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Protective influence of healthful nutrition on mechanisms of environmental pollutant toxicity and disease risks

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Abstract

Human exposures to environmental contaminants around the world contribute to the global burden of disease and thus require urgent attention. Exploring preventive measures against environmental exposure and disease risk is essential. While a sedentary lifestyle and/or poor dietary habits can exacerbate the deleterious effects resulting from exposure to toxic chemicals, much emerging evidence suggests that positive lifestyle changes (e.g., healthful nutrition) can modulate and/or reduce the toxicity of environmental pollutants. Our work has shown that diets high in anti-inflammatory bioactive food components (e.g., phytochemicals or polyphenols) are possible strategies for modulating and reducing the disease risks associated with exposure to toxic pollutants in the environment. Thus, consuming healthy diets rich in plant-derived bioactive nutrients may reduce the vulnerability to diseases linked to environmental toxic insults. This nutritional paradigm in environmental toxicology requires further study in order to improve our understanding of the relationships between nutrition and other lifestyle modifications and toxicant-induced diseases.

Keywords

nutrition; environmental pollutants; anti-inflammatory nutrients; antioxidants

Introduction

Environmental pollution affects nearly every country in the world, and exposure to environmental pollutants is involved in the pathogenesis of numerous non-communicable diseases, including cardiovascular disease, diabetes, and obesity.[1] Recent evidence from the World Health Organization revealed that China and India are two of the most affected countries in terms of indoor and outdoor air pollution exposures with approximately 6.5

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Competing interests

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million associated deaths each year.[2] Pollution from non-airborne exposures (e.g., contaminated foods and water) are more difficult to determine but should be expected to further increase these high death rates. Despite our knowledge of the adverse health effects of pollution exposure, levels of environmental pollutants have continued to rise over the past few years, especially in developing countries. Great strides have been made over the past decade to substantially reduce the amount of pollution generated; while total elimination is ideal, it is not a realistic or feasible goal in the immediate future.[3] The next question then becomes, What can we do now, as individuals, to protect ourselves and future generations from pollutant toxicity and associated diseases? Thus, if we can better understand the mechanisms associated with exposure to environmental pollutants and effects on disease risk we may be able to develop appropriate and effective means to tackle such issues.

Effects of pollutants on the Human Body

Pollutants affect nearly every system of the human body. We are exposed to pollution through a variety of routes, including air, the water we drink, and the foods that we consume.[1,4] These routes of exposure introduce complications throughout the pulmonary system, digestive tract, liver and circulation, and ultimately affect peripheral tissues.[1] The impact of exposure within these systems not only contributes to localized inflammatory responses, but may also influence whole-body metabolic, vascular, and immune health, thus increasing the risk of non-communicable diseases.

Pulmonary system

One common route of pollutant exposure is through inhalation, thus exerting detrimental effects on the pulmonary system.[4] Exposure to air pollution has been consistently linked with the development of conditions, including asthma, chronic obstructive pulmonary disease, and respiratory infections.[5] There is a well-documented interplay between air pollution exposure and increased airway reactivity in children with asthma, and chronic exposure may also increase the risk of asthma development in children.[5,6] Furthermore, exposure to air pollutants during gestational and early life has also been associated with disturbances in lung development and prevalence of respiratory conditions in childhood that may persist throughout life.[7] For example, short-term exposure to particulate matter ($PM_{2.5}$), NO_2, and ozone is associated with lower forced vital capacity and lower forced expiratory volume.[8] Additionally, a recent study reported that, in adult patients with acute respiratory distress syndrome, chronic exposure to air pollution (i.e., ozone and particulate matter) is associated with an increase rate of mortality.[9] Importantly, the initiation of inflammatory responses within the lungs from pollutant exposure can affect other organ systems, contributing to further disease pathologies.[10] For example, acute or chronic exposure to airborne particulate matter can accelerate the pathology of atherosclerosis through increases in vascular inflammation, macrophage infiltration, and generation of reactive oxygen species.[11,12]

Gastrointestinal tract

The gastrointestinal tract plays critical roles in human health and has recently garnered more attention in the scientific community, specifically regarding the intestinal barrier and gut microbiome. The principle function of the intestine is to regulate the absorption of water and nutrients into circulation while also serving as a barrier to the infiltration of pathogens and toxic compounds.[13] Additionally, the gut harbors trillions of bacteria that play critical roles in numerous facets of host metabolism and health.[14] Alterations in gut microbial composition is termed *dysbiosis* and has been linked to increased disease risk. These perturbations in gut microbial populations are associated with a decrease in microbial diversity and are observed in conditions of obesity and diabetes.[14] Importantly, there is current evidence that an altered gut microbiome may actually be causal in the development of such chronic inflammatory conditions.[15,16] Because the primary routes of exposure to many pollutants is through water and foods, the gastrointestinal tract is exposed to high levels of pollutants and may thus be greatly affected. Indeed, it has been observed that exposure to polychlorinated biphenyls (PCBs) disrupts intestinal barrier function through dysregulation of tight junction proteins.[17] Furthermore, oral exposure to the pollutant benzo[a]pyrene resulted in intestinal inflammation and ileal lesions, which was associated with shifts in gut microbial composition.[18] Importantly, Zhang *et al.*[19] demonstrated that exposure to the persistent organic pollutant tetrachlorodibenzofuran (TCDF) can result in alterations of gut microbial populations at the level of phylum, class, and genus, and these changes were associated with disruptions in bile acid and short-chain fatty acid (SCFA) metabolism.[19] This study is one of the first to indicate a link between the effects of pollutant exposure in the gut to overall metabolic health.

