Nutrition Solutions to Counter Health Impact of Air Pollution: Scientific Evidence of Marine Omega-3 Fatty Acids and Vitamins Alleviating Some Harmful Effects of PM2.5

Weiguo Zhang1,*, Manfred Eggersdorfer2, Norman Salem Jr3, Jiong Jack Chen4, Szabolcs Peter2, Li-Qiang Qin5

1DSM Nutrition Products, Human Nutrition and Health, Beijing, China
2DSM Nutrition Products, Human Nutrition and Health, Kaiseraugst, Switzerland
3DSM Nutrition Products, Nutritional Lipids, Columbia, MA, USA
4DSM Nutrition Products, China Innovation Center, Shanghai, China
5School of Public Health, Soochow University, Suzhou, China

Corresponding author: Zhang, W. DSM Nutrition Products, Human Nutrition and Health, Beijing, China. E-mail: weiguozha@yahoo.com

Citation: Zhang, W. et al. Nutrition Solutions to Counter Health Impact of Air Pollution: Scientific Evidence of Marine Omega-3 Fatty Acids and Vitamins Minimizing Some Harms of PM2.5. (2015) J Food Nutr Sci 2(2): 1-6.

Keywords: Air pollution/pollutants; Fine particulate matter (PM2.5); Vitamins; Docosahexaenoic and eicosapentaenoic acids (DHA and EPA); Heart rate variability (HRV); Oxidative stress

Introduction

Air pollution is one of the most important environmental issues in today’s world. To address its importance, the World Health Organization (WHO) published the Global Update of Air Quality Guidelines (AQG) in 2005, in which the WHO has seriously emphasized that “clean air is considered to be a basic requirement of human health and well-being” (WHO 2005).

Major contaminants in the atmosphere include particulate matter, ozone, nitrogen dioxide and sulfur dioxide, which are mainly emitted when fossil fuels (especially coal and petroleum) and biomass are combusted. Among the major pollutants, particulate matter with aerodynamic diameter smaller than 2.5 micrometers is referred to as PM2.5. PM2.5 consists of a complex mixture of solid and liquid components, with organic and inorganic substances including sulfate, nitrates, ammonia, sodium chloride, carbon, mineral dust and water, which can travel deep into the lungs when inhaled. While the ambient PM2.5 concentration is reported hourly and daily in some countries, the use of an annual mean is preferred for evaluating its long-term impact on human health. According to the AQG, the recommended PM2.5 concentration, selected to minimize likely health effects based on existing literature, is an annual mean of 10 μg/m³ and a 24 hours mean of 25 μg/m³. The WHO also sets an annual mean of 35 μg/m³ as an interim target-1 (IT-1).

In this two-part literature review, we first describe an overview of current understanding about the harmful effects of PM2.5 and then summarize data from human studies on nutritional solutions as intervention for the detrimental responses to PM2.5 exposure. To identify the appropriate studies for inclusion for the second part, only scientific publications in peer-reviewed journals were considered, and the PubMed database was used. Specific nutritional interventions included vitamins and marine-derived long-chain polyunsaturated fatty acids (LCPUFA, i.e. fish oil or omega-3 fatty acids). Studies targeting populations composed exclusively of cigarette smokers were excluded, as cigarette smoke largely represents a self-induced PM2.5 exposure in addition to air pollution and is better managed differently (e.g. by lifestyle modification). Studies without human subjects were cited only when mechanisms were introduced.

Overview of Health Harms of PM2.5

PM2.5 is a Human Health Threat

According to the 2005 WHO Guidelines, exposure to PM2.5 at the 35 μg/m³ level (i.e. IT-1) is associated with an ap-
proximately 15% increase in mortality risk, relative to the AQG of 10μg/m³. A statement made by the American Heart Association in 2010, concluded that “the overall evidence from the cohort studies demonstrates on average an approximate 10% increase in all-cause mortality per 10 μg/m³ elevation in long-term average PM2.5 exposure⁵[1].

