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The role of micronutrients in the response to ambient air pollutants: Potential mechanisms and suggestions for research design

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Abstract

People living in regions of low socioeconomic status are thought to be prone to higher exposures to environmental pollutants, poor nutrition, and numerous preventable diseases and infections. Poverty correlates with pollution and malnutrition; however, limited studies examined their interrelationship. The well-studied, deleterious health effects attributed to environmental pollutants and poor nutrition may act in combination with produce more severe adverse health outcomes than any one factor alone. Deficiencies in specific nutrients render the body more susceptible to injury which may influence the pathways that serve as the mechanistic responses to ambient air pollutants. This review (1) explores specific micronutrients that are of global concern, (2) explains how these nutrients may impact the body's response to ambient air pollution, and (3) provides guidance on designing animal models of nutritional deficiency. It is likely that those individuals who reside in regions of high ambient air pollution are similarly malnourished. Therefore, it is important that research identifies specific nutrients of concern and their impact in identified regions of high ambient air pollution.

Introduction

Micronutrients, inclusive of both vitamins and minerals, need to be consumed in necessary quantities for normal physiologic functions. Micronutrients (1) serve as cofactors for enzymes involved in metabolism, (2) are required for DNA synthesis and cell division, (3) are necessary for oxygen transport, and (4) carry out thousands of other essential reactions that sustain life. Deficiencies most commonly generated as a result of poor nutritional intake may lead to mental and physical stunting, physiological impairments such as blindness, and increased incidence of cancer and infections. Worldwide, malnutrition and micronutrient deficiencies are strongly associated with up to 19% of childhood deaths and contribute significantly to reduced life expectancy (Black 2003). While sub-chronic nutritional

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deficiencies are not immediately life threatening, these deficiencies increase susceptibility to other challenges resulting in additive and synergistic reductions in health.

Disproportionate exposure to ambient air pollutants and environmental contaminants is associated with concurrent poor nutritional status (Hennig et al. 2007; Kannan et al. 2006). Such nutrients of concern, at-risk populations, and their relationship to ambient air pollution are summarized in Tables 1 and 2. The purpose of the current review was to (1) provide an understanding of the known micronutrients of concern worldwide (based off of classifications from the World Health Organization, World Food Programme, and the 2015 Dietary Guidelines for Americans), (2) identify connections between nutrient deficiencies and ambient air pollution associated adverse health outcomes, and (3) recommend appropriate animal research models of nutrition to explore these connections.

Vitamin A

Major physiologic functions and consequences of deficiency

Vitamin A is the encompassing name for a class of compounds that exerts activity through the retinoic receptors that are expressed throughout the body and interact with other regulatory transcription factors (Kliwer et al. 1992). Dietary vitamin A is consumed in the form of retinyl esters from animal products, and as carotenoids from plants, which express limited vitamin A activity (Harrison and Hussain 2001). Additional forms of vitamin A include the storage form, retinol and the active form, retinal. Vitamin A is best known for its role in vision and is essential for the ability to see in lowly lit environments. Increasing evidence of vitamin A's role in immunoregulation suggests that it is necessary for mucosal integrity and host defense (Rojanapo, Lamb, and Olson 1980; Tei et al. 2000; Wiedermann et al. 1996). Not surprisingly vitamin A deficiency (VAD) plays a causative role in increased susceptibility and severity of infectious diseases, correlating with nearly 250,000 childhood deaths annually (Ching et al. 2000).

The clinical manifestation of VAD is night blindness estimated to affect approximately 5 million preschool-aged children globally (Black 2014). Asian countries displayed an increased prevalence of VAD with 50% of the population consuming less than the estimated average requirement (Torheim et al. 2010). While the prevalence of VAD outside of Asia is low, typical United States. Vitamin A intake is also below the recommended amounts (Dietary Guidelines Advisory Committee 2015; Torheim et al. 2010). Because of the systemic distribution of vitamin A receptors, reduced consumption may affect many tissue systems and disrupt normal homeostatic functions.

Potential interactions with ambient air pollutants

A limited number of studies investigated connections between ambient air pollution and VAD on health outcomes. Levels of the vitamin A precursor, β carotene, are often lower in populations exposed to environmental tobacco smoke, nitrogen dioxide, and in lung cancer patients (Bernard et al. 1998; Huang et al. 1992; Shibata et al. 1992; Widome et al. 2010). In rodent models, supplementation of β carotene with vitamin E mitigated myocardial damage in rats exposed to tobacco smoke (Van Jaarsveld, Kuyl, and Alberts 1992). It is possible that

the connection with lung cancer may be related to dosing and/or an interaction with tobacco smoke that may not be seen with other pollutants. However, in humans β carotene, supplementation may enhance the risk of cancer in smokers (Goralczyk 2009); therefore, caution needs to be taken with vitamin A-related nutrients. The highly toxic environmental pollutant, 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8- TCDD), compromises vitamin A status (Brouillette and Quirion 2008; Elabbas et al. 2014). Further, VAD increases hepatic sensitivity to TCDD and may lead to enhanced carcinogenesis, suggesting vitamin A's role in TCDD metabolism (Flodstrom et al. 1991). As vitamin A may regulate the aryl hydrocarbon and cytochrome P450 systems, its status may be important for the metabolism of various toxins in both air pollution and other environmental exposures.

Animal models and research design considerations

Animal studies provide a unique model to induce VAD that lacks the ethical concerns of conducting experiments in humans. The rodent diet can be chronically supplemented with up to 4000 IUs and still be well tolerated. However, as a fat-soluble vitamin, it is difficult to establish VAD in the adult rodent as stores are developed early in life. Thus, in the rodent model, it is recommended to begin VAD in utero to ensure adequate signs of deficiency, including growth retardation, by adolescence (Moore and Holmes 1971). A continuation of the VAD diet needs to be followed through lactation, weaning, and adulthood to adequately develop the effects associated with VAD in humans. Lastly, as with humans, vitamin A is a teratogen, and supplementation needs to be avoided in pregnant rodents. The β carotene isoform is considered safe as it does not convert to the storage form of vitamin A, retinol; however, overconsumption carries the potential of carotenemia, the development of an orange pigment to the skin.

Vitamin C

Major physiologic functions and consequences of deficiency

Vitamin C is an antioxidant that comprises the L-enantiomer of ascorbic acid and dehydroascorbic acid. Vitamin C is part of the cell's first line of defense and reduces oxidized vitamin E in response to lipid peroxidation. Vitamin C also mediates the immune response by protecting cellular pools of endothelial nitric oxide synthase (eNOS) through inhibiting oxidation of tetrahydrobiopterin, preventing eNOS depletion (Oudemans-Van Straaten, Spoelstra-De Man, and De Waard 2014). Additional functions of vitamin C include participatory roles in dopamine and carnitine synthesis, tyrosine metabolism, and collagen synthesis (Padayatty et al. 2003). The latter lends to bone deformations seen during scurvy, the clinical manifestation of vitamin C deficiency.

Vitamin C deficiency is rare in the U.S.; however, its prevalence is increasing due to the poor nutritional quality of the westernized diet (Al-Dabagh et al. 2013). The prevalence for vitamin C deficiency is approximately 45–70% in certain segments of the global population, including India and South Asia, and within the low income and aged (Ravindran et al. 2011). Further, it is possible that certain populations require higher doses than the estimated average requirement due to increased utilization of this water-soluble vitamin. Smokers have

an elevated incidence of vitamin C insufficiency, postulated to be a result of oxidative stress leading to increased nutrient utilization (Tribble, Giuliano, and Fortmann 1993).

Potential interactions with ambient air pollutants

The reduced intake of this vitamin is linked to asthma and lung cancer, suggesting a supportive effect on the health of the respiratory system (Gao 1996; Harik-Khan, Muller, and Wise 2004). Vitamin C imparts protection to oxidative damage induced by ambient air pollution. Vitamin C is rapidly utilized for following exposure to a variety of pollutants such as particulate matter (PM), biomass combustion smoke, ozone, and tobacco smoke (Dietrich et al. 2003; Kadiiska et al. 2011; Padhy and Padhi 2009; Snow et al. 2014). In vitro, vitamin C protects against DNA strand breaks following PM exposure (Senthilkumar et al. 2014). In those exposed to tobacco smoke, vitamin C supplementation reduced both lipid peroxidation and oxidized low-density lipoprotein (Panda et al. 2000; Valkonen and Kuusi 2000). However, supplementation failed to lower blood pressure following PM and ozone exposure (Bahk and Oh 1998). Further when combined with vitamin E, supplementation did not prevent adverse changes in lung performance and function following an exercise-ozone challenge (Gomes et al. 2011; Mudway et al. 2006). It is important to note, however, that these studies found reduced levels of biomarkers of lung injury, suggesting some benefit of antioxidant supplementation and the need for even higher doses than used in previous investigations particularly under extreme exposure circumstances.

Animal models and research design considerations

Vitamin C is synthesized in nearly all mammalian vertebrates with the exception of humans and guinea pigs. Because of this, the guinea pig is the accepted model for vitamin C research. Within murine models, several genetic models of vitamin C deficiency exist and include the Osteogenic Disorder Shionogi (ODS) rat, which expresses a mutated enzyme that is responsible for the endogenous synthesis of vitamin C, and various knockout mouse models (reviewed in Yu and Schellhorn 2013). These animals require vitamin C within the diet or water (1000 mg/kg or 1 g/L) or will develop scurvy. Lastly, vitamin C is sensitive to oxidation and might be depleted quickly (Zerdin, Rooney, and Vermue 2003). Therefore, one needs to be cognizant of dietary formulation, storage, and expiration date of rodent diets and supplements.

