

## Cardiovascular effects of indoor air pollutants

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In the last decades, research on the causes of cardiovascular disease has made great progress. Multiple pharmaceutical and surgical approaches have been devised to prevent, treat, or otherwise manage heart disease, yet it remains the leading cause of death both in Europe and United States. There are important gaps in the understanding the leading causes of cardiovascular disease and the underlying pathological mechanisms. Prevention is likely to provide the most effective gains against highly unpredictable events, such as acute myocardial infarction, stroke or arrhythmia, so it is essential to identify the preventable and the modifiable causes of heart disease. Lifestyle choices such as smoking, diet, and exercise are viewed as the most important factors, but in the past years many studies has focused on the contribution of air pollutants in the onset and/or exacerbation of cardiovascular disease.

### **DEFINITION OF CARDIOVASCULAR DISEASE**

Cardiovascular disease (CVD) is a broad term used to describe a range of diseases that affect heart and the circulatory system. Heart disease develops as a result of complex interactions between genes and environment. The most frequent forms of CVD are coronary heart disease and stroke, and other forms include hypertensive heart disease, arrhythmia and heart failure.

### **EPIDEMIOLOGY, TIME TREND AND SOCIAL COST**

Cardiovascular disease is the leading cause of death in the industrialized world: CVD accounts for over 4.35 million deaths (49% of all death) each year in Europe and over 1.9 million deaths (42%) in the European Union (EU). The most common forms of cardiovascular disease are coronary heart disease (CHD) and stroke that are by themselves the two most common causes of death in the EU: accounting respectively for over 744,000 (17%) and 490,000 (11%) deaths in the EU each year. CVD mortality, incidence and case fatality are falling in most Northern, Southern and Western European Countries but either not falling as fast or rising in Central and Eastern European countries.

Overall CVD is estimated to cost the EU economy €169 billion a year. Of the total cost of CVD in the EU, around 62% is due to health care costs, 21% due to productivity losses and 17% due to the informal care of people with CVD (European

## **TRADITIONAL RISK FACTORS**

The seminal Framingham Heart Study framed determinants of heart disease as “risk factors” that can quantitatively predict cardiovascular disease [1] [2]. Major risk factors for CVD could be classified in fixed and modifiable. Fixed risk factors are age (older than 65), gender (male) and heredity (including race). Factors that could be modified are hypertension, high blood cholesterol levels (in particular low-density lipoprotein), diabetes mellitus (especially adult-onset or Type 2 diabetes), obesity and overweight, cigarette smoke, physical inactivity.

Besides major risk factors, other exposures, like stress and high alcohol intake (called contributing risk factors) have been associated with increased risk of cardiovascular disease, but their significance and prevalence have not yet been precisely determined.

## **OTHER FACTORS that could be involved in CVD determination and/or exacerbation: the role of environment**

The so called major risk factors identified in the frame of Framingham Heart Study account for a major portion of but not for the total CVD risk [3, 4]. Many patients suffering from heart disease have no established risk [5], suggesting that quantitatively important determinants of CVD are currently unknown [6]. Moreover, the identification of modifiable risk factors, such as smoking and diet, fosters the perception that the environment significantly influences cardiovascular health. This view is further reinforced by studies showing that CVD rates differ 5- to 100-fold among population groups of similar genetic background. These rates change quickly within the same ethnic group, and they increase when populations migrate from low to high-risk environments [7, 8].

Despite these studies, our understanding of environmental influences has been limited to lifestyle choices such as diet, smoking, and exercise, and it is only in the last few years that disparate lines of evidences have congealed into a coherent idea that environmental exposure to pollutants and chemicals contribute to CVD risk [9-11].

Indoor air pollutants that have been associated, or could be related, to an increase risk of CVD are secondhand smoke, carbon monoxide, particulate matter, ozone, nitrogen oxides, carbon monoxide and sulphur dioxide.

Sources of indoor air pollution are both indoor and outdoor. While many studies have been conducted on carbon monoxide and secondhand smoke effects on heart, less scientific work has been done on CVD risk related to exposure to indoor particulate matter and gaseous pollutants other than CO. Several studies have shown some link between outdoor PM and gases exposure and cardiovascular disease mortality and morbidity [10].