Carrying many toxic substances and getting to the alveoli deep within the lungs, PM2.5 can evoke a series of responses locally and systemically when inhaled. At the cellular and molecular level, exposure to PM2.5 causes an increased inflammatory response and a decreased anti-oxidative capability which would normally counteract reactive oxygen species (ROS), leading to oxidative stress⁵[3]. Some investigations also showed that more antioxidants in circulation system are consumed in response to air pollution⁵[6]. Decreased antioxidant capability or increased oxidative stress is repeatedly implicated as an important (if not the sole) mechanism⁵[7,8] in translating toxicity of PM2.5 into disease pathogenesis.

An example of PM2.5-induced cardiovascular damage is endothelial dysfunction and accelerated development of atherosclerosis⁵[9,10]. In a rodent model, larger arterial atherosclerotic plaque was demonstrated by histopathology after apoE deficient mice exposed to PM2.5 at a concentration of 85 μg/m³ for 6 hours/day, 5 days/week for 6 months versus the same animals that had filtered clean air. In the recent Multi-Ethnic Study of Atherosclerosis (MESA) with 5,362 human subjects over age 60, the intima-media thickness (IMT) of carotid artery was examined by ultrasound as a surrogate marker for arterial hypertrophy and lumen narrowing as well as atherosclerotic development⁵[11]. The results from the MESA population showed that the average annual progression of carotid IMT was 14 μm. An increase of 2.5 μg/m³ in residential PM2.5 level was associated with an additional 5 μm increase in IMT progression annually. This concentric arterial hypertrophy narrows arterial lumen, therefore causing hemodynamic disorders (e.g. blood flow turbulence and blood flow reduction in the distal end of the artery) and augmenting the risk of vascular events (e.g. thrombosis, vessel spasm and ischemia). An example of PM2.5-induced respiratory damage is the increased risk of lung cancer development. A recent meta-analysis from ESCAPE (European Study of Cohorts for Air Pollution Effects), showed a statistically significant association between risk for lung cancer and PM2.5 concentration with hazard ratio (HR) of 1.18 (95% CI 0.96-1.46) per 5 μg/m³ increase (for PM10, the HR was 1.22 with 95% CI 1.03-1.45 per 10 μg/m³). For lung adenocarcinomas, with the same increments of 2.5 μg/m³ in residential PM2.5 level was associated with a 5.0% reduction in HRV-HF⁵[23]. In subjects with an allele for glutathione-S-transferase M1 (GSTM1), a 10 μg/m³ increase in PM2.5 during the 48 hours before HRV measurement was associated with as much as 34% decrease in HRV-HF (95% confidence interval from −9% to −52%)⁵[24]. This polymorphic “null” genotype was reported in about half of the Caucasian population⁵[25].

**PM2.5 pollution is a long-term issue.**

To control and reduce PM2.5 emission at its source is ideal, but very challenging to practically implement. In the United States for example, according to the Environmental Protection Agency, it took over 12 years (from 2000 to 2012) to make a modest 37% reduction in PM2.5 concentration; in large metropolitan areas, however, PM2.5 remains an important pollutant⁵[25].

In developing countries, such as China, even the most aggressive plan for PM2.5 reduction would reduce PM2.5 by only 25% by 2017 (compared to 2012 levels in the Beijing-Tianjin and Hebei area); even if this goal is achieved by then, the annual PM2.5 concentration is projected to be 60 μg/m³, which is still 6-fold higher than the AQG recommendation.

Clearly, reduction of PM2.5 emission requires many coordinated efforts and resources including education, novel and affordable technology, legislation and law enforcement, and most importantly, time. Therefore, in the interim, large populations remain exposed to levels of PM2.5 above the WHO recommendations on a daily basis.