Vitamin D

Major physiologic functions and consequences of deficiency

Vitamin D is synthesized in the epidermal skin layer as cholecalciferol upon exposure to ultraviolet irradiation. Cholecalciferol is subsequently converted into calcidiol in liver and to calcitriol in kidney. Calcitriol is the biologically active form of vitamin D and binds to a specific high affinity nuclear receptor protein, the 1,25-dihydroxyvitamin D3 receptor, which is expressed in nearly every tissue in the body (Hedlund, Moffatt, and Miller 1996). Vitamin D receptors are ubiquitous throughout the body suggesting potential for systemic activity leading to studies exploring the effects of vitamin D on a variety of tissues.

Vitamin D is most known for its effects on bone health and is necessary for calcium absorption. Vitamin D-dependent calcium binding proteins are upregulated in the presence of vitamin D, thereby increasing intestinal calcium absorption. Under normocalcemic conditions, the intestine is the primary target of vitamin D, whereas the skeletal effects of vitamin D become more prominent under negative calcium balance. Hypocalcemia results in elevated plasma levels of both vitamin D and parathyroid hormone (PTH) and together these stimulate osteoclastic bone resorption to achieve calcium homeostasis (Underwood and DeLuca 1984). By contrast, vitamin D is important for prevention of osteomalacia. Thus, the skeletal effects of vitamin D are mediated via both osteogenic and osteoclastogenic properties of the molecule.

Because of vitamin D's critical role in bone development and maintenance, including rickets and osteoporosis, cardiovascular disease, certain cancers, and type 1 diabetes mellitus, deficiency is a global health problem (Holick 2005, 2012a, 2012b, 2012c). Serum 25(OH)D, the inactive form of vitamin D, is the gold standard for assessing vitamin D status (Holick et al. 2011). One third of the U.S. population displays serum 25 (OH)D levels less than 20 ng/ml, while more than 70% of non-Hispanic black individuals and more than 40% of Hispanic individuals were reported to be at risk for deficiency (Ganji, Zhang, and Tangpricha 2012). Further, lower serum 25(OH)D levels are present consistently throughout Asia including India, Thailand, and Malaysia (Chailurkit, Aekplakorn, and Ongphiphadhanakul 2011; Harinarayan et al. 2007; Lu et al. 2009) [reviewed in (Nimitphong and Holick 2013)]. Vitamin D status varies greatly among individuals and is significantly influenced by factors including natural aging process, gender, milk and meat consumption, skin pigmentation, and seasonal changes in climate.

Potential interactions with ambient air pollutants

According to the U.S. Census Bureau, more than 15% of Americans reside at or below the poverty brink and a large segment of this population is concentrated in urban areas with limited access to healthy lifestyle practices including proper nutrition, physical activity, and reduced exposure to harmful chemicals. Due to high crime in many low-income communities, outdoor activities and play are adversely impacted leading to diminished sunlight exposure (Burdette and Whitaker 2004). Since sunshine is a major source of vitamin D, limited outdoor recreation in neighborhoods that house low-income residents might result in inadequate ultraviolet radiation leading to vitamin D deficiency. Perception of the neighborhood safety influences family decisions on outside recreation linking socioeconomic status with low serum 25 (OH)D levels (Lopez and Hynes 2006). Since high levels of atmospheric pollutants reduce ground levels of ultraviolet radiation significantly, ambient air pollution is also a physical risk for vitamin D deficiency (Hosseinpanah et al. 2010). Therefore, living in a polluted area may further compound vitamin D deficiency through several mechanisms and exaggerate the known effects of deficiency on bone and many other tissue systems.

Animal models and research design considerations

There are several limitations in inducing vitamin D deficiency in animal models. Given that vitamin D is a fat-soluble vitamin, it requires longer periods of time to induce deficiency

through diet. In addition, vitamin D deficiency also alters PTH, calcium, and phosphorus levels complicating the interpretation of animal studies. In humans, vitamin D deficiency is often sub-clinical and requires years of deficiency to impact disease risk. Moreover, vitamin D deficiency may occur in humans without significant changes in calcium or phosphorus. Due to time constraints of rodent models, vitamin D deficiency is initiated to a more severe extent. Although animal studies showed that hypocalcemia is not necessary to manifest vitamin D deficiency, the onset of vitamin D deficiency during neonatal life also influences calcium homeostasis (Lester et al. 1982). Stavenuiter et al. (2015) are working on strategies to induce vitamin D deficiency in rodent models with minimal changes to PTH, serum calcium, and phosphorus levels. Such improvements are necessary to better elucidate the role of exclusive vitamin D deficiency in exacerbating the risk of exposure to environmental pollutants.

Zinc

Major physiologic functions and consequences of deficiency

Zinc is one of the most abundant trace elements in the body, and while present throughout, it is predominately stored and utilized in skeletal muscle and bone. Zinc is an integral structural component of several proteins and has regulatory roles in cellular biochemical mechanisms (Boreiko 2010). It is also a component of various metalloenzymes that are required for metabolism of carbohydrate, fat, and protein (Vallee and Falchuk 1993). In addition, zinc is necessary for insulin-like growth factor—I (IGF-I), which is required for normal growth during childhood (MacDonald 2000). Thus, children who are zinc deficient are often physically stunted which is in part due to disruptions in IGF-1 signaling.

One-third of the world population lives in countries with a high prevalence of zinc deficiency which is reported to contribute to 11% of the global total disease burden (Black et al. 2008). Zinc deficiency is a predisposing risk factor for diarrhea, pneumonia, and malaria in children accounting for about 800,000 deaths and about 20% of perinatal mortality worldwide (Black et al. 2008; Boreiko 2010). Zinc deficiency correlates with stunting and supplementation in low-income preschool children increases the linear growth rates (Brown et al. 2002; Hambidge et al. 1972; Walravens, Krebs, and Hambidge 1983).

The most common cause of zinc deficiency is inadequate intake or absorption from the diet. While zinc deficiency is not common in the United States, the elderly population is at elevated risk of deficiency due poor diet and age-related decline in absorption. NHANES III data revealed that 40% of adults aged 60 years or older have zinc intake below the estimated average daily requirement (Alaimo et al. 1994). Globally, deficiency is far more prevalent in South Asia, most of sub-Saharan Africa, and parts of Central and South America. Increased consumption of phytate-rich foods, which chelates dietary metals, accompanied by limited dietary intake of zinc is one of the major contributing factors to zinc deficiency in south Asian countries (Chandyo et al. 2009). Diets rich in fiber and phytate act as chelators and decrease absorption of zinc, requiring vegetarians to consume 50% more of the recommended daily allowance for zinc (Livingstone 2015). Further, children with sickle cell disease, which displays a higher prevalence in African Americans (1 in 700) (Ashley-Koch, Yang, and Olney 2000), demonstrated an increased risk of zinc deficiencies with etiologies

suspected to be related to both insufficient dietary consumption and enhanced nutrient requirements (Leonard et al. 1998; Zemel et al. 2002).

Potential interactions with ambient air pollutants

Zinc is a free radical scavenger and antioxidant (Powell 2000). Considering the antioxidant properties and anabolic functions of zinc on growth, it is reasonable to postulate that zinc deficiency elevates the risk of toxicity induced by environmental pollution (Kim and Hong 2012; Powell 2000). Further, zinc also protects against cadmium toxicity. Cadmium is a hazardous ambient air pollutant that presents a threat to people living in urban areas in the United States (Shi et al. 2012). Since zinc and cadmium share structural similarity, cadmium replaces zinc in conditions of zinc deficiency resulting in inhibition of physiological functions of this metal. Hence, zinc deficiency greatly increases cadmium storage and toxicity (Haas and Levin 2006). Maintaining adequate cadmium: zinc ratios in plant foods are important to decrease cadmium accumulation in the body. Interestingly, refined foods tend to have higher cadmium: zinc ratios than whole foods (Haas and Levin 2006).

Animal models and research design considerations

Zinc deficiency in rodents reduces feed intake, resulting in stunting malnutrition in growing animals that complicates research designs (Giugliano and Millward 1984). To control for the effects of anorexia, it is recommended to match zinc-deficient animals with pair-fed control animals limited to the amount of feed consumed by its zinc deficient paired mate on the previous day (Panemangalore and Bebe 1997). The anorexogenic effect of zinc deficiency also complicates the use of the mouse model due to their rapid growth, with little body weight difference between the mouse neonatal period and adulthood relative to the rat. Since severe zinc deficiency is not seen in humans, another valuable control group that may be included in the study is a marginally zinc-deficient group, where animals receive sufficiently lower zinc levels in the diet that does not induce anorexia and weight loss, thus representing more accurately the degree of zinc deficiency prevalent in humans (Hosea Blewett, Rector, and Taylor 2008).

Iron

Major physiologic functions and consequences of deficiency

Iron is essential for numerous functions; however, this metal is most well known as the necessary cofactor for hemoglobin which carries oxygen in red blood cells. Anemia produced by iron deficiency reduces oxygen delivery to tissues. Further, iron is a requirement for cytochrome c oxidase and cytochrome P450 activity, energy metabolism, and enzymes that help mediate the immune response (Beard 2001). Iron is also a cofactor in the early synthesis of neurotransmitters including epinephrine and norepinephrine. Because of these widespread roles, deficiency during pregnancy might induce a variety of poor outcomes including birth defects and low birthweight which lead to lifelong impacts on development, learning, and autonomic responses (Bakoyiannis et al. 2015; Lozoff, Jimenez, and Wolf 1991).