## Secondhand smoke

Secondhand smoke (SHS), also known as environmental tobacco smoke (e.g. spousal smoking, cohabitant smoking, work exposure), is a complex mixture of gases and particles that includes smoke from the burning cigarette, cigar, or pipe tip (sidestream smoke) and exhaled mainstream smoke [12].

Many reviews have been published summarizing the epidemiological studies about the association between SHS and increase risk for CVD, here we summarized the most important and recent ones. Law and colleagues [13] conducted a meta-analysis of all 19 studies of risk of ischaemic heart disease in lifelong non-smokers who live with a smoker and in those who live with a non-smoker and concluded that people who have never smoked have an estimated 30% greater risk of ischaemic heart disease if they live with a smoker, The Australian 1997 NHMRC Working Party Report [14] reviewed the data from 22 analysis from 16 studies of SHS and CHD, finding a statistically significant increase in the risk of coronary events in nonsmokers exposed to SHS. The Californian 1997 CalEPA Report [15] considered 10 cohort studies and 8 case-control studies of SHS and CHD and concluded that epidemiological data in western and eastern countries are supportive of a causal association between SHS exposure from spouses and CHD mortality in nonsmokers, in both genders. The U.S. 2001 Surgeon General's Report *Women and Smoking* [16] reviewed 10 cohort and 10 case-control studies concluded that data from these studies support a causal association between SHS and CHD mortality, morbidity and symptoms. The U.S. 2006 Surgeon General's Report *The Health Consequences of Involuntary Exposure to Tobacco Smoke* [17] reviewed 9 cohort and 7 case-control studies (between June 1998 and April 2002) concluded that the evidence is sufficient to infer a causal relationship between exposure to SHS and increase risk for CHD morbidity and mortality.

All these reviews concluded that the estimate risk for CHD related to SHS is about 25-30 percent and is within range of risk estimates observed for active smoking and CHD[14, 15, 17] [16]

In the 2006 USDHHS report were also reviewed 6 studies (4 case-control, 1 cross-sectional and 1 cohort) about the association between SHS and risk of stroke, and 12 studies about the link between SHS and subclinical vascular disease, particularly carotid arterial wall thickening. The conclusion was that the analysed studies were "suggestive but not sufficient to infer a causal relationship between exposure to second hand smoke" and an increased risk of stroke and atherosclerosis [17].

## Carbon monoxide

See the paper *Health effects of carbon monoxide intoxication* by P. Carrer et al. on page 187 of this proceedings.

## Particulate matter

Particulate matter (PM) is a complex mixture of airborne solid particles and liquid droplets (aerosols) that vary in size and composition, depending upon the location and time of its source. PM is generally divided, according to the aerodynamic diameter

( $D_a$ ), into  $PM_{10}$  ( $D_a < 10 \mu m$ ),  $PM_{2.5}$  ( $D_a < 2.5 \mu m$ ), ultrafine particles (UFPs;  $D_a < 100 \text{ nm}$ ). Despite its modest contribution to overall volume, the ultrafine fraction represents the largest number of particles and, therefore, presents the largest surface area.

Indoor sources of PM include fuel/tobacco combustion, cleaning operations and cooking [18]. Moreover, fine and ultrafine particles may be formed by reactions between ozone and some VOCs (the so called *indoor chemistry*), in particular terpenes. The highest terpene concentrations also produced high particle levels [19-21]. Particles from outdoor air may contribute to particle load in indoor air, and exposure studies carried out in the United States and Europe showed that particles in outdoor air contributed substantially to personal exposures and to temporal variation in personal exposures, *also in the indoor environment* [22].

The concern about indoor particulate matter cardiovascular effects arises from the epidemiological evidences of health effect of exposure to PM. During the past 15 years, the magnitude of evidence and number of studies linking outdoor air pollution to cardiovascular diseases has grown substantially [23, 24] and there is concern that the association of airborne particles ( $PM_{10}$  and  $PM_{2.5}$ ) with adverse cardiovascular outcomes is causal, as summarized in a review by a committee of the American Heart Association [10].

Long-term exposure to  $PM_{2.5}$  have been demonstrated to be independently related to cardiovascular mortality in general [25], and in particular to mortality for ischemic heart disease, arrhythmia, heart failure and cardiac arrest [26].

