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# Study Protocol for the AIRCARD Study: A Prospective Cohort Study Utilizing DANCAVAS and VIVA Screening Trials

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## Abstract

**Background:** The AIRCARD study is designed to investigate the relationship between long-term exposure to air and noise pollution and cardiovascular disease incidence and mortality.

**Aim:** To conduct a robust prospective cohort analysis assessing the cumulative and differential impacts of air and noise pollution exposure on cardiovascular disease and mortality. This study will adjust for relevant confounders, including traditional cardiovascular risk factors, socioeconomic indicators, and medication use.

**Methods:** This prospective cohort study will include male participants aged 65-74, recruited from the two large Danish DANCAVAS and VIVA trials, both population-based randomized, multicentered, clinically controlled studies. We will assess long-term exposure to air pollutants using the state-of-the-art DEHM/UBM/AirGIS modelling system and noise pollution through the Nord2000 and SoundPLAN models, covering data from 1979 to 2019. The primary analysis will utilize Cox proportional hazards models, adjusted for confounders identified in the cohort (age, body mass index, hypertension, diabetes, smoking status, family history of heart disease, socioeconomic factors, and medication use).

**Discussion:** The AIRCARD study will address global concerns about the impact of air and noise pollution on cardiovascular disease. This research is crucial for understanding how the pollutants contribute to cardiovascular disease. We aim to provide valuable insights into this area, emphasizing the need for public health measures to mitigate pollution exposure. Our goal is to provide policymakers and healthcare professionals with information on the role of environmental factors in cardiovascular health that could influence global strategies to reduce the cardiovascular disease burden associated with pollution.

## Attachments

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## Guidelines

**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, Professor Kenneth Egstrup, Stephan Peronard Mayntz, MD, MPH, and Roda A. Mohamed, MD.
- Department of Environmental Science, Aarhus University, Roskilde; Associate 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.
- OPEN – Open Patient data Explorative Network, Odense University Hospital, Region of Southern Denmark; Anna Mejldal, Jens-Jakob Kjer Møller.

**Funding:**
Supported by the Region of Southern Denmark and by Shipowner Per Henriksen’s Foundation.

**Availability of data and materials:**
A Data Management Plan and Sharing Statement has been developed and is publicly available at dmp.deic.dk with ID: 6570

## Project design

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

## Study population

2 DANCAVAS (39-41) was a 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, aged 65-74 years, living in the southern part of Denmark.

3 For each participant, all relevant CVD risk factors were measured or determined.

The screening included:

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.

4 The Viborg Vascular (VIVA) screening trial (42) was 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 (43).

5 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 (44).

- 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.

## Danish national registries

6 The study will use Danish National Registries through Statistics Denmark and the Danish Health Data Authority.

7 These registries include the Cause of Death Register, the National Patient Register, the Civil Registration System, the Income Statistics Register, the Danish Education Registers, the Family Income Register, the National Prescription Registry, and the Employment Classification Module.

8 Each registry offers unique and comprehensive data, from mortality statistics to socioeconomic variables, contributing to a multifaceted understanding of the impacts of pollution on CVD. The participants were followed in the registries from 1979 to 2019.

## Air pollution

9 In Denmark a validated and reliable air pollution model system is available. 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.

10 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 data 40 years back.

11 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, 45). This multi-scale model system is unique, capable of running on very high temporal (hourly) and spatial (address level) resolutions.

12 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

13 Noise is modelled using state-of-the-art algorithms implemented in a well-known software, the SoundPLAN.

14 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.

15 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 (46, 47).

## Statistics

16 The entire study population is monitored until December 31. 2019, 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 CVD morbidity and mortality when adjusting for inclusion date, sex, and other potential confounding factors at baseline.

17 A Statistical Analysis Plan (SAP) is underway and is currently being revised. We refer to the SAP for all relevant statistics.

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