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Studying the effect of air pollutants on health

Submission date 10/02/2023	**Recruitment status** No longer recruiting	[_] Prospectively registered [X] Protocol
Registration date 20/03/2023	**Overall study status** Completed	[_] Statistical analysis plan [_] Results
Last Edited 04/12/2024	**Condition category** Other	[_] Individual participant data [_] Record updated in last year

Plain English summary of protocol

Background and study aims
Outdoor and indoor pollutants have been linked to a variety of adverse health effects including increasing the risk of heart disease and lung diseases. It is thought that air pollution may also cause problems with memory and the brain's ability to process information. This study is investigating the effect of common air pollutants on brain function in healthy human participants who have family members with brain disorders such as dementia.

Who can participate?
Healthy volunteers aged 50 years or over who have a close family relative with dementia

What does the study involve?
Participants are exposed to a controlled concentration of pollutants (diesel fumes, wood smoke, cleaning products, such as diesel and wood smoke) and the researchers measure their ability to complete a variety of tasks that assess their cognition. Blood samples, nasal washouts and breathing tests will also be collected to look at the effects of pollutant exposures on the immune system.

What are the possible benefits and risks of participating?
There are no direct benefits to taking part in this study. Indirect benefits include the further advancement of the understanding of how pollution exposures affect us all. This is a relatively safe study. The main risk will be exposure to pollutants. Some studies have shown that pollution exposure can be associated with cardiovascular conditions. However, the levels of pollutants used in this study are all within the same levels that we are exposed to in normal day-to-day life. As part of the safety mechanisms of the study, a breathing test will be performed and medical history will be checked to ensure that anyone who is at an increased risk of a side effect from pollutant exposure will be NOT included in the study. The team will also be continuously monitoring the levels of the pollutants during the exposure.

Where is the study run from?
The University of Manchester and the NIHR Clinical Research Facility based at Manchester University Foundation NHS Trust (UK)

When is the study starting and how long is it expected to run for?
September 2022 to December 2025

Who is funding the study?
UK Research and Innovation (UK)

Who is the main contact?
Prof Jacky Smith, jacky.smith@manchester.ac.uk (UK)

Contact information

Type(s)
Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
314890

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
IRAS 314890, CPMS 54794

Study information

Scientific Title
Hazard identification platform to assess the health impacts of indoor and outdoor air pollution exposures, through mechanistic toxicology (HIPTOX)

Acronym
HIPTOX

Study objectives
Currently, there are two hypotheses as to how air pollution might manifest its acute and chronic impacts on the brain. The first is by direct interaction of inhaled particles, or desorbed chemical constituents, with non-neuronal glial cells and neurons in the brain, based either on their uptake via translocation along olfactory neurons to the olfactory bulb; or their entry across the blood-brain barrier from the circulation. This has been the dominant hypothesis within the field, supported by evidence of combustion-like nanoparticles in the brains of sentinel animals and humans from polluted environments, associated in autopsy samples with histopathological features of early dementia, microglia immune defence activation and neuronal injury. The second hypothesis proposes that the neurological damage reflects an indirect impact of air pollution induced systemic inflammation and its transmission to the brain across the glial-neurovascular unit. Support for this assertion comes from toxicological studies that have shown similar neurological impacts, attributed to particulate challenges, following experimental exposures of animals to the pollutant gas ozone, which cannot access the brain, due to its high reactivity with antioxidants and macromolecules at the air-lung interface. The neurological

impacts observed may arise from the release of secondary mediators from the lung and their capacity to induce systemic inflammation and oxidative stress. The indirect action therefore implies a lung-to-brain axis, mediated through the vasculature. This study will investigate the acute and chronic impacts and the likely axis to neuroinflammation induction, through: (A) human challenges to defined source-specific pollutant aerosols using acute physiological readouts through changes in cognitive domains and the detection of peripheral markers of neuroinflammation and neuronal injury

