# Impact of Lifetime Exposure to Air and Noise Pollution on Cardiovascular Disease and Mortality - the AIRCARD Study.

**NCT04353232**

**17/10/2023**

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## INTRODUCTION

The purpose of this study is to determine the impact of individually lifetime accumulated exposure to air and noise pollution on the incidence and prevalence of cardiovascular diseases (CVD) and mortality.

Air as well as noise pollution have harmful effects on human health (1). Experimental and clinical studies have shown a strong impact between particulate matter ($PM_{2.5}$) and cardiovascular disease (CVD) (2, 3). Prolonged exposure to $PM_{2.5}$ has been associated with the development of atherosclerosis and adverse cardiovascular events. However, also short-term exposure has been linked to acute coronary events (4, 5). $PM_{2.5}$ is, however, a combination of many components of specific pollutants that have a size of two and a half microns or less in width. However, there is a knowledge gap, as investigation into which specific components of air pollutants that contribute the most to the development of CVD is lacking. There is a need to adopt and encourage preventive measures but also put in place environmental policies that are effective in promoting the reduction of exposure to pollutants. We want to aid in this shift by showing which specific pollutants contribute the most to the development of CVD so that we can better target these specific air pollutants for better prevention initiatives.

We will determine the contribution of sulfate, nitrate, ammonium, elemental carbon, organic carbon, silicon, or sodium ion, all contained in $PM_{2.5,}$ to CVD. More relevant is that we can demonstrate which pollutants emitted from power plants, industries, and automobiles have the worst impact**.** We can provide insightful information to decision- and policymakers and this can help better target interventions against harmful pollution discharges and hereby significant prevention of many diseases with special emphasis on CVD and mortality.

The results from our pollution study can be implemented immediately when new roads, buildings or industries are planned as well as aid industries in limiting their pollution burden and aid government officials in making new legislative regulations on air pollution. This will have an impact on the general health of the population and therefore for every individual and at all decades of life. The results will have a huge impact within both clinical research, prevention, and the broader public health not only in Denmark, but globally.

From a societal perspective, it is already known that socioeconomic status, personal health, and housing is correlated (6). The Danish Health Authority reported that cardiovascular death can be halved if people from the lowest socioeconomic classes have the same risk of developing CVD as people from the upper socioeconomic classes. If we confirm that air or noise pollution poses the risk as has been suggested, we will be able to bridge the gap created by social inequality in CVD if social inequality also relates to pollution.

## BACKGROUND

Cardiovascular disease and its thrombotic complications are currently one of the deadliest and most disabling diseases; each year CVD causes 3.9 million deaths in Europe and loss of 26 million disability-adjusted living years in the EU (7). The occurrence of CVD is the effect of lifetime exposure to various risk factors (8, 9). Subclinical coronary artery disease as determined by revealing coronary artery calcification (CAC) has been shown to provide powerful prognostic

information beyond that of traditional Framingham risk factors across a wide range of ages and ethnicities (10-13). Social inequality is a known CVD risk factor and the Danish National Board of Health has reported that CVD carries the second largest socioeconomic difference in burden of disease, and if the people with lowest socioeconomic status had the same risk as those with the highest status, the rate of cardiovascular death would be reduced by half (14, 15). However, known genetic and environmental risk factors cannot explain all CVD prevalence, and there is an increasing need for population-based identification of novel risk factors (16).

In a previous study, we demonstrated that living in a city center contributes to the presence of calcification in the coronary arteries (17). Air pollution is a major environmental factor associated with health impacts (18, 19), which disposes significantly to the incidence and prevalence of CVD (20). Furthermore, epidemiological studies suggest that long-term exposure to air pollution (21-24) relates to progression of CAC.

