Cardiovascular Disease: Peer-Reviewed Analysis

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Heart Disease and the Environment

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Heart disease can be caused by birth defects, abnormalities of the heart muscle (cardiomyopathies), the blood vessels supplying the heart, the heart valves, and the conduction system that transmits electrical impulses that regulate the heartbeat. Rarely, the heart can be the site of tumors. This summary paper focuses primarily on abnormalities of the blood vessels due to atherosclerosis. Atherosclerotic heart disease is also called coronary heart disease or coronary artery disease.

Atherosclerosis results from the accumulation of fatty deposits (lipids), fibrous elements, and inflammatory cells in the inner layer of the walls of arteries. As these deposits (plaques) build up, the lumen of the blood vessel narrows, restricting the passage of blood. The surface of atherosclerotic plaques may erode or rupture, releasing substances that encourage platelets to adhere and a blood clot to form, causing blockage of the artery (Hansson 2005).

When blood flow is sufficiently restricted, reduced oxygen supply to the heart muscle causes chest pain (angina). Muscle death or myocardial infarction occurs when the blood flow to a portion of the heart muscle is blocked for a sufficient period of time.

Epidemiology

Overall death rates from heart disease and stroke declined in the 1980s and 1990s, primarily due to modification of risk factors and improvement in medical care. (Fine 1992). Nevertheless, cardiovascular disease (CVD) remains the leading cause of death in the U.S. According to the American Heart Association and the National Center for Health Statistics of the Centers for Disease Control and Prevention, in 2002, heart disease accounted for approximately 38% of deaths in the US and was a primary or contributing cause in many more. Almost 17% of those deaths occurred among persons aged <65 years. (AHA 2005 , Kochanek 2004).

Although mortality rates from heart disease have decreased, the decline has not been uniform for all populations (Cooper et al. 2000). According to the CDC, the proportion of premature deaths due to heart disease was greatest among American Indians/Alaskan Natives (36.0%) and blacks (31.5%) and lowest among whites (14.7%). Premature death was higher for Hispanics (23.5%) than non-Hispanics (16.5%), and for males (24.0%) than females (10.0%). (CDC 2005) The highest proportions of all deaths occurred among persons aged 55--64 years. Cardiac mortality rates across all age groups were highest among blacks and lowest among Asians and Pacific Islanders.

Several factors are likely to be determinants of these disparities. Differences by sex might be attributed in part to the cardioprotective effects of estrogen in pre-menopausal women (Mendelsohn and Karas 1999). Specific racial/ethnic variations probably reflect differences in demographics, including income and stress, access to medical care, and risk factors for heart disease, such as hypertension, high cholesterol, lack of exercise, overweight, smoking, and diabetes. A recent survey by the Centers for Disease Control and Prevention concluded that the prevalence of having two or more of these risk factors was highest among blacks (48.7%) and American Indians/Alaska Natives (46.7%) and lowest among Asians (25.9%). (CDC 2004) Environmental agents discussed in this paper are risk factors as well.

Causes of Cardiovascular Disease (CVD)

Risk Factors
In addition to age, major risk factors for CVD include smoking, physical inactivity, diet, serum lipids/cholesterol, obesity, hypertension, gender, and family history (genetics).

Other environmental factors can also play a role in cardiovascular disease. Air pollution, some synthetic chemicals, metals, and pharmaceuticals can cause or exacerbate preexisting cardiovascular disease. The following sections of this paper briefly summarize the medical literature addressing those environmental agents, with the exception of pharmaceuticals.

Environmental Agents
Metals, air pollutants and other environmental contaminants, synthetic chemicals, and the mineral content of drinking water can affect the heart by altering heart rate or rhythm, contractility and excitability of heart muscle, the conduction of electrical impulses, or by causing or accelerating atherosclerosis. Induction or enhancement of atheroma (plaque) formation involves cholesterol metabolism favoring fatty deposition beneath the surface of endothelial cells lining arterial walls, inflammation, injury to the endothelial cells, and/or thickening of smooth muscle cells in the wall of the arteries. (Ramos et al. 1994, Hansson 2005)

Metals
Arsenic. Arsenic exists in several inorganic and organic forms with varying toxicity profiles. Exposure to inorganic arsenic occurs in the diet, the workplace (mining; smelting; manufacture of chemicals, pesticides, glass, pharmaceutical, electronics), through contaminated drinking water, or from living near facilities that emit arsenic into the environment. Wood preserved with chromated-copper-arsenate (CCA) used in playgrounds, decking, and for other construction purposes has also received considerable recent attention. Arsenic leaches from the wood and can get onto people's hands and into the surrounding soil. Hand-to-mouth activity leads to ingestion.