Iron deficiency is the most prevalent nutritional disorder contributing up to 841,000 deaths annually worldwide (Bailey, West, and Black 2015; Stoltzfus 2003). Rates of deficiency are close to 50% in those residing in the developing world and 11% in Westernized countries (Viteri 1994). Because of the widespread deficiency reported, iron is considered one of the 10 greatest global health risks identified by the World Health Organization (Rosenthal 2003). Further, pregnant women are at an elevated risk of anemia due to increased needs of the nutrient during this time period. Iron deficiency anemia during pregnancy is responsible for 40% of maternal deaths globally (WHO 1962).

Potential interactions with ambient air pollutants

Iron is both an essential nutrient and a component of PM (Ghio, Carraway, and Madden 2012). Bronchial epithelial cells express the divalent metal transporter-1 (DMT-1), which clears lungs of heavy metals (Wang et al. 2002). Expression of DMT-1 is linked to dietary iron intake. Supplemental iron increases DMT-1 expression within airway alveolar epithelial cells and macrophages, improving clearance of heavy metals following PM exposure and reduces injury (Ghio et al. 2005). Deficiency in iron might decrease DMT-1 expression and result in reduced clearance of metals from the airway. Kwong, Friello, and Semba (2004) also showed that in children with lead poisoning, iron deficiency often coexists. Further, data suggest that sufficient iron intake may diminish the severity of lead poisoning possibly through increasing DMT-1 expression.

Iron-deficient women exposed to cookstove smoke have raised serum hemoglobin compared to iron-sufficient women (Neufeld et al. 2004). Hemoglobin does not always reflect iron status and further, is often found elevated during disease (Yip 2000). Elevated hemoglobin lowers blood flow either through increased blood viscosity or direct effects on blood pressure. This might be further complicated in iron deficient, anemic individuals who have decreased oxygen delivery due to lack of iron that binds to oxygen for transport. Lastly, both iron deficiency-related anemia and chronic ambient air pollutant exposure may independently enhance the risk of asthma and cardiovascular disease (Brook et al. 2010; Chang, Chen, and Yang 2015; Chen et al. 2015; Costa et al. 2014; Greenberg et al. 2016; Lapice, Masulli, and Vaccaro 2013; Stojic et al. 2016). Thus, it is possible that in combination, iron deficiency and ambient air pollution increase the risk for complications to the cardiorespiratory systems.

Animal models and research design considerations

In rodents dietary, iron restriction produces deficiency; however, between-strain susceptibility differences exist. Sprague Dawley rats are not as susceptible to iron deficiency compared to Wistar and Fischer 344 rats (Rao and Jagadeesan 1995). Various knockout mouse models exist that also produce iron deficiency. However, some of these mutations, in particular, the transferrin knockout mouse, result in lethality within 2 weeks of life unless weekly transferrin injections are utilized (Latunde-Dada, McKie, and Simpson 2006). Lastly, neurologic damage from iron deficiency may be permanent in offspring. Despite iron supplementation in iron-deficient newborn pups, cognitive defects are not rescued and rats maintain lifelong learning deficits (Kobiler, Lustig, and Shapira 2001). Consequently, timing

is critical and needs to be considered when developing a rodent model incorporating iron deficiency.

Iodine

Major physiologic functions and consequences of deficiency

Iodine is required for the synthesis of thyroid hormone, which heterodimerizes with the retinoic acid receptors (Zhang and Pfahl 1993). Accordingly, some actions of thyroid hormone function are dependent on vitamin A status. Because the thyroid gland is an endocrine organ that regulates metabolism, impairment of thyroid signaling impacts growth and maturation in children. Iodine deficiency induces goiter (swelling of thyroid gland), hypo- and hyperthyroidism (depending on severity and timing), and increases susceptibility to thyroid cancer following radiation exposure (Braverman et al. 2014; Delange 1994; Zimmermann and Boelaert 2015). Further, iodine deficiency reduces mental acuity and is a major cause of mental retardation in children (Creasy et al. 2013). The extreme manifestation of iodine deficiency is referred to as cretinism and may result in stunted physical and mental development that leads to lifelong dependency. Cretinism is estimated to impact up to 15% of the population in regions with severe deficiency including parts of Indonesia and Bolivia (Creasy et al. 2013).

Approximately 2.2 billion individuals reside in areas with iodine deficiency (Zimmermann and Andersson 2012). Iodine is supplemented through elective and mandatory programs worldwide. In countries with such programs, great strides have been made to lower rates of deficiency; U.S. clinical iodine deficiency has decreased from 70% in certain regions during the 1920s to near zero today (Leung, Braverman, and Pearce 2012). However, based on the reports of levels of deficiency, supplementation programs are not ubiquitous globally. U.S. rates of iodine intake have declined due to increased consumption of processed foods lacking in iodized salt and suggests a reemergence of iodide deficiency in the U.S. (Perrine et al. 2010).

Potential interactions with ambient air pollutants

Iodine deficiency increases the susceptibility to chemical toxicity. This has been well characterized in areas exposed to nuclear radiation where iodine supplementation is important for preventing thyroid cancers (Braverman et al. 2014). Additional chemicals impact thyroid health by acting as iodine uptake inhibitors and include waterborne percholate, thiocyanate from cigarette smoke, and nitrates which are found in both contaminated water and PM (Ozpinar et al. 2014). PM10 exposure correlates with higher thyroid cancer incidence (Yanagi, Assuncao, and Barrozo 2012). Following a single PM exposure direct reduction in thyroid hormones, both T4 (inactive form) and T3 (active form) were noted (Alink, Brouwer, and Heussen 1994). Further, cookstove pollution has also been shown to impact thyroid-stimulating hormone, thyroid hormones, and is associated with enlargement of the thyroid gland (Yagil et al. 1982).

Few studies examined connectivity between airway pollutants and thyroid function. Taking into consideration what is known regarding chemical derivatives present in air pollutants,

iodine deficiency may increase the severity of PM effects (Pearce and Braverman 2009). An increased iodine requirement may be necessary in those exposed to pollutants that competitively inhibit iodine transport. The sodium–iodide symporter is expressed in the mammary gland and is necessary for iodine incorporation into breastmilk (Kogai and Brent 2012). Thus, competitive anions may not only get incorporated into the breastmilk but may also compromise iodine uptake. Considering that pregnancy and breastfeeding raises dietary iodine requirements, proper supplementation in regions with high PM and lack of dietary fortification to prevent iodine deficiency is of public health importance.

Animal models and research design considerations

In rodents, deficiency may be achieved through commercial diet formulations or through an in house preparation of 25 µg (iodine)/kg of diet on a base casein diet (Gilbert et al. 2013). Deficiency is determined by measuring thyroid hormone in the serum, and rodents develop similar outcomes of deficiency to humans. Lastly, while some factors of deficiency such as goiter and hypothyroidism may be reversed, physical and mental deficiencies as a result of early life iodine deficiency are irreversible in both humans and animal models.

Folate

Major physiologic functions and consequences of deficiency

Folate, also known as vitamin B9 or folic acid (synthetic form), is necessary for cell division, DNA synthesis and repair, and epigenetic regulation of gene expression (Crider, Bailey, and Berry 2011). Deficiencies in folate induce physical and mental malformations in offspring, megaloblastic anemia, and may contribute to cardiovascular disease and cancer. Since the body's reserves for folate are low, deficiency arises within weeks of inadequate intake. As a methyl donor, folate regulates the epigenetic mechanism of DNA methylation. Folate deficiency reduces global DNA methylation levels (Mejos et al. 2013), whereas supplementation may protect against epigenetic changes induced by chemical exposure in utero (Dolinoy, Huang, and Jirtle 2007).

Folate has been added in the manufacturing process of wheat flour within the U.S. diet since 1996 (Crider, Bailey, and Berry 2011). The folic acid fortification program is regarded as one of the major public health advances in the twentieth century. Since its adoption, rates of neural tube defects have dropped up to 50% (Rader and Schneeman 2006); however, some subpopulations in the U.S. still are deficient (i.e., African Americans and low-income families) (Dowd and Aiello 2008). Not all countries mandate folic acid fortification; some developed countries in Europe, Asia, and much of Africa do not have folic acid fortification. Consequently, folate deficiency and neural tube defects remain a significant public health burden globally (Crider, Bailey, and Berry 2011).

Potential interactions with ambient air pollutants

Folate status may be related to childhood asthma, a condition which is markedly exacerbated by ambient air pollution (Matsui 2014). Numerous studies demonstrated compromised folate status in those exposed to tobacco smoke, cadmium, and PM (Hodson et al. 2011; Mannino et al. 2003; Wang et al. 2012). Conclusions from these findings are difficult to interpret,

particularly considering that folate supplementation in smokers failed to protect against birth defects (Caspers et al. 2013; Feldkamp et al. 2014).

The most promising link between folate and pollution may be through the exploration of the CT/TT methylenetetrahydrofolate reductase gene (MTHFR) mutation. MTHFR synthesizes the active form of folate. Those with the polymorphism have a greater risk of neural tube defects in offspring, mimicking dietary folate deficiency (Botto and Yang 2000). Further, as folate metabolism involves methylation of homocysteine to methionine, homocysteine levels are elevated in those with the MTHFR polymorphism (Varga et al. 2005). Not surprisingly, those with the MTHFR mutation have higher rates of heart disease than the normal population (Klerk et al. 2002). In those with the polymorphism, PM_{2.5} exposure increases heart rate variability compared to controls (Baccarelli et al. 2008). As the MTHFR polymorphism is quite prevalent in North Americans and Europeans, up to 17 and 39% depending on the mutation (Deloughery et al. 1996), the effects of ambient air pollution in this cardiovascular-sensitive population need to be determined.