While it is commonly thought that air pollution only affects lung health, it is important to note that this exposure can also affect the digestive tract and, subsequently, organ systems. It has been documented that, upon inhalation, airborne pollutants are quickly cleared from the lungs and transported to the intestine via mucociliary transport.[13] Therefore, even airborne pollutants can alter overall gut health and microbial populations. For example, it has been demonstrated that ingestion of airborne particulate matter (PM) can cause intestinal inflammation and alter the gut microbiota, contributing to alterations of SCFA production in mice.[20] Additionally, in colonic cells, exposure to PM caused reactive oxygen species production, nuclear factor κb (NF-κB) activation, and disruptions in tight junction proteins, indicating that PM may disrupt intestinal permeability and increase intestinal inflammation.[21] Because the gut lies at the interface of the outside environment and our internal organ systems, maintenance of a healthy intestinal environment and microbiome may aid in prevention of pollutant-associated diseases.

Liver

Many nutrients and toxicants travel from the gut to the liver via the portal vein. Thus, the liver is one of the most critical organs in the body, contributing greatly to metabolism, secretory, excretory, and vascular functions. In the United States, the incidence of liver disease has increased with expanding levels of obesity and is thought to be due to an increase in non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis

(NASH).[22] While these liver pathologies can be developed through poor dietary and lifestyle choices, there is recent evidence that environmental pollutants can also greatly influence liver disease.[23] The term toxicant-associated fatty liver disease (TAFLD) is a relatively new type of liver disease and exhibits similar pathologies to other liver diseases.[23] TAFLD and its more severe form, toxicant associated steatohepatitis (TASH), have been observed in workers highly exposed to industrial chemicals, such as vinyl chloride.[24] These observations of TASH were associated with increased levels of inflammatory cytokines as well as insulin resistance, indicating the widespread metabolic complications that pollutant exposure can exert via the liver.[24] Furthermore, there is evidence that low-level pollutant exposure may also influence the development of liver pathologies. For example, epidemiological data from the general population revealed associations between PCBs and increased levels of serum alanine aminotransferase (ALT), a widely used biomarker of liver injury.[25] These findings support a potential association of chronic, low level pollutant exposure and the development of TAFLD and liver disease. Because the liver is such a vital organ for metabolism, environmental exposures affecting the liver may also contribute to obesity and diabetes through disruption in glucose and lipid metabolism. Therefore, further research is warranted to better understand the mechanisms behind pollutant-induced liver injury and avenues of potential protection against these pathologies.

Vascular tissues

Circulating nutrients, toxicants, and their metabolites can modulate vascular responses that can either be pro- or antiatherogenic. One of the key events in the progression of atherosclerosis is endothelial cell dysfunction. It has been documented that exposure to PM air pollution can disrupt the vasculature, resulting in endothelial cell dysfunction.[26] Furthermore, there is also evidence that arsenic exposure is associated with endothelial cell dysfunction, as evidenced by the presence of circulating soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular cell adhesion molecule-1 (sVCAM-1) in Bangladeshi individuals exposed to arsenic.[27] In support of this, in mouse models of atherosclerosis ($APOE^{-/-}$), exposure to arsenic resulted in increased accumulation of arsenic within the vessel walls as well as exacerbated aortal lesion formation.[28] There is also evidence that persistent organic pollutants (POPs), including PCBs, can increase atherosclerotic risk. Specifically, coplanar PCBs, such as PCB-77 and PCB-126, bind to the aryl hydrocarbon receptor (AhR) within vascular endothelial cells, triggering a cascade of events that leads to production of reactive oxygen species and disruption of cellular redox status.[29] These events ultimately lead to upregulation of NF-κB, resulting in induction of proinflammatory gene products, such as cytokines, chemokines, and cell adhesion molecules that contribute to endothelial cell dysfunction and the early stages of atherosclerosis.[30] More recent evidence suggests that dioxin-like pollutant exposure (PCB-126) can result in upregulation of the enzyme flavin-containing monooxygenase 3 (FMO3) and subsequently increase circulating levels of trimethylamine-*N*-oxide (TMAO), a biomarker strongly associated with cardiovascular disease.[31]

