., pesticides coming in from outside and radon gas from the ground under a building, for example [70].

Epidemiological studies have linked exposure to indoor air pollution from dirty fuels with at least four major categories of illness such as acute respiratory tract infections (ARTI) in children, chronic obstructive pulmonary disease (COPD), lung cancer and pregnancy related problems [91,92]. Accordingly, 4.3 million people a year died from the exposure to household air pollution in 2012 [94]. Almost all occurred in low and middle income countries, with the South East Asian and Western Pacific regions bearing most of the burden (1.69 and 1.62 million deaths, respectively); in contrast, 99,000 people died in Europe [94]. It is estimated that the overall disease burden associated with indoor air pollution exceeds that from outdoor air pollution five-fold [95]. ARTI are the leading cause of disease burden worldwide, causally linked to pollutants from domestic biomass fuels in developing countries [96]. Because of their customary involvement in cooking, women and young children in developing countries spend a lot of their time indoors near the domestic hearth, often with little ventilation, and so are particularly at risk of disease resulting from indoor air pollution [70,91,92,96,97]. However, the absolute burden of disease is larger in men due to larger underlying disease rates in men [94]. Evidence suggests that indoor air pollution mainly caused by burning of biomass fuel can increase oxidative stress and impair several immune functions in the respiratory tract [31,93,98-103].

Sick Building Syndrome

Most people at work (or home) occasionally feel unwell because they have a headache, blocked nose or sore eyes, for example. But in some buildings, people may experience these common symptoms more often than is usual, and for no obvious reason. The symptoms tend to increase in severity with time spent in the building and usually disappear away from the building [104]. If at least 20% of occupants report health symptoms and discomfort associated with staying in a building, but no definitive cause can be identified, the building is termed a 'sick building' [105]. The non-specific mucosal, skin and general symptoms that are temporally related to working or living in a sick building comprise the 'sick building syndrome' (SBS) [37]. The most common symptom of SBS is a general feeling of tiredness or lethargy (affecting 57% of sufferers), while the most common mucous membrane symptom is nasal congestion, affecting 47% of sufferers [106]. Dry (27%) and itchy eyes (28%) are the least prevalent mucous

membrane symptoms, [106] but can cause particular problems in those wearing contact lenses, who may not be able to use them throughout the day [37]. Other symptoms include dry throat (46% of sufferers), headache (43%), runny nose (23%), flu (23%) and difficulty breathing (9%) [106]. All symptoms should improve within a few hours of leaving a sick building apart from dryness of the skin, which may take a few days to improve [37].

Although there is not a single, specific cause of SBS, and risk factors causally associated with SBS remain debatable, there are a number of factors that appear to be related to its increased prevalence [37]. A recent analysis determined that poor lighting, poor ventilation, lack of sunlight, absence of air currents, high noise, high temperature, humidity, environmental tobacco smoke, use of photocopiers, poor job satisfaction and inadequate office cleaning were statistically associated with SBS symptoms [107]. Poor ventilation in particular is a major factor, [107] and buildings with natural ventilation were found to have lower symptom rates than those with mechanical systems that used chillers and humidifiers [88,106]. Insufficient ventilation in offices may cause indoor air pollutants to accumulate gradually [32]. Studies have indicated that both carbon dioxide (CO_2) and VOCs are the major air pollutants resulting from insufficient ventilation in offices [32]. Lower ventilation rates also increase the residence time of indoor airborne pollutants and promote gas phase chemistry [108]. Higher concentrations of VOCs, bacteria and moulds have been found in buildings with low ventilation, [109] while inadequate cleaning led to higher dust levels [110] – both situations can affect the upper airways and cause swelling of the nasal mucosa [109,110]. Another major factor for SBS is a high indoor temperature, [107] which increases the rate at which most indoor chemical processes occur, as well as the emission rate of certain chemicals that participate in these processes [108]. The circumstances that favour chemical reactions among indoor pollutants have increased markedly in the last half-century (e.g. greater ozone levels, decrease in ventilation rates as the cost of energy has risen) [108].

SBS is increasingly a major occupational hazard; [111] for example, in 1980 only 6% of the total requests made to the US National Institute for Occupational Health and Safety (NIOSH) were to evaluate office environments with regard to SBS; since 1992, such requests made up 75% of all requests [112]. In severe cases of SBS, symptoms can affect attitudes to work and may represent a significant cost to business in the form of reduced staff efficiency, increased absenteeism and staff turnover, extended breaks and reduced overtime, lost time complaining and dealing with complaints, and decreased productivity [111,113]. In the late 1990s in the USA, financial benefits gained from improving indoor air quality and reducing SBS symptoms, and thus increasing work productivity, were estimated to be between $10 to $30 billion [114,115].

There is little data on the pathogenesis of SBS. However at any given time, indoor air contains a wide array of pollutants (e.g. ozone, VOCs, terpene, exposure to CO_2) that can react to generate short-lived, highly reactive compounds such as hydroxyl, hydroperoxy and nitrate radicals [108]. Current evidence indicates that the symptoms of SBS – as with outdoor air pollution – are likely to be associated with oxidative stress and that certain conditions such as poor ventilation or lighting or the presence of VOCs or CO_2 can increase the risk of oxidative stress and therefore increase the likelihood of SBS and associated symptoms [32-34,36,116].

Who is Most at Risk?

Pollution is a major environmental health problem affecting everyone [21]. Nevertheless, the degree of sensitivity to pollutants is different for each individual, depending on age, health condition, genetic and lifestyle factors [55]. The immune system is particularly vulnerable to chemical exposure during development in young children; function peaks at around puberty [117] and gradually declines with age, [118] resulting in increased risk of adverse health outcomes from exposure to chemicals in air pollution at the extremes of age [25,119]. Defence against pathogens is compromised mainly because of age-related changes in adaptive immunity mediated by T and B lymphocytes; however, all components of the immune system are affected [118]. Older individuals are more sensitive to infections than younger adults and are frequently classified as being particularly susceptible to air pollution [25]. Oxidative stress from gaseous air pollutants such as O_3 and NO_2 may be a particular problem in the elderly, as these oxidants can cause injury to the delicate cells in the respiratory tract lining fluid (RTLF); small molecular weight antioxidant defences present in RTLF represent the first line of defence against a range of oxidants that enter the lung [25]. As several RTLF antioxidants are of dietary origin, the elderly, who often have different dietary patterns to younger individuals, may have decreased availability of important antioxidants [25]. In general, nutritional factors play a major role in the immune responses in elderly people and nutritional influences on immune responses are of great consequence in aged individuals, even in the very healthy elderly [52].