Animal models and research design considerations

Rodents are susceptible to diet-induced folate deficiency and develop the majority of the signs noted in human deficiency. Early life deficiency produces impaired cognition, elevated homocysteine, and global DNA methylation changes (Berrocal-Zaragoza et al. 2014; Mejos et al. 2013). In adult models, deficiency increased DNA errors and instability, atherosclerosis, and elevated homocysteine (Duthie et al. 2000a; 2000b; Partearroyo et al. 2013; Zhang et al. 2004). However, folate deficiency did not induce neural tube defects in rodents and requires the use of genetic models to study such defects (Heid et al. 1992).

Finally, there have been concerns regarding folate oversupplementation and adverse epigenetic outcomes. To date, there is no definitive evidence supporting that oversupplementation increases the risk of cancer, cardiovascular disease, or any other diseases. However, evidence indicates that the beneficial effect of folate supplementation in such diseases may be absent in a sufficient individuals (Sauer, Mason, and Choi 2009).

Conclusions

It is postulated that ambient air pollution exposure may be higher in impoverished communities or countries and that synergism between nutritional deficiencies and excessive ambient air pollutant exposure may lie at the crux of many of the adverse health outcomes associated with pollutant exposures. Various nutrients have been identified as at-risk for deficiency by well-respected health agencies. Deficiencies in many of the nutrients described herein impact oxidative stress and inflammatory pathways, which increase susceptibility to ambient air pollution and/or infection. Better designed studies to assess the role of the synergistic properties of nutrient deficiencies and environmental pollution are needed. Investigation of combinations of nutrients together with various pollutants may provide a better indicative model of the human condition and provide objective data in the cobenefits of mitigating nutritional deficiency in those exposed to ongoing, disproportionate pollutant levels. Finally, while not reviewed here, one also needs to be cognizant of protein-energy malnutrition (caloric deficiency) and the increased global prevalence of the double burden,

the occurrence of both obesity and micronutrient deficiency, which exert their own unique consequences on the body.

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References

- Alaimo K, McDowell MA, Briefel RR, Bischof AM, Caughman CR, Loria CM, and Johnson CL. 1994 Dietary intake of vitamins, minerals, and fiber of persons ages 2 months and over in the United States: Third national health and nutrition examination survey, phase 1, 1986–91. Advance data from vital and health statistics no 258. Hyattsville, Maryland: National Center for Health Statistics.
- Al-Dabagh A, Milliron BJ, Strowd L, and Feldman SR. 2013 A disease of the present: Scurvy in “well-nourished” patients. *Journal of the American Academy of Dermatology* 69:e246–247. doi: 10.1016/j.jaad.2013.04.051. [PubMed: 24124845]
- Alink GM, Brouwer A, and Heussen GA. 1994 Effects of outdoor and indoor airborne particulate matter on thyroid hormone and vitamin A metabolism. *Toxicology Letters* 72:73–81. doi: 10.1016/0378-4274(94)90012-4. [PubMed: 8202959]
- Ashley-Koch A, Yang Q, and Olney RS. 2000 Sick cell hemoglobin (HbS) allele and sick cell disease: A HuGE review. *American Journal of Epidemiology* 151:839–45. doi:10.1093/oxfordjournals.aje.a010288. [PubMed: 10791557]
- Baccarelli A, Cassano PA, Litonjua A, Park SK, Suh H, Sparrow D, Vokonas P, and Schwartz J. 2008 Cardiac autonomic dysfunction: Effects from particulate air pollution and protection by dietary methyl nutrients and metabolic polymorphisms. *Circulation* 117:1802–09. doi:10.1161/CIRCULATIONAHA.107.726067. [PubMed: 18378616]
- Bakh JH, and Oh YS. 1998 A new and simple maneuver to position the left-sided double-lumen tube without the aid of fiberoptic bronchoscopy. *Anesthesia and Analgesia* 86:1271–75. [PubMed: 9620518]
- Bailey RL, West KP, Jr., and Black RE. 2015 The epidemiology of global micronutrient deficiencies. *Annals of Nutrition & Metabolism* 66 (Suppl 2):22–33. doi:10.1159/000371618.
- Bakoyiannis I, Gkioka E, Daskalopoulou A, Korou LM, Perrea D, and Pergialiotis V. 2015 An explanation of the pathophysiology of adverse neurodevelopmental outcomes in iron deficiency. *Reviews in the Neurosciences* 26:479–88. doi:10.1515/revneuro-2015-0012. [PubMed: 25951130]
- Beard JL 2001 Iron biology in immune function, muscle metabolism and neuronal functioning. *The Journal of Nutrition* 131:568S–580S. [PubMed: 11160590]
- Bernard N, Saintot M, Astre C, and Gerber M. 1998 Personal exposure to nitrogen dioxide pollution and effect on plasma antioxidants. *Archives of Environmental Health: An International Journal* 53:122–28. doi:10.1080/00039896.1998.10545973.
- Berrocal-Zaragoza MI, Sequeira JM, Murphy MM, Fernandez-Ballart JD, Abdel Baki SG, Bergold PJ, and Quadros EV. 2014 Folate deficiency in rat pups during weaning causes learning and memory deficits. *The British Journal of Nutrition* 112:1323–32. doi:10.1017/S0007114514002116. [PubMed: 25313575]
- Black R 2003 Micronutrient deficiency—an underlying cause of morbidity and mortality. *Bulletin of the World Health Organization* 81:79. [PubMed: 12751414]
- Black RE 2014 Global distribution and disease burden related to micronutrient deficiencies. *Nestle Nutrition Institute Workshop Series* 78:21–28. [PubMed: 24504203]
- Black RE, Allen LH, Bhutta ZA, Caulfield LE, De Onis M, Ezzati M, Mathers C, Rivera J, and Maternal and Group Child Undernutrition Study. 2008 Maternal and child undernutrition: Global

and regional exposures and health consequences. *The Lancet* 371:243–60. doi:10.1016/S0140-6736(07)61690-0.

- Boreiko CJ 2010 Overview of health risk assessments for zinc. *Journal of Toxicology and Environmental Health, Part A* 73:166–74. doi:10.1080/15287390903340427. [PubMed: 20077287]
- Botto LD, and Yang Q. 2000 5,10-Methylenetetrahydrofolate reductase gene variants and congenital anomalies: A HuGE review. *American Journal of Epidemiology* 151:862–77. doi:10.1093/oxfordjournals.aje.a010290. [PubMed: 10791559]
- Braverman ER, Blum K, Loeffke B, Baker R, Kreuk F, Yang SP, and Hurley JR. 2014 Managing terrorism or accidental nuclear errors, preparing for iodine-131 emergencies: A comprehensive review. *International Journal of Environmental Research and Public Health* 11:4158–200. doi:10.3390/ijerph110404158. [PubMed: 24739768]
- Brook RD, Rajagopalan S, Pope CA, 3rd, Brook JR, Bhatnagar A, Diez-Roux AV, Holguin F, Hong Y, Luepker RV, Mittleman MA, Peters A, Siscovick D, Smith SC, Jr., Whitsel L, Kaufman JD, and American Heart Association Council on Epidemiology and Prevention, Council on the Kidney in Cardiovascular Disease, and Council of Nutrition, Physical Activity and Metabolism. 2010 Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. *Circulation* 121:2331–78. doi:10.1161/CIR.0b013e3181d8bec1. [PubMed: 20458016]
- Brouillette J, and Quirion R. 2008 The common environmental pollutant dioxin-induced memory deficits by altering estrogen pathways and a major route of retinol transport involving transthyretin. *Neurotoxicology* 29:318–27. doi:10.1016/j.neuro.2007.12.005. [PubMed: 18294692]
- Brown KH, Peerson JM, Rivera J, and Allen LH. 2002 Effect of supplemental zinc on the growth and serum zinc concentrations of prepubertal children: A meta-analysis of randomized controlled trials. *The American Journal of Clinical Nutrition* 75:1062–71. [PubMed: 12036814]
- Burdette HL, and Whitaker RC. 2004 Neighborhood playgrounds, fast food restaurants, and crime: Relationships to overweight in low-income preschool children. *Preventive Medicine* 38:57–63. doi:10.1016/j.ypmed.2003.09.029. [PubMed: 14672642]
- Caspers KM, Romitti PA, Lin S, Olney RS, Holmes LB, Werler MM, and Study National Birth Defects Prevention. 2013 Maternal periconceptional exposure to cigarette smoking and congenital limb deficiencies. *Paediatric and Perinatal Epidemiology* 27:509–20. doi:10.1111/ppe.2013.27.issue-6. [PubMed: 24134526]
- Chailurkit LO, Aekplakorn W, and Ongphiphadhanakul B. 2011 Regional variation and determinants of vitamin D status in sunshine-abundant Thailand. *BMC Public Health* 11:853. doi:10.1186/1471-2458-11-853. [PubMed: 22074319]
- Chandyo RK, Strand TA, Mathisen M, Ulak M, Adhikari RK, Bolann BJ, and Sommerfelt H. 2009 Zinc deficiency is common among healthy women of reproductive age in Bhaktapur, Nepal. *Journal of Nutrition* 139:594–97. doi:10.3945/jn.108.102111. [PubMed: 19158229]
- Chang CC, Chen PS, and Yang CY. 2015 Short-term effects of fine particulate air pollution on hospital admissions for cardiovascular diseases: A case-crossover study in a tropical city. *Journal of Toxicology and Environmental Health, Part A* 78:267–77. doi:10.1080/15287394.2014.960044. [PubMed: 25674828]
- Chen YC, Weng YH, Chiu YW, and Yang CY. 2015 Short-term effects of coarse particulate matter on hospital admissions for cardiovascular diseases: A case-crossover study in a tropical city. *Journal of Toxicology and Environmental Health, Part A* 78:1241–53. doi:10.1080/15287394.2015.1083520. [PubMed: 26408041]
- Ching P, Birmingham M, Goodman T, Sutter R, and Loevinsohn B. 2000 Childhood mortality impact and costs of integrating vitamin A supplementation into immunization campaigns. *American Journal of Public Health* 90:1526–29. doi:10.2105/AJPH.90.10.1526. [PubMed: 11029982]
- Costa S, Ferreira J, Silveira C, Costa C, Lopes D, Relvas H, Borrego C, Roebeling P, Miranda AI, and Teixeira JP. 2014. Integrating health on air quality assessment —review report on health risks of two major European outdoor air pollutants: PM and NO₂. *Journal Toxicological Environment Health B* 17:307–40. doi:10.1080/10937404.2014.946164.
- Creasy RK, Resnik R, Iams JD, Lockwood CJ, Greene MF, and Moore TR. 2013 *Creasy and Resnik's maternal- fetal medicine*. Philadelphia, PA: Principles and Practice: Elsevier Science Health Science.