Previous studies have shown an association between CVD and short-term exposure to increased air pollution levels. The literature on the impact of long-term effect of air pollution is, however, limited. A prospective 10-year cohort Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air) examined more than 7,000 men and women in the age of 45-84 years from six cities in the United States. Data from 5,000 US Environmental Protection Agency monitors and more than 7,420 MESA Air stationary location monitors in six MESA cities were collected with recent and 20-year historical exposure data from participants home addresses (23, 25). The MESA Air study found a strong association with accelerated atherosclerosis in the coronary arteries over a 10-year period related to air pollution (26). However, a limitation of the MESA Air study involves the collection of the air pollution data. The predicted air pollution data for each participant in the study was a collection of questionnaires, and the measurements were averaged data from a two-week period. Strengths in the MESA Air study are the repeatedly measured CAC with CT to evaluate the accelerated atherosclerosis in participants (25). It has also been reported in the German Heinz-Nixdorf Recall (HNR) study (27) and from Lambrechtsen J et al in the Danish DANRISK sub study (17) that CAC was higher in participants living near roads and in city centers, respectively. But the identity of the pollutants that carry the highest risk is unknown.

In Denmark, a unique temporal and spatial epidemiological model for retrospective calculation of accumulated individual air pollution exposure exists (28-32), and it is possible to calculate the air pollution retrospectively to 1979. These data include concentrations of atmospheric particles with diameter less than 2.5 μm ($PM_{2.5}$), which consist of several components. Furthermore, the model system calculates concentrations of health relevant gases, and nitrogen dioxide (NO2), ozone (O3) and sulfur dioxide (SO2) (33, 34).

This study will provide more detailed data as we can model pollution levels hourly compared to the MESA Air's two-week periods. Furthermore, we will incorporate work addresses where previous studies are limited to home addresses only. The MESA Air study is the most comprehensive to date but limited as they divide the contributions into $PM_{2.5}$ and $NO_X$ only. Previous studies have provided air pollution data as an accumulated amount where we have the possibility to show if the air pollution is of local origin (e.g., traffic, wood stoves), national origin (e.g., power plants, industries, agriculture), or international origin (e.g., other countries, shipping). We can show which component contributes most and where the pollutant(s) comes from.

The American Journal of Hypertension released a call for clinical trials on the correlation between air pollution and CVD in 2018 (35), and a joint opinion was released in April 2021 by the World Heart Federation, American College of Cardiology, American Heart Association, and the European Society of Cardiology due to the increasing concern about air pollution in the development of cardiovascular disease (36). They state that *50% of the 6,7 million deaths that can be attributed to air pollution are due to CVD* (36), which is concerning due to the fact that the disease burden of air pollution seems to be "larger and higher-ranking" than some of the presently recognized CVD risk factors (37).

We published a method article in 2020 (38) accounting for the aims of our study and the release of the concerning joint opinion in Circulation has reinforced the importance of this study. Hence, this project will contribute with unique and precise data to show if a correlation between air pollution and CVD burden truly exists.

Another aspect of environmental risk factors is environmental noise. The first article about this subject was published in 1985, nevertheless, it is only in recent years we are seeing both growing quality and quantity of articles in esteemed

journals about environmental noise. These articles unanimously report an increased risk of hypertension, coronary heart disease, stroke, heart failure and atrial fibrillation with even slightly increased levels of environmental noise (specifically road traffic noise and aircraft noise). One of these studies (39) was a cross-sectional study of residents in London who lived close to Heathrow Airport. The study found an increased relative risk for admission due to coronary heart disease and CVD. Another study relating to another cardiovascular complication, hypertension, found that long-term residential exposure to noise was associated with increased incidence of (self-reported) hypertension (40).

## HYPOTHESIS

The purpose of this study is to determine the impact of individually accumulated exposure to air and noise pollution, as well as exposure fluctuations (peaks), on the incidence and prevalence of CVD. Noise pollution can be a significant confounder for the relation investigated and we will therefore include accumulated data for noise over time together with air pollution data.

The ICD or SKS disease classification code system will be used to identify clinical events for patients from the two trials (described below). CVD mortality and total mortality as well as clinical events from myocardial infarctions, percutaneous coronary interventions, coronary artery bypass grafts, heart failure, apoplexies, and bypass will be examined. The analysis will be stratified by socioeconomic status to determine if there is a social inequality in the air and noise pollution impact.