Short-term effects of  $PM_{10}$  exposure include an increase in the overall cardiovascular mortality [27, 28]. Observations in Europe [29, 30] and North America [31, 32] have demonstrated higher rates of hospitalizations for all cardiovascular causes. Direct associations have also been identified with respect to incidence of ischemic heart disease, arrhythmias, and heart failure. Elevations in air pollution have also been associated with increased blood pressure during a prolonged air stagnation episode in Europe [33]. Finally, recent studies from Seoul, South Korea [34], Taiwan [35] and Kuopio, Finland [36] have reported higher incidences of ischemic strokes in direct relation to changes in ambient particle concentrations. In summary, these findings imply that short-term elevations in ambient particle levels are capable of evoking cardiac arrhythmias, worsening heart failure, and triggering acute atherosclerotic/ischemic cardiovascular complications.

To date, there have been only a limited number of studies on the association of measures of ultrafine particles with risk of cardiovascular effects [37-42]. The available literature suggests that ultrafine particles may induce cardiovascular health effects immediately, with a 2–4-day lag, and in association with cumulative exposures [18].

### Gaseous pollutants

Gaseous pollutants, other than carbon monoxide, that could affect cardiovascular system are ozone, nitric dioxide and sulphur dioxide.

Ozone ( $O_3$ ) and other photochemical oxidants are pollutants that are not directly emitted by primary sources. Rather, they encompass a group of chemical species formed through a series of complex reactions in the atmosphere driven by the energy transferred to nitrogen dioxide ( $NO_2$ ) molecules when they absorb light from solar radiation. In most buildings indoor ozone has been transported from outdoors [43]. Indoor ozone concentrations track outdoor concentrations with a slight time lag that depends on the air exchange rate.

There is solid evidence that ozone acutely increases morbidity [18]. To date, data about cardiovascular effects of ozone exposure are poor also because in studies of acute responses to pollutants in humans it is generally not possible to separate effects due to peaks in PM concentrations from those that may be due to ozone. In a review presented in the Air Quality Guidelines of WHO – Europe 2005, 10 of the 15 reviewed studies, focusing on cardiovascular diseases, showed no significant effects of ozone. In addition, there is no clear positive effect of ozone on any of the particular end-points evaluated (myocardial infarction, sudden death, stroke, congestive heart failure and peripheral arterial diseases). Thus, on the basis of the available information, it is clear that the effects of ozone on cardiovascular morbidity need further evaluation [18]. However a recent analysis of the link between ambient air pollution and the risk of hospital cardiac readmissions of MI survivors suggests that the strength of associations with same-day CO,  $O_3$ , or  $NO_2$  was similar to that for  $PM_{10}$  (von Klot S 2005) suggesting a significant contribution of ozone among gaseous co-pollutants.

Nitrogen dioxide ( $NO_2$ ) is a reddish brown gas with a characteristic pungent odour. Nitric oxide spontaneously produces the dioxide when exposed to air. Nitrogen dioxide gas is a strong oxidant, and reacts with water to produce nitric acid and nitric oxide. Significant human exposure to  $NO_2$  can occur in non-occupational indoor settings [44, 45]. Gas-burning appliances, such as unvented furnaces and stoves, are the principal sources of indoor  $NO_x$ , although kerosene space heaters and tobacco smoke may also play a role. [46]. In urban areas, infiltration of ambient  $NO_2$  from vehicular emissions may also influence indoor exposures.

Epidemiological evidences of cardiovascular effects of  $NO_2$  exposure proceed from studies on outdoor air pollution. Moreover, it is very difficult to differentiate the effects of nitrogen dioxide from those of other pollutants in epidemiological studies.

Short-term effects of  $NO_2$  exposure have been investigated in time-series studies on mortality and morbidity in Europe and North America [28, 29, 31, 47-60]. These studies suggest that daily concentrations of nitrogen dioxide are significantly associated with increased cardiovascular mortality. Moreover, the results of time series include an increase in mortality for cardiovascular disease, and in hospital admissions for heart failure, arrhythmia and ischemic heart disease. Controlling for other pollutants at times lowers the effect estimates and at others makes them not statistically significant, and this makes the conclusions less clear. To date, no cardiovascular long-term effect of  $NO_2$  has been demonstrated.