**Nutrition on PM2.5-Associated Heart Rate Variability**

Heart rate variability (HRV) or cardiac cycle length variability is a measurement of interval oscillations between consecutive heartbeats, reflecting beat-to-beat control in the heart by autonomic regulation. Generally, HRV declines with aging. In clinical settings, a reduction of HRV predicts adverse cardiovascular outcomes including ventricular arrhythmia, sudden cardiac death and myocardial infarction⁵[15-17]. HRV is derived from an electrocardiogram (ECG) that registers each QRS complex. Between adjacent QRS complexes, so-called normal-to-normal intervals (all intervals resulting from sinus node cyclic depolarization) are calculated. The standard deviations of normal-to-normal intervals (SDNN) reflect the time-domain differences of cardiac cycles in the period of ECG recording. Other HRV indices are low frequency (LF) and high frequency (HF). Both LF and HF are derived from power spectral density (PSD) analysis and provide information about how power (variance) distributes as a function of frequency. The HF and LF are considered to predominantly reflect parasympathetic (vagal) nerve activity and sympathetic drive (with some parasympathetic influence), respectively, from the central nervous system to the heart⁵[16,17].

The link between PM2.5 exposure and HRV abnormalities was noticed in late 1990s and confirmed repeatedly afterwards⁵[18-22]. For example, in the elderly residing in a nursing home in Mexico City where daily indoor and outdoor PM2.5 ranged from 15-67 and 9-87 μg/m³, a 10 μg/m³ increase in PM2.5 was associated with a 5.0% reduction in HRV-HF⁵[23]. In subjects without the allele for glutathione-S-transferase M1 (GSTM1), a 10 μg/m³ increase in PM2.5 during the 48 hours before HRV measurement was associated with as much as 34% decrease in HRV-HF (95% confidence interval from −9% to −52%)⁵[24]. This polymorphic “null” genotype was reported in about half of the Caucasian population⁵[25].
Fish Oil Prevents HRV Reduction Associated with PM2.5

In a double-blind clinical trial, 50 subjects over 60 years old were randomized to receive 2 g fish oil containing 52% docosahexaenoic acid (C22:6 n-3 DHA) and 25% eicosapentaenoic acid (C20:5 n-3 EPA) or 2 g soy oil for the placebo arm for a period of 6 months (1 month pre-supplementation and 5 months supplementation)[26]. During this time, the ambient PM2.5 levels varied from 5.1 to 49 μg/m³. The 24-hour average of PM2.5 concentration was 18.6±8.0 μg/m³ (mean±SD). For every 8 μg/m³ increase in PM2.5 (one standard deviation), the corresponding reduction of HRV-HF before supplementation was 54%. After 5 months of fish oil supplementation, the reduction was only 7%. In other words, a 47% reduction of HRV-HF was prevented by fish oil, compared to 31% by placebo (P=0.11) (Figure 1).

In addition, SDNN reduction was 27% before supplementation and was 0.5% after fish oil intervention (p<0.01). The effect of placebo oil on SDNN was not statistically significant. Biochemically, there were large increases of both EPA and DHA in erythrocytes from pre-supplementation levels (394% and 140%, respectively). The increase in EPA (87%) and no statistical increase in DHA[26]

Figure 1: Indices of heart rate variability (HRV), i.e. high frequency (HF), low frequency (LF) and standard deviations of normal-to-normal intervals (SDNN) were all reduced in response to each 8 μg/m³ increase in indoor PM2.5, which was largely prevented by fish oil supplement with statistical significance.

In another randomized trial, 29 healthy, middle-aged subjects were randomly assigned to receive olive oil as placebo or 3 g fish oil (containing 65% n-3 fatty acids) daily for 4 weeks, before being placed in an experimental chamber and exposed to concentrated PM2.5 and ultrafine particles with concentration ranging from 83 to 470 μg/m³ with an average of 278±19 μg/m³ [27]. After an acute exposure for 2 hours, the ratio of HF/LF of HRV was lowered and stayed low for 20 hours in subjects who had received placebo, signifying an altered balance between sympathetic and parasympathetic nerve activity. The reduction of the HF/LF ratio, however, was prevented in subjects who had received intervention with 3 g/day fish oil. Plasma assay revealed that there was more than a 5-fold increase in EPA and more than a 2-fold increase in docosapentaenoic acid (DPA) in subjects who received fish oil[27].