We will examine the individual air pollution exposure as well as noise exposure to understand each pollutants' contribution to the accumulated risk and demonstrate the impact of air and noise pollution on CVD morbidity and mortality. We hypothesize that:

1. the amount of accumulated air as well as noise pollution is a highly independent significant risk factor for clinical CVD, when accounting for all traditional cardiovascular risk factors.
2. certain subdivisions of the air pollution exposure carry the highest contribution for development of clinical CVD. This will provide novel and valuable information as this has never been investigated with the precision we can deliver.
3. accumulated air and noise pollution from both individual home addresses and work addresses together better predicts clinical CVD than models based solely on home addresses. No study has evaluated this before.

Furthermore, the impact on the result of social inequality will be thoroughly examined.

## METHOD

### Project design

This study is designed as a prospective registry-based observational study using modelled air/noise pollution data. The population is predominantly males from two Danish clinical trials (DANCAVAS and VIVA trials)

### Study population

DANCAVAS I and II (41-43) are two similar population-based randomized, multicentered, clinically controlled studies designed to evaluate the benefits of 7-step multiple cardiovascular screening and modern vascular prophylaxis in a population of men and a small subpopulation of females, aged 60-74 years, living in the southern part of Denmark. For each participant, all relevant CVD risk factors were measured or determined.

The screening included (figure 1): 1) low-dose non-contrast CT scan to detect CAC and aortic/iliac aneurysms, 2) ankle-brachial blood pressure index (ABI) to detect peripheral arterial disease (PAD) and hypertension, 3) a telemetric assessment of the heart rhythm, and 4) a measurement of the cholesterol and plasma glucose levels.

The Viborg Vascular (VIVA) screening trial (44) is a randomized, multicentered, population-based clinically controlled study designed to evaluate the benefits of vascular screening and modern vascular prophylaxis in men between 65-74 years of age living in the region of Mid Denmark (Viborg County). For each participant, abdominal ultrasound scanning of the infrarenal aorta were performed to detect abdominal aortic aneurism (AAA), and ABI were measured to detect PAD and hypertension (45). In all, 18,749 men were screened.

A total of 33,723 participants in the age of 60-74 are included from the two cohorts. In both trials, an AAA was defined as maximal infrarenal diameter of 30 mm or more, and PAD was defined as an ABI < 0.90 or >=1.40 using the same validated hand held Doppler-based methodology (46). We have accounted for traditional CVD confounders in all participants. This is unique for our study. Previous studies on air pollution and CVD burden have not been able to prospectively consider these confounding variables to the same extent.

**Air pollution**

In Denmark a validated and reliable air pollution model system is available (figure 2). The system is named DEHM/UBM/AirGIS (28, 30-32) and consists of three coupled models; the Danish Eulerian Hemispheric Model (DEHM) (28, 32), the Urban Background Model (UBM) (29) and the Operational Street Pollution Model (OSPM) (30, 31) and a GIS system (AirGIS) that couples the modelled concentrations with the address level of the population. The system calculates air pollution concentrations of 80 chemical species as well as air pollution levels in cities, in streets and on address level even on both side of the street. These pollution levels can be calculated back to 1979 giving retrospectively data 40 years back. The model system is validated in relation to air pollution measurements throughout Denmark back to 1990 with high correlation between model estimated values and measured values (28, 30, 31, 47). This multi-scale model system is unique, capable of running on very high temporal (hourly) and spatial (address level) resolutions. The development of the models and the calculation of air pollution and measurements is performed at Aarhus University, Department of Environmental Science (ENVS). The model is robust; taking all necessary factors into account that could contribute to the individual life-long air pollution exposure and the model is one of the best in the world.

