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Environmental Determinants of Cardiovascular Disease

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Abstract

Many features of the environment have been found to exert an important influence on cardiovascular disease (CVD) risk, progression, and severity. Changes in the environment due to migration to different geographic locations, modifications in lifestyle choices, and shifts in social policies and cultural practices alter CVD risk, even in the absence of genetic changes. Nevertheless, the cumulative impact of the environment on CVD risk has been difficult to assess and the mechanisms by which some environment factors influence CVD remain obscure. Human environments are complex; and their natural, social and personal domains are highly variable due to diversity in human ecosystems, evolutionary histories, social structures, and individual choices. Accumulating evidence supports the notion that ecological features such as the diurnal cycles of light and day, sunlight exposure, seasons, and geographic characteristics of the natural environment such altitude, latitude and greenspaces are important determinants of cardiovascular health and CVD risk. In highly developed societies, the influence of the natural environment is moderated by the physical characteristics of the social environments such as the built environment and pollution, as well as by socioeconomic status and social networks. These attributes of the social environment shape lifestyle choices that significantly modify CVD risk. An understanding of how different domains of the environment, individually and collectively, affect CVD risk could lead to a better appraisal of CVD, and aid in the development of new preventive and therapeutic strategies to limit the increasingly high global burden of heart disease and stroke.

Keywords

Coronary artery disease; stroke; circadian rhythms; sunlight; altitude; latitude; air pollution; built environment; social networks; socioeconomic status; diet; nutrition; exercise; smoking

INTRODUCTION

Despite many notable advances in treatment and management, cardiovascular disease (CVD) remains the most frequent cause of mortality in all human populations. In the developed world, it kills more people than any other disease, and in low and middle income countries its prevalence is on the rise. Deaths from ischemic heart disease and stroke have increased worldwide. Even in the US, where the rates of CVD mortality have been steadily decreasing from their peak in the 1960s, this rate of decline has substantially slowed down since the

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1990s[1], and by 2030, 40.5% of the population is projected to have some form of CVD.[2] While some of this increase may be due to an aging population, the near universal pervasiveness of CVD reflects our inability to prevent its escalating occurrence or to understand its fundamental nature.

The received view is that CVD is due to a set of chronic conditions that arise from a complex interplay between genetic predisposition and environmental influences that lead to progressive deterioration in the structure and the function of cardiovascular tissues. It is generally believed that even though genetic defects underlie some infrequent forms of heart disease, most CVD is due to interactions between several gene variants and lifestyle factors. Although the specific contribution of the genes and the environment remains poorly understood, it is thought that environmental factors and lifestyle play a more dominant role in CVD development. This belief is based on the results of many studies showing that, to a large extent, CVD could be prevented by maintaining a healthy lifestyle. For instance, data from the Nurses' Health Study[3] suggest that 82% of coronary events could be prevented by maintaining a healthy lifestyle. Similarly it was found that 62% of all coronary events may have been avoided if men in the Health Professionals Follow-up Study had adhered to a low-risk lifestyle. Data combined from both these studies show that 47% of stroke in women and 35% in men could be attributed to the lack of adherence to low-risk lifestyle choices.[4] In a cohort of Swedish women low-risk behavior was associated with a 92% decrease in risk of myocardial infarction (MI).[5] Taken together, these data suggest that, for the most part (50–90%), CVD is a modifiable and preventable condition.

The modifiable nature of CVD is further supported by studies showing that even in the absence of large genetic changes, CVD risk in a population is affected by changes in the environment. This is most strikingly demonstrated by data from China, which show that the age-adjusted CVD mortality rates in Beijing increased by 50% for men and 27% for women due to environmental changes between 1984 and 1999.[6] Changing environmental conditions have also been linked to a 75% decrease in CVD risk in Finland within 20 years,[7] and a 24% drop in coronary mortality in Poland in 9 years.[8] In England and Wales the mortality rate for coronary heart disease (CHD) between 1981 and 2000 have decreased by 62% in men and 45% in women; and more than half of this decline was attributed to a reduction in environmental risk factors.[9] Additionally, a recent study of the decrease in CHD deaths from 1980 to 2000 in the US suggested that approximately 44% of the decrease could be attributable to environmental changes.[10]

Additional support for modifiable nature of CVD risk comes from migrant studies showing that moving to a new environment could substantively modify CVD risk. Data collected between 1960s–1970s indicate a significant increase in the rates of CHD deaths in Japanese men who moved from Japan to the US.[11] Similarly, Indians living in the UK[12] have higher CVD risk than their counterparts living in India. Such data strengthen the view that changes in the environment could dramatically alter CVD risk, even without significant genetic changes. The primacy of the environment is further enforced by studies on genetically-identical twins. In a study of Finnish immigrants it was found that those who moved to Sweden had lower rates of CHD than those living in Finland;[13] and this decrease in risk was

evident even in migrant twins, suggesting that changes in the environment modify CVD risk, independent of genetics.

CVD and the human environment

If CVD is largely preventable, and if it is dramatically affected by environmental changes, it is important to understand how the environment affects CVD. Which components of the environment affect CVD risk? How this risk is imparted? And why the environment affects CVD? To answer these questions, we have to understand the complexity of the human environment. Unlike other animals, who exist primarily in their natural environment, humans live in elaborate, self-created microenvironments. They form large social networks fashioned by history and culture and they survive in diverse geographic ecosystems to which they have variably adapted during the course of their evolution. Hence to understand the totality of human circumstance, we have to examine the social, personal and natural domains of the human environment which collectively make up the human envirome (Figure 1). We have to apprehend how these domains interact, and we have to understand how they individually and collectively bear upon CVD risk.

The most primeval component of the human environment is the natural ecosystem. This includes the recurrent day/night cycle, the changing seasons, and the local features of geography; a rather invariant set of conditions that have been the primary determinants of human evolution to date, and which continue to exert a powerful influence on human physiology, psychology, and health. During early human evolution and history other living things such as bacteria, viruses, predators, parasites, and pests were important health-relevant component of the natural environment. However, with increasing civilization, these threats were progressively minimized. Now, the rates of parasitic and infectious diseases have plummeted and, even in developing countries, non-communicable diseases have emerged as major threats to human health. Moreover, with increasing acculturation, humans have created complex social environments. These environments have become the primary domains of human activity and they moderate both the salutogenic and pathogenic influences of the natural environment on humans. Within such natural and social domains; however, humans, with their advanced rational and cognitive abilities, create personal environments, which they populate by their own individual choices. Being a proximal and malleable domain, the personal environment is a powerful determinant of human health. Nevertheless, as reviewed below, all – personal, social and natural - domains of the human environment individually and collectively affect CVD risk.

THE NATURAL ENVIORNMENT

Nature is the primordial domain of the human environment. In common with all living things, humans have evolved by adapting to their natural environment. And even though, during the course of civilization, the influence of nature has been moderated by increasingly complex social environments, the natural environment still exerts a powerful influence on human health. Therefore, living in artificial environments or in a state of dyssynchrony with the rhythms of the nature may be one reason for the high rates of CVD in modern environments. High contemporary risk of CVD may also be due to a mismatch between

ancient human genes and current human environments. This mismatch may be because rapid changes in human environments have outpaced genetic adaptation. Ancestral alleles adapted to ancient environments have become maladapted to modern environments therefore confer disease risk. Key features of the natural environment that have been linked to CVD risk are:

Circadian Rhythms

The day/night cycle is a fundamental, invariant feature of the natural environment. All life is entrained to this cycle, which in turn exerts a pervasive control over both plants and animals. In mammals, sunlight regulates the master clock in the suprachiasmatic nucleus, which synchronizes the light-insensitive peripheral clocks to coordinate a 24 h cycle. This day/night cycle controls both cardiovascular health and function; heart rate and blood pressure are lowest at night and during sleep and begin to rise before waking-up, coinciding with a period of vagal dominance, in anticipation of daytime activities. Circadian cues also regulate the expression of cardiovascular genes and the abundance of cardiovascular proteins,[14, 15] as well as the levels of neurohormones that regulate cardiovascular function, such angiotensin II, renin, aldosterone, growth hormone and atrial naturetic peptide.[16] Given this tight diurnal regulation, it is not surprising that the incidence of adverse cardiovascular events varies with the time of day. Myocardial infarctions occur most frequently between 6 – 12 PM (mostly between 3 – 6 AM),[17, 18] and are 3 times more likely to occur in early morning than at night. The frequency of stokes, arrhythmias, and sudden cardiac death and the rupture of abdominal aortic aneurisms also show matutinal clustering.[19–21] The timing of adverse cardiovascular events appears to be linked to the intrinsic clock mechanism, but not to the stress of waking up, as it has been reported that when in a new geographic location, the frequency of cardiovascular events in travelers peaks, for a few days, at times that correspond to their time zone of origin.[16]

In addition to increasing CVD susceptibility, the diurnal cycle also affects CVD severity. Myocardial infarcts that occur in the middle of the night are larger[22] and angioplasties performed at night are less successful.[23] A similar circadian dependence has been observed in animals; mice subjected to coronary ligation at the sleep-to-wake transition exhibit a dramatic increase in myocardial infarct size compared with those at the wake-to-sleep transition,[24] indicating that the extent of tissue injury depends upon the circadian phase, synchronized with the day/night cycle. Hence, disruption of this synchrony could impair cardiovascular function and health. Indeed, frequent disturbances in the sleep-wake cycle increase the risk of diabetes,[25, 26] obesity,[25, 26] and hypertension[27] in shift workers, transmeridian flight crews,[28, 29] and patients with sleep apnea or other sleep disturbances.[16] Even short-term circadian misalignment increases blood pressure and inflammation,[30] as well as postprandial levels of blood glucose and insulin.[31] Although it is unclear why disruption of the circadian rhythm elevates CVD risk, it is evident that significant cardiovascular benefits could be derived from maintaining diurnal rhythms, treating sleep disorders, restoring neuroendocrine hormonal profiles, (by imposing a fixed or regular schedule of zeitgebers, or timekeepers such as light, activity, or eating).”[16] Additional benefits may be derived from pharmacologically targeting clock proteins or therapy with varying light wavelengths or intensity. Collectively, the work on circadian rhythms reinforces the view that the both human physiology and disease susceptibility are

inextricably linked to the natural environment and exquisitely attuned to its primordial rhythms.