Peripheral tissues

Upon circulation of these environmental pollutants, as discussed above, numerous peripheral tissues become exposed, including highly vascularized adipose tissue.[32] With the worldwide obesity epidemic, research on the toxicological interplay between pollutants and adipose tissue has become increasingly important. It is no longer believed that adipose tissue is solely storage of excess energy, but it in fact plays numerous metabolic and endocrine roles within the body. In regard to pollutant exposure, adipose tissue is capable of storing lipophilic pollutants, specifically persistent organic pollutants (POPs).[32] While such storage can be protective to reduce availability to other organ systems in situations of acute and high pollutant exposures, there is evidence that a low and chronic release of POPs from adipose tissue can exert some toxic effects to other lipophilic tissues, such as the brain and the liver.[33] Furthermore, it has been demonstrated that pollutants can alter adipose tissue structure and function through metabolic disruption and inflammation, which may increase the risk of chronic metabolic diseases.[32,34] Some pollutants also have been associated with increases in adiposity and weight gain and are thus termed *obesogens*.[35] These pollutants, including bisphenol A (BPA), benzo[a]pyrene, and certain organophosphate pesticides, are thought to play a role in the development of obesity by disrupting lipid storage and metabolic mechanisms and promotion of adipocyte hyperplasia.[35,36]

As evidenced by the above-discussed findings, pollution has diverse and body-wide effects on human health, thus increasing the risk of disease. Therefore, identifying what makes an individual more at risk and understanding how lifestyle choices influence pollutant toxicity is of utmost importance.

What influences disease risk associated with environmental insults?

One major question to be addressed is why certain people are more susceptible to pollutant-associated diseases. It has been demonstrated that compromised health or suboptimal lifestyles may exacerbate the toxicity of environmental pollutants. For example, it has been shown that pollutant toxicity is worsened in animal models with NAFLD.[37] This illustrates the idea that individuals in poor health or with underlying disease conditions may be more susceptible to environmental insult or other chemical or non-chemical stressors. Additionally, it is now appreciated that events occurring during pregnancy can play a significant role in the future health and disease risk of the offspring. It has been documented that the offspring of mothers exposed to environmental pollutants during pregnancy exhibit effects that may be detrimental and persist into adulthood. For example, PM exposure throughout pregnancy was observed to be associated with an increased fetal C-reactive protein (CRP) level upon delivery, indicating that prenatal pollution exposure may increase fetal inflammatory responses and thus potentially alter long-term health outcomes.[38] Moreover, data from a longitudinal birth cohort study revealed an association between prenatal exposure to dichlorodiphenyltrichloroethane (DDT) and hypertension later in life, further indicating the long-term negative effects of early-life pollutant exposure.[39] Aside from compromised health and prenatal exposures, some individuals may be susceptible to disease development associated with environmental insults due to genetic predisposition to these non-communicable diseases. For example, certain genetic polymorphisms in oxidative

stress genes and inflammatory genes have been demonstrated to influence the respiratory effects and susceptibility to air pollution.[40]

Lifestyle and nutrition as a modulator of disease risk

As discussed above, the risk of pollutant-induced toxicity may be increased by underlying diseases, prenatal exposures, and genetic predispositions. Because certain unhealthy lifestyle choices can predispose an individual to disease, it can be expected that this may allow for greater pollutant-induced toxicity. Thus, finding ways to achieve a healthy lifestyle and therefore reduce disease risk are significant and highly important.

Recent evidence has shown that, while genetics play a role in disease risk, it may be smaller than once thought. In a recent study by Khera *et al.*,[41] it was observed that, in participants with a high genetic risk of coronary artery disease, those living a "favorable lifestyle" (i.e., no obesity, no smoking, regular physical activity, and a healthy diet) had approximately a 50% lower relative risk of coronary artery disease compared with those living an "unfavorable lifestyle."[41] These findings demonstrate just how influential our lifestyle choices are on overall disease risk independent of genetic risk. For individuals looking to achieve favorable lifestyle choices, a logical place to start is examination of dietary habits. Because nutrition is such a critical aspect of life, with food being a fundamental component for survival, understanding how nutrition affects our health is essential. Research has established that certain nutrition practices can worsen health outcomes, while others can provide benefits. This is well demonstrated by the present global obesity epidemic, which has been attributed to a reliance on processed, high-fat, and nutrient-poor foods that contribute to excess energy intake relative to actual nutrient requirements.[42] While body fat gain is the first visible complication of this chronic positive energy balance, the internal inflammatory processes and metabolic complications elicited pose a greater threat to overall well-being. These less visible metabolic complications can even occur before any weight gain. For example, consumption of high-fat diets, with greater proportions of saturated, *trans*-, and omega-6 fatty acids (e.g., linoleic acid), can increase inflammatory processes rapidly and thus long-term cardiovascular disease risks.[43,44] Additionally, research examining the effects of consumption of processed meats has become a source of great interest and controversy in the field of nutrition. As defined by the American Institute for Cancer Research, processed meats are "meats preserved by smoking, curing or salting, or addition of chemical preservatives." Interestingly, a meta-analysis conducted by Micha *et al.*[45] revealed that a single serving per day of processed meat was associated with a 42% increase in risk of coronary heart disease and a 19% higher risk of diabetes mellitus.[45]