There is also a link between air pollution and the severity of illness associated with respiratory infection; thus individuals with pre-existing lung disease may be at greater risk [120]. As might be supposed, living near to areas of high pollution (e.g. in cities or industrial areas) is significantly associated with poor health outcomes such as asthma and reduced lung function, particularly in children [121-123]. Frequent travelling can also increase exposure to air pollution, particularly when travelling by car and bike [77,124]. Smoking is a major risk factor, and is associated with higher concentrations of 8-OHdG (a marker of oxidative stress to DNA) compared with non-smokers – partly the result of the thousands of chemicals in tobacco smoke, including ROS, and partly due to oxidative stress as a result of poor indoor air quality [32,125]. Smoking also reduces the concentration of the antioxidant vitamin C in the body, [126,127] partly due to a higher metabolic turnover of ascorbic acid compared to non-smokers [128-130]. Reductions in plasma ascorbic acid have been observed in heavy smokers, but also those regularly exposed to passive smoking [131]. Significantly lower serum levels of vitamin C were seen in children with a high or low exposure to environmental tobacco smoke [132]. It has been demonstrated that low plasma concentrations of vitamin C can significantly increase the risk of obstructive airways disease (OAD) [133]. The risk of developing OAD in current smokers within the lowest quintile of plasma vitamin C concentration was almost six times greater compared to never smokers; this risk decreased with increasing vitamin C concentration [133]. Office workers may also be at risk of adverse health effects resulting from reduced air quality at work, particularly those who are feeling stressed, unloved or powerless to change their situation [134-136]. Finally, a poor nutrient status can also exacerbate the adverse risks of air pollution. In particular, a diet deficient in direct antioxidants (e.g. vitamins C and E) or components of antioxidant enzymes (e.g. copper, zinc, selenium) may increase the effects of oxidative stress [15].

Certain environments may also increase the transmission of pathogens and consequently the risk of developing an infection. For example, travelling in a train or an airplane, where people are in prolonged and close proximity to each other, may increase the risk of infections such as cold, flu or gastroenteritis [58-60]. The diet may also be adversely affected by frequent travelling, which can impact immune

Citation: Haryanto B, Suksmasari T, Wintergerst E, Maggini S (2015) Multivitamin Supplementation Supports Immune Function and Ameliorates Conditions Triggered By Reduced Air Quality. Vitam Miner 3: 128.

Page 8 of 15

function [16]. In the workplace, microorganisms may be spread in a number of ways, such as contact, droplet, airborne or vector-borne (i.e. insect) transmission. Therefore, office workers are also at increased risk of infections such as the common cold, respiratory infections, sinus and middle ear infections, tonsillitis, etc [61,62]. This may be of particular concern in workers whose immune function may be suboptimal, such as those with an insufficient diet [39,40,43,44,63].

Micronutrients, Immune Function and Pollution

In addition to the beneficial effects of micronutrients on immune function in general, which help to maintain immune functions within the normal range, [16,39] certain micronutrients are also vital to protect against oxidative stress. They play an essential role in the antioxidant defence system, either as direct antioxidants (vitamins C and E) or as components of antioxidant enzymes: SOD (e.g. copper, zinc) or glutathione peroxidase (selenium) [15]. The synergy of endogenous and exogenous antioxidants plays a key role in the protection against the development of inflammation of the respiratory passage and aggravation of asthma and ARTI caused by air pollutants, for example [55].

Vitamin E is a lipid-soluble, radical-scavenging antioxidant that is present in all cellular membranes [137,138] and can act directly with a variety of oxy radicals, including the peroxyl, hydroxyl and superoxide radicals [138]. The α-tocopherol form of vitamin E protects cell membranes from oxidation by reacting with lipid radicals produced in the lipid peroxidation chain reaction [139,140]. This removes the free radical intermediates and prevents the propagation reaction from continuing; in doing so, oxidised α-tocopheroxyl radicals are produced that can be recycled back to the active reduced form through reduction by other antioxidants, such as vitamin C [141]. As a potent peroxyl radical scavenger, vitamin E especially protects polyunsaturated fatty acids within the phospholipid biological membrane and in plasma lipoproteins [142]. Thus it can help to protect immune cells in particular, which contain a high percentage of polyunsaturated fatty acids in their plasma membranes. It also decreases production of prostaglandin E2, which is produced by lipid peroxidation of lung cells after O_3 exposure [143]. Vitamin E appears to have a major role as an integral constituent of alveolar surfactant, whose quantity and composition affects lung function [144].

Vitamin C is a water-soluble free radical scavenger [137,138]. Intracellular vitamin C can prevent protein oxidation and regulate gene expression and mRNA translation, which is particularly relevant for the lungs as they are exposed to oxidative substances [24]. Extracellular vitamin C protects against oxidants and oxidant-mediated damage, [145] and contributes to antioxidant activity in vitro by scavenging a variety of free radicals and oxidants, including the superoxide and peroxyl radicals, hydrogen peroxide, hypochlorous acid, oxidant air pollutants and oxidants that leak from activated neutrophils and macrophages [89,145]. Zinc has been shown to have antioxidant activity in vitro and in vivo (cofactor of SOD; binding and stabilization of protein thiols) and is involved in the cytosolic defence against oxidative stress caused by ROS produced and released by activated macrophages [3]. Zinc has a stabilising effect on membranes, possibly by displacing bound transition metal ions and thereby preventing peroxidation of membrane lipids [146]. The antioxidant effect of selenium is mediated through glutathione peroxidases that remove an excess of potentially damaging lipid hydroperoxides, hydrogen peroxide and peroxinitrite produced during oxidative stress [3,138]. Thus, selenium plays an important role in redox regulation, contributes to membrane integrity and protection against DNA damage, and helps to protect the host from

oxidative stress generated by the microbicidal effects of macrophages and during inflammatory reactions [3]. Copper (along with zinc) is a component of the enzyme SOD, which works with catalase and glutathione peroxidases in the antioxidant defence against ROS; the enzyme is essential in the dismutation of superoxide anion to oxygen and hydrogen peroxide, and diminishes damage to lipids, proteins and DNA [3].

In the lungs, both the extracellular compartment (RTLF) and the intracellular components are well endowed with antioxidant defences, which are the first-line of defence against ROS [24]. Vitamins C and E, SOD and glutathione peroxidase act as free-radical scavengers, while vitamin C also functions as a sacrificial target for O_3, for example, reacting rapidly with this oxidant to limit its interaction with RTLF lipids and proteins [90]. Thus, antioxidants are essential to protect the respiratory system against damage from free radicals generated by air pollution and increase resistance to infection.

When nutrition is inadequate, immune function may be compromised particularly in those who may already be at risk of impaired immunity (e.g. children, the elderly, smokers, etc.) [40,52,90]. For example, micronutrient deficiency can impair innate, cell-mediated and adaptive immunity, induce inflammation and potentiate existing inflammation, diminish phagocytic and respiratory burst of macrophages, reduce NK cell activity, alter the production of cytokines (e.g. IL-12, TNFα, IFNγ), reduce lymphocyte growth, proliferation and activity, and decrease antigen-specific responses (Table 1) [3,16]. Such changes lead to dysregulation of the balanced host response, which can increase susceptibility to infections; in turn, infections aggravate micronutrient deficiencies by reducing nutrient intake, increasing losses, and interfering with utilization by altering metabolic pathways [147]. These changes may be particularly important in individuals with a greater exposure to pathogens, such as frequent travellers or those in close contact with fellow workers (e.g. such as in open-plan offices) [58,148].