Seasons

In most places, the natural environment is characterized not only by diurnal rhythms, but by a change in seasons as well. In most locations, this leads to wide variations in temperature and humidity as well as the length of day. A change of season alters sunlight exposure, physical activity, and feeding behavior; changes which, by modifying physiological responses and metabolism, could affect cardiovascular function and disease. In both Northern and Southern hemispheres, the levels of blood pressure and plasma HDL, LDL, and glucose are slightly higher in winter than in summer,[32] and it has been reported that more patients on statin therapy achieve their target LDL level in summer than in winter, suggesting that plasma lipoprotein metabolism in humans may be regulated by the seasons.[33] Similar seasonal variations have been reported in animals. In European badgers, for instance, the plasma cholesterol levels are 650% higher in winter than in summer; LDL levels peak in autumn/winter, while HDL predominates in early spring.[34] In humans, seasonal variations have also been observed in fibrinogen,[35] tissue plasminogen activator antigen, and von Willebrand factor.[36]

Seasonal changes in CVD risk factors are associated with variations in cardiovascular mortality, which is significantly higher in winter than summer at geographic locations both north[37] and south[38] of the equator. The difference between the winter peak and summer trough could be large. In England and Wales the winter peak accounts for 20,000 additional deaths per year,[39] in the US 53% more cases of MI are reported in winter than in summer.[40] This increase in mortality may be because in winter, the elderly succumb to CVD due to exacerbation of pre-existing disease,[41] or respiratory infections that trigger an acute phase response. But age may not be the only reason. In winter mortality spikes in both the young (ages <55 to 74 years) and the aged (>75).[40] Another explanation could be that hemodynamic changes due to cold temperature destabilize vulnerable lesions, leading to plaque rupture and occlusive thrombosis more frequently in winter than in summer. Cold outdoor ambient temperature, by itself, may be an important factor, as colder days, both in winter and in summer, are associated with an excessive number of infarctions.[42] Exposure to ambient cold temperature increases vascular resistance and blood pressure, leading to an increase in oxygen demand,[43, 44] and in the Framingham Offspring Cohort, ambient temperature was found to be a strong determinant of microvascular function.[45] Cold ambient temperature can also increase coronary artery resistance or induce coronary vasospasm and has been linked to acute myocardial infarction,[46, 47] and acute presentation of abdominal aortic aneurysms.[47] However, low temperatures do not appear to be the only important factor, because excessive mortality during winter months has also been reported in areas where there is little seasonal change in temperature e.g., Los Angeles.[48] Although, understanding and delineating the contributions of temperature and seasons on cardiovascular mortality would require further research, extant data support the notion that seasons exert a powerful influence on CVD risk and mortality.

While ambient cold temperatures are linked to acute cardiovascular events, high temperatures may be equally significant. Heat waves in different regions of the world are associated with increased cardiovascular mortality particularly in susceptible individuals such as the elderly who cannot rapidly adapt to rapid changes in temperature.[49] Extant literature suggests that cardiovascular effects relate not only to extremes of temperature, but to transitions and variability in temperature.[49] A 10 °F increase in same day temperature, for instance, has been found to be associated with increased risk of hospitalization, ischemic heart disease and ischemic stroke.[50] Such variability in temperature and its associated CVD risk is likely to increase with climate change, which could profoundly affect human health. The earth's average surface temperature is now higher than it has been in the last 100,000 years. This increase in temperature and is likely to affect global climate patterns and increase temperature fluctuations leading to changes in food production as well as social and economic conditions, which could significant increase the global burden of CVD, particularly among resource-scare vulnerable populations.

Sunlight

The reasons underlying the seasonal clustering of CVD deaths remain obscure, but a particularly attractive hypothesis is that lower levels of sunlight reaching the earth in winter could increase CVD susceptibility. But could sunlight affect cardiovascular health? Some studies suggest that high levels of exposure to sunlight early in life delays CVD by 0.6 to 2.1 years,[51, 52] and that spending times outdoors (presumably leading to greater sunlight exposure) is inversely related to CVD mortality.[53] Significantly, in these studies the extent of increase in CVD mortality due to a lack of sunlight exposure was similar to smoking.[52] In a survey of all the 200 districts in the UK, the hours of sunshine per annum were negatively associated with CVD mortality.[54] Although the possibility of residual confounding or exposure misclassification cannot be completely ruled out, these results support that notion that sunlight exposure is beneficial for cardiovascular health.

Sunlight exposure could affect CVD risk for many reasons, but the most well supported hypothesis relates to vitamin D, which is synthesized only in the presence of sunlight. However, the efficiency of this photosynthetic process depends upon the number of photons that penetrate the endothelium, which in turn depends upon the extent of melanin pigmentation of the skin.[55] Therefore, individuals with darker skin require longer exposure to sunlight to synthesize the same amount of vitamin D as those with lighter skin. Because exposure to UVB radiation is essential for this process, the efficiency of vitamin D depends upon the level of UVB radiation reaching the earth's surface. When the sun is low in the sky (during winter or during early morning and late evening) incoming radiation has to travel longer and is subject to more scattering and absorption than when the sun is directly overhead. Consequently, the ability of synthesize vitamin D is affected by the time of the day, the season and the latitude. As a result, there is greater prevalence of vitamin D deficiency in fall and winter than in summer and spring.[56, 57]

Seasonal and latitudinal variations in vitamin D levels have been associated with geographic and seasonal variations in blood pressure. With increasing distance from the equator, there is a progressive increase in blood pressure, which correlates with a gradual fall in ambient

UVB radiation.[58] The prevalence of hypertension shows a similar latitudinal distribution. Moreover, blood pressure is higher in winter,[43, 58] when UVB levels are low and decreases in summer when sunnier days arrive. Although a causal relationship between blood pressure and sunlight remains to be fully clarified (see below), it has been reported that exposure to UVB radiation[59] skin tanning in salons[60] or treatment with high-dose vitamin D2[61] reduces blood pressure.

In addition to blood pressure, vitamin D regulates other cardiovascular functions as well. All cardiovascular tissues express vitamin D receptor (VDR),[62] which regulates the expression of nearly 200 genes.[62] Overall, 3% of the human genome is regulated by the vitamin D. In mice, the lack of functional VDR leads not only to a bone and growth plate phenotype, but also to high rennin hypertension, cardiac hypertrophy, and increased thrombogenicity.[63] In humans, vitamin D deficiency is associated with an increased risk of adverse cardiovascular events such as myocardial infraction, stroke, heart failure, and sudden cardiac death.[64, 65] In a meta-analysis of cohort studies, 10 ng/ml increment in baseline vitamin D was associated with a 0.88 risk of incident hypertension.[66] The association is supported by Mandelian randomization studies, which show that an increase in genetically determined vitamin D levels is associated with a decrease in blood pressure and hypertension risk, supporting a causal relationship.[64, 65] However, the results of randomized controlled trials with vitamin D supplementation have generated mixed results. While meta-analysis of early RCTs showed that vitamin D intake (>500 IU/day) decreases all-cause mortality in part by decreasing cardiovascular deaths,[67] the results of recent RCTs have found no significant effects.[65] Nonetheless, a Cochrane review of extant data suggests that all-cause mortality might be reduced with vitamin D supplementation,[68] and in the VINDICATE study, vitamin D supplementation was found to improve cardiac function and reserve LV remodeling in heart failure patients.[69] The inconsistent results of RCTs have been attributed to methodological issues, such as improper dosing, lack of measurement of vitamin D levels at baseline or after intervention, and inclusion of participants regardless of their vitamin D status. To address these issues, several large, well-controlled trials are in progress.[65]

Despite the well-studied relationship between sunlight and vitamin D, it remains plausible that vitamin D levels reflect general health status and that there may be additional unidentified factors linking sunlight to cardiovascular health. Recent work has shown that brief whole-body irradiation of healthy humans with UVA, which does not synthesize vitamin D, causes a rapid and sustained decrease in blood pressure.[70] This was attributed to UVA-induced release of NO from cutaneous photolabile NO derivatives. It has been suggested that UVA-liberated NO diffuses to deeper tissue layers, where it enhances local levels of metastable nitroso compounds such as S-nitrosoglutathione, which then are distributed via blood circulation and subsequently evoke systemic responses such as a decrease in blood pressure. The human skin contains high levels of nitrite and nitrosothiols and because UVA penetrates the epidermis, this mechanism could in principle generate significant levels of nitrite in the blood and explain the effects of sunlight on blood pressure. The increase in NO production by sunlight could also have beneficial effects on metabolism. In animal models, NO prevents myocardial ischemic injury[71] and diet-induced obesity.[72] And it has been reported that UV irradiation reduces weight gain and metabolic syndrome, effects that were not duplicated by vitamin D supplementation, but prevented by treating

mice with a NO scavenger,[73] suggesting that decreased exposure to sunlight, leading to lower levels of NO could result in metabolic dysfunction and disease. Whether sunlight regulates NO production in humans remains unknown, but intriguing data from elite athletes showing that combination of UVA radiation and oral nitrite supplementation increases exercise performance.[74] suggest that further investigations might reveal new links between sunlight, diet and cardiometabolic health (Figure 2).