On the other hand, it is well appreciated that many chronic diseases, such as cardiovascular disease and type 2 diabetes, can be prevented or attenuated with healthful dietary practices. This includes diets similar to that of the Mediterranean diet, rich in omega-3 fatty acids, fruits, vegetables, and whole grains.[46,47] These dietary components, which are rich in antioxidant and anti-inflammatory compounds (e.g., phytochemicals and polyphenols), may reduce or prevent the proinflammatory events associated with chronic metabolic diseases.[46,47] Additionally, there is also evidence that consumption of polyphenolic compounds, such as resveratrol, tea polyphenols, and curcumin can protect against

inflammation and chronic disease through alterations in proinflammatory gene expression both directly and through epigenetic modifications.[48] For example, curcumin, a principle component of the spice turmeric, has been demonstrated to suppress or inhibit the expression of tumor necrosis factor α (TNF-α), as well as cyclooxygenase 2 (COX-2), the target of nonsteroidal anti-inflammatory drugs (NSAIDs).[49,50] Additionally, the consumption of table grapes, rich in polyphenolic compounds, including resveratrol and anthocyanins, have been shown to attenuate systemic inflammatory responses, hepatic lipogenesis, and adiposity in mice fed a high-fat diet.[51] Thus, dietary choices are very powerful, and when chosen appropriately can vastly influence the development of numerous metabolic diseases.

Influence of nutrition on pollutant toxicity

The underlying denominator of non-communicable diseases, such as those observed from pollutant exposure, is oxidative stress and inflammation. An inflammatory process usually precedes other health effects, and thus is a critical step to understand and identify means to protect against inflammation. Similar to the way in which nutrition can contribute to or protect from non-communicable diseases, nutrition can also modulate the toxicity of environmental pollutants, thereby altering overall disease risk. It has been established that certain unhealthy nutrition practices can actually worsen the toxicity of pollutant exposure. The overconsumption of processed and refined foods contributes to diets high in inflammatory fatty acids, which not only exacerbate diet-induced metabolic complications, but also pollutant-associated inflammatory processes.[52,53] These high-fat processed foods are also low in protective bioactive nutrients, thus leading to increased oxidative stress and inflammation. Additional stressors, such as environmental insults, added to this may result in a greater inflammatory response, which could be due to the fact that the mechanisms of pollutant-induced toxicity and dietary-induced inflammatory responses are similar.[53] This detrimental interplay of nutrition and pollutants was illustrated comparing the effects of PCB exposure in mice fed corn oil (high in linoleic acid) versus mice fed olive oil (high in oleic acid). In corn oil–fed mice, PCB exposure resulted in further increases in expression of aortic vascular cell adhesion molecule 1 (VCAM-1). Importantly, this observation was not observed in mice fed olive oil, indicating the selective interaction of specific dietary fats with PCB inflammatory processes.[54] Others have also observed this toxic interplay of pollutants and nutrition. For example, it has been shown that high-fat diets can exacerbate arsenic-associated liver inflammation and fibrosis.[55] Additionally, diet-induced obesity and NAFLD are worsened in the presence of PCB-153, further illustrating the detrimental interplay of poor nutrition and pollutant exposure.[56]

As discussed above, individuals consuming a healthful diet already have a lower risk of chronic inflammatory disease and thus may be less susceptible to environmental insults and associated disease risks. This is important when considering the observed increase in air pollution in many overpopulated parts of the world and the link to risks of pulmonary and peripheral diseases. In fact, biological and epidemiological evidence suggest that exposure to particulate matter and related components of air pollution can contribute to oxidative stress and inflammation, suggesting that intake of diets enriched in antioxidant and anti-inflammatory nutrients should be advised to downregulate pulmonary disease risks.[57,58,59]

There is evidence that specific nutrients can actually reduce the toxicity and health complications associated with pollutant exposure. Diets rich in bioactive food components, such as omega-3 fatty acids and polyphenols, contain high levels of antioxidant and anti-inflammatory compounds that are capable of blunting the toxic and inflammatory effects of pollutant exposure.[60] Resveratrol, a polyphenol found abundantly in grapes, berries, and other plants, has been shown attenuate hepatic steatosis and oxidative stress in mice exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD).[61] Furthermore, resveratrol has also been documented to combat PCB-induced disruptions in adipocyte glucose homeostasis, which may protect against the development of type 2 diabetes associated with pollutant exposure.[62] Another phenolic compound, epigallocatechin gallate (EGCG), found in green tea, is capable of attenuating cardiovascular inflammation and toxicity associated with arsenic exposure.[63] In support of this, our lab has observed that consumption of green tea can reduce oxidative and inflammatory responses associated with PCB-126 exposure through upregulation of antioxidant enzymes.[64] Importantly, EGCG exhibits epigenetic regulation of NF-κB target genes, reducing PCB-126–induced endothelial cell inflammation mechanisms.[65]

