EXPOSOMICS - Enhanced exposure assessment and OMIC profiling for high priority environmental exposures in Europe.

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The primary objective is to improve prediction of individual disease risk related to air pollution, by characterizing the internal and external exposome related to air pollution in Europe. The specific research questions are:1. Can novel biomarkers...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON40311

Source
ToetsingOnline

Brief title
EXPOSOMICS

Condition

- Other condition

Synonym
Acute changes in blood pressure; Acute changes in lung function

Health condition

Biomarkers of response

Research involving

Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: EU□s Seventh Framework Programme for Research (FP7)

Intervention

Keyword: Air pollution, Biomarker, OMICs profiling

Outcome measures

Primary outcome

PEM measurements:

Personal monitoring includes particles smaller than 2.5 µm (PM2.5), the soot content of PM2.5 (marker for diesel emissions) and ultrafine particles (UFP, particulates less than 1 µm). BGI PM2.5 cyclones will be used to collect PM2.5 on a Teflon filter over 24h (van Roosbroeck, 2008). Filters will be weighed to assess ambient PM2.5 concentrations and filter reflectance will be measured to assess soot levels using procedures of the ESCAPE study (Eeftens, 2012). The DiSCMini will be used to measure UFP continuously. At the same time, subjects will carry a belt with a Samsung Galaxy S3 mobile phone with a project developed application to log location and physical activity at 1 second intervals, obtained from the telephone*s internal GPS and Accelerometer. For validation, a regular GPS to track location and an Accelerometer to track physical activity will be used as well. The GPS device will be a Trac King GPS tracker, logging GPS coordinates at 1 second intervals. Actigraph ActiSleep+ Wireless motion sensors will be used for activity measurements, logging activity at 1 second intervals.

Biological samples:

Blood sample collection

20 ml of whole blood, divided over 3 tubes, will be collected by the standard phlebotomy technique of venipuncture of forearm veins. 10ml will be collected in one EDTA tube, 5 ml will be collected in a Serum tube, and 5 ml will be collected in a PAX-tube.

After processing, OMIC analyses will be assessed on the freshly collected samples and on archived blood samples, obtained from the EPIC-NL biobank.

Buccal scrapes and Nasal Swabs

Since the mouth or the nose are target organs, direct or intermediate responses to air pollution may be detectable in these organs. Therefore, buccal scrape samples will be collected with a special designed sterile plastic scraper and nasal swab samples will be collected from each nostril with a sterile nasal swab. Samples will be analyzed for:

- RNA expression
- DNA methylation

Buccal scrapes are collected by scraping the inside of the cheek, towards the rear of the mouth, with a patented small plastic device. From each cheek, one sample is collected by going 10 times from top to bottom with a scraper. The straight portion of the scraper is broken and stored in separate Eppendorf vials containing preservation fluid. This procedure has been previously applied

in the Asia Lung Study and Nano Exposure study in which IRAS, Utrecht University participates.

Nasal swabs are collected by swabbing the inside of the nostril with a small floss tip swab. From each nostril, one sample is collected by twisting the swab inside the back of the nose (lower turbinate) for 5 seconds. The tip of the swab is snipped and stored in separate Eppendorf vials containing preservation fluid. This procedure is previously applied in the Asia Lung Study, and Nano Exposure study in which IRAS, Utrecht University participates.

OMICS analyses:

Metabolomics analysis will be performed to identify novel biomarkers that reflect exposure to a large diversity of pollutants, contributing to an understanding of how exposures to air pollution is mechanistically related to adverse health outcomes. The adductome will be analyzed on a non-targeted investigation of the internal exposome based on measurement of human serum albumin (HSA) adductomes for 1) identification of particular HSA adducts associated with known pollution sources followed by 2) measurements of identified adducts in human samples. Transcriptomics, Epigenomics, and Proteomics will contribute to the characterization of the internal exposome, and its relationship with the external exposome. This is done by applying a series of omics technology platforms to bio-samples for which data of the external exposome, the air pollution data, will be measured. In addition to

contributing to the discovery of novel biomarkers of environmental exposure or risk of health effects, Transcriptomics, Epigenomics, and Proteomics, describing multiple levels of cellular function, will provide mechanistic information of value in establishing cause-effect relationships.