**Noise pollution**

Noise is calculated using state-of-the-art algorithms implemented in a well-known software, the SoundPLAN. The algorithms, reflecting advanced physics and mathematics-based knowledge, consider the propagation of sound in the atmosphere as well as the sound originating from the source, e.g., road transport, railway. Here, information from various national registers, such as the national traffic database, including traffic counts, travel speeds, the building register, the address register, and the Danish surface and elevation model, to name a few. In addition, advanced weather classes reflecting all meteorological conditions in Denmark are used in noise calculations. The model output is a noise estimate at the address location or any location of interest in Denmark, which can be subsequently used to investigate the health impacts of short-term and/or long-term noise exposure (48, 49).

**Statistics**

The entire study population is monitored until December 31. 2022, in the Danish national registers.

Primarily a multivariate Cox proportional hazards regression model will be used to examine the associations between air- and noise pollution and all-cause mortality and CVD morbidity and mortality when adjusting for inclusion date, sex, and other potential confounding factors at baseline.

Descriptive statistics of the main study variables to examine noise pollution will be presented in tables, frequencies with percentages of dichotomous/ordinal variables and medians with quartiles for numeric variables. Outcomes will be analyzed both as dichotomized variables, present CAC, severe CAC (CAC score above 400), AAA and PAD, and as the underlying continuous variables, CAC score, aortic diameter, and lowest measured ankle-brachial blood pressure index. Confounding CVD variables will be considered and adjusted for (e.g., lifestyle, medical history, QoL, weight,

height, waist circumference, blood pressure, ABI, calcium score for coronary arteries, aortic dimensions, HbA1c and lipid parameters).
To investigate hypothesis about noise we will, for each dichotomized outcome, estimate adjusted odds ratios using multivariable logistic regression, with cumulated noise pollution as exposure and the Framingham risk factors as confounders. The continuous variables will be analyzed in multivariable linear regression models and the cardiovascular risk factors as confounders.
To investigate the impact of work versus home address, we will compare regression models with accumulated air pollution from both work and home addresses with models with air pollution only from home addresses. ROC curves from both models will be compared to evaluate the hypothesis.

**Ethics approval and consent**
The DANCAVAS and VIVA studies were approved from "Videnskabsetisk Komité" (S20140028, S20160164 and M20080028). Access to the participants' former residential addresses has been approved from "Sundhedsdatastyrelsen" (FSEID-00005213).

**Feasibility**
We have formed the group of researchers that will perform the study and we have received all the necessary approvals. The group includes professors in the areas where special skills are needed.

**COLLABORATION**
This project is a collaboration across disciplines and sectors (cardiology, physics, environmental sciences, surgery, public health). The study will be performed as a collaboration between:

- Cardiovascular Research Unit, Odense University Hospital - Svendborg; Professor Jess Lambrechtsen and Professor Kenneth Egstrup
- Kræftens Bekæmpelse; Professor Ole Raaschou-Nielsen and Ulla Hvidtfeldt, senior researcher
- Department of Environmental Science, Aarhus University, Roskilde; Associated professor Lise M. Frohn, Professor Jørgen Brandt, Associate professor Matthias Ketzel, and postdoctoral fellow Jibran Khan
- Department of Cardiology, Odense University Hospital; Professor Axel Cosmus Pyndt Diederichsen
- Department of Cardiac, Thoracic and Vascular Surgery, Odense University Hospital; Professor Jes Sanddal Lindholt

Jess Lambrechtsen is PI on the study and has taken care of all applications to the "Sundhedsdatastyrelsen". Axel Cosmus Pyndt Diederichsen and Jes Sanddal Lindholt are the owners of the DANCAVAS study data and Jes is the owner of the VIVA study data. The Department of Environmental Science, Aarhus University, administrates the air and noise pollution database and delivers analysis of the air and noise pollution data to the study. Kræftens Bekæmpelse is included in the project due to their many years of experiences with research on environment and health.
We anticipate publishing at least six papers in high-ranked scientific papers, hopefully more. Realistically, one or more papers can be published in one of the top five journals in the specific area and if the results go in the anticipated direction, a main publication in The Lancet is realistic.

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