Benefits of Micronutrient Supplementation

A sufficient and balanced diet should cover daily micronutrient requirements [16]. However, many people both in developing and industrialized countries do not get adequate amounts of essential micronutrients through the diet; in such cases, micronutrient supplementation may be necessary [16]. Various animal and human studies have shown that adding the deficient nutrient back to the diet can restore immune function to the normal range (Table 1) and increase resistance to infection [39]. It is now widely believed that diet-derived antioxidants play a role in the prevention of human disease [15]. Thus, maintaining adequate antioxidant status may provide a useful approach in attenuating the cellular injury and dysfunction observed in some inflammatory disorders [5]. In children, supplementation can represent a valid method to support nutrition, especially in developing regions [149]. Table 1 outlines some of the general benefits that micronutrient supplementation can confer to the immune system [3,16]. Among its other benefits on the immune system, there is evidence to suggest that the negative physiological and functional impact of air pollution may be modulated by dietary supplementation [24,26,35,90,150]. Boosting the plasma concentrations of antioxidants above the normal range could have a protective effect on the respiratory system, if this strategy resulted in augmented RTLF antioxidant concentrations [90]. For example, vitamin C and E supplementation above the minimum dietary requirement in asthmatic children with a low intake of vitamin E provided some protection against the nasal acute inflammatory response to O_3 and alleviated oxidative stress associated with

photochemical oxidant pollution [26]. Antioxidants such as vitamin C act as powerful scavengers of O_3 and NO_2 radicals in body fluids and are likely to protect lung lining fluids against inhaled oxidizing air pollutants [151]. In non-smoking healthy adults, for example, dietary supplementation including the vitamins C and E protected against O_3-induced pulmonary function decrements [152]. Although there was no apparent effect on the severity of the inflammation provoked by O_3 exposure, the exposure parameters used could have been inadequate to induce sufficient pulmonary inflammation for detection of a protective effect of antioxidant supplementation [152]. It was concluded that antioxidant supplementation may represent a safe and effective strategy with which to decrease pulmonary function responses to this common air pollutant [152]. Supplementation with vitamin C may also be beneficial in smokers and could have a protective role in the aetiology of OAD, acting as an important effect modifier of smoking on the risk of OAD [133]. It is thought that vitamin C supplementation may reduce the risk of OAD from smoking, particularly in those who have the lowest levels of plasma vitamin C [133]. A recent systematic review of the evidence determined that antioxidants (vitamin C and E were most often studied) can partially attenuate the negative effects of air pollutants (usually O_3), with modulation of the pollutant-induced airway hyper-responsiveness and diminution in lung function [150]. In people chronically exposed to arsenic in drinking water who were supplemented with vitamin E and selenium, there was a trend towards a greater decrease in protein carbonyl levels (a marker of oxidative damage) compared with placebo [153].

Thus, the evidence indicates that supplementation with micronutrients, and antioxidants in particular, have an important role in the restoration of the immune system and in the management of conditions associated with poor air quality. With this in mind, a community design trial was conducted in Jakarta, Indonesia to investigate the effects of a tailored multivitamin supplement containing several antioxidants (Table 3) in workers exposed to poor air quality. Poor air quality is a fact of life in Jakarta, [154] which is among the most populated and polluted cities in the world [77].

The study was conducted to investigate the effects of intervention with a multivitamin supplement containing antioxidants (Table 3) on the frequency of SBS, ARTI and diarrhoea in employees in Jakarta, Indonesia. The study was supported by Bayer Indonesia [155]. Eighteen companies were chosen to participate in this community design trial. Of these, 11 companies were randomly assigned to the intervention group, while seven formed the control group. Twenty employees were randomly selected from each company; those in the intervention group consumed a once-daily multivitamin supplement (Redoxon Vita Immune, Bayer Consumer Care; Table 3) for 3 months, while the control group received no intervention during this time. A placebo was not used in the non-intervention group because the companies were in a different location and the subjects were unaware that there was an intervention group. Further study details can be found in Table 4. Patient demographics were recorded before the start of treatment. During the 3-month follow-up, the presence of any symptoms of SBS (e.g. headache, watery eyes, nasal congestion, throat irritation, dry cough, dry and itchy skin, dizziness, sickness, fatigue, inability to concentrate, sensitivity to smell), ARTI (cough, cold or flu) and diarrhoea (soft and watery stool >3 times/day) were documented using an ordinal Yes/No scale. Antioxidant intake from food was quantitatively and qualitatively assessed at the start and the end of the 3-month follow-up using a 24 h recall and standard food frequency questionnaire (FFQ).

Data were available for 350 subjects; 212 received the multivitamin supplement and 138 formed the control group. Overall, demographic characteristics and behaviors of company employees, and the source and the risk of exposure in the working places, in Jakarta were not different among those who consumed or not the multivitamin supplement every day for 3 months. However, some differences were found with regard to age (greater in the control group, p=0.002), body weight (greater in the control group, p=0.002), education (higher level of education in the control group, p=0.004), house location (a greater number lived in a house in the control group, p=0.02), type of company (more subjects worked in a private company in the control group, while a greater number worked in a government capacity in the intervention group, p=0.02), perception of a bad smell at work (recorded by more subjects in the control group, p=0.04) and noise (recorded by more subjects in the control group p=0.006). More than half of the subjects in each group travelled to work via motorcycle or car. Most subjects overall had insufficient food intake at the start (75.7%) and the end of study (71.1%), including insufficient consumption of vitamin C (76.9% and 77.9%, respectively) and zinc (96.9% and 74.9%); however, there were no significant differences between the groups in the amount of antioxidants consumed from food. The risk of suffering illness was greater in the intervention group than the control group, with a significantly greater exposure to a photocopying machine (p=0.002), laser printer (p=0.0003), a plastic or wooden screen/curtain (p=0.0002) and a production machine (p=0.0003).

At the end of the study, there was a significantly lower risk of

Active ingredients	Effervescent tablet (1 tablet/day)	Recommended dietary allowance [a]	Tolerable upper intake level [b]
Vitamins			
Vitamin C, mg	1000	75	2000
Vitamin E, mg	45	15	1000
Vitamin A, µg	700	700	3000
Vitamin D, µg	10	15	100
Vitamin B6, mg	6.5	1.3	100
Folate, µg	400	400	1000
Vitamin B12, µg	9.6	2.4	ND
Trace elements			
Selenium, µg	110	55	400
Zinc, mg	10	8	40
Copper, mg	0.9	0.9	10
Iron, mg	5	18	45

[a,b]US Institute of Medicine Dietary Reference Intakes 1997-2011 (women, 19–50 yr) [157,158]; ND: Not Determined (no data to identify risk).

Table 3: Composition of Redoxon Vita Immune (Bayer Consumer Care).

Study date	Jun 2008–Jan 2009
Location	Jakarta, Indonesia
Randomization method	A total of 18 companies were randomly divided into two groups; 11 companies were assigned to the case group and seven were assigned to the control group. Each company contained 20 purposefully-selected respondents
Inclusion criteria	Adults (18+ years), otherwise no specific inclusion criteria
Exclusion criteria	No exclusion criteria
Patient consent	Written informed consent was provided after a clear explanation of the study aims and before treatment allocation
Ethics approval committee	Ethical clearance was gained after revisions from the Institute for Health Research and Development at the Ministry of Health, Indonesia
Intervention	Redoxon Vita Immune (Bayer Consumer Care), one effervescent tablet per day for 90 continuous days
Statistical analysis	Descriptive statistics (univariate analysis), T-test, linear regression, ordered logit regression

Table 4: Summary of study protocol details.