Secondary outcome

Home Outdoor measurements:

Air monitors will be used to measured air pollution at the subject*s home address. This is allowing a comparison between measured outdoor and personal exposure and a comparison between modelled and measured home outdoor concentrations. The modeled home outdoor concentrations will be calculated based in models, previously developed in the ESCAPE project.

Biological samples:

Blood pressure measurements

Blood pressure will be measured after each PEM session using automatic blood pressure meters (Omron M6, Omron Healthcare Europe BV, Hoofddorp, the Netherlands) according to the recommendations of the American Heart Association (Pickering et al., 2005). The cuff (an adjustable pre-shaped cuff of 22-42 cm, dependent on the mid-upper arm circumference) will be placed at the non-dominant arm. Systolic and diastolic blood pressure will be measured at least two times with 5 minutes intervals according to a standard protocol while the subject is seated. Only if there are two reproducible measurements (difference < 5 mmHg), the mean of the measurements will be used in the analyses.

Spirometry data:

FVC, FEV1, MEF, MMEF and PEF will be measured after each PEM session using the EASYONE Spirometer (ndd Medical Technologies, Zurich, Switzerland) (Boogaard, 2013). Calibration will be checked daily. At least three manoeuvres will be performed per person, and the best values from the technically correct manoeuvres will be selected according to European Respiratory Society criteria.

Height measurement

Height measurements will be performed after the first PEM session using a ruler (up to 220cm). Subject*s body height will be measured after taking off shoes at a 1cm accuracy. Height data will be used for general anthropometrics and for spirometry preparations.

Seated height measurement

Seated height will be measured after the first PEM session using a ruler (up to 220cm). Subject*s torso height will be measured after sitting down on a chair at a 1cm accuracy. Subsequently, the height of the seat will be measured. Seated height data will be used for general anthropometrics and for spirometry preparations.

Weight measurement

Weight measurements will be performed after the first PEM session using a scale (up to 150kg). Subject*s body weight will be measured after taking off shoes at a 1kg accuracy. Weight data will be used for general anthropometrics and for

spirometry preparations.

Study description

Background summary

EXPOsOMICS is a multicenter study, performed in 5 study areas in Italy, Spain, Switzerland, the United Kingdom and the Netherlands from the end of 2013 until the end of 2014. Every center will perform the same Personal Exposure Monitoring (PEM) procedures, followed by biological sample collection. The EXPOsOMICS study will be performed in a subsample of an existing cohort, where a blood sample is available from the moment of cohort inclusion.

This application for the Medical Ethical Committee covers the procedures in the Netherlands, where the Institute for Risk Assessment Sciences (IRAS), part of Utrecht University, is the only center involved in implementation of the study. Subjects will be recruited from the cohorts EPIC-Morgen and EPIC-Prospect, together referred as EPIC-NL.

A considerable number of longitudinal cohorts in both children and adults have explored associations between non-genetic risk factors and health outcomes using detailed information on major risk factors, confounders, and health outcomes (Brunekreef, 2002; Van Roosbroeck, 2008a; Van Roosbroeck, 2008b; Kaufman, 2012). The assessment of environmental exposure in such studies is often not optimal resulting in uncertainties in the quantification of exposure and associated health risks. The quality of exposure assessment approaches can be improved by improving the quality of traditional approaches focused on assessment of concentrations in the environment (air, water). In addition, assessment of biological markers that reflect the human body*s response to exposure might contribute as well.

The exposome concept, which refers to the comprehensive description of lifelong environmental (i.e. non-genetic) exposure history, has been proposed to draw attention to the critical need for more complete environmental exposure assessment in epidemiological studies (Wild, 2005; Rappaport, 2010; Wild, 2011). The exposome refers to the individual exposure to multiple stressors in critical periods of life. The current challenge is to apply the concept in observational studies (Wild, 2011), as exposures are difficult to characterize since they significantly vary in space and time.