- Crider KS, Bailey LB, and Berry RJ. 2011 Folic acid food fortification-its history, effect, concerns, and future directions. *Nutrients* 3:370–84. doi:10.3390/nu3030370. [PubMed: 22254102]
- Delange F 1994 The disorders induced by iodine deficiency. *Thyroid* 4:107–28. doi:10.1089/thy.1994.4.107. [PubMed: 8054857]
- Deloughery TG, Evans A, Sadeghi A, McWilliams J, Henner WD, Taylor LM, Jr., and R. D. Press. 1996 Common mutation in methylenetetrahydrofolate reductase: Correlation with homocysteine metabolism and late onset vascular disease. *Circulation* 94:3074–78. doi:10.1161/01.CIR.94.12.3074. [PubMed: 8989110]
- Dietary Guidelines Advisory Committee. 2015 Part D. Chapter 1: Food and nutrient intakes, and health: Current status and trends - continued. Washington D.C.: Office of Disease Prevention and Health Promotion.
- Dietrich M, Block G, Norkus EP, Hudes M, Traber MG, Cross CE, and Packer L. 2003 Smoking and exposure to environmental tobacco smoke decrease some plasma antioxidants and increase gamma-tocopherol in vivo after adjustment for dietary antioxidant intakes. *The American Journal of Clinical Nutrition* 77:160–66. [PubMed: 12499336]
- Dolinoy DC, Huang D, and Jirtle RL. 2007 Maternal nutrient supplementation counteracts bisphenol A-induced DNA hypomethylation in early development. *Proceedings of the National Academy of Sciences* 104:13056–61. doi:10.1073/pnas.0703739104.
- Dowd JB, and Aiello AE. 2008 Did national folic acid fortification reduce socioeconomic and racial disparities in folate status in the US? *International Journal of Epidemiology* 37:1059–66. doi:10.1093/ije/dyn066. [PubMed: 18456713]
- Duthie SJ, Grant G, and Narayanan S. 2000a Increased uracil misincorporation in lymphocytes from folate-deficient rats. *British Journal of Cancer* 83:1532–37. doi:10.1054/bjoc.2000.1481. [PubMed: 11076664]
- Duthie SJ, Narayanan S, Brand GM, and Grant G. 2000b DNA stability and genomic methylation status in colonocytes isolated from methyl-donor-deficient rats. *European Journal of Nutrition* 39:106–11. doi:10.1007/s003940070026. [PubMed: 10918992]
- Elabbas LE, Esteban J, Barber X, Hamscher G, Nau H, Bowers WJ, Nakai JS, Herlin M, Åkesson A, Viluksela M, Borg D, and Håkansson H. 2014 In Utero and Lactational exposure to a mixture of environmental contaminants detected in Canadian Arctic human populations alters retinoid levels in rat offspring with low margins of exposure. *Journal of Toxicology and Environmental Health. Part A* 77:223–45. doi:10.1080/15287394.2013.861776. [PubMed: 24588224]
- Feldkamp ML, Srisukhumbowornchai S, Romitti PA, Olney RS, Richardson SD, Botto LD, and Study National Birth Defects Prevention. 2014 Self-reported maternal cigarette smoke exposure during the periconceptional period and the risk for omphalocele. *Paediatric and Perinatal Epidemiology* 28:67–73. doi:10.1111/ppe.12093. [PubMed: 24313669]
- Flodstrom S, Busk L, Kronevi T, and Ahlborg UG. 1991 Modulation of 2,3,7,8-tetrachlorodibenzo-p-dioxin and phenobarbital-induced promotion of hepatocarcinogenesis in rats by the type of diet and vitamin A deficiency. *Fundamental and Applied Toxicology* 16:375–91. doi:10.1016/0272-0590(91)90122-K. [PubMed: 2055368]
- Ganji V, Zhang X, and Tangpricha V. 2012 Serum 25-hydroxyvitamin D concentrations and prevalence estimates of hypovitaminosis D in the U.S. population based on assay-adjusted data. *Journal of Nutrition* 142:498–507. doi:10.3945/jn.111.151977. [PubMed: 22323766]
- Gao YT 1996 Risk factors for lung cancer among nonsmokers with emphasis on lifestyle factors. *Lung Cancer* 14 (Suppl 1):S39–S45. doi:10.1016/S0169-5002(96)90209-3. [PubMed: 8785666]
- Ghio AJ, Carraway MS, and Madden MC. 2012 Composition of air pollution particles and oxidative stress in cells, tissues, and living systems. *Journal of Toxicology and Environmental Health, Part B* 15:1–21. doi:10.1080/10937404.2012.632359.
- Ghio AJ, Piantadosi CA, Wang X, Dailey LA, Stonehuerner JD, Madden MC, Yang F, Dolan KG, Garrick MD, and Garrick LM. 2005 Divalent metal transporter-1 decreases metal-related injury in the lung. *AJP: Lung cellular and Molecular Physiology* 289:L460–L467. doi:10.1152/ajplung.00154.2005. [PubMed: 15908475]
- Gilbert ME, Hedge JM, Valentin-Blasini L, Blount BC, Kannan K, Tietge J, Zoeller RT, Crofton KM, Jarrett JM, and Fisher JW. 2013 An animal model of marginal iodine deficiency during

- development: The thyroid axis and neurodevelopmental outcome. *Toxicological Sciences* 132:177–95. doi:10.1093/toxsci/kfs335. [PubMed: 23288053]
- Giugliano R, and Millward DJ. 1984 Growth and zinc homeostasis in the severely Zn-deficient rat. *British Journal of Nutrition* 52:545–60. doi:10.1079/BJN19840122. [PubMed: 6498147]
- Gomes EC, Allgrove JE, Florida-James G, and Stone V. 2011 Effect of vitamin supplementation on lung injury and running performance in a hot, humid, and ozone polluted environment. *Scandinavian Journal of Medicine & Science in Sports* 21:e452–e460. doi:10.1111/j.1600-0838.2011.01366.x. [PubMed: 22092484]
- Goralczyk R 2009 Beta-carotene and lung cancer in smokers: Review of hypotheses and status of research. *Nutrition and Cancer* 61:767–74. doi:10.1080/01635580903285155. [PubMed: 20155614]
- Greenberg N, Carel RS, Derazne E, Bibi H, Shpriz M, Tzur D, and Portnov BA. 2016 Different effects of longterm exposures to SO₂ and NO₂ air pollutants on asthma severity in young adults. *Journal of Toxicology and Environmental Health, Part A* 79:342–51. doi:10.1080/15287394.2016.1153548. [PubMed: 27092440]
- Haas EM, and Levin B. 2006 *Staying healthy with nutrition: The complete guide to diet and nutritional medicine*. Berkeley, CA: Celestial Arts.
- Hambidge KM, Hambidge C, Jacobs M, and Baum JD. 1972 Low levels of zinc in hair, anorexia, poor growth, and hypogeusia in children. *Pediatric Research* 6:868–74. doi:10.1203/00006450-197212000-00003. [PubMed: 4509185]
- Harik-Khan RI, Muller DC, and Wise RA. 2004 Serum vitamin levels and the risk of asthma in children. *American Journal of Epidemiology* 159:351–57. doi:10.1093/aje/kwh053. [PubMed: 14769638]
- Harinarayan CV, Ramalakshmi T, Prasad UV, Sudhakar D, Srinivasarao PV, Sarma KV, and Kumar EG. 2007 High prevalence of low dietary calcium, high phytate consumption, and vitamin D deficiency in healthy south Indians. *The American Journal of Clinical Nutrition* 85:1062–67. [PubMed: 17413106]
- Harrison EH, and Hussain MM. 2001 Mechanisms involved in the intestinal digestion and absorption of dietary vitamin A. *The Journal of Nutrition* 131:1405–08. [PubMed: 11340090]
- Hedlund TE, Moffatt KA, and Miller GJ. 1996 Stable expression of the nuclear vitamin D receptor in the human prostatic carcinoma cell line JCA-1: Evidence that the antiproliferative effects of 1 alpha, 25-dihydroxyvitamin D₃ are mediated exclusively through the genomic signaling pathway. *Endocrinology* 137:1554–61. [PubMed: 8612485]
- Heid MK, Bills ND, Hinrichs SH, and Clifford AJ. 1992 Folate deficiency alone does not produce neural tube defects in mice. *The Journal of Nutrition* 122:888–94. [PubMed: 1552363]
- Hennig B, Ettinger AS, Jandacek RJ, Koo S, McClain C, Seifried H, Silverstone A, Watkins B, and Suk WA. 2007 Using nutrition for intervention and prevention against environmental chemical toxicity and associated diseases. *Environmental Health perspectives* 115:493–95. doi:10.1289/ehp.9549. [PubMed: 17450213]
- Hodson KE, Bowman RJ, Mafwiri M, Wood M, Mhoro V, and Cox SE. 2011 Low folate status and indoor pollution are risk factors for endemic optic neuropathy in Tanzania. *British Journal of Ophthalmology* 95:1361–64. doi:10.1136/bjo.2010.197608. [PubMed: 21733919]
- Holick MF 2005 Vitamin D: Important for prevention of osteoporosis, cardiovascular heart disease, type 1 diabetes, autoimmune diseases, and some cancers. *Southern Medical Journal* 98:1024–26. doi:10.1097/01.SMJ.0000140865.32054.DB. [PubMed: 16295817]
- Holick MF 2012a D-fending the cardiovascular benefits of vitamin D. *Menopause* 19:1065–66. doi:10.1097/gme.0b013e31826e2cc5. [PubMed: 23014136]
- Holick MF 2012b Nutrition: Diabetes and death defying vitamin D. *Nature Reviews. Endocrinology* 8:388–90. doi:10.1038/nrendo.2012.84.
- Holick MF 2012c Vitamin D: Extraskelatal health. *Rheumatic Disease Clinics of North America* 38:141–60. doi:10.1016/j.rdc.2012.03.013. [PubMed: 22525849]
- Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, and Weaver CM. 2011 Evaluation, treatment, and prevention of vitamin D deficiency: An Endocrine