In addition to combatting pollutant-induced inflammation and toxicity directly, there is evidence that certain nutritional components can actually aid in reducing the overall body burden of pollutants. Interestingly, it has been observed that individuals consuming vegetarian or vegan diets exhibit trends toward lower body burden of organochloride compounds.[66] These diets tend to be high in polyphenols and antioxidant compounds due to their plant-based focus, and thus it is possible that specific bioactive and plant-derived compounds may be promoting greater excretion of pollutants. However, these associations need to be further explored to determine if this is indeed the case. Because nutrition and pollutants often interact with and alter similar mechanistic pathways, it is possible that nutritional targeting of some of these pathways may be able to modulate pollutant metabolism and excretion. One example of the overlap in nutritional and pollutant interactions can be observed between arsenic and folate. For the body to facilitate excretion of arsenic, it must undergo methylation, with *S*-adenosylmethionine (SAM) functioning as the methyl donor. Interestingly, synthesis of SAM relies on a one-carbon metabolism that is folate dependent.[67] Therefore, supplementation with folate may enhance the methylation and subsequent excretion of arsenic. Indeed, Peters *et al.*[67] recently observed that 12- and 24-week supplementations of 800 μg/day of folic acid significantly reduced blood arsenic concentration in an arsenic-exposed Bangladeshi population.[67] This finding is especially important owing to the prevalence of chronic arsenic exposure worldwide and supports the importance of fostering a better understanding of the metabolism and excretion pathways of pollutants as potential targets of intervention. In addition to nutritional modulation of molecular mechanisms to enhance pollutant excretion, direct disruption or binding of these pollutants via the enterohepatic circulation may also provide a means of intervention to reduce body burden. For example, during this process, these pollutants become exposed to the intestinal environment, thus providing an avenue for potential dietary intervention. Indeed, it has been observed that consumption of the dietary fat substitute Olestra, a sucrose polyester, can enhance the excretion rate of PCBs and hexochlorobenzene in mice and also in highly exposed individuals.[68–70] This enhanced excretion is believed to be through

interference with the enterohepatic circulation of these pollutants. Because of these findings, there is the potential that other nutritional components may act similarly and be able to bind and increase pollutant excretion and ultimately reduce the body burden of certain pollutants.

Conclusions

Levels of environmental pollution are on the rise worldwide, especially in densely populated areas, including China and India. Environmental pollution affects virtually every aspect of the human body, including the pulmonary and gastrointestinal systems, liver, vasculature, and other peripheral tissues, such as adipose tissue. The diverse and detrimental impacts that pollutant exposure has on these systems contribute to the increasing occurrence of chronic inflammatory conditions observed worldwide. While efforts to reduce and remediate pollution are underway, means of immediate protection at an individual level is of upmost importance. Nutrition can have a drastic impact on the development of or protection against non-communicable diseases, such as those associated with pollutant exposure. There is increasing evidence of the protective mechanisms of healthful nutrition on pollutant toxicity, specifically regarding components of the Mediterranean diet (i.e., omega-3 fatty acids and anti-inflammatory polyphenols), suggesting a means by which individuals may be able to control the development of pollutant-associated disease risks. Because nutrition is such a critical aspect of daily life, it is important to continue to foster a better understanding of the ways in which the foods we consume can affect the toxicity of environmental pollutants. Positive lifestyle changes, such as healthful nutrition (e.g., diets high in phytochemicals or polyphenols), may provide the most sensible means to develop primary prevention strategies of diseases associated with many environmental toxic insults.

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References

1. Carpenter DO. Polychlorinated biphenyls (PCBs): routes of exposure and effects on human health. Rev Environ Health. 2006; 21:1–23. [PubMed: 16700427]
2. World Health Organization. [Accessed Feb 12, 2017] WHO releases country estimates on air pollution exposure and health impact. 2016. http://www.who.int/mediacentre/news/releases/2016/air-pollution-estimates/en/
3. Fulekar, M. Bioremediation Technology. Springer Netherlands; 2010. Global Status of Environmental Pollution and Its Remediation Strategies; p. 1-6.
4. Kampa M, Castanas E. Human health effects of air pollution. Environ Pollut. 2008; 151:362–367. [PubMed: 17646040]
5. Kurt OK, Zhang J, Pinkerton KE. Pulmonary health effects of air pollution. Curr Opin Pulm Med. 2016; 22:138–143. [PubMed: 26761628]
6. Ierodiakonou D, Zanobetti A, Coull BA, et al. Ambient air pollution, lung function, and airway responsiveness in asthmatic children. J Allergy Clin Immunol. 2016; 137:390–399. [PubMed: 26187234]
7. Veras MM, de Oliveira Alves N, Fajersztajn L, et al. Before the first breath: prenatal exposures to air pollution and lung development. Cell Tissue Res. 2017; 367:445–455. [PubMed: 27726025]