Altitude

Altitude is additional aspect of the natural environment that has an important bearing upon human health. Nearly 400 million people live in areas more than 1500 m (4,900 feet) above sea level[75] and human populations living in these areas have developed significant anatomical, physiologic, and metabolic adaptation to cold temperature and low oxygen levels. Of the several highland populations, native Tibetans and Nepalese Sherpas are best adapted to high altitudes. Tibetans have the oldest altitude ancestry, and through successive generations they have attained a high grade of adaptation to high altitudes. They rarely exhibit systolic hypertension and have lower levels of cholesterol and apoB than sea level dwellers.[76] They also show lower pulmonary pressure in response to exercise with less increase in ventilation rates and better preservation of cardiac output. In contrast, Andean natives who have a shorter history of living at high altitudes are less well adapted and they show greater muscularlization of the distal pulmonary arterial branches and LV hypertrophy. [77] A similar difference is evident in animals. Species native to mountainous areas (yaks, pika) have better cardiopulmonary responses than domestic animals recently transported to high altitudes.[78]

In lowlanders not adapted to high altitude ascent to high altitude (>2500 m) results in an increase in pulmonary artery pressure due to hypoxic pulmonary vasoconstriction (HPV). This is usually accompanied by increased erythropoiesis, and an increased pressure load on the right ventricle.[79] If the ascent is slow, the changes are well tolerated by otherwise healthy individuals, but in susceptible individuals, or when the ascent is rapid, pulmonary edema develops due to uneven HPV and high capillary pressures in the lung, leading to an extensive inflammatory response. Such symptoms could be avoided by slow ascent or by pharmacological treatment with calcium channel blockers or phosphodiesterase inhibitors.[79] However, populations permanently in areas of high elevation have lower CVD risk and mortality. Results of some small studies show that individuals who live at high altitudes (1000 to 5500 m) have lower total cholesterol and/or LDL-cholesterol[80–82] and higher HDL levels,[81, 83] and low levels of serum leptin.[84] That living at high altitudes could be beneficial for cardiovascular health is supported also by data showing that arterial accumulation of cholesterol is decreased in rabbits born and raised at high altitude.[85] Even brief sojourns at high altitudes could lead to favorable changes in blood lipids,[86] and insulin resistance,[87] and stimulate lipolysis of plasma triglycerides.[88] Living in high altitude lowers the rates of CHD and myocardial infarctions. Populations living in high altitudes in Switzerland, Greece, US and the Andes consistently show lower rates of mortality than lowland dwellers.[75] Among highland dwellers in Switzerland, the mortality rate for coronary heart disease decreases by 22% per 1000 m increase in altitude. Similarly, people in mountainous villages in Greece have lower total and coronary mortality than those in lowland villages.[89] Remarkably, the

hazard ratios for coronary mortality in highland dwelling men and women were 0.39 and 0.46, indicating a strong protective effect of residence in mountainous areas. Residence in higher land elevation in the US has also been associated with lower death rates in both Blacks and Whites (effect size>0.7).[90]

How could altitude affect CVD? Difference in diet, physical activity, air pollution could potentially account for the beneficial effects of altitude on cardiovascular health. However, stable differences in the natural environment are likely to important, as illustrated by a study in Switzerland,[91] which showed that being born at high altitude had an independent beneficial effect on CVD. People who were born at a higher residence and then moved down in altitude had a lower risk than those who were lived in low altitudes their entire life. Differences in solar UV exposure could be another reason. With every 300 m increase in altitude, UV levels increase by 10%[92] and as a result vitamin D synthesis is increased at high altitudes.[93] But differences in sunshine or temperature may not account for the entirety of the effect. A recent study, which included 4.2 million individuals aged 40–84 (nearly the complete adult population of Switzerland), found an inverse relationship between altitude and ischemic heart disease even after adjustment for sunshine, precipitation, temperature and road distance.[94] Although potential confounding by risk factors such as physical activity, obesity, high blood pressure and pollution levels, which all vary with altitude,[75] cannot be ruled out, the findings of the study support the concept that high altitude has an independent effect on cardiovascular health. Therefore, further studies are required to understand how altitude affects cardiovascular health and why it diminishes CVD risk.

Greenspaces

Throughout evolution, interaction with natural vegetation has been an invariant feature of the human environment. Even though the project of civilization is to immure human activity in artificial built environments, humans display innate biophilic preferences. Believed to a product of evolution, these tendencies counter the instinctive fear of natural threats and predators and may underlie the well-known restorative effects of nature and natural vegetation on mental health. Whether interactions with nature is important also for physical health remains less clear, but an association between vegetation and physical health is consistent with the results of many recent studies showing that even in modern urban environments of sprawling metropolises and congested conurbations, residential proximity to vegetation is associated with lower levels of stress, diabetes, stroke and CVD.[95, 96]

Living in artificial environments minimizes contacts with natural elements such as sunlight, animals and plants that have salutary effects on health.[97] Previous studies have shown that residential proximity to vegetation is associated with lower levels of stress, diabetes, stroke and CVD,[95, 96] and individual level data indicate that children living in greener areas have lower levels of asthma[98], blood pressure,[99] and insulin resistance.[100] In adults, residential proximity to greenness has been associated with better general health, enhanced social support, and physical activity.[95, 101] In an analysis of the entire population of England, the rate of CVD mortality in least green areas was found to be twice that of greenest areas.[102] Similarly, it was found that the odds of hospitalization for CVD were 37% lower among adults who lived in areas of highly variable greenness in Perth, Australia.[103] In a

longitudinal follow up of 575,000 adults for 4 years in Ontario, Canada, higher levels of greenness were associated with lower risk of CVD and stroke mortality.[104] In the US, residential proximity to greenspaces has been associated with higher survival rates after ischemic stroke, even after adjustment for socioeconomic factors.[105] Taken together, these data support the notion that exposure to vegetation decreases CVD risk, mortality and severity. However, most such studies are cross-sectional and therefore limited in their attribution of causality. Hence to obtain prospective data, Donovan *et al.*,[106] studied the effects of a natural experiment – loss of 100 million trees in Northern US to emerald ash borer infestation. They found that loss of trees increased both CVD and respiratory deaths. Progressive loss of tree canopy was associated with 16.7 additional deaths per year per 100,000 adults, corresponding to a 15,080 excessive deaths from 2002–2007. The reasons why CVD deaths should be related to a loss of tree canopy remain obscure, but the relationship between mortality and greenness was further reinforced by the recent analysis of the 108,630 participants of the Nurses' Health Study, which showed that women who lived in areas with the highest levels of greenness had 12% lower rates of mortality than those living in less green areas.[107] It could be speculated that some of the beneficial cardiovascular effects of greenery might relate to a decrease in the levels of local air pollution, increased proximity to walking spaces, or lower levels of mental stress. Although the contribution of these mechanisms has not been delineated, extant associations support the presence of a primordial bond between nature and health. Further elucidation of this bond, and how it is modified by urban and social domains of the environment, might be fruitful areas of future investigation.

THE SOCIAL ENVIRONMENT

Like other hominids, humans live in discrete communities. Settlement into small cohesive communities has several advantages: it provides a network of social support; it promotes cooperation, collaboration, and commerce; and it helps in creating a cultural and social identity. Cohesive communities fashion rich social environments consisting of houses, cities, and roads, with the purpose of promoting human health and optimizing human flourishing. They create artificial environments to protect against the elements; the vagaries of nature; and the threat of natural predators and pests. The creation of these artificial, but safe, environments may have been particularly critical for human evolution, as humans have long, protracted childhoods, when they are much more vulnerable to natural threats than other animals. However, built environments alienate humans from nature and they modify the influence of the natural environment on human health and development. Artificial environments create new problems, such as crowding, noise, and pollution; problems that ultimately limit health and promote disease. Moreover, the need for elaborate built environments necessitates the development of complex social hierarchy to afford and preserve private property and to enable division of labor. These hierarchical organizations engender economic disparity and lead to the development of social institutions that award more wealth and power to some members of the community, while marginalizing others. As discussed below, extensive evidence documents a strong influence of components of the social environment - the built environment, pollution, and socioeconomic status (SES) on both CVD risk and cardiovascular mortality.

The Built Environment

By moderating or modifying the influence of local ecology and by creating artificial, non-natural living spaces, the built environment could either promote or prevent disease. It could prevent disease by creating sanitary, climate regulated, safe spaces, but it could also promote disease by generating unconducive living conditions. Socio-environmental characteristics appear to contribute to CVD mortality risk, and the rates of CVD mortality vary across communities with different area characteristics, such as social cohesion, neighborhood identity, and stimatization.[108] Within communities, social inequalities are related to mortality; and within cities, living in deprived neighborhoods is associated with increased CVD prevalence.[109] Residents of disadvantaged neighborhoods have been found to have a higher incidence of CVD (RR = 3.1 for Whites and 2.5 for Blacks),[110] independent of personal income, education and occupation or established CVD risk factors.