This project is designed to move the field forward by collecting data on the individual external exposome (by repeated personal exposure monitoring of key pollutants including real-time monitoring of activity and location) and the

individual internal exposome (by profiling large sets of biological molecules for new and integrated biomarkers), in relationship to air pollution exposure. To improve quality of assessment of relationships, differences in short-term perturbations and long-term or natural progression in biomarker levels will be analyzed using an archived blood sample, requested from the cohort*s biobank.

Developed tools will improve the quality of air pollution exposure estimates for epidemiological studies, eventually resulting in reduced uncertainty in disease risk assessment.
This study is among the first attempts to apply the exposome concept in large scale human studies. A unique feature of the project is the integration of both external and internal detailed measurements. Though personal monitoring studies have been performed before (Kaur, 2005; Briggs, 2008; Boogaard, 2010; Dons, 2012), there are very few on assessing long-term air pollution exposures (Aldgate, 2007; Van Roosbroeck, 2007) and none that included ultrafine particles (UFPs).

This multidisciplinary study will create significant new information regarding:
1. Validity of standard exposure assessment approaches in assessing individual exposure to key air pollutants, including ultrafine particles
2. Relationships between external and internal markers of exposures, resulting in potential new biomarkers of air pollution exposure
3. Acute effects of air pollution through more detailed exposure assessment

Study objective

The primary objective is to improve prediction of individual disease risk related to air pollution, by characterizing the internal and external exposome related to air pollution in Europe. The specific research questions are:
1. Can novel biomarkers of exposure for major outdoor air pollutants be identified through characterization of the internal exposome using untargeted OMIC analyses (corrected for variations in OMIC levels in archived blood sample from cohort*s biobank, due to long-term or natural progression) and detailed assessment of the external exposome using personal exposure monitoring?
2. Can novel biomarkers of exposure for major outdoor air pollutants be identified in target tissue for air pollution, such as the nose and the mouth?
3. What is the agreement between modelled exposure to air pollution and measured personal exposure of key particulate pollutants (external exposome)?
4. Does short-term exposure to outdoor air pollutants affect lung function and blood pressure?

Study design

In the proposed study, forty (40) subjects from five European study areas will perform three 24 hour Personal Exposure Monitoring (PEM) sessions, spread over one year (total 160 adults and 40 children). In Italy, the Netherlands,

Switzerland and the United Kingdom adults from existing cohorts will be included, whereas in Spain children will be included. In the remainder of this protocol we will discuss only the four adult cohorts, focusing the Dutch situation, since this application to the METC only covers work in the Netherlands.
In the Netherlands forty (40) subjects, aged 50-70 , will be selected from the EPIC-NL cohort, where a blood sample is available at study baseline (mid 1990*s).

All eligible volunteers, based on EPIC-NL records, will receive a Letter of Recruitment (including study details and Letter of Agreement) and a Screening Questionnaire (SQ). Interested volunteers will be asked to fill out the SQ and the Letter of Agreement and send this back to IRAS, Utrecht University. Based on data from the SQ, final eligibility will be concluded.

When eligible, subjects will be visited by a fieldworker (a) to determine whether the subject is motivated to participate, (b) to explain the setup of the study and show the backpack and belt with air monitors, (c) to answer the subject*s questions. When the subject agrees with procedures, the subject will fill out a Baseline Questionnaire (BQ). The fieldworker will record home and outdoor characteristics in a Home Characterization Form (HCF) and an Outdoor Characterization Form (OCF). When finishes, (provisional) appointments will be made for all three 24h PEM sessions.