Organic arsenic is present in seafood and is generally less toxic than inorganic forms. Large amounts of organic arsenic, Roxarsone, are also used in commercial poultry-raising operations to prevent and treat parasites and to stimulate growth. As a consequence, chicken consumption has become a significant source of arsenic exposure in the general population. (Lasky et al. 2004) People who consume chicken regularly are exposed to arsenic from that source alone at levels that supply a substantial fraction of the tolerable daily intake. (The World Health Organization tolerable daily intake is 2 microgm/kg/day inorganic As) Approximately 65% of the arsenic in chicken meat is in the inorganic form. Moreover, the

manure of chickens treated with arsenic is spread on the ground where organic arsenic is converted into the inorganic form and leaches into ground and surface waters. (Brown 2003)

Drinking water arsenic from geological sources varies considerably from place to place. High levels of arsenic in drinking water cause thickening of the walls of arteries and are associated with Blackfoot disease in Taiwan due to progressive narrowing of peripheral vessels. (Tseng 1977) Drinking water levels of arsenic in this area of Taiwan generally range from 170 to 800 ppb, though some are higher. Progressively higher levels of arsenic in drinking water are associated with increased risk of vascular disease.

The coronary arteries are also thickened and mortality from cardiovascular disease is elevated in arsenic-exposed populations in Taiwan. (Tseng et al. 2003) High levels of arsenic exposure were also associated with thickening of the arteries in the hearts of children who died from arsenic poisoning in Northern Chile. (Rosenberg 1974)

The threshold exposure at which cardiovascular effects of arsenic exposure begins to appear and the extent to which arsenic contributes to cardiovascular disease in the general population are unclear. One survey of 1185 people with well water contaminated with arsenic from 0-2389 ppb (median 2 ppb) self-reported significantly more depression, hypertension, circulatory problems, and cardiac bypass surgery when water levels of As were between 2-10 ppb compared to < 2 ppb. (Zierold et al. 2004).

Other health effects, including skin lesions and increased skin, lung, and bladder cancer risks, begin to appear at drinking water levels as low as 10 ppb. (Yoshida et al. 2004) The US EPA has established a maximum contaminant level of drinking water at 10 ppb, though a number of areas in the US have naturally occurring groundwater levels of arsenic that are higher than 10 ppb.

Lead. Cumulative low-level lead exposures are associated with elevated blood pressure and thereby may increase the risk of atherosclerotic cardiovascular disease. (Cheng et al. 2001).

Mercury. Recent information identifies mercury exposure as a risk factor for the development of cardiovascular disease. An ongoing study of over 1800 men in Finland has reported an association between mercury exposures and risk of myocardial infarction and death. In their first report in 1995, after 7 years of follow up, men with hair mercury levels exceeding 2 ppm had a 2-fold higher risk of myocardial infarction than those men with the lowest hair mercury levels, after adjusting for age and other risk factors. (Salonen et al. 1995) The men in the highest mercury exposure group also had a 2.9-fold increased risk of cardiovascular death compared with those with lower hair mercury content. A recent update of the Finnish study, after an average 14 year follow up, finds that higher hair mercury levels were associated with 60% increased risk of acute myocardial infarction and 38% increased risk of death from any cause over an average 14 year period of follow up. (Virtanen et al. 2005)

A 2002 study of 684 European and Israeli men with first diagnosis of myocardial infarction reported that the mercury content of their toenails (used as an integrated measure of mercury exposure over time) was significantly higher than the mercury levels in a matched control population. (Guallar et al. 2002) The investigators also measured levels of docosahexaenoic acid (DHA), a fatty acid present in fish, and thought to be protective against developing heart disease. They found that the men with heart attacks had lower levels of this protective fatty acid than the controls. In men with similar levels of the fatty acid,

however, mercury levels were higher in cases than in controls, suggesting that mercury had an independent adverse impact. The investigators concluded that high mercury levels may diminish the protective effects of fish consumption.

Another study reported at the same time, however, did not find a correlation between mercury levels in toenails and subsequent risk of myocardial infarction, after controlling for age, smoking, and other risk factors. (Yoshizawa et al. 2002)

Proposed mechanisms for adverse effects of mercury on the heart include damage to lipids in the blood or in cellular membranes (lipid peroxidation) and damage to the autonomic nervous system that controls heart rate and heart rate variability.