Even though over 40 published studies report that living in socially-deprived areas increases CVD risk,[108] it remains unclear how this risk is imparted. In disadvantaged neighborhoods, the availability and costs of various types of foods, publicity and availability of cigarettes, the distribution of recreational spaces and differences in the built environment are likely to be important contributors to excessive CVD mortality. In addition, transportation services, healthcare resources, social interactions and neighborhood identity might be important as well. Moreover, it may be necessary to consider experiential factors such as affective experience (attachment, sense of community), cognitive experience (satisfaction with the neighborhood) and relational experience (social integration, social support and stressful interactions) as well.[108] Clearly, comprehensive environmental assessment is needed to capture all the dimension of complex entities such as communities and neighborhoods, entities that are composite products of local economics, history, social structure, public policy, and cultural practices.

The clearest impact of the built environment could be seen with obesity. Meta-analyses of over 60 studies show that aspects of the built environment are positively correlated with obesity[111], particularly in disadvantaged groups[112]. Strongest evidential support was found for food stores (supermarkets instead of smaller grocery stores), places to exercise, and safety. Each of these neighborhood characteristics were found to be correlated with body mass index[112]. Greater neighborhood physical activity resources were associated with lower insulin resistance[113] and high walkability neighborhoods were associated with decreases in weight and waist circumference[114]. These measures of obesity were also associated with high density of fast-food restaurants[114]. For neighborhoods with a high-density of fast-food restaurants an odds ratio of 1.8 has been reported[115]. Each quartile increase in land-use mix has been found to be associated with a 12% reduction in the likelihood of obesity.[116] Moreover, each additional hour spent in car per day was associated with a 6% increase in obesity risk and each kilometer walked per day with a 55% reduction in the likelihood of obesity. These effects of obesity mediate some of the effects on the built environment on CVD risk; more than half of the inverse association between neighborhood education and blood pressure could be explained by differences in BMI.[117] Factors contributing to the other half of the association remain unknown. Overall, CVD risk seems to aggregate in disadvantaged neighborhoods because of multiple sources of vulnerability that relate to the

characteristics of the built environment, stress, nutritional resources, lack of places to exercise, decreased interaction with nature and exposure to multiple environmental toxicants and pollutants.

Pollution

The modern environment is awash with synthetic chemicals and pollutants. By some estimates, > 30,000 synthetic chemicals are in current use, of these at least 5,500 are produced at > 100 tons per year.[118] Almost all major rivers and lakes show significant contamination by synthetic chemicals, pesticides or metals. Pesticides such as lindane, chlordane and DTT from Asia have been detected in Canadian Rockies and mercury generated by human activity has been detected in Arctic wild-life.[119] As a result, there are no pristine, un-polluted places left on the entire planet. High levels of pollutants are also released in the air. Although the level of air pollution in the developed world today is much lower than during its peak in the 1950s–1970s, the levels of air pollution in the developing world remain extraordinarily high.

Most air pollution is a mixture of complex aerosols containing both particles and gases. Particulate air pollution consists of particulate matter (PM), which when analyzed for mass fall into two peaks, corresponding to coarse particles (10-2.5 μm) and fine particles (0.1 to 2.5 μm). The fine particle mode also contains a small fraction of ultrafine particles, which despite its modest contribution to the overall volume of PM, contains the largest number of particles. Aerosols emitted in the environment directly are composed mostly of minerals, soot, salt particles, pollens and spores, whereas secondary aerosols are generated by sulfates, nitrates and organic compounds. In addition, both indoor and outdoor air contains a variety of gaseous pollutants, such as volatile organic chemicals (VOCs), nitrogen and sulfur oxides, and ozone. The composition of ambient air particles and gases in the atmosphere varies with meteorological conditions, local sources, geography, and seasons and could be quite complex, making it difficult to link constituents with health effects.

The WHO estimates that globally air pollution could be linked to 7 million premature deaths per year. This includes 1.6 million deaths in China and 1.3 million death in India. Estimates of premature mortality in the US from outdoor air pollution vary from 55,000[120] to 200,000.[121] In its health impact, air pollution rivals the effects of hypertension, smoking and physical inactivity.[122] Exposure to air pollution is pervasive and in some place, ubiquitous and unavoidable. In parts of the developing world, >95% of the urban population lives in cities where the levels of air pollution exceeds the air quality guidelines of the WHO.[122] The estimated contribution of the major sources of outdoor air pollution to premature mortality in different geographic locations is listed in Table 1. Notably most of this mortality in developing countries such as China and India is associated with residential and commercial energy use, which has been linked to over 10 million excessive deaths.[120] This estimate, however, does not include an additional 3.54 million death per year due to household air pollution due to biomass burning. In the US and Western Europe, agriculture, power generation and land traffic appear to be the major source categories. Agriculture, which contributes to $PM_{2.5}$ formation by releasing ammonia from fertilizers use and domestic

animals, contributes to nearly 20% of the global burden of outdoor air pollution, corresponding to an estimated 6.6 million death per year worldwide.[120]

While exposure to $PM_{2.5}$ has been linked premature mortality due to respiratory diseases and cancer, between 70–80% of premature deaths due to exposure to $PM_{2.5}$ are due to cardiovascular causes.[123] Reasons for the unique vulnerability of cardiovascular tissues to air pollution remain unclear, but extensive evidence has documented acute exacerbations of cardiovascular events upon exposure to particulate air pollution and chronic increase in CVD in individuals exposed recurrently to air pollution. Even brief exposures to polluted air are associated with MI, stoke, arrhythmias, atrial fibrillation and hospitalization for exacerbation of heart failure in susceptible individuals.[122–124] There is equally strong evidence suggesting that chronic and persistent exposure to air pollution increases the progression of atherosclerotic lesions and has adverse effects on blood pressure regulation, peripheral thrombosis, endothelial function, and insulin sensitivity.[49, 122–124]

The effects of air pollution on cardiovascular health seem to depend upon individual susceptibility. Individuals with pre-existing CVD, diabetes or those who smoke seem to be particularly vulnerable to the adverse effects of air pollution. Age, sex, ethnicity, and nutritional and socioeconomic status may be additional factors that might affect susceptibility, but no consistent evidence has emerged to implicate an important contribution of these factors.[49] It does appear; however, that individuals in good health are less likely to be affected by exposure to air pollution. For instance, in a study to 17,545 male health professionals, no association was found between CVD and long-term PM exposure.[125] This lack of effect was attributed to the higher SES and healthier lifestyle of this population. Nevertheless, other studies suggest that even young, healthy adults show signs of endothelial injury,[126] suggesting that although exposure to air pollution could induce cardiovascular injury in healthy individuals, clinical manifestation of this injury may be attenuated in individuals with good physical health and low CVD risk burden.

In addition to individual susceptibility factors, vulnerability to ambient air pollution is also moderated by environmental factors, such as the built environment, noise, ambient temperature, neighborhood greenspaces and proximity to major roadways or co-exposure to other pollutants and toxins. Individuals who live with close proximity to major roadways have been found to have increased carotid-intima thickness with increased exposure to traffic[127] and increased CVD risk as reflected by an increase in chronic inflammation,[128] circulating levels of angiogenic cells,[129] abdominal adiposity,[130] and incident hypertension.[131] Roadway proximity has been associated with elevated risk of acute myocardial infarction,[132] sudden cardiac death,[133] fatal coronary disease,[133] post-stroke mortality,[134] and mortality risk after hospitalization with acute heart failure.[135] In aggregate, this evidence reveals the significance of residential location as an important determinant of CVD risk and incidence, and survival after major CVD events. Whether ambient and roadway pollutant exposure have synergistic effects remains unclear, but it is generally believed that fresh emission containing high levels of ultrafine PM are particularly toxic and may account for the high CVD risk associated with residential proximity to major roadways. In addition to ultrafine PM, emissions from vehicular traffic also contain volatile organic chemicals (VOCs) such as acrolein, benzene, and butadiene, which by themselves have been found to

exert significant cardiovascular toxicity.[136] Acute exposure to the VOC acrolein in particular can cause dyslipidemia[137], vascular injury,[138–140] endothelial dysfunction,[141] and platelet activation[142], whereas chronic exposures accelerate atherogenesis[143], destabilize atherosclerotic lesions[144], disrupt cardioprotective signaling[145] and induce dilated cardiomyopathy.[146] Thus VOCs and other gaseous pollutants such as CO, NO_2, O_3 and sulfates, which constitute more than 98% of the mixture we breathe in urban locations[124] could significant modify to the effects of PM and contribute to CVD risk burden, particularly in urban locations.