Symptom	Respondents (%)		P-value[*]
	With antioxidant (n=212)	Without antioxidant (n=138)	
Headache			
Yes	18.9	37.0	0.0003
No	81.1	63.0	
Sore eyes			
Yes	17.4	31.9	0.001
No	82.6	68.1	
Nasal congestion			
Yes	14.6	30.4	0.0004
No	85.4	69.6	
Throat inflammation			
Yes	16.9	23.2	0.005
No	83.1	76.8	
Dry cough			
Yes	16.0	23.2	0.05
No	84.0	76.8	
Skin irritation			
Yes	15.1	13.8	0.30
No	84.9	86.2	
Dizziness			
Yes	19.3	29.7	0.05
No	80.7	70.3	
Sickness			
Yes	15.6	13.0	0.07
No	84.4	87.0	
Lack of concentration			
Yes	16.0	14.5	0.10
No	84.0	85.5	
Tired/pain			
Yes	19.3	32.6	0.003
No	80.7	67.4	
Sensitive to smell			
Yes	7.6	10.9	0.08
No	92.4	89.1	

[*]P-value of the linear regression calculation to differentiate numeric independent variables by group.

Table 5: Proportion of employees in Jakarta, Indonesia, reporting symptoms associated with sick building syndrome after daily consumption of a multivitamin supplement containing antioxidants for 3 months.

developing many symptoms associated with SBS after supplementation compared with no intervention, with significantly fewer subjects reporting headache, sore eyes, nasal congestion, throat inflammation and tiredness/pain in particular (Table 5). For example, the proportion of subjects who reported nasal congestion was 51.9% lower in the supplementation group compared with no intervention (Figure 2).

In addition, a significantly smaller proportion of subjects who consumed the multivitamin supplement reported symptoms of ARTI and diarrhoea over 3 months (Table 6). For example, the proportion of subjects who reported diarrhoea or cough was 64.4% and 46.2% lower, respectively, in the supplementation group compared with no intervention (Figure 3).

The risk of developing symptoms of SBS and ARTI is associated with prolonged contact with environmental factors that act as vehicles for
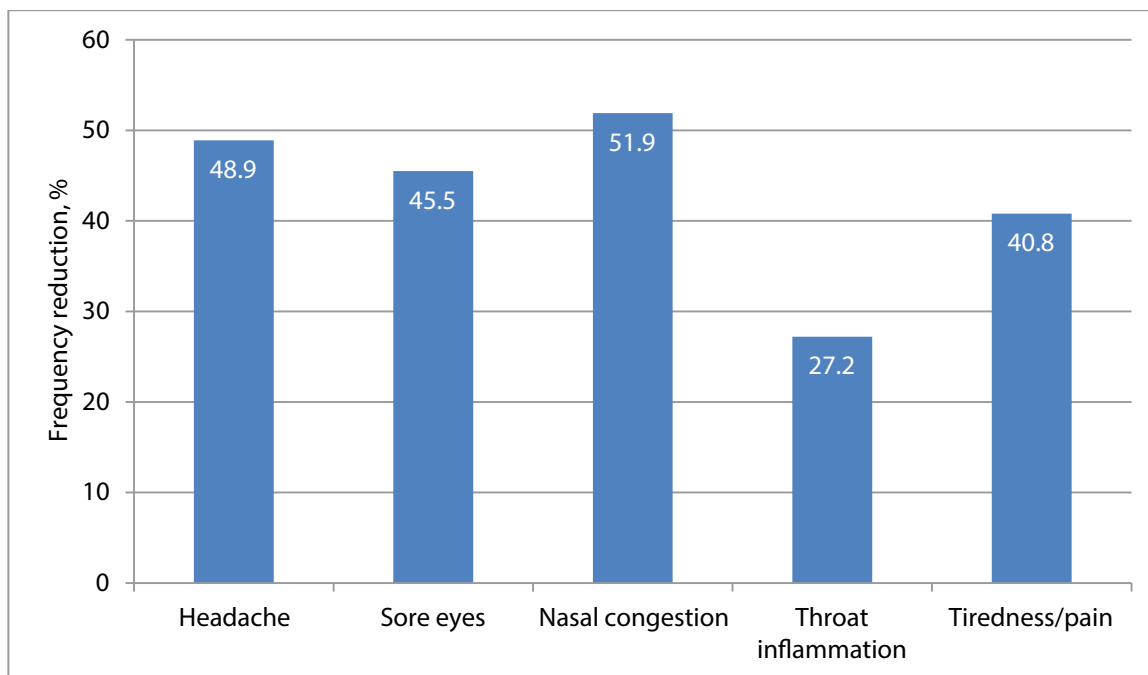
Figure 2: Intervention with a multivitamin supplement containing antioxidants for 3 months reduces symptoms associated with sick building syndrome compared with no intervention in employees in Jakarta, Indonesia.

Symptoms	Respondents (%)		P-value*
	With antioxidant (n=212)	Without antioxidant (n=138)	
ARTI			
Cough			
Yes	26.9	50.0	0.0001
No	73.1	50.0	
Cold			
Yes	30.2	50.0	0.0002
No	69.8	50.0	
Flu			
Yes	24.5	38.4	0.01
No	75.5	61.6	
Diarrhoea			
Yes	11.8	33.3	0.0004
No	88.2	66.7	

*P-value of the linear regression calculation to differentiate numeric independent variables by group.
Table 6: Proportion of employees in Jakarta, Indonesia, reporting symptoms of acute respiratory tract syndrome (ARTI) or diarrhoea after daily consumption of a multivitamin supplement containing antioxidants for 3 months.

physical, chemical, biological and radiation pollutants [32,73,82,107]. The employees in this study were in contact with certain risk factors (e.g. photocopying machines, cloth printing equipment, use of screens or curtains, etc.) for at least 8 hours per day and consequently were at an increased of illness. It should also be noted that most respondents in the study had an insufficient intake of energy, vitamin C and zinc from food at baseline. This insufficiency is likely to impair immunity and thus increase the risk of developing disease [40,52,90]. A potential limitation of the study is that the multivitamin supplement consumed is a well-known brand that is readily available OTC. Therefore, the intervention group would have already been familiar with its potential health benefits – or even in some cases, its perceived lack of efficacy – which could have biased the results. Thus, a placebo-controlled study would

be useful to confirm these promising results. In addition, it would have been useful in this study to also evaluate the urinary 8-OHdG levels, for example, to evaluate whether antioxidant supplementation ameliorated the effects of oxidative stress. Nevertheless, the results of this study confirm that micronutrient supplementation including antioxidants can significantly reduce the symptoms of SBS, ARTI and diarrhoea in employees exposed to the habitual levels of pollution experienced in a big city such as Jakarta. The potential impact on employees' long-term health as well as the economic impact on their work performance deserves further investigation.