8. Rice MB, Ljungman PL, Wilker EH, et al. Short-term exposure to air pollution and lung function in the Framingham Heart Study. Am J Respir Crit Care Med. 2013; 188:1351–1357. [PubMed: 24200465]
9. Rush B, McDermid RC, Celi LA, et al. Association between chronic exposure to air pollution and mortality in the acute respiratory distress syndrome. Environ Pollut. 2017
10. Wong J, Magun BE, Wood LJ. Lung inflammation caused by inhaled toxicants: a review. Int J Chron Obstruct Pulmon Dis. 2016; 11:1391–1401. [PubMed: 27382275]
11. Sun Q, Wang A, Jin X, et al. Long-term air pollution exposure and acceleration of atherosclerosis and vascular inflammation in an animal model. JAMA. 2005; 294:3003–3010. [PubMed: 16414948]
12. Marchini T, Wolf D, Michel NA, et al. Acute exposure to air pollution particulate matter aggravates experimental myocardial infarction in mice by potentiating cytokine secretion from lung macrophages. Basic Res Cardiol. 2016; 111:44. [PubMed: 27240856]
13. Salim SY, Kaplan GG, Madsen KL. Air pollution effects on the gut microbiota: a link between exposure and inflammatory disease. Gut Microbes. 2014; 5:215–219. [PubMed: 24637593]
14. Kinross JM, Darzi AW, Nicholson JK. Gut microbiome-host interactions in health and disease. Genome Med. 2011; 3:14. [PubMed: 21392406]
15. Ellekilde M, Selfjord E, Larsen CS, et al. Transfer of gut microbiota from lean and obese mice to antibiotic-treated mice. Sci Rep. 2014; 4:5922. [PubMed: 25082483]
16. Turnbaugh PJ, Backhed F, Fulton L, et al. Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome. Cell Host Microbe. 2008; 3:213–223. [PubMed: 18407065]
17. Choi YJ, Seelbach MJ, Pu H, et al. Polychlorinated biphenyls disrupt intestinal integrity via NADPH oxidase-induced alterations of tight junction protein expression. Environ Health Perspect. 2010; 118:976–981. [PubMed: 20299304]
18. Ribiere C, Peyret P, Parisot N, et al. Oral exposure to environmental pollutant benzo[a]pyrene impacts the intestinal epithelium and induces gut microbial shifts in murine model. Sci Rep. 2016; 6:31027. [PubMed: 27503127]
19. Zhang L, Nichols RG, Correll J, et al. Persistent Organic Pollutants Modify Gut Microbiota-Host Metabolic Homeostasis in Mice Through Aryl Hydrocarbon Receptor Activation. Environ Health Perspect. 2015; 123:679–688. [PubMed: 25768209]
20. Kish L, Hotte N, Kaplan GG, et al. Environmental particulate matter induces murine intestinal inflammatory responses and alters the gut microbiome. PLoS One. 2013; 8:e62220. [PubMed: 23638009]
21. Mutlu EA, Engen PA, Soberanes S, et al. Particulate matter air pollution causes oxidant-mediated increase in gut permeability in mice. Part Fibre Toxicol. 2011; 8:19. [PubMed: 21658250]
22. Cave M, Deaciuc I, Mendez C, et al. Nonalcoholic fatty liver disease: predisposing factors and the role of nutrition. J Nutr Biochem. 2007; 18:184–195. [PubMed: 17296492]
23. Wahlang B, Beier JI, Clair HB, et al. Toxicant-associated steatohepatitis. Toxicol Pathol. 2013; 41:343–360. [PubMed: 23262638]
24. Cave M, Falkner KC, Ray M, et al. Toxicant-associated steatohepatitis in vinyl chloride workers. Hepatology. 2010; 51:474–481. [PubMed: 19902480]
25. Cave M, Appana S, Patel M, et al. Polychlorinated biphenyls, lead, and mercury are associated with liver disease in American adults: NHANES 2003–2004. Environ Health Perspect. 2010; 118:1735–1742. [PubMed: 21126940]
26. Brook RD, Rajagopalan S, Pope CA 3rd, et al. Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. Circulation. 2010; 121:2331–2378. [PubMed: 20458016]
27. Chen Y, Santella RM, Kibriya MG, et al. Association between arsenic exposure from drinking water and plasma levels of soluble cell adhesion molecules. Environ Health Perspect. 2007; 115:1415–1420. [PubMed: 17938729]
28. Simeonova PP, Hulderman T, Harki D, et al. Arsenic exposure accelerates atherogenesis in apolipoprotein E(−/−) mice. Environ Health Perspect. 2003; 111:1744–1748. [PubMed: 14594625]

