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REVIEW ARTICLE

Environment and cardiovascular disease: rationale of the Corinthia study

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Abstract Environmental factors constitute an important but underappreciated risk factor towards the development and progression of cardiovascular disease (CVD). Environmental exposure to variable pollutants is implicated in the derangement or propagation of adverse pathophysiological processes linked with atherosclerosis, including genetic, hemodynamic, metabolic, oxidative and inflammation parameters. However, no data exist on environmental pollution in rural or semi-rural areas. Therefore, the purpose of the "Corinthia" study is to examine the impact of environmental pollution in indices of cardiovascular morbidity and mortality in a cross-sectional and longitudinal design. The Corinthia study began in October 2015 and is planned to recruit 1,500 individuals from different regions of Corinthia country with different environmental exposures to pollutants and different patterns of soil/ground and/or air pollution until December 2016. Baseline measurements will include lifestyle measurements, anthropometric characteristics and a comprehensive cardiovascular examination. The follow-up is planned to extend prospectively up to 10 years and this study is anticipated to provide valuable data on the distinct impact of soil and air pollution on early markers of

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atherosclerosis and cardiovascular disease and on the overall impact of environment pollution to cardiovascular morbidity and mortality.

1. Introduction

Despite major advances in cardiovascular (CV) medicine during the the past few decades, deaths and morbidity from cardiovascular diseases (CVD) are increasing globally.[1,2] It appears that population aging and population growth have balanced out the decline in age-specific death rates from CVD that could be attributed to more effective prevention and treatment strategies.[2]

Interestingly, although progress in confronting CVD has been evident worldwide, it has been notably heterogeneous. Regions with the fastest growing population dynamics have experienced relative increases in CV deaths in line with global trends. In contrast, developed regions have reported no detectable changes or small decreases in CV mortality as rapid aging of the population has offset the declines in age-specific death rates.[3] Residual CV risks beyond traditional risk factors should be reassessed and further explored in the quest to uncover new underlying mechanisms that may provide the basis for innovative preventive interventions and therapeutic goals.

In this light, environmental factors constitute an important but underappreciated risk factor towards the development and progression of CVD.[4] Environmental exposure to variable pollutants has been implicated in the derangement or propagation of adverse pathophysiological processes linked with atherosclerosis, including genetic, hemodynamic, metabolic, oxidative and inflammation parameters.[4] Recent studies have suggested that chronic environmental stress is an important determinant of CVD risk, even below current regulatory standards for exposure levels.[4,5]

One of the most important studies in the field of environmental cardiology, the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air) investigated the association between long-term air pollution exposure and the progression of subclinical atherosclerosis and the incidence of CVD in an urban dwelling population.[6] However, no data exist concerning environmental pollution in rural or semi-rural areas. Therefore, the purpose of the "Corinthia" study was to examine the impact of environmental pollution in indices of CV morbidity and mortality in a cross-sectional and longitudinal design.

2. Study rationale

Nationwide data for Greece concerning environment pollution and CVD morbidity and mortality are markedly scarce. Research activity has focused on soil and groundwater anthropogenic contamination in river basin of heavily polluted industrialized areas but without reporting associations with CVD.[7] Moreover, certain prospective or retrospective studies have examined the association of long-term exposure to air pollution with CVD morbidity in urban population.[8,9] The region of Corinthia has rural and semi-rural areas with high exposure to soil and air contamination in distinct territorial patterns. We hypothesized that long term exposure to environmental pollutants mediates detrimental epigenetic, oxidative, inflammatory and pro-atherogenic effects that could accelerate the progress and the severity of CVD as well as the quality of life and the overall morbidity and mortality. Therefore, we sought to investigate with a cross-sectional and longitudinal design the impact of different types of environmental pollution on indices of subclinical atherosclerosis, on rates of CV morbidity and mortality and on CVD risk. The study hypotheses are:

I. The primary hypothesis of the study is that individual exposed to different environmental pollutants have increased rate of all-cause mortality.
II. The secondary hypothesis of the study is that individuals exposed to different environmental pollutants have an increased rate of CV mortality and increased incidence of non-fatal CVD (i.e., acute coronary syndromes, peripheral aortic disease, cerebrovascular disease).
III. Additional hypotheses of the study are:
   a. Individuals exposed to different environmental pollutants present an adverse cardiometabolic profile in terms of surrogate markers of early atherosclerosis and oxidative stress
   b. Environmental pollution affects adversely the quality of life in exposed subjects
   c. Environmental pollution confers epigenetic alterations (telomere shortening, microRNAs mobilization and circulation) in subjects exposed to different pollutants.

3. Experimental details and design of the Corinthia study

The present study began in October 2015 and is planned to recruit 1,500 individuals from different regions of Corinth with different environmental exposure to pollutants and different patterns of soil/ground and/or air pollution until December 2016.