Dietary Methyl Nutrients May Prevent HRV Reduction Associated With PM2.5

Dietary methyl nutrients include folate, pyridoxine (vitamin B6), cyanocobalamin (B12) and methionine[28]. The effects of different intakes of methyl nutrients on PM2.5-induced HRV were investigated in the Normative Aging Study in elderly men. In all subjects, adjusted changes in SDNN, HF and LF for each 10 g/m³ of PM2.5 in the 48 hours before nutrient intake measurement were -7.1% (p=0.03), -18.7% (p=0.01) and -11.8% (p=0.08), respectively. In this study, lower dietary intake of vitamin B6 (<3.65 mg/d), B12 (<11.1 µg/d) and methionine (<1.88 mg/d) were accompanied by a pronounced reduction in SDNN, HF and LF for each 10 g/m³ increase in PM2.5 concentration. In contrast, higher intake of vitamin B6 (≥3.65 mg/d), B12 (≥11.1 µg/d) and methionine (≥1.88 mg/d) abrogated HRV reduction (Figure 2). The effects of folate intake on HRV reduction were not statistically significant. Although PM2.5 attenuated both HF and LF, the LF reduction was greater, indicating an imbalance between sympathetic and parasympathetic drive to the heart or relative activation of sympathetic nervous system. Figure 2 shows the effects of different methyl nutrients on SDNN. Similarly, the higher daily intake of these methyl nutrients prevented LF and HF from PM2.5-associated reduction. Of note, this study was not a randomized, placebo-controlled trial and the nutrient intake was estimated by dietary questionnaire, rather than precisely administered. Although the results favor increased methyl nutrient intake, these benefits are only correlations and need to be confirmed with more rigorous clinical trials.

Figure 2: PM 2.5 reduced HRV-SDNN significantly in subjects who had less vitamin B6, B12 and methionine intakes. Such reductions were prevented in those who had higher methyl nutrient intakes.

Gene and environmental interactions were observed in a subset analysis. Subjects with methylene tetrahydrofolate reductase (MTHFR) 677CT and 677TT polymorphisms had lower SDNN compared with 677CC before dietary examination; each 10 g/m³ increase in PM2.5 in the 48 hours before the examination was associated with a further 8.8% decrease in SDNN in MTHFR CT and TT, which was absent in the CC genotype. In cytoplasmic serine hydroxyl methyltransferase (cSHMT) 1420CC phenotype, PM2.5 caused an 11.8% decrease in SDNN, which was absent in cSHMT 1420CT and 1420TT carriers[29]. In a subset analysis, subjects with methylene tetrahydrofolate reductase (MTHFR) 677CT and 677TT polymorphisms had lower SDNN compared with 677CC before dietary examination; each 10 g/m³ increase in PM2.5 in the 48 hours before the examination was associated with a further 8.8% decrease in SDNN in MTHFR CT and TT, which was absent in the CC genotype. In cytoplasmic serine hydroxyl methyltransferase (cSHMT) 1420CC phenotype, PM2.5 caused an 11.8% decrease in SDNN, which was absent in cSHMT 1420CT and 1420TT carriers[29]. Both MTHFR and cSHMT polymorphisms were linked to cardiovascular risk as they involve in biological processes such as methyl group transfer, homosysteine metabolism and redox reactions[29-31] which were previously shown to be altered by exposure to air pollution[32,33,24]. Working as coenzymes or substrates in the methionine cycle that contributes to controlling the biological processes[29]. B vitamins and methionine may play a role in protecting this genetically vulnerable population against PM2.5-induced HRV change.
Nutrition on PM2.5–Induced Biochemical Alterations