Several factors are likely to be at play in determining cardiovascular risk from mercury. The beneficial fatty acids in fish have heart protective effects, but sufficient mercury exposure is likely to ultimately outweigh those beneficial effects. Dietary selenium is yet a third variable, inasmuch as selenium appears to mitigate the toxic impacts of mercury to some degree. (Cuvin-Aralar and Furness 1991) Consequently, studies investigating the impacts of mercury on the heart will need to consider each of these variables, as well as others such as smoking, blood pressure, and age.

Most environmental mercury comes from human activities (coal burning power plants, medical and municipal waste incinerators, etc), though naturally occurring volcanoes, fires, and rock weathering also contribute. Inorganic mercury is converted to the organic form, methylmercury, by bacteria in the sediments of water bodies. In turn, the organic mercury bioconcentrates as it moves up through the food web, concentrating at significant levels in predatory fish. The primary source of organic mercury exposure is fish consumption, and for people who eat fish, the kind and amount of fish they eat determines tissue mercury levels.

Some fish, particularly larger predatory fish like shark, swordfish, large tuna, king mackerel, and tilefish are contaminated with significant amounts of mercury. (FDA) Some freshwater species are also heavily contaminated with mercury in many states and advisories warn people to limit their intake or altogether avoid those species.

Dental amalgam tooth fillings and occupational sources can also add significantly to total mercury exposures. (Lindberg et al. 2004)

Cadmium. Blood cadmium levels are positively associated with development of atherosclerotic peripheral artery disease. (Navas-Acien et al. 2004, Houtman 1993) Like lead, cadmium may also contribute to development of hypertension at relatively low levels of exposure. Diet is the major source of cadmium for most people, though smokers have substantially higher cadmium intake from that source, and some occupations result in cadmium exposures. (metal smelting; electroplating; battery, pigment, and plastics manufacturing)

Cobalt. In the 1960's in Quebec a group of people who were heavy beer drinkers developed cardiomyopathy that was ultimately linked to excessive cobalt exposure. Cobalt had been added to the beer as a foam stabilizer, now a discontinued practice. Heart disease from cobalt is unlikely to be an issue in the general population.

Air Pollution

Air pollution is a mixture of contaminants, including small particles (particulates), ozone, carbon monoxide, nitrous oxides, sulfur oxides, heavy metals like lead and mercury, polycyclic aromatic hydrocarbons, and toxic chemicals. Considerable data have accumulated indicating conclusively that air pollution contributes to cardiovascular disease, including mortality.

Particulate air pollution (PM). The strongest and most consistent link between air pollution exposure and cardiovascular morbidity and mortality is for particulate matter. Particulate matter (PM) is a mixture of solid particles and liquid droplets that vary in size and origin. Sources include vehicle emissions, road dust, tire fragmentation, power generation and other industrial combustion sources, agriculture, construction, wood burning, pollen, fires, and volcanoes. Environmental tobacco smoke is an important indoor source of particulates. Soil, road dust, and construction debris create larger particles; fossil fuel combustion in motor vehicles and from power generation produces fine and ultrafine particles.

Particulates are chemically and physically diverse. Fine particles, less than 10 micrometers in diameter (PM 10), are more easily inhaled deeply into the lungs than larger particles. These fine particles are often sub-classified into coarse (between 2.5-10 microns), fine (less than 2.5 micrometers, PM 2.5), and ultrafine (less than 0.1 micrometer) sizes because of differing health effects and sources. Ultrafine particles are deposited in alveoli and are able to enter the systemic circulation. Smaller particles contain complex mixtures of many different chemicals, including carbon, sulfates, nitrates, ammonium compounds (an important source is fertilizer used on farms), metals, and a wide variety of organic chemical compounds emitted from large and small industrial operations.

A large number of short term and long term epidemiologic studies consistently show that exposure to particulate air pollution is associated with increased risk of premature death from cardiopulmonary disease. (Brook et al. 2004) In the Harvard Six-Cities study, investigators followed over 8000 participants from six cities with varying levels of air pollution for 14-16 years and reported a significant 26% increase in mortality from all causes in the most heavily polluted city when compared to the least polluted. (Dockery et al. 1993) Cardiopulmonary deaths accounted for most of the increase. After adjusting for individual risk factors including smoking, gender, body mass index, education, occupation, hypertension, and diabetes, the relationship between air pollution and mortality remained. Among the air pollutants, elevations of PM 2.5 and sulfates showed the strongest association.

Similarly, an American Cancer Society study followed over 500,000 individuals from all 50 states over 16 years and reported a 6% increase in cardiopulmonary deaths for every 10 micrograms/m3 elevation in annual average PM 2.5. The relationship between PM 2.5 and adverse health effects was linear and showed no evidence of a "safe" threshold. Further analysis of the data showed a 12% increased risk of cardiovascular mortality for a 10-microgm/m3 increase in PM 2.5, and the largest single increase in risk was for atherosclerotic heart disease. (Pope et al. 2004) Risks for arrhythmia and heart failure were also increased.

Another study in the Netherlands followed 5000 adults for up to 8 years and concluded that exposure to traffic-related air pollutants was more highly related to mortality than were city-wide background levels

of air pollution. Risk of cardiopulmonary death was almost doubled in people living near a major road when compared to those living at some distance. (Hoek et al. 2002)

Other studies of millions of people in many different cities in Europe and in the US have examined short-term effects of air pollution. They also show a similar relationship between risk of cardiopulmonary death and particulate air pollution. (Samet et al. 2000, Katsouyanni et al. 2001; Health Effects Institute) In the European study, daily cardiovascular deaths were increased 0.6% for every 10 microgm/m3 increase in PM 2.5. In the US study, the corresponding increase was 0.31%. Analyses of these and other data, looking at longer lag times between air pollution levels and risk of cardiac death, indicate that the observed relationships are not simply a matter of accelerating the death of people who were already close to their time of death. Mechanistic investigations suggest that particulate air pollution can have short and long-term effects, promoting the development of cardiovascular disease as well as initiating an acute cardiac event. (Brook et al. 2004)

Particulate air pollution is complex and is likely to cause cardiovascular impacts through a variety of mechanisms. (Brook et al. 2004) An inflammatory response in the lungs and even systemically through release of a variety of substances triggered by PM exposure is an important contributor. Some studies show that blood factors that promote blood clotting, including fibrinogen levels and platelet aggregation, are increased. Blood viscosity increases with PM exposure. Heart rate variability decreases, which is associated with an increased risk of subsequent arrhythmias or other cardiac events. Each of these factors may contribute to an increased risk of cardiovascular disease.

Carbon monoxide. Carbon monoxide (CO) is another air pollutant that can have adverse cardiovascular impacts. Carbon monoxide avidly binds to hemoglobin, interfering with oxygen delivery to tissues causing hypoxic stress. CO also causes direct damage to the lining of arteries in animals at exposure levels of 180 ppm, a concentration to which people may be exposed from environmental sources (air pollution, cigarette smoke, exhaust from vehicles), particularly in enclosed spaces. (Ramos et al. 1996) Carbon monoxide is often mixed with other pollutants making it difficult to sort out those changes that are due to CO alone.

Studies are inconclusive with respect to whether or not there is an increased mortality from coronary artery disease among workers exposed to CO. A study of bridge and tunnel workers suggests an increased risk at levels above 50 ppm. (Stern, 1988) CO levels of 35 ppm can reduce exercise tolerance and the threshold for angina in people with coronary artery disease.

Ambient urban CO levels (<9-ppm/8 hr average) have been associated with angina, cardiac arrhythmia, and cardiac arrest. (Allred et al. 1991, Peters et al. 2000, Schwartz 1999, Leaf and Kleinman 1996, Balzan et al. 1994). However, these reports should be interpreted with caution for several reasons. General ambient measurements may not accurately reflect individual CO exposure levels. The effects may actually be result of exposure to a mixture of air pollutants since CO and particulate air pollution are somewhat correlated. Finally, low-level CO effects are more likely to occur in individuals with significant pre-existing cardiovascular disease.

Air pollution and public policy: Although exposure to ambient air pollution poses smaller individual risks for cardiovascular disease than diabetes or smoking, the absolute number of people affected is enormous because it is ubiquitous and exposure occurs over a lifetime. Pope has estimated an average loss of life

expectancy directly related to chronic air pollution exposure from between 1.8 and 3.1 years for those living in the most polluted cities in the United States. (Pope 2000) A recent report estimates that the health impacts in the US from particulate air pollution attributable just to diesel exhaust from cars, trucks, and construction equipment includes 21,000 premature deaths, 3,000 lung cancer deaths, 15,000 hospital admissions. 15,000 emergency visits for asthma, 27,000 non-fatal myocardial infarctions, 410,000 asthma attacks, 12,000 cases of chronic bronchitis, and 2,400,000 work loss days. (CAFT 2005)

In 1997, the US EPA promulgated 24-hour and annual average standards for PM 2.5. The existing federal PM10 standards were retained, however, to address health effects that could be related to the "coarse fraction". Currently, a separate PM10-2.5 standard is under consideration.

Current US EPA National Ambient Air Quality Standards for PM (1997 NAAQS):

Time Period	PM_{10}, µg/m^3	$PM_{2.5}$, µg/m^3
Annual	50	15
Daily	150	65

The annual standard is satisfied when the 3-year average of the mean PM levels measured in a community is less than or equal to the indicated number. The daily standard is met when the 3-year average of the 98th or 99th percentile of 24-hour PM levels in each community is less than or equal to the indicated number.

Current EPA estimates suggest that attainment of these standards would reduce total mortality by 23,000 deaths annually and cardiovascular hospital admissions by 42,000 per year in the United States. Nevertheless, 19% of all US counties with air-quality monitoring systems are presently not meeting these standards. This percentage is substantially greater in regions such as the industrial Midwest (41%) and southern California (60%).

Data also show that improved air quality results in decreased cardiovascular mortality, and the "real" effects of air pollution on cardiovascular health may be even stronger than the estimates described above. A ban on coal sales in Dublin, Ireland resulted in a 36 microgrm/m3 (70%) reduction in PM. Death rates for respiratory and cardiovascular deaths over the 6-year period after the ban declined by 15.5% and 10.3%, respectively, as compared to the 6-year period before the ban. (Clancy, 2002) This decrease in mortality is more than twice what would be predicted by the short-term analyses (Brook et al. 2004).

Drinking Water: Mineral Content (Hard vs. Soft Water)
A number of studies in various countries have reported an inverse correlation between the hardness of drinking water and risk of coronary artery disease—the harder the water, the lower the risk (reviewed in Sauvant and Pepin 2002). Water hardness is determined by calcium and magnesium content. Most studies show that, of the two minerals, magnesium is likely to be the most heart protective, and some studies suggest that the magnesium/calcium ratio is most important. A high ratio appears to be more protective than a low one. The general consistency of these findings in a number of studies suggests that the mineral content of drinking water is a risk factor for heart disease. However, its relative importance, compared to other risk factors like smoking, overweight, diet, and high blood pressure, is unclear.

Industrial Chemicals

Solvents. A large number of industrial solvents can cause cardiac arrhythmias. (Fine 1992, Ramos et al. 1996). However, the doses required to have that effect are usually large, such as might occur in a poorly designed or ventilated workplace where industrial solvents are used. Benzene, chloroform, heptane, toluene, trichloroethylene, and fluorocarbons are among the many solvents that can cause cardiac arrhythmias (Fine 1992).

1,1,1 trichloroethane can also depress cardiac muscle contractility at high doses (Herd et al. 1974). Methylene chloride, a solvent that is sometimes present in paint and varnish strippers, is metabolized to carbon monoxide and thereby interferes with oxygen delivery to the heart and other tissues by strongly binding to hemoglobin. Ethanol (the alcohol in alcoholic beverages), particularly in chronically large amounts, can also cause cardiomyopathy and increase the risk of atrial and ventricular fibrillation (Klatsky 2002, Fine 1992).

Nitroglycerin and Other Nitrates

Workers exposed to nitroglycerine, ethylene glycol dinitrate, and other nitrates used in the manufacture of explosives are at risk of angina, myocardial infarction, and sudden death after prolonged exposure followed by withdrawal from exposure (Hogstedt and Andersson 1977). Although nitroglycerin is used therapeutically to dilate coronary arteries during an episode of angina, in workers exposed to higher levels over longer periods of time, coronary artery spasm is thought to occur after withdrawal from exposure.

Carbon disulphide. Carbon disulphide is a gas used in the manufacture of rayon and soil disinfectants. Exposure to this gas in laboratory animals and people causes the development of atherosclerotic cardiovascular disease (Tolonen 1975, Sweetnam et al. 1987). Workers exposed to carbon disulphide are at substantially increased risk of developing coronary artery disease. The mechanism of toxicity is not well understood, but may involved direct injury to the cells (endothelial) lining the coronary arteries, leading to plaque formation.

Summary

Risk factors for development of cardiovascular disease are numerous. Historically, diet, exercise, smoking, serum cholesterol, high blood pressure, diabetes, obesity, age, and family history have received most attention. Modifying those variables where possible has had beneficial effects on reducing the incidence of cardiovascular disease in the general population. However, other environmental factors that have not received much attention in the past also influence cardiovascular disease and mortality risks. Some, like air pollution or drinking water hardness affect large populations of people throughout the world and are of significant public health concern. Others like mercury, arsenic, and lead increase cardiovascular risks, but their relative contribution to heart disease in the general population is uncertain. Significant exposures to certain industrial chemicals affect smaller subpopulations though they may be highly relevant in certain circumstances. Attention to these environmental risk factors through health-protective public policies, workplace modifications, and individual behavioral changes is likely to decrease the substantial public health burden of cardiovascular disease.

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