The link between air pollution exposure and cardiovascular disease is supported by extensive evidence from animal models, which show that in controlled conditions, increased exposure to concentration ambient particles increases atherogenesis, insulin resistance, and thrombosis.[123] While this evidence attests to the biological plausibility of the relationship between CVD and air pollution, the underlying mechanisms remain opaque; however, unraveling physiological and molecular mechanisms, is critical to understand how air pollution exposure affects cardiovascular health, which specific conditions regulate individual susceptibility to PM toxicity and how the CVD burden of PM could be mitigated. Although we currently lack a comprehensive understanding of the varied cardiovascular effects of PM, important themes are being to emerge that relate PM exposure to an increase in systemic inflammation and imbalance of the autonomic nervous system. Inhalation of PM could create a state of heightened inflammation, by a “spillover” of proinflammatory or oxidative mediators from the lung to systemic circulation. This could lead to endothelial dysfunction and increased thrombosis that chronically could result in hypertension and accelerated atherogenesis. A spillover effect is consistent with recent observations showing that oxidants generated in the lung by PM exposure could accelerate the formation of atherosclerotic lesions[147] and that increased superoxide dismutation in the lung could prevent PM-induced insulin resistance.[148] Additionally, activation of several lung receptors and nerve endings by PM could lead to change in heart rate, heart rate variability and electrocardiographic changes reflective of an increase in sympathetic tone. Such changes and the resulting hemodynamic and electrophysiological changes could account for the acute cardiovascular effects of PM. While, further work is required to fully understand the pathophysiology of PM inhalation and to devise therapeutic strategies to minimize the impact of air pollution on cardiovascular health, the extensive evidence documenting the cardiovascular consequences of PM exposure highlights the important relationship between clean air and cardiovascular health and the dependence of CVD risk on external, environmental factors.

Environmental Noise

Like air pollution, noise is another important environmental factor that has an important bearing on cardiovascular health and disease. Noise generated from several sources, such as roadway traffic, railroads, and aircrafts interferes with communication, causes annoyance and disturbs sleep. In the US, nearly 46% of the population (145.5 million) is exposed to noise at levels exceeding 55 dBA L_{DN} (weighted day-night 24h average noise level) and 43.8 million individuals are exposed to noise levels exceeding 65 dBA L_{DN}.[149] In Europe, 40% of the population is exposed to road traffic noise exceeding 55 dBA L_{DN} and >30% to

>55 dB at night.[150] Constant exposure to noise induces stress, and affects cognitive function, autonomic homeostasis and sleep quality, all of which could increase CVD risk. Direct exposure studies with humans have shown that simulated traffic noise increases blood pressure, heart rate and cardiac output; effects that are likely to be mediated by the release of catecholamines, cortisol, and other stress hormones. Similarly, exposure to air craft noise, particularly at night, induces endothelial dysfunction measured by flow-dependent dilation, as well as an increase in blood pressure.[150] In animal models, chronic exposure to continuous noise (80–100 dB) has been reported to increase heart rate and mean systemic arterial blood pressure, functional changes that were associated with an increase in plasma corticosterone, adrenaline and endothelin-1.[151] Therefore, it is not surprising that exposure to environmental noise has been found to be associated with increased CVD risk in several epidemiological studies. In a recent meta-analysis of 14 studies on the association between road traffic noise and CHD, the pooled estimate of RR was found to be 1.08. Within the range of 52–77 dBA L_{DN}, an increase in noise by 10 dB was associated with an 8% increase in CHD risk.[152] Exposure to noise within this range has also been associated with an increase in hypertension.[149, 150] The effect size of this association seems to be inconsistent between studies, with larger effects reported for men, aged individuals and diabetics.[150] Associations of similar magnitude have been reported for stroke as well.[150] Although the exposure-response relationship does not suggest a biological threshold of effect,[152] the effect appears to be higher at higher levels of exposure due to occupational conditions or residential proximity to major sources of noise pollution such as airports, and there is suggestive evidence that individuals living in the vicinity of major airports have higher risk of developing arterial hypertension, CHD and stroke as well as a higher risk of CVD hospitalization.[150] Often noise pollution is confounded by air pollution and the effects of the two have been difficult to separate. In addition, the effects of noise could be moderated by greenspaces and other features of the built environment such as house design and orientation. The contribution of these factors has not been fully assessed. Nevertheless, current estimates suggest that a 5 dB L_{DN} reduction in environmental noise would reduce hypertension cases by 1.2 million and CHD cases by 279,000 per year in the US alone,[149] indicating that noise is an important contributor to CVD in modern, urban environments. Importantly, the link between noise and CVD reinforces the view that much of CVD is derived from unconducive environmental influences and that minimizing the impact of such exposures could significant diminish CVD burden.

Social Networks

Even though components of the physical environment such as land use and air pollution strongly influence CVD risk, the most important component of any human environment is not its physical attributes, but other people. Human groups form complex social networks of families, communities and nations, and interactions within and between these networks regulate important determinants of health such as health care access, civic policies, economic activity, the structuring of neighborhoods and cities or the generation of environmental pollutants. Consistent with the high impact of social interactions, it has been found that CVD risk factors such as obesity[153] and smoking[154] form distinct clusters within social networks and CVD risk factors such as obesity spread through social ties. For instance, it has been reported that a person’s chances of becoming obese increase by 57% is

he or she had a friend who became obese within the same period. The strength of social interactions in modifying disease risk seem to exceed the major known genetic influences. For instance, genome screening have identified that the FTO gene is strongly associated with obesity; however, persons carrying this gene have a 67% increase in the risk of obesity, compared with a 171% increase in risk by having just one friend who is obese,[155] suggesting that in this analysis at least, friends have a stronger influence on CVD risk than genetics.

Like friends, family members also influence CVD risk, which segregates in families. Family history is used to define risk status in the National Cholesterol Education Program (NCEP), [156] and has been found to be a risk correlate also in the Framingham study as well.[157] However, family history is not included in Framingham risk score because it is not clear whether its effects are independent of the major CVD risk factors.[158] Nevertheless, data from twin studies show that an individual's risk of CVD is increased when he or she has a relative with CVD by 57 % for men and 38 % for women.[159] Similar levels of CVD heritability have been found in the Danish twin registry (53 % for men and 58% for women). [160] While on face value these data suggest that much of CVD risk is heritable, observe evidence from studies on the social determinants of health suggest that the effects of shared genes cannot be separated from shared environments. Families are genetically related, but they also share the same environment and usually the same SES, and often the same neighborhood. They have similar diets and lifestyle choices, and members of a family dynamically affect each other's behavior. For instance, social network studies report that if one sibling becomes obese the chances that the other would becoming obese increases by 40 %.[153] Hence, families might have similar CVD risk not only because they share similar genes, but also because they share similar environments. Even in studies in which twins are separated at birth the change in environment is often not large enough to allow for a clear distinction between genes and environment.

Socioeconomic Status

Documented effects of SES on CVD also support the role of the environment. Poverty has always been known to be associated with poor health, but perhaps not in the same context as in modern societies. In the early part of the century, CVD was considered to be a disease of affluence, as during the 1930s and 1940s the rates of CVD in the West were higher in men with higher SES,[161] but since 1961, CVD mortality have been robustly and negatively associated with SES[162] In developing countries; however, CVD rates have increased with increasing affluence and adoption of the Western lifestyle. Reasons for the change in the relationship between SES and CVD remain unclear, but at least in the US, there is consistent evidence that low education is a significant predictor of MI and sudden death. In a remarkable study on 270,000 Bell employees in the US, Hinkle *et al.*[163], found that men who entered the organization with a college degree had a lower incidence and death rate from CHD in every part of the country and in all departments. Many other investigators have found a similar association of low education and income with excessive CVD mortality.[162] Several studies to assess the contribution of psychosocial factors such as social support, coping styles, behavior, job strain or stress, and anger or hostility are currently in progress, but a direct role of such factors in contributing to CVD risk remains uncertain.

SES, as reflected the level of education, was also inversely related to hypertension. Interestingly, even at higher education levels, the adjusted prevalence of hypertension remained nearly twice as high in blacks as in whites[164]. Reasons for this disparity may relate to other environmental and genetic factors such as differences in fluid regulation and/or vitamin D synthesis. However, the dependence of CVD risk factors does not entirely account of the strong effect of SES. For instance, in the Whitehall study men in the lowest SES has 2.7 times the 10-year CHD death risk than those in the highest grade. After adjusting for classical risk factors, the relative risk was reduced to only 2.1,[165] suggesting that the risk imparted by low SES is relatively independent of the major CVD risk factors. At best, conventional risk factors seem to account for only 15–30 % of the CVD risk imposed by SES. Clearly, other unappreciated environmental factors are at work. Indeed, recent work suggests that the some of the effects of SES may be due to the unique structuring, civic architecture and characteristics of disadvantaged neighborhoods particularly in the US and other industrialized countries.

THE PERSONAL ENVIRONMENT

Within the context of the social environment, the personal environment is created by personal lifestyle choices and individual preferences. The most persuasive evidence supporting a role of the personal environment comes from studies reporting a direct and robust association between lifestyle choices that affect CVD risk. However, the influence of the environment begins with the earliest stages of CVD development. Several studies show that the *in utero* environment determines CVD susceptibility later in life. An unfavorable *in utero* environment could induce the formation of atherosclerotic lesions during fetal development. The aorta of premature human fetuses shows fatty streaks, inflammation and the accumulation of oxidized lipids and the coronary arteries show intimal thickening.[166] Low birth weight, which is an indicator of an unfavorable uterine environment, shows a strong negative correlation with ischemic heart disease. This association persists even when adjusted for gestational duration, indicating that high CVD risk could be attributed to fetal growth restriction rather than to premature birth.[167]

In face of adversity the fetus attempts to adapt to the unfavorable environment. It undergoes predictive adaptive programming to diminish the impact of the adverse environment. These adaptations persist and could be beneficial if the *in utero* conditions continue upon birth, however, very often the post-natal environment is different and therefore the individual, already set off on a different course by fetal reprogramming, fails as an adult to adequately adapt to the new post-natal environment. An adverse fetal environment may be created by a variety of conditions such as the obstruction of the uterine artery, maternal under nutrition, smoking, alcohol consumption, diabetes or drugs and pharmaceuticals. While our understanding of the contribution of each of these factors to CVD risk is still in its infancy, both human and animal studies show that maternal hypercholesterolemia is associated with an increase in fatty streak formation in fetal arteries. The Fate of Early Lesions in Children (FELIC) study showed that the progression of atherosclerosis was markedly faster in offspring of hypercholesterolemic than normocholesterolemic mothers.[166] Thus the disease risk burden of the mother is at least partially transmitted to the fetus. This view is reinforced by the observation that immunization of the mother protects against postnatal atherogenesis,

even in the absence of gestational diabetes or maternal hypercholesterolemia.[167] Similarly, we have found that in mice prenatal exposure to low levels of environmental tobacco smoke affects offspring weight gain and induces a lipid profile that could alter the offspring's CVD risk in later life.[168] These findings are consistent with human data showing that infants of mothers who smoke during pregnancy have increased risk of subsequent obesity.[169] Thus, exposure to environmental pollutants or other adverse environmental factors that contribute to CVD in mother could induce fetal reprogramming that could alter the child's future CVD risk.