Local and systematic inflammation and oxidative stress represent a major biochemical response to the exposure to PM2.5. To date, a large family of inflammatory biomarkers and reactive oxygen species (ROS) were unfavorably changed by PM2.5, including C-reactive protein (CRP), interleukin-6 (IL-6), IL-1β, tumor necrosis factor-α (TNF-α), superoxide dismutase (SOD), glutathione (GSH), lipid peroxidation (LPO), and glutathione S-transferase (GST). The alteration of these bioactive molecules are well known in mediating a physiological (e.g. aging) and pathological (e.g. atherosclerosis) cascade, relevant to the pathogenesis of various non-communicable diseases. While the anti-inflammatory and anti-oxidative effects of omega-3 have been recognized for a long time, some of the important mechanisms have been recently unveiled. For example, omega-3 binds to the G protein coupled receptor GPR120, alters cell membrane fatty acid composition and lipid rafts, and inhibits the activation of pro-inflammatory transcriptional factor (i.e. NF-κB), thereby reducing the expression of inflammatory genes and activating the anti-oxidative and anti-inflammatory transcription factor (e.g. peroxisome proliferator-activated receptors or PPAR-γ) [34-36]. In addition, lipophilic vitamin E and hydrophilic vitamin C have also been established as nutritional antioxidants [37,38], which can be obtained either from diet or supplementation.

Fish Oil Improves PM2.5-Induced Pro-atherosclerotic Lipid Profile

Both plasma triglycerides (TG) and very low-density lipoprotein (VLDL) increased significantly after inhalation of polluted air [27,39]. The changes of VLDL and TG were also studied in the randomized clinical trial cited previously, where subjects received either olive oil as placebo or fish oil and were placed in an experimental chamber inhaling polluted air with PM2.5 and ultrafine particles at an average level of 278±19 μg/m³ [28]. The elevations of TG and VLDL were observed after 2 hours of exposure and lasted for about 22 hours in subjects pretreated with placebo. However, the pro-atherosclerotic lipid change was prevented in subjects who received pretreatment with fish oil [37]. The mechanism for these lipid-lowering effects may involve the activation of PPAR pathway by fish oil treatment [34-36].

Fish Oil Reduces Oxidative Stress Associated With PM2.5

In a double-blind study in a nursing home in Mexico City, 52 participants over 60 years old were assigned randomly to either fish oil or placebo oil to test the protective effects of fish oil against PM2.5-induced oxidative stress. The mean amount of fish oil against PM2.5 was 38.7 μg/m³.

In a double-blind study in a nursing home in Mexico City, 52 participants over 60 years old were assigned randomly to either fish oil or placebo oil to test the protective effects of fish oil against PM2.5-induced oxidative stress. The mean amount of fish oil against PM2.5 was 38.7 μg/m³.

Vitamin E and C May Reduce Oxidative Stress Associated With PM2.5

In a Brazilian study to evaluate occupational exposure in a coal-electric power plant, a total of 80 individuals were randomly selected, controlled for age and sex, and divided into four groups (n=20 each): directly exposed (working in the coal burning areas), indirectly exposed (office workers located about 200 m from the plant), residents (about 2 km from the plant), and non-exposed subjects as controls. The study evaluated oxidative status based on exposure category. In response to direct exposure to airborne contamination, GSH was reduced in whole blood; thiobarbituric acid reactive substances (TBARS) and protein carbonyls (PC) were increased in plasma, and the activities of SOD and catalase (CAT) were increased in red blood cells. Compared with non-exposed subjects, GST was increased in all subjects regardless of exposure category. These biochemical changes suggest the occurrence of oxidative damage and the initiation of an endogenous detoxification process. Daily supplementation with vitamins C (500 mg) and E (800 mg) for 6 months effectively normalized these unfavorable alterations [42]. It should be noted that, in this study, while the baseline comparisons of the oxidative status were made with a control group as reference, the effects of active treatment with vitamin C and E were not compared with a placebo-treated control group, representing a shortcoming in study design.

Of particular interest, although there were no differences in dietary nutrient intake profile in the various groups in the Brazilian study, it is worth noting that the α-tocopherol levels were reduced in those exposed directly (by 51%) or indirectly (by 36%) to contaminated air or living in surrounding areas (by 37%) compared with controls who had no exposure (Figure 4). Previously, plasma and tissue vitamin E depletion have been found in ovine models with burn and smoke inhalation injury and in human cigarette smokers [5,6], although it is unclear if air pollution affects vitamin E metabolism in a similar manner. However, vitamin E and C are proven antioxidants [37,38]. Dietary vitamin E and C intake also improved asthmatic-related parameters in children who were exposed to atmospheric air mainly polluted by PM10 [41]. Taken together, these findings may suggest that supplementation with vitamin C and E is beneficial in subjects inhaling contaminated air in order to maintain an appro-
Nutrition Solutions to Counter Air Pollution Harms

private level of α-tocopherol and to augment overall anti-oxidant capability[42].