29. Lim EJ, Majkova Z, Xu S, et al. Coplanar polychlorinated biphenyl-induced CYP1A1 is regulated through caveolae signaling in vascular endothelial cells. Chem Biol Interact. 2008; 176:71–78. [PubMed: 18786521]
30. Majkova Z, Smart E, Toborek M, et al. Up-regulation of endothelial monocyte chemoattractant protein-1 by coplanar PCB77 is caveolin-1-dependent. Toxicol Appl Pharmacol. 2009; 237:1–7. [PubMed: 19265715]
31. Petriello MC, Hoffman JB, Sunkara M, et al. Dioxin-like pollutants increase hepatic flavin containing monooxygenase (FMO3) expression to promote synthesis of the pro-atherogenic nutrient biomarker trimethylamine N-oxide from dietary precursors. J Nutr Biochem. 2016; 33:145–153. [PubMed: 27155921]
32. La Merrill M, Emond C, Kim MJ, et al. Toxicological function of adipose tissue: focus on persistent organic pollutants. Environ Health Perspect. 2013; 121:162–169. [PubMed: 23221922]
33. Kim MJ, Marchand P, Henegar C, et al. Fate and complex pathogenic effects of dioxins and polychlorinated biphenyls in obese subjects before and after drastic weight loss. Environ Health Perspect. 2011; 119:377–383. [PubMed: 21156398]
34. Arsenescu V, Arsenescu RI, King V, et al. Polychlorinated biphenyl-77 induces adipocyte differentiation and proinflammatory adipokines and promotes obesity and atherosclerosis. Environ Health Perspect. 2008; 116:761–768. [PubMed: 18560532]
35. Grun F. Obesogens. Curr Opin Endocrinol Diabetes Obes. 2010; 17:453–459. [PubMed: 20689419]
36. Holtcamp W. Obesogens: an environmental link to obesity. Environ Health Perspect. 2012; 120:a62–68. [PubMed: 22296745]
37. Wahlang B, Perkins JT, Petriello MC, et al. A Compromised Liver Alters Polychlorinated Biphenyl-Mediated Toxicity. Toxicology. 2017; 80:11–22.
38. van den Hooven EH, de Kluizenaar Y, Pierik FH, et al. Chronic air pollution exposure during pregnancy and maternal and fetal C-reactive protein levels: the Generation R Study. Environ Health Perspect. 2012; 120:746–751. [PubMed: 22306530]
39. La Merrill M, Cirillo PM, Terry MB, et al. Prenatal exposure to the pesticide DDT and hypertension diagnosed in women before age 50: a longitudinal birth cohort study. Environ Health Perspect. 2013; 121:594–599. [PubMed: 23591545]
40. Yang IA, Fong KM, Zimmerman PV, et al. Genetic susceptibility to the respiratory effects of air pollution. Thorax. 2008; 63:555–563. [PubMed: 18511640]
41. Khera AV, Emdin CA, Drake I, et al. Genetic Risk, Adherence to a Healthy Lifestyle, and Coronary Disease. N Engl J Med. 2016; 375:2349–2358. [PubMed: 27959714]
42. Kopelman PG. Obesity as a medical problem. Nature. 2000; 404:635–643. [PubMed: 10766250]
43. Baum SJ, Kris-Etherton PM, Willett WC, et al. Fatty acids in cardiovascular health and disease: a comprehensive update. J Clin Lipidol. 2012; 6:216–234. [PubMed: 22658146]
44. Kuipers RS, de Graaf DJ, Luxwolda MF, et al. Saturated fat, carbohydrates and cardiovascular disease. Neth J Med. 2011; 69:372–378. [PubMed: 21978979]
45. Micha R, Wallace SK, Mozaffarian D. Red and processed meat consumption and risk of incident coronary heart disease, stroke, and diabetes mellitus: a systematic review and meta-analysis. Circulation. 2010; 121:2271–2283. [PubMed: 20479151]
46. Sofi F, Cesari F, Abbate R, et al. Adherence to Mediterranean diet and health status: meta-analysis. BMJ. 2008; 337:a1344. [PubMed: 18786971]
47. Sofi F, Macchi C, Abbate R, et al. Mediterranean diet and health status: an updated meta-analysis and a proposal for a literature-based adherence score. Public Health Nutr. 2014; 17:2769–2782. [PubMed: 24476641]
48. Joven J, Micol V, Segura-Carretero A, et al. Polyphenols and the modulation of gene expression pathways: can we eat our way out of the danger of chronic disease? Crit Rev Food Sci Nutr. 2014; 54:985–1001. [PubMed: 24499117]
49. Aggarwal S, Ichikawa H, Takada Y, et al. Curcumin (diferuloylmethane) down-regulates expression of cell proliferation and antiapoptotic and metastatic gene products through suppression of IkappaBalpha kinase and Akt activation. Mol Pharmacol. 2006; 69:195–206. [PubMed: 16219905]