- Society clinical practice guideline. The Journal of Clinical Endocrinology & Metabolism 96:1911–30. doi:10.1210/jc.2011-0385. [PubMed: 21646368]
- Hosea Blewett HJ, Rector ES, and Taylor CG. 2008 Altered ex vivo cytokine production in zinc-deficient, pairfed and marginally zinc-deficient growing rats is independent of serum corticosterone concentrations. British Journal of Nutrition 100:820–28. doi:10.1017/S0007114508942148. [PubMed: 18307831]
- Hosseiniapanah F, Pour SH, Heibatollahi M, Moghbel N, Asefzade S, and Azizi F. 2010 The effects of air pollution on vitamin D status in healthy women: A cross sectional study. BMC Public Health 10:519. doi:10.1186/1471-2458-10-519. [PubMed: 20799984]
- Huang C, Zhang X, Qiao Z, Guan L, Peng S, Liu J, Xie R, and Zheng L. 1992 A case-control study of dietary factors in patients with lung cancer. Biomedical and Environmental Sciences 5:257–65. [PubMed: 1333225]
- Kadiiska MB, Hatch GE, Nyska A, Jones DP, Hensley K, Stocker R, George MM, Van Thiel DH, Stadler K, Barrett JC, and Mason RP. 2011 Biomarkers of oxidative stress study IV: Ozone exposure of rats and its effect on antioxidants in plasma and bronchoalveolar lavage fluid. Free Radical Biology and Medicine 51:1636–42. doi:10.1016/j.freeradbiomed.2011.07.013. [PubMed: 21824516]
- Kannan S, Misra DP, Dvonch JT, and Krishnakumar A. 2006 Exposures to airborne particulate matter and adverse perinatal outcomes: A biologically plausible mechanistic framework for exploring potential effect modification by nutrition. Environmental Health Perspectives 114:1636–42. [PubMed: 17107846]
- Kim JH, and Hong YC. 2012 GSTM1, GSTT1, and GSTP1 polymorphisms and associations between air pollutants and markers of insulin resistance in elderly Koreans. environmental Health perspectives 120:1378–84. doi:10.1289/ehp.1104406. [PubMed: 22732554]
- Klerk M, Verhoef P, Clarke R, Blom HJ, Kok FJ, Schouten EG, and Mthfr Studies Collaboration Group. 2002 MTHFR 677C–>T polymorphism and risk of coronary heart disease: A meta-analysis. JAMA 288:2023–31. doi:10.1001/jama.288.16.2023. [PubMed: 12387655]
- Kliwer SA, Umesono K, Mangelsdorf DJ, and Evans RM. 1992 Retinoid X receptor interacts with nuclear receptors in retinoic acid, thyroid hormone and vitamin D3 signalling. Nature 355:446–49. doi:10.1038/355446a0. [PubMed: 1310351]
- Kobiler D, Lustig S, and Shapira S. 2001 Brain iron uptake and transport in animal model of iron deficiency, Tardive Dyskinesia and neurodegenerative diseases. New York: Springer US.
- Kogai T, and Brent GA. 2012 The sodium iodide symporter (NIS): Regulation and approaches to targeting for cancer therapeutics. Pharmacology & Therapeutics 135:355–70. doi:10.1016/j.pharmthera.2012.06.007. [PubMed: 22750642]
- Kwong WT, Friello P, and Semba RD. 2004 Interactions between iron deficiency and lead poisoning: Epidemiology and pathogenesis. Science of the Total environment 330:21–37. doi:10.1016/j.scitotenv.2004.03.017. [PubMed: 15325155]
- Lapice E, Masulli M, and Vaccaro O. 2013 Iron deficiency and cardiovascular disease: An updated review of the evidence. Current Atherosclerosis Reports 15:358. [PubMed: 24057693]
- Latunde-Dada GO, McKie AT, and Simpson RJ. 2006 Animal models with enhanced erythropoiesis and iron absorption. Biochimica Et Biophysica Acta (BBA) -Molecular Basis of Disease 1762:414–23. doi:10.1016/j.bbadis.2005.12.007. [PubMed: 16459059]
- Leonard MB, Zemel BS, Kawchak DA, Ohene-Frempong K, and Stallings VA. 1998 Plasma zinc status, growth, and maturation in children with sickle cell disease. The Journal of Pediatrics 132:467–71. doi:10.1016/S0022-3476(98)70022-8. [PubMed: 9544903]
- Lester GE, VanderWiel CJ, Gray TK, and Talmage RV. 1982 Vitamin D deficiency in rats with normal serum calcium concentrations. Proceedings of the National Academy of Sciences 79:4791–94. doi:10.1073/pnas.79.15.4791.
- Leung AM, Braverman LE, and Pearce EN. 2012 History of U.S. iodine fortification and supplementation. Nutrients 4:1740–46. doi:10.3390/nu4111740. [PubMed: 23201844]
- Livingstone C 2015 Zinc: Physiology, deficiency, and parenteral nutrition. Nutrition in Clinical Practice 30:371–82. doi:10.1177/0884533615570376. [PubMed: 25681484]

- Lopez RP, and Hynes HP. 2006 Obesity, physical activity, and the urban environment: Public health research needs. *Environmental Health* 5:25. [PubMed: 16981988]
- Lozoff B, Jimenez E, and Wolf AW. 1991 Long-term developmental outcome of infants with iron deficiency. *The New England Journal of Medicine* 325:687–94. doi:10.1056/NEJM199109053251004. [PubMed: 1870641]
- Lu L, Yu Z, Pan A, Hu FB, Franco OH, Li H, Li X, Yang X, Chen Y, and Lin X. 2009 Plasma 25-hydroxyvitamin D concentration and metabolic syndrome among middle-aged and elderly Chinese individuals. *Diabetes Care* 32:1278–83. doi:10.2337/dc09-0209. [PubMed: 19366976]
- MacDonald RS 2000 The role of zinc in growth and cell proliferation. *The Journal of Nutrition* 130:1500S–1508S. [PubMed: 10801966]
- Mannino DM, Mulinare J, Ford ES, and Schwartz J. 2003 Tobacco smoke exposure and decreased serum and red blood cell folate levels: Data from the third national health and nutrition examination survey. *Nicotine & Tobacco research* 5:357–62. doi:10.1080/1462220031000094330. [PubMed: 12791531]
- Matsui EC 2014 Environmental exposures and asthma morbidity in children living in urban neighborhoods. *Allergy* 69:553–58. doi:10.1111/all.12361. [PubMed: 24697316]
- Mejors KK, Kim HW, Lim EM, and Chang N. 2013 Effects of parental folate deficiency on the folate content, global DNA methylation, and expressions of FRalpha, IGF-2 and IGF-1R in the postnatal rat liver. *Nutrition Research and Practice* 7:281–86. doi:10.4162/nrp.2013.7.4.281. [PubMed: 23964315]
- Moore T, and Holmes PD. 1971 The production of experimental vitamin A deficiency in rats and mice. *Laboratory Animals* 5:239–50. doi:10.1258/002367771781006492. [PubMed: 5126333]
- Mudway IS, Behndig AF, Helleday R, Pourazar J, Frew AJ, Kelly FJ, and Blomberg A. 2006 Vitamin supplementation does not protect against symptoms in ozone responsive subjects. *Free radical Biology and Medicine* 40:1702–12. doi:10.1016/j.freeradbiomed.2005.10.050. [PubMed: 16767844]
- Neufeld LM, Haas JD, Ruel MT, Grajeda R, and Naeher LP. 2004 Smoky indoor cooking fires are associated with elevated hemoglobin concentration in iron-deficient women. *Revista Panamericana De Salud Publica* 15:110–18. doi:10.1590/S1020-49892004000200006. [PubMed: 15030656]
- Nimitphong H, and Holick MF. 2013 Vitamin D status and sun exposure in southeast Asia. *Dermatoendocrinology* 5:34–37. doi:10.4161/derm.24054.
- Oudemans-Van Straaten HM, Spoelstra-De Man AM, and De Waard MC. 2014 Vitamin C revisited. *Critical Care* 18:460. [PubMed: 25185110]
- Ozpinar A, Kelestimur F, Songur Y, Can O, Valentin L, Caldwell K, Arian E, Unsal I, Serteser M, Inal T, Erdemgil Y, Coskun A, Bakirci N, Sezgin O, and Blount B. 2014 Iodine status in Turkish populations and exposure to iodide uptake inhibitors. *PLoS One* 9:e88206. doi:10.1371/journal.pone.0088206. [PubMed: 24505430]
- Padayatty SJ, Katz A, Wang Y, Eck P, Kwon O, Lee JH, Chen S, Corpe C, Dutta A, Dutta SK, and Levine M. 2003 Vitamin C as an antioxidant: Evaluation of its role in disease prevention. *Journal of the American College of Nutrition* 22:18–35. doi:10.1080/07315724.2003.10719272. [PubMed: 12569111]
- Padhy PK, and Padhi BK. 2009 Effects of biomass combustion smoke on hematological and antioxidant profile among children (8–13 years) in India. *Inhalation Toxicology* 21:705–11. doi:10.1080/08958370802448961. [PubMed: 19555227]
- Panda K, Chattopadhyay R, Chattopadhyay DJ, and Chatterjee IB. 2000 Vitamin C prevents cigarette smoke induced oxidative damage in vivo. *Free radical Biology and Medicine* 29:115–24. doi:10.1016/S0891-5849(00)00297-5. [PubMed: 10980400]
- Panemangalore M, and Bebe FN. 1997 Zinc diets: *Deficiency and excess* In Trace elements in laboratory rodents, ed. Watson RR, 191–214. Boca Raton, FL, USA: CRC Press.
- Partearroyo T, Perez-Miguelsanz J, Ubeda N, Valencia-Benitez M, Alonso-Aperte E, and Varela-Moreiras G. 2013 Dietary folic acid intake differentially affects methionine metabolism markers and hippocampus morphology in aged rats. *European Journal of Nutrition* 52:1157–67. doi:10.1007/s00394-012-0426-1. [PubMed: 22832899]

- Pearce EN, and Braverman LE. 2009 Environmental pollutants and the thyroid. *Best Practice & Research Clinical Endocrinology & Metabolism* 23:801–13. doi:10.1016/j.beem.2009.06.003. [PubMed: 19942155]
- Perrine CG, Herrick K, Serdula MK, and Sullivan KM. 2010 Some subgroups of reproductive age women in the United States may be at risk for iodine deficiency. *Journal of Nutrition* 140:1489–94. doi:10.3945/jn.109.120147. [PubMed: 20554903]
- Powell SR 2000 The antioxidant properties of zinc. *The Journal of Nutrition* 130:1447S–1454S. [PubMed: 10801958]
- Rader JI, and Schneeman BO. 2006 Prevalence of neural tube defects, folate status, and folate fortification of enriched cereal-grain products in the United States. *Pediatrics* 117:1394–99. doi:10.1542/peds.2005-2745. [PubMed: 16585338]
- Rao J, and Jagadeesan V. 1995 Development of a rat model for iron deficiency and toxicological studies: Comparison among Fischer 344, Wistar, and Sprague Dawley strains. *Laboratory Animal Science* 45:393–97. [PubMed: 7474878]
- Ravindran RD, Vashist P, Gupta SK, Young IS, Maraini G, Camparini M, Jayanthi R, John N, Fitzpatrick KE, Chakravarthy U, Ravilla TD, and Fletcher AE. 2011 Prevalence and risk factors for vitamin C deficiency in north and south India: A two centre population based study in people aged 60 years and over. *PLoS One* 6:e28588. doi:10.1371/journal.pone.0028588. [PubMed: 22163038]
- Rojanapo W, Lamb AJ, and Olson JA. 1980 The prevalence, metabolism and migration of goblet cells in rat intestine following the induction of rapid, synchronous vitamin A deficiency. *The Journal of Nutrition* 110:178–88. [PubMed: 7354380]
- Rosenthal AM 2003 WHO names top 10 health risks. *Environmental Health perspectives* 111:A456. doi:10.1289/ehp.111-a456. [PubMed: 12842792]
- Sauer J, Mason JB, and Choi SW. 2009 Too much folate: A risk factor for cancer and cardiovascular disease? *Current Opinion in Clinical Nutrition and Metabolic Care* 12:30–36. doi:10.1097/MCO.0b013e32831cec62. [PubMed: 19057184]
- Senthilkumar S, Manju A, Muthuselvam P, Shalini D, Indhumathi V, Kalaiselvi K, Palanivel M, Chandrasekar PP, and Rajaguru P. 2014 Characterization and genotoxicity evaluation of particulate matter collected from industrial atmosphere in Tamil Nadu state, India. *Journal of Hazardous Materials* 274:392–98. doi:10.1016/j.jhazmat.2014.04.017. [PubMed: 24797908]
- Shi G, Chen Z, Teng J, Bi C, Zhou D, Sun C, Li Y, and Xu S. 2012 Fluxes, variability and sources of cadmium, lead, arsenic and mercury in dry atmospheric depositions in urban, suburban and rural areas. *Environmental Research* 113:28–32. doi:10.1016/j.envres.2012.01.001. [PubMed: 22280823]
- Shibata A, Paganini-Hill A, Ross RK, Yu MC, and Henderson BE. 1992 Dietary beta-carotene, cigarette smoking, and lung cancer in men. *Cancer Causes Control* 3:207–14. doi:10.1007/BF00124253. [PubMed: 1610967]
- Snow SJ, De Vizcaya-Ruiz A, Osornio-Vargas A, Thomas RF, Schladweiler MC, McGee J, and Kodavanti UP. 2014 The effect of composition, size, and solubility on acute pulmonary injury in rats following exposure to Mexico city ambient particulate matter samples. *Journal of Toxicology and Environmental Health, Part A* 77:1164–82. doi:10.1080/15287394.2014.917445. [PubMed: 25119738]
- Stavenuiter AW, Arcidiacono MV, Ferrantelli E, Keuning ED, Vila Cuenca M, Ter Wee PM, Beelen RH, Vervloet MG, and Dusso AS. 2015 A novel rat model of vitamin D deficiency: Safe and rapid induction of vitamin D and calcitriol deficiency without hyperparathyroidism. *Biomed research International* 2015:604275. doi:10.1155/2015/604275. [PubMed: 25815325]
- Stojic SS, Staniši N, Stoji A, and Šoštari A. 2016 Single and combined effects of air pollutants on circulatory and respiratory system-related mortality in Belgrade, Serbia. *Journal of Toxicology and Environmental Health, Part A* 79:17–27. doi:10.1080/15287394.2015.1101407. [PubMed: 26699658]
- Stoltzfus RJ 2003 Iron deficiency: Global prevalence and consequences. *Food and Nutrition Bulletin* 24:S99–S103. doi:10.1177/15648265030244S206. [PubMed: 17016951]

- Tei M, Spurr-Michaud SJ, Tisdale AS, and Gipson IK. 2000 Vitamin A deficiency alters the expression of mucin genes by the rat ocular surface epithelium. *Investigative Ophthalmology & Visual Science* 41:82–88. [PubMed: 10634605]
- Torheim LE, Ferguson EL, Penrose K, and Arimond M. 2010 Women in resource-poor settings are at risk of inadequate intakes of multiple micronutrients. *Journal of Nutrition* 140:2051S–2058S. doi:10.3945/jn.110.123463. [PubMed: 20881075]
- Tribble DL, Giuliano LJ, and Fortmann SP. 1993 Reduced plasma ascorbic acid concentrations in nonsmokers regularly exposed to environmental tobacco smoke. *The American Journal of Clinical Nutrition* 58:886–90. [PubMed: 8249873]
- Underwood JL, and DeLuca HF. 1984 Vitamin D is not directly necessary for bone growth and mineralization. *The American Journal of Physiology* 246:E493–E498. [PubMed: 6742112]
- Valkonen MM, and Kuusi T. 2000 Vitamin C prevents the acute atherogenic effects of passive smoking. *Free radical Biology and Medicine* 28:428–36. doi:10.1016/S0891-5849(99)00260-9. [PubMed: 10699755]
- Vallee BL, and Falchuk KH. 1993 The biochemical basis of zinc physiology. *Physiological Reviews* 73:79–118. [PubMed: 8419966]
- Van Jaarsveld H, Kuyl JM, and Alberts DW. 1992 Antioxidant vitamin supplementation of smoke-exposed rats partially protects against myocardial ischaemic/reperfusion injury. *Free radical Research Communications* 17:263–69. doi:10.3109/10715769209079518. [PubMed: 1473735]
- Varga EA, Sturm AC, Misita CP, and Moll S. 2005 Cardiology patient pages. Homocysteine and MTHFR mutations: Relation to thrombosis and coronary artery disease. *Circulation* 111:e289–e293. doi:10.1161/01.CIR.0000165142.37711.E7. [PubMed: 15897349]
- Viteri FE 1994 The consequences of iron deficiency and anaemia in pregnancy on maternal health, the foetus and the infant. *SCN News* 11:14–18.
- Walravens PA, Krebs NF, and Hambidge KM. 1983 Linear growth of low income preschool children receiving a zinc supplement. *The American Journal of Clinical Nutrition* 38:195–201. [PubMed: 6881078]
- Wang TC, Song YS, Wang H, Zhang J, Yu SF, Gu YE, Chen T, Wang Y, Shen HQ, and Jia G. 2012 Oxidative DNA damage and global DNA hypomethylation are related to folate deficiency in chromate manufacturing workers. *Journal of Hazardous Materials* 213–214:440–46. doi:10.1016/j.jhazmat.2012.02.024.
- Wang X, Ghio AJ, Yang F, Dolan KG, Garrick MD, and Piantadosi CA. 2002 Iron uptake and Nramp2/DMT1/DCT1 in human bronchial epithelial cells. *American Journal of Physiology Lung Cellular and Molecular Physiology* 282:L987–L995. doi:10.1152/ajplung.00253.2001. [PubMed: 11943663]
- WHO. 1962 11 special subjects: Causes of death. 1. Anaemias. *World Health Statistics Quarterly* 15:594.
- Widome R, Jacobs DR, Jr., Hozawa A, Sijtsma F, Gross M, Schreiner PJ, and Iribarren C. 2010 Passive smoke exposure and circulating carotenoids in the CARDIA study. *Annals of Nutrition & Metabolism* 56:113–18. doi:10.1159/000277662. [PubMed: 20110671]
- Wiedermann U, Chen XJ, Enerback L, Hanson LA, Kahu H, and Dahlgren UI. 1996 Vitamin A deficiency increases inflammatory responses. *Scandinavian Journal of Immunology* 44:578–84. doi:10.1046/j.1365-3083.1996.d01-351.x. [PubMed: 8972739]
- Yagil R, Etzion Z, Rovner M, Meyerstein M, Abu-Rabiya U, Roiz Y, and Walfish S. 1982 Cooking-smoke as a factor affecting thyroid metabolism and oxygen transport capability. *Comparative Biochemistry and Physiology Part A: Physiology* 73:181–86. doi: 10.1016/0300-9629(82)90052-4.
- Yanagi Y, Assuncao JV, and Barrozo LV. 2012 The impact of atmospheric particulate matter on cancer incidence and mortality in the city of Sao Paulo, Brazil. *Cadernos De Saude Publica* 28:1737–48. doi:10.1590/S0102-311X2012000900012. [PubMed: 23033188]
- Yip R 2000 Significance of an abnormally low or high hemoglobin concentration during pregnancy: Special consideration of iron nutrition. *The American Journal of Clinical Nutrition* 72:272S–279S. [PubMed: 10871593]

- Yu R, and Schellhorn HE. 2013 Recent applications of engineered animal antioxidant deficiency models in human nutrition and chronic disease. *Journal of Nutrition* 143:1–11. doi:10.3945/jn.112.168690. [PubMed: 23173175]
- Zemel BS, Kawchak DA, Fung EB, Ohene-Frempong K, and Stallings VA. 2002 Effect of zinc supplementation on growth and body composition in children with sickle cell disease. *The American Journal of Clinical Nutrition* 75:300–07. [PubMed: 11815322]
- Zerdin K, Rooney ML, and Vermue J. 2003 The vitamin C content of orange juice packed in an oxygen scavenger material. *Food chemistry* 82:387–95. doi:10.1016/S0308-8146(02)00559-9.
- Zhang R, Ma J, Xia M, Zhu H, and Ling W. 2004 Mild hyperhomocysteinemia induced by feeding rats diets rich in methionine or deficient in folate promotes early atherosclerotic inflammatory processes. *The Journal of Nutrition* 134:825–30. [PubMed: 15051832]
- Zhang XK, and Pfahl M. 1993 Hetero- and homodimeric receptors in thyroid hormone and vitamin A action. *Receptor* 3:183–91. [PubMed: 8167569]
- Zimmermann MB, and Andersson M. 2012 Update on iodine status worldwide. *Current Opinion in Endocrinology & Diabetes and Obesity* 19:382–87. doi:10.1097/MED.0b013e328357271a.
- Zimmermann MB, and Boelaert K. 2015 Iodine deficiency and thyroid disorders. *The Lancet Diabetes & Endocrinology* 3:286–95. doi:10.1016/S2213-8587(14)70225-6. [PubMed: 25591468]

Table 1.

Roles of identified at-risk nutrients.

Nutrient	Estimated average requirement*	At risk populations [§]	Major roles
Vitamin A	<ul style="list-style-type: none"> Children: 210 – 275 ug/d Males: 445 – 630 ug/d Females: 420 – 500 ug/d Pregnancy: 550 ug/d Lactation: 900 ug/d 	<ul style="list-style-type: none"> Asian countries Pre-school aged children Women of childbearing age 	<ul style="list-style-type: none"> Vision Maintenance of mucosal lining. Host response
Vitamin C	<ul style="list-style-type: none"> Children: 13 – 22 mg/d Males: 39 – 75 mg/d Females: 39 – 60 mg/d Pregnancy: 70 mg/d Lactation: 100 mg/d 	<ul style="list-style-type: none"> Low income Tobacco smokers Elderly 	<ul style="list-style-type: none"> Antioxidant Neurotransmitter synthesis Bone formation Energy metabolism
Vitamin D	<ul style="list-style-type: none"> Children: 10 ug/d Males: 10 ug/d Females: 10 ug/d Pregnancy: 10 ug/d Lactation: 10 ug/d 	<ul style="list-style-type: none"> Asian countries Hispanics and non-hispanic blacks Poor sun exposure Elderly Malabsorptive diseases and bariatric surgery patients 	<ul style="list-style-type: none"> Calcium and phosphorus absorption (bone health) Adaptive immunity (cardiovascular and systemic health)
Zinc	<ul style="list-style-type: none"> Children: 2.5 – 4.0 mg/d Males: 7.0 – 9.4 mg/d Females: 6.8 – 7.0 mg/d Pregnancy: 9.5 mg/d Lactation: 10.4 mg/d 	<ul style="list-style-type: none"> South Asia, Sub-Saharan Africa, South and Central Americas Elderly Vegans/vegetarians Sickle cell anemia 	<ul style="list-style-type: none"> Energy metabolism Immunity Motor and neurodevelopment Antioxidant
Iron	<ul style="list-style-type: none"> Children: 3.0 – 4.1 mg/d Males: 5.9 – 7.7 mg/d Females: 5.0 – 8.1 mg/d Pregnancy: 22 mg/d Lactation: 6.5 mg/d 	<ul style="list-style-type: none"> Adolescent and pre-menopausal females Pregnant women Malabsorptive diseases and bariatric surgery patients 	<ul style="list-style-type: none"> Hemoglobin (oxygen transport) Drug and energy metabolism Neurotransmitter synthesis Motor and neurodevelopment

Nutrient	Estimated average requirement*	At risk populations [§]	Major roles
Iodine	<ul style="list-style-type: none"> • Children: 65 ug/d • Males: 73 – 95 ug/d • Females: 73 – 95 ug/d • Pregnancy: 160 ug/d • Lactation: 209 ug/d 	<ul style="list-style-type: none"> • Regions with no fortification programs • Pregnant and lactating women • Children under 3 years of age 	<ul style="list-style-type: none"> • Thyroid hormone synthesis • Energy metabolism • Motor and neurodevelopment
Folate	<ul style="list-style-type: none"> • Children: 120 – 160 ug/d • Males: 250 – 320 ug/d • Females: 250 – 320 ug/d • Childbearing aged females: 400 ug/d • Pregnancy: 520 ug/d • Lactation: 450 ug/d 	<ul style="list-style-type: none"> • U.S. African Americans and low income families • Regions with no fortification programs • Pregnant women and those of childbearing age • Malabsorptive diseases including alcoholism • MTHFR polymorphism 	<ul style="list-style-type: none"> • Cell division • DNA synthesis and repair • Epigenetics • Homocysteine metabolism

* Estimated average requirement obtained from the dietary reference intakes published by the Food and Nutrition board, Institute of Medicine, National Academies.

[§]When not referring to a specific geographical region, at risk populations are global.

Table 2.

Summary of the interplay between nutrients and pollutants.

Nutrient	Risk of deficiency on pollutant exposure	Effects of pollutants on vitamin status	Study design caveats
Vitamin A	Increases sensitivity to infections and toxic compounds.	Compromises status.	<ul style="list-style-type: none"> Animal deficiency models must start early in life.
Vitamin C	Increases oxidative stress and injury.	Compromises status.	<ul style="list-style-type: none"> Most animal models synthesize Vitamin C.
Vitamin D	Compromises immunity.	May compromise status by reducing outdoor time and sunlight exposure.	<ul style="list-style-type: none"> Vitamin status does not change acutely. Deficiency often causes disturbances to parathyroid hormone and calcium.
Zinc	Compromises immunity and oxidative stress response.	May increase status depending on pollutant.	<ul style="list-style-type: none"> Pair-fed animals should be used for control groups. Consider marginally-deficient models.
Iron	Increases sensitivity to toxic compounds.	May increase status depending on pollutant	<ul style="list-style-type: none"> Rodent strains have differences in susceptibility to deficiency.
Iodine	Increases sensitivity to toxic compounds.	May reduce status through competitive uptake.	<ul style="list-style-type: none"> Mental retardation due to deficiency is irreversible.
Folate	Compromises regeneration and elevates cardiovascular risk.	Compromises status.	<ul style="list-style-type: none"> Consider screening for MTHFR gene polymorphisms in humans. Rodent models of deficiency do not develop neural tube defects, genetic models must be used.