The environment continues to exert its influence after birth. Breast-fed infants show a dose-dependent reduction in obesity and formula-fed infants have a higher fat mass perhaps because breast milk contains leptin, which suppresses appetite and increases fat consumption.[169] Environmental factors may be related also to the epidemic of childhood obesity. In the last 30 years, the prevalence of obesity has increased 3-fold in children 2- to 5-years of age and 4-fold in children 6 to 11 years. Overweight children tend to grow into obese adults. In one study it was found that 80% of the overweight children were obese adults. The increase in childhood obesity has resulted in the higher prevalence of CVD risk factors such as high blood pressure and hypercholesterolemia leading to premature atherosclerosis and T2D. These diseases, particularly T2D, once thought to be occur only in late adulthood have now been shown to occur in children and adolescents, and it has been predicted that current generation of children may have a shorter lifespan than their parents, in part because of a higher incidence of diabetes and cardiovascular disease[169]. Because such sudden changes across the entire population are unlikely to be genetic, but may be related to technological advances, urbanization and economic issues that impact a child's eating and physical activity behavior.[169] These behaviors are heavily influenced by the social and physical environments, which to some extent dictate specific lifestyle choices relating to diet, exercise and smoking. Indeed extensive research suggests that individual lifestyle choices are key determinants of CVD risk. These are discussed below:

Nutrition

Personal food choices are important determinants of CVD risk. But the choice is not entirely arbitrary; it is defined, in part, by cultural and social conditions. Dietary traditions of obtaining and preparing food are unique to each culture, and like language; they provide cultural identity that is preserved across generations. Individuals from different dietary traditions display relatively stable dietary choices, despite occasional deviations. Dietary choices are also constrained by the social environment and conditions relating to food distribution and availability and often socioeconomic factors such as affordability. Hence, differences in individual eating behaviors and segregation of heart disease among different communities, families, and socioeconomic strata may be related to culturally transmitted or socially constrained dietary patterns.

Although diet is generally believed to be a critical determinant of health, its effects on CVD risk and progression are difficult to study. For such studies, large populations are required, but they are often heterogeneous in their health characteristics and genetic backgrounds, making it difficult to draw firm conclusions. It is also difficult to vary a single dietary

component in one group and not the other or to maintain large groups of people on specified diets for the long time required to assess changes in CVD risk and progression. Nevertheless, several studies have found significant cardiovascular effects of dietary components. These studies show that changes in diet alone could alter CVD risk. In the Nurses' Study, replacement of just 5 % energy from saturated fat with unsaturated fat was associated with a 42% reduction in CVD risk,[170] indicating that independent of energy content, CVD risk is affected by the composition of the diet. This view is reinforced by data on *trans* fats. In a meta-analysis of 4 studies, a 2% increase in energy consumption from *trans* fats was found to be associated with a 23% increase in cardiovascular events. A diet high in *trans* fatty acids has also been associated with 3-fold increase in sudden cardiac death[171]. Conversely, men who adhered to a "prudent" diet (consisting of vegetables, fruits, whole grains, fish and poultry) have half the CVD risk of men on a "Western" diet (red meat, processed meat, refined grains, sweets and dairy products).[172] Similarly, in the PREDIMED trial in which 7447 persons were followed for 4.8 years, a Mediterranean diet supplemented with extra-virgin olive oil or nuts improved the atheroprotective effects of HDL[173], delayed atherogenesis[174], and reduced the incidence of major cardiovascular events (HR=0.7),[175] further underscoring the profound influence of diet on CVD risk and outcomes.

Diet affects all the major CVD risk factors. Consumption of saturated fat increases cholesterol levels and high salt intake, the prevalence of hypertension. *Trans* fats raise LDL cholesterol, but reduce HDL and the size of the LDL particle, making LDL more atherogenic.[171] In communities where the consumption of sodium is <1 g/day, the prevalence of hypertension is only 1% of that in industrialized societies, and Tarahumara Indians of Mexico, who consume low (<100 mg/day) levels of cholesterol and fat, have low LDL levels and very low rates of CVD.[176] Dietary patterns also affect obesity and T2D, both of which are strongly associated with Western diet,[177] saturated fat intake, and frequent consumption of processed meat.[178] The association between CVD risk factors, such as T2D, is substantiated by dietary intervention studies, which show that modification in diet are particularly effective in reducing the rate of progression from glucose intolerance to frank diabetes.[179] Appropriate changes in nutrition can even reverse CVD. In the DIRECT-Carotid trial, a low-fat Mediterranean diet was associated with a decrease in both the carotid-wall volume and carotid artery thickness.[180] However, the molecular and the cellular mechanisms by which dietary components affect CVD risk factors are likely complex and as yet incompletely understood.

Physical Activity

Physical activity is a central feature of healthy living and throughout evolution. It must have been important for obtaining means for survival (food, material goods, protection, mates, etc) and for avoiding natural or predatory threats. Whatever the reasons, physical inactivity in contemporary humans is strongly associated with CVD risk. It increases the risk of coronary disease by 45%; stroke by 60%; hypertension by 30%; and T2D by 50%, and it has been estimated that 13% of all premature deaths in US could be attributed to physical inactivity.[181] Physical inactivity due to prolonged bed rest leads to a decrease in whole body insulin sensitivity within the first 3 days of inactivity,[181] and after 12 weeks, to an 8%

decrease in LV mass.[182] Conversely, regular exercise reduces CVD risk.[183] The effects are dose-dependent; moderate physical activity is associated with a 26% reduction in CVD risk, whereas high intensity activities with 42% risk reduction. Moderate to high intensity exercise has been shown to increase life expectancy by 1.3 to 3.7 years and active individuals remain free of CVD 1–3 years longer than their sedentary peers.[184]

Several mechanisms can account for the salubrious effects of exercise.[183] Vigorous physical activity increases myocardial oxygen supply and improves myocardial contraction and electrical stability. In addition, exercise increases HDL levels, while decreasing LDL-C, blood pressure, blood coagulation, systemic inflammation and insulin resistance. Even moderate levels of activity improve lipoprotein profiles and glucose homeostasis. At least some of these effects may be related to an improvement in NO production. Nevertheless, it is unclear how physical activity impacts CVD risk correlates such as cholesterol, blood pressure and insulin sensitivity - which specific metabolic, cellular and metabolic processes are affected and how does physical activity modify the nature and the inter-relationships between different processes that regulate cardiovascular homeostasis and health. Moreover, changes in CVD risk factors and inflammatory/hemostatic factors account for only about 60% of beneficial effects of exercise.[185] Factors that contribute to the other 40% of the protective effects of exercise on CVD remain unknown.

A better understanding of the effects of physical activity is required not only to devise new strategies to promote cardiovascular health and improve athletic performance, but to identify the environmental factors that promote or prevent physical activity. Depression may be one such barrier to physical activity. Individuals who are depressed are physically inactive and therefore the association between depression and CVD could be largely explained by physical inactivity.[186] Other barriers to physical activity in modern environments include labor saving devices, efficient transportation, and entertainment modalities that do not require physical activity. Moreover, the built environment, particularly in the US, does not demand, support, or even encourage physical activity. Thus like diet, physical inactivity is not just a lifestyle choice, but a social problem. Therefore, even though personal education and individual motivation remain the bedrock of prevention, community-wide changes in neighborhood characteristics, the built environment, recreational opportunities, and academic curricula are required to create an environment conducive to physical activity.

Smoking

No other personal choice has a more negative impact on cardiovascular health than smoking. On average, adults who smoke die 13 to 14 years earlier than non-smokers. In the US, smoking is associated with 443,000 premature deaths per annum, resulting in a yearly loss of over 5 million potential life years and $193 billion in direct medical costs and lost productivity.[187] Yet, nearly 16% Americans continue to smoke and each day nearly 2,100 youth and young adults become daily smokers (CDC 2016). World-wide, nearly 20% people smoke. About 5 trillion cigarettes are manufactured each year – nearly 1,000 cigarettes for every person on the planet; 15 billion cigarettes are sold daily, which corresponds to 10 million cigarettes every minute. Although in developed countries, smoking has declined by

40–50% from its peak in the 1960s[187], worldwide nearly one billion people continue to smoke.