We plan to recruit individuals living in three different areas according to environmental pollution (Figure 1):

I. Subjects living in areas with no evidence of soil/ground or air pollution
II. Subjects living in areas with air pollution
III. Subjects living in areas with soil/ground pollution

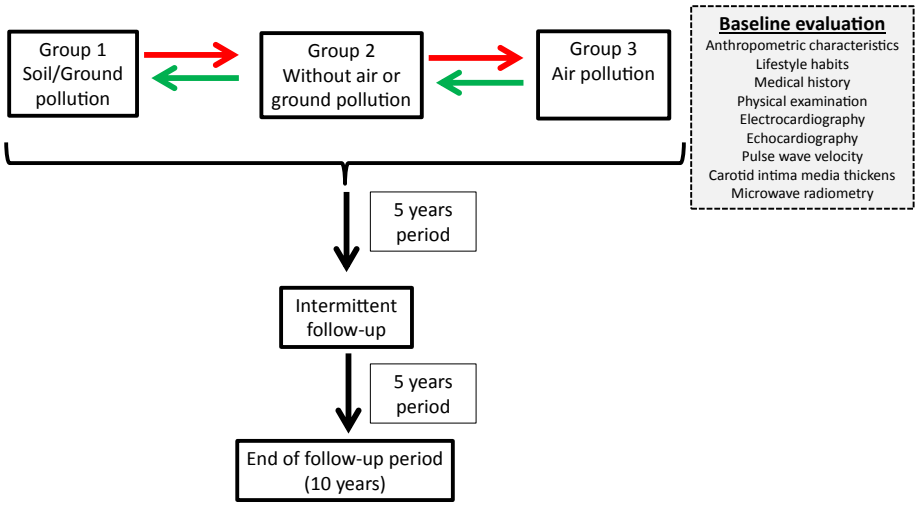

Figure 1 Study design and follow-up schedule.

Residents of the selected regions who are not planning to move within the next 10 years will be approached. An acceptance rate of participation of approximately 80% of those eligible subjects is anticipated. Exclusion criteria for the study would be

1. The inability and unwillingness to provide informed consent
2. Individuals less than 40 years of age

The recruitment into Corinthia study will be community-based, with an emphasis on balancing recruitment across the three areas, census blocks, age categories (per decades) and gender. The sampling frame will implement information from the latest national Census and will proceed along geographic boundaries. As a sampling unit, we will use each household, with a goal of including no more than 2 eligible participants from different households per census block. Initial contact will be performed by telephone or door-to-door. Telephone recruitment will be based on a list built from the specified geographic boundaries. Initial contact included a screening questionnaire and household enumeration of all eligible persons. The recruitment goal is 500 participants from each of the three areas of interest. During this period, the research team will communicate with the local authorities and with health services in these areas to organize the volunteering selection of the participants in each area. Responsibility of the research team is also the organization of the places where field research will take place. Pilot measurements will take place; accordingly, the research team will estimate the validity of the tests and will calculate the variability coefficients of the tests.

The first 14 months will be devoted to recruitment (October 2015-December 2016).

3.1. Quality Control and repeatability of measures

The research fellow recruited for this study will perform all vascular and anthropometric measurements and will undergo a two-month training and accreditation for these measurements. Echocardiographic measurements will be performed by the same trained cardiac physiologist.

3.2. Study Measurements

Baseline measurements for participants in the "Corinthia" Study will include parameters affecting daily lifestyle such as smoking habits, physical activity and diet. Anthropometric (height, weight, waist circumference), socio-economic and lifestyle characteristics (marital status, educational level, economic and professional status), as well as family history and history of cardiovascular risk factors and diseases will be recorded. We are also planning to identify the psychological state of individuals (using a valid Depression Scale ZUNG) and their mental status (MMSE-Mini Mental State Examination). We will record the presence and the treatment in use, if any, of hypertension, diabetes mellitus and hypercholesterolemia. Subjects will be submitted to a full cardiac examination, including physical examination, electrocardiography, echocardiography (evaluation of left ventricle ejection fraction, of left ventricle dimensions, evaluation of valvular function, of transmittal flow pattern, of right ventricle systolic pressure, of aortic distensibility, etc.), blood pressure measurements, arterial wall properties measurement with the non-invasive estimation of pulse wave velocity and estimation of atherosclerotic burden with evaluation of carotid intima media thickness and of atherosclerotic plaques in carotid arteries. Peripheral blood samples will be gathered for DNA analysis, routine biochemical tests and measurement of inflammatory markers and markers of oxidative stress. Subsequent examinations, which will include repetitions of certain baseline measurements as well as new measures, will be scheduled at approximately adjacent two-year intervals.

3.3. Selection of regions-Environmental measurements

Data on soil/ground contamination with pollutants (pesticides, fertilizers, etc.) and of air pollution from industrial

gasses and exposures will be provided from records and measurements of the Faculty of Geology and Geoenvironment and the faculty of Environmental Physics of the National and Kapodistrian University of Athens.

3.4. Follow-up

The study investigators will prospectively perform five- and 10-year follow-up studies of the participants' (a) vital status (death from any cause or due to CVD); (b) development of coronary heart disease (CHD) (i.e., myocardial infarction, angina pectoris, other identified forms of ischemia, heart failure of different types and chronic arrhythmias); and (c) development of cerebrovascular disease.

With an anticipated loss to follow-up of approximately 15%,[10] the 10-year follow-up data are expected to decipher the effect of long-term exposure to pollution on overall and cardiovascular mortality and morbidity as well as on interim endpoints of surrogate markers of subclinical atherosclerosis. Respectively, with a type I error predefined to 0.05 and all considered to be two-tailed, a sample size of 1,500 subjects would yield adequate power (>80%) to detect a 1.5-fold change in the Hazzard ratio per area-group change in the aforementioned index variable towards the secondary endpoint (all-cause mortality) taking into account an event rate of 6%, a follow-up period of minimum 60 months and an anticipated loss to follow-up of less than 15%. Type I error was predefined at 0.05, and all tests were considered to be two-tailed.

4. Conclusion

The Corinthia study is an interesting epidemiological study of environmental importance with a cross-sectional and prospective longitudinal design planning to provide data on the distinct impact of soil and air pollution in indices of cardiovascular morbidity and mortality and on the overall health status of a rural or semi-rural population in Greece.

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