Sulfure dioxide ( $SO_2$ ) is a colourless gas that is readily soluble in water. Sulfur dioxide is derived from the combustion of sulfur-containing fossil fuels. In nonoccupational

settings, SO<sub>2</sub> is generally found at substantially lower concentrations indoors than outside; however, the use of kerosene space heaters can generate significant indoor concentrations.

Literature about cardiovascular effects of SO<sub>2</sub> is poor, and it prevalently include studies on outdoor air pollution health effects. A review of literature on Health effects of outdoor air pollution in developing countries in Asia [61] is suggestive for a positive association between SO<sub>2</sub> levels and hospital admission for cardiovascular disease, in studies from Hong Kong. The European APHEA 2 project single pollutant models resulted in positive and significant sulfur dioxide risk estimates for all of the cardiac outcomes except stroke. However, these estimates were reduced when carbon monoxide, nitrogen dioxide, black smoke or PM<sub>10</sub> were included in the model. The authors noted that sulfur dioxide could be a surrogate of urban pollution mixtures that in some cases is more strongly associated with cardiovascular hospital admissions than particles [62-65]. In an analysis of morbidity after the step-change in ambient sulfur dioxide concentration in Hong Kong, Wong et al. [66] concluded that for sulfur dioxide concentrations in the 5–40-µg/m<sup>3</sup> range in Hong Kong, there were non-threshold and nearly linear relationships between sulfur dioxide on the one hand and cardiac admissions on the other, but no trends for ischemic heart disease.

Moreover, the influence of SO<sub>2</sub> levels on PM<sub>10</sub> risk estimates has been investigated in the U.S. NNMAP [52] (re-analysis by Schwartz et al in 2003 [67]). The authors concluded that there was little evidence of PM<sub>10</sub> effects confounded by sulfur dioxide.

## **IDENTIFICATION OF SUSCEPTIBLE POPULATION SUBGROUPS**

People who already have heart disease are at especially high risk of acute events if exposed to SHS [17].

It is now reasonably well established that both short-term and chronic air pollution (including PM and gaseous pollutants) exposures are related to cardiovascular diseases. Whether there are specific individuals or subsets of patients at increased relative risk is less well documented. Some observations have suggested that people suffering from cardiovascular diseases are more vulnerable to particles and NO<sub>2</sub> and persons suffering from asthma and other respiratory diseases are more susceptible to particles [18, 61, 68, 69]. Moreover, the elderly [25, 28, 70-72] and those with less than a high school education (low socioeconomic status) may be particularly susceptible populations [71, 73]. According to a few recent studies women gender seems to be more prone to cardiovascular effects of PM than men [74, 75].

## **CONCLUSIONS**

Environmental cardiology is a emerging field of research. The identification of modifiable risk factors for cardiovascular disease such as smoking and diet, supports the perception that the environment significantly influences cardiovascular health. The indoor environment represents an important microenvironment in which people

spend a large part of their time each day, so that exposure to cardio-toxic indoor air pollutants could have a role in the cardiovascular etiopathology.

There are consistent evidences that SHS exposure is associated with increase risk of cardiovascular disease, in particular CHD (similar risk estimates observed for active smoking).

Cardiovascular effects of particles, in particular PM<sub>10</sub> and PM<sub>2.5</sub>, have been suggested in a consistent number of studies on outdoor pollution, and short-term elevation of particles seem to evoke cardiac arrhythmias, to worse heart failure, and to trigger acute atherosclerotic/ischemic cardiovascular complications. As highlighted by Hänninen and Jantunen in a recent letter to the Journal of Epidemiology and Community Health, the observed seasonal variation in mortality due to particles could be due to the variation in the infiltration of outdoor air particles indoors, that mostly depends on ventilation via open windows[76].

More research is needed to identify the role of the ultrafine fraction.

Cardiovascular toxicity of gaseous pollutants, i.e. ozone, nitrogen dioxide and sulfur dioxide, has been investigated in the outdoor environment. To date, literature about cardiovascular effects of the exposure in indoor environments to these pollutants is too poor, and no conclusions could be made.

All together, these studies suggest a potential role of indoor particles, both generated indoor or infiltrated from outdoor, in the causation and/or exacerbation of cardiovascular disease. Additional studies on gaseous pollutants effects on cardiovascular system are much needed and more refined epidemiological studies on indoor pollutants effects on cardiovascular system are required.

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