During a PEM session, a fieldworker will visit the subject*s home address to distribute PEM devices. The subject will carry a backpack and a belt with PEM monitors for fine and ultrafine particles for a period of 24 hours, while performing daily activities. Simultaneously, the same set of air pollution monitors will run outdoors at the subject*s home address. During the 24 hour PEM session, the subject will fill out a PEM Session Questionnaire (PSQ) on smoke and fine dust exposure, a Time-Activity Diary (TAD) on past 24h activities and a Food Questionnaire (FQ) on food intake in the past 48h. At the end of each PEM session, a nurse and a fieldworker will visit the subjects home address. The nurse will collect a blood sample for OMIC analyses (20 ml), perform a blood pressure measurement, a spirometry test and collect two buccal scrapes, two nasal swabs, and health data in the Health Questionnaire (HQ). The fieldworker will shut down and check PEM devices.
Biological samples will be transported to a center, processed and stored at -80 degrees Celsius.

When all PEM sessions are finished, fresh blood samples (used for long and short-term perturbations of the biomarker response), archived blood sample from the cohort*s biobank (used for correction for variations in biomarker levels due to long-term or natural progression of the biomarker response), and buccal scrapes and nasal swabs (to assess biomarker levels in target tissues) will be sent for OMIC analysis. Metabolomics, Adductomics, Transcriptomics, Epigenomics, and Proteomics analyses will be applied on these samples to detect

systemic biomarkers, relevant for air pollution exposure. All analyses for a specific OMIC technology will be conducted in the same laboratory for all five study areas.

Spirometry and blood pressure measurements will be conducted to get more detailed information on direct respiratory and cardiovascular effects of air pollution. These effect have been described in literature, but the methods of this study provides the opportunity to investigate these effects in more depth.

Study burden and risks

The healthy participants in this study may experience minor physiological discomfort, related to the PEM sessions (n=3) or the collection of biological samples (n=3, at the end of each PEM session). Performing the PEM sessions may cause slight discomfort because of the attention that is required to correctly fulfill the carrying of the pumps, but previous studies including up to six repeats have not identified this as an important issue. Collecting blood may be unpleasant, and may provoke a hematoma that usually disappears fast. The risk associated to collecting blood is small. Performing spirometry may induce short term dizziness, because a maximal respiratory effort is made. Symptoms usually disappear fast.
The collection of cells from the nose and the mouth can cause a mild irritation. This usually disappears fast and does not lead to any health risk for the subject.

Subjects* privacy will be guarded by storing the data encrypted on a protected server at IRAS. A unique Subject ID, consisting of a 3 number code, is created for each eligible volunteer, based in SQ data. Personal information from the Letter of Agreement will be processed at IRAS, protected by professional secrecy. The Subject ID will be used for all computer files, forms, tubes and filters. Researchers and fieldworkers, performing measurements, processing samples or analyzing filters, will not have the possibility to trace subject*s name or home address. When samples are shipped to partners, again only the Subject ID will be used on all files and tubes. Individual data will under no circumstances be communicated. Procedures are in place to ensure compliance with professional secrecy and confidentiality. Each person involved in data entry and analysis is bound to respect these rules.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Subject is enrolled in the EPIC-NL cohort or lives close to a busy road
Subject enrolled in the EPIC-NL cohort has provided a baseline blood sample by the time of inclusion in the cohort (which is still available)
The EXPOsOMICS project obtained approval from EPIC-NL to contact participants via the cohort.

Exclusion criteria

Subject is younger than 50 years or over 70yrs of age by the time of performing the first monitoring session.
Subject is a smoker or ex-smoker (less than 6 months) since baseline of cohort inclusion.
Subject is currently living with a smoker or ex-smoker (less than 6 months).
Subject has a doctor diagnosed chronic disease (e.g. IHD, CVD, COPD, Asthma, Diabetes, Crohn).
Subject has/had cancer excluding non-melanoma skin cancer.
Subject is restricted in daily activities due to physical limitations.
Subject has a job that involves contact with diesel exhaust.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-02-2014
Enrollment:	40
Type:	Actual

Ethics review

Approved WMO Date:	24-12-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	10-03-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	23-04-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL45499.041.13

Study results

Date completed: 01-03-2015

Actual enrolment: 43