Figure 4: Despite similar profiles of nutrient intakes, circulation levels of α-tocopherol in subjects exposed to air pollution were decreased compared with that in control subjects. After vitamin E and C were administered, α-tocopherol levels in subjects inhaling polluted air were normalized.

Conclusions

The findings from recent scientific literature have shown that nutritional intervention is a promising preventative approach for PM2.5-induced pathophysiological and biochemical disorders. This does not reduce the responsibility of polluters or remove the pressure from authorities that legislate and enforce environmental protection policies and regulations; nor does it alter the disagreeable somatic and psychological impacts of the polluted environment on individuals. However, nutritional supplementation is simple and inexpensive, and may help in minimizing some of the harm accompanying PM2.5 exposure in the interim prior to reaching compliance with the WHO AQG[42].

It is clear, however, that this field is in need of further research. Aside from several placebo-controlled trials involving fish oil, similar human studies for other nutrients to combat the detrimental effects of air pollution on health are lacking. While both the interventional study with vitamins E and C and the observational study with dietary methyl nutrients are with positive results and tend to favor supplementation as well, in the absence of placebo control, these benefits are correlational and cannot be completely attributed to the effects of nutritional intervention. In this regard, the authors believe that future studies should include randomized, controlled trials to further verify the results, in particular those derived from observational studies. Additionally, while existing studies focus on fish oil, methyl nutrients, vitamins E and C, dietary compounds and ingredients, especially ones with anti-oxidant and anti-inflammatory activity, should be explored for potential health benefits against air pollution. Finally, the existing studies cited in this review are of limited duration; the long-term benefits or sequela of nutritional intervention, especially with regard to relevant PM2.5 clinical outcomes, such as hospitalizations, cardiovascular disease or pulmonary disease, still require further investigation. Overall, given that micronutrient intake deficiency is a common problem worldwide, we believe that the health benefits of nutritional supplementation deserve emphasis in both academic research and commercial product development.

Acknowledgment:

W.Z. initiated the literature search and was in charge of drafting the text and drawing the figures. All authors critically reviewed and revised the manuscript, and approved the final manuscript. W.Z. and M.E. took the responsibility of the final editing.