Although smoking increases the risk of developing lung cancer and respiratory disease, nearly half of the premature mortality associated with smoking is due to CVD. Smokers have a nearly 2-fold higher risk of coronary disease and a 10-fold higher risk of developing peripheral artery disease.[188] Smokers are also more susceptible to arrhythmias, stroke and sudden cardiac death.[189] Smoking decreases regional left ventricular function even in asymptomatic individuals and significantly (45–80%) increases the risk of heart failure. Compared with non-smokers, even light smoker who smoke 6–9 cigarettes per day have a relative MI risk of 2.1.[190] That even low level exposure to tobacco smoke can increase CVD risk is amply supported by studies showing the high CVD risk of exposure to secondhand smoke[191] and the significant decrease in CVD mortality in communities after smoking ban.[192] The high vulnerability of smokers to heart disease underscores the high susceptibility of cardiovascular tissues to inhaled pollutants. Studies on air pollution, secondhand smoke exposure, and smoking have consistently demonstrated cardiovascular injury at levels and durations of exposure much smaller than those associated with lung cancer or even respiratory disease. In addition, exposure to several chemicals including bisphenol A and phthalates,[193] persistent organic pollutants[194], as well as VOCs such as acrolein, benzene and butadiene[136] have been found to be associated with increased CVD risk. Indeed, the WHO estimates that CVD is the leading cause of death due to exposure to environmental pollutants and the number of CVD deaths far exceed those due to cancer and respiratory disease (Figure 3). Reasons for the high vulnerability of cardiovascular tissue remain unclear, but may relate to poor xenobiotic metabolism in these tissues and their direct exposure to blood borne toxins.

While the mechanisms by which smoking increases CVD risk are not fully understood, it seems to affect CVD independent of other risk factors.[158] A meta-analysis of 54 different studies suggests that smoking increases LDL-C and decreases HDL, but changes in lipids account for <10% of the excessive CVD risk in smokers.[189] Similarly, even though smoking acutely affects blood pressure, smokers tend to maintain a lower blood pressure and anti-hypertensive therapy does not completely mitigate the CVD risk of smoking. The contribution of insulin resistance is also uncertain; some studies show that smoking increases insulin resistance but others have found no association between smoking and incident diabetes.[195] The mechanisms that mediate the risk of smoking remain to be identified, and even though cardiovascular injury due to tobacco smoke exposure has been directly demonstrated in animal models,[189] it is unclear which processes are most vulnerable to exposure and which components of tobacco smoke inflict cardiovascular injury. The problem stems in part from the complexity of the tobacco smoke, which contains more than 4000 different chemicals, making it difficult to attribute cardiovascular injury to specific chemicals, or to generate dose-response relationships. Nevertheless, it is generally believed that the volatile organic compounds (VOCs) generated by combustion contribute to the harmful effects of smoking. Based on this assumption, new devices have been developed that deliver nicotine in an aerosol of propylene glycol and vegetable glycerin. Some investigators believe that these devices – e-cigarettes – are less harmful than combustible cigarettes[196] and that they promote cessation,[197] a view that is shared by many in the general

public. As a result the use of e-cigarette is spreading. In 2014, 3.7% of American adults (9 million people) used e-cigarettes and the use of e-cigarettes among middle and high school students has tripled from 2013 to 2014, accounting for more than 13% of high school students. Currently nearly 2.5 million youth use e-cigarettes (CDC 2014). However, the safety profile of e-cigarettes is unknown.[198] While they do not contain many of the harmful or potentially harmful substances generated by combustion, they emit significant levels of reactive aldehydes that have been found to cause cardiovascular toxicity[199] as well as PM[200] of the same size range that increases CVD risk and mortality.[124] Nevertheless, some health advocates find the residual risk associated with e-cigarettes acceptable.[201] They believe that e-cigarettes are a safer alternative to combustible cigarettes and their widespread use and acceptance could lessen the burden of tobacco-induced disease. Others, however, are less certain and remain concerned about the potential health effects of nicotine as well as the chemicals present in e-cigarette aerosols.[201] They are also concerned about the uptake of e-cigarettes by youth who would not otherwise smoke cigarettes and the renormalization of smoking,[198] which has been a major contributing factor to the decline in the number of smokers in the last 5 decades. Regardless, of the impact e-cigarettes might have on cardiovascular health in future, the advent and spread of e-cigarettes is an important case study of how environmental factors – society, culture, advertisement and regulatory policy – influence CVD risk and affect cardiovascular health.

Perspective

Overall, the evidence discussed here provides ample support to the view that the CVD is an environmental disease. The disease stems largely from living in unconducive environments, and is sustained, in part, by a state of constant dyssynchrony with the rhythms of the natural environment and a mismatch between our ancient genes and our contemporary environments. This view provides a new perspective on CVD prevention and treatment, which suggests that enduring gains against the disease may be made by investigations into environmental origins of the disease, investigations that might be beyond the confines of the laboratory or the clinic, but within the domain of empiric inquiry.

An integrated environmental view of CVD also underscores the importance of prevention. As discussed, much of CVD is preventable and since the 1960s, primary prevention has been the major reason for the decline in CVD mortality.[1] In comparison with improved clinical care and treatment, preventive measures are likely to garner more widespread and enduring gains and, if not cost-prohibitive, could be adopted worldwide, even in resource-poor countries, which now seemed destined to bear the largest brunt of this epidemic. But most prevention strategies to date have been focused on individual interventions. However, if a majority of CVD is attributable to the environment, more widespread gains against the disease could be accrued by collective actions such as restructuring cities, minimizing pollution, increasing access to better nutrition, walkable areas, and urban greenspaces, rather than targeting individual behaviors and choices alone. Additional gains could be accrued by addressing both temporal and genetic dyssynchrony with the environment, in order to develop more individualized preventive approaches, approaches that recognize that each individuals is a unique product of his or her evolutionary, social and cultural history. Such a recognition of the role of the environment may also help in addressing social, economic and

cultural differences that fuel and sustain health disparities, even in affluent societies. But to fully redeem the promise of this approach, we would have to commit significant resources to this line of investigation, which has traditionally received less attention and funding than other approaches. But given the predominant role of the environment, unprecedented efforts have to be made to assess individually the impact of the natural, social and personal domains of the environment, and to understand how these domains influence the effects of other domains, and how such interactions collectively affect CVD. Hence, the challenge to future investigators is not only to systematically unweave the strands of environmental influences, but to integrate the effects of the various components of the environment into a comprehensive model. Such a model might explain how the effects of the natural environment are moderated or amplified by the social and personal environments and how the effects of the social and personal environment are limited or modified by the natural environment. Much work remains to done to develop and test such a model, but even an incremental advance in our understanding of the environmental bases of CVD might help in devising more effective prevention and intervention strategies that could meaningfully slow down or halt the ominous progression and spread of CVD in modern societies.

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Nonstandard Abbreviations and Acronyms

CVD	cardiovascular disease
MI	myocardial infarction
CHD	coronary heart disease
UV	ultraviolet
SES	socioeconomic status
RR	Relative risk
HR	Hazard ratio
PM	particulate matter
VOC	volatile organic chemicals
dB	decibel
T2D	Type 2 Diabetes
CDC	Centers for Disease Control

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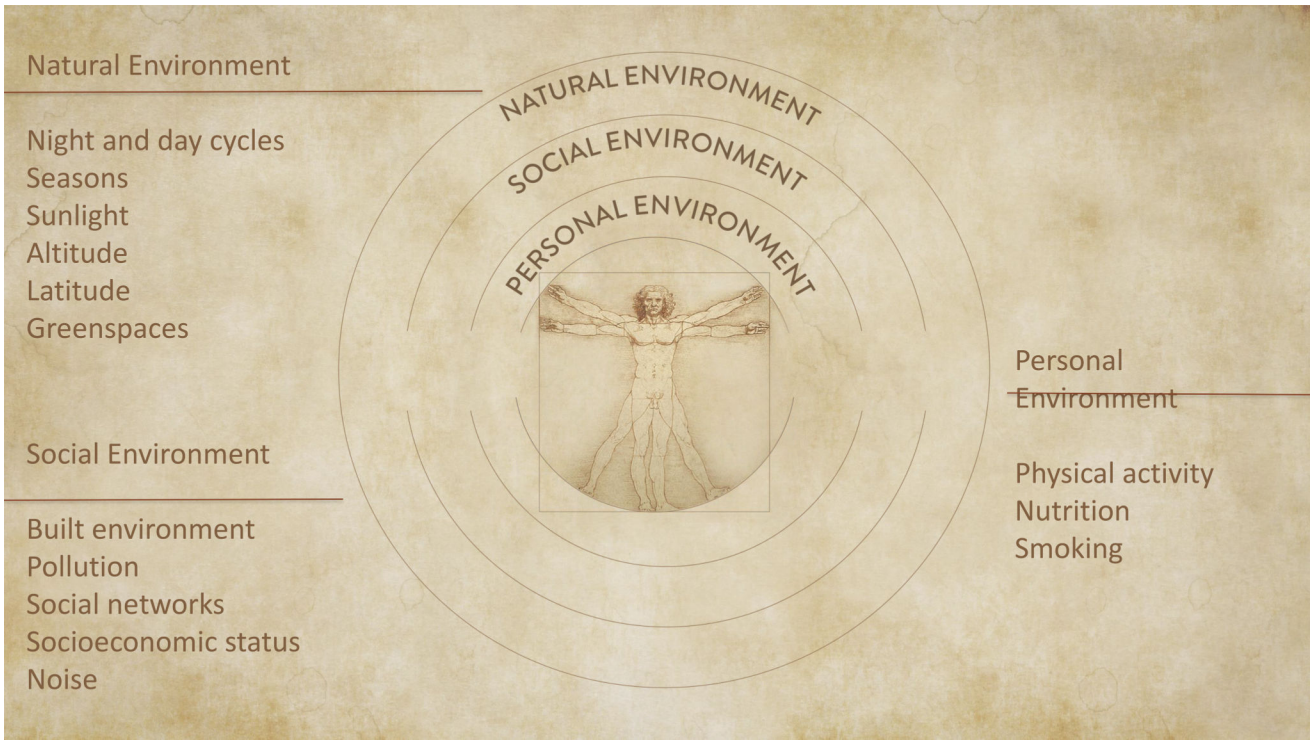

Figure 1.

The human envirome. The human environment is categorized into natural, social and personal domains. The natural domain of the environment is characterized both by natural ecology and geology, as well as the diurnal cycles, seasons and greenspaces. The influence of the natural environment is moderated both by the physical attributes of the social environment as well as social and networks and socioeconomic status of the individual within society. Features of social environments, such as pollution and occupation also affect CVD risk. The social environment, permits, promotes, facilitates or constrains lifestyle choices such as physical activity, nutritional choices and smoking that constitute important domains of the personal environment. Collective influences of these nested domains of the environment have been found to profound influence CVD risk, incidence, prevalence and severity.

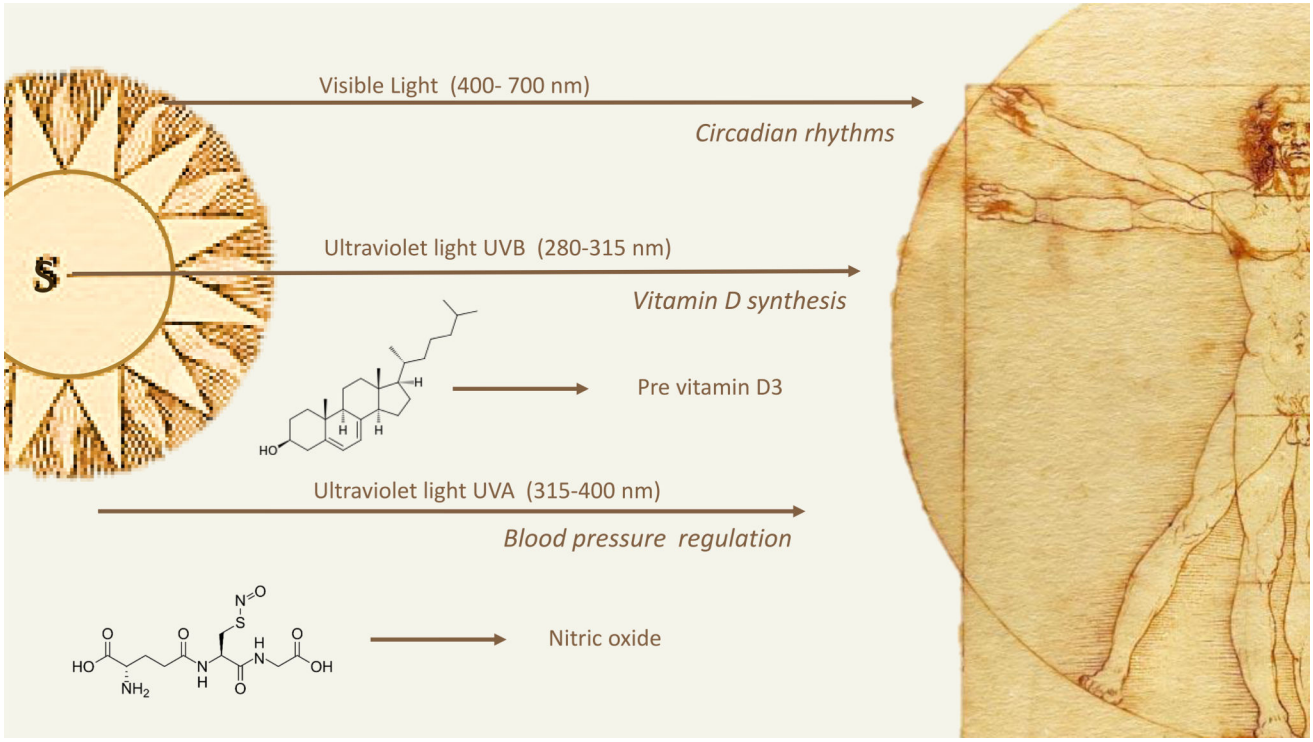

Figure 2.

The effect of sunlight on cardiovascular health. The visible range of sunlight regulates the master clock located in the pacemaker neurons of the suprachiasmatic nucleus, which sets the intrinsic 24 h cycle and synchronizes the light-insensitive peripheral clocks to coordinate cycles of waking, sleeping and feeding. The UVB radiation converts 7-dehydrocholesterol in the epidermis to previtamin D3, which undergoes thermal isomerization to vitamin D. Vitamin D3 formed in the skin appear in the circulation and is then transported to the liver where it is converted to 25(OH)D3. In kidney, 25(OH) D3 undergoes hydroxylation to form biologically active 1,25(OH)2D. The UVA radiation induces the photo-degradation of nitrosothiols, such as S-nitrosylglutathione, which leads to the generation of NO, an important regulator of blood pressure.

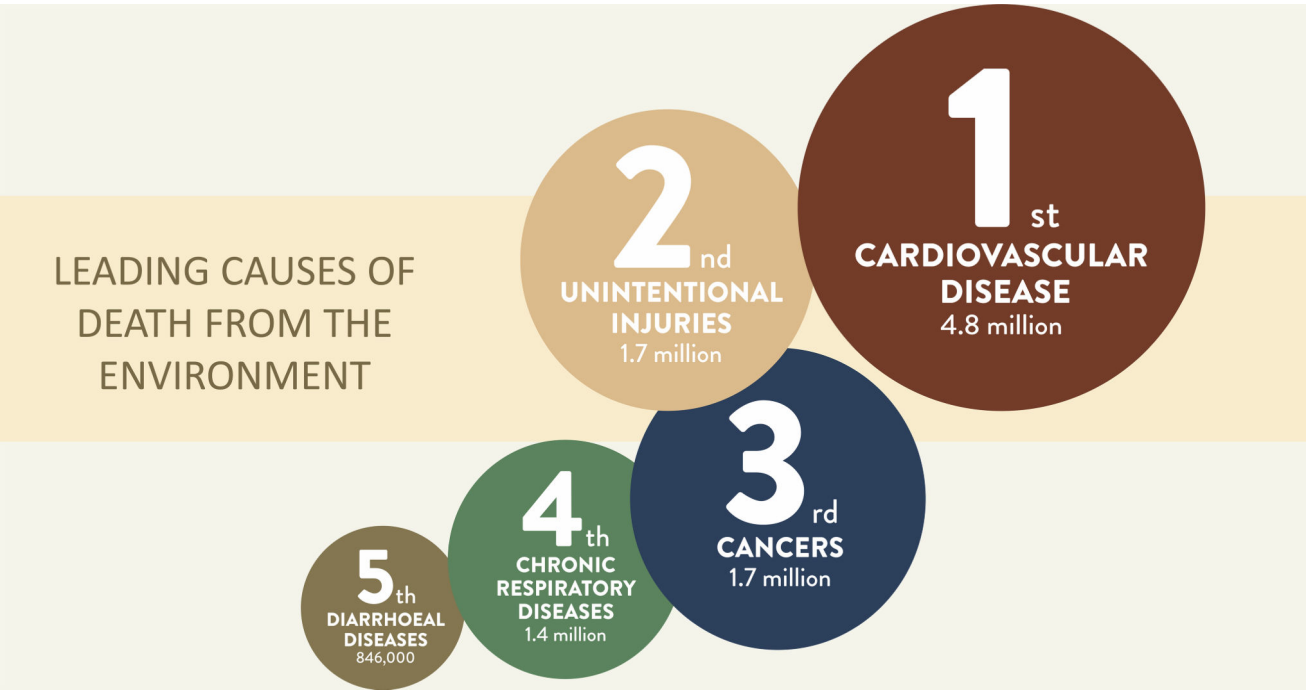

Figure 3.
Data from the World Health Organization showing cause-specific deaths attributable to the environment per year worldwide.

Table I

Estimated premature mortality associated with different source categories of outdoor air pollution in different geographic areas (2010)

Source Category	% mortality global	% mortality USA	Geographic Area	Major constituents
Residential energy	31	6	China, India, Indonesia, Vietnam	CO_2, CO, VOCs, NOx, SO_2, Hg, $PM_{2.5}$
Agriculture	20	29	Europe, Russia, Japan, Eastern USA	Inorganic $PM_{2.5}$, NH_3, sulfates nitrates
Power generation	14	31	USA, Russia, Korea, Turkey	Sulfate and nitrate containing $PM_{2.5}$, Hg
Industry	7	6	Japan, Germany, China	Sulfate containing $PM_{2.5}$, VOCs, hydrocarbons
Biomass burning	5	5	Canada, Africa, South America, Australia, Southeast Asia	$PM_{2.5}$, NOx, CO, SO_2, Pb, Hg
Land traffic	5	21	USA, Germany, Russia, Japan	Ultrafine PM, $PM_{2.5}$, NOx, VOCs, ozone
Natural sources	18	2	Africa and Middle East	PM_{10}, Airborne dust

Data from Lelieveld et al., 2017[120]