Conclusions

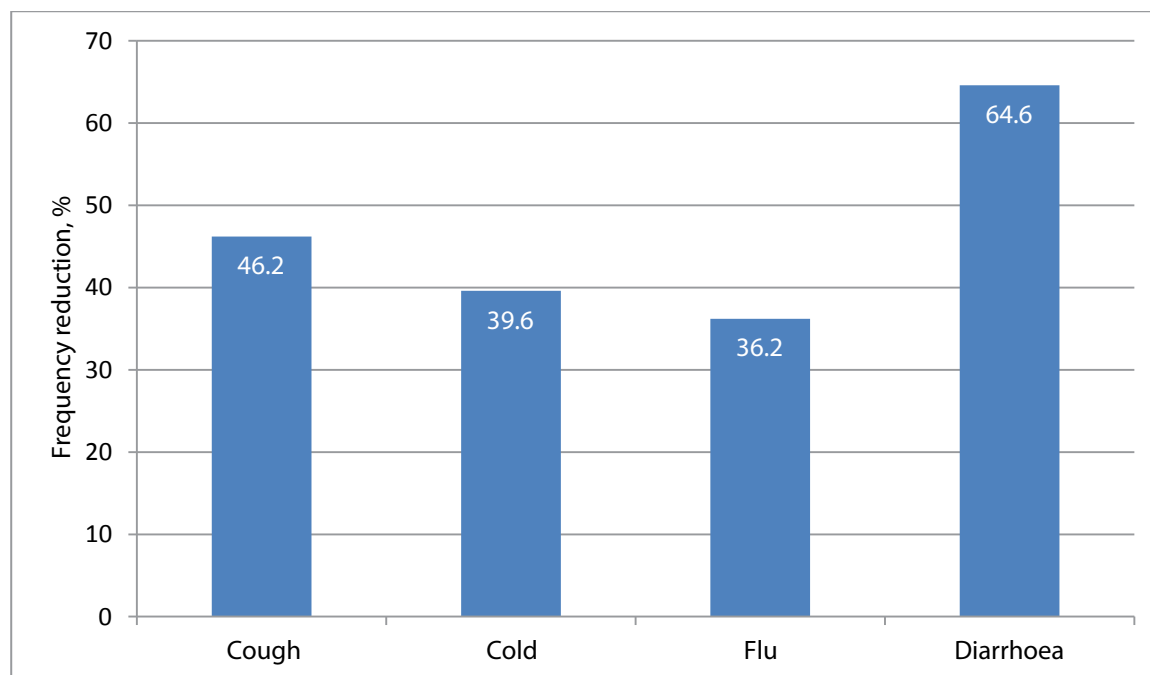Air pollution is a major problem, particularly in developing

Figure 3: Intervention with a multivitamin supplement containing antioxidants for 3 months reduces symptoms associated with acute respiratory tract infections and diarrhoea compared with no intervention in employees in Jakarta, Indonesia.

countries, and contributes towards 7 million premature deaths each year [19]. Air pollution can increase the risk of ARTI, and 14% of air pollution-related deaths are due to lung or respiratory diseases [21]. Evidence suggests that dietary supplementation may moderate the acute effects of air pollutants [24] and increase resistance to infection [39]. Nutritional status can determine a person's susceptibility to the oxidative stress-related effects of air pollution, [156] as insufficient intake of antioxidants upsets the oxidant-antioxidant balance further in favour of ROS, with a resulting increase in oxidative stress [43]. Furthermore, even relatively mild nutritional deficiencies can alter immunocompetence and increase the risk of infection and inflammation [40,63].

Acknowledgements

Conflicts Of Interest

References

1. Parkin J, Cohen B (2001) An overview of the immune system. Lancet 357: 1777-1789.

2. Goldman L, Schafer AI (2011) The innate and adaptive immune systems, Cecil Medicine (24thedn.) Elsevier, Philadelphia.

3. Wintergerst ES, Maggini S, Hornig DH (2007) Contribution of selected vitamins and trace elements to immune function. Nutr Metab 51: 301-323.

4. Babior BM (1984) The respiratory burst of phagocytes. J Clin Invest 73: 599-601.

5. Conner EM, Grisham MB (1996) Inflammation, free radicals, and antioxidants. Nutrition 12: 274-277.

6. Knight JA (2000) Review: free radicals, antioxidants, and the immune system. Ann Clin Lab Sci 30: 145-158.

7. Berger A (2000) Th1 and Th2 responses: what are they?. BMJ 321: 424.

8. Forman HJ, Torres M, Fukuto J (2002) Redox signaling. Mol Cell Biochem 234: 49-62.

9. Meydani SN, Wu D, Santos MS, Hayek MG (1995) Antioxidants and immune response in aged persons: overview of present evidence. Am J Clin Nutr 62: 1462S-1476S.

10. Rahman K (2007) Studies on free radicals, anti-oxidants and co-factors. Clin Interven Aging 2: 219-236.

11. Delfino RJ, Staimer N, Vaziri ND (2011) Air pollution and circulating biomarkers of oxidative stress. Air Qual Atmos Health 4: 37-52.

12. Adly AAM (2010) Oxidative stress and disease: an updated review. Res J Immunol 3: 129-145.

13. Halliwell B (1996) Antioxidants in human health and disease. Annu Rev Nutr 16: 33-50.

14. Kelly F (2003) Oxidative stress: its role in air pollution and adverse health effects. Occup Environ Med 60: 612-616.

15. Evans P, Halliwell B (2001) Micronutrients: oxidant/antioxidant status. Br J Nutr 85: S67-S74.

16. Maggini S, Beveridge S, Sorbara PJP, Senatore G (2000) Feeding the immune system: the role of micronutrients in restoring resistance to infections. CAB Reviews: Perspectives in Agricaulture, Veterinary Science, Nutrition and Natural Resources 3: 1-21.

17. Hughes DA (2000) Dietary antioxidants and immune function. Nutrition Bulletin 25: 35-41.

18. Albers R, Bourdet-Sicard R, Braun D, Calder PC, Herz U, et al. (2013) Monitoring immune modulation by nutrition in the general population: identifying and substantiating effects on human health. Br J Nutr 2013; 110: S1-S30.

19. (2014) 7 million deaths annually linked to air pollution, World Health Organization.

20. Pruss-Ustun A, Corvalan C (2006) Preventing disease through healthy environments. Towards an estimate of the environmental burden of disease. World Health Organization.

21. (2014) Air pollution, World Health Organization.

22. (2014) Water sanitation health: burden of disease and cost-effectiveness estimates, World Health Organization.

23. Chuang KJ, Chan CC, Su TC, Lee CT, Tang CS (2007) The effect of urban air pollution on inflammation, oxidative stress, coagulation, and autonomic dysfunction in young adults. Am J Respir Crit Care Med 176: 370-376.

24. Romieu I, Castro-Giner F, Kunzli N, Sunyer J (2008) Air pollution, oxidative stress and dietary supplementation: a review. Eur Resp J 31: 179-197.

25. Kelly FJ, Dunster C, Mudway I (2003) Air pollution and the elderly: oxidant/antioxidant issues worth consideration. Eur Resp J 21: 70s-75s.

26. Sienra-Monge JJ, Ramirez-Aguilar M, Moreno-Macias H, Reyes-Ruiz NI, Del Río-Navarro BE, et al. (2004) Antioxidant supplementation and nasal inflammatory responses among young asthmatics exposed to high levels of ozone. Clin Exp Immunol 138: 317-322.

27. Moller P, Loft S (2010) Oxidative damage to DNA and lipids as biomarkers of exposure to air pollution. Environ Health Perspect 118: 1126-1136.

28. D'Amato G, Baena-Cagnani CE, Cecchi L, Annesi-Maesano I, Nunes C, et al. (2013) Climate change, air pollution and extreme events leading to increasing prevalence of allergic respiratory diseases. Multidiscip Respir Med 8: 12.

29. Auerbach A, Hernandez ML (2012) The effect of environmental oxidative stress on airway inflammation. Curr Opin Alllergy Clin Immunol 12: 133-139.

30. Liu L, Poon R, Chen L, Frescura AM, Montuschi P, et al. (2009) Acute effects of air pollution on pulmonary function, airway inflammation, and oxidative stress in asthmatic children. Environ Health Perspect 117: 668-674.

31. Repine JE, Bast A, Lankhorst I (1997) Oxidative stress in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1997 156: 341-357.

32. Lu CY, Ma YC, Lin JM, Li CY, Lin RS (2007) Oxidative stress associated with indoor air pollution and sick building syndrome-related symptoms among office workers in Taiwan. Inhalation Toxicol 19: 57-65.

33. Jung CC, Liang HH, Lee HL, Hsu NY, Su HJ (2014) Allostatic load model associated with indoor environmental quality and sick building syndrome among office workers. PLoS ONE 9: e95791.

34. Lu CY, Ma YC, Lin JM, Chuang CY, Sung FC (2007) Oxidative DNA damage estimated by urinary 8-hydroxydeoxyguanosine and indoor air pollution among non-smoking office employees. Environment Res 103: 331-337.

35. Hope J (2013) A review of the mechanism of injury and treatment approaches for illness resulting from exposure to water-damaged buildings, mold, and mycotoxins, Scientific World Journal 2013.

36. Bernstein JA, Alexis N, Bacchus H, Bernstein IL, Fritz P, et al. (2008) The health effects of nonindustrial indoor air pollution. J Allergy Clin Immunol 121: 585-591.

37. Burge P (2004) Sick building syndrome. Occup Environ Med 61: 185-190.

38. Sabir M, Shashikiran U, Kochar SK (1999) Building related illnesses and indoor air pollution. J Assoc Physicians India 47: 426-430.

39. Calder PC, Kew S (2002) The immune system: a target for functional foods?. Br J Nutr 88: S165-S176.

40. Chandra RK (1997) Nutrition and the immune system: an introduction. Am J Clin Nutr 66: 460S-463S.

41. Hamer M, Wolvers D, Albers R (2004) Using stress models to evaluate immuno-modulating effects of nutritional intervention in healthy individuals. J Am Coll Nutr 23: 637-646.

42. Field CJ, Johnson IR, Schley PD (2002) Nutrients and their role in host resistance to infection. J Leukocyte Biol 71: 16-32.

43. Beck MA (2000) Nutritionally induced oxidative stress: effect on viral disease. Am J Clin Nutr 71: 1676s-1681s.

44. Katona P, Katona-Apte J (2008) The interaction between nutrition and infection. Clin Infect Dis 46: 1582-1588.

45. Albers R, Antoine JM, Bourdet-Sicard R, Calder PC, Gleeson M, et al. (2005) Markers to measure immunomodulation in human nutrition intervention studies. Br J Nutr 94: 452-481.

46. Knight JA (2000) The biochemistry of aging. Adv Clin Chem 35: 1-62.

47. Chandra RK (2002) Nutrition and the immune system from birth to old age. Eur J Clin Nutr 56(Suppl 3): S73-S76.

48. Calder PC, Krauss-Etschmann S, de Jong EC, Dupont C, Frick JS, et al. (2006) Early nutrition and immunity - progress and perspectives. Br J Nutr 96: 774-790.

49. Morein B, Blomqvist G, Hu K (2007) Immune responsiveness in the neonatal period. J Comp Pathol 137(Suppl 1): S27-S31.

50. West LJ (2002) Defining critical windows in the development of the human immune system. Hum Exp Toxicol 21: 499-505.

51. Jonsdottir I (2007) Maturation of mucosal immune responses and influence of maternal antibodies. J Comp Pathol 137(Suppl 1): S20-S26.

52. Lesourd B, Mazari L (1999) Nutrition and immunity in the elderly. Proc Nutr Soc 58: 685-695.

53. Lesourd B (1999) Immune response during disease and recovery in the elderly. Proc Nutr Soc 58: 85-98.

54. Castle S (2000) Clinical relevance of age-related immune dysfunction. Clin Infect Dis 31: 578-585.

55. Majkowska-Wojciechowska B, Kowalski ML (2012) Allergens, air pollutants and immune system function in the era of global warming. In: Mukesh Khare (ed.) Air Pollution - Monitoring, Modelling, Health and Control.

56. (2013) Review of evidence on health aspects of air pollution - REVIHAAP Project, World Health Organization, Europe.

57. (2013) Air quality in Europe - 2013 report, European Environment Agency.

58. Furuya H (2007) Risk of transmission of airborne infection during train commute based on mathematical model. Environ Health Prev Med 12: 78-83.

59. Mangili A, Gendreau M (2005) Transmission of infectious diseases during commercial air travel. Lancet 365: 989-996.

60. Gerard E (2002) Infectious diseases in air travellers arriving in the UK. J R Soc Promot Health 122: 86-88.

61. Jaakkola JJ, Heinonen OP (1995) Shared office space and the risk of the common cold. Eur J Epidemiol 11: 213-216.

62. Jaakkola MS, Yang L, Ieromnimon A, Jaakkola JJ (2007) Office work exposures and respiratory and sick building syndrome symptoms. Occup Environ Med 64: 178-184.

63. K Keen CL, Gershwin ME (1990) Zinc deficiency and immune function. Annu Rev Nutr 10: 415-431.

64. Lodovici M, Bigagli E (2011) Oxidative stress and air pollution exposure. J Toxicol 2011: 487074.

65. Lemos AO, Oliveira NC, Lemos CT (2011) In vitro micronuclei tests to evaluate the genotoxicity of surface water under the influence of tanneries. Toxicol In Vitro 25: 761-766.

66. Escher BI, van Daele C, Dutt M, Tang JY, Altenburger R (2013) Most oxidative stress response in water samples comes from unknown chemicals: the need for effect-based water quality trigger values. Environ Sci Technol 47: 7002-7011.

67. (2006) Principles and methods for assessing autoimmunity associated with exposure to chemicals. Environmental Health Criteria 236, World Health Organisation.

68. (2009) Global health risks: mortality and burden of disease attributable to selected major risks, World Health Organisation.

69. Kuehn BM (2014) More than 7 million air pollution deaths each year. JAMA 311: 1486.

70. Smith KR, Mehta S (2003) The burden of disease from indoor air pollution in developing countries: comparison of estimates. Int J Hyg Environ Health 206: 279-289.

71. (1999) European Centre for Environment and Health Bilthoven. Strategic approaches to indoor air policy-making, World Health Organisation.

72. Norback D (2009) An update on sick building syndrome. Curr Opin Allergy Clin Immunol 9: 55-59.

73. (2014) Ambient (outdoor) air quality and health, Fact sheet no. 313, World Health Organisation.

74. Brandt J, Silver JD, Christensen JH, Andersen MS, Bonlokke JH, et al. (2013) Contribution from the ten major emission sectors in Europe and Denmark to the health-cost externalities of air pollution using the EVA model system – an integrated modelling approach. Atmos Chem Phys Discuss 13: 5871-5922.

75. (2007) Cost of pollution in China: Economic estimates of physical damages, The World Bank.

76. (1994) Indonesia environment and development: challenges for the future, The World Bank.

77. Both AF, Westerdahl D, Fruin S, Haryanto B, Marshall JD (2013) Exposure to carbon monoxide, fine particle mass, and ultrafine particle number in Jakarta, Indonesia: effect of commute mode. Sci Total Environ 443: 965-972.

78. (2010) Improving Air Quality in Mexico City, SEDEMA: Ministry of Environment.

79. De Araujo Vormittag EdM, Guimaraes Rodrigues C, Jorge de Miranda M, Cavalcante JA, Rodrigues da Costa R, et al. (2013) Avaliação do impacto da poluição atmosférica sob a visão da saúde no Estado de São Pauloa.

80. (2006) Air quality guidelines for particulate matter, ozone, nitrogen dioxide and sulfer dioxide, Global update 2005, World Health Organisation.

81. (2013) PM10, country level (micrograms per cubic meter), The World Bank.

82. (2004) Health aspects of air pollution. Results from the WHO project "systematic review of health aspects of air pollution in Europe",World Health Organisation.

83. Sardar K, Ali S, Hameed S, Afzal S , Fatima S, et al. (2013) Heavy metals contamination and what are the impacts on living organisms. Greener Journal of Environmental Management and Public Safety 2: 172-179.

84. (2014) Air quality: data and statistics, World Health Organization, Europe.

85. (2011) Tackling the global clean air challenge, World Health Organization.

86. Apte JS, Bombrun E, Marshall JD, Nazaroff WW (2012) Global intraurban intake fractions for primary air pollutants from vehicles and other distributed sources. Environ Sci Technol 46: 3415-3423.

87. Pozzer A, Zimmermann P, Doering UM, van Aardenne J, Tost H, et al. (2012) Effects of business-as-usual anthropogenic emissions on air quality. Atmos Chem Phys 12: 6915-6937.

88. Bascom R (1991) The upper respiratory tract: mucous membrane irritation. Environ Health Perspect 95: 39-44.

89. Kelly FJ, Mudway IS (2003) Protein oxidation at the air-lung interface. Amino Acids 25: 375-396.

90. Kelly FJ (2004) Dietary antioxidants and environmental stress. Proc Nutr Soc 63: 579-585.

91. (2014) Indoor air pollution, World Health Organization.

92. Yeasir Azad SM, Bahauddin K, Uddin H, Parveen S (2014) Indoor air pollution and prevalence of acute respiratory infection among children in rural area of bangladesh. J Biol Agriculture Healthcare 4: 60-71.

93. Bautista LE Correa A, Baumgartner J, Breysse P, Matanoski GM (2009) Indoor charcoal smoke and acute respiratory infections in young children in the Dominican Republic. Am J Epidemiol 169: 572-580.

94. (2014) Burden of disease from household air pollution for 2012. World Health Organization.

95. Moturi NW (2010) Risk factors for indoor air pollution in rural households in Mauche division, Molo district, Kenya. Afr Health Sci 10: 230-234.

96. Ezzati M, Kammen DM (2001) Quantifying the effects of exposure to indoor air pollution from biomass combustion on acute respiratory infections in developing countries. Environ Health Perspect 109: 481-488.

97. Bruce N, Perez-Padilla R, Albalak R (2000) Indoor air pollution in developing countries: a major environmental and public health challenge. Bull World Health Organ 78: 1078-1092.

98. Leem JH, Kim JH, Lee KH, Hong Yc, Lee KH, et al. (2005) Asthma attack associated with oxidative stress by exposure to ETS and PAH. J Asthma 42: 463-467.

99. Li N Sioutas C, Cho A, Schmitz D, Misra C, et al. (2003) Ultrafine particulate pollutants induce oxidative stress and mitochondrial damage. Environ Health Perspect 111: 455-460.

100. Banerjee A, Mondal NK, Das D, Ray MR (2012) Neutrophilic inflammatory response and oxidative stress in premenopausal women chronically exposed to indoor air pollution from biomass burning. Inflammation 35: 671-683.

101. Mondal NK, Roy A, Mukherjee B, Das D, Ray MR (2010) Indoor air pollution from biomass burning activates Akt in airway cells and peripheral blood lymphocytes: a study among premenopausal women in rural India. Toxicol Pathol 38: 1085-1098.

102. Beck B, Brain J (1982) Prediction of the pulmonary toxicity of respirable combustion products from residential wood and coal stoves. Proceedings: residential wood & coal combustion specialty conference, Louisville, Kentucky, PA: Air Pollution Control Association 264-280.

103. Houtmeyers E, Gosselink R, Gayan-Ramirez G, Decramer M (1999) Regulation of mucociliary clearance in health and disease. Eur Respir J 13: 1177-1188.

104. (1991) Indoor Air Facts No. 4: sick building syndrome, United States Environmental Protection Agency.

105. Fanger P (1988) Hidden olfs in sick buildings. ASHRAE 30: 40-43.

106. Israeli E, Pardo A (2011) The sick building syndrome as a part of the autoimmune (auto-inflammatory) syndrome induced by adjuvants. Mod Rheumatol 21: 235-239.

107. Abdel-Hamid MA, A Hakim S, Elokda EE, Mostafa NS (2013) Prevalence and risk factors of sick building syndrome among office workers. J Egypt Public Health Assoc 88: 109-114.

108. Weschler CJ (2004) Chemical reactions among indoor pollutants: what we've learned in the new millennium. Indoor Air 14 Suppl 7: 184-194.

109. Walinder R, Norbäck D, Wieslander G, Smedje G, Erwall C (1997) Nasal congestion in relation to low air exchange rate in schools. Evaluation by acoustic rhinometry. Acta Otolaryngol 117: 724-727.

110. Walinder R, Norbäck D, Wieslander G, Smedje G, Erwall C, et al. (1999) Nasal patency and lavage biomarkers in relation to settled dust and cleaning routines in schools. Scand J Work Environ Health 25: 137-143.

111. Joshi SM (2008) The sick building syndrome. Indian J Occup Environ Med 12: 61-64.

112. (1995) Indoor environmental quality (IEQ), Centers for Disease Control and Prevention.

113. (2000) How to deal with sick building syndrome (SBS). Guidance for employers, building owners and building managers, Health and Safety Executive.

114. Fisk WJ, Rosenfeld AH (1997) Estimates of improved productivity and health from better indoor environments. Indoor Air 7: 158-172.

115. Fisk WJ (2000) Health and productivity gains from better indoor environments and their relationship with building energy efficiency. Ann Rev Energy Environ 25: 537-566.

116. Wiseman H, Halliwell B (1996) Damage to DNA by reactive oxygen and nitrogen species: role in inflammatory disease and progression to cancer. Biochem J 313 : 17-29.

117. Hirokawa K, Utsuyama M, Kasai M, Kurashima C (1992) Aging and immunity. Acta Pathol Jpn 42: 537-548.

118. Pawelec G (2007) Immunosenescence comes of age. Symposium on Aging Research in Immunology: The Impact of Genomics. EMBO Rep 8: 220-223.

119. (2012) Guidance for immunotoxicity risk assessment for chemicals. International Program on Chemical Safety, Harmonization Project Document No. 10, World Health Organization.

120. Chauhan AJ, Johnston SL (2003) Air pollution and infection in respiratory illness. Br Med Bull 68: 95-112.

121. Beelen R, Raaschou-Nielsen O, Stafoggia M, Andersen ZJ, Weinmayr G, et al. (2014) Effects of long-term exposure to air pollution on natural-cause mortality: an analysis of 22 European cohorts within the multicentre ESCAPE project. Lancet 383: 785-795.

122. Huang YL, Batterman S (2000) Residence location as a measure of environmental exposure: a review of air pollution epidemiology studies. J Expo Anal Environ Epidemiol 10: 66-85.

123. Brugge D, Durant JL, Rioux C (2007) Near-highway pollutants in motor vehicle exhaust: a review of epidemiologic evidence of cardiac and pulmonary health risks. Environ Health 6: 23.

124. Zuurbier M Hoek G, Oldenwening M, Lenters V, Meliefste K, et al. (2010) Commuters' exposure to particulate matter air pollution is affected by mode of transport, fuel type, and route. Environ Health Perspect 118: 783-789.

125. Lu CY, Ma YC, Chen PC, Wu CC, Chen YC (2014) Oxidative stress of office workers relevant to tobacco smoking and inner air quality. Int J Environ Res Public Health 11: 5586-5597.

126. Wintergerst ES, Maggini S, Hornig DH (2006) Immune-enhancing role of vitamin C and zinc and effect on clinical conditions. Ann Nutr Metab 50: 85-94.

127. Kallner AB, Hartmann D, Hornig DH (1981) On the requirements of ascorbic acid in man: steady-state turnover and body pool in smokers. Am J Clin Nutr 34: 1347-1355.

128. Schectman G, Byrd JC, Hoffmann R (1991) Ascorbic acid requirements for smokers: analysis of a population survey. Am J Clin Nutr 53: 1466-1470.

129. Preston AM, Rodriguez C, Rivera CE, Sahai H (2003) Influence of environmental tobacco smoke on vitamin C status in children. Am J Clin Nutr 77: 167-172.

130. Valkonen M, Kuusi T (1998) Passive smoking induces atherogenic changes in low-density lipoprotein. Circulation 97: 2012-2016.

131. Tribble DL, Giuliano LJ, Fortmann SP (1993) Reduced plasma ascorbic acid concentrations in nonsmokers regularly exposed to environmental tobacco smoke. Am J Clin Nutr 58: 886-890.

132. Strauss RS (2001) Environmental tobacco smoke and serum vitamin C levels in children. Pediatrics 107: 540-542.

133. Sargeant LA, Jaeckel A, Wareham NJ (2000) Interaction of vitamin C with the relation between smoking and obstructive airways disease in EPIC Norfolk. European Prospective Investigation into Cancer and Nutrition. Eur Respir J 16: 397-403.

134. Edvardsson B, Bergdahl J, Eriksson N, Stenberg B (2013) Coping and self-image in patients with symptoms attributed to indoor environment. Arch Environ Occup Health 68: 145-152.

135. Marmot AF, Eley J, Stafford M, Stansfeld SA, Warwick E, et al. (2006) Building health: an epidemiological study of "sick building syndrome" in the Whitehall II study. Occup Environ Med 63: 283-289.

136. Thorn A (2000) Emergence and preservation of a chronically sick building. J Epidemiol Community Health 54: 552-556.

137. Lobo V, Patil A, Phatak A, Chandra N (2010) Free radicals, antioxidants and functional foods: Impact on human health. Pharmacogn Rev 4: 118-126.

138. Machlin LJ, Bendich A (1987) Free radical tissue damage: protective role of antioxidant nutrients. FASEB J 1: 441-445.

139. Traber MG, Atkinson J (2007) Vitamin E, antioxidant and nothing more. Free Radic Biol Med 43: 4-15.

140. Burton GW, Ingold KU (1981) Autooxidation of biological molecules. 1. The antioxidant activity of vitamin E and related chain-breaking phenolic antioxidants in vitro. J Am Chem Soc 103: 6472-6477.

141. Wang X, Quinn PJ (1999) Vitamin E and its function in membranes. Prog Lipid Res 38: 309-336.

142. Traber MG (2006) Vitamin E. In: Shils ME, Shike M, Ross AC, Caballero B, Cousins RJ (eds.) Modern nutrition in health and disease. Lippincott Williams & Wilkins, Philadelphia, pp. 396-411.

143. Singh U, Devaraj S, Jialal I (2005) Vitamin E, oxidative stress, and inflammation. Annu Rev Nutr 25: 151-174.

144. Kolleck I, Sinha P, Rüstow B (2002) Vitamin E as an antioxidant of the lung: mechanisms of vitamin E delivery to alveolar type II cells. Am J Respir Crit Care Med 166: S62-66.

145. Levine M, Katz A, Padayatt SJ (2006) Vitamin C. In: Shils ME (ed.) Modern nutrition in health and disease (10thedn.) Lippincott Williams & Wilkins, Philadelphia, pp. 507-524.

146. Bettger WJ, Reeves PG, Savage JE, O'Dell BL (1980) Interaction of zinc and vitamin E in the chick. Proc Soc Exp Biol Med 163: 432-436.

147. Maggini S, Wintergerst ES, Beveridge S, Hornig DH (2007) Selected vitamins and trace elements support immune function by strengthening epithelial barriers and cellular and humoral immune responses. Br J Nutr 98(Suppl 1): S29-S35.

148. Bodin Danielsson C, Chungkham HS, Wulff C, Westerlund H (2014) Office design's impact on sick leave rates. Ergonomics 57: 139-147.

149. Maggini S, Wenzlaff S, Hornig D (2010) Essential role of vitamin C and zinc in child immunity and health. J Int Med Res 38: 386-414.

150. Tashakkor AY, Chow KS, Carlsten C (2011) Modification by antioxidant supplementation of changes in human lung function associated with air pollutant exposure: a systematic review. BMC Public Health 11: 532.

151. Yang W, Omaye ST (2009) Air pollutants, oxidative stress and human health. Mutat Res 674: 45-54.

152. Samet JM, Hatch GE, Horstman D, Steck-Scott S, Arab L, et al. (2001) Effect of antioxidant supplementation on ozone-induced lung injury in human subjects. Am J Respir Crit Care Med 164: 819-825.

153. Mahata J, Argos M, Verret W, Kibriya MG, Santella RM, et al. (2008) Effect of selenium and vitamin e supplementation on plasma protein carbonyl levels in patients with arsenic-related skin lesions. Nutr Cancer 60: 55-60.

154. Resosudarmo BP, Napitupulu L (2004) Health and economic impact of air pollution in Jakarta. Economic Record 80: S65-S75.

155. Haryanto B, Purnama H (2010) Multivitamin supplementation reduces sick building syndrome in employees in Jakarta, Indonesia. Proc Nutr Soc 69(OCE3): E315.

156. Kleeberger SR (2005) Genetic aspects of pulmonary responses to inhaled pollutants. Exp Toxicol Pathol 57 Suppl 1: 147-153.

157. (2011) Dietary reference intakes (DRIs): recommended daily allowances and adequate intakes, vitamins and elements, Food and Nutrition Board, Institute of Medicine, National Academies.

158. (2011) Dietary reference intakes (DRIs): tolerable upper intake levels, vitamins and elements, Food and Nutrition Board, Institute of Medicine, National Academies.