References

1. Brook, R. D., Rajagopalan, S., Pope, C. A. 3rd, et al. Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the american heart association. (2010) Circulation 121(21): 2331-2378.
2. Hou, L., Zhang, X., Dion, L., et al. Inhalable particulate matter and mitochondrial DNA copy number in highly exposed individuals in Beijing, china: A repeated-measure study. (2013) Part Fibre Toxicol 10: 17.
3. Oluzole, O., Arinola, G.O., Ana, G. R., et al. Relationship between household air pollution from biomass smoke exposure, and pulmonary dysfunction, oxidant-antioxidant imbalance and systemic inflammation in rural women and children in nigeria. (2013) Glob J Health Sci 5(4) :28-38.
4. Farchi, S., Forastiere, F., Pistelli, R., et al. Exposure to environmental tobacco smoke is associated with lower plasma beta-carotene levels among nonsmoking women married to a smoker. (2001) Cancer Epidemiol Biomarkers Prev 10(8): 907-909.
5. Handelman, G. J., Packer, L., Cross, C. E. Destruction of tocopherols, carotenoids, and retinol in human plasma by cigarette smoke. (1996) Am J Clin Nutr 63(4): 559-565.
6. Shimoda, K., Nakazawa, H., Traber, M. G., et al. Plasma and tissue vitamin E depletion in sheep with burn and smoke inhalation injury. (2008) Burns 34(8): 1137-1141.
7. Menzel, D. B. Antioxidant vitamins and prevention of lung disease. (1992) Ann N Y Acad Sci 669: 141-155.
8. Rossner, P. Jr., Svecova, V., Milcova, A., et al. Oxidative and nitrosative stress markers in bus drivers. (2007). Mutation Res 617(1-2): 23-32.
9. Montiel-Davalos, A., Ibarra-Sanchez Mde. J., Ventura-Gallegos, J. L., et al. Oxidative stress and apoptosis are induced in human endothelial cells exposed to urban particulate matter. (2010) Toxicol In Vitro 24(1): 135-141.
10. Sun, Q., Wang, A., Jin, X., et al. Long-term air pollution exposure and acceleration of atherosclerosis and vascular inflammation in an animal model. (2005) J Am Med Assoc 294(23): 3003-3010.
11. Adar, S. D., Sheppard, L., Vedal, S., et al. Fine particulate air pollution and the progression of carotid intima-medial thickness: A prospective cohort study from the multi-ethnic study of atherosclerosis and air pollution. (2013) PLoS Med 10(4): e1001430.
12. Van Donkelaar, A., Martin, R. V., Brauer, M., et al. Global estimates of ambient fine particulate matter concentrations from satellite-based aerosol optical depth: Development and application. (2010) Environ Health Perspect 118(6): 847-855.
13. Kleiger, R. E., Miller, J. P., Bigger, J. T. Jr., et al. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. (1987) Am J Cardiol 59(4): 256-262.
14. Lahiri, M. K., Kannankeril, P. J., Goldberger, J. J. Assessment of autonomic function in cardiovascular disease: Physiological basis and prognostic implications. (2008) J Am Coll Cardiol 51(18): 1725-1733.
15. Tsuji, H., Larson, M. G., Venditti, F. J., Jr. Impact of reduced heart rate variability on risk for cardiac events. The Framingham heart study. (1996) Circulation 94(11): 2850-2855.
16. Mainardi, L. T., Bianchi, A. M., Cerutti, S. Time-frequency and time-varying analysis for assessing the dynamic responses of cardiovascular control. (2002) Crit Rev Biomed Eng 30(1-3): 175-217.
17. Reyes del Paso, G. A., Langewitz, W., Mulder, L. J., et al. The utility of low frequency heart rate variability as an index of sympathetic cardiac tone: a review with emphasis on a reanalysis of previous studies. (2013) Psychophysiology 50(5): 477-487.
18. Devlin, R. B., Ghiio, A. J., Kehrl, H., et al. Elderly humans exposed to concentrated air pollution particles have decreased heart rate variability. (2003) Eur Respir J Suppl 40: 76s-80s.
19. Gold, D. R., Litonjua, A., Schwartz, J., et al. Ambient pollution and heart rate variability. (2000) Circulation 101(11): 1267-1273.
20. Liao, D., Creason, J., Shy, C., et al. Daily variation of particulate air pollution and poor cardiac autonomic control in the elderly. (1999)
Nutrition Solutions to Counter Air Pollution Harms

Environ Health Perspect 107(7): 521-525.

21. Magari, S. R., Hauser, R., Schwartz, J., et al. Association of heart rate variability with occupational and environmental exposure to particulate air pollution. (2001) Circulation 104(9): 986-991.

22. Pope, C. A. 3rd, Verrier, R. L., Lovett, E. G., et al. Heart rate variability associated with particulate air pollution. (1999) Am Heart J 138(5 pt 1): 890-899.

23. Holguin, F., Tellez-Rojo, M. M., Hernandez, M., et al. Air pollution and heart rate variability among the elderly in Mexico City. (2003) Epidemiology 14(5): 521-527.

24. Schwartz, J., Park, S. K., O’Neill, M. S., et al. Glutathione-S-transferase M1, obesity, statins, and autonomic effects of particles: Gene-by-drug-by-environment interaction. (2005) Am J Respir Crit Care Med 172(12): 1529-1533.