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 04/10/2022, the University of Manchester Research Ethics Committee (Research Governance, Ethics and Integrity, 2nd-floor Chrsitie Building, The University of Manchester, Oxford Road, Manchester, M13 9PL, UK; telephone not available; research.ethics@manchester.ac.uk), ref: 2022-14762-25491
2. Approved 06/12/2022, HRA and Health and Care Research Wales (HCRW) (Castlebridge 4, 15-19 Cowbridge Road East, Cardiff, CF11 9AB, UK; +44 (0)1686 252101, (0)2920 230457, (0)7920 565664; approvals@hra.nhs.uk), ref: 22/HRA/4925

Study design
Single-centre observational cohort study

Primary study design
Observational

Study type(s)
Other

Health condition(s) or problem(s) studied
This is a study of healthy volunteers aged 50 years or above who have a close relative with dementia

Interventions
Healthy volunteers will be recruited and will undergo cognitive testing, spirometry, blood tests for biomarkers, and nasal lavage and will then undergo controlled pollutant exposures:
1. Diesel
2. Clean air (control)
3. Wood smoke
4. Secondary organic aerosol
5. Cooking emissions
6. Clean air with nitrogen oxides (NOx)
7. Wood smoke with NOx
They will then undergo all the pre-exposure measures.

Evidence of impairment in cognitive function post-exposure measured using any of these cognitive tasks compared to clean air on each visit both at baseline (pre-pollutant exposure) and 3.5 hours post-exposure:
1. Socio-emotional cognitive functioning is measured by Approach bias using the Expression Recognition Task. The team expects a change in approach bias between pre- and post-pollutant exposure measures compared to pre- and post-clean air exposure.

2. Executive cognitive functioning measured by 'Cognitive Control' using the Face Identification Task. The team expects a change in cognitive control between pre- and post-pollutant exposure measures compared to pre- and post-clean air exposure.
3. Working memory ability is measured using the Spatial n-back task. The team expects a change in discrimination ability between pre- and post-pollutant exposure measures compared to pre- and post-clean air exposure.

1. Change in any of these cognitive tasks post pollutant exposure compared to clean air:
1.1. Sustained Attention measured by 'Long Response Time (RT)' and Psychomotor Speed measured by 'Short Response Time (RT)'. Both these metrics are measured using the Psychomotor Vigilance Task on each visit both at baseline (pre-pollutant exposure) and 3.5 hours post-exposure. The team might expect a change in sustained attention between pre- and post-pollutant exposure measures compared to pre- and post-clean air exposure. However, changes in Psychomotor Speed are not anticipated.
1.2. Coarse and fine motor movements are measured using the Pegboard Test on each visit both at baseline (pre-pollutant exposure) and 3.5 hours post-exposure. The team might expect a change in both coarse and fine motor movement between pre- and post-pollutant exposure measures compared to pre- and post-clean air exposure.
2. Change in lung function post-exposure to pollutants compared to clean air measured using spirometry
3. Change in the DNA post pollutant exposure compared to clean air measured using blood tests for biomarkers

Intervention Type
Other

Primary outcome(s)
Evidence of impairment in cognitive function post-exposure measured using any of these cognitive tasks compared to clean air on each visit both at baseline (pre-pollutant exposure) and 3.5 hours post-exposure:
1. Socio-emotional cognitive functioning measured by 'Approach bias', calculated as Δd (change in "dee-prime"), a sensitivity towards positive-affective (smiling face) stimuli comparative to negative-affective (fearful face) stimuli, using the Expression Recognition Task
2. Executive cognitive functioning measured by 'Cognitive Control', calculated as ΔRT (change in response time), a difference between response time on trials of high conflict (more distracting two-face trials following less distracting one-face trials) compared to low conflict (two-face trials following two-face trials), using the Face Identification Task
3. Working memory ability is measured by 'discrimination', calculated as d ("dee-prime"), a measure of discrimination for if the location of a square is in the same (or a different) position as a square shown 2 squares previously