50. Lev-Ari S, Maimon Y, Strier L, et al. Down-regulation of prostaglandin E2 by curcumin is correlated with inhibition of cell growth and induction of apoptosis in human colon carcinoma cell lines. J Soc Integr Oncol. 2006; 4:21–26. [PubMed: 16737669]
51. Baldwin J, Collins B, Wolf PG, et al. Table grape consumption reduces adiposity and markers of hepatic lipogenesis and alters gut microbiota in butter fat-fed mice. J Nutr Biochem. 2016; 27:123–135. [PubMed: 26423887]
52. Hennig B, Ormsbee L, McClain CJ, et al. Nutrition can modulate the toxicity of environmental pollutants: implications in risk assessment and human health. Environ Health Perspect. 2012; 120:771–774. [PubMed: 22357258]
53. Hoffman JB, Petriello MC, Hennig B. Impact of nutrition on pollutant toxicity: an update with new insights into epigenetic regulation. Rev Environ Health. 2017; 32:65–72. [PubMed: 28076319]
54. Hennig B, Reiterer G, Toborek M, et al. Dietary fat interacts with PCBs to induce changes in lipid metabolism in mice deficient in low-density lipoprotein receptor. Environ Health Perspect. 2005; 113:83–87. [PubMed: 15626652]
55. Wu J, Liu J, Waalkes MP, et al. High dietary fat exacerbates arsenic-induced liver fibrosis in mice. Exp Biol Med (Maywood). 2008; 233:377–384. [PubMed: 18296743]
56. Wahlang B, Falkner KC, Gregory B, et al. Polychlorinated biphenyl 153 is a diet-dependent obesogen that worsens nonalcoholic fatty liver disease in male C57BL6/J mice. J Nutr Biochem. 2013; 24:1587–1595. [PubMed: 23618531]
57. Romieu I, Castro-Giner F, Kunzli N, et al. Air pollution, oxidative stress and dietary supplementation: a review. Eur Respir J. 2008; 31:179–197. [PubMed: 18166596]
58. Li XY, Hao L, Liu YH, et al. Protection against fine particle-induced pulmonary and systemic inflammation by omega-3 polyunsaturated fatty acids. Biochim Biophys Acta. 2017; 1861:577–584. [PubMed: 28011301]
59. Tong H. Dietary and pharmacological intervention to mitigate the cardiopulmonary effects of air pollution toxicity. Biochim Biophys Acta. 2016; 1860:2891–2898. [PubMed: 27189803]
60. Hennig B, Ettinger AS, Jandacek RJ, et al. Using nutrition for intervention and prevention against environmental chemical toxicity and associated diseases. Environ Health Perspect. 2007; 115:493–495. [PubMed: 17450213]
61. Ishida T, Takeda T, Koga T, et al. Attenuation of 2,3,7,8-tetrachlorodibenzo-p-dioxin toxicity by resveratrol: a comparative study with different routes of administration. Biol Pharm Bull. 2009; 32:876–881. [PubMed: 19420757]
62. Baker NA, English V, Sunkara M, et al. Resveratrol protects against polychlorinated biphenyl-mediated impairment of glucose homeostasis in adipocytes. J Nutr Biochem. 2013; 24:2168–2174. [PubMed: 24231106]
63. Sun TL, Liu Z, Qi ZJ, et al. (−)-Epigallocatechin-3-gallate (EGCG) attenuates arsenic-induced cardiotoxicity in rats. Food Chem Toxicol. 2016; 93:102–110. [PubMed: 27170490]
64. Newsome BJ, Petriello MC, Han SG, et al. Green tea diet decreases PCB 126-induced oxidative stress in mice by up-regulating antioxidant enzymes. J Nutr Biochem. 2014; 25:126–135. [PubMed: 24378064]
65. Liu D, Perkins JT, Hennig B. EGCG prevents PCB-126-induced endothelial cell inflammation via epigenetic modifications of NF-kappaB target genes in human endothelial cells. J Nutr Biochem. 2016; 28:164–170. [PubMed: 26878794]
66. Arguin H, Sanchez M, Bray GA, et al. Impact of adopting a vegan diet or an olestra supplementation on plasma organochlorine concentrations: results from two pilot studies. Br J Nutr. 2010; 103:1433–1441. [PubMed: 20030906]
67. Peters BA, Hall MN, Liu X, et al. Folic Acid and Creatine as Therapeutic Approaches to Lower Blood Arsenic: A Randomized Controlled Trial. Environ Health Perspect. 2015; 123:1294–1301. [PubMed: 25978852]
68. Jandacek RJ. Intervention to reduce PCBs: learnings from a controlled study of Anniston residents. Environ Sci Pollut Res Int. 2016; 23:2022–2026. [PubMed: 25721531]
69. Jandacek RJ, Anderson N, Liu M, et al. Effects of yo-yo diet, caloric restriction, and olestra on tissue distribution of hexachlorobenzene. Am J Physiol Gastrointest Liver Physiol. 2005; 288:G292–299. [PubMed: 15513954]

70. Jandacek RJ, Heubi JE, Buckley DD, et al. Reduction of the body burden of PCBs and DDE by dietary intervention in a randomized trial. J Nutr Biochem. 2014; 25:483–488. [PubMed: 24629911]