25. Gilliland, F. D., Li, Y. F., Saxon, A., et al. Effect of glutathione-S-transferase M1 and P1 genotypes on xenobiotic enhancement of allergic responses: Randomised, placebo-controlled crossover study. (2004) Lancet 363(9403): 119-125.

26. Romieu, I., Tellez-Rojo, M. M., Lazo, M., et al. Omega-3 fatty acid prevents heart rate variability reductions associated with particulate matter. (2005) Am J Respir Crit Care Med 172(12): 1534-1540.

27. Tong H, Rappold AG, Diaz-Sanchez D, et al. Omega-3 fatty acid supplementation appears to attenuate particulate air pollution-induced cardiac effects and lipid changes in healthy middle-aged adults. (2012) Environ Health Perspect 120(7): 952-957.

28. Selhub, J. Folate, vitamin B12 and vitamin B6 and one carbon metabolism. (2002) J Nutr Health Aging 6(1): 39-42.

29. Baccarelli, A., Cassano, P. A., Litonjua, A., et al. Cardiac autonomic dysfunction: Effects from particulate air pollution and protection by dietary methyl nutrients and metabolic polymorphisms. (2008) Circulation 117(14):1802-1809.

30. Aguilar, B., Rojas, J. C., Collados, M. T. Metabolism of homocysteine and its relationship with cardiovascular disease. (2004) J Thromb Thrombolysis 18(2): 75-87.

31. Friso, S., Choi, S. W. Gene-nutrient interactions in one-carbon metabolism. (2005) Curr Drug Metab 6(1): 37-46.

32. Baccarelli, A., Zanobetti, A., Martinelli, I., et al. Effects of exposure to air pollution on blood coagulation. (2007a) J Thromb Haemost 5(2): 252-260.

33. Baccarelli, A., Zanobetti, A., Martinelli, I., et al. Air pollution, smoking, and plasma homocysteine. (2007b) Environ Health Perspect 115(2): 176-181.

34. Berger, J., Moller, D. E. The mechanisms of action of PPARs. (2002) Annu Rev Med 53: 409-435.

35. Calder, P. C. Omega-3 polyunsaturated fatty acids and inflammatory processes: Nutrition or pharmacology? (2013) Br J Clin Pharmacol 75(3): 645-662.

36. Oh, D. Y., Olefsky, J. M. Omega 3 fatty acids and gpr120. (2012) Cell Metab 15: 564-565.

37. Bruno, R. S., Traber, M. G. Vitamin E biokinetics, oxidative stress and cigarette smoking. (2006) Pathophysiology 13(3): 143-149.

38. Sram, R. J., Binkova B, Rossner P. Jr. Vitamin C for DNA damage prevention. (2012) Mutat Res 733(1-2): 39-49.

39. Yeatts, K., Svendsen, E., Creason, J., et al. Coarse particulate matter (pm2.5-10) affects heart rate variability, blood lipids, and circulating eosinophils in adults with asthma. (2007) Environ Health Perspect 115(5): 709-714.

40. Romieu I, Garcia-Esteban R, Sunyer J, et al. 2008. The effect of supplementation with omega-3 polyunsaturated fatty acids on markers of oxidative stress in elderly exposed to PM(2.5). (2008) Environ Health Perspect 116(9): 1237-1242.

41. Nair, U., Bartsch, H., Nair, J. Lipid peroxidation-induced DNA damage in cancer-prone inflammatory diseases: A review of published adduct types and levels in humans. (2007) Free Radic Biol Med 43(8): 1109-1120.

42. Possamai, F. P., Junior, S. A., Parisotto, E. B., et al. Antioxidant intervention compensates oxidative stress in blood of subjects exposed to emissions from a coal electric-power plant in south Brazil. (2010) Environ Toxicol Pharmacol 30(2): 175-180.

43. Su, H. J., Chang, C. H., Chen, H. L. Effects of vitamin C and E intake on peak expiratory flow rate of asthmatic children exposed to atmospheric particulate matter. (2013) Arch Environ Occup Health 68(2): 80-86.

44. Air quality guidelines - global update 2005. Public Health and Environment (PHE) WHO.