Key secondary outcome(s))
1. Change in any of these cognitive tasks post pollutant exposures compared to clean air on each visit both at baseline (pre-pollutant exposure) and 3.5 hours post-exposure:
1.2 Sustained Attention measured by 'Long Response Time (RT)', the speed at which stimuli are responded to after a long wait (25-35 seconds). Psychomotor Speed is measured by 'Short Response Time (RT)', the speed at which stimuli presented rapidly (less than two seconds of each other) are responded to. Both these metrics are measured using the Psychomotor Vigilance Task.
1.2. Coarse motor movement is measured by 'Right + Left + Both' score, the number of metal pegs participants can move into a plastic board in 30 seconds with their right hand, left hands, and both hands together. Fine motor movement is measured by the 'Assembly' score, the

number of metal parts participants can build into a plastic board in 60 seconds alternating their dominant and non-dominant hand. These are measured using the Pegboard Test.

2. Change in lung function post-exposure to pollutants compared to clean air measured using spirometry, FEV1 in litres and FVC in litres, pre and post exposures
3. Change in the DNA post pollutant exposure compared to clean air measured using blood tests for biomarkers and fluid samples collected from the nasal wash/lavage pre and post exposures

Completion date
31/12/2025

Eligibility

Key inclusion criteria
1. Aged ≥50 years old
2. Family history of dementia
3. Provision of signed, written and dated informed consent, prior to any study-specific procedures

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
50 years

Sex
All

Key exclusion criteria
1. Neurological or psychiatric disorder
2. General Practitioner Assessment of Cognition Score of ≤7
3. Current smoker (including e-cigarettes) or ex-smoker of less than 6 months abstinence, and >20 pack-year history
4. Current pregnancy
5. Significantly abnormal spirometry
6. History of cardiac disease
7. History of chronic respiratory or airways disease
8. History of inflammatory diseases (e.g. rheumatoid arthritis, chronic periodontitis, inflammatory bowel disease)
9. History of neurological or psychiatric disorders
10. History of organ transplant
11. Consumption of >3 units of alcohol in the 24 hours preceding the testing visit
12. Any vaccination in the week prior to the testing visit
13. Cold or flu in the 48 hours prior to the testing visit

14. Visual impairment not correctable with glasses/contact lenses.
15. Significant claustrophobia preventing the participant from wearing a mask over the nose and mouth for an hour
16. Concomitant medication use of neurologically active drugs such as opiates/benzodiazepines /anti-epileptics etc
17. Substance misuse

Date of first enrolment
13/12/2022

Date of final enrolment
30/11/2023

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
NIHR Manchester Clinical Research Facility
Manchester Royal Infirmary
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Sponsor information

Organisation
University of Manchester

ROR
https://ror.org/027m9bs27

Funder(s)

Funder type
Government

Funder Name

UK Research and Innovation

Alternative Name(s)
UKRI

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The dataset generated and analysed will be stored in a non-publicly available repository: the University of Manchester RedCAP database.

• The type of data stored: Participant contact details, participant GP contact details, participant demographics (including date of birth, height, weight and ethnicity), participant medical history and current medications for eligibility. Measurements will include clinical measures such as lung function test results (continuous data), and cognitive test results measured in (ms) Data collected in this study will be quantitative data, with repeat measures within individuals. Blood samples will be collected for immune cell analysis and DNA analysis. Fluid samples will be collected from the nasal wash/lavage, to look at inflammatory markers.
• The process for requesting access (if non-publicly available): Not publically available. Anonymised summary study data will be shared as part of the publication of the results of the study.
• Dates of availability: After the study is completed and published.
• Whether consent from participants was required and obtained: Fully informed consent was obtained.
• Comments on data anonymization: All subjects will be allocated a pseudonymised ID number and data collected during visits will be analysed under this number.
• Any ethical or legal restrictions: Personally identifiable is held securely and will not be available to secondary parties. Data remains the property of the University of Manchester.

IPD sharing plan summary
Stored in non-publicly available repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		29/02/2024	04/12/2024	Yes	No
Participant information sheet	version 1.5	16/01/2023	20/03/2023	No	Yes
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes