

Assessing the impact of prenatal exposure to air pollution on neonatal brain development using air pollution modelling and structural and diffusion MRI

Brendan Bos

School of Public Health

Faculty of Medicine

Imperial College London

Submitted in part fulfilment of the requirements for the degree of Doctor of
Philosophy at Imperial College London, October 2023.

Abstract

Prenatal exposure to air pollution has been shown to disrupt neurodevelopment in animals as well as in children. The impact on childhood neurodevelopment was previously investigated using cognitive and behavioural testing, with few studies using magnetic resonance imaging. To date, no research has been conducted on the impacts of prenatal exposure to air pollution on neonatal neurodevelopment.

To assess whether prenatal exposure to air pollution affects neonatal neurodevelopment, I used modelled ambient exposures to investigate two previously imaged cohorts. The first cohort consisted of healthy, term-born infants who underwent structural and diffusion imaging in the neonatal period ($n = 469$), utilising a novel biophysical model to process the diffusion imaging data. The second cohort consisted of infants born extremely preterm ($n = 249$). Ambient air pollution exposures were modelled at residence. Associations between prenatal air pollution exposure and neonatal neuroimaging metrics were assessed using canonical correlation analysis (CCA), which is capable of incorporating multiple correlated variables and robust significance testing. I found that increased prenatal exposure to PM_{10} and decreased exposure to NO_2 but not $PM_{2.5}$ is associated with multiple structural measures of the brain in healthy neonates. When investigating diffusion tensor imaging as well as neurite orientation dispersion and density imaging, I found no associations in the same cohort between prenatal exposure to $PM_{2.5}$, PM_{10} , and NO_2 and neonatal white matter microstructure metrics. Infants born preterm are at risk of adverse neurodevelopment. When investigating this vulnerable cohort, prenatal exposure to $PM_{2.5}$, PM_{10} , and NO_2 was not related to any metric of neonatal brain morphology or white matter microstructure.

Pregnant women may be vulnerable to the effects of air pollution exposure; however, no guidance for personal exposure reduction is available. Specific personal exposure reduction interventions were suggested and classified based on their scale, cost, and evidence of an effect.

Copyright declaration

The copyright of this thesis rests with the author. Unless otherwise indicated, its contents are licensed under a Creative Commons Attribution-Non Commercial 4.0 International Licence (CC BY-NC). Under this licence, you may copy and redistribute the material in any medium or format. You may also create and distribute modified versions of the work. This is on the condition that: you credit the author and do not use it, or any derivative works, for a commercial purpose. When reusing or sharing this work, ensure you make the licence terms clear to others by naming the licence and linking to the licence text. Where a work has been adapted, you should indicate that the work has been changed and describe those changes. Please seek permission from the copyright holder for uses of this work that are not included in this licence or permitted under UK Copyright Law.

Statement of Originality

I hereby declare that the work in this thesis is my own original research and that I have appropriately cited any work that is not my own.

Covid-19 Impact Statement

This thesis was originally planned to include a personal exposure measurement study conducted on a cohort of pregnant women as a part of the MobileAir project. Due to the impact of Covid-19 this aspect of the project was delayed and could not be undertaken as part of this PhD. The research question was therefore limited to assessing the impact of prenatal exposure to air pollution on fetal brain development using air pollution modelling and neonatal structural and diffusion MRI.

Acknowledgements

I am very grateful to my supervisors Professor Ben Barratt and Professor Serena Counsell for their guidance and support throughout my PhD. Ben, for being a cheerful, kind, and enthusiastic supervisor who can always find time, no matter how packed his schedule is. Serena, for making me feel welcome in her team, for pushing me when I needed it, and for always working hard to ensure my work is as good as can be. I would also like to thank Dr Dafnis Batalle and Dr Oliver Gale-Grant for helping me overcome several obstacles with their brilliant guidance.

This work would not have been possible without the Exposure Science Team, whose members may have changed over the years, but whose friendship and support has not. I want to acknowledge the wider Environmental Research Group for their support, and for many excellent conversations and shared laughs over the years. I would also like to thank the Medical Research Council for funding my PhD.

I am grateful to my parents, who have supported me from afar, and have always been there to listen and encourage me. Thank you to my friends and family for distracting me from my research whenever I needed it. Lastly, I will always be grateful to Eileen for her love and for patiently listening to all my worries over the years.

TABLE OF CONTENTS

Chapter 1 - Background	17
1.1 Air pollutants.....	18
1.1.1 Particulate Matter.....	18
1.1.2 Ultrafine Particles.....	19
1.1.3 Oxides of nitrogen.....	20
1.1.4 Ozone	20
1.1.5 Polycyclic aromatic hydrocarbons	20
1.1.6 Carbon monoxide.....	21
1.1.7 Assessing ambient air pollution exposure	21
1.2 Fundamentals of magnetic resonance imaging	23
1.2.1 T1 recovery and T2 relaxation	25
1.2.2 Registration	28
1.2.3 Segmentation.....	29
1.2.4 Principles of diffusion MRI	31
1.2.5 Diffusion Tensor Model.....	33
1.2.6 Neurite Orientation Dispersion and Density Imaging	34
1.2.7 Tractography	35
1.3 Effects of prenatal exposure to air pollution on early life neurodevelopment assessed with MRI	36
1.3.1 Structural MRI	37
1.3.2 Diffusion MRI	40
1.3.3 Animal models	41
1.3.4 Sex-specificity.....	43
1.3.5 Periods of susceptibility to air pollution	43
Chapter 2 - Data description and methods.....	45
2.1 Cohort overview.....	45
2.1.1 The developing Human Connectome Project (dHCP)	45
2.1.2 The evaluation of Preterm Imaging Study (ePrime)	46
2.2 Imaging.....	46
2.2.1 Developing Human Connectome Project MRI protocol.....	46
2.2.2 The evaluation of Preterm Imaging Study (ePrime) MRI protocol	48
2.3 Air pollution modelling	49
2.4 Data processing and analysis	51
Chapter 3 - Impacts of prenatal exposure to air pollution on white matter microstructure in the healthy neonatal brain.....	54

3.1 Introduction	54
3.2. Methods.....	55
3.2.1 Subjects	55
3.2.2 MRI acquisition	56
3.2.3 Image processing	56
3.2.4 Air pollution modelling	56
3.2.5 Statistical analysis	56
3.3. Results.....	57
3.3.1 Subjects	57
3.3.2 Air pollution exposure.....	58
3.3.3 White matter microstructure.....	60
3.3.4 Single pollutant linear regression results.....	62
3.3.5 CCA of exposure to air pollution and WM microstructure metrics	64
3.4. Discussion.....	66
3.5 Conclusion.....	68
Chapter 4 - Structural impacts of prenatal exposure to air pollution on the healthy neonatal brain .	69
4.1 Introduction	69
4.2 Methods.....	70
4.2.1 Subjects	70
4.2.2 MRI acquisition	70
4.2.3 Image processing	70
4.2.4 Air pollution modelling	71
4.2.5 Statistical Analysis.....	71
4.3 Results.....	72
4.3.1 Subjects	72
4.3.2 Pollution exposure	72
4.3.3 Brain Volumes.....	76
4.3.4 Single pollutant linear regression results.....	78
4.3.5 CCA results	79
4.4 Discussion.....	84
4.5 Conclusions	86
Chapter 5 - Prenatal exposure to air pollution and neonatal neurodevelopment in a prematurely born cohort assessed with structural and diffusion MRI	87
5.1. Introduction	87
5.2 Methods.....	89
5.2.1 Subjects	89

5.2.2 MRI acquisition	89
5.2.3 Image processing	89
5.2.4 Air pollution modelling	89
5.2.5 Statistical analysis	90
5.3 Results	90
5.3.1 Subjects	90
5.3.2 Air pollution exposure.....	92
5.3.3 Brain volumes	93
5.3.4 Single pollutant linear regression	94
5.3.5 CCA	95
5.4 Discussion.....	99
5.5 Conclusions	101
Chapter 6 – Reducing pregnant women’s exposure to air pollution.....	102
6.1 The health effects of prenatal air pollution exposure	102
6.2 The case for exposure reduction interventions	103
6.3 Prenatal exposure and maternal behaviour	104
6.4 Types of exposure environments and existing guidance	105
6.5 Interventions to reduce personal exposure to air pollution.....	107
6.5.1 Interventions in outdoor behaviour.....	107
6.5.2 Transport interventions	107
6.5.3 Indoor interventions	109
6.6 Behavioural change in pregnant women	110
6.6.1 Lessons from interventions in nutrition.....	112
6.7 Preliminary recommendations for interventions to reduce personal exposure to air pollution in pregnant women.....	114
6.7.1 Further considerations.....	116
6.8 Conclusions	117
Chapter 7 - General discussion	119
7.1 Overall summary.....	119
7.2 Analysis chapters	119
7.2.1 Air pollution exposure assessment.....	119
7.2.2 Cohort data	122
7.2.3 Analysis method.....	122
7.3 Reducing pregnant women’s exposure to air pollution	123
7.4 Statistical limitations.....	124
7.4.1 CCA	124

7.4.2 Covariates and confounding information	125
7.5 Conclusions and future work	126

List of tables

TABLE 3.1: DISTRIBUTION OF AGE AT MRI, AGE AT BIRTH, SEX, AND INDEX OF MULTIPLE DEPRIVATION OF THE DHCP SUBJECTS.....	57
TABLE 3.2: DESCRIPTIVE STATISTICS OF MODELLED POLLUTION EXPOSURE FOR EACH TRIMESTER AND THE WHOLE PREGNANCY IN $\mu\text{G}/\text{M}^3$ FOR THE SUBJECTS FROM THE DEVELOPING HUMAN CONNECTOME PROJECT (DHCP).	59
TABLE 3.3: THE LIST OF ANALYSED WM TRACTS, THEIR TRACT TYPE AND BILATERALITY.....	61
TABLE 3.4: SIGNIFICANT SINGLE LINEAR REGRESSION RESULTS PRIOR TO FALSE-DISCOVERY CORRECTION BETWEEN POLLUTION EXPOSURE OVER THE ENTIRE GESTATIONAL PERIOD AND DMRI MEASURES IN ALL TRACTS, ADJUSTED FOR SEX, IMD, PMA AT SCAN, AND GA AT BIRTH.	62
TABLE 4.1: DISTRIBUTION OF AGE AT MRI, AGE AT BIRTH, SEX, AND INDEX OF MULTIPLE DEPRIVATION OF THE DHCP SUBJECTS.....	72
TABLE 4.2: DESCRIPTIVE STATISTICS OF MODELLED POLLUTION EXPOSURE FOR EACH TRIMESTER AND THE WHOLE PREGNANCY IN $\mu\text{G}/\text{M}^3$ FOR THE SUBJECTS FROM THE DEVELOPING HUMAN CONNECTOME PROJECT (DHCP).	72
TABLE 4.3: MEDIAN BRAIN VOLUMES FOR THE SUBJECTS FROM THE DEVELOPING HUMAN CONNECTOME PROJECT (DHCP).	76
TABLE 4.4: SINGLE POLLUTANT LINEAR REGRESSION RESULTS FOR EACH RELATIVE BRAIN VOLUME FROM THE DHCP SUBJECTS AND $\text{PM}_{2.5}$, PM_{10} , AND NO_2 , ADJUSTED FOR SEX, IMD, PMA AT SCAN, AND GA AT BIRTH; BETA = EFFECT SIZE; CI = CONFIDENCE INTERVAL (95%); Q-VALUE = P-VALUE AFTER FDR CORRECTION.	78
TABLE 4.5: SPEARMAN'S R AND R^2 FOR EACH RELATIVE REGION OF THE BRAIN AND THE ASSOCIATION WITH THE FIRST MODE OF THE CCA.	81
TABLE 4.6: SPEARMAN'S R AND R^2 FOR NO_2 , PM_{10} , AND $\text{PM}_{2.5}$ AND THE ASSOCIATION WITH THE FIRST MODE OF THE CCA.	82
TABLE 5.1: DISTRIBUTION OF AGE AT MRI, AGE AT BIRTH, SEX, AND INDEX OF MULTIPLE DEPRIVATION OF THE EPRIME SUBJECTS.....	91
TABLE 5.2: DESCRIPTIVE STATISTICS OF MODELLED POLLUTION EXPOSURE FOR EACH TRIMESTER AND THE WHOLE PREGNANCY IN $\mu\text{G}/\text{M}^3$ OF THE EPRIME COHORT.	92
TABLE 5.3: MEDIAN AND RANGE OF ABSOLUTE TOTAL BRAIN VOLUME AND RELATIVE BRAIN VOLUMES OF THE EPRIME COHORT.	93
TABLE 5.4: SINGLE POLLUTANT LINEAR REGRESSION RESULTS FOR EACH RELATIVE BRAIN VOLUME FROM THE DHCP SUBJECTS AND $\text{PM}_{2.5}$, PM_{10} , AND NO_2 , ADJUSTED FOR SEX, IMD, PMA AT SCAN, GA AT BIRTH, BIRTH WEIGHT Z-SCORE (BWZ), AND DAYS VENTILATED; BETA = EFFECT SIZE; CI = CONFIDENCE INTERVAL (95%); Q-VALUE = P-VALUE AFTER FDR CORRECTION.	94
TABLE A1: SINGLE LINEAR REGRESSION RESULTS BETWEEN POLLUTION EXPOSURE OVER THE ENTIRE GESTATIONAL PERIOD AND DMRI MEASURES IN ALL TRACTS, ADJUSTED FOR SEX, IMD, PMA AT SCAN, AND GA AT BIRTH. ..	157
TABLE A2: SINGLE POLLUTANT LINEAR REGRESSION RESULTS FOR EACH RELATIVE BRAIN VOLUME AND POLLUTANT, FOR THE FIRST TRIMESTER, ADJUSTED FOR SEX, IMD, PMA AT SCAN, AND GA AT BIRTH; BETA = EFFECT SIZE; CI = CONFIDENCE INTERVAL (95%); Q-VALUE = P-VALUE AFTER FDR CORRECTION. SIGNIFICANT P-VALUES ARE MARKED IN RED.	178
TABLE A3: SINGLE POLLUTANT LINEAR REGRESSION RESULTS FOR EACH RELATIVE BRAIN VOLUME AND POLLUTANT, FOR THE SECOND TRIMESTER, ADJUSTED FOR SEX, IMD, PMA AT SCAN, AND GA AT BIRTH; BETA = EFFECT SIZE; CI = CONFIDENCE INTERVAL (95%); Q-VALUE = P-VALUE AFTER FDR CORRECTION. SIGNIFICANT P-VALUES ARE MARKED IN RED.	179
TABLE A4: SINGLE POLLUTANT LINEAR REGRESSION RESULTS FOR EACH RELATIVE BRAIN VOLUME AND POLLUTANT, FOR THE THIRD TRIMESTER, ADJUSTED FOR SEX, IMD, PMA AT SCAN, AND GA AT BIRTH; BETA = EFFECT SIZE; CI =	

CONFIDENCE INTERVAL (95%); Q-VALUE = P-VALUE AFTER FDR CORRECTION. SIGNIFICANT P-VALUES ARE MARKED IN RED.	180
TABLE A5: DESCRIPTIVE STATISTICS OF THE ABSOLUTE BRAIN VOLUMES OF THE DHCP SUBJECTS INCLUDED IN THIS STUDY.....	181
TABLE A6: ADDITIONAL DESCRIPTIVE STATISTICS OF THE EPRIME SUBJECTS.....	183
TABLE A7: ABSOLUTE BRAIN VOLUMES OF THE EPRIME SUBJECTS.	184
TABLE A8: SINGLE LINEAR REGRESSION RESULTS BETWEEN POLLUTION EXPOSURE OVER THE ENTIRE GESTATIONAL PERIOD AND DMRI MEASURES IN ALL TRACTS, ADJUSTED FOR SEX, IMD, PMA AT SCAN, GA AT BIRTH, BIRTH WEIGHT Z-SCORE (BWZ), AND DAYS VENTILATED.	184
TABLE A9: SINGLE LINEAR REGRESSION RESULTS BETWEEN POLLUTION EXPOSURE OVER THE FIRST TRIMESTER AND DMRI MEASURES IN ALL TRACTS FOR ALL SUBJECTS IN THE EPRIME COHORT, ADJUSTED FOR SEX, IMD, PMA AT SCAN, GA AT BIRTH, BIRTH WEIGHT Z-SCORE (BWZ), AND DAYS VENTILATED.....	189
TABLE A10: SINGLE LINEAR REGRESSION RESULTS BETWEEN POLLUTION EXPOSURE OVER THE SECOND TRIMESTER AND DMRI MEASURES IN ALL TRACTS FOR ALL SUBJECTS IN THE EPRIME COHORT, ADJUSTED FOR SEX, IMD, PMA AT SCAN, GA AT BIRTH, BIRTH WEIGHT Z-SCORE (BWZ), AND DAYS VENTILATED.....	194
TABLE A11: SINGLE LINEAR REGRESSION RESULTS BETWEEN POLLUTION EXPOSURE OVER THE FIRST TRIMESTER AND DMRI MEASURES IN ALL TRACTS FOR ALL SUBJECTS IN THE EPRIME COHORT, ADJUSTED FOR SEX, IMD, PMA AT SCAN, GA AT BIRTH, BIRTH WEIGHT Z-SCORE (BWZ), AND DAYS VENTILATED. BETA = EFFECT SIZE; CI = CONFIDENCE INTERVAL (95%); Q-VALUE = P-VALUE AFTER FDR CORRECTION.	198
TABLE A12: SINGLE LINEAR REGRESSION RESULTS BETWEEN POLLUTION EXPOSURE OVER THE SECOND TRIMESTER AND DMRI MEASURES IN ALL TRACTS FOR ALL SUBJECTS IN THE EPRIME COHORT, ADJUSTED FOR SEX, IMD, PMA AT SCAN, GA AT BIRTH, BIRTH WEIGHT Z-SCORE (BWZ), AND DAYS VENTILATED. BETA = EFFECT SIZE; CI = CONFIDENCE INTERVAL (95%); Q-VALUE = P-VALUE AFTER FDR CORRECTION.	200

List of figures

FIGURE 1.1: SIZE COMPARISONS FOR PM PARTICLES. REPRODUCED FROM THE ENVIRONMENTAL PROTECTION AGENCY (EPA.GOV).	19
FIGURE 1.2: A PRECESSING PROTON IN A MAGNETIC FIELD. IMAGE REPRODUCED FROM GRANDE-BARRETO ET AL (2017).	24
FIGURE 1.3: Z-AXIS GRADIENT COIL APPLYING A SPATIALLY VARYING MAGNETIC FIELD. REPRODUCED FROM UOMUS.EDU.IQ.	24
FIGURE 1.4: <i>T1 RECOVERY (LEFT) AND T2 DECAY (RIGHT) IN FAT AND WATER BASED ON SHORT AND LONG TR AND SHORT AND LONG TE. TIME IN MILLISECONDS. M_{xy} = TRANSVERSE MAGNETIZATION, M_z = LONGITUDINAL MAGNETIZATION. IMAGE REPRODUCED FROM BITAR ET AL (2006).</i>	25
FIGURE 1.5: CONVENTIONAL SPIN ECHO SEQUENCE. TR = REPETITION TIME, TE = ECHO TIME, RF = RADIOFREQUENCY PULSE. REPRODUCED FROM RADIOPAEDIA.ORG.	26
FIGURE 1.6: T1- AND T2-WEIGHTED IMAGES IN INFANTS AND CHILDREN. REPRODUCED FROM MILLER ET AL (2020). ..	27
FIGURE 1.7: A BESPOKE NEONATAL BRAIN IMAGING SYSTEM, CONSISTING OF (I) THE NEONATAL HEAD COIL, (II) THE FRAME, AND (III) THE POSITIONING SHELL. REPRODUCED FROM HUGHES ET AL (2017).	28
FIGURE 1.8: LINEAR AND NON-LINEAR REGISTRATION IN MRI. LINEAR REGISTRATION ADJUSTS THE SHAPE AND SIZE OF THE ENTIRE IMAGE, WHEREAS NON-LINEAR REGISTRATION CAN MAKE LOCAL CHANGES. REPRODUCED FROM FSL COURSE MATERIAL (FSL, 2022).	29
FIGURE 1.9: TISSUE SEGMENTATION AND NEONATAL ATLAS PARCELLATION FOR THE SAME INFANT. ANATOMICAL IMAGES WERE SEGMENTED INTO 9 TISSUE CLASSES (A) AND PARCELLATED INTO 87 BRAIN REGIONS (B). REPRODUCED FROM EDWARDS ET AL (2022).	31
FIGURE 1.10: (A) ISOTROPIC DIFFUSION AND (B) ANISOTROPIC DIFFUSION AND THE EIGENVECTORS λ_1 , λ_2 , AND λ_3 . ..	32
FIGURE 1.11: MEAN DIFFUSIVITY (MD) AND FRACTIONAL ANISOTROPY (FA) MAPS FOR NEONATES, 2-YEAR-OLDS, AND ADULTS. REPRODUCED FROM OISHI ET AL (2013).	34
FIGURE 1.12: VECTOR FIELD OF LOCAL PREDOMINANT FIBRE ORIENTATIONS AND TWO OF ITS STREAMLINES DEPICTED ON A CORONAL VIEW OF THE HUMAN BRAIN. REPRODUCED FROM JEURISSEN ET AL. (2017).	36
FIGURE 3.1: RESIDENTIAL SUBJECT DISTRIBUTION OF THE DEVELOPING HUMAN CONNECTOME PROJECT (dHCP) PER LOWER SUPER OUTPUT AREA (LSOA) IN GREATER LONDON. THE SUBJECTS WERE SCANNED AT ST. THOMAS' HOSPITAL IN CENTRAL LONDON, WHICH IS INDICATED ON THE MAP.	58
FIGURE 3.2: CORRELOGRAM OF MODELLED POLLUTION EXPOSURE FOR EACH TRIMESTER AND THE WHOLE PREGNANCY IN $\mu\text{G}/\text{M}^3$ FOR THE SUBJECTS FROM THE DEVELOPING HUMAN CONNECTOME PROJECT (dHCP). (A) POLLUTANT CORRELATION OVER THE ENTIRE GESTATIONAL PERIOD; (B) POLLUTANT CORRELATION OVER THE FIRST TRIMESTER; (C) POLLUTANT CORRELATION OVER THE SECOND TRIMESTER; (D) POLLUTANT CORRELATION OVER THE THIRD TRIMESTER.	60
FIGURE 3.3: OBSERVED CCA CORRELATIONS (Y-AXIS), THE MEDIAN, AND THE 5TH TO 95TH PERCENTILES OF THE NULL DISTRIBUTION OF THE PERMUTED CCA CORRELATIONS ESTIMATED VIA PERMUTATION TESTING ACROSS THE THREE CCA MODES (X-AXIS). EXPOSURE TO $\text{PM}_{2.5}$, PM_{10} , AND NO_2 OVER THE ENTIRE GESTATIONAL PERIOD FOR ALL SUBJECTS AND WM MICROSTRUCTURE METRICS (A), OVER THE FIRST TRIMESTER (B), OVER THE SECOND TRIMESTER (C), AND OVER THE THIRD TRIMESTER (D).	65
FIGURE 4.1: AVERAGE ANNUAL CONCENTRATIONS OF NO_2 IN $\mu\text{G}/\text{M}^3$ IN GREATER LONDON, 2016. REPRODUCED FROM LONDONAIR.ORG.UK.	74
FIGURE 4.2: AVERAGE ANNUAL CONCENTRATIONS OF PM_{10} IN $\mu\text{G}/\text{M}^3$ IN GREATER LONDON, 2016. REPRODUCED FROM LONDONAIR.ORG.UK.	75
FIGURE 4.3: A SEGMENTED IMAGE IN A NEONATE AT 40 WEEKS PMA SHOWING THE ANALYSED BRAIN REGIONS IN THE SAGITTAL, AXIAL, AND CORONAL PLANES. LEFT (L) TO RIGHT (R), SUPERIOR (S) TO INFERIOR (I), ANTERIOR (A) TO POSTERIOR (P), CORTICAL GREY MATTER (DARK BLUE), WHITE MATTER (LIGHT BROWN), DEEP GREY MATTER	

(BROWN), EXTRACEREBRAL CSF (BEIGE), CEREBELLUM (PURPLE), BRAINSTEM (TURQUOISE), AMYGDALA AND HIPPOCAMPUS (RED), AND VENTRICLES (LIGHT GREEN).....	77
FIGURE 4.4: OBSERVED CCA CORRELATIONS (Y-AXIS), THE MEDIAN, AND THE 5TH TO 95TH PERCENTILES OF THE NULL DISTRIBUTION OF THE PERMUTED CCA CORRELATIONS ESTIMATED VIA PERMUTATION TESTING ACROSS THE THREE CCA MODES (X-AXIS). EXPOSURE TO PM _{2.5} , PM ₁₀ , AND NO ₂ OVER THE ENTIRE GESTATIONAL PERIOD FOR ALL SUBJECTS AND WM MICROSTRUCTURE METRICS (A), OVER THE FIRST TRIMESTER (B), OVER THE SECOND TRIMESTER (C), OVER THE THIRD TRIMESTER (D), OVER THE ENTIRE GESTATIONAL PERIOD FOR MALE SUBJECTS ONLY (E), AND OVER THE ENTIRE GESTATIONAL PERIOD FOR FEMALE SUBJECTS ONLY (F).	81
FIGURE 4.5: CANONICAL CORRELATION OF THE POLLUTANTS USING SPEARMAN’S RANK TEST, IN THE FOLLOWING ORDER: (A) 1. NO ₂ , 2. PM ₁₀ , 3. PM _{2.5} . CANONICAL CORRELATIONS OF THE RELATIVE BRAIN VOLUMES USING SPEARMAN’S RANK TEST, IN THE FOLLOWING ORDER: (B) 1. WHITE MATTER, 2. CORTICAL GREY MATTER, 3. VENTRICLES, 4. CEREBELLUM, 5. DEEP GREY NUCLEI, 6. BRAINSTEM, 7. AMYGDALA & HIPPOCAMPUS, 8. Ex. CEREBRAL CSF.	83
FIGURE 5.1: RESIDENTIAL SUBJECT DISTRIBUTION OF THE EPRIME COHORT PER LOWER SUPER OUTPUT AREA (LSOA) IN GREATER LONDON. THE SUBJECTS WERE SCANNED AT QUEEN CHARLOTTES & CHELSEA HOSPITAL IN WEST LONDON, WHICH IS INDICATED ON THE MAP.....	92
FIGURE 5.2: OBSERVED CCA CORRELATIONS (Y-AXIS), THE MEDIAN, AND THE 5TH TO 95TH PERCENTILES OF THE NULL DISTRIBUTION OF THE PERMUTED CCA CORRELATIONS ESTIMATED VIA PERMUTATION TESTING ACROSS THE THREE CCA MODES (X-AXIS).	96
FIGURE 5.3: OBSERVED CCA CORRELATIONS (Y-AXIS), THE MEDIAN, AND THE 5TH TO 95TH PERCENTILES OF THE NULL DISTRIBUTION OF THE PERMUTED CCA CORRELATIONS ESTIMATED VIA PERMUTATION TESTING ACROSS THE THREE CCA MODES (X-AXIS).	98
FIGURE 6.1: DAILY AIR QUALITY INDEX AND RECOMMENDATIONS FOR AT-RISK INDIVIDUALS AND THE GENERAL POPULATION IN THE UK, REPRODUCED FROM HTTPS://UK-AIR.DEFRA.GOV.UK/AIR-POLLUTION/DAQI (DEPARTMENT FOR ENVIRONMENT FOOD & RURAL AFFAIRS (DEFRA)).	105
FIGURE 6.2: DIAGRAM OF INTERVENTIONS TO REDUCE PERSONAL EXPOSURE TO AIR POLLUTION IN PREGNANT WOMEN WITH INFORMATION ABOUT THE EVIDENCE OF EFFECT OF IMPLEMENTATIONS STRATEGIES AND INTERVENTIONS, AS WELL AS THEIR REACH AND COST, RESPECTIVELY.	115
FIGURE 6.3: INTERVENTIONS AND THEIR CONTRIBUTION TO EXPOSURE REDUCTION BY INTERRUPTING EXPOSURE PATHWAYS. THIS CHART DEPICTS THE PATH FROM SOURCES OF AIR POLLUTION TO THE INHALED DOSE AND SHOWS THE INCREASED BURDEN AND RISK OF UNINTENDED HARM FROM THE INTERVENTION TO THE INDIVIDUAL. REPRODUCED FROM LAUMBACH ET AL (2022).	117
FIGURE A1: OUTPUT OF THE DMRI PROCESSING PIPELINE FROM 38 TO 44 WEEKS POST-MENSTRUAL AGE (20 SUBJECTS PER BIN) SHOWING MAXIMUM INTENSITY PROJECTIONS OF THE AUTOMATED PROBABILISTIC TRACTOGRAPHY RESULTS AVERAGED ACROSS 80 dHCP SUBJECTS (20 PER AGE BIN). ALL TRACTS ARE VISUALIZED USING THE SAME THRESHOLDS (0.005, 0.05). THESE THRESHOLDS EXTRACT THE MAIN BODY OF THE TRACTS AND MIGHT REMOVE LATERAL PROJECTIONS DUE TO THE VARIABLE AND LOW NUMBER OF CROSSINGS THAT CAN BE ESTIMATED ESPECIALLY AT THE VERY YOUNG AGE.....	177
FIGURE A2: SUBJECT DISTRIBUTION OF MY SUBJECTS FROM THE DEVELOPING HUMAN CONNECTOME PROJECT (dHCP) PER LOWER SUPER OUTPUT AREA (LSOA) IN GREATER LONDON. THE SUBJECTS WERE SCANNED AT ST. THOMAS’ HOSPITAL IN CENTRAL LONDON, WHICH IS INDICATED ON THE MAP.	182
FIGURE A3: CORRELATION BETWEEN PM _{2.5} , PM ₁₀ , AND NO ₂ . MODELLED OVER THE ENTIRE GESTATIONAL PERIOD (A), THE FIRST TRIMESTER (B). THE SECOND TRIMESTER (C), AND THE THIRD TRIMESTER (D).	183

List of Acronyms

AD	Alzheimer's disease
ADC	Apparent diffusion coefficient
ADHD	Attention deficit hyperactivity disorder
ADMS	Atmospheric dispersion modelling system
AOD	Aerosol optical depth
APOE	Apolipoprotein E
AQI	Air quality index
ASD	Autism spectrum disorder
BREATHE	Brain Development and Air Pollution Ultrafine Particles in School Children
BWZ	Birth weight z-score
CAPS	Concentrated ambient particles
CC	Corpus callosum
CCA	Canonical correlation analysis
CMAQ	Community multiscale air quality
CO	Carbon monoxide
CO₂	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CORINE	Coordination of Information on the Environment
CPAP	Continuous positive airway pressure
CSF	Cerebrospinal fluid
DAQI	Daily air quality index
DEFRA	Department for Environment Food & Rural Affairs
DEP	Diesel exhaust particles
dHCP	Developing human connectome project
dMRI	Diffusion MRI
DT	Diffusion tensor
DTI	Diffusion tensor imaging
EC	Elemental carbon
EMEP	European Monitoring and Evaluation Programme
EPA	Environmental protection agency
EPETR	European pollutant Release and Transfer Register
ETS	Environmental tobacco smoke
FA	Fractional anisotropy
FDR	False-discovery rate
FMRIB	Functional MRI of the brain
FOV	Field of view
FSL	FMRIB software library
GA	Gestational age
GIS	Geographic Information Systems
GM	Grey matter
HAP	Household air pollution
HARDI	High angular resolution diffusion imaging
HEPA	High efficiency particulate air
HIC	High-income countries

ICV	Intracranial volume
IMD	Index of multiple deprivation
LAEI	London atmospheric emissions inventory
LMICs	Low- and middle-income countries
LSOA	Lower super output area
LUR	Land use regression
MD	Mean diffusivity
MRI	Magnetic resonance imaging
NAEI	National atmospheric emissions inventory
NDI	Neurite density index
NO	Nitric oxide
NO₂	Nitrogen dioxide
NO_x	Oxides of Nitrogen
NODDI	Neurite Orientation Dispersion and Density Imaging
OC	Organic carbon
ODI	Orientation dispersion index
PAHs	Polycyclic aromatic hydrocarbons
PM	Particulate matter
PM₁₀	Particles with a diameter smaller than 10 microns
PM_{2.5}	Particles with a diameter smaller than 2.5 microns
PMA	Postmenstrual age
PRS	Polygenic risk score
RF	Radiofrequency
ROI	Region of interest
SENSE	Sensitivity encoding
SNR	Signal-to-noise ratio
TBSS	Tract-based spatial statistics
TBV	Total brain volume
TE	Echo time
TPN	Total parenteral nutrition
TR	Repetition time
TRAP	Traffic-related air pollution
TSA	Tract-specific analysis
TSE	Turbo spin echo
UFPs	Ultrafine Particles Ultrafine particles
ULEZ	Ultra-low emission zone
VOCs	Volatile organic compounds
WM	White matter

CHAPTER 1 - BACKGROUND

Exposure to air pollution is the leading environmental contributor to the global burden of disease, causing an estimated 6.7 million premature deaths globally in 2019 (Fuller et al., 2022), and up to 40000 deaths per year in the UK (Holgate, 2017). Air pollution exposure contributes substantially to noncommunicable cardiovascular and respiratory diseases, especially in low- and middle-income countries (LMICs) (Murray et al., 2020). It has been associated with the development of cognitive impairment and neurodegenerative diseases such as dementias (Cristaldi et al., 2022), among which Alzheimer's disease (Fu and Yung, 2020), Parkinson's disease (Murata et al., 2022), and cognitive aging (Power et al., 2016).

In rodents, histopathological consequences of air pollution exposure have been shown in the brain, along with increased inflammation (Fu et al., 2020, Nephew et al., 2020). Particulate matter (PM) has been detected in human brain tissue (Maher et al., 2016), and PM exposure may impact both upon the structure as well as the functioning of the human brain (Herting et al., 2019). There is evidence that the effect of air pollution on the brain may start early in life (Rodulfo-Cárdenas et al., 2023). Periods characterised by strong neurodevelopment such as childhood and in utero may be especially vulnerable to the effects of air pollution, due to immature defence mechanisms and immune systems of fetuses and children (Grandjean and Landrigan, 2014). The developmental processes taking place during this period are fragile, and any disruption can have life-long consequences (Lopuszanska and Samardakiewicz, 2020). Whilst there is a growing body of evidence that exposure to air pollution can contribute to disrupted neurodevelopment, there is a paucity of evidence in childhood, adolescence, and prenatally within this area of research. Neuroimaging studies have been identified as a critical component of studying the impact of air pollution on the developing brain (Zundel et al., 2022).

Magnetic resonance imaging (MRI) can provide detailed images of the brain throughout the developmental period. Improvements in brain imaging in the neonatal period allow detailed images of the neonatal brain to be taken to evaluate brain morphometry and perform volumetric analysis (Counsell et al., 2019). Further, different MR approaches such as diffusion MRI can reveal the movement of water molecules in brain tissue over time, and characterising diffusion in the brain allows quantification of the underlying tissue microstructure of the white matter (WM) and can give insight into patterns of brain injury. Using MRI to investigate the effect of prenatal exposure to air pollution on the neonatal brain could therefore yield insight into impacts on brain morphology and WM microstructure.

1.1 Air pollutants

The following section will describe and give background information on the pollutants that have previously been shown to impact neurodevelopment. Air pollution is a complex mixture of gases and particles, and many of these pollutants are ubiquitous and are responsible for a variety of health effects.

1.1.1 Particulate Matter

PM can be a primary (directly emitted to the atmosphere) or secondary (a result of chemical reactions in the atmosphere) pollutant, and is mainly emitted via combustion or abrasion processes (DEFRA, 2020). Particles in the atmosphere exist in both solid and liquid state. Primary sources include human sources such as vehicle exhausts, solid fuel burning, tyre wear, and brake wear, and natural sources such as sea salt, soil particles, forest fires, and pollen.

Particles originating from fossil fuel combustion usually have a carbonaceous core which is coated in metallic elements such as cadmium, arsenic, vanadium, beryllium, and selenium, with organic components such as benzene, other polyaromatic hydrocarbons, and sulphur compounds absorbed into the surface (Chithra and Shiva Nagendra, 2013, Manisalidis et al., 2020). Many of the absorbed materials also originate from fossil fuel combustion. Secondary PM is typically made up of nitrates, sulphates, and ammonia. Particulate matter is conventionally split into two components, particles with a diameter smaller than 10 microns (PM_{10}) and particles with a diameter smaller than 2.5 microns ($PM_{2.5}$) (Figure 1.1). Penetration into the body is dependent on the size of the particle. PM_{10} can pass through the upper respiratory tract and into the larynx and trachea. The smaller components of $PM_{2.5}$ (see UFP below) can invade the lungs deeply and pass into the bloodstream (Wilson and Suh, 1997) and then to all organs in an adult, such as the brain and the placenta, and organs in the foetus including the brain (Bové et al., 2019, Bongaerts et al., 2022, Peters et al., 2006).

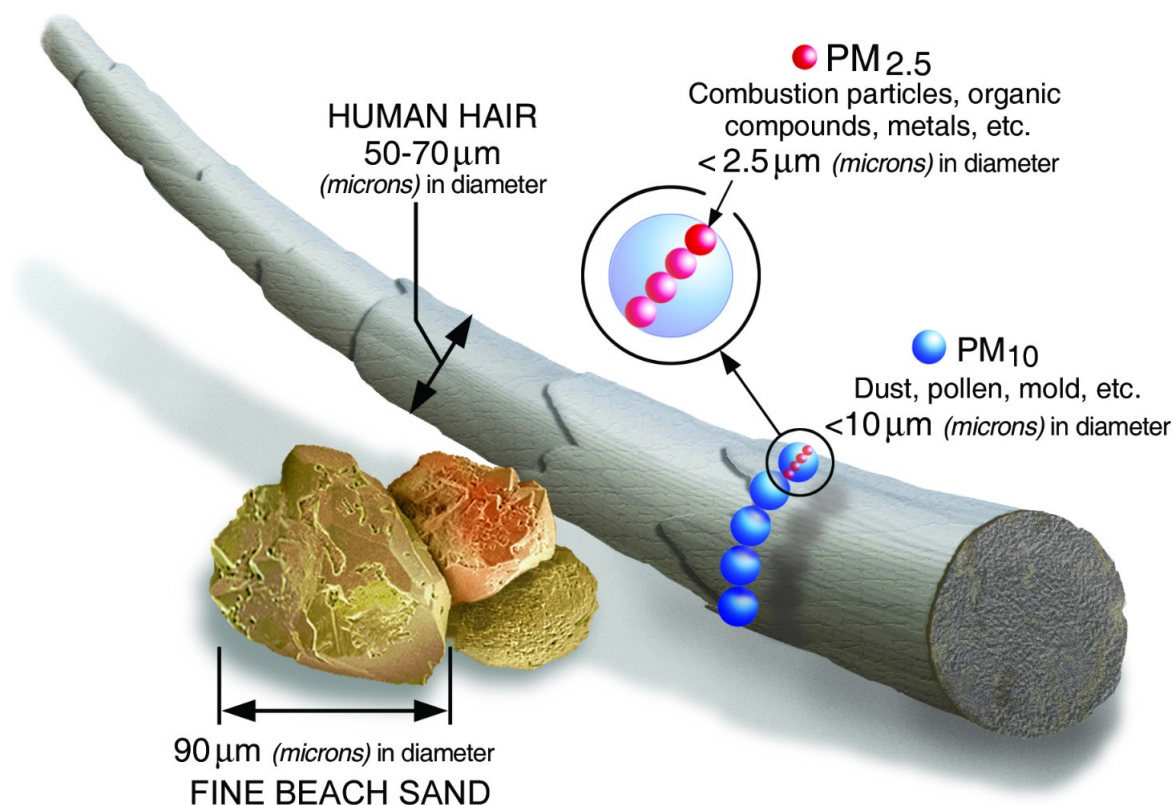


Figure 1.1: Size comparisons for PM particles. Reproduced from the Environmental Protection Agency (epa.gov).

Both short- and long-term exposure to PM_{2.5} and PM₁₀ have been associated with adverse human health effects. Overall mortality, mortality of cardiopulmonary diseases as well as lung cancer risk increases with increased long-term exposure to PM_{2.5} and PM₁₀ (Xing et al., 2016, Lu et al., 2015). Increased short-term exposure to PM_{2.5} is related to an increase in mortality and increased short-term exposure to PM₁₀ is related to increased cardiovascular and respiratory mortality (Kloog et al., 2013, Analitis et al., 2006). The health effects of PM are dependent on its size and may also depend on the composition of the particle (Bates et al., 2019, Ali et al., 2019).

1.1.2 Ultrafine Particles

Ultrafine particles (UFPs) are the component of PM_{2.5} that is smaller than 100 nm in diameter and are emitted primarily by fossil fuel and solid fuel combustion (Knibbs et al., 2011). While PM₁₀ and PM_{2.5} are measured by mass, UFPs are typically measured by count (number of particles per unit volume). High concentrations are found in close proximity to sources, such as cooking, smoking, and traffic, as particles coalesce rapidly, and concentrations are usually higher in urban settings than rural settings. Traditionally only measured as a component of PM_{2.5}, UFPs have in recent years come under increased scrutiny due to their ability to pass into the bloodstream and disperse throughout the body,

translocating to essentially all organs (Schraufnagel, 2020). In animal studies, UFPs have been shown to translocate to the brain via the olfactory bulb, which may lead to direct impacts on the brain (Oberdörster et al., 2004). UFPs have so far been linked to systemic inflammation, reduced lung function, and cardiovascular disease, but their precise role in many illnesses remains unknown (Olsen et al., 2014, Downward et al., 2018).

1.1.3 Oxides of nitrogen

Oxides of nitrogen (NO_x) are a group of nitrogen-based gases which are emitted into the atmosphere, the most prevalent being nitric oxide (NO) and nitrogen dioxide (NO_2). Dominant sources are combustion sources such as traffic and industry, however, household boilers and cooking can also be significant sources (National Atmospheric Emissions Inventory, 2022). NO is not considered harmful to health, but readily reacts to NO_2 . NO_2 is a respiratory irritant and can penetrate deeply into the lung. Short-term exposure can inflame the tissue and increase the risk of respiratory infections (Chen et al., 2007). Long-term exposure to NO_2 increases risk of respiratory and cardiovascular mortality (Faustini et al., 2014).

NO_x can contribute to the formation of secondary inorganic particles in the atmosphere adding to PM concentrations. Further, NO_x can react with volatile organic compounds (VOCs) to produce photochemical pollutants such as ozone (O_3) (Crutzen, 1970).

1.1.4 Ozone

Ozone (O_3) is a secondary pollutant generated by the reaction of fossil fuel combustion products with NO_x and VOCs in the presence of sunlight. O_3 concentrations are therefore higher in summer in the UK (National Atmospheric Emissions Inventory, 2022).

O_3 is a strong oxidant and has low water-solubility, enabling penetration deep into the lungs (Hatch et al., 1994). Short-term exposure may exacerbate pre-existing conditions such as asthma, and long-term exposure is associated with increased general mortality, respiratory mortality, and cardiovascular mortality (Gryparis et al., 2004).

1.1.5 Polycyclic aromatic hydrocarbons

Polycyclic aromatic hydrocarbons (PAHs) are a group of chemical compounds that occur as complex mixtures in the environment. They are a product of incomplete combustion, such as from industrial processes, vehicles, or solid fuel use. Many PAHs are organic compounds that accumulate in the human body and have toxic and carcinogenic effects (DEFRA, 2020, Kumar et al., 2014). Many PAHs have toxic and carcinogenic properties (Abdel-Shafy and Mansour, 2016). Long-term exposure to PAHs

may cause cancer and adverse reproductive and developmental effects in animals (Wells et al., 2010, Diggs et al., 2012). In humans, long-term exposure may cause kidney and liver damage (ATSDR, 1995).

1.1.6 Carbon monoxide

Carbon monoxide (CO) is emitted by incomplete combustion of fossil fuels when insufficient oxygen is available for a reaction to carbon dioxide (CO₂). The main outdoor source in the UK is road transport, however, cigarette smoke and faulty or unserviced cooking or heating appliances may be significant indoor sources of CO (National Atmospheric Emissions Inventory, 2020). CO has a greater tendency to bind to haemoglobin than oxygen, reducing the capacity to circulate oxygen throughout the body. This has well-known consequences for health, including greater risk of respiratory disease (Zhao et al., 2019), myocardial infarction (Lee et al., 2020b), and overall mortality (Chen et al., 2021).

1.1.7 Assessing ambient air pollution exposure

Ambient air pollution is traditionally monitored primarily in urban areas via often sparsely distributed fixed monitoring sites using expensive and highly sophisticated equipment. This serves regulatory purposes and gives a broad overview of pollutant concentrations across a city over time, with detailed information in specific locations (Kanakoglou et al., 2005). In the UK, monitoring sites are separated into kerbside, roadside, and background locations (LAQN, 2018). They are often located at pollution “hotspots”, such as heavily trafficked intersections or street canyons with poor dispersion conditions to test compliance with air pollution legislation.

Early landmark studies such as the six-city study have used air quality measurements from monitoring sites to establish the health effects of air pollution over a city’s population (Dockery et al., 1993). However, using data from monitoring sites to estimate an individual’s personal exposure to air pollution has shown high levels of uncertainty (Evangelopoulos et al., 2020). This approach is now seen as a sub-optimal way to assess exposure to air pollution (Health Effects Institute, 2010), and instead researchers commonly extrapolate measurements across urban areas using models or use a more personalised approach with small portable monitors (Jerrett et al., 2005, Brokamp et al., 2019).

Personal monitoring is sometimes seen as the gold standard of exposure assessment, as the small and cheap instruments can be carried around over long periods by individuals, giving unparalleled insight into their exposure and avoiding the issue of exposure misclassification (Brokamp et al., 2019, Health Effects Institute, 2010, Snyder et al., 2013). However, the instruments are often of subpar quality, with low precision between instruments and low accuracy especially when measuring gaseous pollutants (Lewis and Edwards, 2016, Lewis et al., 2016). They also typically assess total exposure to air pollution, combining both indoor and outdoor sources, which complicates interpretation and mitigation.

Further, cohort sizes are limited by the cost and logistical effort of distributing air pollution sensors, lowering statistical power (de Nazelle et al., 2013).

Some of these problems can be overcome using models. Models are used to predict ambient air pollution exposures using a variety of techniques incorporating data such as land use data, meteorological conditions, and traffic density, and air pollution measurements from satellites, monitoring sites, and sensors (Jones et al., 2020, Eeftens et al., 2012, de Hoogh et al., 2018, Brokamp et al., 2019). Ambient air pollution models can achieve high spatial resolution and cover large areas over long periods of time. They may suffer from nondifferential exposure misclassification, as researchers are often unable to incorporate measures of spatiotemporal mobility and indoor exposure. Hybrid models attempt to include these measures, but often have to contend with limited data, both in setting up the model and validating it, and high individual variability in behaviour and exposure characteristics (Tang et al., 2018, Smith et al., 2016).

Specific measurement and modelling approaches are suited to different air pollutants. UFPs and gases such as VOCs react, aggregate, or deposit rapidly after being emitted and are therefore highly localised. This can lead to difficulties in using monitoring networks and models to assess these pollutants accurately. However, regional pollutants such as PM_{2.5} and PM₁₀ vary less over space and concentrations can be more accurately characterised with a monitoring network or a model.

Different types of modelling approaches are commonly used. Land use regression (LUR) models are empirical models, and their predictions of air pollutant concentrations are based on regression techniques using air pollution measurements (Briggs et al., 1997, Chen et al., 2019). Geographic information systems (GIS) are used to add predictor data such as traffic, land use, and land cover, and to feed in data from monitoring sites to estimate pollutant concentrations at locations without any monitoring site cover. LUR models are capable of predicting concentrations across large areas and have been used in studies assessing air quality across continents, though these large studies are usually limited by the monitoring site network (Hoek, 2017). Some LUR models also incorporate satellite-based estimates, which use aerosol optical depth (AOD) measurements to assess air pollutant concentrations. However, satellite based measurements are unable to capture microscale variations in air quality (Michanowicz et al., 2016). LUR can be limited in its assumptions about the distribution of pollutants around sources and receptors, often assuming isotropic distribution and not taking into account meteorological variability and its influence on pollution gradients (Tularam et al., 2021). To improve their estimates, meteorological covariates such as measures of atmospheric stability have been incorporated into LUR models (Chen et al., 2012). Further, dedicated measurements campaigns have been conducted to feed into LUR models, increasing the density of data and model accuracy. LUR

models typically perform well and explain a high degree of variance of the measured spatial variation (Hoek, 2017).

Dispersion and chemical transport models are deterministic models which use physical and chemical predictors to model air pollutant dispersion and chemical transformation from source to receptor in the atmosphere. Dispersion models take into account the chemical and physical properties of the pollutants, as well as how these are affected by meteorology and topography. The spatial resolution can vary between address level and continental scale, and validating the model estimates with monitoring data is essential, as no empirical data is used in the pollutant estimates prior to validation (Hoek, 2017, Holmes and Morawska, 2006).

1.2 Fundamentals of magnetic resonance imaging

The following section will provide an overview of the fundamentals of MRI which underlie the research conducted in this thesis. MRI is a non-invasive imaging technique that can provide detailed images of the body. A strong magnetic field (B_0) is used to align protons in the hydrogen atoms, parallel or antiparallel to the magnetic field. The strength of the field is expressed in Tesla (T), and scanners are usually 1.5T or 3T, though more recently high-field MRI at 7T has become more common (Grover et al., 2015, Trattnig et al., 2018).

This strong magnetic field is required to interact with hydrogen nuclei (protons) in the brain. Hydrogen nuclei are most abundant within water molecules in the brain, though those in fatty molecules are also relevant. After alignment, the hydrogen nuclei rotate around the axis of the B_0 field (Figure 1.2) at a frequency that is proportional to the strength of the magnetic field (also called resonance frequency), and the exact relationship between field strength and rotation frequency can be calculated using the Larmor equation (Pooley, 2005), which can be expressed as follows:

$$f_0 = \gamma B_0$$

Where f_0 is the precession frequency, γ is the gyromagnetic ratio, and B_0 is the strength of the magnetic field. The rotating hydrogen atoms create oscillating fields which induce a voltage inside the radiofrequency coils (RF coils) placed around the head or body of the subject. Multiple coils are usually used, depending on the region being scanned, as a higher number of coils increases the signal-to-noise ratio (SNR) and can reduce the amount of time needed to acquire an image. Head coils typically have 8, 12, 16, 32, or 64 coils (Jenkinson and Chappell, 2018).

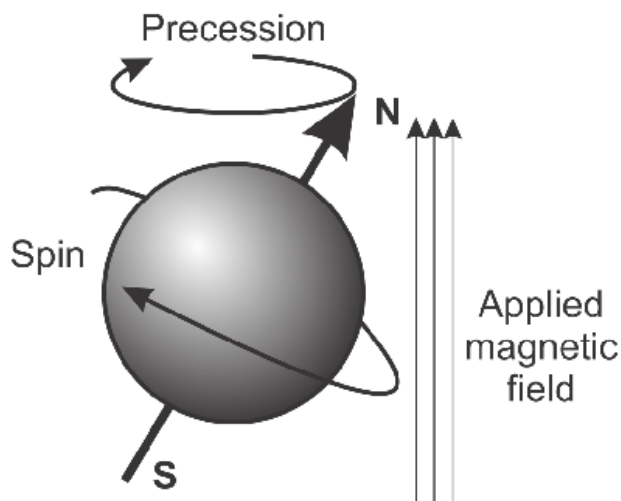


Figure 1.2: A precessing proton in a magnetic field. Image reproduced from Grande-Barreto et al (2017).

The observed MRI signal is the total sum of all the signals received from nuclei, but with no information on the location of the nuclei. Using gradient coils, a secondary, spatially varying magnetic field is applied on the x, y, and z-axis (Figure 1.3). This secondary application gives the nuclei a frequency that depends on their location in the brain, and this property is used to link the now varying frequency to the exact location of where the signal originates in the brain.

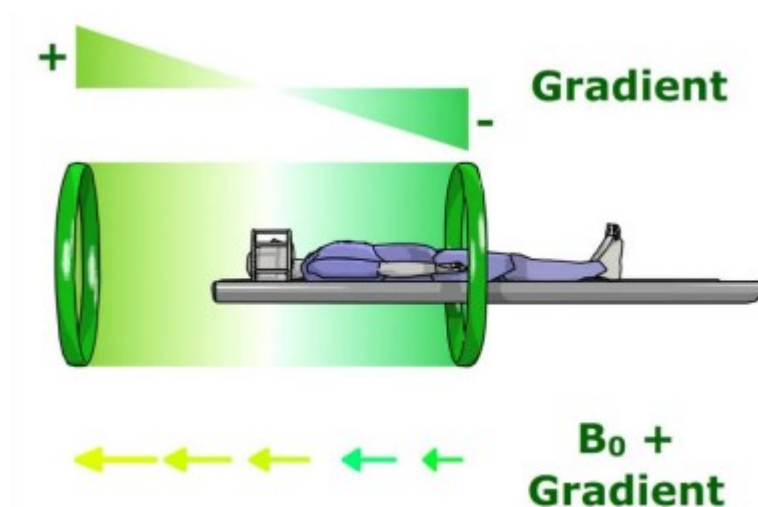


Figure 1.3: Z-axis gradient coil applying a spatially varying magnetic field. Reproduced from uomus.edu.iq.

High SNR is desirable to enable qualitative and quantitative analysis. SNR is inversely related to spatial resolution, as increasing image resolution decreases the signal per voxel due to a lower number of protons per voxel. However, higher spatial resolution images carry more information and may improve the accuracy of the delineation of brain structures in the processing stage. A longer acquisition time

improves the SNR, as more signal can be sampled. Therefore, the acquisition time, the SNR, and spatial resolution must be traded off against each other (Jenkinson and Chappell, 2018).

1.2.1 T1 recovery and T2 relaxation

Contrast between different tissue types in MRI is dependent on their properties. The local microscopic environment of hydrogen nuclei determines how fast the molecules realign with the b_0 field after being excited by a magnetic field. This property is described using T1 and T2 relaxation constants. T1 recovery time is the time it takes protons to realign with the b_0 field after being excited by a radiofrequency (RF) pulse. T2 decay describes the process of precessing protons dephasing after a RF pulse. T1 recovery and T2 decay are dependent on each tissue type and their environment, protons in fat have a short T1 and T2 time and protons in water have a long T1 and a long T2 time (Figure 1.4).

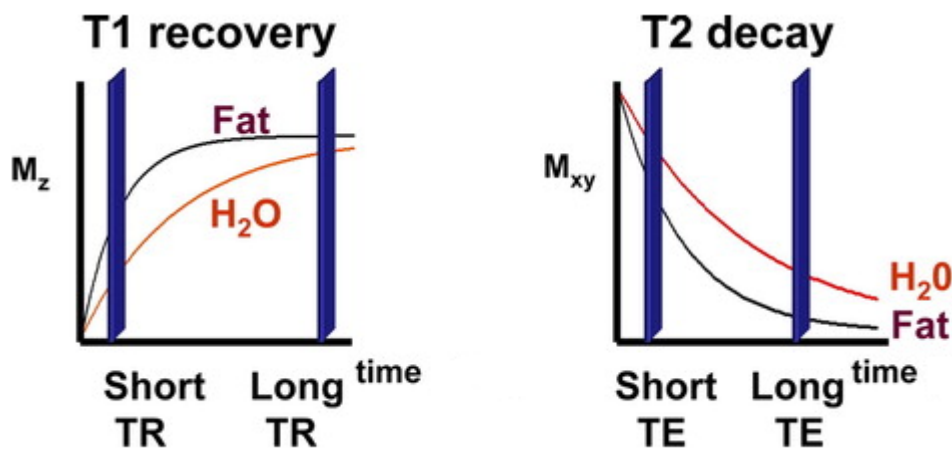


Figure 1.4: T1 recovery (left) and T2 decay (right) in fat and water based on short and long TR and short and long TE. Time in milliseconds. M_{xy} = transverse magnetization, M_z = longitudinal magnetization. Image reproduced from Bitar et al (2006).

These properties are used to create contrast in an MRI by changing the repetition time (TR) and echo time (TE). TR is the time between excitations of the same region and TE is the time between excitation and measurement of the signal (Figure 1.5) (Chappell et al., 2018).

Conventional Spin Echo

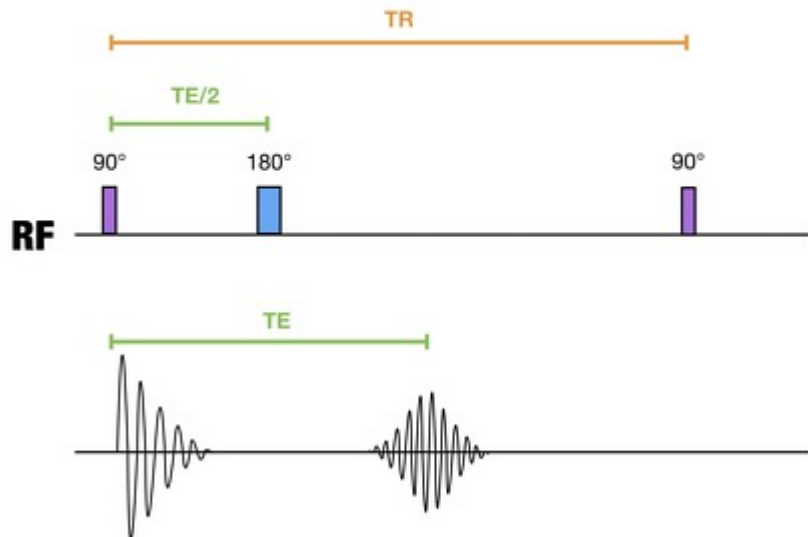


Figure 1.5: Conventional Spin Echo sequence. TR = Repetition Time, TE = Echo Time, RF = Radiofrequency Pulse. Reproduced from Radiopaedia.org.

A short TE will produce a strong signal, as relatively little time has passed for the excited molecules to revert to their original state. However, there will also be little difference in intensity and therefore contrast in tissue types, as recovery states between tissue types will not have had time to differentiate themselves. Longer TE will produce a weaker signal but a stronger differentiation between tissue types. A short TR means net magnetization has not had time to recover, leading to a reduced signal strength at the next excitation. The difference between tissue types though, will be more pronounced, as the difference in the state of recovery between tissue types is greater. By contrast, a long TR will lead to greater signal, as net magnetization has had time to recover, but little difference between tissue types (Symms et al., 2004).

$T1$ -weighted images are created using a short TE and short TR , leading to tissue with a high fat content appearing bright and tissue with high water content appearing dark. $T2$ -weighted images are created using a long TE and long TR , and therefore tissue with high water content appears bright and high fat content appears dark, the exact opposite of $T1$ (Chappell et al., 2018).

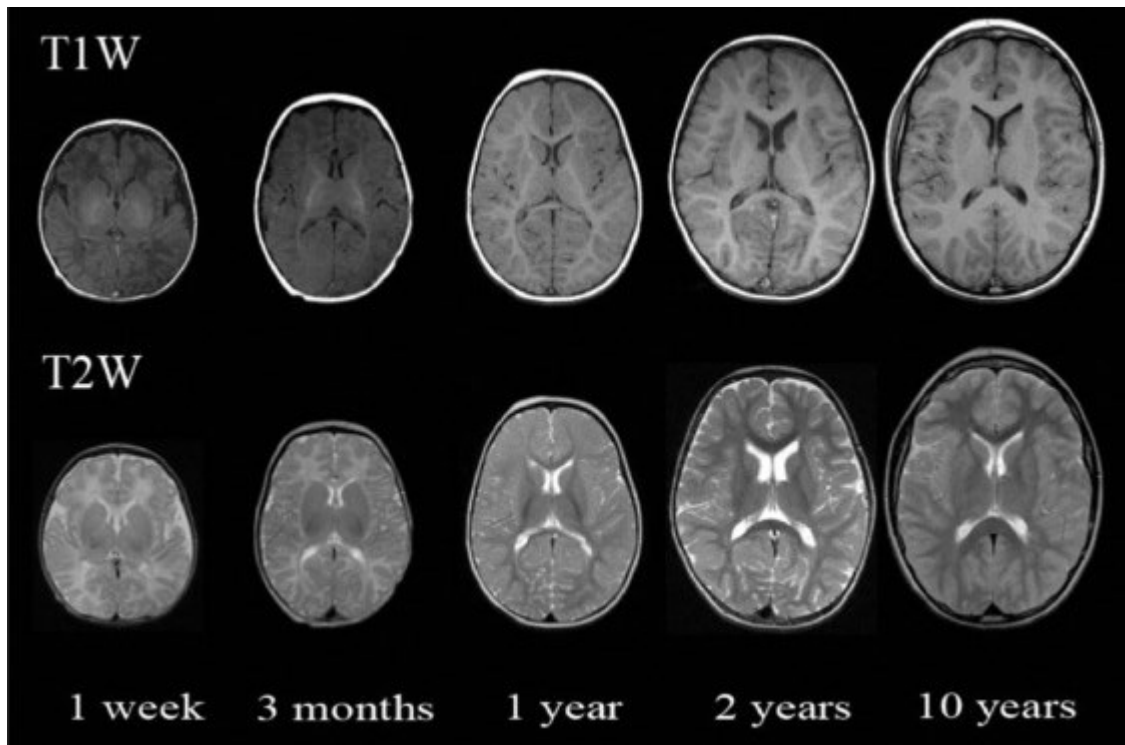


Figure 1.6: T1- and T2-weighted images in infants and children. Reproduced from Miller et al (2020).

MRI can provide more detailed images of the developing brain than any other imaging modality. However, most of the imaging and processing tools for MRI were developed for the adult brain and had to be adapted to the neonatal brain. The brain of neonates has not fully developed yet and has a greater water content and lower fat content than the adult brain, leading to a different appearance in T2- and T1-weighted images. Both T1- and T2-weighted images are used extensively in neonatal MRI, but contrast between grey matter (GM) and WM is greater in T2- than in T1-weighted images (Figure 1.6) (Miller et al., 2020, Counsell et al., 2019).

Myelin is largely responsible for the difference in appearance of the brain in adult and neonatal MRI. Myelin is a fatty sheath that acts as an insulating layer, it forms around WM tracts in part during gestation but mostly during post-term development (Gilles et al., 1976). Only small amounts of myelin are therefore present in the neonatal brain, and these can be assessed using MRI. Myelinated WM exhibits high signal intensity on T1-weighted images but low signal intensity on T2-weighted images due to myelin's fatty composition.

Neonatal MR brain imaging faces unique challenges compared with adult MR brain imaging. The smaller size of neonatal heads means that using adult head coils leads to low SNR compared with bespoke close-fitting array coils (Figure 1.7) (Keil et al., 2011, Hughes et al., 2017). Brain sizes are also much smaller when compared with adults, requiring higher resolution to obtain the same amount of information (Kelly et al., 2019). Further, neonatal MR imaging suffers from motion artefacts, as infants

are an inherently uncooperative cohort. In the past this has led to neonatal MR imaging being performed on sedated infants, but as sedation is not without risk, alternative techniques have been developed to decrease subject motion and sedation is no longer standard practice (Tocchio et al., 2015). As infants still move even when sleeping, motion correction techniques are usually applied in image processing (Cordero-Grande et al., 2018).

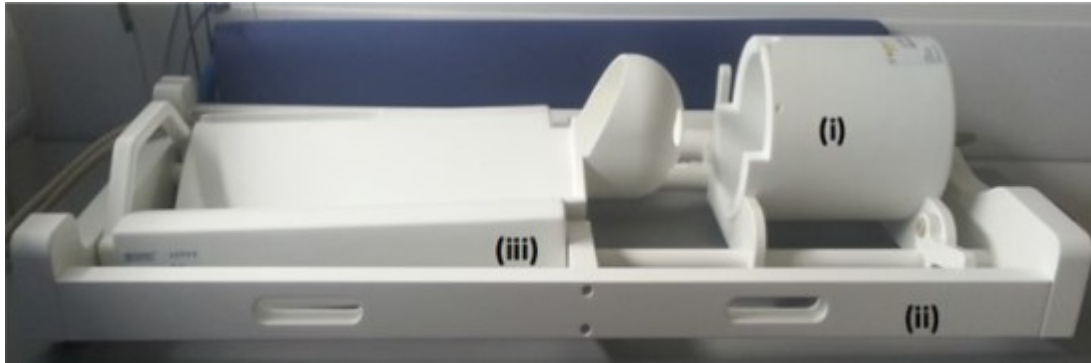


Figure 1.7: A bespoke neonatal brain imaging system, consisting of (i) the neonatal head coil, (ii) the frame, and (iii) the positioning shell. Reproduced from Hughes et al (2017).

1.2.2 Registration

Image registration brings images into the same space, aligning the same anatomy in different images and even different modalities to the same coordinates to allow for consistency in subsequent comparison and analysis (Jenkinson and Chappell, 2018). This step is essential as the resolution of imaging data, the position of the subject's head, and the field of view of the image may vary between acquisitions.

In the same subject, image registration is termed “within” subject registration, and is commonly done to correct for subject motion during the imaging process. Within subjects, linear transformations such as rigid-body transformation (6 degrees of freedom) and affine transformation (12 degrees of freedom) are sufficient to align images, as the anatomy stays the same between images (Figure 1.8). Between subjects, the anatomy may vary substantially, requiring non-linear transformation of the images. Non-linear transformations can have as many degrees of freedom as there are voxels, and this enables changing the brain geometry locally to account for individual differences (Figure 1.8) (Song et al., 2017). For example, cortical folding patterns are uniquely different between each individual neonate and need flexibility in transformation to get good alignment (Dubois et al., 2008).

Subject images are often registered to a subject template or atlas, which is an average image from a demographic subset. These atlases represent an average anatomy to which individuals can be registered to enable a standardised way of describing the location of brain tissues (Dickie et al., 2017).

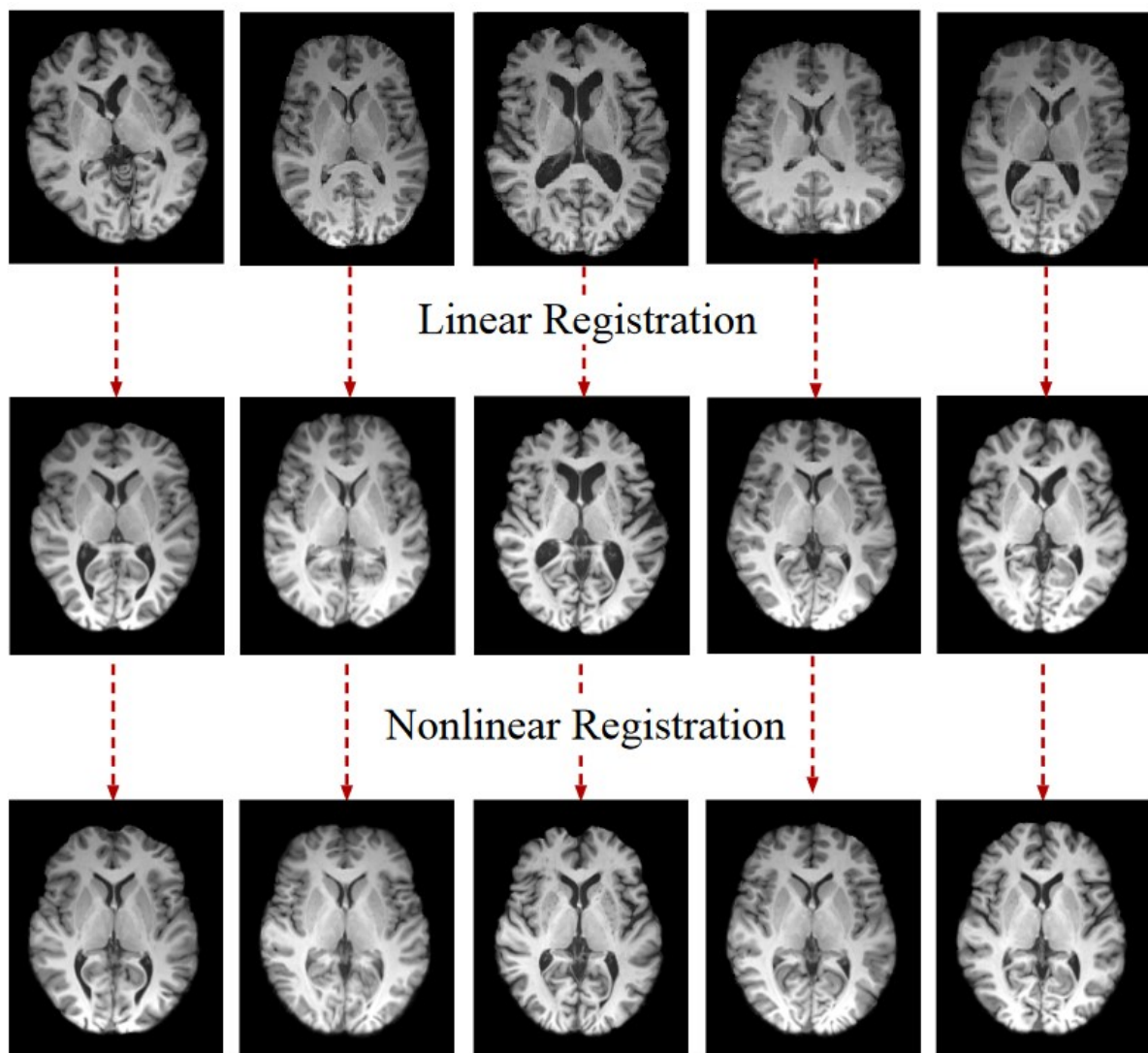


Figure 1.8: Linear and non-linear registration in MRI. Linear registration adjusts the shape and size of the entire image, whereas non-linear registration can make local changes. Reproduced from FSL course material (FSL, 2022).

1.2.3 Segmentation

Segmentation refers to the process of delineating different tissues or structures within the brain. Most segmentation processes use a combination of modelled tissue intensity distributions along with information about each voxel's spatial neighbourhood to determine tissue types. The tissue intensity distributions usually show well differentiated peaks in intensities for each of the major tissue types (GM, WM, and cerebrospinal fluid (CSF)) that can be used to create probability distribution functions (González-Villà et al., 2016). In neonates, however, the intensity distribution of WM and CSF can be very similar since most of the WM is unmyelinated and therefore has high signal in T2-weighted images (Makropoulos et al., 2014). This problem requires special care in automated segmentation algorithms.

Spatial neighbourhood information can be used to smoothen tissue distributions and can aid an automatic segmentation algorithm's accuracy (Devi et al., 2015). This is particularly helpful if isolated points in the middle of a tissue type, for example the GM, get classified as another tissue type, e.g. WM. Spatial dependency can be used to tell the algorithm that if the neighbouring voxels are classified as GM, it is highly likely that this voxel should also be classified as GM. Care should be taken that neighbourhood information is not weighted too strongly, otherwise this could lead to misclassification errors.

As the size of each voxel is much larger than the size of the underlying tissue, several tissue types are often present in one voxel, which can lead to partial voluming errors. The term partial voluming error describes the misclassification of voxels due to loss of contrast between two adjacent tissue types. It may be helpful to describe voxels as partially attributable to different tissue types. The fraction of each volume described as a tissue type can be used to delineate error-prone boundaries between tissue types more accurately (Sharma and Aggarwal, 2010). Moreover, prior knowledge about brain anatomy can be used to make segmentation more accurate. Atlases of previously segmented subjects in the same demographic group are used in atlas-based segmentation methods. The accuracy is dependent on quality of the template and how closely aligned the demographics of the atlas and the target group are. Figure 1.9 shows an example of a tissue segmentation and neonatal atlas parcellation for the same infant.

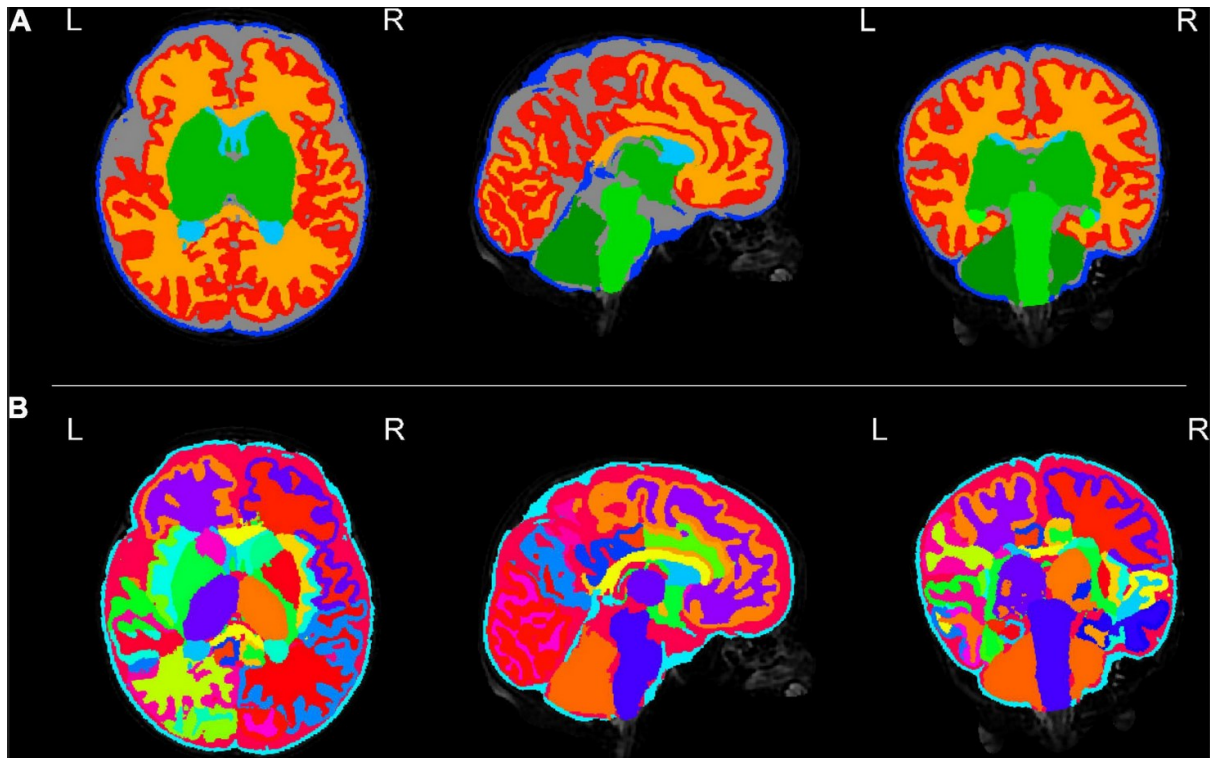


Figure 1.9: Tissue segmentation and neonatal atlas parcellation for the same infant. Anatomical images were segmented into 9 tissue classes (A) and parcellated into 87 brain regions (B). Reproduced from Edwards et al (2022).

1.2.4 Principles of diffusion MRI

The contrast in diffusion MRI is determined by the movement of water molecules in the brain. Water diffuses randomly throughout the brain in a process called Brownian motion. In the CSF, where there are no obstacles to diffusion, Brownian motion occurs isotropically, i.e., equally in all directions. Brownian motion is affected by tissues and structures within the brain, as water molecules cannot pass through cell membranes easily. The WM is made up of tightly packed and elongated axonal bundles, which hinder diffusion perpendicular to the orientation of the axons and preferentially allow water molecules to diffuse along the orientation of axon bundles, i.e., the water molecules diffuse in an anisotropic fashion (Figure 1.10).

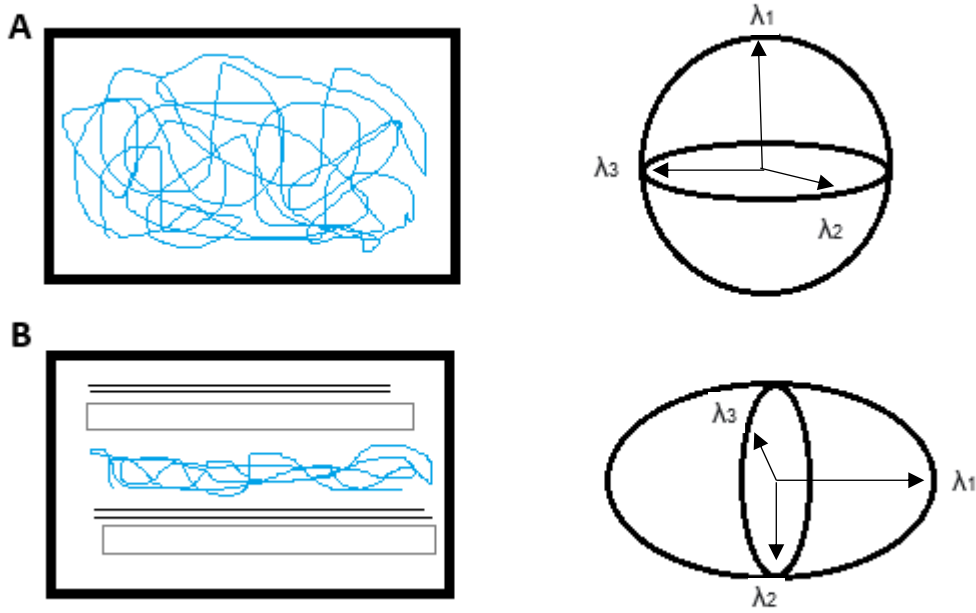


Figure 1.10: (A) Isotropic diffusion and (B) anisotropic diffusion and the eigenvectors λ_1 , λ_2 , and λ_3 .

The movement of water molecules is therefore dependent on the underlying tissue microstructure of the brain. It is important to note the distinction, however, that diffusion MRI quantifies the properties of diffusing molecules over time instead of biological quantities (Jenkinson and Chappell, 2018). Information about the underlying microstructure can only be inferred. Further, no distinction can be made between active displacement of water and Brownian motion, and the degree of diffusion depends on the extent of diffusion weighting and the microstructural environment. Therefore, the estimated diffusion coefficient is termed the apparent diffusion coefficient (ADC).

Diffusing water molecules lead to dephasing of the MRI signal, reducing its amplitude. In diffusion MRI however, by deliberately applying steep magnetic field gradients, this effect can be made into the dominant contrast mechanism. To accurately quantify diffusion, a diffusion weighted image needs to be compared to an image with no diffusion weighting, called a b_0 image. The b -value is a metric for the degree of diffusion weighting applied, with higher b -values leading to greater diffusion sensitivity at the cost of a lower SNR. It can be calculated as follows:

$$b = \gamma^2 G^2 \delta^2 \left(\Delta - \frac{\delta}{3} \right)$$

Where γ is the gyromagnetic ratio, G is the amplitude, δ is the time of applied gradients, and Δ is the duration between paired gradients. Typical b -values range between 750 and 1500 (s/mm^2) in clinical settings, but the ranges tend to be wider when imaging for research purposes (Tusor et al., 2014).

As each image is only sensitive to diffusion in one direction, a complete sequence requires many different images to capture diffusion in many directions. These images need to be acquired quickly in fast imaging sequences for the acquisition not to take very large amounts of time and put a heavy burden on subjects. The speed of the acquisition comes at the cost of image resolution and increased sensitivity to artefacts such as geometric distortion, which then need to be corrected for in the image processing stage.

1.2.5 Diffusion Tensor Model

A common model that is used to interpret diffusion data is the diffusion tensor (DT) model (Basser and Jones, 2002, Basser et al., 1994). It uses directional diffusion data from each voxel, compared with the signal measured with no diffusion gradient applied (b0 image), to calculate metrics such as mean diffusivity (MD) and fractional anisotropy (FA). It requires a minimum of six phase encoding directions to be solvable. The three principal diffusion directions are called the eigenvectors, and the diffusion along these vectors is denoted by the eigenvalues. MD describes the overall diffusion and can be calculated using the following formula:

$$MD = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3}$$

Where $\lambda_{1,2,3}$ are the eigenvalues. Thus, MD is the mean of the three eigenvalues of the diffusion tensor. FA is the normalised variance of diffusion along the eigenvectors, and can be calculated as follows:

$$FA = \sqrt{\frac{1}{2} \frac{\sqrt{(\lambda_1 - \lambda_2)^2 + (\lambda_2 - \lambda_3)^2 + (\lambda_3 - \lambda_1)^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}}$$

FA values range between 0 and 1, where 0 represents isotropic diffusion and 1 represents pure anisotropy. The principal diffusion direction is further characterised using the axial diffusivity, which is the eigenvalue of the primary eigenvector. Radial diffusivity refers to the mean of the eigenvalues of the second and third eigenvectors (Jenkinson and Chappell, 2018). An example of a visualisation of MD and FA in neonates, 2-year-olds, and adults can be found in Figure 1.11.

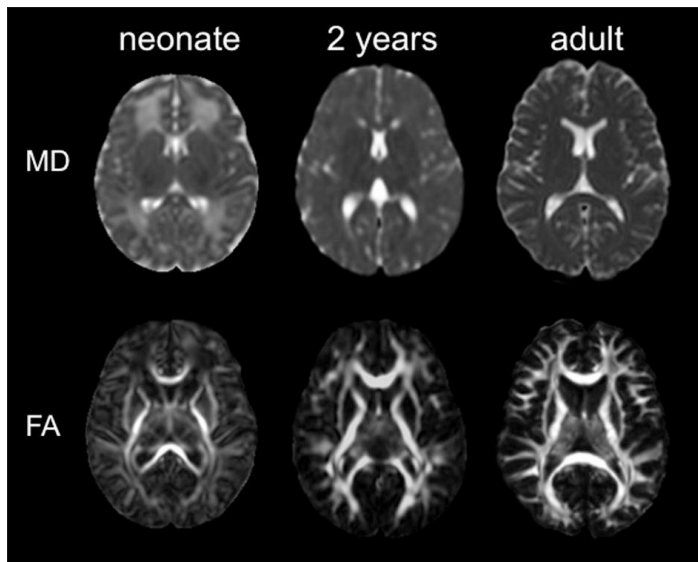


Figure 1.11: Mean diffusivity (MD) and fractional anisotropy (FA) maps for neonates, 2-year-olds, and adults. Reproduced from Oishi et al (2013).

Diffusion tensor imaging (DTI) thus provides information about the directionality of the water diffusion process (Martinez-Heras et al., 2021). DTI has high sensitivity to relatively small microstructural changes in WM tissue. WM fibre bundles can be visualised using this technique by using the directional dependence of water diffusion in the brain in a process called diffusion tractography. Diffusion tractography allows the reconstruction of WM fibre bundles and gives insight into the developing structure of neonatal WM (See Section 1.27) (Counsell et al., 2019). DTI is limited in its ability to characterise complex diffusion topology, such as when diffusion displacement is multidirectional, in so called crossing fibres (Alexander, 2005). Moreover, DTI is restricted in its biological specificity and its ability to discern several microstructural tissue properties within one voxel. Scanner parameters, subject motion, and quality of the data further impact upon the quality of DTI analysis (Jones and Cercignani, 2010). In order to address these shortcomings of DTI, other diffusion MRI techniques have been proposed.

1.2.6 Neurite Orientation Dispersion and Density Imaging

Several other biophysical models attempt to model microstructure using diffusion MRI data (Alexander et al., 2019). One widely used model is the Neurite Orientation Dispersion and Density Imaging (NODDI) model (Zhang et al., 2012). NODDI enables quantification of changes in microstructure in GM and WM. Its indices have been shown to be clinically relevant and able to capture microstructural changes in fibre density, myelination, and orientation distribution of neurites in the developing brain (Kunz et al., 2014, Chang et al., 2015).

NODDI models signal contributions separated into tissue (GM and WM) and non-tissue signal (CSF). The non-tissue compartment is modelled assuming isotropic Gaussian diffusion, whereas the tissue compartment models the space around neurites as anisotropic diffusion and the neurites themselves as orientationally dispersed sticks. The model assumes that diffusion along the direction of the sticks is unhindered, while diffusion perpendicular to the sticks is strongly hindered. NODDI provides two main metrics, the orientation dispersion index (ODI), and the neurite density index (NDI). The orientation of the sticks in the intra-neurite model is expressed in the ODI, which is a value between 0 and 1. A value of 0 indicates that all neurites are perfectly aligned, whereas a value of 1 indicates a perfectly random dispersion. The ODI thus quantifies the degree at which neurites are orientationally coherent. The intra-neurite volume fraction, calculated using the intra-neurite and extra-neurite signal, gives an estimate of the neurite density (NDI), which is expressed as a value between 0 and 1. NODDI also provides the isotropic volume fraction (f_{iso}), which is a quantification of the amount of partial volume that is water. An increased NDI and f_{iso} indicate an increase in the density of neurites and local water, respectively.

NODDI has several limitations. NODDI requires the acquisition of multiple high angular resolution diffusion imaging (HARDI) shells to be estimated accurately. Further, the assumption of multiple Gaussian compartments in NODDI limits the model and may lead to neglect of factors that could be of importance, such as inter-compartmental exchange and non-Gaussian effects (Kamiya et al., 2020). In order to guarantee model stability, some of the parameters are constrained and may introduce bias if not handled carefully. However, NODDI has been used successfully in many studies (Lemkaddem et al., 2014, Billiet et al., 2015, Kunz et al., 2014, Chang et al., 2015), showing clinical relevance of the model metrics. Additionally, when compared with histological findings, ODI has shown a stronger correlation with orientation dispersion than FA, which suggests that NODDI is able to represent orientation dispersion more clearly than the diffusion tensor model (Schilling et al., 2018, Grussu et al., 2017).

1.2.7 Tractography

Tractography is a technique primarily used to delineate WM tracts using diffusion MRI data, allowing visualization and quantification of the complex network of connections in the brain (Figure 1.12). The WM is composed of bundles of nerve fibres called axons, which connect different regions of the brain to each other. Fibre tractography uses the dominant orientation of each imaging voxel to piece together a trajectory through the brain (Jeurissen et al., 2017). The DT model can only identify a single fibre orientation per voxel, and will therefore run into problems when it comes to more complex fibre orientations, such as fanning, crossing, and kissing fibres (Alexander et al., 2001, Tuch et al., 2002).

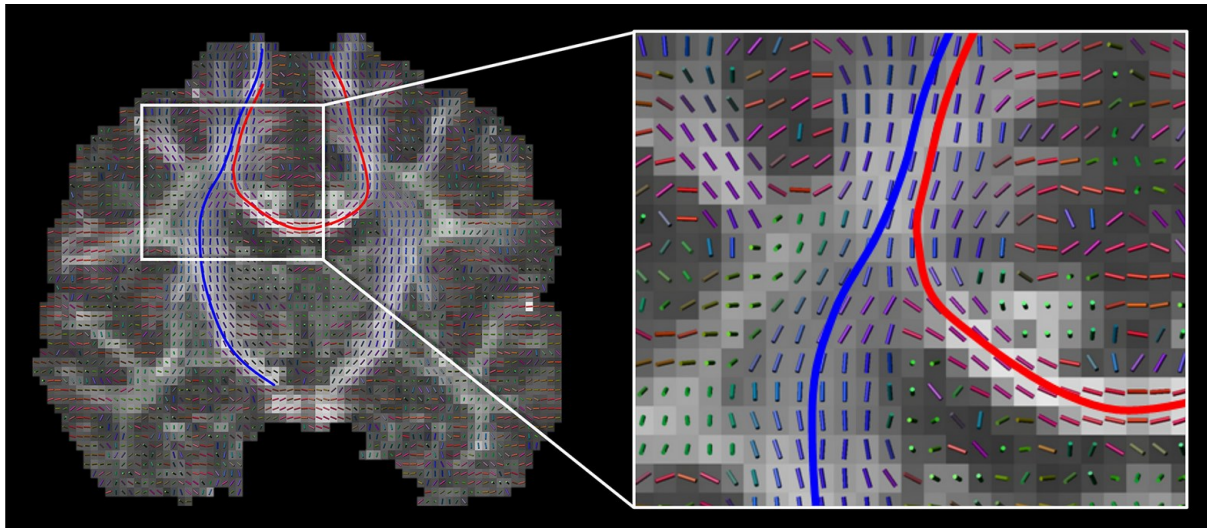


Figure 1.12: Vector field of local predominant fibre orientations and two of its streamlines depicted on a coronal view of the human brain. Reproduced from Jeurissen et al. (2017).

Tractography algorithms are commonly split between deterministic and probabilistic algorithms. In deterministic tractography the streamlines connecting voxels are delineated according to a fixed direction in each voxel (Sarwar et al., 2019). Deterministic algorithms are unable to account for uncertainty, only estimating the principal direction of diffusion, and are susceptible to noise (Jones, 2008, Descoteaux et al., 2009). Probabilistic tractography uses the dominant orientation of local water diffusion along with the mean orientation of WM fibres from voxel to voxel in order to infer the location and extent of tracts in the brain (Beaulieu, 2002, Ciccarelli et al., 2006). This enables the algorithm to quantify uncertainty in each voxel, allowing tracking even in regions of high uncertainty (Jeurissen et al., 2017). In general, caution is warranted when examining and interpreting diffusion MRI tractography (Kroenke, 2018), as direct examinations and correlations between imaging and histological examinations of the developing human brain are scarce (Dean et al., 2013, Huang et al., 2012).

1.3 Effects of prenatal exposure to air pollution on early life neurodevelopment assessed with MRI

Research on the impacts of air pollution on the brain has been conducted for around two decades. Some of the first studies to do research on this subject examined brain tissues in canines exposed to high levels of air pollution in Mexico City and found evidence of brain inflammation and neurodegeneration (Calderón-Garcidueñas et al., 2002, Calderón-Garcidueñas et al., 2003). Since then, exposure to air pollution has been linked to a wide range of impacts on the brain, including increased risk of dementia (Power et al., 2016), cognitive decline (Clifford et al., 2016), and neurodegenerative diseases such as Parkinson's disease (Cristaldi et al., 2022). The developmental

period came under scrutiny a few years later, with studies assessing exposure to air pollution both during pregnancy and childhood (Perera et al., 2006, Perera et al., 2009, Calderón-Garcidueñas et al., 2008). The immature brain is especially susceptible to the effects of environmental exposures due to its swift development, leading to vulnerability in key maturation processes (Grandjean and Landrigan, 2014). There are several studies that examine the link between postnatal exposure to air pollution, in childhood or adolescence, and neurodevelopment in children (Jedrychowski et al., 2015, Rivas et al., 2019). This thesis focuses on prenatal exposure to air pollution, and there is now a sizeable amount of literature on prenatal exposure to air pollution and its effects on cognitive performance, mental health, and behavioural disorders in childhood (Shang et al., 2020, Chun et al., 2020, Zundel et al., 2022). However, the use of brain MRI in this field has been limited, with studies mostly examining structural MRI. Additionally, all imaging was done in childhood, when subjects were between the ages of 6 – 15 years old.

1.3.1 Structural MRI

The impact of prenatal exposure to air pollution on early life brain morphology has been examined in school age children using MRI in several studies, resulting in mostly adverse associations, with a few null findings. Structural MRI was explained in Section 1.2, and in this section, I will detail the evidence on whether prenatal exposure to air pollution affects brain structural morphology in early life.

Intracranial volume (ICV) and total brain volume TBV increase rapidly during gestation, especially in the third trimester (Vasung et al., 2019). This growth is shared unequally between different parts of the brain. The cerebellum can grow as much as three to four times in volume in the third trimester, whereas the brain stem will grow more slowly, with TBV doubling in size in this period. Conversely, ventricular volume generally decreases during the third trimester (Clouchoux et al., 2012).

In an early study, prenatal exposure to PAHs was inversely correlated with distance from the template surface, an index of local volume for GM and WM in the left but not the right hemisphere of the brain of children aged 7 – 9 years old (Peterson et al., 2015). Further investigation using the distance from surface measures found that the inverse correlation with local volumes derived from spatially larger impacts on underlying WM of the left hemisphere. The cohort consisted of 255 subjects, though only 40 out of 255 children included in this cohort underwent MRI after stratified sampling in which the authors selected 20 subjects above and 20 subjects below the median PAH exposure level of the cohort. The authors conducted a 48-hour personal air monitoring campaign in the third trimester of pregnancy to measure exposure to PAHs, validated by a two-week monitoring campaign in a subset of homes. The correlation between the sampling campaigns was moderate ($r = 0.44$), raising questions about how representative the measurements are of PAH exposure levels throughout pregnancy.

Prenatal exposure to coarse PM (PM_{10} - $PM_{2.5}$), $PM_{2.5}$ absorbance, and $PM_{2.5}$ were inversely correlated to cortical thickness in several brain regions in both hemispheres in a large cohort of children aged 6 – 10 years old ($n = 783$), though no effects were found for NO_2 (Guxens et al., 2018). Exposures were modelled at residential level using LUR models. This study also assessed the impact on global brain volumes, finding no effects of any pollutants on TBV, cortical GM volume, cortical WM volume, subcortical GM volume, and ventricular volume.

Further null findings were found in a study of 186 children aged 8 – 12 years old who were imaged as part of the Brain Development and Air Pollution Ultrafine Particles in School Children (BREATHE) study (Mortamais et al., 2019). The authors used LUR models to assess residential exposure to $PM_{2.5}$ during pregnancy and found an association between an increase in $PM_{2.5}$ exposure and decreasing corpus callosum (CC) volume, which did not survive false-discovery rate (FDR) correction for multiple comparisons. No associations were found with WM, GM, and ventricular volume.

A comprehensive study by Lubczyńska et al examined prenatal exposure air pollution for a large imaging cohort of children aged 9 – 12 years old ($n = 3133$) (Lubczyńska et al., 2021). Residential exposure to PM_{10} , $PM_{2.5}$, coarse PM, $PM_{2.5}$ absorbance, UFP, composition of PM, and NO_2 was estimated using a LUR model, and oxidative potential of $PM_{2.5}$ was measured. In their single-pollutant model, higher levels of PM_{10} , $PM_{2.5}$, coarse PM, and $PM_{2.5}$ absorbance were related to an increase in the relative size of the cerebellum. Increased coarse PM exposure was related in a larger relative size of the putamen and pallidum, and increased exposure to silicone was related to a larger relative size of the amygdala. Further, increased exposure to PM components benzo(a)pyrene (B[a]P), PAHs, and copper were related to a smaller relative size of the hippocampus, and oxidative potential of $PM_{2.5}$ was associated with a smaller relative size of the CC. Prenatal exposure to air pollution was not associated with volumes of the total brain, cortical and subcortical GM, cerebral WM, thalamus, caudate nucleus, and nucleus accumbens.

In their multi-pollutant model, increased oxidative potential of $PM_{2.5}$ was associated with a smaller relative size of the CC. Increased coarse PM exposure was associated with larger relative size of the cerebellum, whereas increased oxidative potential of $PM_{2.5}$ was associated with smaller relative size of the cerebellum. Increased exposure to PAHs was associated with a smaller relative size of the hippocampus, and increased exposure to PAHs and organic carbon (OC) were related to a smaller relative size of the amygdala, while silicone was related to a larger relative size of the amygdala.

The same cohort was used to study whether having the apolipoprotein E (APOE) genotype or a high or low polygenic risk score (PRS) for Alzheimer's Disease (AD) had a modifying effect on prenatal air pollution exposure and structural brain morphology in adolescents (Essers et al., 2023). The APOE

gene is responsible for cholesterol metabolism and lipid homeostasis, and carriers of the allele are at higher risk of neurodegenerative processes (Kloske and Wilcock, 2020, Piers, 2018, Fernandez et al., 2019). Using the same pollution measures as described in Lubczynska et al (2021) described above, Essers et al (2023) found that in their single-pollutant analysis, higher prenatal exposure to NO_x, PM₁₀, PM_{2.5}, coarse PM, and PM_{2.5} absorbance was differentially associated in APOE ε4 carriers compared to non-carriers with larger cortical GM volumes. Higher prenatal exposure to NO_x, PM₁₀, PM_{2.5}, and coarse PM was also related to larger cerebral WM in APOE ε4 carriers compared to non-carriers. Higher exposure to multiple air pollutants was differentially associated with larger CC volumes, and with smaller subcortical GM, putamen, thalamus, hippocampus, and nucleus accumbens volumes in APOE ε4 carriers compared to non-carriers. In their multi-pollutant analysis, only prenatal exposure to coarse PM was differentially associated with larger cerebral WM volume in APOE ε4 carriers compared to non-carriers.

A high or low PRS for AD also modified the associations between prenatal exposure to air pollution and childhood brain morphology. Prenatal exposure to several air pollutants was differentially associated with larger cortical GM volume, and smaller subcortical GM, pallidum, putamen, thalamus, amygdala, and hippocampus volumes per increase in PRS for AD. Again, only coarse PM remained significantly associated with larger cortical GM volume in their multipollutant analysis per increase in PRS for AD. Associations with prenatal exposure to air pollution and cerebral WM and cortical GM were not modified by polygenic risk scores.

Peterson et al (2022) estimated prenatal residential exposure to PM_{2.5} and PAHs using a spatiotemporal exposure model and measured PAH exposures for 48-hour periods in the third trimester. MR imaging of children aged 6 – 14 years old was undertaken in a larger subsample of the same cohort of their 2015 study (n = 332). Exposure to both PM_{2.5} and PAHs was associated with thicker posterior inferior, lateral temporal, and mesial wall surfaces in the cortical GM, as well as thinner dorsal parietal surfaces. Both pollutant exposures were also associated with smaller local WM volumes in the cingulate gyrus and the inferior parietal lobes, and larger WM volumes at the posterior inferior brain surface, the superior frontal gyrus, and the brain's dorsal convexity. Stratifying by sex revealed stronger associations with PM_{2.5} for males, and stronger associations with PAHs for females.

None of the above studies found any associations of prenatal exposure to NO₂ with childhood brain morphology. The most researched pollutants were PM_{2.5} and PAHs, and these showed the strongest associations with brain morphology measures. Prenatal exposure to PM₁₀ was assessed by Guxens et al (2018) and Lubczynska et al (2021) and increased exposure to PM₁₀ was not associated with any metric of brain morphology except larger relative size of the cerebellum in the latter study.

In summary, only five studies were found that researched prenatal exposure to air pollution and brain morphology. Two out of these five studies found no association between volumetric measures of the brain and prenatal exposure to air pollution (Guxens et al., 2018, Mortamais et al., 2019). Peterson inferred local WM volume in their 2015 study and did not assess volumes of the brain in their 2022 study other than WM surface area and local volumes. Studies also varied in cohort size, the exposure assessment method used, and ages at which subjects were scanned, with ages ranging from age 6 to 14 years old.

1.3.2 Diffusion MRI

The effect of prenatal exposure to air pollution on childhood WM microstructure using diffusion MRI has been the subject of only two studies to date. Diffusion MRI is an MRI method which measures diffusion in the brain, giving insight into tissue microstructure. The various aspects of diffusion MRI were explained in Section 1.2, and in this section, I will detail the evidence on whether prenatal exposure to air pollution affects any of the metrics measured by diffusion MRI and by extension whether brain tissue microstructure in early life is impacted. If these metrics are affected by prenatal exposure to air pollution this could give insight into WM injury on a much smaller scale than structural MRI.

The most common metrics of diffusion MRI, FA and MD, change with maturation. Prenatally, FA increases as the WM becomes more organised in the third trimester, and the inverse of this trend is generally true for MD for most tracts (Wilson et al., 2021). In the WM, these changes reflect variations in water content, axonal calibre, myelination and oligodendrocyte proliferation (Tusor et al., 2014). MD and FA are strongly correlated with maturity (Wilson et al., 2021, Pannek et al., 2014), and any impacts prenatal exposure to air pollution may have on these metrics could give insight into the vulnerability of the developing brain. However, as outlined in Section 1.2.5, DTI is sensitive to underlying microstructure but lacks specificity. FA, for example, is modulated by many factors such as partial voluming, axonal and dendritic density and number, and orientation dispersion, making interpretation more difficult (Jones et al., 2013).

Utilising the same models to estimate prenatal exposure to air pollution and studying the same cohort as in the above study on structural MRI, albeit with a slightly smaller sample ($n = 2954$), Lubczyńska et al found that in their single pollutant model higher exposures to PM_{10} , $PM_{2.5}$, $PM_{2.5}$ absorbance, and NO_x during pregnancy were associated with lower global FA (Lubczyńska et al., 2020). Also in their single pollutant model, higher prenatal exposures to PM_{10} , $PM_{2.5}$, $PM_{2.5}$ absorbance, NO_2 , NO_x , copper, iron, silicone, UFP, and higher oxidative potential of $PM_{2.5}$ were associated with higher global MD. The multipollutant model showed a significant association between higher $PM_{2.5}$ exposure and lower

global FA, and when PAHs and PM_{2.5} were included, they showed positive and negative associations with global FA, respectively. Silicone exposure during pregnancy was associated with higher MD in the cingulate gyrus part of the cingulum of the left hemisphere, the left superior longitudinal fasciculus, and the forceps minor (Lubczyńska et al., 2020).

Peterson et al (2022) found that prenatal exposure to PM_{2.5} and PAH were associated with higher FA values in the basal ganglia, anterior cingulate gyrus, and thalamus. As with the structural imaging, sex differences were found, with PM_{2.5} associations being stronger in males and PAH associations stronger in females. Further, higher PM_{2.5} exposures were associated with greater diffusivity in the anterior CC and the anterior corona radiata, suggesting a possible decrease in myelination, more fibre crossings, or lower cell density. Myelination is difficult to assess using imaging and histological assessment is still the gold standard of quantifying myelination (Laule et al., 2007, Wang et al., 2019). Higher exposures to PAH were also associated with lower diffusivity in the internal capsule, which could be indicative of increased myelination, or higher cell density, or higher axonal fibre coherence in the internal capsule.

In summary, only two studies were found that researched prenatal exposure to air pollution and WM microstructure. Both studies discovered significant associations between prenatal air pollution exposure and FA and MD in several tracts, and Lubczynska et al also found associations with global FA and MD. PM_{2.5} and PAH were studied in overlapping age groups in both studies and findings are comparable, adding some significance to the very small number of studies.

1.3.3 Animal models

A larger body of work has examined the relationship between prenatal exposure to air pollution and early life neurodevelopment in animals. Direct comparison between results in animal and human air pollution exposure studies is complicated by the differences in exposure, the lack of spatiotemporal heterogeneity in animal studies, and differences in composition and levels of exposure. Further, exposure time frames may not be comparable, since e.g., the neonatal period in mice is equivalent to the human third trimester. However, animal studies give great insight into windows of vulnerability and potential mechanistic pathways of how air pollution affects early life neurodevelopment. Some important findings which are complementary to the studies outlined in humans above are summarised below.

Prenatal air pollution exposure to concentrated ambient particles (CAPS) and traffic-related air pollution (TRAP) in mice has been shown to induce microglial activation in both sexes and reduce the number of microglia (Klocke et al., 2017). Also in mice, neuronal and astrocyte apoptosis in the cortex and hippocampus was shown as a result of chronic prenatal exposure to high doses of PM_{2.5} (Zhang et al., 2018b, Zheng et al., 2019). Further, prenatal exposure to diesel exhaust particles (DEP) induced

change in morphology of astrocytes and microglia (Bolton et al., 2017, Kulas et al., 2018), PM_{2.5} and UFP exposure led to increased cell apoptosis in the cerebral cortex (Zhang et al., 2018b) and in the nucleus accumbens in male offspring (Cory-Slechta et al., 2019), and prenatal exposure to TRAP increased microglial infiltration in the hippocampus in mice offspring (Patten et al., 2020). The microglia are the immune cells of the brain and are activated in response to disease or neuroinflammation (Colonna and Butovsky, 2017). Greater numbers of microglia are required for neuro- and oligodendrogenesis through the release of cytokines (Shigemoto-Mogami et al., 2014), however, an ongoing inflammatory response may make microglia more vulnerable to dysfunction or cell death (Allen et al., 2017).

Aside from effects on a cellular level, several studies have shown impacts of prenatal exposure to air pollution on brain morphology in animal offspring. Klocke et al (2017), which was described above, also discovered that dams exposed to CAPS gave birth to offspring with ventriculomegaly, increased CC area, and reduced hippocampal area. TRAP exposure during pregnancy decreased lateral ventricle size in female mice, with no effect in male mice (Patten et al., 2020). This last finding was opposed by evidence of persistently increased ventricular area in female adult mice exposed prenatally to CAPS (Klocke et al., 2018a).

Some of the effects of prenatal exposure to air pollution only became apparent in later life, once the mice were fully grown. Di Domenico et al compared brain morphology in mice pre- and postnatally exposed to CAPS, and only the prenatally exposed group had lower CC volume in adulthood (Di Domenico et al., 2020). Prenatal exposure to TRAP also led to a decrease in neurogenesis in male adult mice (Woodward et al., 2018). Further, increased cortical volume in male mice found postnatally after prenatal exposure to DEP reversed in adulthood, changing to declining volume (Bolton et al., 2017). Bolton et al theorise that inflammatory activation and/or a developmental delay, caused by air pollution exposure in a critical developmental window, impairs the ability of microglia to reduce the neuron precursor pool, resulting in an excess of neurons postnatally.

WM maturation was also affected by prenatal exposure to air pollution. Myelination, which is the process of coating WM axons in a fatty, protective sheath called myelin, was shown to be impacted in several studies. Both male-specific hypermyelination of the cerebellum (Klocke et al., 2018b), and hypermyelination of the CC in both sexes was evidenced histologically (Klocke et al., 2018a, Klocke et al., 2017). Interestingly, Klocke et al researched prenatal exposure and found increased CC area and hypermyelination, and Allen et al researched postnatal exposure and found decreased CC area and hypomyelination (Allen et al., 2017). This implies that besides being sex and region-specific, these impacts are also timing specific, indicating that prenatal vulnerability to air pollution exposure is

specific to certain time windows of pregnancy. It strengthens the evidence base for the impacts of air pollution exposure on myelination, as both pre- and postnatal exposure to air pollution affect myelination.

In summary, several animal studies found impacts of prenatal exposure to air pollution on early life neurodevelopment in the form of effects on morphology, WM microstructure, and cell damage. Effects on the size of the CC in both directions were found in animal models, whereas in humans the CC was smaller due to air pollution exposure. Peterson et al (2022) also found greater diffusivity in the anterior CC, which may be the result of decreased myelination. In mice, both hyper- and hypomyelination have been histologically evidenced in the CC (Klocke et al., 2018b, Allen et al., 2017, Klocke et al., 2017). No effects on ventricles were discovered in any of the studies on humans, whereas several animal studies found increased and decreased size of the ventricles as a consequence of prenatal exposure to air pollution, with stronger effects in females (Klocke et al., 2018a, Patten et al., 2020, Klocke et al., 2017).

1.3.4 Sex-specificity

Sex-specificity of results was evidenced less frequently in human studies compared with animal studies. Both studies conducted by Peterson et al (2022, 2015) found a stronger effect of PAH on female brains and of PM_{2.5} on male brains. In the 2015 study, prenatal PAH exposure was more strongly associated with WM measures in girls, though this was driven by relatively few subjects. In the 2022 study, prenatal PM_{2.5} exposure was associated with cortical thickening in boys and thinning in girls, and with increased volumes in the dorsal convexity and smaller volumes in the left hemisphere posterior mesial and lateral surfaces in boys, and PAH was associated with smaller inferior parietal volumes. When examining DTI measures, PM_{2.5} was associated more strongly with FA in male children and PAH with FA in female children. None of the other human studies found evidence of a sex-specific effect.

In mice, there is some evidence of a male-specific effect of prenatal exposure to PM on microglial activation and astrogliosis (Allen et al., 2017, Allen et al., 2014, Bolton et al., 2017, Morris-Schaffer et al., 2019). However, impacts on both increased and decreased ventricle size was more pronounced in females, opposing this view (Klocke et al., 2018a, Klocke et al., 2017, Patten et al., 2020). This conflicting body of evidence suggests that it is currently unclear whether a sex-specific neurodevelopmental vulnerability to prenatal air pollution exposure exists.

1.3.5 Periods of susceptibility to air pollution

There is some evidence that there are specific gestational timeframes in which vulnerability to air pollution exposure is greater. A study examining impacts on adverse birth outcomes identified the

third trimester as a period of vulnerability to prenatal PM_{2.5} exposure (Yuan et al., 2020). Neurodevelopmentally, Allen et al (2017) pointed towards the third trimester as a window of vulnerability in mice, however, this period is difficult to compare to humans as the neurodevelopmental period that is equivalent to the third trimester in humans takes places postnatally in mice. Higher residential concentrations of PM_{2.5} during the third trimester were associated with smaller CC volume in 8 – 12 year olds, though this finding did not survive correction for multiple comparisons (Mortamais et al., 2019). Binter et al (2022) identified pregnancy as a period of vulnerability to PM_{2.5} and its effects on WM microstructure as assessed by MRI in childhood, though this study did not investigate trimesters separately. When investigating periods of susceptibility to air pollution of brain volumes, the pregnancy period did not survive correction for multiple comparisons. Thus, there is some evidence that the third trimester is a period of particular susceptibility to the impacts of air pollution exposure on neurodevelopment, but further research is required to state this conclusively.

CHAPTER 2 - DATA DESCRIPTION AND METHODS

This chapter describes the methodology for the studies presented in this thesis. An overview is provided of MRI data collection and processing in the evaluation of Preterm Imaging Study (ePrime) and developing Human Connectome Project (dHCP) cohorts. The air pollution model used, data processing, and statistical analysis techniques employed in this thesis are described here. I was not involved in the development of the exposure model, recruitment of subjects, image acquisition, or image processing.

2.1 Cohort overview

2.1.1 The developing Human Connectome Project (dHCP)

The studies in Chapters 3 and 4 were based on an existing dataset from a sample of neonates participating in the developing Human Connectome Project (dHCP, <http://www.developingconnectome.org/>). The cohort was recruited in Greater London, UK, and written informed consent was obtained from parents. The principal inclusion criteria of the neonatal dHCP were infants born between 23 – 44 weeks gestational age (GA), estimated from the mothers last menstrual period and where possible confirmed by early ultrasound scanning. Participants were excluded if they had any contraindication to MRI, such as metallic implants, or if language difficulties prevented proper communication about the trial and consent process (<http://www.developingconnectome.org/study-inclusion-and-exclusion-criteria/>). The subjects were born between the years 2015 to 2020 and were scanned in the neonatal period. A total of 782 infants were included in the dHCP project at the time of this thesis (367 male, 415 female).

MRI data were acquired on a Philips 3T (Philips Medical Systems) magnetic resonance system using a 32-channel receive coil. Imaging was performed in the neonatal period for each of the 782 infants. Fetal scans as well as follow-up neurodevelopmental assessment between 17 and 24 months was acquired, but for the purposes of this thesis only the neonatal MRI data and details related to it were considered.

The index of multiple deprivation (IMD) was calculated from postcode at birth for all infants in the ePrime cohort using an online tool (<https://tools.npeu.ox.ac.uk/imd/>). This tool uses socioeconomic data from the 2010 census, which matches the time period in which the subjects in the ePrime cohort were born. A different tool was used to calculate IMD for the dHCP cohort, as it was updated and uses data from 2019 (<https://www.fscbiodiversity.uk/imd/>) which more closely matches the period in which the subjects in the dHCP cohort were born. IMD is a composite measure of socioeconomic status in England, and it encompasses factors such as income, employment, education, health, and crime,

and will be expressed in quintiles throughout this thesis (<https://opendatacommunities.org/data/societal-wellbeing/imd/indices>).

2.1.2 The evaluation of Preterm Imaging Study (ePrime)

The study in Chapter 5 was based on an existing dataset from the Evaluation of Preterm Imaging Study (ePrime; European Clinical Trials Database: EudraCT 2009-011602-42; NCT01049594) (Edwards et al., 2018). The cohort was recruited from neonatal units in 14 hospitals within the North and Southwest London Perinatal Network in Greater London, UK. Participants were recruited at birth in 2010 – 2013 and were included in the ePrime cohort if born before 33 weeks GA, their mother was over 16 years old and not a hospital inpatient. Subjects were excluded if they had major congenital malformation, had prior MRI taken, care in a centre where preterm MRI was routine, metallic implants, parents unable to speak English, or were subject to child protection proceedings. Written informed consent was obtained from the participant's carers. A total of 511 infants took part in the study, and 510 subjects remained after one withdrawal (253 male, 247 female).

MRI data from each infant was acquired on a Philips 3T (Philips Medical Systems) magnetic resonance system using an 8-channel phased array head coil. Imaging was performed at term-equivalent age (38 – 44 weeks GA) for 507 subjects. Clinical characteristics of the baby, such as birthweight, GA at birth, time spent on ventilation, and time spent on total parenteral nutrition were also collected. The subject's parents were also asked to complete several questionnaires. For the purposes of this thesis only the MRI data and details related to it were considered.

2.2 Imaging

2.2.1 Developing Human Connectome Project MRI protocol

All infants were scanned in the neonatal period during natural sleep without sedation following feeding and swaddling using a dedicated protocol (Hughes et al., 2017), including a bespoke transport system, positioning device and a customized 32-channel receive coil with a custom-made acoustic hood. The bespoke imaging system allowed subjects to be placed in a standardised pose which fixed the imaging geometry for each subject, and the position could only be altered in head-foot direction before the examination. The field of view was sufficient to include 95% of late-term neonates, informed by a biometric analysis of data from 91 term-born infants (Hughes et al., 2017). All scans were supervised by a neonatal nurse and/or paediatrician who monitored heart rate, oxygen saturation and temperature throughout the scan.

T2-weighted, T1-weighted, and diffusion-weighted MR images were acquired using the dHCP protocol optimised for neonatal imaging (Edwards et al., 2022). T2-weighted images were obtained using a

turbo spin echo (TSE) sequence, acquired in two stacks of 2D slices (in sagittal and axial planes), using parameters: TR = 12000 ms, TE = 156 ms, with SENSE factor 2.11 (axial) and 2.58 (sagittal) with overlapping slices (resolution $0.8 \times 0.8 \times 1.6$ mm).

High angular resolution diffusion MRI was acquired using parameters TR = 3800 ms, TE = 90 ms, SENSE factor = 1.2, multiband factor = 4, resolution $1.5 \times 1.5 \times 3.0$ mm with 1.5 mm slice overlap. Diffusion gradient encoding included images collected on four different shells at $b = 0$ s/mm² (20 repeats), $b = 400$ s/mm² (64 directions), $b = 1000$ s/mm² (88 directions), $b = 2600$ s/mm² (128 directions), and images were reconstructed to a final resolution of $1.5 \times 1.5 \times 1.5$ mm³ (Hutter et al., 2018). All images were reviewed by a perinatal neuroradiologist.

Image processing

Structural MRI data were processed using the dHCP structural pipeline. Motion-correction and slice-to-volume image reconstruction were carried out retrospectively using a dedicated algorithm to obtain 0.8 mm³ isotropic T2-weighted images (Cordero-Grande et al., 2018, Kuklisova-Murgasova et al., 2012). In order to register the images, labelled atlases developed by Gousias et al (2012) were registered to each subject in a multi-channel approach, using the original intensity T2-weighted images and GM probability maps (Makropoulos et al., 2018). The GM probability maps are developed using an initial tissue segmentation developed with the aid of a preterm probabilistic tissue atlas that is registered to each subject (Serag et al., 2012). Since preterm subjects typically have higher CSF volume compared with term-born subjects, the CSF intensities were eroded to perform registration and initial tissue segmentation. The GM probability maps are then registered together with the intensity T2-weighted images in a multi-channel registration of the labelled atlases.

The segmentation process uses multiple labelled atlases which are registered to the target image (Makropoulos et al., 2018, Makropoulos et al., 2016, Makropoulos et al., 2014). These are used as a spatial prior along with an intensity model of the image in an Expectation-Maximization algorithm. This resulted in the following tissue types; WM, cortical GM, ventricles, extracerebral CSF, cerebellum, hippocampus & amygdala, deep GM, and brainstem.

Diffusion MRI data were pre-processed according to the dHCP's diffusion MRI pre-processing pipeline (Bastiani et al., 2019). This includes corrections for motion and distortion (Andersson and Sotiropoulos, 2016). Fibre orientations were modelled (up to three per voxel) with FSL's bedpost (FMRIB Software Library), using a model-based deconvolution against a zeppelin response kernel, to accommodate for the low anisotropy inherent in data from this age group (Hernández et al., 2013, Bastiani et al., 2019, Sotiropoulos et al., 2016).

Standardised tractography protocols were used to map WM tracts in each subject. The protocols consist of a set of masks defined in template space that provide rules for the propagation and retention of streamlines. Streamlines are propagated from a seed mask and are included in the tract if they pass through the target mask. Exclusion and stop masks are used to remove and terminate streamlines, respectively. The protocols had been defined for neonatal tractography by Bastiani et al. (2019), manually redrawn in a different 40 post-menstrual week template space (Schuh et al., 2018). This template was used as it has been shown to preserve cortical details better than other atlases that are available for this age group (Schuh et al., 2018).

To run tractography, the protocol masks were transformed from template space to the subject's native space, using a non-linear warp field (Avants et al., 2011). Probabilistic tractography was performed in native space, using FSL's probtrackx (Behrens et al., 2007), and the results directly resampled to standard space. The resultant spatial maps were used to generate population atlases for each tract. Normalised path density distributions were thresholded at 0.1% for each subject, and binarised. These binary masks were averaged across subjects to generate the population averages, which describe the proportion of subjects for which a given tract is present at a given voxel.

Microstructural metrics were derived from both the DT model and the NODDI model. FSL's dtifit tool was used to fit the DT model on the $b=1000$ s/mm² shell. FA and MD were calculated from the DT in each voxel. The NODDI model was also fit to the data with a Watson distribution (Zhang et al., 2012), using the CUDA diffusion imaging toolbox (cuDIMOT) (Hernandez-Fernandez et al., 2019). This provided estimates of the voxel-wise fibre orientation dispersion, intra-neurite volume fraction and isotropic compartment volume fraction.

The population atlases described above were registered to the subjects' native space and binarised above a threshold of 30% to generate a subject-specific region of interest (ROI) for each tract. These microstructural measures were summarised for each subject in each of the tracts considered and the median values of the microstructural measures were recorded within the ROIs.

2.2.2 The evaluation of Preterm Imaging Study (ePrime) MRI protocol

MRI data for each infant was acquired at term-equivalent age on a Philips 3T (Philips Medical Systems) magnetic resonance system using an 8-channel phased array head coil. 445 infants (87%) were sedated with oral chloral hydrate before undergoing MRI, and an expert reviewer inspected T2-weighted images for motion artifacts, and subjects with evidence of motion were excluded (Edwards et al., 2018).

T2-weighted fast-spin echo MRI were acquired with TR = 14.7s, TE = 160 ms, flip angle = 90°, FOV = 220mm, with 1-mm overlapping slices (resolution 0.86 x 0.86 x 2 mm). T1-weighted MRI was acquired with TR = 17 ms, TE = 4.6ms, flip angle = 13°, FOV = 210 mm (resolution 0.82 x 0.82 x 0.8 mm). Single-shot echo-planar diffusion weighted imaging was acquired in the transverse plane in 32 non-collinear directions with a single b0 volume with TR = 8s, TE = 49ms, slice thickness = 2mm, FOV = 224mm, b-value = 750s/mm², and SENSE = 2 (resolution 1.75 x 1.75 x 2mm).

Image processing

The structural images were registered, and morphometric analysis was performed using FMRIB Software Library (FSL 5.0.1, www.fmrib.ox.ac.uk/fsl). T2 images were registered to a gestation appropriate template, which was created by combining cortical GM parcellations from the University of North Carolina infant brain atlas (Shi et al., 2011) and subcortical GM parcellations from the Gousias-Makropoulos atlas (Makropoulos et al., 2016, Makropoulos et al., 2014).

The segmentation process followed the same pipeline by Makropoulos et al described in the dHCP section above (Makropoulos et al., 2018, Makropoulos et al., 2016, Makropoulos et al., 2014). The resulting images were segmented into the following tissue types: cortical GM, WM, cerebellum, ventricles, deep GM, brainstem, amygdala, thalamus, and hippocampus.

Diffusion MR images affected by motion were excluded, and images were corrected for eddy current artefacts using *eddy correct* (Andersson et al., 2016), and the tensor model was fitted using FSL's *dtifit* (FMRIB; <http://fsl.fmrib.ox.ac.uk>). Tract-specific analysis (TSA) was employed to obtain diffusion MRI measures for WM tracts (Pecheva et al., 2017). After registration to a study-specific template (Zhang et al., 2006), diffusion data were projected onto skeleton models of individual WM tracts using deterministic tractography for each subject (Mori et al., 1999). Tractography for the whole brain was obtained from a WM mask with FA threshold of 0.1 (Wakana et al., 2007). The projection used the maximum FA value along unit normal from the centre of the tract to the boundary in order to account for residual misalignment and inter-subject correspondence (Smith et al., 2006).

2.3 Air pollution modelling

Prenatal exposure to ambient air pollution for both the ePrime and dHCP cohort was modelled using the London Air Pollution Toolkit (Beevers et al., 2012). The Air Pollution Toolkit is the result of coupling the Community Multiscale Air Quality (CMAQ) modelling system (Byun and Ching, 1999) with the Atmospheric Dispersion Modelling System (ADMS) Roads model (CERC, 2006). In the CMAQ component of the model, a combination of the European Monitoring and Evaluation Programme (EMEP), the European pollutant Release and Transfer Register (EPETR), the National Atmospheric Emissions Inventory (NAEI) (Murrells et al., 2010) and the London Atmospheric Emissions Inventory

(LAEI) were used to derive anthropogenic and natural emissions. Normalised traffic counts taken from 37 automatic sites in London were used to create hourly emissions for road traffic, and biogenic emissions were estimated using Coordination of Information on the Environment (CORINE) land cover data combined with meteorological data from Weather Research and Forecasting (Sanderson, 2002, Guenther et al., 1995). NO and NO₂ emissions from road transport and primary exhaust were taken from the NAEI and the LAEI, respectively. Large industrial plants in Europe and the UK, and gas combustion from commercial and domestic sources in London, were also fed into the model. The ADMS component of the model was used to describe dispersion and dilution of emissions away from roadways using meteorological inputs for each hour of the year, taking into account road geography such as street canyons and motorways. Chemistry near roads was simulated using a model described by Carslaw and Beevers (Carslaw and Beevers, 2005).

The toolkit is capable of modelling over one million individual sources of pollution with different source characteristics in a grid resolution of 20 x 20 metres. Pollution concentrations were modelled at postcode level, and the value used was dependent on one or several centroids within the postcode. The location of the centroid depended on the environment of the postcode, whether there are green spaces within it, it is fully built up, and its surrounding road type. More details on the Air Pollution Toolkit and its quality assurance and quality control can be found at: <https://www.healtheffects.org/system/files/Kelly-LEZ-AppendixB.pdf> (Kelly et al., 2011).

Maternal residence was used as the subjects' location for the entire duration of pregnancy. Air pollution exposure was modelled at postcode level. Postcode units in the UK are very small, covering 15 households on average, and there are over 150000 postcode units in Greater London. The period between estimated date of conception and date of birth was used to obtain an average exposure over the gestational period. Trimesters were separated into time periods of 13 weeks and 2 days each (total of 93 days). Subjects' exposure to air pollution was modelled based on their GA, i.e., different weeks of gestation were modelled independently so as not to introduce exposure misclassification.

The modelled pollutants were PM_{2.5}, PM₁₀, and NO₂. These pollutants were chosen as prenatal exposure to them has been implicated in various studies as affecting neurodevelopmental performance in infancy and childhood as assessed by cognitive performance tests (Rivas et al., 2019, Sentís et al., 2017b, Kim et al., 2014). Further, studies using animal models have related prenatal exposure to TRAP and UFP to changes in myelination and brain morphology, including increased inflammation, in the neonatal and postnatal brain (Klocke et al., 2018a, Klocke et al., 2018b, Bolton et al., 2017). NO₂ best represents air pollution exposure heterogeneity from traffic sources. PM_{2.5} and coarse PM were also related to thinner cortices in a previous study (Guxens et al., 2018). Coarse PM

was not included in the analysis due to its high uncertainty which is the result of subtracting two values with inherent uncertainty, resulting in a small value with high uncertainty ranges. O₃ and NO_x were not included in the analysis due to lack of evidence associating these pollutants with neurodevelopment, brain morphology, or WM microstructure in the neonatal period. Further evidence relating prenatal air pollution exposure to impacts on the brain emerged after the pollutants were selected, and this evidence was described in detail in Section 1.3.

Temporal adjustment was applied to annual mean model estimates using aggregated measurements from the London Air Quality Network (www.londonair.org.uk) using the method described in Walton et al (Walton et al., 2016). Annual averages were transformed to acute exposure estimates by scaling annual mean concentrations with a factor for each pollutant for periods prior to imaging. This factor is determined by the ratio between concentrations measured by local monitoring sites in the prior period and the annual mean of concentrations measured at those sites.

The model was run separately for each cohort, with each subjects' exposure to air pollution based on their GA at birth. For each week of GA one model run was performed per cohort. For example, if a subject was born at 38 weeks + 5 days gestation, this was rounded up to 39 weeks and the subject was included in a model run for 39 weeks. Air pollution concentrations for each trimester were modelled separately in one model run for the entire cohort, as trimester time periods are uniform between subjects. The model output was one average value over the time period for each pollutant per subject. A number of subjects lived outside of Greater London and were therefore outside of the geographical range of the model. These subjects were excluded from the analysis as no pollution data were available.

2.4 Data processing and analysis

All data were visualised to observe general distributions and ensure values are sensible. Missing MRI data and modelling data could not be imputed, and subjects missing these data were removed. Air pollution exposures were generally log-normally distributed; hence the descriptive statistics are primarily given as median and range. All statistical tests and analysis were performed using R (Multiple versions, <https://www.r-project.org/>). Several of the volumetric and diffusion data in both cohorts were non-normally distributed, as assessed by the Shapiro-Wilk test (Shapiro and Wilk, 1965), therefore the descriptive statistics here were also primarily given as median and range. The Benjamini-Hochberg method was used to correct for multiple comparisons. Results with Benjamini-Hochberg corrected p-values (referred to as q-values throughout the thesis) at a threshold of $q < 0.05$ were considered to be significant. Linear regressions were performed to assess the relationships between exposure to air pollution and different MRI metrics, and an example of a linear regression script is

included

at:

https://github.com/brendanbos/Thesis_Code/blob/master/Simple_Linear_Regression_Script.R. All regressions were performed as single pollutant linear regressions, due to strong correlation between pollutants, as assessed by Spearman's rank correlation coefficient. WM microstructure metrics in the left and right hemisphere were assessed separately, due to evidence of differential impacts of prenatal exposure to air pollution on the left and right hemisphere in childhood (Lubczyńska et al., 2020).

CCA was performed in order to include multiple strongly correlated and colinear pollution and MRI variables (using the CCA package in R (<https://cran.r-project.org/web/packages/CCA/CCA.pdf>, version 1.2.1, (González et al., 2008)). CCA is a method of correlating linear relationships between two sets of variables first developed by Hotelling in 1936 (Hotelling, 1936). The technique tries to solve the problem of finding basis vectors for two sets of variables in a way that maximises the correlation between the projections of the variables onto the basis vectors (Hardoon et al., 2003). Any analysis of correlation is dependent on the coordinate system in which the variables are placed, as even very strongly correlated sets of multidimensional variables described in different coordinate systems might not result in finding this correlation. CCA creates linear transformations of each set of variables to pair the sets of variables and maximise the correlation between the corresponding coordinates (Zhuang et al., 2020). Due to non-normality of parts of the air pollution and structural and diffusion MRI data, spearman's rank correlation coefficient was used to estimate canonical correlations between corresponding pairs of sets of variables. The canonical correlations between corresponding pairs indicate how the strength of the direction of the variation of dependent variables (in this case the clinical variables) and the independent variables (in this case air pollution concentrations) are related (Yu et al., 2019). Each set of canonical variates contribute to a mode of the CCA. Since the CCA model has no noise component, measures to remove confounding were applied as a step prior to the CCA. A regression model was created which assessed the variation in the data explained by the confounders, and the resulting residuals were used in the CCA with potential confounding information removed (Wang et al., 2020). For each mode, a permutation testing procedure to test the significance of the corresponding canonical correlation was used as a validation step (Nichols and Holmes, 2002, Smith et al., 2015). The rows of both inputs (brain variable and pollution variables) were permuted 1000 times, and the CCA was re-run and canonical correlations re-computed after each permutation. This formed a null distribution of canonical correlations which could then be compared to observed canonical correlations. A mode of the resulting CCA was only considered significant if the Spearman's r was greater than the 95th percentile of random permutation tests. After finding a significant mode, the correlation of the original variables to the CCA mode was assessed. This was done by correlating the multivariate transformation of the MRI variables (volumes or tract metrics) with the original

univariate MRI variables, and by correlating the multivariate transformation of the air pollution variables with the original univariate air pollution variables, allowing an assessment of the contribution of the air pollution and MRI variables to a given mode. To summarise, CCA is a multivariate statistical method that detects and quantifies associations between two sets of variables by looking for a weighted linear composite for each variate (sets of dependent and independent variables) to maximize the overlap in their distributions (Krzanowski, 1988, Härdle and Simar, 2015). Each pair of canonical variates that jointly share variance in both variable sets is known as a mode. CCA is applicable in instances where linear regression is used, whilst simultaneously addressing multicollinearity. An example of a full analysis done using CCA in my thesis can be found at: https://github.com/brendanbos/Thesis_Code/blob/master/CCA_Example_Script.R.

In secondary analyses, seasons were defined as meteorological seasons, starting on the first day of December, March, June, and September, for winter, spring, summer, and autumn, respectively. Volumetric data in both the ePrime and dHCP cohorts were adjusted for available metrics of head size (TBV and ICV, respectively), and relative volumes were used in the analysis. This adjustment was done as neonatal head size (and consequently brain volume) can differ significantly between subjects. Subjects with evidence of major lesions were excluded from both cohorts.

Maps of the residential distribution of the subjects in both the ePrime and dHCP cohorts in Greater London were created using shapefiles of the lower super output areas (LSOA) obtained from the London datastore (<https://data.london.gov.uk/>). The subjects' distribution was not shown at postcode level to maintain anonymity.

CHAPTER 3 - IMPACTS OF PRENATAL EXPOSURE TO AIR POLLUTION ON WHITE MATTER MICROSTRUCTURE IN THE HEALTHY NEONATAL BRAIN

3.1 Introduction

The foetal brain undergoes rapid development during pregnancy. In the second and third trimester, WM pathways develop and form the basis of structural connectivity in the brain which underlie cognitive, behavioural, and motor abilities (Johnson, 2001). Abnormal WM development has been linked to several pathologies, including autism spectrum disorder, attention deficit hyperactivity disorder, and other neurodevelopmental disorders (Ameis et al., 2016, Dean et al., 2016, Fitzsimmons et al., 2013).

Diffusion MRI is used frequently to assess tissue microstructure in the neonatal brain and enables measures such as MD and FA to be determined (Basser et al., 1994). While these measures are sensitive to microstructural changes during development, they lack specificity (Beaulieu, 2009). Neurite orientation dispersion and density imaging (NODDI) is a biophysical model that provides quantitative measures that correlate to tissue microstructure with greater specificity (Zhang et al., 2012). For instance, NDI estimates correlate more strongly with both optical myelin staining intensity and stereological estimation of neurite density than traditional DTI markers (Jespersen et al., 2010). Further, NODDI is able to represent orientation dispersion more clearly than the DT model (Schilling et al., 2018, Grussu et al., 2017).

DTI metrics exhibit specific changes through the late second and the third trimester, which can be linked to underlying developmental processes. Diffusivities decrease rapidly with GA across the WM, with regional differences of the rate and mean (Pieterman et al., 2015, Partridge et al., 2004). Conversely, FA increases across the WM, and these processes are reflective of the development of the myelin sheath, which imposes tortuosity on the water motion. Axial diffusivity generally decreases more slowly than radial diffusivity, which is further driven by the restrictions to water motion that occur due to the development of the myelin sheath (Beaulieu, 2002). Another factor is the decreasing amount of total water present as myelinogenesis advances.

F_{iso} was found to be increased in adult cohorts with autism spectrum disorder (ASD) and multiple sclerosis (Andica et al., 2021, Johnson et al., 2021), and no difference was found between neonates with congenital heart disease compared with healthy controls (Karmacharya et al., 2018) (both NODDI and DTI are described in more detail in Sections 1.2.5 and 1.2.6). NODDI has not previously been used to assess the impacts of prenatal air pollution exposure on WM microstructure.

Prenatal exposure to air pollution has been shown to affect WM microstructure in children and preadolescents. Two previous studies have examined the impact of prenatal exposure to air pollution on WM microstructure in school age children using MRI, as outlined in detail in Section 1.3.2, and results have shown adverse findings. Briefly, Lubczyńska et al found that in their single pollutant model higher exposures to several air pollutants during pregnancy were associated with lower global FA and higher global MD ($n = 2954$) (Lubczyńska et al., 2020). The multipollutant model showed mixed findings of prenatal exposure to $PM_{2.5}$ and PAH on global FA, with a negative and positive association, respectively. No associations were found between pollutants and FA in any single WM tract. The latest study was conducted by Peterson et al (2022). In this study prenatal exposure to $PM_{2.5}$ and PAH were associated with higher FA values in the basal ganglia, thalamus, and the anterior cingulate gyrus ($n = 332$). These results were sex-specific, with $PM_{2.5}$ associations being stronger in males and PAH associations stronger in females. Prenatal exposure to $PM_{2.5}$ and PAH was also related to lower and higher average diffusivity coefficient in several brain regions.

In this chapter I aimed to examine the relationship between in utero exposure to air pollutants and neonatal brain development using diffusion MRI data acquired shortly after birth in a healthy, term-born, cohort. I hypothesised that prenatal exposure to air pollution is associated with altered neonatal WM microstructure in term-born neonates. I assessed the relationship between NO_2 , $PM_{2.5}$, and PM_{10} exposure during gestation and WM microstructure employing DTI measures, MD, and FA, and NODDI measures, ODI, F_{iso} , and NDI, in a large cohort of healthy term-born neonates. I hypothesised that prenatal exposure to NO_2 , $PM_{2.5}$, and PM_{10} would disrupt WM microstructural development, and therefore be related to a decrease in ODI, NDI and FA, and an increase in MD and F_{iso} .

3.2. Methods

3.2.1 Subjects

This study is based on a sample of neonates participating in the Developing Human Connectome Project (dHCP, <http://www.developingconnectome.org/>), described in detail in Section 2.1.1. The dHCP is a London, UK, based cohort of neonatal MRI scans taken in the days following delivery. Research Ethics Committee approval was granted for this project (14/LO/1169) and written informed consent was obtained from parents. 490 infants were included in the dHCP project at the time of this study. Infants were excluded if their GA was <37 weeks ($n = 82$), their post-menstrual age at scan >44 weeks ($n = 0$), or there was evidence of major focal lesions on MRI ($n = 12$). In cases of multiple pregnancies ($n = 5$), only one infant of the twin pair was included. Subjects with smoking parents were excluded ($n = 1$). In addition, 141 infants were excluded as the mother's residential address was outside of the air pollution model domain. The final sample consisted of 249 infants. IMD at postcode

resolution was used to describe socioeconomic status for all subjects. The processing of diffusion MRI data took place earlier than for the structural data, which is why fewer subject data are available in this study.

3.2.2 MRI acquisition

Diffusion MRI acquisition of the dHCP cohort is described in detail in the methodology chapter in Section 2.2.1.

3.2.3 Image processing

Processing of the diffusion MRI data of the dHCP cohort is described in detail in the methodology chapter in Section 2.2.1. Image processing resulted in two DTI and three NODDI metrics of WM microstructure for each tract assessed per subject, namely MD and FA, and NDI, ODI, and F_{iso} , respectively (Bastiani et al., 2019).

The following tracts were delineated: anterior commissure, arcuate fasciculus, acoustic radiation, anterior thalamic radiations, dorsal cingulum, peri-genual cingulum tract, temporal cingulum, corticospinal tract, arcuate fasciculus, forceps major, forceps minor, fornix, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, middle cerebellar peduncle, middle longitudinal fasciculus, optic radiation, superior longitudinal fasciculi (1,2,3), superior thalamic radiation, uncinate fasciculus, and the vertical occipital fasciculus (Warrington et al., 2020, Bastiani et al., 2019).

3.2.4 Air pollution modelling

Air pollution was modelled as described in detail in the methodology chapter in Section 2.3. Air pollution modelling resulted in three estimates of air pollution exposure per subject, one value for $PM_{2.5}$, PM_{10} , and NO_2 each.

3.2.5 Statistical analysis

A correlogram between pollutants within each exposure window was calculated using Spearman's R . The relationship between prenatal pollution exposure and WM microstructure metrics, ODI and NDI, was first explored using single pollutant linear regression analysis, adjusting for postmenstrual age (PMA) at scan, GA at birth, sex, and IMD. Results were FDR corrected using Benjamini-Hochberg false discovery rate method (Benjamini and Hochberg, 1995).

To account for potential confounding factors relevant to neonatal diffusion MRI, ODI and NDI were adjusted for PMA at scan, GA at birth, and sex. Further, to account for socioeconomic status, the residuals of pollutant variables were determined and adjusted for IMD as it has been shown to be correlated with pollution exposure (Hajat et al., 2015). For each CCA mode, I used a permutation testing procedure to test the significance of the corresponding canonical correlation as a validation

step. To perform this, the rows of both inputs (brain variable and pollution variables) were permuted 1000 times, CCA was re-run and canonical correlations re-computed after each permutation. A mode of the resulting CCA was only considered significant if the Spearman's r was greater than the 95th percentile of random permutation tests (Yu et al., 2019). Since none of the modes passed the 95th percentile of random permutation tests, no further analysis steps were taken.

A secondary analysis was performed to examine the impact of trimester specific exposures on neonatal WM microstructure. All metrics of WM microstructure were adjusted for ICV, PMA at scan, GA at birth, sex, and IMD in a single pollutant linear regression analysis. Further, trimester specific air pollution exposure estimates were adjusted for seasonality due to the disproportionate effect of seasonality on shorter exposure periods. A CCA was then performed for each trimester as outlined above. Sex-specific associations were not investigated in a CCA, as separated into male and female, the number of subjects was lower than the number of variables. An interaction term between sex and pollutant was introduced into the linear regression analysis in order to assess the differential impact of pollution exposure on different sexes.

3.3. Results

3.3.1 Subjects

The subject group comprised 249 infants (112 male) born at a median (range) GA of 40.14 (37.14-42.14) weeks and imaged at 40.86 (37.43 – 44.43) weeks PMA (Table 1). The median IMD for the study group was 4 (1-5). Male subjects age at birth and age at scan did not differ significantly from female subjects (Shapiro-wilk, $p > 0.05$) and were scanned at a median age of 41.14 weeks, whereas female subjects were scanned at a median date of 40.71 weeks (Table 3.1). Subjects' residential distribution in greater London is shown in Figure 3.1. This map shows the subject distribution per Lower Super Output Area (LSOA), not per postcode, to preserve anonymity. Subjects were concentrated around the Boroughs of Southwark and Lambeth, close to St. Thomas' Hospital where the imaging was performed, and very few subjects resided in north and west London.

Table 3.1: Distribution of age at MRI, age at birth, sex, and index of multiple deprivation of the dHCP subjects.

	Male	Female	Total
Subjects (n, %)	112 (45%)	137 (55%)	249
Age at MRI, weeks (median, range)	41.14 (37.43 – 44.43)	40.71 (37.71 – 44.14)	40.86 (37.43 – 44.43)

Age at birth, weeks (median, range)	40.29 (37.29 – 42.14)	40 (37.14 – 42)	40.14 (37.14 – 42.14)
IMD quintile (median, range)	4 (1 – 5)	4 (1 – 5)	4 (1 – 5)

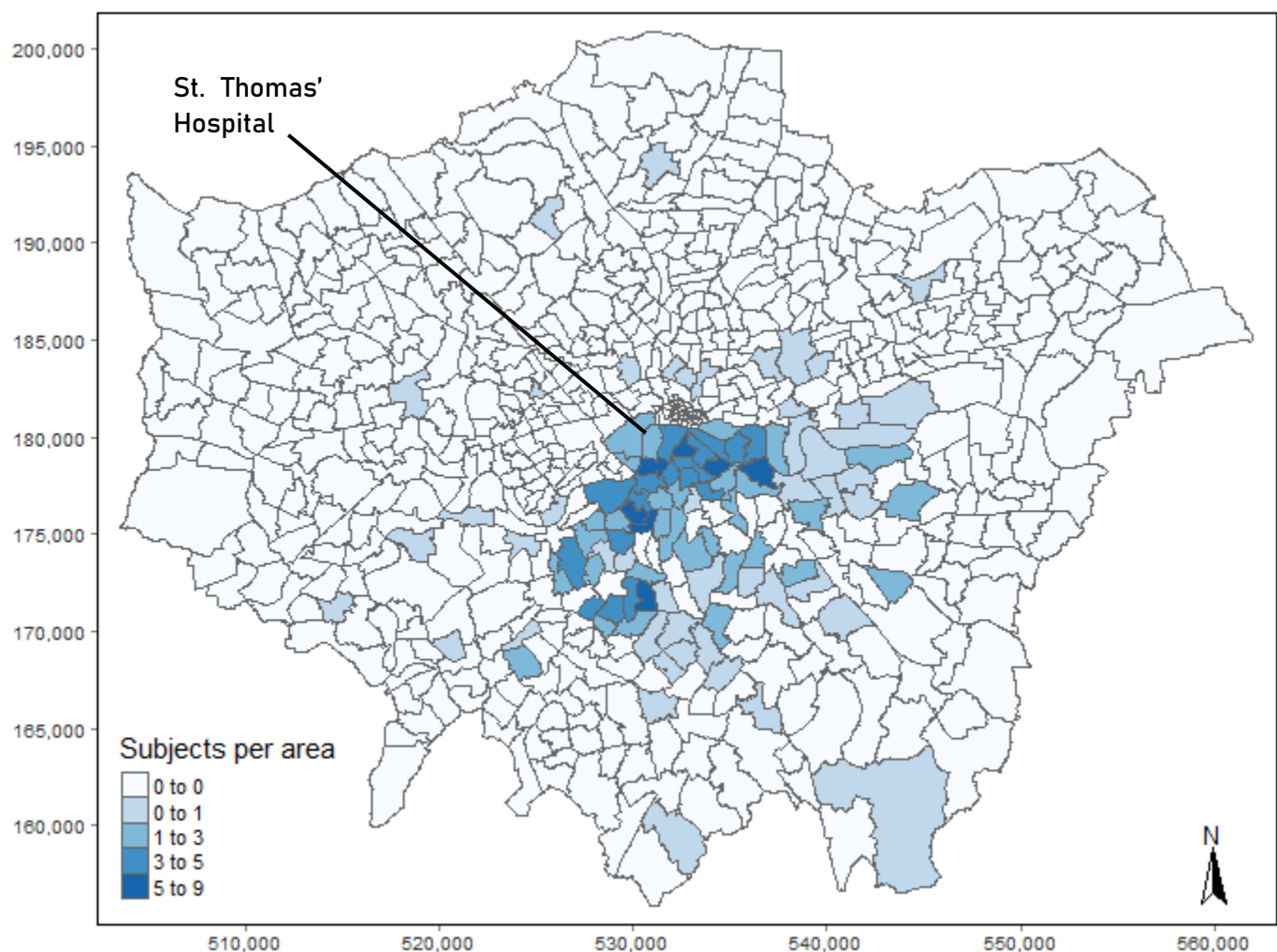


Figure 3.1: Residential subject distribution of the developing human connectome project (dHCP) per lower super output area (LSOA) in Greater London. The subjects were scanned at St. Thomas' Hospital in central London, which is indicated on the map.

3.3.2 Air pollution exposure

Descriptive statistics of subjects' pollution exposure are detailed below (Table 2). NO_2 , $\text{PM}_{2.5}$, and PM_{10} were non-normally distributed, summary statistics are therefore presented as median and range. Modelled median PM_{10} exposure was $24.0 \mu\text{g}/\text{m}^3$ over the entire gestational period, $\text{PM}_{2.5}$ exposure was $13.6 \mu\text{g}/\text{m}^3$, and NO_2 was $41.8 \mu\text{g}/\text{m}^3$. The range of exposures varied by pollutant, with a range of $20.8 - 32.2 \mu\text{g}/\text{m}^3$ for PM_{10} , $10.8 - 19.1 \mu\text{g}/\text{m}^3$ for $\text{PM}_{2.5}$, and $28.0 - 68.5 \mu\text{g}/\text{m}^3$ for NO_2 . Trimester

specific median exposures were very similar to exposure over the entire gestational period, however, the range of values tended to be greater.

Table 3.2: Descriptive statistics of modelled pollution exposure for each trimester and the whole pregnancy in $\mu\text{g}/\text{m}^3$ for the subjects from the developing human connectome project (dHCP).

PM₁₀, $\mu\text{g}/\text{m}^3$ (median, range)	
1st trimester of pregnancy	23.0 (16.6 – 36.0)
2nd trimester of pregnancy	23.3 (15.3 – 32.0)
3rd trimester of pregnancy	23.2 (17.5 – 35.4)
Whole pregnancy	24.0 (20.8 – 32.2)
PM_{2.5}, $\mu\text{g}/\text{m}^3$ (median, range)	
1st trimester of pregnancy	13.7 (9.4 – 23.3)
2nd trimester of pregnancy	13.2 (8.8 – 21.3)
3rd trimester of pregnancy	13.4 (9.7 – 22.5)
Whole pregnancy	13.6 (10.8 – 19.1)
NO₂, $\mu\text{g}/\text{m}^3$ (median, range)	
1st trimester of pregnancy	40.3 (23.8 – 61.2)
2nd trimester of pregnancy	40.2 (19.3 – 57.5)
3rd trimester of pregnancy	39.2 (26.9 – 63.6)
Whole pregnancy	41.8 (28.0 – 68.5)

A correlogram of correlation between pollutants for the entire gestational period and for each trimester is shown below (Figure 3.2). Correlations were high (r between 0.62 and 0.94) between all

pollutants, and correlations between PM_{2.5} and PM₁₀ were higher than between PM_{2.5} or PM₁₀ and NO₂.

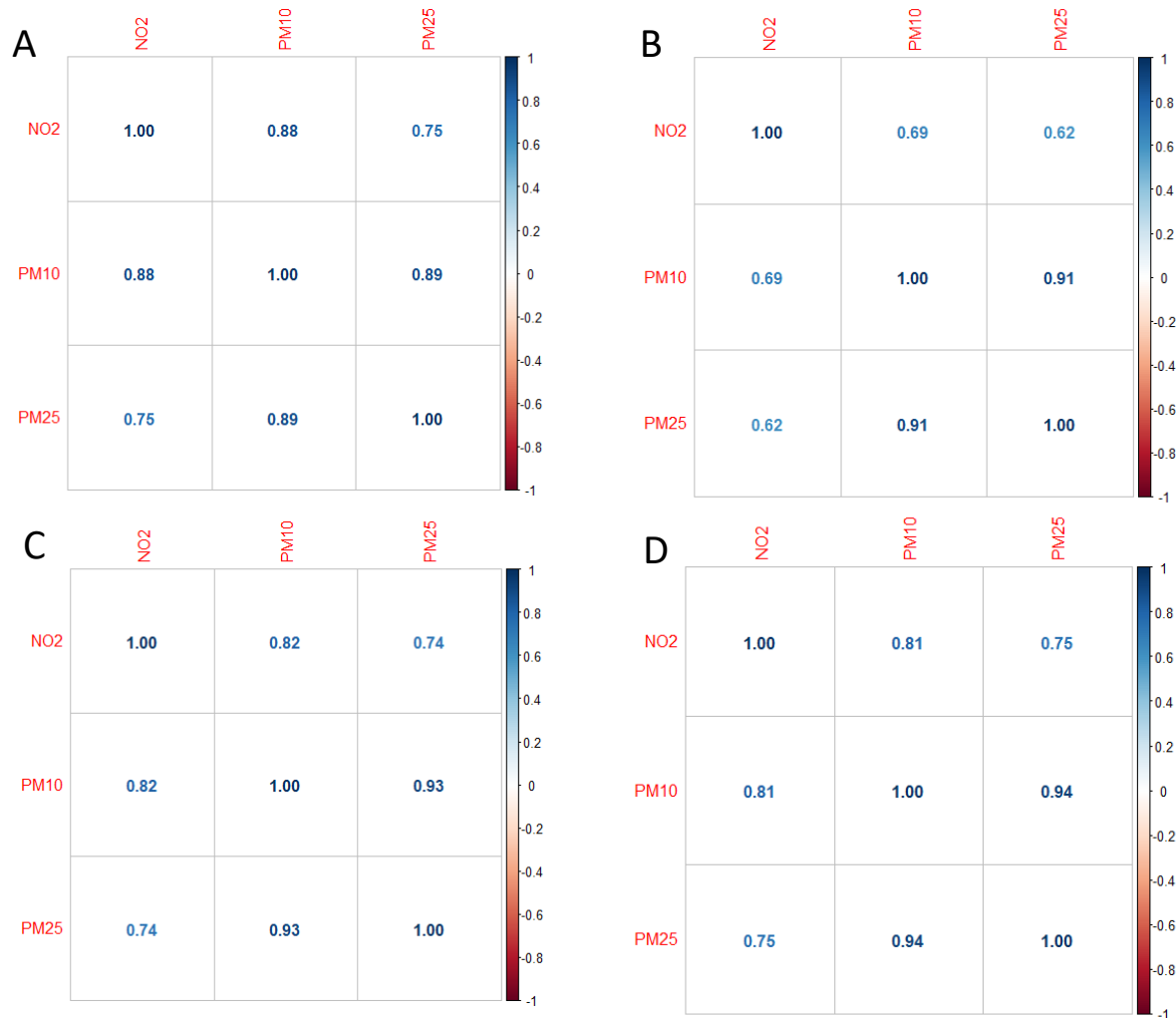


Figure 3.2: Correlogram of modelled pollution exposure for each trimester and the whole pregnancy in $\mu\text{g}/\text{m}^3$ for the subjects from the developing human connectome project (dHCP). (A) pollutant correlation over the entire gestational period; (B) pollutant correlation over the first trimester; (C) pollutant correlation over the second trimester; (D) pollutant correlation over the third trimester.

3.3.3 White matter microstructure

The specific WM tracts that were analysed can be found in Table 3.3. Descriptive statistics of subjects' WM microstructure metrics are detailed in the GitHub repository https://github.com/brendanbos/Thesis_Code/blob/master/Descriptive_data_dHCP_WM_microstructure.docx (Table G4, File = Descriptive_data_dHCP_WM_microstructure.docx). An image of the

tractography results averaged over 80 dHCP subjects at 38-, 40-, 42-, and 44-weeks PMA can be found in the appendix (Figure A1).

Table 3.3: The list of analysed WM tracts, their tract type and bilaterality.

Type	Name	Bilaterality
Projection fibres	Corticospinal tract (cst)	Y
	Acoustic radiation (ar)	Y
	Anterior thalamic radiation (atr)	Y
	Superior thalamic radiation (str)	Y
	Optic radiation (or)	Y
Association fibres	Superior longitudinal fasciculus (slf1, 2, and 3)	Y
	Inferior longitudinal fasciculus (ilf)	Y
	Inferior fronto-occipital fasciculus (ifo)	Y
	Uncinate fasciculus (unc)	Y
	Arcuate fasciculus (af)	Y
	Frontal aslant tract (fa)	Y
	Uncinate fasciculus (uf)	Y
	Vertical occipital fasciculus (vof)	Y
Commissural fibres	Forceps minor (fmi)	N
	Forceps major (fma)	N
	Middle cerebellar peduncle (mcp)	N
	Anterior commissure (ac)	N
Limbic system fibres	Fornix (fx)	Y
	Cingulum subsection: Dorsal (cbd)	Y
	Cingulum subsection: Perigenual (cbp)	Y

	Cingulum subsection: Temporal (cbt)	Y
--	--	---

3.3.4 Single pollutant linear regression results

Table A1 shows the results of the single pollutant linear regression model assessing the relationship between pollution exposure over the entire gestational period and WM microstructure metrics. Air pollutants were statistically significantly related to WM microstructure metrics prior to FDR correction in several instances (38 WM microstructure metrics related to at least one air pollutant, Table 3.4). All three pollutants, NO₂, PM_{2.5}, and PM₁₀, were significantly related to the orientation dispersion index in the anterior commissure, the right anterior thalamic radiation, the right dorsal cingulum, and the right fornix ($p < 0.05$). However, none of the associations survived FDR correction ($q > 0.05$). This was also the case when examining exposure per trimester (Table G1, G2, and G3, $q > 0.05$, https://github.com/brendanbos/Thesis_Code/blob/master/dHCP_dMRI_Trimester_results_SLR.docx). Adding an interaction term between sex and pollutant into the linear regression analysis did not alter the statistical significance of the results.

Table 3.4: Significant single linear regression results prior to false-discovery correction between pollution exposure over the entire gestational period and diffusion MRI measures in all tracts, adjusted for sex, IMD, PMA at scan, and GA at birth. Beta = effect size; CI = Confidence interval (95%); q-value = p-value after FDR correction. WM microstructure metrics are coded as follows: First the type of metric, followed by the tract, and l = left, or r = right hemisphere, respectively. FA = fractional anisotropy; fintra = neurite density index (NDI); fiso = isometric volume fraction; MD = mean diffusivity; OD = orientation dispersion index (ODI). Tract abbreviations: ac = anterior commissure; af = arcuate fasciculus; ar = acoustic radiation; atr = anterior thalamic radiations; cbd = dorsal cingulum; cbp = peri-genual cingulum tract; cbt = temporal cingulum; cst = corticospinal tract; fa = arcuate fasciculus; fma = forceps major; fmi = forceps minor; fx = fornix; ifo = inferior fronto-occipital fasciculus; ilf = inferior longitudinal fasciculus; mcp = middle cerebellar peduncle; mdlf = middle longitudinal fasciculus; or = optic radiation; slf(1,2,3) = superior longitudinal fasciculi; str = superior thalamic radiation; uf = uncinate fasciculus; vof = vertical occipital fasciculus.

WM microstructure metric	Pollutant	<i>beta</i> (in 10 ⁻³)	Std. error (in 10 ⁻³)	Lower CI (in 10 ⁻³)	Upper CI (in 10 ⁻³)	p-value	q-value
FA_af_r	PM _{2.5}	-1.313	0.549	-2.394	-0.232	0.017	0.65

FA_af_r	PM ₁₀	-1.068	0.511	-2.074	-0.061	0.038	0.65
FA_atr_l	PM _{2.5}	-1.354	0.618	-2.571	-0.138	0.029	0.65
FA_atr_l	PM ₁₀	-1.261	0.574	-2.391	-0.131	0.029	0.65
FA_atr_r	PM _{2.5}	-1.43	0.609	-2.63	-0.23	0.02	0.65
FA_cbt_r	PM _{2.5}	-1.11	0.447	-1.99	-0.23	0.014	0.65
FA_cst_r	PM _{2.5}	-1.527	0.764	-3.031	-0.022	0.047	0.65
FA_ifo_l	PM _{2.5}	-1.327	0.668	-2.642	-0.011	0.048	0.65
FA_slf2_r	PM _{2.5}	-1.376	0.575	-2.508	-0.244	0.017	0.65
FA_slf3_r	PM _{2.5}	-1.011	0.503	-2.002	-0.019	0.046	0.65
FA_uf_l	PM _{2.5}	-1.314	0.6	-2.496	-0.132	0.03	0.65
FA_uf_r	PM _{2.5}	-1.255	0.552	-2.342	-0.169	0.024	0.65
fintra_ac	PM _{2.5}	-1.398	0.597	-2.575	-0.222	0.02	0.65
fintra_atr_r	PM _{2.5}	-1.978	0.726	-3.407	-0.549	0.007	0.65
fintra_atr_r	PM ₁₀	-1.429	0.678	-2.764	-0.093	0.036	0.65
fintra_fx_l	NO ₂	-0.466	0.221	-0.902	-0.03	0.036	0.65
fintra_vof_l	NO ₂	0.416	0.187	0.047	0.785	0.027	0.65
fiso_mdif_l	PM ₁₀	0.779	0.368	0.054	1.503	0.035	0.65
fiso_mdif_l	NO ₂	0.29	0.122	0.05	0.531	0.018	0.65
MD_ac	PM _{2.5}	0.002	0.001	0	0.004	0.032	0.65
OD_ac	PM _{2.5}	-1.534	0.631	-2.777	-0.291	0.016	0.65
OD_ac	PM ₁₀	-1.452	0.586	-2.606	-0.298	0.014	0.65
OD_ac	NO ₂	-0.385	0.196	-0.771	0.001	0.049	0.65
OD_atr_l	PM _{2.5}	-1.864	0.768	-3.376	-0.352	0.016	0.65
OD_atr_r	PM _{2.5}	-2.63	0.804	-4.214	-1.047	0.001	0.65
OD_atr_r	PM ₁₀	-1.97	0.753	-3.452	-0.487	0.009	0.65
OD_atr_r	NO ₂	-0.535	0.251	-1.03	-0.04	0.034	0.65
OD_cbd_r	PM _{2.5}	-1.972	0.813	-3.574	-0.371	0.016	0.65
OD_cbd_r	PM ₁₀	-2.003	0.754	-3.488	-0.519	0.008	0.65
OD_cbd_r	NO ₂	-0.585	0.251	-1.079	-0.09	0.021	0.65
OD_cbp_r	PM _{2.5}	-3.459	1.381	-6.178	-0.739	0.013	0.65
OD_cbp_r	PM ₁₀	-3.226	1.282	-5.752	-0.7	0.013	0.65
OD_fmi	PM _{2.5}	-2.247	0.978	-4.172	-0.321	0.022	0.65
OD_fx_r	PM _{2.5}	-2.045	0.682	-3.387	-0.702	0.003	0.65
OD_fx_r	PM ₁₀	-1.617	0.636	-2.871	-0.364	0.012	0.65
OD_fx_r	NO ₂	-0.462	0.212	-0.88	-0.044	0.031	0.65

OD_uf_r	PM _{2.5}	-1.804	0.822	-3.422	-0.185	0.029	0.65
OD_vof_l	PM _{2.5}	2.44	1.067	0.339	4.541	0.023	0.65

3.3.5 CCA of exposure to air pollution and WM microstructure metrics

The CCA examining the relationship between exposure to air pollution over the entire gestational period and WM microstructure metrics identified three modes. None of the modes exceeded the 95th percentile of random permutations (Figure 3.3A), which was the threshold of significance, and no further analysis steps were performed. The CCA of exposure to air pollution over the first, second, and third trimesters and relative brain volumes also identified three modes, and none of these exceeded the 95th percentile of random permutations (Figure 3.3B, 3.3C, and 3.3D). Mode 1 in the analysis over the entire gestational period had an observed correlation of $r = 0.96$, whereas the 95th percentile was $r = 0.97$. Similarly, mode 1 in the first trimester had an observed correlation of $r = 0.96$, and the 95th percentile was $r = 0.97$. In the third trimester the observed correlation was $r = 0.95$, and the 95th percentile was $r = 0.96$. The second and third modes displayed similar patterns and did not come close to the 95th percentile of random permutations, with lower than random correlations. Only in the second trimester did the second mode display slightly better correlation than the first mode, though both did not pass permutation testing either.

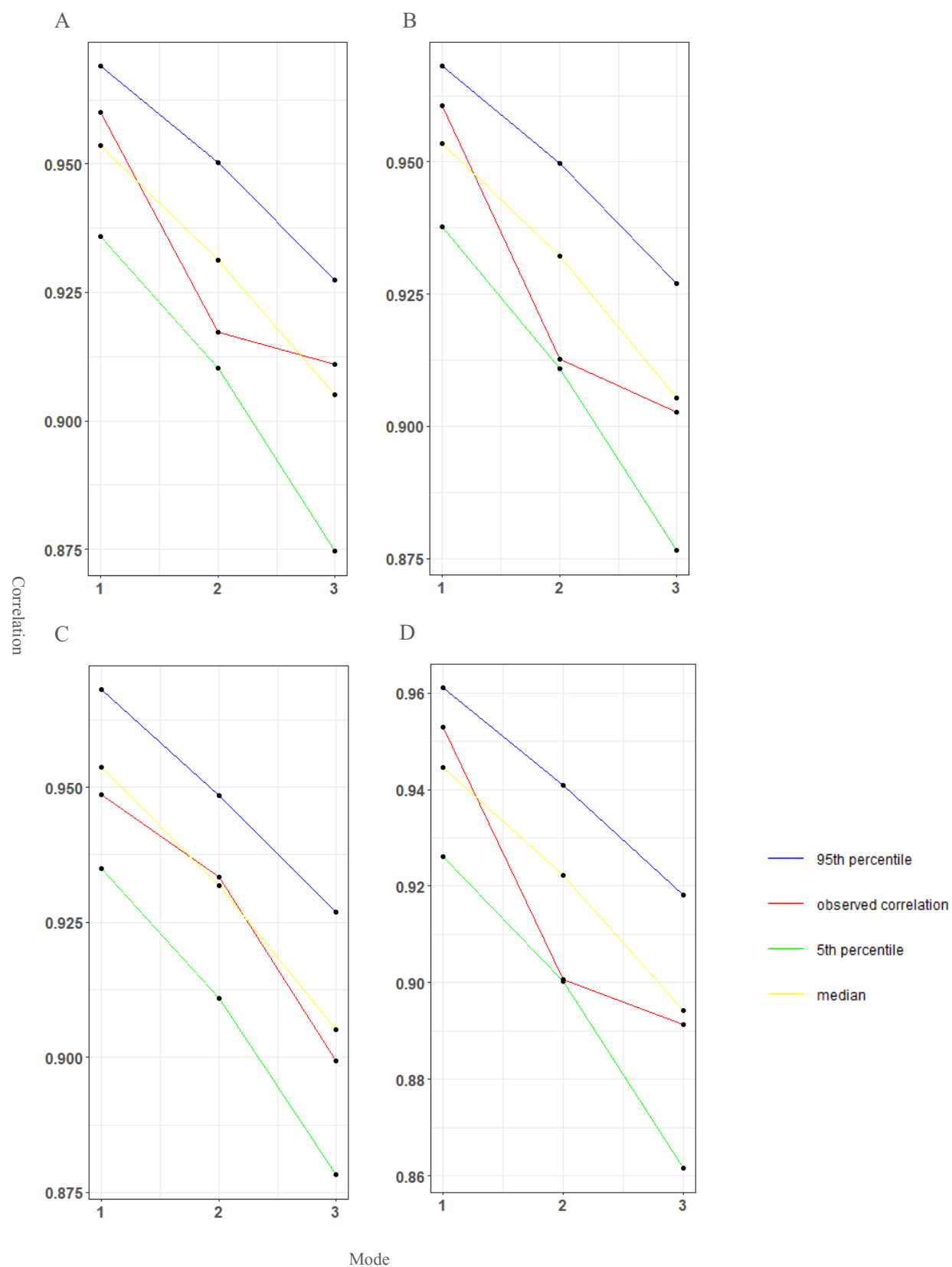


Figure 3.3: Observed CCA correlations (y-axis), the median, and the 5th to 95th percentiles of the null distribution of the permuted CCA correlations estimated via permutation testing across the three CCA

modes (x-axis). Exposure to PM_{2.5}, PM₁₀, and NO₂ over the entire gestational period for all subjects and WM microstructure metrics (A), over the first trimester (B), over the second trimester (C), and over the third trimester (D).

3.4. Discussion

In this study I assessed the relationship between prenatal exposure to air pollution and WM microstructure in the neonatal period in a cohort of healthy term born babies using state-of-the-art diffusion neuroimaging. I assessed WM tracts in regions that have been implicated in previous studies assessing prenatal pollution exposure in animal models (Klocke et al., 2018a, Klocke et al., 2018b), and in humans in childhood (Peterson et al., 2022, Lubczyńska et al., 2020) and found that prenatal exposure to all three pollutants modelled, NO₂, PM_{2.5}, and PM₁₀, were not associated with any metrics of WM microstructure assessed in this chapter. The secondary analyses performed in this study, examining the relationship of trimester-specific exposures on neonatal WM microstructure also yielded no significant results after correction for FDR ($q > 0.05$). No sex-specific associations between pollutants and neonatal WM microstructure were found.

A few studies have used diffusion MRI to assess the effects of prenatal exposure on brain development in childhood (more details for these studies can be found in Chapter 1.3). These studies used DTI metrics to assess WM microstructure, which is sensitive to changes in microstructural tissue structure but lacks specificity (Basser et al., 1994, Martinez-Heras et al., 2021). Lubczyńska et al found that in their single pollutant model higher exposures to PM₁₀, PM_{2.5}, PM_{2.5} absorbance, and NO_x during pregnancy were associated with lower global fractional anisotropy (FA) in children aged 9 – 12 years old ($n = 2954$) (Lubczyńska et al., 2020). Also in their single pollutant model, higher prenatal exposures to PM₁₀, PM_{2.5}, PM_{2.5} absorbance, NO₂, NO_x, copper, iron, silicone, UFP, and higher oxidative potential of PM_{2.5} were associated with higher global MD. The multipollutant model showed a significant association between higher PM_{2.5} exposure and lower global FA, and when PAHs and PM_{2.5} were included, they showed positive and negative associations with global FA, respectively. Only prenatal exposure to silicon was associated with any single WM tract microstructure metrics, namely with higher MD in the cingulate gyrus part of the cingulum of the left hemisphere, the left superior longitudinal fasciculus, and the forceps minor. I did not measure or model exposure to silicon as a part of this study, and none of the pollutants in my study were associated with the cingulum, the left superior longitudinal fasciculus, and the forceps minor (cbd, slf_I, and fm in Table 4). No analysis of the effect of prenatal exposure to air pollution on global FA or MD was conducted. The MD and FA data in the dHCP dataset were not processed for the purpose of creating a global FA and MD metric,

and creating a metric of global FA and MD would constitute a data reduction method with consequent loss of information.

Peterson et al (2022) found that prenatal exposure to PM_{2.5} and PAH were associated with higher FA values in the basal ganglia, anterior cingulate gyrus, and thalamus in children aged 6 – 14 years old (n = 332). In my study, PM_{2.5} was not related to these tracts in the neonatal period. It may be that the effects only become apparent in childhood. Peterson et al (2022) did not adjust for postnatal exposure, and postnatal exposure may be responsible for the effect that is being observed. Pujol et al measured pollution exposure in childhood and undertook diffusion MRI in a sample of 263 children aged 8 – 12 years (Pujol et al., 2016b), though the final sample of subjects with DTI metrics was 177. This study assessed the relationship between elemental carbon (EC) and NO₂ and childhood brain development in a voxel-wise analysis between individual brain images and pollutant measurements and found no association with MD and FA in the WM microstructure in childhood.

This is the first study to employ NODDI metrics in assessing the impact of prenatal exposure to air pollution on neonatal WM microstructure. DTI is limited in its ability to represent complex intravoxel fibre topologies, and DTI metrics are biologically non-specific (Martinez-Heras et al., 2021). NODDI assesses neurite density, orientation dispersion, and the isotropic volume fraction within a voxel, and in this study none of these metrics were related to gestational or trimester-specific air pollution exposure.

Concentrations of PM_{2.5}, PM₁₀, and NO₂ modelled in this study (Table 3.2) were all above the 2021 World Health Organisation annual air quality guidelines for these pollutants (5 µg/m³, 15 µg/m³, and 10 µg/m³, respectively) (World Health Organization, 2021), but they were below the UK standards (20 µg/m³, 40 µg/m³, and 40 µg/m³, respectively) (DEFRA, 2010). Air pollution concentrations modelled for my London-based cohort are comparable to those found in other studies examining pregnancy cohorts in European cities (Guxens et al., 2022). Air pollution exposure levels were significantly lower than those found in pregnancy cohorts in low to middle income countries (Wylie Blair et al., 2017, Zhou et al., 2022), and higher than exposures found in pregnancy cohorts in north America (Zhang et al., 2022, Zhang et al., 2018a). Trimester specific exposures varied more strongly than exposures over the entire gestational period, largely due to an effect of seasonality on trimesters which did not impact the longer gestational periods. This seasonality was adjusted for in the analysis.

In my study, the single linear regression analysis over the entire gestation led to 36 tracts being related to prenatal air pollution exposure. None of these associations survived FDR rate correction and since the number of dependent variables is high (n = 168) compared with the number of subjects (n = 249), these findings may just be chance findings (Austin and Steyerberg, 2015). I did not observe any

significant associations between exposure to air pollution over the entire gestational period and neonatal WM microstructure in the CCA. Several DTI metrics measured in childhood have previously been related to prenatal exposure to air pollution, however, I did not replicate these findings in the neonatal period. The sample size of my study (249 subjects) was relatively small, especially compared to Lubczynska et al (2021) (n = 2954), which may have had a significant impact on the results of this study. Power calculations can determine the minimum number of subjects required for adequate statistical power (Jones et al., 2003). In future work, further processing of dHCP dMRI data can increase the cohort size which can then be compared to estimated sample size requirements for adequate statistical power. Impacts of prenatal exposure to air pollution on NODDI metrics ODI, F_{iso} , and NDI have not been previously assessed, but no significant results were found in this study. Further, I did not observe any associations between individual trimester exposure and WM microstructure, additionally, no sex-specific associations between prenatal exposure to air pollution and WM microstructure were found.

3.5 Conclusion

I found no significant associations between prenatal exposure to NO_2 , $PM_{2.5}$, and PM_{10} and DTI and NODDI metrics of WM microstructure in a healthy term-born cohort. This is the only study to assess the impact of prenatal exposure to air pollution on neonatal WM microstructure in term born infants and longitudinal studies with MRI taken at several time points throughout early life are required to confirm these findings.

CHAPTER 4 - STRUCTURAL IMPACTS OF PRENATAL EXPOSURE TO AIR POLLUTION ON THE HEALTHY NEONATAL BRAIN

Parts of this chapter appear in the publication “*Prenatal exposure to air pollution is associated with structural changes in the neonatal brain*” (Bos et al., 2023) which can be found under <https://doi.org/10.1016/j.envint.2023.107921>. In the previous chapter I assessed the impact of prenatal exposure to air pollution on neonatal WM microstructure in a cohort of healthy, term-born infants as measured by diffusion MRI, finding no significant effects after correcting for FDR. In this chapter I will examine the impact of prenatal exposure to air pollution on neonatal brain morphology, a macrostructural measure of the brain, as assessed by structural MRI, in the same cohort of healthy, term-born, infants.

4.1 Introduction

Exposure to a wide range of pollutants in childhood has been associated with developmental delay (Clifford et al., 2016). In addition, maternal exposure during pregnancy may adversely impact brain development, disrupting neurodevelopment and increasing the risk of cognitive dysfunction (Jedrychowski et al., 2015, Volk et al., 2021). Healthy neurodevelopment is based on a complex chain of cellular events which lead to the development of morphological brain features such as the GM, WM, and CSF. These developmental processes are particularly susceptible to disruption, and environmental toxicants have been previously implicated (Grandjean and Landrigan, 2014, Horton et al., 2014). Structural MRI allows quantification of morphological brain features to investigate the impacts of air pollution exposure on structural brain measures.

A few studies have examined the impact of prenatal exposure to air pollution on brain morphology in school age children using MRI, as outlined in detail in Section 1.3, and results have shown mostly adverse findings. Briefly, prenatal exposure to PM_{2.5} was associated with thinner cortex in children aged 6 to 10 years old (Guxens et al., 2018), but not with global brain volumes. Mortamais et al (2019) found that higher residential concentrations of PM_{2.5} in the third trimester were related to smaller CC in 8 – 12-year-olds prior to FDR correction. Prenatal exposure to PAH was associated with reduced WM surface area in children aged 7 to 9 years old (Peterson et al., 2015). Further, a study which considered the effect of prenatal exposures to a wide range of pollutants in children aged 9 to 12 years old while also adjusting for postnatal exposures detected associations between increased exposure and larger amygdala, cerebellum, putamen and pallidum volume, smaller CC and hippocampal volume (Lubczyńska et al., 2021). In addition, a recent study associated prenatal exposures to PM_{2.5} and PAH

with smaller WM volumes (Peterson et al., 2022). None of these studies undertook neonatal brain MRI and it is unclear whether prenatal exposure to air pollution affects neonatal brain morphology.

In this study I aimed to examine the relationship between in utero exposure to ambient air pollutants and neonatal brain development using structural brain MRI data acquired shortly after birth in a healthy, term-born, cohort. I hypothesised that prenatal exposure to air pollution is associated with altered neonatal brain morphology in term-born neonates, with no hypothesis about the directionality of this effect. Prenatal air pollution exposure could accelerate fetal brain development as an adaptation to unfavourable circumstances (Amiel-Tison et al., 2004), as well as impair fetal brain growth due to impacts on e.g. neurogenesis (Woodward et al., 2018), therefore the direction of the impact was unclear. I assessed the impact of prenatal exposure to three ubiquitous air pollutants, PM₁₀, PM_{2.5}, and NO₂, which have previously been linked to altered brain development in older children.

4.2 Methods

4.2.1 Subjects

This study is based on a sample of neonates participating in the Developing Human Connectome Project (dHCP, <http://www.developingconnectome.org/>), described in detail in Section 2.1.1. Infants were recruited at St. Thomas' Hospital, London and imaged at the Evelina Newborn Imaging Centre, Centre for the Developing Brain, King's College London, United Kingdom. The subjects were born between the years 2015 to 2020 and were scanned in the neonatal period. 782 infants were included in the dHCP project at the time of this study. Infants were excluded if their mothers smoked during pregnancy (n = 16), GA at birth was 37 weeks or less (n = 94), or 44 weeks or more (n = 0), or there was evidence of major focal lesions on MRI (n = 29). In cases of multiple pregnancies (n = 46), only one infant of the twin pair was included. In addition, 128 infants were excluded as the mother's residential address was outside of the air pollution model domain. The final sample consisted of 469 infants. The IMD at postcode resolution was used to describe socioeconomic status for all subjects.

4.2.2 MRI acquisition

MRI acquisition of the dHCP cohort is described in detail in Section 2.2.1.

4.2.3 Image processing

MRI processing of the dHCP cohort is described in detail in Section 2.2.1. Image processing resulted in segmentation into the following tissue types: WM, cortical GM, ventricles, extracerebral CSF, cerebellum, hippocampus & amygdala, deep grey nuclei, and the brainstem.

4.2.4 Air pollution modelling

Air pollution was modelled as described in detail in the methodology chapter in Section 2.2.

4.2.5 Statistical Analysis

All volumes were adjusted for ICV to remove the effect of individual differences in head size and will be referred to as “relative” volumes throughout this chapter. The relationship between prenatal pollution exposure and brain morphology was first explored using single pollutant linear regression analysis, adjusting for PMA at scan, GA at birth, sex, and IMD. Results were FDR corrected using Benjamini-Hochberg FDR method (Benjamini and Hochberg, 1995).

To account for potential confounding factors relevant to neonatal MRI, all brain volumes included in the analysis were adjusted for PMA at scan, GA at birth, and sex. Further, to account for socioeconomic status, the residuals of pollutant variables were determined and adjusted for IMD as it has been shown to be correlated with pollution exposure (Hajat et al., 2015). For each CCA mode, I used a permutation testing procedure to test the significance of the corresponding canonical correlation as a validation step. To perform this, the rows of both inputs (brain variable and pollution variables) were permuted 1000 times, CCA was re-run and canonical correlations re-computed after each permutation. A mode of the resulting CCA was only considered significant if the Spearman’s r was greater than the 95th percentile of random permutation tests (Yu et al., 2019). Significance of the association between modes that passed this test was corrected for multiple comparisons using the Benjamini-Hochberg FDR method (Benjamini and Hochberg, 1995). Finally, the correlation of each original variable to the CCA mode testing for univariate correlation was assessed between each of the brain measures and pollutants using Spearman’s r test.

A secondary analysis was performed to examine the impact of trimester specific exposures on neonatal brain morphology. All volumes were adjusted for ICV, PMA at scan, GA at birth, sex, and IMD in a single pollutant linear regression analysis. Further, trimester specific air pollution exposure estimates were adjusted for seasonality due to the disproportionate effect of seasonality on shorter exposure periods. A CCA was then performed for each trimester as outlined above. I examined sex-specific associations between prenatal exposure to air pollution and neonatal brain morphology and investigated the correlations between exposures by trimester using Spearman’s rank correlation. To this end I separated the subjects into male and female and conducted CCA analysis as outlined above.

4.3 Results

4.3.1 Subjects

The subjects comprised 469 infants (207 male) born at a median (range) GA of 40.14 (36.14 – 43.57) weeks and imaged at 41.29 (36.71 – 45.14) weeks PMA (Table 4.1). The median IMD for the study group was 4 (1 – 5). Male subjects were scanned at a median age of 41.43 weeks, whereas female subjects were scanned at a median date of 41.07 weeks (Table 4.1). Subjects were concentrated around the Boroughs of Southwark and Lambeth, close to where the MRI was performed (Figure A2).

Table 4.1: Distribution of age at MRI, age at birth, sex, and index of multiple deprivation of the dHCP subjects.

	Male	Female	Total
Subjects (n, %)	207 (44.1%)	262 (55.9%)	469
Age at MRI, weeks (median, range)	41.43 (36.86 – 45.14)	41.07 (36.71 – 44.86)	41.29 (36.71 – 45.14)
Age at birth, weeks (median, range)	40.14 (36.29 – 43)	40.14 (36.14 – 43.57)	40.14 (36.14 – 43.57)
IMD quintile (median, range)	4 (1 – 5)	4 (1 – 5)	4 (1 – 5)

4.3.2 Pollution exposure

Descriptive statistics of subjects' pollution exposure are detailed below (Table 4.2). NO₂ and PM₁₀ were non-normally distributed, summary statistics are therefore presented as median and range. Modelled median PM₁₀ exposure was 23.4 µg/m³ over the entire gestational period, PM_{2.5} exposure was 13.5 µg/m³, and NO₂ was 39.7 µg/m³. The range of exposures varied by pollutant, with a range of 18.2 – 30.5 µg/m³ for PM₁₀, 10.2 – 18.5 µg/m³ for PM_{2.5}, and 24.7 – 58.0 µg/m³ for NO₂. Trimester specific median exposures were very similar to exposure over the entire gestational period, however, the range of values tended to be greater.

Table 4.2: Descriptive statistics of modelled pollution exposure for each trimester and the whole pregnancy in µg/m³ for the subjects from the developing human connectome project (dHCP).

PM ₁₀ , µg/m ³ (median, range)	
1st trimester of pregnancy	23.1 (17.1 – 37.1)

2nd trimester of pregnancy	23.2 (15.6 – 38.5)
3rd trimester of pregnancy	22.9 (11.9 – 39.6)
Whole pregnancy	23.4 (18.2 – 30.5)

PM_{2.5}, µg/m³ (median, range)

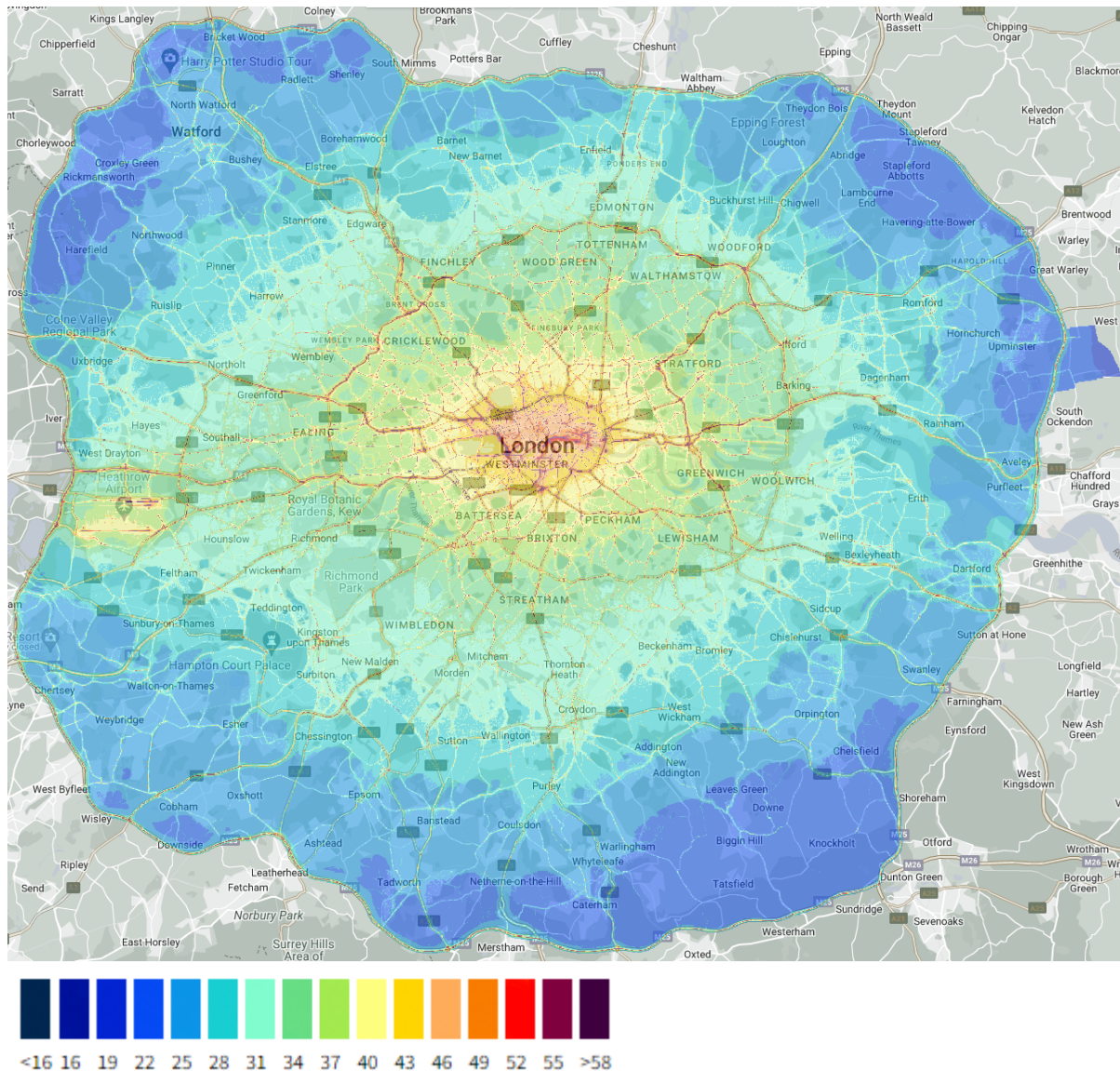
1st trimester of pregnancy	13.4 (9.0 – 24.2)
2nd trimester of pregnancy	13.5 (8.5 – 25.2)
3rd trimester of pregnancy	13.3 (8.9 – 22.5)
Whole pregnancy	13.5 (10.2 – 18.5)

NO₂, µg/m³ (median, range)

1st trimester of pregnancy	39.4 (23.3 – 59.1)
2nd trimester of pregnancy	39.7 (20.2 – 71.7)
3rd trimester of pregnancy	38.3 (21.9 – 62.3)
Whole pregnancy	39.7 (24.7 – 58.0)

A map of annual mean PM₁₀ and of annual mean NO₂ concentrations across Greater London in 2016 is included to illustrate spatial exposure gradients (Figure 4.1 and 4.2). Pollutant concentrations for both PM₁₀ and NO₂ decrease steadily moving from central London to outer London, with a steeper

gradient for NO₂, which is more influenced by local sources. Subjects resided mostly in the heavily polluted areas in central London, with fewer subjects in the outer, less polluted areas of the city.



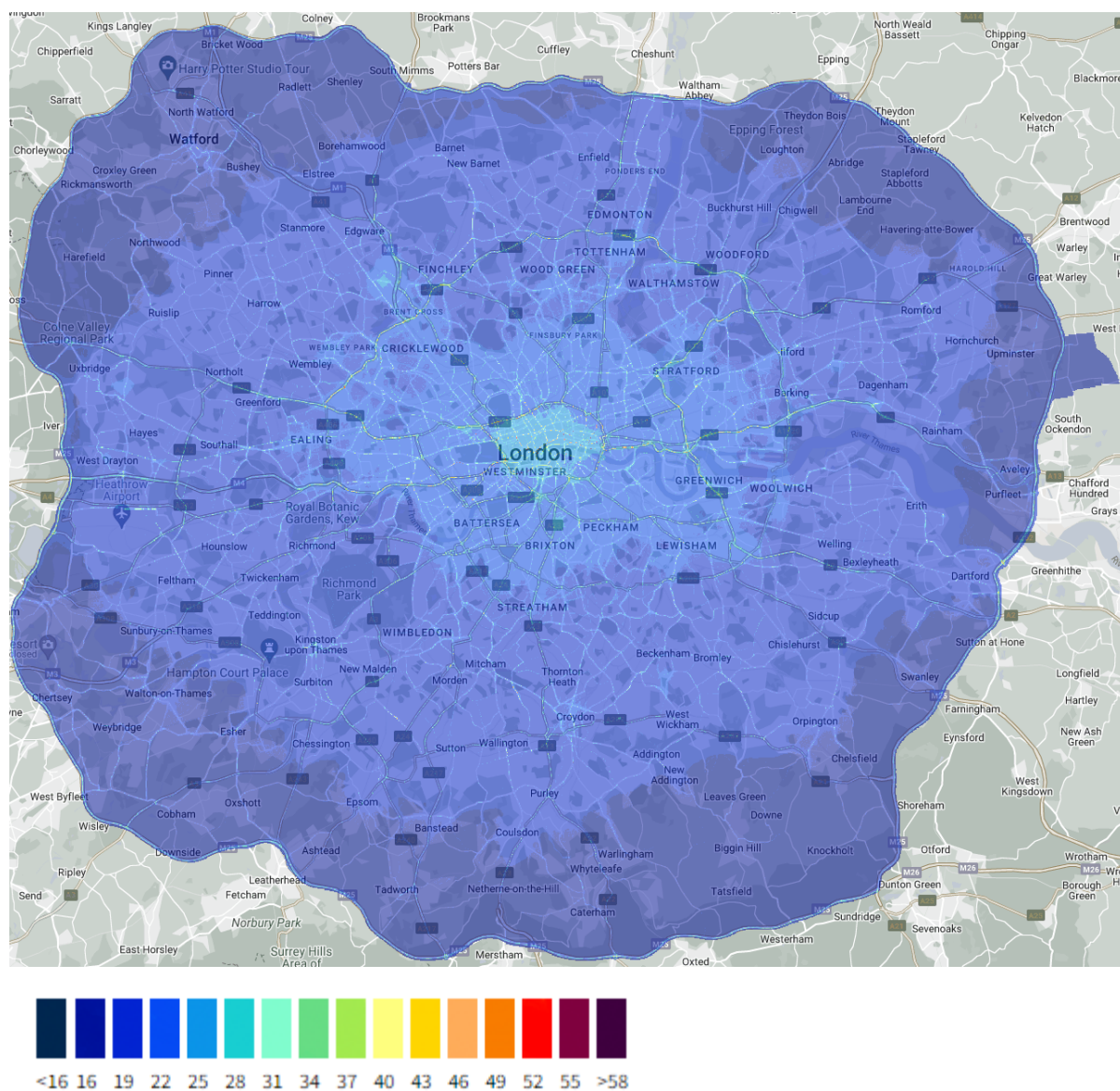


Figure 4.2: Average annual concentrations of PM_{10} in $\mu g/m^3$ in Greater London, 2016. Reproduced from Londonair.org.uk.

A correlogram of correlation between pollutants for the entire gestational period and for each trimester can be found in the appendix (Figure A3). Pollutants were highly correlated, with correlations ranging from 0.69 to 0.93.

4.3.3 Brain Volumes

Descriptive statistics of subjects' brain volumes are detailed below (Table 4.3). TBV and relative cerebellum were non-normally distributed and so summary statistics are presented as median and range. A table with descriptive statistics of absolute volumes can be found in the appendix (Table A5).

Table 4.3: Median brain volumes for the subjects from the developing human connectome project (dHCP).

Volume	Median	Range
Intracranial Volume (mm ³)	439103	273072 – 664283
Total Brain Volume (mm ³)	361807	223962 – 532365
Relative Cortical Grey Matter	0.419	0.365 – 0.496
Relative White Matter	0.422	0.342 – 0.466
Relative Cerebellum	0.07	0.054 – 0.089
Relative Ventricles	0.013	0.007 – 0.047
Relative Deep Grey Nuclei	0.075	0.063 – 0.087
Relative Brainstem	0.018	0.015 – 0.022
Relative Amygdala & Hippocampus	0.007	0.0058 – 0.0088
Relative Extracerebral CSF	0.168	0.112 – 0.253

A segmented image of the neonatal brain at 40 weeks PMA showing the regions of the brain analysed in this chapter is shown in Figure 4.3. Images included are shown in the sagittal, axial, and coronal

planes, and from left to right, superior to inferior, and anterior to posterior, giving a detailed view of the neonatal brain.

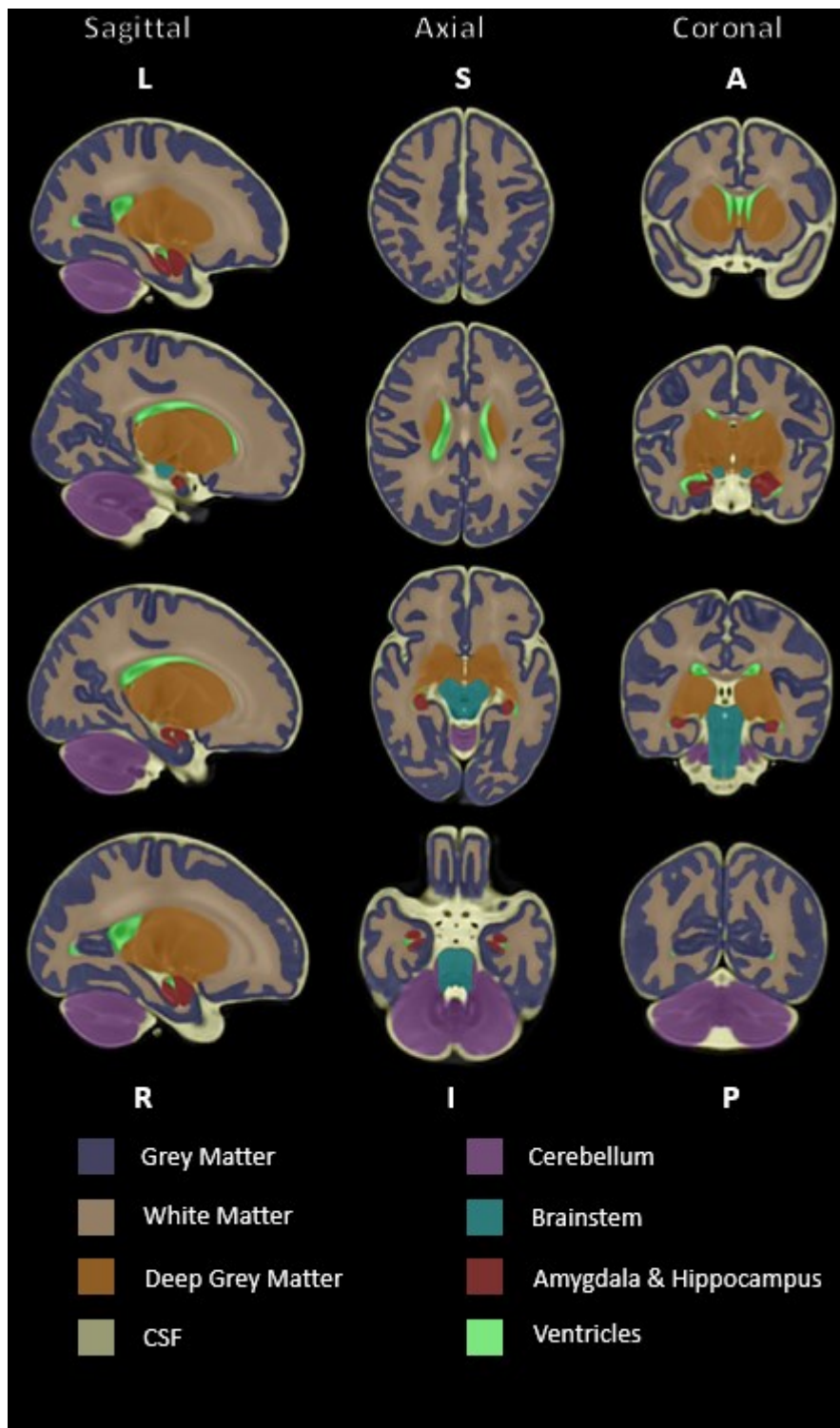


Figure 4.3: A segmented image in a neonate at 40 weeks PMA showing the analysed brain regions in the sagittal, axial, and coronal planes. Left (L) to right (R), superior (S) to inferior (I), anterior (A) to posterior (P), cortical grey matter (dark blue), white matter (light brown), deep grey matter (brown),

extracerebral CSF (beige), cerebellum (purple), brainstem (turquoise), amygdala and hippocampus (red), and ventricles (light green).

4.3.4 Single pollutant linear regression results

Table 4.4 shows the results of the single pollutant linear regression model assessing the relationship between pollution exposure over the entire gestational period and relative brain volumes. Prenatal exposure to PM_{2.5} and PM₁₀ was related to an increase in the relative volume of the extracerebral CSF ($p < 0.05$), however, none of the associations survived FDR correction ($q > 0.05$). This was also the case when examining exposure per trimester (Table A2, A3, and A4, $q < 0.05$).

Table 4.4: Single pollutant linear regression results for each relative brain volume from the dHCP subjects and PM_{2.5}, PM₁₀, and NO₂, adjusted for sex, IMD, PMA at scan, and GA at birth; beta = effect size; CI = Confidence interval (95%); q-value = p-value after FDR correction.

Brain Region	Pollutant	<i>beta</i> (in 10 ⁻³)	Std. error (in 10 ⁻³)	Lower CI (in 10 ⁻³)	Upper CI (in 10 ⁻³)	p-value	q-value
Relative White Matter	PM _{2.5}	-0.156	0.322	-0.788	0.477	0.629	0.961
	PM ₁₀	-0.102	0.260	-0.612	0.409	0.695	0.961
	NO ₂	-0.042	0.100	-0.237	0.154	0.675	0.961
Relative Grey Matter	PM _{2.5}	0.049	0.336	-0.612	0.710	0.884	0.981
	PM ₁₀	0.020	0.272	-0.513	0.554	0.940	0.981
	NO ₂	0.067	0.104	-0.137	0.272	0.517	0.961
Relative Amygdala	PM _{2.5}	-0.001	0.014	-0.029	0.027	0.927	0.981
	PM ₁₀	-0.004	0.012	-0.026	0.019	0.758	0.961
	NO ₂	0.001	0.004	-0.007	0.010	0.761	0.961
Relative Cerebellum	PM _{2.5}	-0.002	0.147	-0.290	0.286	0.990	0.99
	PM ₁₀	0.009	0.118	-0.223	0.242	0.937	0.981
	NO ₂	-0.050	0.045	-0.139	0.039	0.273	0.819
Relative Basal Ganglia	PM _{2.5}	0.069	0.097	-0.122	0.259	0.479	0.961
	PM ₁₀	0.031	0.078	-0.123	0.184	0.696	0.961
	NO ₂	0.013	0.030	-0.046	0.072	0.656	0.961
	PM _{2.5}	0.115	0.114	-0.110	0.339	0.315	0.839

Relative Ventricles	PM ₁₀	0.154	0.092	-0.027	0.335	0.094	0.51
	NO ₂	-0.017	0.035	-0.086	0.053	0.638	0.961
Relative Brainstem	PM _{2.5}	0.040	0.029	-0.017	0.097	0.172	0.688
	PM ₁₀	0.042	0.024	-0.004	0.088	0.076	0.51
	NO ₂	0.011	0.009	-0.007	0.028	0.236	0.811
Relative Extracerebral CSF	PM _{2.5}	1.290	0.569	0.172	2.409	0.024	0.286
	PM ₁₀	1.046	0.460	0.143	1.949	0.023	0.286
	NO ₂	0.286	0.177	-0.061	0.633	0.106	0.51

4.3.5 CCA results

CCA of exposure to air pollution over the entire gestational period identified three modes. Only mode 1 exceeded the 95th percentile of random permutations (Figure 4.4A). The CCA over the first, second, and third trimester also identified three modes, and none of these exceeded the 95th percentile of random permutations (Figure 4.4B, 4.4C, and 4.4D). The same was true when the cohort was separated by sex, neither in the male nor in the female group did any of the modes exceed the 95th percentile of random permutations (Figure 4.4E and 4.4F). Mode 2 in the analysis of exposures over the second trimester and brain morphology had an observed correlation of $r = 0.15$, whereas the 95th percentile was $r = 0.16$. Mode 1 for male subjects had an observed correlation of $r = 0.32$, and the 95th percentile was $r = 0.33$. Mode 1 for female subjects was $r = 0.27$, and the 95th percentile was $r = 0.3$ (Figure 4.4E and 4.4F). None of the other modes had an observed correlation close to the 95th percentile.

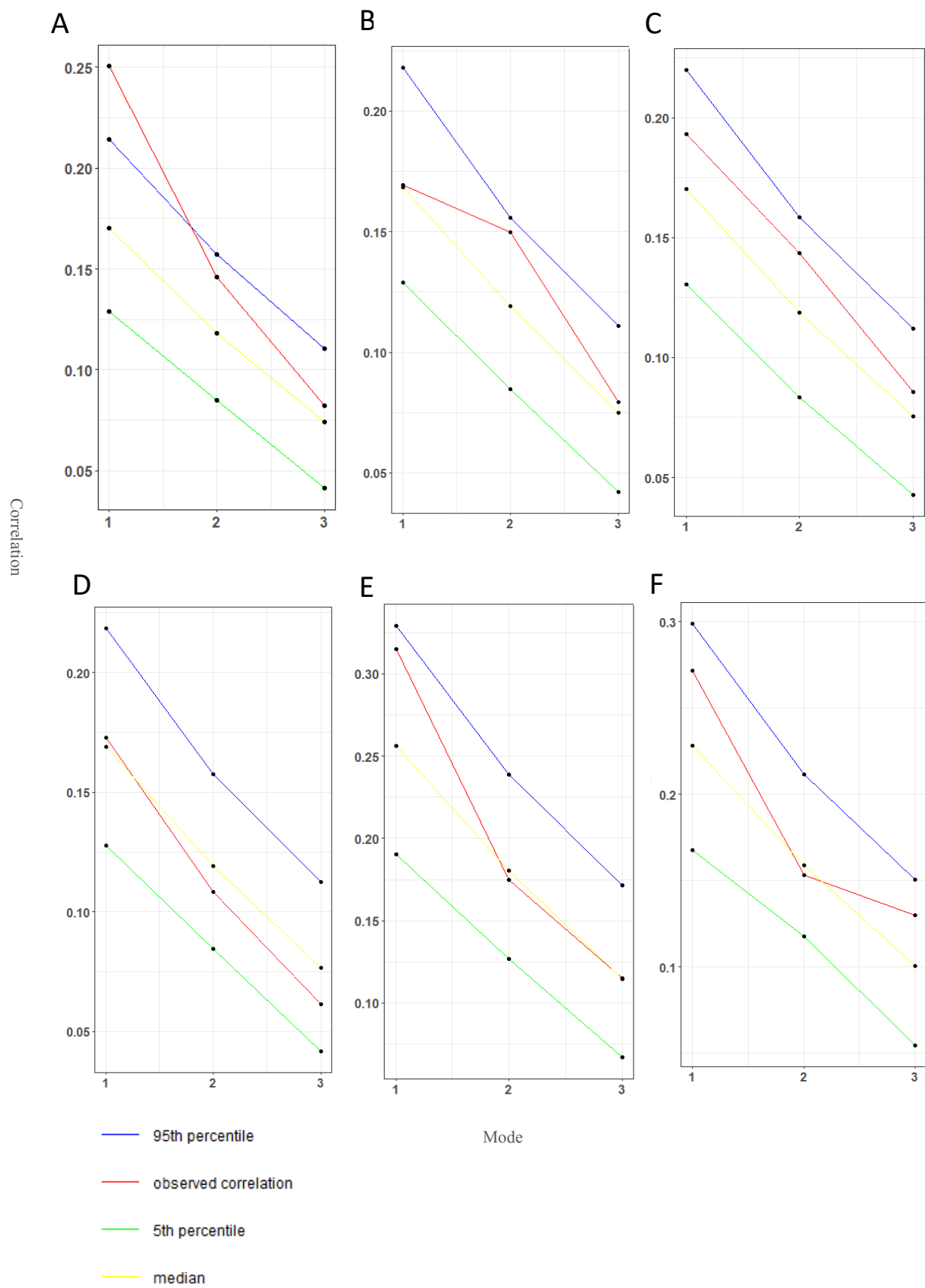


Figure 4.4: Observed CCA correlations (y-axis), the median, and the 5th to 95th percentiles of the null distribution of the permuted CCA correlations estimated via permutation testing across the three CCA modes (x-axis). Exposure to PM_{2.5}, PM₁₀, and NO₂ over the entire gestational period for all subjects and WM microstructure metrics (A), over the first trimester (B), over the second trimester (C), over the third trimester (D), over the entire gestational period for male subjects only (E), and over the entire gestational period for female subjects only (F).

Higher PM₁₀ concentrations and lower NO₂ concentrations were strongly canonically correlated to a larger relative size of the ventricles, moderately associated with larger relative size of the cerebellum, and modestly associated with smaller size of cortical GM, amygdala & hippocampus, and a larger brainstem and extracerebral CSF in the first mode (Table 4.5 and 4.6, Figure 4.6). Exposure to PM_{2.5} was not significantly associated with any brain volume measures. All brain region associations with the first mode except WM and deep grey nuclei survived FDR correction.

Table 4.5: Spearman's R and R² for each relative region of the brain and the association with the first mode of the CCA.

Brain Region	Spearman's R	R ²	p-value	q-value
White Matter	0.055	0.003	0.24	0.24
Cortical Grey Matter	-0.251	0.063	<0.001	<0.001
Ventricles	0.735	0.540	<0.001	<0.001
Cerebellum	0.450	0.202	<0.001	<0.001
Deep Grey Nuclei	-0.087	0.007	0.06	0.07
Brainstem	0.281	0.079	<0.001	<0.001
Amygdala & Hippocampus	-0.261	0.068	<0.001	<0.001
Extracerebral CSF	0.215	0.046	<0.001	<0.001

Spearman's R was modest for NO₂ and PM₁₀, at -0.2 and 0.2, respectively, and R² was 0.04 for both pollutants (Table 4.6). Spearman's R for PM_{2.5} was very low at 0.06. NO₂ and PM₁₀ were significantly

associated with the first mode. $PM_{2.5}$ was not associated with the first mode, before and after FDR correction.

Table 4.6: Spearman's R and R^2 for NO_2 , PM_{10} , and $PM_{2.5}$ and the association with the first mode of the CCA.

Pollutant	Spearman's R	R^2	p-value	q-value
NO_2	-0.2	0.04	<0.001	<0.001
PM_{10}	0.2	0.04	<0.001	<0.001
$PM_{2.5}$	0.06	0.004	0.2	0.2

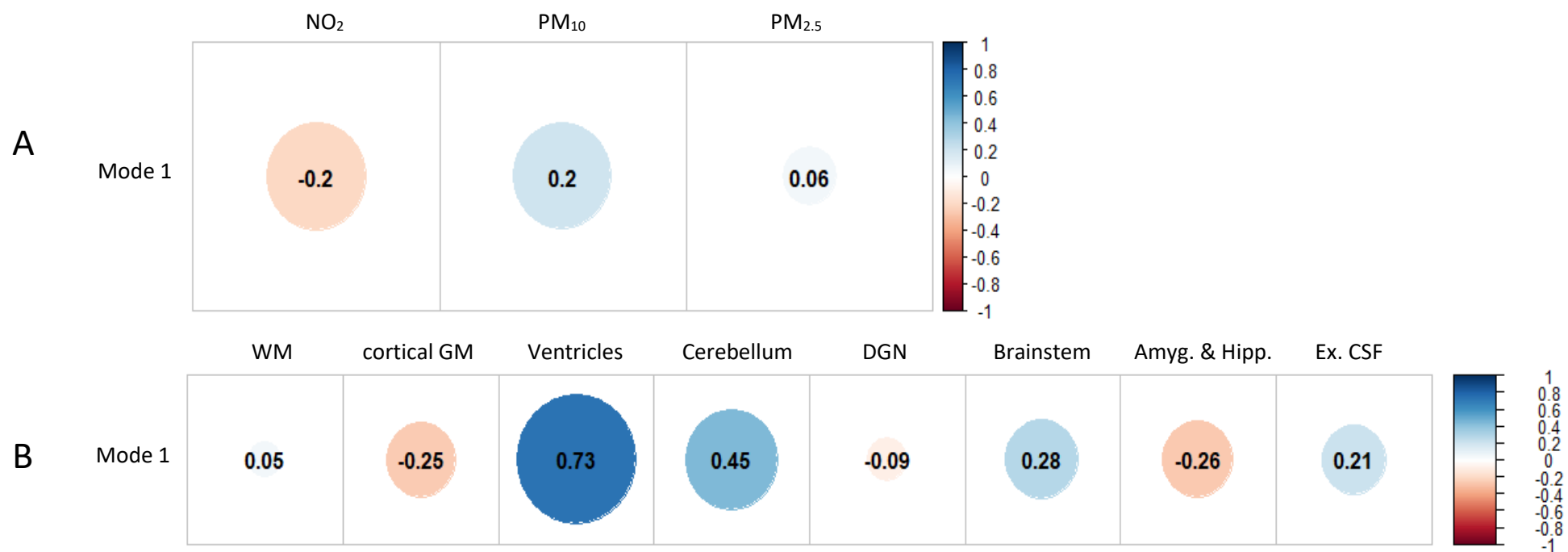


Figure 4.5: Canonical correlation of the pollutants using Spearman's rank test, in the following order: (A) 1. NO₂, 2. PM₁₀, 3. PM_{2.5}. Canonical correlations of the relative brain volumes using Spearman's rank test, in the following order: (B) 1. White Matter, 2. Cortical Grey matter, 3. Ventricles, 4. Cerebellum, 5. Deep Grey Nuclei, 6. Brainstem, 7. Amygdala & Hippocampus, 8. Ex. Cerebral CSF.

4.4 Discussion

In this study I assessed the relationship between prenatal exposure to ambient air pollution and brain morphology in the neonatal period using MRI, and to my knowledge this was the first study to do so. Using CCA, I observed associations between air pollution in utero and neonatal brain structure with higher gestational exposure to PM₁₀ and lower exposure to NO₂ related to larger relative ventricular and cerebellar volume, along with modest associations with smaller cortical GM, amygdala and hippocampus volumes, and larger volumes of brainstem and extracerebral CSF.

To date, studies assessing prenatal exposure to air pollutants and its impacts on brain morphology in childhood provide conflicting results (as outlined in detail in Section 1.3.1). Lubczynska et al found an association between increased exposure to coarse PM (which is a derivative of the PM exposures assessed in this chapter, PM₁₀ - PM_{2.5}) during pregnancy and increased cerebellar size in children age 9 – 12, and an association between increased exposure to PM_{2.5} and smaller cerebellar volume in their multipollutant model, though this latter finding was not statistically significant in their single-pollutant model (Lubczyńska et al., 2021). A study examining TRAP exposure during the first year of life showed an association with smaller cerebellum in children aged 12 years old (Beckwith et al., 2020). These findings relate to MRI scans taken in childhood, however, and as such are not directly comparable to my data.

I found larger relative ventricle volumes in relation to increased exposure to PM₁₀, and decreased exposure to NO₂. In mice, Allen et al (2017) detected an association between increased ultrafine particle exposure during pregnancy and male-specific ventriculomegaly. Ventriculomegaly occurred in concert with inflammation and microglial activation, aberrant WM development and hypomyelination in the CC. Klocke et al (2017) also related higher gestational exposure to concentrated ambient particles in mice with ventriculomegaly. In my study I observed larger relative size of the ventricles as a result of exposure to higher levels of PM₁₀. Ventriculomegaly could reflect an expansion of the ventricles to fill available space due to cell loss and/or altered brain development (Allen et al., 2017, Leviton and Gilles, 1996).

The finding that lower NO₂ concentrations are related to larger relative ventricle size is unexpected. One other study reported opposing effects of NO₂ and PM_{2.5}, in which the third mode of CCA linked higher concentrations of PM_{2.5} to lower concentrations of NO₂, and was related to lower area and volumes across the cortex as well as WM indices in school-aged children (Alnæs et al., 2020). NO₂ may affect the developing brain in several ways, and prenatal exposure could harm the fetal brain by inducing inflammation, oxidative stress, DNA methylation, and vascular injury (Shang et al., 2020). However, there is some evidence that acute exposure to high concentrations of NO₂ increases nitrite

in the blood stream and lowers blood pressure and that hypertensive disorders of pregnancy increase risk of neurodevelopmental disorders in offspring (Floyd et al., 2020, Maher et al., 2018). In this study I modelled chronic ambient exposures, which tend to be lower than acute exposures via domestic gas appliances as used in Floyd et al (2020), and there is no proven link between long-term exposure to NO₂ and lower blood pressure.

Higher gestational exposure to PM₁₀ and lower exposure to NO₂ was related to larger relative cerebellar volume in my study. The mechanisms relating increased PM exposure in utero and increased cerebellar size are not clear. In rat brains, direct exposure of the cerebellum to PM_{2.5} in solution was shown to cause oxidative stress (Fagundes et al., 2015), and inhaled diesel-extracted particles led to oxidative stress and inflammation in the cerebellum in mice (Kim et al., 2018). Again, however, comparison is difficult as these studies were conducted during different time periods, namely in adult and adolescent animals, respectively. Klocke et al examined young mice and found that gestational exposure to ambient PM_{2.5} was related to hypermyelination in the cerebellum of male mice (Klocke et al., 2018b). This last finding points to accelerated maturation as a result of high gestational exposure to air pollutants, and as theorized by the authors, may be a response to injury.

Air pollution exposure explained a small amount of variance in cortical GM, amygdala & hippocampus, brainstem, and extracerebral CSF volumes. Higher gestational exposure to PM₁₀ and lower exposure to NO₂ was related to smaller cortical GM and amygdala and hippocampus, and larger brainstem and extracerebral CSF. Some of these findings are comparable to previous studies in children. Lubczynska et al (2021) observed that higher pregnancy and childhood exposure to multiple air pollutants was related to smaller hippocampus and larger amygdala in 12-year-olds with no associations found for cortical GM. Beckwith et al also found reduced cortical GM volume in children aged 12 years old after childhood exposure to TRAP (Beckwith et al., 2020).

In mice, decreased volume of the hippocampus was associated with prenatal exposure to ultra-fine particles (Klocke et al., 2017). Woodward et al (2018) also found impaired neurogenesis in the hippocampus in adult rats exposed prenatally to TRAP. Impaired neurogenesis as a consequence of higher exposure to PM₁₀ may contribute to the smaller relative cortical GM, hippocampal and amygdala volumes I observe in my study.

There have been few studies analysing brain volumes in healthy term infants in the neonatal period (Gale-Grant et al., 2022). However, in infants born preterm, increased ventricular volume (Liverani et al., 2023) and decreased cortical GM volume (Liverani et al., 2023, Pagnozzi et al., 2023) in the neonatal period were associated with lower outcome scores at 2 years. In addition, Liverani et al

(2023) demonstrated a relationship between amygdala volumes in the neonatal period and behavioural scores in 5-year-old children born preterm.

I did not observe any associations between individual trimester exposure and brain volumes, nor was prenatal exposure to PM_{2.5} significantly associated with any of the brain volumes studied. Further, I did not observe any significant associations between exposure over the entire gestational period and WM or deep grey nuclei volume, despite previous studies showing associations in children aged 6-14 years old (Pujol et al., 2016a, Mortamais et al., 2017, Cserbik et al., 2020, Lubczyńska et al., 2021, Peterson et al., 2022, Peterson et al., 2015). It is possible that these relationships become apparent only in later childhood. When I divided the participants into male and female, I did not find any sex-specific associations between prenatal exposure to air pollution and brain volumes. This may be due to reduced statistical power resulting from dividing the subjects into male and female subgroups. Including sex as a term in the CCA model was not possible, as categorical variables cannot be included in CCA.

4.5 Conclusions

This study shows for the first time in humans that prenatal particulate air pollution exposure affects neonatal brain morphology, particularly relative cerebellar and ventricle size. The brain is especially vulnerable during this critical period of development and altered brain development in utero may have adverse consequences throughout the life course. This finding is an important addition to the growing body of evidence that gestational exposure to pollution affects health in early life and shows that reducing particulate matter concentrations and exposure during fetal life should be a public health priority. My finding that lower NO₂ exposure is related to larger relative ventricular and cerebellar size is more difficult to interpret and requires further study.

CHAPTER 5 - PRENATAL EXPOSURE TO AIR POLLUTION AND NEONATAL NEURODEVELOPMENT IN A PREMATURELY BORN COHORT ASSESSED WITH STRUCTURAL AND DIFFUSION MRI

In the previous chapter I showed that prenatal exposure to air pollution is associated with neonatal brain morphology in a healthy, term-born, cohort. Preterm born infants, and especially those born extremely preterm, are at risk of adverse neurodevelopment (Johnson and Marlow, 2017), and it is unclear whether air pollution has greater impacts on fetal neurodevelopment of this vulnerable cohort. In this chapter I will examine the impact of prenatal exposure to air pollution on neonatal brain morphology and WM microstructure as assessed by structural and diffusion MRI, respectively, in a cohort of infants born extremely preterm.

5.1. Introduction

Preterm birth is defined as being born before 37 weeks of gestation (World Health Organization, 1977). Globally, approximately 11% of births are estimated to occur prematurely, with 80% of premature births occurring in South Asia or sub-Saharan Africa (Walani, 2020). Prematurity is the most common cause of neonatal death, and preterm infants are vulnerable to multiple morbidities and adverse outcomes such as respiratory infections and cerebral palsy (Platt, 2014). The impact of prematurity on brain development is particularly severe, and a high degree of prematurity is associated with long-term intellectual disability, autism spectrum disorder, attention deficit disorder, and problems with behaviour and language (Johnson and Marlow, 2017, Vanes et al., 2023).

Prenatal exposure to high levels of ambient air pollution increases the risk of preterm birth, with high concentrations of particulate matter implicated most strongly (Nyadanu et al., 2022, Yu et al., 2022). A London-based study found that prenatal exposure to both O_3 and $PM_{2.5}$ were associated with preterm birth, with stronger associations for O_3 (Smith et al., 2020). Prenatal exposure to high levels of air pollution is also associated with changes in brain morphology, both neonatally and at various stages of childhood (Guxens et al., 2022, Peterson et al., 2022, Bos et al., 2023). Impacts on several metrics measuring cognitive function have also been documented (Shang et al., 2020), however, research in this field is in its early stages and evidence is limited.

There is some evidence that preterm born infants are more vulnerable to the effects of air pollution ex utero and in utero. Acute exposure to $PM_{2.5}$ increased risk of bronchiolitis and otitis media more strongly for preterm born infants than for term born infants (Girguis et al., 2018), and preterm born infants show slower repair of oxidative damage and paternal smoking related DNA damage (Vande Loock et al., 2012). One study showed a stronger association between increased prenatal exposure to

PM₁₀ during the second trimester of pregnancy and a decline in neonatal lung function in those born preterm compared with term born infants (Decrue et al., 2022). Further, prenatal residential exposure to intensive traffic was positively associated with hypotonia and lethargy subscales as assessed by the Neonate Intensive Care Unit Network Behavioural Scale (NINS) in hospitalised preterm infants (n = 240). No metrics of air pollution exposure were utilised in this study, only traffic derivatives such as distance to roads and vehicle-mile/km². In this cohort all subjects were born very preterm, in the late second or early third trimester, which is suggestive of an effect on neuromotor development early in gestation (Zhang et al., 2020). None of these studies examined neurodevelopment as assessed by MRI and whether any vulnerability of preterm infants to the effects of air pollution extends to these metrics is unclear.

There are several characteristic differences between the developing preterm brain and the developing fetal brain. At term equivalent age, TBV is reduced in preterm infants compared with healthy infants (Makropoulos et al., 2016, Ball et al., 2012, Ball et al., 2013). The reduction is dependent on the level of prematurity, with white and cortical GM regions affected. Brain growth is slower in preterm infants compared with healthy foetuses with consequences lasting into adulthood (Bouyssi-Kobar et al., 2016). Preterm infants at term-equivalent age showed lower anisotropy in the WM compared to their term-born peers. This relationship was dependent on the prematurity of preterm infants, with greater prematurity leading to lower FA in multiple regions of the brain (Pandit et al., 2013, Young et al., 2018).

Many factors influence brain development in preterm born infants. A significant share of preterm neonates, especially in those born extremely preterm, must be provided with respiratory support using continuous positive airway pressure (CPAP) or mechanical ventilation as their lungs are unable to fulfil the functions of oxygenating and simultaneously removing carbon dioxide from the bloodstream (37% of subjects in the ePrime cohort were mechanically ventilated for at least one day) (Chakkarapani et al., 2020, Ho et al., 2020). Further, preterm neonates may not be able to absorb nutrients through the gastrointestinal tract and are provided nutrition intravenously through total parenteral nutrition (TPN) (Brine and Ernst, 2004). The usage and duration of these measures are related to brain development at term as assessed by diffusion MRI and structural MRI (Kersbergen et al., 2016, De Nardo et al., 2022, Barnett et al., 2018).

Trends in WM microstructure metrics in preterm born infants were described in Section 3.1. Briefly, diffusivities decrease rapidly, and FA increases with GA across the WM, however, these trends are region dependent. How prenatal exposure to air pollution might affect these developmental processes in infants born preterm is unclear. In this chapter I aimed to examine the relationship between in utero exposure to air pollutants in infants born very preterm and brain development using structural and

diffusion MRI acquired at term equivalent age. I examined the impacts on DTI metrics derived from diffusion MRI. I hypothesised that the preterm subjects would be vulnerable to the effects of prenatal exposure to air pollution, and that therefore prenatal exposure to PM₁₀, PM_{2.5}, and NO₂ is associated with altered brain morphology and altered WM microstructure at term equivalent age. No hypothesis was developed about the directionality of these effects on WM microstructure, due to limited information about fetal WM microstructure DTI metrics in infants born extremely preterm. In terms of brain morphology, it was expected that prenatal exposure to PM₁₀, PM_{2.5}, and NO₂ would have stronger effects than on the healthy, term-born neonates described in the previous chapter.

5.2 Methods

5.2.1 Subjects

This study is based on a sample of neonates that were part of the ePrime project, which is described in detail in Section 2.1.2. The subjects were scanned at Queen Charlottes & Chelsea Hospital in west London between 2010 – 2013. For the purposes of this study subjects were excluded if they had major focal lesions on MRI, were scanned earlier than 37 weeks or later than 44 weeks PMA, or in cases of multiple pregnancies, only one infant of the twin or triplet was included. In the structural MRI dataset this led to 2, 0, 40, and 30 exclusions, respectively. In the diffusion MRI dataset this led to 34, 0, 41, and 36 exclusions, respectively. Further, infants were excluded as the mother's residential address was outside of the air pollution model domain (155 in the diffusion MRI dataset, 190 in the structural MRI dataset). A final sample of 244 subjects with structural MRI data and 245 subjects with diffusion MRI data were included, of which 204 had both structural and diffusion MRI data available. IMD was used to describe socioeconomic status for all subjects.

5.2.2 MRI acquisition

MRI acquisition of the ePrime cohort is described in detail in Section 2.1.2.

5.2.3 Image processing

MRI processing of the ePrime cohort is described in detail in Section 2.2.2. The structural MRI data were segmented into the following tissue types: WM, cortical GM, ventricles, cerebellum, hippocampus, amygdala, thalamus, deep grey nuclei, and the brainstem.

The following tracts were delineated using TSA: corpus callosum, corticospinal tract, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, and the uncinate fasciculus.

5.2.4 Air pollution modelling

Air pollution was modelled as described in detail in the methodology chapter in Section 2.3.

5.2.5 Statistical analysis

A correlogram between pollutants within each exposure window was calculated using Spearman's R. All volumes were adjusted for TBV to remove the effect of individual differences in head size and will be referred to as "relative" volumes throughout this chapter. The relationship between prenatal pollution exposure and relative brain morphology was first explored using single pollutant linear regression analysis, adjusting for PMA at scan, GA at birth, sex, IMD, birth weight z-score (BWZ), and days ventilated. Time spent on TPN was not included as a covariate, as it was found to be collinear with days ventilated when testing for collinearity ($r = 0.62$, $p < 0.001$). BWZ is a composite weight score which considers birthweight by parity, sex, and ethnic background (Visser et al., 2009). Results were FDR corrected using the Benjamini-Hochberg method (Benjamini and Hochberg, 1995).

In order to include multiple colinear pollution and brain variables in one model I then performed CCA. All brain volumes and tracts included in the analysis were adjusted for PMA at scan, GA at birth, sex, IMD, BWZ, and by the number of days on ventilation. I used a permutation testing procedure to test the significance of canonical correlation corresponding to each mode in a validation step, with a mode of the CCA only being considered significant if Spearman's r was greater than the 95th percentile of this permutation test (Yu et al., 2019). Since none of the modes passed the 95th percentile of random permutation tests, no further steps were taken.

A secondary analysis was performed to examine the impact of first and second trimester specific exposures on neonatal brain morphology and tractography. The third trimester was not assessed in this specific analysis, as all subjects were born before the midpoint of the third trimester, and some were born before the third trimester began. First, a linear regression analysis was performed, adjusting for the same covariates as described above and further adjusting the trimester specific air pollution exposure for seasonality. Then a CCA was performed as outlined above, also adjusting air pollution exposure for seasonality. Further, sex-specific associations between neonatal brain morphology and tractography and prenatal exposure to air pollution were also assessed in a CCA. To this end I separated the subjects into male and female and conducted CCA analysis as outlined above.

5.3 Results

5.3.1 Subjects

The subjects comprised of 285 subjects (139 male, 146 female) born at a median (range) GA of 30.57 (23.57 – 32.86) weeks and imaged at 42.5 (37.86 – 48) weeks PMA (Table 5.1). The median (range) IMD of the study group was 3 (1-5). Male subjects were scanned at a median age of 42.57 weeks, whereas female subjects were scanned at a median date of 42.43 weeks (Table 5.1). The geographic distribution of subjects' residences can be seen in Figure 5.1. Subjects' residences were concentrated

around West and South London, with few subjects in North and East London (Figure 5.1). A table with additional information on major lesions, BWZ, and time spent on ventilation or TPN can be found in the appendix (Table A6).

Table 5.1: Distribution of age at MRI, age at birth, sex, and index of multiple deprivation of the ePrime subjects.

	Male	Female	Total
Subjects (n, %)	139 (48.8%)	146 (51.2%)	285
Age at MRI, weeks (median, range)	42.57 (37.86 – 47.86)	42.43 (38.28 – 48)	42.5 (37.86 – 48)
Age at birth, weeks (median, range)	30.28 (24 – 32.86)	30.71 (23.57 – 32.86)	30.57 (23.57 – 32.86)
Index of multiple deprivation quintile (median, range)	3 (1 – 5)	3 (1 – 5)	3 (1 – 5)

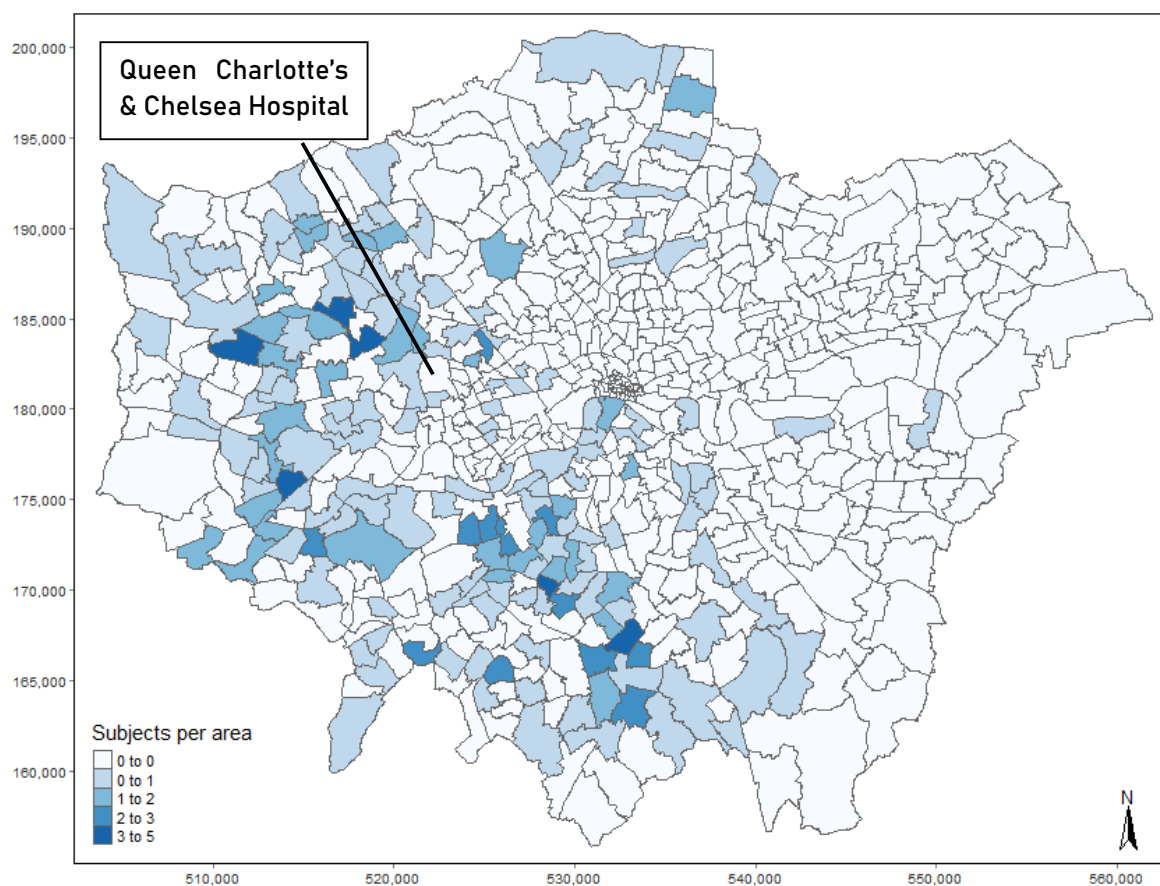


Figure 5.1: Residential subject distribution of the ePrime cohort per lower super output area (LSOA) in Greater London. The subjects were scanned at Queen Charlottes & Chelsea Hospital in west London, which is indicated on the map.

5.3.2 Air pollution exposure

Descriptive statistics of the subjects' exposure to air pollution are outlined below (Table 5.2). None of the pollutants were normally distributed, and the descriptive statistics are therefore presented as median and range. As shown in Table 5.1, subjects were born in the second or third trimester, air pollution exposure is therefore shown only for the entire gestational period, the first, and the second trimester. Modelled median PM₁₀ exposure was 22.9 µg/m³ over the entire gestational period, PM_{2.5} exposure was 13.8 µg/m³, and NO₂ was 35.9 µg/m³. The range of exposures varied by pollutant, with a range of 15.9 – 37.9 µg/m³ for PM₁₀, 7.4 – 24.7 µg/m³ for PM_{2.5}, and 19.3 – 70.0 µg/m³ for NO₂. Trimester specific median exposures were very similar to exposure over the entire gestational period in both range and median values.

Table 5.2: Descriptive statistics of modelled pollution exposure for each trimester and the whole pregnancy in µg/m³ of the ePrime cohort.

PM₁₀ levels, µg/m³ (median, range)	
1st trimester of pregnancy	22.4 (16.1 – 39.9)
2nd trimester of pregnancy	22.2 (17.1 – 36.1)
3rd trimester of pregnancy	-
Whole pregnancy	23.0 (15.9 – 37.9)
PM_{2.5} levels, µg/m³ (median, range)	
1st trimester of pregnancy	13.3 (8.7 – 26.6)
2nd trimester of pregnancy	13.2 (8.9 – 24.0)
3rd trimester of pregnancy	-
Whole pregnancy	13.8 (7.4 – 24.7)

NO₂ levels, µg/m³ (median, range)

1st trimester of pregnancy	36.1 (20.1 – 72.5)
2nd trimester of pregnancy	35.6 (21.1 – 67.0)
3rd trimester of pregnancy	-
Whole pregnancy	35.9 (19.3 – 70.0)

5.3.3 Brain volumes

Descriptive statistics of the subjects' brain volumes are summarised below (Table 5.3). The volume of the ventricles was non-normally distributed, therefore summary statistics are presented as median and range. A table with absolute brain volumes was added to the appendix (Table A7).

Table 5.3: Median and range of absolute total brain volume and relative brain volumes of the ePrime cohort.

Brain region	Median	Range
Total Brain Volume (mm³)	377090	271017 – 529459
Relative Cortical Grey Matter	0.501	0.412 – 0.594
Relative White Matter	0.322	0.248 – 0.41
Relative Cerebellum	0.089	0.074 – 0.122
Relative Ventricles	0.022	0.013 – 0.061
Relative Deep Grey Nuclei	0.086	0.075 – 0.098
Relative Brainstem	0.016	0.013 – 0.019
Relative Amygdala	0.002	0.002 – 0.003
Relative Thalamus	0.024	0.017 – 0.028

Relative Hippocampus	0.004	0.003 – 0.005
-----------------------------	-------	---------------

5.3.4 Single pollutant linear regression

The results of the single pollutant linear regression model examining the relationship between pollution exposure over the entire gestational period and relative brain volumes are detailed below (Table 5.4). Prenatal exposure to PM_{2.5} was related to a decrease in the relative size of the brainstem ($p < 0.05$), though this association does not survive FDR correction ($q > 0.05$). No other association was statistically significant ($p > 0.05$, $q > 0.05$). The linear regression analysis of exposure to air pollution over the first and second trimesters and relative brain volumes did not find any significant results after FDR correction (Table A11 and A12, $q > 0.05$).

Table 5.4: Single pollutant linear regression results for each relative brain volume from the dHCP subjects and PM_{2.5}, PM₁₀, and NO₂, adjusted for sex, IMD, PMA at scan, GA at birth, birth weight z-score (BWZ), and days ventilated; beta = effect size; CI = Confidence interval (95%); q-value = p-value after FDR correction.

Brain Region	Pollutant	<i>beta</i> (in 10 ⁻³)	Std. error (in 10 ⁻³)	Lower CI (in 10 ⁻³)	Upper CI (in 10 ⁻³)	p-value	q-value
Relative White Matter	PM _{2.5}	0.577	0.420	-0.251	1.405	0.171	0.595
	PM ₁₀	0.574	0.353	-0.121	1.268	0.105	0.595
	NO ₂	0.279	0.174	-0.065	0.622	0.111	0.595
Relative Grey Matter	PM _{2.5}	-0.388	0.417	-1.210	0.434	0.353	0.654
	PM ₁₀	-0.444	0.350	-1.133	0.246	0.206	0.595
	NO ₂	-0.269	0.173	-0.609	0.071	0.120	0.595
Relative Amygdala	PM _{2.5}	-0.002	0.003	-0.009	0.004	0.493	0.802
	PM ₁₀	-0.003	0.003	-0.008	0.003	0.333	0.654
	NO ₂	-0.002	0.001	-0.004	0.001	0.220	0.595
Relative Hippocampus	PM _{2.5}	-0.001	0.007	-0.014	0.012	0.913	0.974
	PM ₁₀	0.001	0.006	-0.010	0.012	0.892	0.974
	NO ₂	0.001	0.003	-0.005	0.006	0.974	0.974
	PM _{2.5}	-0.145	0.116	-0.375	0.084	0.213	0.595

Relative Cerebellum	PM ₁₀	-0.114	0.098	-0.307	0.079	0.247	0.605
	NO ₂	-0.003	0.049	-0.098	0.093	0.953	0.974
Relative Deep Grey Nuclei	PM _{2.5}	-0.044	0.071	-0.183	0.095	0.535	0.802
	PM ₁₀	-0.016	0.059	-0.133	0.101	0.787	0.957
	NO ₂	-0.007	0.029	-0.065	0.051	0.815	0.957
Relative Ventricles	PM _{2.5}	0.130	0.142	-0.151	0.410	0.363	0.654
	PM ₁₀	0.132	0.120	-0.104	0.367	0.271	0.61
	NO ₂	0.018	0.059	-0.098	0.135	0.756	0.957
Relative Brainstem	PM _{2.5}	-0.036	0.018	-0.071	-0.001	0.045	0.595
	PM ₁₀	-0.026	0.015	-0.056	0.004	0.084	0.595
	NO ₂	-0.010	0.008	-0.025	0.004	0.166	0.595
Relative Thalamus	PM _{2.5}	-0.019	0.030	-0.077	0.039	0.521	0.802
	PM ₁₀	-0.008	0.025	-0.057	0.041	0.748	0.957
	NO ₂	-0.006	0.012	-0.030	0.018	0.620	0.881

The results of the single pollutant linear regression model examining the relationship between pollution exposure over the entire gestational period and WM microstructure are described in the appendix (Table A8). Exposure to PM_{2.5}, PM₁₀, and NO₂ was not related to any of the WM microstructure metrics assessed ($p > 0.05$, $q > 0.05$).

5.3.5 CCA

The CCA examining the relationship between exposure to air pollution over the entire gestational period and relative brain volumes identified three modes. None of these modes exceeded the 95th percentile of random permutations (Figure 5.2A), which was the threshold of significance, and no further analysis steps were performed. The CCA of exposure to air pollution over the first and second trimesters and relative brain volumes also identified three modes, and none of these exceeded the 95th percentile of random permutations (Figure 5.2B and 5.2C). The same was true when the cohort was separated by sex, neither in the male nor in the female group did any of the modes exceed the 95th percentile of random permutations (Figure 5.2D and 5.2E). None of the modes in any of the analyses came close to the 95th percentile of random permutations, and the modes were instead more closely resembled the median.

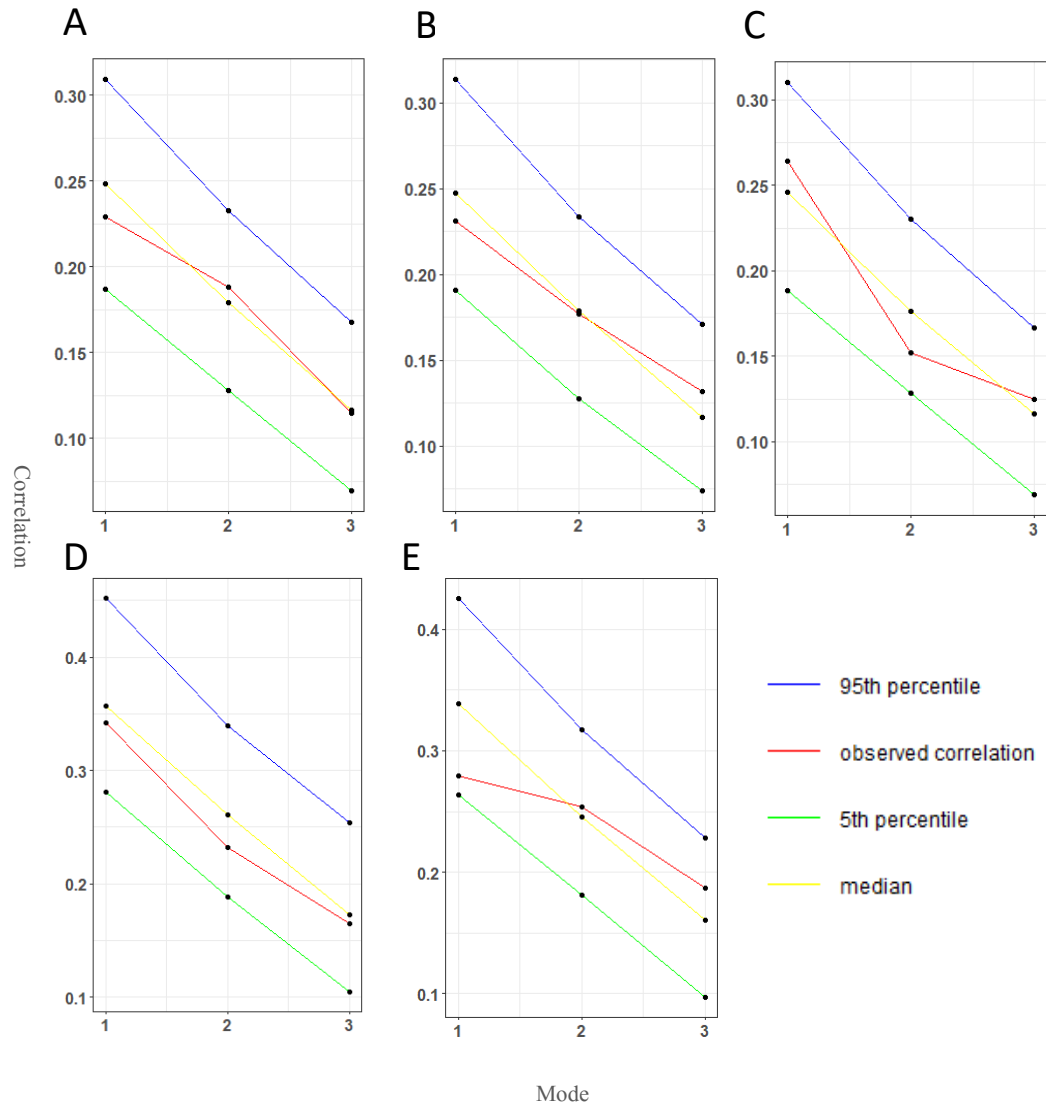


Figure 5.2: Observed CCA correlations (y-axis), the median, and the 5th to 95th percentiles of the null distribution of the permuted CCA correlations estimated via permutation testing across the three CCA modes (x-axis). (A) Exposure to $PM_{2.5}$, PM_{10} , and NO_2 over the entire gestational period for the entire cohort and relative brain volumes. (B) Exposure to $PM_{2.5}$, PM_{10} , and NO_2 over first trimester for the entire cohort and relative brain volumes. (C) Exposure to $PM_{2.5}$, PM_{10} , and NO_2 over the second trimester for the entire cohort and relative brain volumes. (D) Exposure to $PM_{2.5}$, PM_{10} , and NO_2 over the entire gestational period for male subjects and relative brain volumes. (E) Exposure to $PM_{2.5}$, PM_{10} , and NO_2 over the entire gestational period for female subjects and relative brain volumes. White matter microstructure

The CCA examining the relationship of exposure to air pollution over the entire gestational period and WM microstructure identified three modes. None of these modes exceeded the 95th percentile of random permutations (Figure 5.3A). The CCA of exposure to air pollution over the first and second

trimesters and WM microstructure also identified three modes, though none of these exceeded the 95th percentile of random permutations (Figure 5.3B and 5.3C). The same was true when the cohort was separated by sex, neither in the male nor the female group did any of the modes exceed the 95th percentile of random permutations (Figure 5.3D and 5.3E). In the analysis of the second trimester the second mode had an observed correlation of $r = 0.469$, and the 95th percentile was $r = 0.47$. However, none of the other modes in any of the analyses came close to the 95th percentile of random permutations.

The linear regression analysis of exposure to air pollution over the first and second trimesters and WM microstructure did not find any significant results (Table A9 and A10, $p > 0.05$, $q > 0.05$).

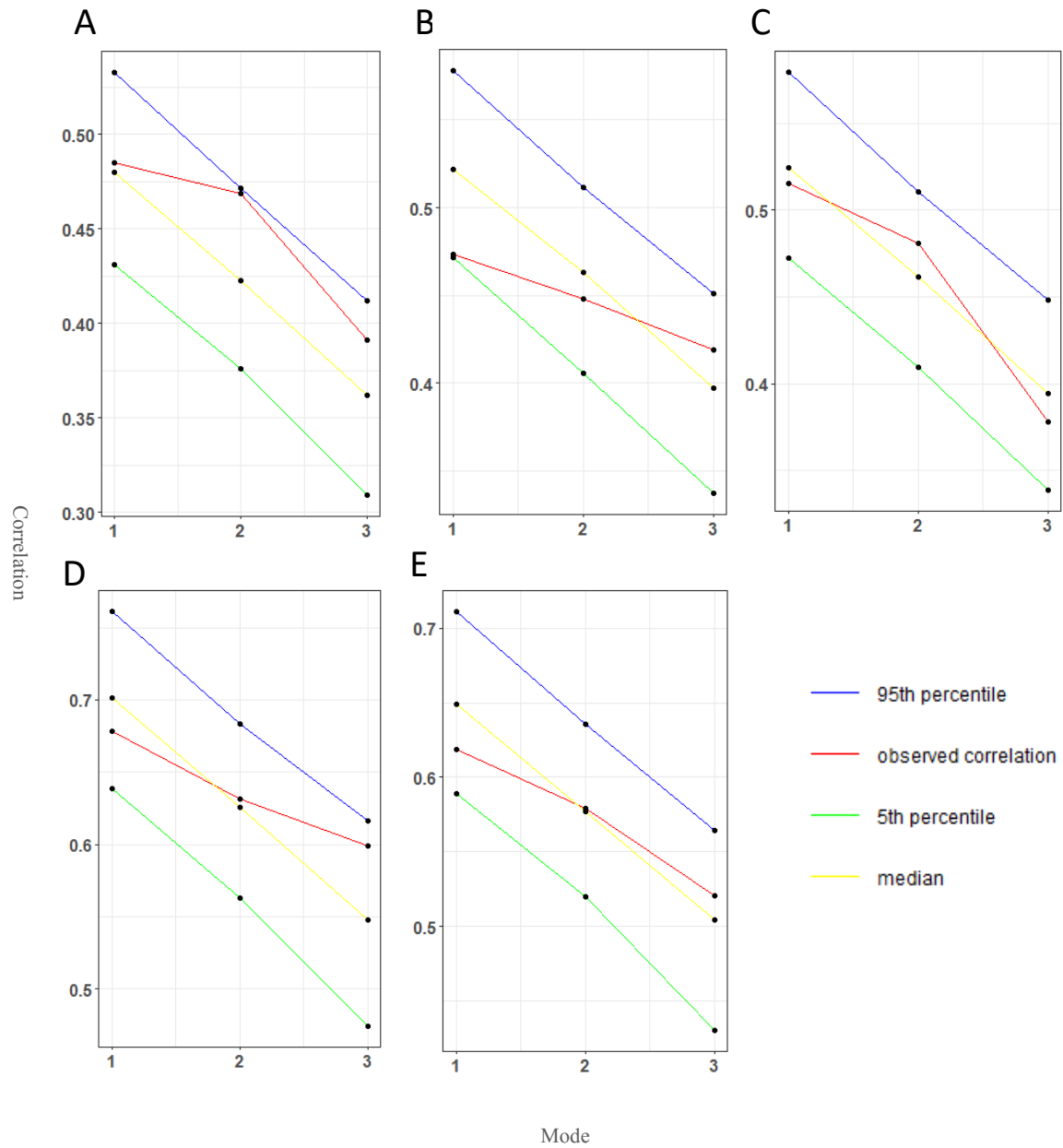


Figure 5.3: Observed CCA correlations (y-axis), the median, and the 5th to 95th percentiles of the null distribution of the permuted CCA correlations estimated via permutation testing across the three CCA modes (x-axis). (A) Exposure to $PM_{2.5}$, PM_{10} , and NO_2 over the entire gestational period for the entire cohort and white matter microstructure. (B) Exposure to $PM_{2.5}$, PM_{10} , and NO_2 over first trimester for the entire cohort and white matter microstructure. (C) Exposure to $PM_{2.5}$, PM_{10} , and NO_2 over the second trimester for the entire cohort and white matter microstructure. (D) Exposure to $PM_{2.5}$, PM_{10} , and NO_2 over the entire gestational period for male subjects and white matter microstructure. (E) Exposure to $PM_{2.5}$, PM_{10} , and NO_2 over the entire gestational period for female subjects' white matter microstructure.

5.4 Discussion

In this chapter I assessed the relationship between prenatal exposure to ambient air pollution in preterm born infants and neonatal brain morphology and WM microstructure as assessed by MRI at term. Using CCA and simple linear regression models I found no associations between prenatal exposure to PM_{2.5}, NO₂, and PM₁₀, and neonatal brain morphology or WM microstructure in preterm infants. Further, investigating specific trimesters of exposure and separating the cohort by sex also revealed no associations between prenatal exposure to air pollution and structural and diffusion MRI measures at term equivalent age.

There are no other studies examining the effects of prenatal exposure to air pollution on neurodevelopment assessed by structural MRI or diffusion MRI in infants born preterm, at term or in later life. In Chapter 4 I showed that in term born infants, higher prenatal exposure to PM₁₀ and lower prenatal exposure to NO₂ are linked to larger relative ventricular and cerebellar volume, along with modest associations with smaller cortical GM, amygdala and hippocampus volumes, and larger volumes of brainstem and extracerebral CSF in healthy term born infants. Several studies examined the effect of prenatal air pollution exposure and neurodevelopment assessed by structural MRI in childhood with mixed results, as previously described in Section 1.3.1. Briefly, no associations between any brain volumes or global brain metrics were found in two studies (Guxens et al., 2018, Mortamais et al., 2019). Prenatal exposure to air pollution was associated with an increase in relative size of the cerebellum, putamen, pallidum, and amygdala, and a smaller relative size of the hippocampus (Lubczyńska et al., 2021). Prenatal exposure to air pollution was not associated with volumes of the total brain, GM, WM, ventricles, and the thalamus (Guxens et al., 2018, Mortamais et al., 2019, Lubczyńska et al., 2021). Peterson et al found an association between prenatal exposure to air pollution and local WM volumes (Peterson et al., 2022). I did not find any associations with brain regions previously implicated in term born infants or in childhood. Two previous studies examined the effect of prenatal air pollution exposure and neurodevelopment assessed by diffusion MRI in childhood (described in detail in Section 1.3.2). Briefly, Lubczynska et al (2020) found an association between multiple air pollutants and lower global FA and higher global MD. Silicone exposure was associated with higher MD in the cingulate gyrus part of the cingulum of the left hemisphere, the left superior longitudinal fasciculus, and the forceps minor. Further, Peterson et al (2022) found an association between higher exposure to PAH and PM_{2.5} and higher FA values in the basal ganglia, anterior cingulate gyrus, and thalamus, higher PM_{2.5} exposures were associated with greater diffusivity in the anterior CC and the anterior corona radiata, and higher exposures to PAH were also associated with lower diffusivity in the internal capsule. I did not find any associations with metrics of WM microstructure implicated in previous studies.

Preterm infants may not be affected by prenatal exposure to air pollution in the same way due to a different timeframe of exposure. The ePrime cohort analysed in this study was born prior to 33 weeks GA, which is less than halfway into the third trimester, with some subjects born much earlier (median 30.57 weeks GA). Thus, most of the prenatal exposure to air pollution was limited to the first and second trimester and much of the third trimester's exposure may be in the ex-utero environment. The third trimester is characterised by rapid brain development, as multiple key neurodevelopmental processes take place, including synaptogenesis, neuronal organisation, and the onset of myelination (Kostović and Jovanov-Milosević, 2006). WM pathways show an increase in whole brain mean FA with GA, and a decrease in MD, however, different sections of the WM showed distinct maturational trends of FA and MD (Wilson et al., 2021). These processes may make the brain uniquely vulnerable to injury in the third trimester. This was also suggested by Allen et al (2017), who studied prenatal UFP exposure in mice and suggested the human third trimester equivalent as a period of vulnerability to neurodevelopmental toxicity of UFP due to rapid neuro- and gliogenesis in this period. However, in mice this period occurs ex utero and may not be transferable to humans (Allen et al., 2017). Further, comparison of WM in mice and humans is complicated by the fact that mice have much less WM (Zhang and Sejnowski, 2000, Ventura-Antunes et al., 2013). Mortamais et al reported an association between higher levels of residential PM_{2.5} exposure and smaller CC volume in 8 – 12 year old school children, but this association did not survive FDR correction (Mortamais et al., 2019). Peterson et al found an association between third trimester exposure to PAH and reductions in WM surface area in children aged 7 – 9 years old, with null results for cortical thickness (Peterson et al., 2015). Further, in Chapter 3 I assessed the impact of third trimester exposure to air pollution on WM microstructure metrics and in Chapter 4 I assessed the impact of third trimester exposure to air pollution on brain morphology at term and found no significant results. There is therefore not enough evidence to suggest that the third trimester of pregnancy is a stage of neurodevelopment uniquely vulnerable to air pollution exposure and that the lack of prenatal exposure in this period in this cohort could explain the null results of this study.

Concentrations of PM_{2.5}, PM₁₀, and NO₂ modelled in this study were all above the 2021 World Health Organisation annual air quality guidelines for these pollutants (5 µg/m³, 15 µg/m³, and 10 µg/m³, respectively) (World Health Organization, 2021), but they were below the UK standards (20 µg/m³, 40 µg/m³, and 40 µg/m³, respectively) (DEFRA, 2010). Concentrations of air pollutants modelled in the ePrime cohort were comparable to those found in the dHCP cohort, with median concentrations of PM_{2.5} at 13.5 µg/m³ compared with 13.8 µg/m³, PM₁₀ at 23.4 µg/m³ and 22.9 µg/m³, and NO₂ at 39.7 µg/m³ and 35.9 µg/m³, respectively. The pregnancy periods in the ePrime cohort occurred between 2010 – 2013 and those included in the dHCP chapter occurred between 2015 – 2020. Roadside

concentrations of PM_{2.5}, PM₁₀, and NO₂ decreased in London between 2010 – 2016 in a heterogeneous manner (Font et al., 2019), with no studies conducted on background air pollution concentrations. Nonetheless, as with the concentrations modelled in the dHCP cohort, the concentrations modelled in the ePrime cohort were comparable to other studies examining pregnancy cohorts in European cities (Guxens et al., 2022), lower than pregnancy cohorts in low to middle income countries (Wyllie Blair et al., 2017, Zhou et al., 2022), and higher than pregnancy cohorts in north America (Zhang et al., 2022, Zhang et al., 2018a).

Neurodevelopment at term as assessed by MRI in preterm infants is strongly associated with GA at birth, PMA at scan, sex, and other factors (Kersbergen et al., 2016). Though I adjusted for several important factors, it may be the case that other factors associated with preterm birth outweigh or confound the small effect air pollution may have on neurodevelopment in a cohort born extremely preterm. Additionally, even though the cohort size may be large for a neonatal cohort, it is small in statistical terms and may have led to a lack of statistical power to detect the association between prenatal exposure to air pollution and neurodevelopment in preterm infants, if any.

I did not find any trimester or sex-specific associations between prenatal exposure to air pollution and brain volumes or WM microstructure. As discussed above, it is unclear whether this is because the first and second trimester are not vulnerable periods of neurodevelopment to air pollution exposure. The sex-specific analysis may have suffered from reduced statistical power, as I divided the subjects into male and female subgroups because including a categorical variable into CCA is not possible.

5.5 Conclusions

In this chapter I found no impact of prenatal air pollution exposure on brain morphology and WM microstructure metrics at term in infants born extremely preterm. I hypothesised that preterm infants' neurodevelopment would be uniquely vulnerable to the impacts of air pollution, but this study indicates a null result. This is the only study to assess the impact of prenatal exposure to air pollution on brain morphology and WM microstructure in preterm infants at term, and longitudinal studies with MRI taken at several time points throughout early life are required to confirm these findings.

CHAPTER 6 – REDUCING PREGNANT WOMEN’S EXPOSURE TO AIR POLLUTION

In the previous chapters I have laid out the evidence of the impact of prenatal exposure to air pollution on neonatal neurodevelopment and summarised the evidence on childhood neurodevelopment as assessed by MRI. Prenatal exposure to air pollution has impacts beyond those described previously in this thesis, and it is clear that mothers and their offspring should be protected from this health burden. In this chapter I will describe potential interventions to reduce personal exposure to air pollution and how these could be applied to pregnant women. Unlike previous chapters, which only assess exposure to ambient air pollution, I will consider exposure from indoor and outdoor sources, under the assumption that health effects from each source type are similar.

This discussive chapter is in lieu of planned personal exposure fieldwork that was not possible due to restrictions arising from the COVID pandemic, but the feasibility and efficacy of its concluding recommendations could be evaluated in future research.

6.1 The health effects of prenatal air pollution exposure

The global burden of prenatal exposure is distributed unequally, and the impact is strongly dependent on geographic location and socioeconomic status of the mother and the fuel sources used. Household air pollution (HAP), generated from the burning of biomass, kerosene, and coal for heating, cooking, and lighting in typically small and under ventilated spaces can lead to very high exposures to multiple air pollutants (Zhu et al., 2022, Rosário Filho et al., 2021). This problem is centred around low- and middle-income countries (LMICs), especially in South Asia and sub-Saharan Africa, and since women customarily spend a lot more of their time at home in many of these countries, they are particularly vulnerable to the high levels of exposure found inside households in LMICs. This exposure leads to substantial health effects in adults and children, causing higher rates of chronic obstructive pulmonary disease (COPD), lung cancer, and cerebrovascular disease in adults, and asthma and acute respiratory infections in both adults and children. HAP exposure disproportionately affects maternal health and that of their offspring, and effects include increased risk of low birthweight, stillbirth, and respiratory and cardiovascular mortality in under-5s (Lee et al., 2020a, Maung et al., 2022).

Several types of interventions have been undertaken to decrease HAP concentrations and exposure associated with domestic solid biomass fuel combustion, and these include improving cookstoves or replacing them with liquefied petroleum gas stove or ethanol stove alternatives (Woolley et al., 2022). However, the success of these interventions has been limited (Masekela et al., 2023), with only four studies achieving an improvement of the risk of low birth weight after intervention, and no effects on

preterm birth and acute respiratory infections, largely due to lack of consideration of community and end-user needs (Thakur et al., 2018, Thomas et al., 2015, Woolley et al., 2022).

In this chapter I will focus on high-income countries (HIC), where generally air pollution concentrations are much lower. Even at these much lower concentrations, prenatal exposure to air pollution has impacts on the offspring's health beyond the evidence presented in this thesis, such as low-birth weight and stillbirth (Smith et al., 2020, Smith et al., 2017, Bekkar et al., 2020). There is also evidence of an association between gestational exposure to particulate matter and hypertensive disorders of pregnancy and preeclampsia (Cao et al., 2021, Bai et al., 2020). In terms of further neurodevelopmental effects, several studies have demonstrated the detrimental impacts of prenatal exposure to air pollution on cognitive performance in childhood, including on full-scale IQ (ages 10.5 and 5 years old on average, respectively) (Holm et al., 2023, Lee et al., 2017), impaired standard error of the hit reaction time and increased omission errors (ages 4 – 5 and 6.5 years old, respectively) (Sentís et al., 2017a, Chiu et al., 2016). The overall evidence on neurobehavioural disorders and prenatal exposure to air pollution is less clear, with both null and significant results for attention deficit hyperactivity disorder (ADHD) (ages 3 – 10 and 10 – 15 years old, respectively) (Forns et al., 2018, Fuertes et al., 2016), and some evidence of an effect on ASD (Chun et al., 2020, Pagalan et al., 2019, Raz et al., 2015).

Whilst there is some uncertainty surrounding the specific impacts of prenatal exposure to air pollution, the general picture of the vulnerability of pregnant women to air pollution is clear. Despite the substantial body of evidence showing detrimental impacts of prenatal exposure to air pollution on infants and children, there is little evidence of how pregnant women could reduce their exposure to air pollution. As even relatively low concentrations of air pollution which are found in HIC are linked to negative outcomes in mother and child, there is a need to create clear, actionable and accessible evidence-based recommendations for the reduction of pregnant women's exposure to air pollution to prevent significant health burdens in early and later life.

6.2 The case for exposure reduction interventions

The need for interventions to reduce personal exposure to air pollution is not immediately obvious, especially since emission reduction strategies are an effective method of reducing exposure to air pollution for large swathes of the population (Carlsten et al., 2020, World Health Organization, 2020, Laumbach et al., 2021). A further argument against personal interventions is that reducing personal exposure is not an equitable approach, as not every individual will have access to an intervention, and it can place a burden of discomfort, cost, and inconvenience on an individual (Laumbach and Cromar, 2022). The onus should not primarily be on the population to reduce their exposure, especially not on

a vulnerable subgroup such as pregnant women, but on the emitter of said air pollution to reduce emissions. However, progress on emission reduction is slow. Exposure to air pollution can have a substantial burden on an individual's health, and when upstream interventions are insufficient and don't effectively reduce exposure, empowering individuals to act on their own behalf can have a significant positive impact (World Health Organization, 2020). Even with effective measures in place, as there is no safe lower limit for air pollution (Pope et al., 2015), there may always be a case for interventions to reduce exposures further, especially in vulnerable people.

Interventions for air pollution exposure reduction are usually aimed at disrupting the pathway from the source to the inhalation or dose of air pollution (Laumbach and Cromar, 2022). In order to effectively reduce an individual's exposure, it is important to understand what their personal exposure consists of and how this relates to their own norms, behavioural, financial, and social situation.

6.3 Prenatal exposure and maternal behaviour

In the case of pregnant women, most studies (including this thesis) have employed modelling techniques to understand ambient air pollution exposure using assumptions about time-activity patterns and generally neglecting subjects' spatiotemporal mobility (Nyadanu et al., 2022). Several studies used measurements or combined measurements with modelling efforts to understand prenatal exposure to air pollution, though these measurements were often made at local measurement sites or only at specific time points during pregnancy (Ha et al., 2020). A slightly dated study found moderate agreement between short-term personal exposure measurements and estimates using LUR models and interpolation of ambient monitors (Nethery et al., 2008). There have been studies to understand HAP exposure in LMICs (Johnson et al., 2022), but there is a lack of understanding of personal exposure to air pollution throughout pregnancy in a maternal cohort in a HIC. A few studies have conducted measurements of personal exposure at various time points throughout pregnancy (Ghassabian et al., 2023), and some have considered urine metabolites (Lozano et al., 2022, Boyle et al., 2016), however, a more comprehensive effort would give greater insights into opportunities for intervention.

There is little evidence of time-activity patterns of pregnant women and how these change during the course of pregnancy. A study from 2009 collected time-activity data for 62 pregnant women in Canada up to three times during pregnancy, with no data collected in the first trimester (Nethery et al., 2009). Pregnant subjects were compared with a group of non-pregnant female controls. Pregnant women spent more time at home the further the pregnancy progressed, and those out of work, from lower income groups, and with previous children also spent more time at home during pregnancy. No other

behaviour such as time spent outdoors or in transit was related to pregnancy status or the progression of pregnancy.

6.4 Types of exposure environments and existing guidance

Air quality information and air pollution exposure reduction guidance in the UK is combined with advice for exercise (Department for Environment Food & Rural Affairs (DEFRA), <https://uk-air.defra.gov.uk/air-pollution/daq>). The advice is tied to the Daily Air Quality Index (DAQI), which ranges from Low (DAQI of 1 – 3), Moderate (DAQI of 4 – 6), and High (7 – 9), to Very High (DAQI of 10). Each of these values is accompanied with behavioural advice, particularly for outdoor air pollution exposure and divided into advice for the at-risk individuals and the general population (Figure 6.1).

Air Pollution Banding	Value	Accompanying health messages for at-risk individuals*	Accompanying health messages for the general population
Low	1-3	Enjoy your usual outdoor activities.	Enjoy your usual outdoor activities.
Moderate	4-6	Adults and children with lung problems, and adults with heart problems, who experience symptoms , should consider reducing strenuous physical activity, particularly outdoors.	Enjoy your usual outdoor activities.
High	7-9	Adults and children with lung problems, and adults with heart problems, should reduce strenuous physical exertion, particularly outdoors, and particularly if they experience symptoms. People with asthma may find they need to use their reliever inhaler more often. Older people should also reduce physical exertion.	Anyone experiencing discomfort such as sore eyes, cough or sore throat should consider reducing activity, particularly outdoors.
Very High	10	Adults and children with lung problems, adults with heart problems, and older people, should avoid strenuous physical activity. People with asthma may find they need to use their reliever inhaler more often.	Reduce physical exertion, particularly outdoors, especially if you experience symptoms such as cough or sore throat.

Figure 6.1: Daily Air Quality Index and recommendations for at-risk individuals and the general population in the UK, reproduced from <https://uk-air.defra.gov.uk/air-pollution/daq> (Department for Environment Food & Rural Affairs (DEFRA)).

Pregnant women are not categorised as part of the at-risk individuals unless they have underlying heart or lung problems. When planning strenuous activity outdoors it is also advised that at-risk individuals check the air pollution forecast, which provides an indication of the air pollution levels to come in the following days. This advice could readily be extended to include pregnant women, who are vulnerable to the effects of air pollution and may be classifiable as at-risk individuals. However, there is a need to balance the beneficial effects of outdoor exercise with the harmful effects of air

pollution exposure in this messaging, as the inhaled dose can be higher when using active travel modes compared with travelling by car or public transport (Nyhan et al., 2014). A 2017 review of ambient air pollution exposure according to mode of transport found higher exposures for active commuters but also higher life expectancy, suggesting that the beneficial effects of exercise outweighed the negative effects of high air pollution exposure (Cepeda et al., 2017). A review from 2021 similarly concluded that in the active transport environment the benefits of physical activity outweigh the risks of air pollution exposure (Tainio et al., 2021). The authors pointed out, however, that the evidence is very limited for LMICs and for sensitive subpopulations, including pregnant women. The evidence for exercise and air pollution may therefore not be generalisable to pregnant women.

Air quality information and air pollution exposure reduction guidance is rarely extended to other areas of life, such as inside the home, the travel microenvironment, and inside schools, where people spend significant amounts of time. Air pollution concentrations can be high in any of these environments and can contribute a significant share of daily exposure. For example, a review of previous studies found that despite the fact that most people spend only a short amount of time each day travelling or commuting, exposure in this microenvironment can account for a sizeable share of daily pollution exposure (Mitsakou et al., 2021). Over the six studies that were reviewed (Marshall et al., 2006, Kaur et al., 2007, Roosbroeck et al., 2008, Dons et al., 2013, Dons et al., 2012, de Nazelle et al., 2013), people only spent around 6% of their time travelling and yet they were exposed to around 30% of their daily cumulative total exposure to air pollutants.

Indoor environments such as the home or the workplace may also differ substantially in their contribution to total exposures, depending on various factors such as behaviour, occupation, and socioeconomic status (Kelly and Fussell, 2018, Flanagan et al., 2019). Occupational exposure is regulated by workplace exposure limits and exposure must be controlled to be as low as is reasonably practicable (Health and Safety Executive, 2020). The workplace exposure limits for air pollutants are very high compared with the concentrations that have been linked to health effects on mother and child, though workplace limits only apply over 15-minute and 8-hour periods and are decided by evidence of short-term effects. In the USA, 90% of women remain employed during pregnancy (United States Census Bureau, 2011), which means workplace exposure could contribute significantly to air pollution exposure during pregnancy. In the UK, workplace risk assessments have to be carried out to protect pregnant workers, though this does not entail more stringent air pollution exposure limits than for non-pregnant workers (Health and Safety Executive, <https://www.hse.gov.uk/mothers/employer/risk-assessment.htm>).

The home environment is viewed as a protected space, and people mistakenly believe they are not exposed to air pollution in their homes as they see it as an outdoor problem (Kelly and Fussell, 2018). As outlined above, pregnant women spend more time at home than the average person of similar age. Therefore, the home environment should be a focus for reducing pregnant women's exposure to air pollution, yet, to date, there is no guidance or advice for pregnant women to reduce their exposure to air pollution in the home environment. Spreading information about key contributors to air pollution exposure and sharing the tools to reducing exposure is essential in improving outcomes related to air pollution exposure in pregnant women. In the next section I will introduce the interventions that are available and have been shown to reduce personal exposure to air pollution.

6.5 Interventions to reduce personal exposure to air pollution

6.5.1 Interventions in outdoor behaviour

There are many actions available to an individual to reduce their exposure to air pollution. As mentioned above, the DAQI is used to communicate risk about concentrations of outdoor air pollution in the UK. Checking the air quality forecast and planning strenuous activities on days that have low levels of outdoor air pollution could effectively reduce exposure, especially since breathing rates and air intake are highly elevated during even moderate exertion. This leads to much higher doses of air pollution exposure in those who are exercising compared with people who are sedentary or doing less strenuous modes of exercise such as walking (Nyhan et al., 2014). Staying indoors and avoiding high outdoor air pollution days could therefore have a high impact on exposure, however, there is little evidence linking modified behaviour depending on outdoor air pollution levels with health benefits. In a study conducted in London, walking beside a busy road was associated with fewer short-term gains in lung function than walking in a park in healthy adults and patients with COPD or ischaemic heart disease (Sinharay et al., 2018). Exercising away from busy roads and high levels of TRAP could significantly reduce exposure to air pollution. The ideal time of day to exercise is not entirely clear, as ozone concentrations are lower in the morning but exposure to TRAP may be higher (Mitsakou et al., 2021). However, it is important not to overcomplicate the advice, as exercise throughout pregnancy is associated with preventing pregnancy related disorders and improving outcomes for both mother and child (Ribeiro et al., 2022).

6.5.2 Transport interventions

The transport microenvironment can contribute significantly to daily cumulative exposure to air pollution (Mitsakou et al., 2021). In a review of urban transport microenvironments, Mitsakou et al (2021) found that active transport was associated with lower exposure to air pollution compared with motorised transport when the car windows were open. When the windows were closed and

ventilation was changed to recirculation mode, particulate air pollution concentrations were lower than in active travel modes. This comparison also depended strongly on where active travel took place. If pedestrian and cyclist routes were separated from the road, exposures decreased, even with only a few metres of separation. Public transport exposures, which consisted of measurements on trains and buses, were generally comparable to those in active travel and depended on factors such as route, air filtration, and location and frequency of stops. The mix of pollutants also differed between modes, with especially particulate matter exposures being dependent on filters inside vehicles and opening or closing windows. This review did not consider inhaled doses, which are likely significantly higher in active travel modes compared with motorised and public transport.

Exposure reduction advice in the transport microenvironment can be highly complex and be different for different microenvironments and situations based on this evidence. For example, when driving through areas with high concentrations of air pollution such as busy intersections or tunnels reducing air inflow into your vehicle by closing the windows and setting the ventilation settings to recirculate lowers concentrations inside the car (de Nazelle et al., 2017, Cepeda et al., 2017). This needs to be balanced against CO₂ concentrations inside the cabin, as high CO₂ concentrations due to lack of ventilation can impair concentration (Hudda and Fruin, 2018). Ventilation of the cabin should be done in areas with low air pollution concentrations, which may be difficult to estimate without significant expertise. Thus, advice related to driving behaviour may be too nuanced and complex to give to pregnant women. It is evident that active travel holds many benefits for pregnant women, especially when undertaken away from pollution sources such as busy roads (Carlsten et al., 2020, Ribeiro et al., 2022). However, there is a lack of evidence comparing the benefits of active travel with the potentially detrimental effects of increased inhaled dose of air pollution on pregnant women and their offspring.

Wearing a face mask or a respirator may be a method of reducing exposure to particulate matter. There is a limited amount of evidence to suggest that this is the case, and efficacy is strongly dependent on proper usage to ensure tightness of fit (Rengasamy and Eimer, 2011). Further, it has been suggested that wearing a facemask makes an individual feel protected from the harmful effects of air pollution which could make them linger for too long in highly polluted areas, whereas the actual level of protection is uncertain (Huang and Morawska, 2019). The usage of respirators has been linked to some benefits on cardiovascular health, such as short term reduction in blood pressure and increased heart rate variability (Langrish et al., 2012, Langrish et al., 2009, Morishita et al., 2019, Shi et al., 2017). No studies have been conducted on long-term use of respirators or face masks and effect on clinical outcomes, nor have studies examined the effect of using loose-fitting masks to reduce exposure (Laumbach and Cromar, 2022). One study suggested there may be adverse effects of wearing a mask or respirator, such as discomfort, stress, headaches, and dermatitis (Johnson, 2016). When

comparing physiological and subjective responses to wearing a N95 filtering facepiece respirator in pregnant women compared with nonpregnant women, no differences were found (Roberge et al., 2014). To be able to recommend the usage of facemasks and respirators in pregnant women, more evidence is required balancing the possible detrimental physiological and psychological effects of wearing masks with the thus far unexplored short and long-term benefits during pregnancy.

6.5.3 Indoor interventions

Indoor air is a mixture of outdoor air infiltrating into a building and combining with indoor sources in a process affected by indoor chemistry (Air Quality Expert Group, 2022). Indoor sources of air pollution include emissions from building materials, cleaning products, personal care products, cooking, environmental tobacco smoke (ETS), and biological sources such as human metabolism, pets, house dust mites, and mould (Kelly and Fussell, 2018, González-Martín et al., 2021). Polluted outdoor air enters buildings and can worsen indoor air quality, and the rate of infiltration is highly dependent on the building type, openings and gaps in the building envelope, and whether natural or mechanical ventilation is employed (Nazaroff, 2021). Being inside a building can be protective and reduce exposure, especially in the case of high outdoor air pollution and low indoor-outdoor ratios (Laumbach and Cromar, 2022). The increased airtightness of modern buildings decreases infiltration of outdoor air pollutants but may come at a trade-off with lower ventilation rates unless mechanical ventilation is employed. Adequate ventilation is important to prevent build-up of indoor air pollutants as well as moisture levels which could lead to mould problems (Air Quality Expert Group, 2022).

Mechanical ventilation systems are often equipped with air filtration systems such as HEPA filters. HEPA filters are the most commonly used indoor air cleaner system and are over 95% efficient in removing particles of all sizes (Bliss, 2006). Particle filtration systems have been shown to reduce exposure to particulate matter by between 20 to 70%, and lower exposures to infiltrated outdoor air have been linked to decreases in morbidity and mortality (Fisk, 2013, Cheek et al., 2021). Barn et al (2018b) equipped the homes of pregnant women with portable air purifiers between on average 11 weeks gestation and birth in Mongolia, which reduced overall concentrations of PM_{2.5} inside homes by 29%. The researchers found no evidence of an effect of the intervention on parent reported behaviour problems and little impact on autism-related behaviour scores in children four years of age compared with a control group (Enkhbat et al., 2021, Enkhbat et al., 2022), however, they found an increase in birth weight in term born babies (Barn et al., 2018a), an increase in full-scale intelligence quotient at age four (Ulziikhuu et al., 2022), and a decrease in weight in two year old children in the intervention group (Tamana et al., 2021). This intervention indicates some benefit of using air filters to reduce prenatal exposure to air pollution. Air purification only started near the end of the first trimester, and filter effectiveness was reduced by 50% after 5 months, indicating that with proper

maintenance of the equipment and an earlier start date exposures might have been decreased more effectively. The concentrations of air pollutants in this study were very high and this finding may not be directly comparable to HIC with lower concentrations.

Gaseous pollutants are not removed by HEPA filters. There are many different types of indoor air purification systems that attempt to remove particulate matter as well as gaseous pollutants, some of which produce harmful by-products such as ozone (US EPA, 2018). Activated carbon filters may provide some effect in reducing indoor exposure to gaseous pollutants without producing any harmful by-products.

Awareness of the effect on air quality of chemical-emitting consumer products such as candles, compressed aerosol devices, and personal care products is important to ensure adequate source control indoors (Air Quality Expert Group, 2022). Replacing combustion appliances such as gas cookers with electric equivalents and using an extractor fan and ensuring adequate ventilation when cooking will further reduce emissions. Introducing legislation to restrict indoor emissions of air pollution would provide benefits for public health for the entire population, including for pregnant women.

6.6 Behavioural change in pregnant women

The pregnancy period is seen as one where women are especially susceptible to health advice and are likely to implement behavioural changes in favour of their own health and their child's health (Zinsser et al., 2020). Current UK guidelines recommend that pregnant women are given lifestyle advice during antenatal appointments (National Institute for Health and Care Excellence, 2021). There are many behavioural and lifestyle changes that women are advised to adopt at the onset of pregnancy and keep up throughout pregnancy, including changes in routine care, abstinence from alcohol and tobacco consumption, changes in physical activity, and improved diet (Zinsser et al., 2020). These changes are considered vital for the health of the mother and child. Intervening in the early stages of pregnancy may improve health outcomes for both mother and child through pregnancy and beyond early life of the child, depending on how effectively behavioural changes are adopted (Rockliffe et al., 2021). Incorporating advice about the impacts of prenatal air pollution exposure and how to reduce exposure into national guidelines may be an effective method of communicating the health risk to pregnant women.

Disseminating information about the risk is crucial. Further, pregnant women need to be given the tools to make informed choices to reduce their exposure, and key to this is making air quality data accessible (McCarron et al., 2023). The UK and especially London has one of the most extensive networks of ambient air quality monitoring sites globally, which provides information about air pollution concentrations and is readily accessible to anyone. As described above, air quality

information is usually provided in the form of an air quality index such as the DAQI in the UK, in order to decrease the level of complexity of the information. In most other locations reliable information about air quality is much more inaccessible, and the quality of the data may not be as high (OpenAQ, 2020). AQI metrics may vary between countries and may not accurately represent the scientific evidence on health impacts of air pollutant concentrations and exposure (Kanchan et al., 2015). For example, the DAQI may indicate that air quality is “good” at concentrations that have been evidenced to impact upon the health of the general public, as well as the health of pregnant women and their offspring, risking miscommunication with this vulnerable group.

The perceived level of personal vulnerability or susceptibility may be a barrier to behaviour change, which increases the importance of communicating the risk of air pollution exposure to pregnant women (D'Antoni et al., 2017). Moreover, being able to access air quality data does not automatically lead to behavioural change which decreases exposure to air pollution, even when being alerted to high pollution days (Noonan, 2014).

Ensuring lasting behavioural change which reduces exposure effectively is a complex endeavour. No single change in behaviour will eliminate personal exposure, and as there is no known risk-free level of air pollution exposure even the target level is uncertain (Pope et al., 2015). According to McCarron et al (2023), air quality dissemination strategies and engagement tools beyond making data accessible to the public are needed. Personal exposure measurements have in previous studies increased the awareness of the threat of air pollution and also resulted in increased awareness of the connection between exposure and behaviour (Wong-Parodi et al., 2018). Further, and more importantly, subjects in some studies took protective action after taking part in personal exposure studies, including keeping the car windows closed and reducing idling, as well as no longer walking on busy roads (Bales et al., 2019, Heydon and Chakraborty, 2020). In a study conducted on school children in London, after a personal measurement campaign and information dissemination about the detrimental impacts of air pollution exposure, 98% of children said they were aware of the problem of air pollution. In total 31% of children reported altering their route to school to reduce their exposure after the intervention, and 24% of parents responded similarly (Varaden et al., 2021). A personal exposure study in Barcelona, Spain, increased motivation and awareness of the problem of air pollution in a group equipped with monitoring devices compared with a control group, yet both groups felt a lack of controllability and self-efficacy with respect to reducing personal exposure (Oltra et al., 2017). As far as I'm aware, no personal exposure studies including pregnant women in order to reduce their exposures were conducted to date. One study examined the efficacy of a behavioural strategy to minimise air pollution exposure in pregnant women in Tehran, Iran, however no air pollution measurements were taken (Araban et al., 2017). This study recruited pregnant women and disseminated information about the

dangers of outdoor air pollution and sent daily reminders via text message to stay inside to reduce the subjects' exposures, with no intervention in a control group. This intervention was effective in increasing time spent indoors in the intervention group, however, what effect this had on exposures and outcomes was not investigated.

McCarron et al (2023) suggests that pairing personal exposure data with enhanced participatory engagement, creating a dialogue between researchers and community, is an effective way of enabling exposure reduction behaviour. Further, co-producing personal exposure studies and exposure reduction interventions with the community led to solutions designed around the need of the community (West et al., 2021). As a unique cohort facing unique challenges, pregnant women's needs and problems must be considered in any interventions to reduce their exposure to air pollution.

In a scoping review of behaviour change in pregnant women conducted by Zinsser et al (2020) behaviour change programs which prioritised empowerment of pregnant women as well as improving their skills and competencies was highlighted as an effective method for behaviour change. Further, the role of midwives as healthcare professionals that can support and drive this change was emphasized. As they play a major role in antenatal care and support self-efficacy and enhance health equity (World Health Organization, 2015), midwives may be able to facilitate behaviour change where other health care professional can't (Zinsser et al., 2020). Educating midwives about the dangers of prenatal air pollution exposure and facilitating them to pass this information on to pregnant women may therefore be a possible approach in enabling pregnant women to lower their exposure to air pollution.

6.6.1 Lessons from interventions in nutrition

It is recommended that pregnant women change their nutritional intake during pregnancy, and guidance should be given during antenatal care visits (National Institute for Health and Care Excellence, 2021, National Institute for Health and Care Excellence, 2014). A significant share of women of childbearing age (19 – 49 years old) in the UK are on average deficient in several key micronutrients (Derbyshire, 2018). The magnitude of deficiency is higher in women of low socioeconomic status and previously obese women (Charnley et al., 2021). Poor maternal nutritional status is a risk factor for fetal complications and poor neonatal outcomes comparable to those related to maternal exposure to air pollution, such as preterm birth and low birth weight (Rogne et al., 2017, Chia et al., 2019).

Interventions in maternal diet during pregnancy are commonplace (Taylor et al., 2017, Zinsser et al., 2020), and lessons learned may be valuable for interventions to reduce maternal personal exposure to air pollution. A key difference is that the awareness of the importance of nutrition during pregnancy

is high (Blondin and LoGiudice, 2018), whereas the awareness of sources and effects of air pollution is rising but comparatively low in the general population (Ramírez et al., 2019, McCarron et al., 2023), and there is no evidence of the level of awareness among pregnant women. It is likely that knowledge about the need to reduce exposure to air pollution during pregnancy is not widespread.

Nutritional assessment and appropriate interventions are effective beginning in the preconception period (Dean et al., 2014), and throughout pregnancy, but especially in the early stages of pregnancy (Carbonneau et al., 2022). The impacts of improved nutrition, as well as adoption of behavioural change were strongest when interventions took place in the first trimester of pregnancy. The quality of antenatal care was an important factor, higher frequency of visits to a dietitian were related to adverse health effects in a multi-ethnic, low-income, high-risk group of pregnant women (Carbonneau et al., 2022). The researchers traced this finding to the lack of personalised advice given by the dietitian, as well as reliance on outdated health guidelines. An individual's exposure to air pollution is highly personal and depends on many environmental and behavioural factors, and changes in air quality may require a modification in guidance (Laumbach and Cromar, 2022). Introducing personal exposure reduction guidance as a component of antenatal care will therefore require personalised care using up to date information.

Attendance at online group sessions was a predictor of beneficial impacts of an intervention (Rhodes et al., 2020). In this review of digital interventions in pregnant women, exclusively digital interventions were found to be less effective than interventions containing an interpersonal engagement element. Using behavioural change techniques in an interpersonal online environment, as well as providing feedback on progress throughout pregnancy drove engagement and increased the effectiveness of the interventions. However, there was no clear evidence of an impact from use of online group forums for participants. This evidence supports the need for interactive expert care throughout pregnancy when trying to enact behavioural change, which needs to be considered when planning air pollution exposure reduction guidance.

Information campaigns are seen as effective methods of disseminating information to allow individuals to improve their decision making concerning their health with increased awareness of the risks associated with unhealthy behaviour (de Chaisemartin et al., 2011). A campaign running since 2005 in France to increase folic acid intake in women of childbearing age, including pregnant women, in order to reduce the incidence of neural tube defects (Lamoureux, 2005), had a small, statistically significant effect (Herrera-Araujo, 2016). The information was shared with at risk individuals and caregivers to women of childbearing age such as generalists, gynaecologists, nurses, and pharmacists and was consequently seen as highly credible by the target group. Similar public information

campaigns for air pollution exposure targeted towards high-risk individuals in childbearing age as well as their caregivers could have beneficial effects.

6.7 Preliminary recommendations for interventions to reduce personal exposure to air pollution in pregnant women

Drawing on interventions in maternal nutrition and the effectiveness of behavioural change interventions in pregnant women, I conceived several suggestions for personal exposure reduction interventions and categorised by the strength of the available evidence as well as cost of the intervention (Figure 6.2). Taking action prior to pregnancy or in the early stages of pregnancy improves efficacy of interventions and this time period should be prioritised (Rockliffe et al., 2021). Not quantified is the complexity and difficulty of implementing these interventions, as well as potential side effects that may occur. Some of these actions might be impossible for individuals to take, due to their ability, financial situation, or due to cultural and social factors (McCarron et al., 2023).

Community led exposure studies which encourage strong participatory engagement with an open dialogue between researchers and community show great promise of increasing uptake of interventions to reduce pregnant women's exposure to air pollution (Varaden et al., 2021). Combining this implementation strategy with simple, cheap, and well evidenced interventions such as increasing ventilation after cooking or installing mechanical air purification systems indoors or inside cabins of vehicles may lead to reduced exposure to air pollution (Lim et al., 2021, Laumbach and Cromar, 2022). However, exposure studies are usually small in scale and may not be able to reach large swathes of pregnant women or women of childbearing age.

Sharing information about the risks of exposure to air pollution with caregivers can have a large reach and may effectively prevent exposure to air pollution (Herrera-Araujo, 2016, Lamoureux, 2005). Digital media campaigns have similar reach; however, the evidence of an effect is weak (Rhodes et al., 2020). Some interventions are effective but come with a high financial cost which may deter action, such as replacing a gas stove with an electric one. The evidence was unclear whether several interventions had a positive effect on air pollution exposure. For example, electronic air filtration methods such as ionizers, plasma air cleaners, or electrostatic precipitators can increase ozone concentrations whilst removing particles, with the effect on total exposures depending on the environment (Liu et al., 2021).

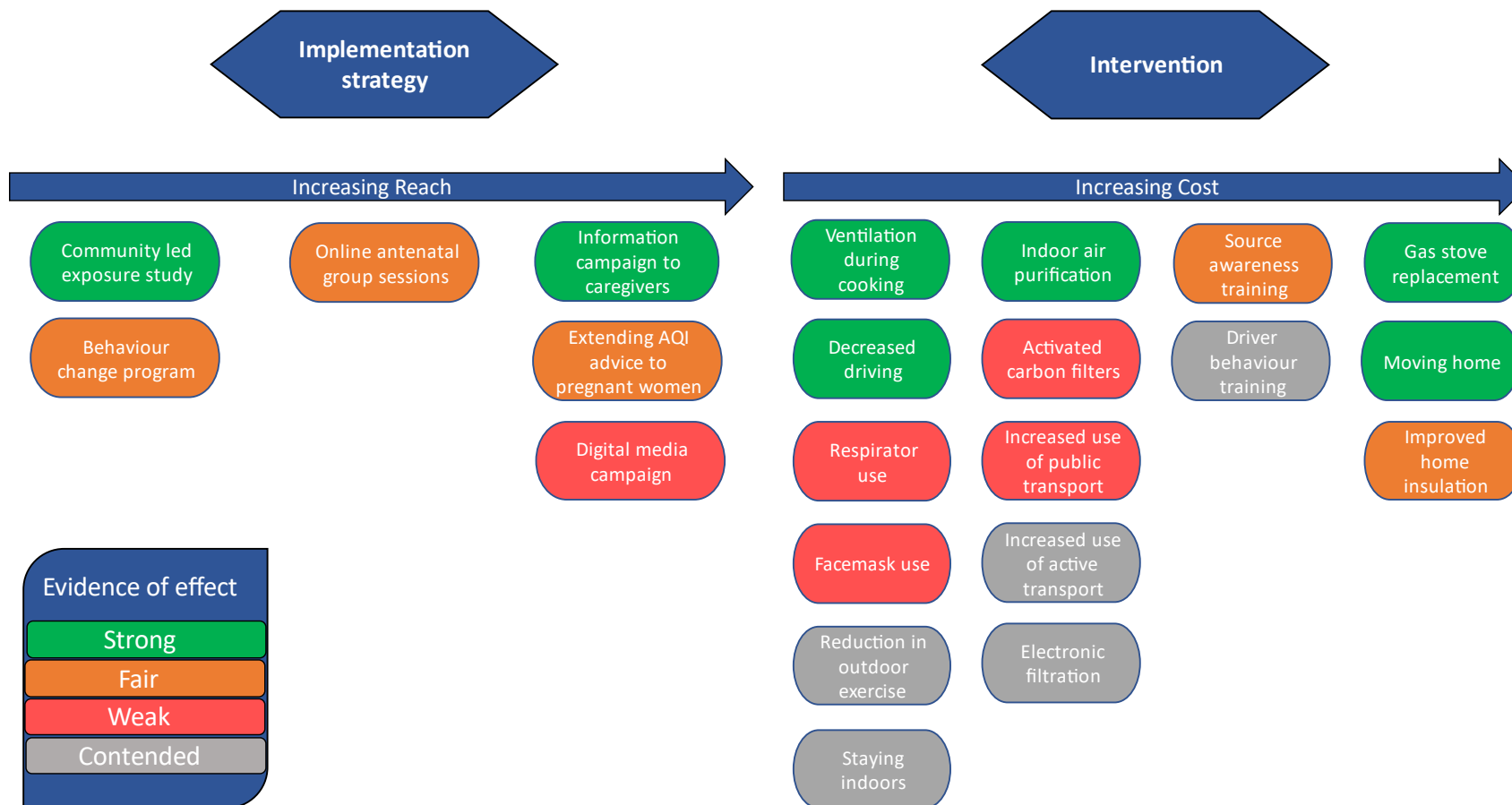


Figure 6.2: Diagram of interventions to reduce personal exposure to air pollution in pregnant women with information about the evidence of effect of implementations strategies and interventions, as well as their reach and cost, respectively.

6.7.1 Further considerations

Air pollution exposure reduction efforts are at their most effective on a population level when source control measures are employed. However, even with source control measures in place, vulnerable subgroups such as pregnant women may not be adequately protected, and personal exposure reductions are desirable. Further, occupational limits are inadequate and do not effectively protect pregnant women from high exposures. Waiting for legislation to be passed and for source control measures to be enacted takes time, and personal exposure reduction measures can be effectively enacted within a short time period. Some activities such as cooking lead to short-term very high peaks in air pollution concentrations. These peaks may not affect long-term averages significantly but could have adverse health effects in and of themselves, and reducing peak exposures can be effectively achieved using personal exposure interventions. Personal exposure reductions should therefore be a key component of maternal health care, but the benefit of an intervention must be balanced with the cost. Some interventions can come at a significant financial burden, such as purchasing and maintaining equipment such as air purifiers or respirators. Other interventions may have unwanted side effects. Staying indoors can be recommended when outdoor air pollution is high, but when the information communicated is unclear or incomplete this may come at the cost of physical activity or lead to social isolation. Figure 6.3 shows the potential increase in individual burden and risk of unintended harm from an intervention, even though air pollution exposure is reduced (Laumbach and Cromar, 2022).

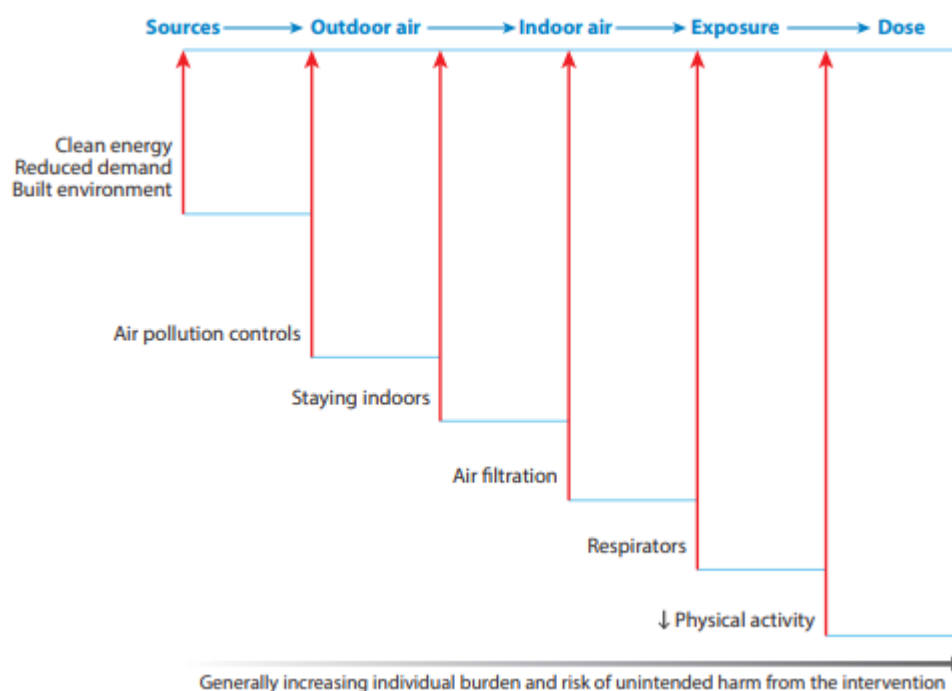


Figure 6.3: Interventions and their contribution to exposure reduction by interrupting exposure pathways. This chart depicts the path from sources of air pollution to the inhaled dose and shows the increased burden and risk of unintended harm from the intervention to the individual. Reproduced from Laumbach et al (2022).

Any interventions must therefore limit the negative impact on pregnant women as much as possible. Equity issues must be considered, and any interventions should account for individual cultural, educational, and socioeconomic context (World Health Organization, 2020). Information should be made available for pregnant women to make informed decisions, and the current information base specific to pregnant women is lacking. More stringent workplace air pollution exposure limits for pregnant workers than for non-pregnant workers are justifiable by the evidence of effects on health outcomes. However, without proper care this could create a barrier for women of childbearing age and pregnant women to be employed.

6.8 Conclusions

Pregnant women and their children could benefit from reduced exposure to air pollution, and behaviour change could have positive effects throughout the life course of both mother and child. There is a need to inform and dispel common misconceptions, such as the idea that the indoor environment is always a clean one. Studies that are co-produced with pregnant women, considering their needs and pairing exposure data with participatory engagement, have shown the greatest effect on behaviour change. The most cost effective and wide reaching interventions to reduce personal exposure to air pollution should be trialled, however, the lack of evidence in key aspects of personal

exposure reduction, such as behaviour characterisation and consideration of the burden of interventions on pregnant women, needs to be resolved.

CHAPTER 7 - GENERAL DISCUSSION

7.1 Overall summary

In this thesis, a high-resolution air pollution model created for London, the Air Pollution Toolkit, was used to model ambient residential air pollution exposures during pregnancy for two cohorts, the ePrime and dHCP cohorts. Both are neonatal MRI cohorts, using bespoke methods to obtain diffusion and structural MRI at term equivalent age. Healthy, term-born, neonates were studied in the dHCP cohort, and neonates born extremely preterm in the ePrime cohort. The diffusion imaging in the dHCP cohort was processed using conventional DTI as well as NODDI, which gives unique insights into WM microstructure. Measures to reduce exposures in pregnant women were investigated in a review of the literature and recommendations were given for interventions. This chapter will consider the results from three analysis chapters and one discursive chapter, discussing the data and analysis methods used, the strengths, and limitations of this thesis as well as the potential for future work.

7.2 Analysis chapters

In the dHCP cohort, which consists of healthy, term born neonates, increased exposure to PM_{10} , and decreased exposure to NO_2 was related to altered brain morphology. None of the other neonatal MRI metrics studied in this thesis were related to prenatal exposure to air pollution. Prenatal exposure to ambient PM_{10} has previously been associated with adverse birth outcomes (Nyadanu et al., 2022), though impacts of increased exposure to $PM_{2.5}$ have been more pronounced. $PM_{2.5}$ has been found in the placenta, as well as in fetal tissue, including in the brain (Bongaerts et al., 2022, Bové et al., 2019). Fine particles are able to pass through the lungs and into the bloodstream, circulating to the fetus. However, the coarse fraction of PM_{10} is only able to pass the trachea and can reach the lung, but not the bloodstream (Fiordelisi et al., 2017). This indicates that the negative effect of prenatal PM_{10} exposure on neonatal brain morphology is not a local effect in the placenta or in the fetus, but an effect on the mother which is affecting the fetus. Decreased exposure to NO_2 was related to altered neonatal brain morphology. NO_2 is a gaseous pollutant, which passes through the upper respiratory tracts to the distal airways where it causes local and systemic inflammation (Ackermann-Lieblich et al., 2019). As with the effect of PM_{10} , this suggests that the impacts of NO_2 on the mother impact upon fetal brain development.

7.2.1 Air pollution exposure assessment

Air pollution exposures in this thesis were modelled using the air pollution toolkit (Kelly et al., 2011). Modelling exposures enables getting estimate of many subjects' exposures to air pollution over a long period of time whilst minimising the financial cost and the time expended on this effort.

However, air pollution modelling has limitations, which are important to consider. In this study I modelled ambient residential exposures, which doesn't take into account differences in the spatiotemporal mobility of subjects, their indoor exposure, or inhaled dose of an individual which could lead to non-differential exposure misclassification (Weisskopf and Webster, 2017, Park and Kwan, 2017). The main types of non-differential exposure misclassification are classified as Berkson and classical error. The Berkson type error, which may decrease the precision of an effect estimate, does not introduce bias. Classical error, however, biases the effect towards the null. As the same model is used for all subjects, the true exposures vary randomly around this proxy estimate, and the error in this study is a Berkson type error (Zeger et al., 2000, Armstrong, 1998).

The air pollution toolkit considers several aspects of the microenvironment, modelling exposure in a 20 by 20 metre grid, and using data on road geography such as road type, street canyons and motorways, the chemistry near roads, and whether the environment consists of green spaces or is fully built up. This categorisation and approximation, as well as the size of the grid, may leave out important aspects of a microenvironment, in part because the ambient environment is modelled, not the indoor environment in which the subjects are likely to spend most of their time. As described in the previous chapter, indoor air is a highly complex mixture of infiltrating outdoor air and indoor air pollution sources such as building materials, cleaning products, personal care products, cooking, environmental tobacco smoke (ETS), and biological sources such as human metabolism, pets, house dust mites, and mould (Kelly and Fussell, 2018, González-Martín et al., 2021). Indoor and personally generated sources of air pollution may contribute significantly to an individual's total exposure (Van Roosbroeck et al., 2008). No previous studies comprehensively characterised personal exposure during pregnancy using measurements. Peterson et al (2015, 2022) measured personal exposure to PAHs during the third trimester for 48 hours and validated these measurements in a two-week monitoring campaign in a subset of homes. The correlation between these measurements was 0.44, indicating that residential measurements may differ substantially from personal exposure, which is influenced by many individual factors. These may have had a strong effect as the personal monitoring time period was very short in this study. The impacts on public health of indoor air pollution in HIC are poorly understood and it is unclear what effect poor indoor air quality may have on pregnant women and neonatal neurodevelopment.

Areas outside of the home indoor environment where individuals spend a significant amount of their time include the work and transport microenvironments, which may have outsized effects on exposures, with evidence for both increased and decreased exposures due to time spent in these environments (de Nazelle et al., 2017, Reis et al., 2018, Yu et al., 2018). This effect may be somewhat mitigated by the fact that pregnant women spend more time at home than non-pregnant individuals

(Nethery et al., 2009). Whilst these are exposures that cannot be captured by most models, including the Air Pollution Toolkit, modelling has advantages over personal monitoring other than reach and cost. The predictors of an ambient exposure estimate are better understood, and uncertainties better quantified and controlled for, than the individual behavioural predictors of personal exposure (Weisskopf and Webster, 2017). For example, differences in personal behaviour may introduce confounding to an association between personal exposure to air pollution and a health outcome, whereas they would not introduce confounding to the association between the modelled exposure and the health outcome (Hernán and Robins, 2010).

There was no statistically significant difference between average air pollution exposures in the ePrime cohort or the dHCP cohort ($p > 0.05$), even though the timeframes were a few years apart (2010 – 2013, 2015 – 2020, respectively). Roadside air pollution concentrations in London decreased slightly between 2010 and 2016 (Font et al., 2019), however, it is unclear if background concentrations also trended downwards. The introduction of the Ultra Low Emission Zone (ULEZ) in 2019 decreased concentrations of PM_{10} , $PM_{2.5}$, and NO_2 in central London, with the highest reduction seen for NO_2 (Greater London Authority, 2019, Greater London Authority, 2023). This area in London covers around 100000 people, and none of the subjects of both the dHCP and ePrime cohorts resided in this area, and only 19 (4%) of subjects in the dHCP cohort were born after April 2019, which was when the ULEZ was first introduced. There may have been some impact from vehicles being upgraded outside of the ULEZ and prior to its introduction, as the introduction was first announced in 2017 and surrounding residents may have acted early in replacing their vehicles. Apart from the study by Font et al (2019) it is unclear how air pollutant concentrations as well as the chemical composition of PM changed in Greater London throughout the study period, and whether this may have had an impact on the results of this thesis. This could be analysed in future studies using data from the Marylebone Road and Honor Oak Park monitoring sites in London, which both record particle composition.

For a significant share of subjects within both the ePrime and the dHCP cohort the range of the pollution model did not reach the residence, as the Air Pollution Toolkit is only capable of modelling air pollution concentrations within Greater London. Subjects outside of Greater London therefore had to be excluded from the analysis. While this lowered the number of subjects and imaging data available, including only subjects residing within Greater London reduces inter-subject variability of factors which may have affected the results, such as particle composition which is strongly influenced by local sources and differs between environments (Kundu and Stone, 2014). Urban PM is associated with greater health risks as well as greater neurotoxicity, which is suspected to be due to the high toxicity of TRAP (Costa et al., 2017, Alemayehu et al., 2020).

7.2.2 Cohort data

As part of the data collection for the dHCP cohort information on the highest age of maternal education was gathered. It was established that this data could not correctly estimate maternal education as women in this cohort may have attended courses, university, or other forms of formal education later in life without it being a clear signifier of the overall level of education. The IMD was used instead for all subjects to quantify socioeconomic status, which created an equal baseline between ePrime and dHCP cohorts. The median IMD of the dHCP cohort was 4, and 3 for the ePrime cohort, which means that there was a significant difference in socioeconomic status between cohorts. Increased income in pregnant women was associated with decreased time spent at home in another study (Nethery et al., 2009). Whilst IMD is not purely an index of income and encompasses other factors such as employment and education, this may be an indication that residential modelling of air pollution exposures more accurately reflects the exposures of pregnant women of lower IMD.

The dHCP subjects' residences were more concentrated around Lambeth and Southwark in central and south London and St. Thomas' Hospital, whereas the ePrime subjects' residences were more spread out around west and south London and the Queen Charlottes & Chelsea Hospital (Figure 13 and Figure 20, in Chapters 3 and 5, respectively). Few subjects in either cohort resided in north and northeast London. Maternal residence information was collected at a single time point upon recruitment to the ePrime and dHCP cohorts, which occurred during pregnancy. Residential subject mobility during pregnancy was not captured. This may have introduced a degree of exposure misclassification, as subjects may not have lived at the same address throughout pregnancy. One review found that 14 to 32% of the population move during pregnancy, with a median of 24% across studies (Bell and Belanger, 2012). Two studies based in the UK found residential mobility rates of 15 (Pearce et al., 2008) and 16% (Tunstall et al., 2010), respectively. Evidence on the timing of the move in pregnancy shows a higher percentage moving in the second trimester than the first or the third (Bell and Belanger, 2012). This misclassification may introduce random variation in the dataset which reduces the power to detect associations. Further, there is some evidence that families with lower socioeconomic status move more often during pregnancy, which would lead to differential variation in the dataset (Tunstall et al., 2010, Bentham, 1988). One study conducted in the Netherlands indicated that pregnant women are more likely to move over short distances than nonpregnant movers (Michielin and Mulder, 2008), which may reduce the degree of exposure misclassification, depending also on the spatial heterogeneity of the pollutant in question.

7.2.3 Analysis method

In this thesis I used CCA to assess the relationship between prenatal exposure to air pollution and neonatal neurodevelopment as assessed by structural and diffusion MRI in both a cohort of healthy,

term born, neonates and a cohort of preterm neonates. Initially, linear regression analysis was performed to assess this relationship, however, the characteristics of air pollutants and the fact that many air pollutants have the same sources make them highly correlated, which makes the use of standard statistical methods complex (Billionnet et al., 2012). Regression especially tends to be unreliable when variables are highly correlated, leading to unstable and inaccurate results (Kiers and Smilde, 2007). Therefore, single pollutant linear regression analysis was used to explore the associations, avoiding the issue of correlation between pollutants by only including a single pollutant in each analysis. However, this approach does not address collinearity between brain MRI data, nor does it sufficiently explore the complexity of the multiple air pollutants that subjects were exposed to. Multiple pollutants may have additive or synergistic effects on health which can lead to difficulty in interpreting single pollutant models (Vedal et al., 2003).

Multiple time varying exposures have previously been related to birth outcomes, and single pollutant models have been found unable to characterise the complex associations (Wilson et al., 2019). CCA was chosen as the statistical analysis technique for these analyses due to its ability to incorporate a large number of correlated variables and because it is a proven method and has been widely applied in neuroscientific applications (Zhuang et al., 2020, Wang et al., 2020). Despite being computationally complex, CCA is able to assess the joint multivariate linear relationship between modalities and has been shown to be an effective data driven analysis method. It allows interpretation beyond techniques that assess one to one or many to one relationships. CCA is capable of incorporating non-normally distributed variables (Wang et al., 2020). To ensure that non-normality does not impact upon the CCA Spearman's rank correlation coefficient was used, which is a non-parametric test of correlation. CCA is therefore a suitable method to evaluate the impact of prenatal exposure to multiple air pollutants and the effects on neonatal brain health as assessed by MRI.

7.3 Reducing pregnant women's exposure to air pollution

In my final results chapter, I outlined the evidence around personal exposure reduction for pregnant women, explaining why personal exposure reduction beyond source mitigation is necessary, especially for vulnerable cohorts. I discussed the existing evidence on personal exposure reduction in general and combined this information with the literature on behaviour change in pregnant women, and implementation strategies of nutritional intervention efforts in pregnant women to generate a diagram (Figure 6.2). The diagram makes suggestions for interventions to reduce personal exposure to air pollution in pregnant women with information about the evidence of effect of implementations strategies and interventions, as well as their reach and cost, respectively.

It is clear that air pollution can contribute to health conditions in pregnant women and their offspring. Source control measures are being implemented in some locations such as in London, and progress here has been remarkable (Hajmohammadi and Heydecker, 2022), but elsewhere efforts to reduce air pollution exposures have been sparse. So far there has been very little evidence to turn to for women of childbearing age in order to protect themselves as well as their children. This chapter was written to provide an initial guideline for policy makers and pregnant women, and all the suggestions are based on existing evidence. However, the nutritional interventions were implemented for the benefit of pregnant women and the air pollution exposure reduction interventions were studied in non-pregnant cohorts, therefore none of the proposed air pollution exposure reduction interventions were trialled on pregnant women specifically, and they can only be seen as suggestions, and not recommendations. Cost effective interventions with the strongest evidence of an effect, as well as those with high reach should be trialled and assessed for their impact on reducing exposure to air pollution in pregnant women. A systematic study investigating pregnant women's behaviour and consequent personal exposure would provide more insight into which interventions would be the most effective. Further, those interventions in which the evidence of an effect was classified as contended should be further investigated to clarify their effect on reducing exposures.

It is essential that not just the short-term impact of any intervention on pregnant women's behaviour and the resulting reduction in personal exposure is quantified, but also how effective these interventions are in the long term. There is evidence that interventions can have an immediate impact on behaviour which leads to exposure reduction (McCarron et al., 2023). However, most studies only assess how effectively any behavioural changes were adopted in the short-term, and don't conduct any follow up reviews to evaluate the longevity of the impact on behaviour of an intervention. The pregnancy period has been established as a period in which women are especially susceptible to behavioural change (Zinsser et al., 2020), however, there is a risk that the improved behaviour and consequent reduced exposure to air pollution could be reduced or reversed once the pregnancy period is over (Rockliffe et al., 2021). While the pregnancy period is an especially vulnerable period, it is important that subjects are informed about the long-term benefits of reducing one's personal exposure to air pollution.

7.4 Statistical limitations

7.4.1 CCA

One of the factors which may have had an impact on the results are the limitations of my analysis technique. CCA can only yield accurate and useful model fits when the number of observations is higher than the number of variables (Giraud, 2021, Hastie et al., 2015). This is the case in all my

analyses; however, the number of diffusion MRI variables is high compared to the number of individuals in my analysis of the dHCP cohort. This may lead to difficulty of the CCA assessing latent dimensions and may lead to error in deriving canonical vectors (Wang et al., 2020). An increased number of variables in one or both sets of the CCA usually leads to increased canonical correlation. In the case of the analysis of the diffusion MRI data in the dHCP cohort, no significant results were found. Therefore, even if the high number of variables erroneously led to increased canonical correlation, this did not impact upon the final result.

A second factor is related to the statistical relationships that CCA can assess in the underlying data. CCA is a linear model, and it assumes additivity in the relationships between covariates, as well as being limited in that it assumes and only detects a linear intermodality relationship (Zhuang et al., 2020). If a non-linear relationship between the air pollution variables and neonatal MRI metrics exists, it may not be detected. These analyses were driven by correlations, and any inferences and interpretations on causalities are not possible.

7.4.2 Covariates and confounding information

A further limitation was lack of information on some confounding factors, such as noise. Noise levels during pregnancy were not available for any of the cohorts, and noise pollution may be a confounder for the health effects of air pollution. Modelling estimates of noise or using proxies such as stress levels may constitute a useful contribution to adjust for confounders. However, a study on the effects of air pollution on cardiovascular health found no change in results when noise was adjusted for (Stafoggia et al., 2014). Whether this lack of confounding also applies to neurodevelopmental outcomes is unclear. Smoking information was available for the dHCP cohort, and subjects with known maternal smoking were excluded. Smoking information was not available for the ePrime cohort, and as maternal smoking during pregnancy affects foetal neurodevelopment and is a risk factor for adverse neurodevelopmental outcomes, this may have had an impact on the results of my analysis (Ylijoki et al., 2019, Ekblad et al., 2015).

IMD does not include individual level variables of socioeconomic status, as it is modelled at postcode level. It therefore does not fully adjust for factors that have been shown to influence fetal brain development, such as maternal education. Ambient air pollution concentrations were also modelled on postcode level. There may be more heterogeneity within postcodes than the Air Pollution Toolkit is able to capture, even if postcodes in the UK are often of small size. Additionally, no information was available on spatiotemporal subject mobility, which could lead to exposure misclassification. However, people spend most of their time at home, and this is especially the case for pregnant women (Nethery et al., 2009), which means any exposure misclassification that occurred was likely limited in its impact.

Subjects may have moved home during the pregnancy period, which was not considered, and air pollution concentrations were averaged over the entire pregnancy period and the individual trimesters, which could mask effects of variations in short-term exposure.

My study analysed brain structure and WM microstructure at a single time-point in the neonatal period. The neonatal brain continues its rapid development postnatally, and interpretation of an effect on growth patterns and impacts on WM microstructural development over time is limited by the design of my study because the single MRI measurement prevents drawing conclusions on potential long-term effects of air pollution.

7.5 Conclusions and future work

To conclude, the research presented in this thesis is highly novel and it is the first time the impact of prenatal exposure to air pollution on neonatal brain morphology and WM microstructure as assessed by MRI was investigated. The results showed that increased prenatal exposure to PM₁₀ and decreased exposure to NO₂ is strongly associated with an increase in the relative size of the ventricles, modestly related to an increase in the relative size of the cerebellum, weakly associated with an increase in the relative size of the GM, and amygdala and hippocampus, and weakly associated with a decrease in the relative size of the brainstem and the extracerebral CSF in neonates. I found no associations in the same cohort between prenatal exposure PM_{2.5}, PM₁₀, and NO₂ and neonatal WM microstructure metrics MD, FA, F_{iso}, NDI, and ODI in 23 tracts. Further, prenatal exposure to PM_{2.5}, PM₁₀, and NO₂ was not related to any metric of neonatal brain morphology or WM microstructure in infants born preterm. A strength of this study is the large sample size for neonatal cohorts, which are comparable to cohorts in studies with MRI taken in childhood. Further, bespoke imaging methods were used to obtain state of the art neonatal imaging, and air pollution data was modelled using a validated high-quality ambient air pollution model. Finally, the statistical method used allowed incorporation of three ubiquitous yet highly correlated pollutants. This research is important as it shows that prenatal exposure to air pollution at levels seen in HIC has effects on neurodevelopment that can be measured neonatally. This adds the neonatal period to the body of evidence linking air pollution exposure to impacts upon neurodevelopment throughout the life course, which previously spanned from childhood to old age. It is also the first time specific interventions were suggested for pregnant women to reduce their exposure to air pollution. These interventions were classified based on their scale, cost, and the evidence of an effect on personal exposure reduction. The guidance given in this thesis for pregnant women to reduce their exposure can be trialled by policy makers and pregnant women alike, empowering this vulnerable cohort to protect themselves from the impacts of personal exposure to

air pollution. It is clear that further to the mixed findings of this thesis, prenatal exposure to air pollution impacts on maternal as well as fetal and infant health, and efforts must be made to mitigate these impacts.

Several different areas of this research should be the focus of future work. Firstly, whilst the ePrime and dHCP cohorts that were studied in this thesis are large for neonatal cohorts, they may not have been large enough to find statistical associations in WM microstructure or in preterm born infants. Further processing of MRI data in the dHCP cohort would allow a larger number of subjects to be assessed and this would add statistical power to the research. Greater statistical power increases the likelihood of rejecting a false null hypothesis (Serdar et al., 2021). Subjects had to be excluded due to limited range of the air pollution model used. Using a model capable of estimating exposure for all subjects in both the dHCP and ePrime cohorts would increase statistical power and may lead to more robust associations. Combining the two cohorts into one analysis would also achieve an increase in statistical power. However, as the subjects in the ePrime cohort were born extremely preterm, and the subjects included in the dHCP cohort were term-born healthy subjects, this would likely have introduced bias. MR imaging was conducted at term equivalent age for both cohorts. All subjects in the ePrime cohort were born extremely preterm and were exposed to the ex-utero environment for a longer period than the subjects in the dHCP cohort prior to imaging. In future work assessing the impact of prenatal exposure to air pollution in preterm infants, adjusting for postnatal exposure should be considered. As part of both the dHCP and ePrime follow up with subjects, neuropsychological outcome data were collected. Future work should assess whether prenatal exposure to air pollution impacts upon these outcome data, and whether any effect found on neonatal neurodevelopment mediates the effects. Longitudinal studies with MRI taken at several time points throughout early life are required to confirm the findings of this thesis as well as give insights into causalities of the impacts of air pollution exposure. This would further allow an assessment of the effects of air pollution exposure on brain development between the neonatal period and early childhood, which has not been characterised.

A previous study by Lubczyńska et al (2020) examined the impact of prenatal exposure to air pollution on global FA and MD. The MD and FA data in the dHCP dataset were not processed for the purpose of creating a global FA and MD metric, and creating a metric of global FA and MD would therefore constitute a data reduction method with loss of information. Future work could construct a global metric of FA and MD using a TBSS approach and assess the impact of prenatal exposure to air pollution on neonatal global MD and FA. Further, previous studies found an effect of prenatal exposure to pollutants not estimated in this study on brain morphology and WM microstructure in childhood (Lubczyńska et al., 2020, Lubczyńska et al., 2021, Peterson et al., 2015, Peterson et al., 2022). This

study did not assess silicone and PAHs, and therefore it is unclear whether these pollutants impact upon neonatal brain morphology and WM microstructure in term born or preterm born infants. Moreover, it is also unlikely that this effect only becomes apparent in childhood, as Lubczynska et al (2020, 2021) adjusted for postnatal exposure in their analysis. Essers et al (2023) found an impact of being a carrier of the *APOE* ϵ 4 gene and having a high or low PRS for AD on associations between prenatal exposure to air pollution and child structural brain morphology. Investigating whether *APOE* ϵ 4 status or PRS for AD has a modifying impact on the effect of prenatal exposure to air pollution on neonatal brain development would give new insights into genetic vulnerabilities earlier in life, with potential for the mitigation of health risks throughout the life course.

There are some indications that the timing of fetal brain stress and injury is essential in determining the health impact, in healthy as well as preterm born infants (Ophelders et al., 2020, Yuan et al., 2020, Chiu et al., 2016). Investigating the importance of time windows of exposure requires high time resolution estimates of air pollution exposure which personal exposure monitoring can provide. Personal exposure measurements of pregnant women were planned to be undertaken as a part of the MobileAir project, which was delayed and could not be incorporated into this thesis. Short-term exposures to air pollution can vary strongly and may have impacts which cannot be quantified by studies using long-term exposure averages. Detailing personal exposure to air pollution in pregnant women may further aid the development of hybrid models, which assess exposure taking into account spatiotemporal mobility as well as indoor environments. Other pollutants than those investigated in this thesis have been linked to neurodevelopmental impacts in childhood, and future studies should investigate the impact of these pollutants on neonatal neurodevelopment.

Little is known about how pregnant women's behaviour shapes their exposure to air pollution, both in the indoor and outdoor environment. A comprehensive characterisation of exposure throughout every trimester of pregnancy would give insight into how to reduce exposure and improve outcomes for both mother and child. It is also unclear how exercising in polluted areas impacts the health of pregnant women (Tainio et al., 2021). There are benefits to active travel in polluted environments for the general population, though these are limited by the impacts of air pollution exposure. Considering the great benefits of exercise for pregnancy outcomes it is important that this area of research is better understood. Intervention implementation strategies previously attempted for nutritional interventions in pregnant women or women of childbearing age should be trialled for personal exposure reduction. Once behaviour change is achieved and exposures are lowered, it is unclear how sustainable any interventions are. Longitudinal studies which assess the sustainability of behaviour change are required (McCarron et al., 2023). Further research is required to be able to quantify and

balance the benefit of reduced exposure in pregnant women, both in the short- and long-term, with increased individual burden of an intervention.

References

- ABDEL-SHAIFY, H. I. & MANSOUR, M. S. M. 2016. A review on polycyclic aromatic hydrocarbons: Source, environmental impact, effect on human health and remediation. *Egyptian Journal of Petroleum*, 25, 107-123.
- ACKERMANN-LIEBRICH, U., FELBER DIETRICH, D. & JOSS, M. K. 2019. Respiratory and Cardiovascular Effects of NO₂. *Reference Module in Earth Systems and Environmental Sciences*. Elsevier.
- AIR QUALITY EXPERT GROUP 2022. Indoor Air Quality. https://uk-air.defra.gov.uk/assets/documents/reports/cat09/2211011000_15062022_Indoor_Air_Quality_Report_Final.pdf: Department for Environment, Food and Rural Affairs.
- ALEMAYEHU, Y. A., ASFAW, S. L. & TERFIE, T. A. 2020. Exposure to urban particulate matter and its association with human health risks. *Environmental Science and Pollution Research*, 27, 27491-27506.
- ALEXANDER, A. L., HASAN, K. M., LAZAR, M., TSURUDA, J. S. & PARKER, D. L. 2001. Analysis of partial volume effects in diffusion-tensor MRI. *Magnetic Resonance in Medicine*, 45, 770-780.
- ALEXANDER, D. C. 2005. Multiple-Fiber Reconstruction Algorithms for Diffusion MRI. *Annals of the New York Academy of Sciences*, 1064, 113-133.
- ALEXANDER, D. C., DYRBY, T. B., NILSSON, M. & ZHANG, H. 2019. Imaging brain microstructure with diffusion MRI: practicality and applications. *NMR in Biomedicine*, 32, e3841.
- ALI, M. U., LIU, G., YOUSAF, B., ULLAH, H., ABBAS, Q. & MUNIR, M. A. M. 2019. A systematic review on global pollution status of particulate matter-associated potential toxic elements and health perspectives in urban environment. *Environ Geochem Health*, 41, 1131-1162.
- ALLEN, J. L., LIU, X., WESTON, D., PRINCE, L., OBERDÖRSTER, G., FINKELSTEIN, J. N., JOHNSTON, C. J. & CORY-SLECHTA, D. A. 2014. Developmental exposure to concentrated ambient ultrafine particulate matter air pollution in mice results in persistent and sex-dependent behavioral neurotoxicity and glial activation. *Toxicol Sci*, 140, 160-78.
- ALLEN, J. L., OBERDÖRSTER, G., MORRIS-SCHAFFER, K., WONG, C., KLOCKE, C., SOBOLEWSKI, M., CONRAD, K., MAYER-PROSCHEL, M. & CORY-SLECHTA, D. A. 2017. Developmental neurotoxicity of inhaled ambient ultrafine particle air pollution: Parallels with neuropathological and behavioral features of autism and other neurodevelopmental disorders. *NeuroToxicology*, 59, 140-154.
- ALNÆS, D., KAUFMANN, T., MARQUAND, A. F., SMITH, S. M. & WESTLYE, L. T. 2020. Patterns of sociocognitive stratification and perinatal risk in the child brain. *Proc Natl Acad Sci U S A*, 117, 12419-12427.
- AMEIS, S. H., LERCH, J. P., TAYLOR, M. J., LEE, W., VIVIANO, J. D., PIPITONE, J., NAZERI, A., CROARKIN, P. E., ARISTOTLE N. VOINESKOS, LAI, M.-C., CROSBIE, J., BRIAN, J., SORENI, N., SCHACHAR, R., SZATMARI, P., ARNOLD, P. D. & ANAGNOSTOU, E. 2016. A Diffusion Tensor Imaging Study in Children With ADHD, Autism Spectrum Disorder, OCD, and Matched Controls: Distinct and Non-Distinct White Matter Disruption and Dimensional Brain-Behavior Relationships. *American Journal of Psychiatry*, 173, 1213-1222.
- AMIEL-TISON, C., CABROL, D., DENVER, R., JARREAU, P.-H., PAPIERNIK, E. & PIAZZA, P. V. 2004. Fetal adaptation to stress: Part I: acceleration of fetal maturation and earlier birth triggered by placental insufficiency in humans. *Early Human Development*, 78, 15-27.
- ANALITIS, A., KATSOUYANNI, K., DIMAKOPOULOU, K., SAMOLI, E., NIKOLOULOPOULOS, A. K., PETASAKIS, Y., TOULOUMI, G., SCHWARTZ, J., ANDERSON, H. R., CAMBRA, K., FORASTIERE, F., ZMIROU, D., VONK, J. M., CLANCY, L., KRIZ, B., BOBVOS, J. & PEKKANEN, J. 2006. Short-term effects of ambient particles on cardiovascular and respiratory mortality. *Epidemiology*, 17, 230-3.
- ANDERSSON, J. L. R., GRAHAM, M. S., ZSOLDOS, E. & SOTIROPOULOS, S. N. 2016. Incorporating outlier detection and replacement into a non-parametric framework for movement and distortion correction of diffusion MR images. *Neuroimage*, 141, 556-572.

- ANDERSSON, J. L. R. & SOTIROPOULOS, S. N. 2016. An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging. *Neuroimage*, 125, 1063-1078.
- ANDICA, C., KAMAGATA, K., KIRINO, E., UCHIDA, W., IRIE, R., MURATA, S. & AOKI, S. 2021. Neurite orientation dispersion and density imaging reveals white matter microstructural alterations in adults with autism. *Molecular Autism*, 12, 48.
- ARABAN, M., TAVAFIAN, S. S., ZARANDI, S. M., HIDARNIA, A. R., BURRI, A. & MONTAZERI, A. 2017. A behavioral strategy to minimize air pollution exposure in pregnant women: a randomized controlled trial. *Environ Health Prev Med*, 22, 26.
- ARMSTRONG, B. G. 1998. Effect of measurement error on epidemiological studies of environmental and occupational exposures. *Occup Environ Med*, 55, 651-6.
- ATSDR, U. 1995. Toxicological profile for polycyclic aromatic hydrocarbons (PAHs). *US Agency for Toxic Substances and Disease Registry, Atlanta, GA*.
- AUSTIN, P. C. & STEYERBERG, E. W. 2015. The number of subjects per variable required in linear regression analyses. *Journal of Clinical Epidemiology*, 68, 627-636.
- AVANTS, B. B., TUSTISON, N. J., SONG, G., COOK, P. A., KLEIN, A. & GEE, J. C. 2011. A reproducible evaluation of ANTs similarity metric performance in brain image registration. *Neuroimage*, 54, 2033-44.
- BAI, W., LI, Y., NIU, Y., DING, Y., YU, X., ZHU, B., DUAN, R., DUAN, H., KOU, C., LI, Y. & SUN, Z. 2020. Association between ambient air pollution and pregnancy complications: A systematic review and meta-analysis of cohort studies. *Environ Res*, 185, 109471.
- BALES, E., NIKZAD, N., QUICK, N., ZIFTCI, C., PATRICK, K. & GRISWOLD, W. G. 2019. Personal pollution monitoring: mobile real-time air quality in daily life. *Personal and Ubiquitous Computing*, 23, 309-328.
- BALL, G., BOARDMAN, J. P., RUECKERT, D., ALJABAR, P., ARICHI, T., MERCHANT, N., GOUSIAS, I. S., EDWARDS, A. D. & COUNSELL, S. J. 2012. The effect of preterm birth on thalamic and cortical development. *Cereb Cortex*, 22, 1016-24.
- BALL, G., SRINIVASAN, L., ALJABAR, P., COUNSELL, S. J., DURIGHEL, G., HAJNAL, J. V., RUTHERFORD, M. A. & EDWARDS, A. D. 2013. Development of cortical microstructure in the preterm human brain. *Proc Natl Acad Sci U S A*, 110, 9541-6.
- BARN, P., GOMBOJAV, E., OCHIR, C., BOLDBAATAR, B., BEEJIN, B., NAIDAN, G., GALSUREN, J., LEGTSEG, B., BYAMBAA, T., HUTCHEON, J. A., JANES, C., JANSSEN, P. A., LANPHEAR, B. P., MCCANDLESS, L. C., TAKARO, T. K., VENNERS, S. A., WEBSTER, G. M. & ALLEN, R. W. 2018a. The effect of portable HEPA filter air cleaner use during pregnancy on fetal growth: The UGAAR randomized controlled trial. *Environ Int*, 121, 981-989.
- BARN, P., GOMBOJAV, E., OCHIR, C., LAAGAN, B., BEEJIN, B., NAIDAN, G., BOLDBAATAR, B., GALSUREN, J., BYAMBAA, T., JANES, C., JANSSEN, P. A., LANPHEAR, B. P., TAKARO, T. K., VENNERS, S. A., WEBSTER, G. M., YUCHI, W., PALMER, C. D., PARSONS, P. J., ROH, Y. M. & ALLEN, R. W. 2018b. The effect of portable HEPA filter air cleaners on indoor PM2.5 concentrations and second hand tobacco smoke exposure among pregnant women in Ulaanbaatar, Mongolia: The UGAAR randomized controlled trial. *Science of The Total Environment*, 615, 1379-1389.
- BARNETT, M. L., TUSOR, N., BALL, G., CHEW, A., FALCONER, S., ALJABAR, P., KIMPTON, J. A., KENNEA, N., RUTHERFORD, M., DAVID EDWARDS, A. & COUNSELL, S. J. 2018. Exploring the multiple-hit hypothesis of preterm white matter damage using diffusion MRI. *Neuroimage Clin*, 17, 596-606.
- BASSER, P. J. & JONES, D. K. 2002. Diffusion-tensor MRI: theory, experimental design and data analysis - a technical review. *NMR Biomed*, 15, 456-67.
- BASSER, P. J., MATTIELLO, J. & LEBIHAN, D. 1994. MR diffusion tensor spectroscopy and imaging. *Biophysical Journal*, 66, 259-267.
- BASTIANI, M., ANDERSSON, J. L. R., CORDERO-GRANDE, L., MURGASOVA, M., HUTTER, J., PRICE, A. N., MAKROPOULOS, A., FITZGIBBON, S. P., HUGHES, E., RUECKERT, D., VICTOR, S., RUTHERFORD,

- M., EDWARDS, A. D., SMITH, S. M., TOURNIER, J. D., HAJNAL, J. V., JBABDI, S. & SOTIROPOULOS, S. N. 2019. Automated processing pipeline for neonatal diffusion MRI in the developing Human Connectome Project. *Neuroimage*, 185, 750-763.
- BATES, J. T., FANG, T., VERMA, V., ZENG, L., WEBER, R. J., TOLBERT, P. E., ABRAMS, J. Y., SARNAT, S. E., KLEIN, M., MULHOLLAND, J. A. & RUSSELL, A. G. 2019. Review of Acellular Assays of Ambient Particulate Matter Oxidative Potential: Methods and Relationships with Composition, Sources, and Health Effects. *Environmental Science & Technology*, 53, 4003-4019.
- BEAULIEU, C. 2002. The basis of anisotropic water diffusion in the nervous system - a technical review. *NMR Biomed*, 15, 435-55.
- BEAULIEU, C. 2009. CHAPTER 6 - The Biological Basis of Diffusion Anisotropy. In: JOHANSEN-BERG, H. & BEHRENS, T. E. J. (eds.) *Diffusion MRI*. San Diego: Academic Press.
- BECKWITH, T., CECIL, K., ALTAYE, M., SEVER, R., WOLFE, C., PERCY, Z., MALONEY, T., YOLTON, K., LEMASTERS, G., BRUNST, K. & RYAN, P. 2020. Reduced gray matter volume and cortical thickness associated with traffic-related air pollution in a longitudinally studied pediatric cohort. *PLoS One*, 15, e0228092.
- BEEVERS, S. D., KITWIROON, N., WILLIAMS, M. L. & CARSLAW, D. C. 2012. One way coupling of CMAQ and a road source dispersion model for fine scale air pollution predictions. *Atmospheric Environment*, 59, 47-58.
- BEHRENS, T. E. J., BERG, H. J., JBABDI, S., RUSHWORTH, M. F. S. & WOOLRICH, M. W. 2007. Probabilistic diffusion tractography with multiple fibre orientations: What can we gain? *NeuroImage*, 34, 144-155.
- BEKKAR, B., PACHECO, S., BASU, R. & DENICOLA, N. 2020. Association of Air Pollution and Heat Exposure With Preterm Birth, Low Birth Weight, and Stillbirth in the US: A Systematic Review. *JAMA Netw Open*, 3, e208243.
- BELL, M. L. & BELANGER, K. 2012. Review of research on residential mobility during pregnancy: consequences for assessment of prenatal environmental exposures. *Journal of Exposure Science & Environmental Epidemiology*, 22, 429-438.
- BENJAMINI, Y. & HOCHBERG, Y. 1995. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society. Series B (Methodological)*, 57, 289-300.
- BENTHAM, G. 1988. Migration and morbidity: Implications for geographical studies of disease. *Social Science & Medicine*, 26, 49-54.
- BILLIET, T., VANDENBULCKE, M., MÄDLER, B., PEETERS, R., DHOLLANDER, T., ZHANG, H., DEPREZ, S., VAN DEN BERGH, B. R. H., SUNAERT, S. & EMSELL, L. 2015. Age-related microstructural differences quantified using myelin water imaging and advanced diffusion MRI. *Neurobiology of Aging*, 36, 2107-2121.
- BILLIONNET, C., SHERRILL, D. & ANNESI-MAESANO, I. 2012. Estimating the Health Effects of Exposure to Multi-Pollutant Mixture. *Annals of Epidemiology*, 22, 126-141.
- BINTER, A.-C., KUSTERS, M. S. W., VAN DEN DRIES, M. A., ALONSO, L., LUBCZYŃSKA, M. J., HOEK, G., WHITE, T., IÑIGUEZ, C., TIEMEIER, H. & GUXENS, M. 2022. Air pollution, white matter microstructure, and brain volumes: Periods of susceptibility from pregnancy to preadolescence. *Environmental Pollution*, 313, 120109.
- BITAR, R., LEUNG, G., PERNG, R., TADROS, S., MOODY, A. R., SARRAZIN, J., MCGREGOR, C., CHRISTAKIS, M., SYMONS, S., NELSON, A. & ROBERTS, T. P. 2006. MR Pulse Sequences: What Every Radiologist Wants to Know but Is Afraid to Ask. *RadioGraphics*, 26, 513-537.
- BLISS, S. 2006. Best Practices Guide to Residential Construction: Materials. *Finishes and Details*, John Wiley & Sons, New York, NY.
- BLONDIN, J. H. & LOGIUDICE, J. A. 2018. Pregnant women's knowledge and awareness of nutrition. *Applied Nursing Research*, 39, 167-174.
- BOLTON, J. L., MARINERO, S., HASSANZADEH, T., NATESAN, D., LE, D., BELLIVEAU, C., MASON, S. N., AUTEN, R. L. & BILBO, S. D. 2017. Gestational Exposure to Air Pollution Alters Cortical Volume,

- Microglial Morphology, and Microglia-Neuron Interactions in a Sex-Specific Manner. *Frontiers in synaptic neuroscience*, 9, 10-10.
- BONGAERTS, E., LECANTE, L. L., BOVÉ, H., ROEFFAERS, M. B. J., AMELOOT, M., FOWLER, P. A. & NAWROT, T. S. 2022. Maternal exposure to ambient black carbon particles and their presence in maternal and fetal circulation and organs: an analysis of two independent population-based observational studies. *The Lancet Planetary Health*, 6, e804-e811.
- BOS, B., BARRATT, B., BATALLE, D., GALE-GRANT, O., HUGHES, E. J., BEEVERS, S., CORDERO-GRANDE, L., PRICE, A. N., HUTTER, J., HAJNAL, J. V., KELLY, F. J., DAVID EDWARDS, A. & COUNSELL, S. J. 2023. Prenatal exposure to air pollution is associated with structural changes in the neonatal brain. *Environ Int*, 174, 107921.
- BOUYSSI-KOBAR, M., DU PLESSIS, A. J., MCCARTER, R., BROSSARD-RACINE, M., MURNICK, J., TINKLEMAN, L., ROBERTSON, R. L. & LIMPEROPOULOS, C. 2016. Third Trimester Brain Growth in Preterm Infants Compared With In Utero Healthy Fetuses. *Pediatrics*, 138.
- BOVÉ, H., BONGAERTS, E., SLENDERS, E., BIJNENS, E. M., SAENEN, N. D., GYSELAERS, W., VAN EYKEN, P., PLUSQUIN, M., ROEFFAERS, M. B. J., AMELOOT, M. & NAWROT, T. S. 2019. Ambient black carbon particles reach the fetal side of human placenta. *Nature Communications*, 10, 3866.
- BOYLE, E. B., VIET, S. M., WRIGHT, D. J., MERRILL, L. S., ALWIS, K. U., BLOUNT, B. C., MORTENSEN, M. E., MOYE, J., JR. & DELLARCO, M. 2016. Assessment of Exposure to VOCs among Pregnant Women in the National Children's Study. *Int J Environ Res Public Health*, 13, 376.
- BRIGGS, D. J., COLLINS, S., ELLIOTT, P., FISCHER, P., KINGHAM, S., LEBRET, E., PRYL, K., VAN REEUWIJK, H., SMALLBONE, K. & VAN DER VEEN, A. 1997. Mapping urban air pollution using GIS: a regression-based approach. *International Journal of Geographical Information Science*, 11, 699-718.
- BRINE, E. & ERNST, J. A. 2004. Total parenteral nutrition for premature infants^{1, 2, 3} Deborah Scanga, MS, RD is acknowledged for assistance with the referencing. ²²William Buss, PharmD is acknowledged for his assistance with sections related to pharmaceutical management and solution stability and compatability.^{1 33}CE—FEATURE ARTICLE: Link to www.nainr.com, click “CE Articles” to access the approved and accredited Continuing Education Questions for this featured article. Approval and accreditation are through Mosby Continuing Education and Training. Specific instructions and information on the number of credits available and the testing processes can be viewed on the website. *Newborn and Infant Nursing Reviews*, 4, 133-155.
- BROKAMP, C., BRANDT, E. B. & RYAN, P. H. 2019. Assessing exposure to outdoor air pollution for epidemiological studies: Model-based and personal sampling strategies. *J Allergy Clin Immunol*, 143, 2002-2006.
- BYUN, D. & CHING, J. K. S. 1999. Science algorithms of the EPA Models-3 Community Multiscale Air Quality (CMAQ) Modeling System. *EPA/600/R-99/030*.
- CALDERÓN-GARCIDUEÑAS, L., AZZARELLI, B., ACUNA, H., GARCIA, R., GAMBLING, T. M., OSNAYA, N., MONROY, S., MR, D. E. L. T., CARSON, J. L., VILLARREAL-CALDERON, A. & REWCASTLE, B. 2002. Air pollution and brain damage. *Toxicol Pathol*, 30, 373-89.
- CALDERÓN-GARCIDUEÑAS, L., MARONPOT, R. R., TORRES-JARDON, R., HENRÍQUEZ-ROLDÁN, C., SCHOONHOVEN, R., ACUÑA-AYALA, H., VILLARREAL-CALDERÓN, A., NAKAMURA, J., FERNANDO, R., REED, W., AZZARELLI, B. & SWENBERG, J. A. 2003. DNA damage in nasal and brain tissues of canines exposed to air pollutants is associated with evidence of chronic brain inflammation and neurodegeneration. *Toxicol Pathol*, 31, 524-38.
- CALDERÓN-GARCIDUEÑAS, L., MORA-TISCAREÑO, A., ONTIVEROS, E., GÓMEZ-GARZA, G., BARRAGÁN-MEJÍA, G., BROADWAY, J., CHAPMAN, S., VALENCIA-SALAZAR, G., JEWELLS, V., MARONPOT, R. R., HENRÍQUEZ-ROLDÁN, C., PÉREZ-GUILLÉ, B., TORRES-JARDÓN, R., HERRIT, L., BROOKS, D., OSNAYA-BRIZUELA, N., MONROY, M. E., GONZÁLEZ-MACIEL, A., REYNOSO-ROBLES, R., VILLARREAL-CALDERON, R., SOLT, A. C. & ENGLE, R. W. 2008. Air pollution, cognitive deficits

- and brain abnormalities: A pilot study with children and dogs. *Brain and Cognition*, 68, 117-127.
- CAO, L., WANG, L., WU, L., WANG, T., CUI, X., YU, L., DIAO, R. & MAO, H. 2021. Particulate matter and hypertensive disorders in pregnancy: systematic review and meta-analysis. *Public Health*, 200, 22-32.
- CARBONNEAU, E., DUMAS, A., BRODEUR-DOUCET, A. & FONTAINE-BISSON, B. 2022. A Community Prenatal Intervention in Social Nutrition: Evaluating the Impact on Pregnancy and Birthweight Outcomes. *Nutrients* [Online], 14.
- CARLSTEN, C., SALVI, S., WONG, G. W. K. & CHUNG, K. F. 2020. Personal strategies to minimise effects of air pollution on respiratory health: advice for providers, patients and the public. *Eur Respir J*, 55.
- CARSLAW, D. C. & BEEVERS, S. D. 2005. Estimations of road vehicle primary NO₂ exhaust emission fractions using monitoring data in London. *Atmospheric Environment*, 39, 167-177.
- CEPEDA, M., SCHOUFOUR, J., FREAK-POLI, R., KOOLHAAS, C. M., DHANA, K., BRAMER, W. M. & FRANCO, O. H. 2017. Levels of ambient air pollution according to mode of transport: a systematic review. *The Lancet Public Health*, 2, e23-e34.
- CERC 2006. AMDS-Roads, An air quality management system user guide. Cambridge Environmental Research Consultants Ltd Cambridge, UK.
- CHAKKARAPANI, A. A., ADAPPA, R., MOHAMMAD ALI, S. K., GUPTA, S., SONI, N. B., CHICOINE, L. & HUMMLER, H. D. 2020. "Current concepts of mechanical ventilation in neonates" - Part 1: Basics. *Int J Pediatr Adolesc Med*, 7, 13-18.
- CHANG, Y. S., OWEN, J. P., POJMAN, N. J., THIEU, T., BUKSHUPUN, P., WAKAHIRO, M. L. J., BERMAN, J. I., ROBERTS, T. P. L., NAGARAJAN, S. S., SHERR, E. H. & MUKHERJEE, P. 2015. White Matter Changes of Neurite Density and Fiber Orientation Dispersion during Human Brain Maturation. *PLOS ONE*, 10, e0123656.
- CHAPPELL, M., OKELL, T. & JENKINSON, M. 2018. *Short introduction to MRI Physics for Neuroimaging*, Oxford Neuroimaging Primers.
- CHARNLEY, M., NEWSON, L., WEEKS, A. & ABAYOMI, J. 2021. Pregnant Women Living with Obesity: A Cross-Sectional Observational Study of Dietary Quality and Pregnancy Outcomes. *Nutrients*, 13, 1652.
- CHEEK, E., GUERCIO, V., SHRUBSOLE, C. & DIMITROULOPOULOU, S. 2021. Portable air purification: Review of impacts on indoor air quality and health. *Science of The Total Environment*, 766, 142585.
- CHEN, J., DE HOOGH, K., GULLIVER, J., HOFFMANN, B., HERTEL, O., KETZEL, M., BAUWELINCK, M., VAN DONKELAAR, A., HVIDTFELDT, U. A., KATSOUYANNI, K., JANSSEN, N. A. H., MARTIN, R. V., SAMOLI, E., SCHWARTZ, P. E., STAFOGGIA, M., BELLANDER, T., STRAK, M., WOLF, K., VIENNEAU, D., VERMEULEN, R., BRUNEKREEF, B. & HOEK, G. 2019. A comparison of linear regression, regularization, and machine learning algorithms to develop Europe-wide spatial models of fine particles and nitrogen dioxide. *Environment International*, 130, 104934.
- CHEN, K., BREITNER, S., WOLF, K., STAFOGGIA, M., SERA, F., VICEDO-CABRERA, A. M., GUO, Y., TONG, S., LAVIGNE, E., MATUS, P., VALDÉS, N., KAN, H., JAAKKOLA, J. J. K., RYTI, N. R. I., HUBER, V., SCORTICHINI, M., HASHIZUME, M., HONDA, Y., NUNES, B., MADUREIRA, J., HOLOBĂCĂ, I. H., FRATIANNI, S., KIM, H., LEE, W., TOBIAS, A., ÍÑIGUEZ, C., FORSBERG, B., ÅSTRÖM, C., RAGETTLI, M. S., GUO, Y.-L. L., CHEN, B.-Y., LI, S., MILOJEVIC, A., ZANOBBETTI, A., SCHWARTZ, J., BELL, M. L., GASPARRINI, A. & SCHNEIDER, A. 2021. Ambient carbon monoxide and daily mortality: a global time-series study in 337 cities. *The Lancet Planetary Health*, 5, e191-e199.
- CHEN, L., WANG, Y., LI, P., JI, Y., KONG, S., LI, Z. & BAI, Z. 2012. A land use regression model incorporating data on industrial point source pollution. *Journal of Environmental Sciences*, 24, 1251-1258.
- CHEN, T. M., GOKHALE, J., SHOFRER, S. & KUSCHNER, W. G. 2007. Outdoor air pollution: nitrogen dioxide, sulfur dioxide, and carbon monoxide health effects. *Am J Med Sci*, 333, 249-56.

- CHIA, A. R., CHEN, L. W., LAI, J. S., WONG, C. H., NEELAKANTAN, N., VAN DAM, R. M. & CHONG, M. F. 2019. Maternal Dietary Patterns and Birth Outcomes: A Systematic Review and Meta-Analysis. *Adv Nutr*, 10, 685-695.
- CHITHRA, V. S. & SHIVA NAGENDRA, S. M. 2013. Chemical and morphological characteristics of indoor and outdoor particulate matter in an urban environment. *Atmospheric Environment*, 77, 579-587.
- CHIU, Y.-H. M., HSU, H.-H. L., COULL, B. A., BELLINGER, D. C., KLOOG, I., SCHWARTZ, J., WRIGHT, R. O. & WRIGHT, R. J. 2016. Prenatal particulate air pollution and neurodevelopment in urban children: Examining sensitive windows and sex-specific associations. *Environment International*, 87, 56-65.
- CHUN, H., LEUNG, C., WEN, S. W., MCDONALD, J. & SHIN, H. H. 2020. Maternal exposure to air pollution and risk of autism in children: A systematic review and meta-analysis. *Environ Pollut*, 256, 113307.
- CICCARELLI, O., BEHRENS, T. E., ALTMANN, D. R., ORRELL, R. W., HOWARD, R. S., JOHANSEN-BERG, H., MILLER, D. H., MATTHEWS, P. M. & THOMPSON, A. J. 2006. Probabilistic diffusion tractography: a potential tool to assess the rate of disease progression in amyotrophic lateral sclerosis. *Brain*, 129, 1859-1871.
- CLIFFORD, A., LANG, L., CHEN, R., ANSTEY, K. J. & SEATON, A. 2016. Exposure to air pollution and cognitive functioning across the life course – A systematic literature review. *Environmental Research*, 147, 383-398.
- CLOUCHOUX, C., GUIZARD, N., EVANS, A. C., DU PLESSIS, A. J. & LIMPEROPOULOS, C. 2012. Normative fetal brain growth by quantitative in vivo magnetic resonance imaging. *American Journal of Obstetrics and Gynecology*, 206, 173.e1-173.e8.
- COLONNA, M. & BUTOVSKY, O. 2017. Microglia Function in the Central Nervous System During Health and Neurodegeneration. *Annu Rev Immunol*, 35, 441-468.
- CORDERO-GRANDE, L., HUGHES, E. J., HUTTER, J., PRICE, A. N. & HAJNAL, J. V. 2018. Three-dimensional motion corrected sensitivity encoding reconstruction for multi-shot multi-slice MRI: Application to neonatal brain imaging. *Magnetic Resonance in Medicine*, 79, 1365-1376.
- CORY-SLECHTA, D. A., SOBOLEWSKI, M., MARVIN, E., CONRAD, K., MERRILL, A., ANDERSON, T., JACKSON, B. P. & OBERDORSTER, G. 2019. The Impact of Inhaled Ambient Ultrafine Particulate Matter on Developing Brain: Potential Importance of Elemental Contaminants. *Toxicologic Pathology*, 47, 976-992.
- COSTA, L. G., COLE, T. B., COBURN, J., CHANG, Y. C., DAO, K. & ROQUÉ, P. J. 2017. Neurotoxicity of traffic-related air pollution. *Neurotoxicology*, 59, 133-139.
- COUNSELL, S. J., ARICHI, T., ARULKUMARAN, S. & RUTHERFORD, M. A. 2019. Fetal and neonatal neuroimaging. *Handb Clin Neurol*, 162, 67-103.
- CRISTALDI, A., FIORE, M., OLIVERI CONTI, G., PULVIRENTI, E., FAVARA, C., GRASSO, A., COPAT, C. & FERRANTE, M. 2022. Possible association between PM(2.5) and neurodegenerative diseases: A systematic review. *Environ Res*, 208, 112581.
- CRUTZEN, P. J. 1970. The influence of nitrogen oxides on the atmospheric ozone content. *Quarterly Journal of the Royal Meteorological Society*, 96, 320-325.
- CSERBIK, D., CHEN, J.-C., MCCONNELL, R., BERHANE, K., SOWELL, E. R., SCHWARTZ, J., HACKMAN, D. A., KAN, E., FAN, C. C. & HERTING, M. M. 2020. Fine particulate matter exposure during childhood relates to hemispheric-specific differences in brain structure. *Environment International*, 143, 105933.
- D'ANTONI, D., SMITH, L., AUYEUNG, V. & WEINMAN, J. 2017. Psychosocial and demographic predictors of adherence and non-adherence to health advice accompanying air quality warning systems: a systematic review. *Environ Health*, 16, 100.
- DE CHAISEMARTIN, C., GEOFFARD, P. Y. & LE FAOU, A. L. 2011. Workplace smoking ban effects on unhappy smokers. *Health Econ*, 20, 1043-55.

- DE HOOGH, K., CHEN, J., GULLIVER, J., HOFFMANN, B., HERTEL, O., KETZEL, M., BAUWELINCK, M., VAN DONKELAAR, A., HVIDTFELDT, U. A., KATSOUYANNI, K., KLOMPMAKER, J., MARTIN, R. V., SAMOLI, E., SCHWARTZ, P. E., STAFOGGIA, M., BELLANDER, T., STRAK, M., WOLF, K., VIENNEAU, D., BRUNEKREEF, B. & HOEK, G. 2018. Spatial PM_{2.5}, NO₂, O₃ and BC models for Western Europe – Evaluation of spatiotemporal stability. *Environment International*, 120, 81-92.
- DE NARDO, M. C., MARIO, C. D., LACCETTA, G., BOSCARINO, G. & TERRIN, G. 2022. Enteral and parenteral energy intake and neurodevelopment in preterm infants: A systematic review. *Nutrition*, 97, 111572.
- DE NAZELLE, A., BODE, O. & ORJUELA, J. P. 2017. Comparison of air pollution exposures in active vs. passive travel modes in European cities: A quantitative review. *Environment International*, 99, 151-160.
- DE NAZELLE, A., SETO, E., DONAIRE-GONZALEZ, D., MENDEZ, M., MATAMALA, J., NIEUWENHUIJSEN, M. J. & JERRETT, M. 2013. Improving estimates of air pollution exposure through ubiquitous sensing technologies. *Environmental Pollution*, 176, 92-99.
- DEAN, D. C., TRAVERS, B. G., ADLURU, N., TROMP, D., DESTICHE, D., SAMSIN, D., PRIGGE, M., ZIELINSKI, B., FLETCHER, T., ANDERSON, J., FROELICH, A., BIGLER, E., LANGE, N., LAINHART, J. & ALEXANDER, A. 2016. Investigating the Microstructural Correlation of White Matter in Autism Spectrum Disorder. *Brain Connectivity*, 6, 415-433.
- DEAN, J. M., MCCLENDON, E., HANSEN, K., AZIMI-ZONOOZ, A., CHEN, K., RIDDLE, A., GONG, X., SHARIFNIA, E., HAGEN, M. & AHMAD, T. 2013. Prenatal cerebral ischemia disrupts MRI-defined cortical microstructure through disturbances in neuronal arborization. *Science translational medicine*, 5, 168ra7-168ra7.
- DEAN, S. V., LASSI, Z. S., IMAM, A. M. & BHUTTA, Z. A. 2014. Preconception care: nutritional risks and interventions. *Reprod Health*, 11 Suppl 3, S3.
- DECRUE, F., GORLANOVA, O., SALEM, Y., VIENNEAU, D., DE HOOGH, K., GISLER, A., USEMANN, J., KORTEN, I., NAHUM, U., SINUES, P., SCHULZKE, S., FUCHS, O., LATZIN, P., RÖÖSLI, M. & FREY, U. 2022. Increased Impact of Air Pollution on Lung Function in Preterm versus Term Infants: The BILD Study. *Am J Respir Crit Care Med*, 205, 99-107.
- DEFRA 2010. Air Quality Standards Regulations 2010. Department for Environment, Food and Rural Affairs.
- DEFRA. 2020. *Air Pollution in the UK 2020* [Online]. https://uk-air.defra.gov.uk/library/annualreport/viewonline?year=2020_issue_1#report_pdf. [Accessed 30/06 2022].
- DERBYSHIRE, E. 2018. Micronutrient Intakes of British Adults Across Mid-Life: A Secondary Analysis of the UK National Diet and Nutrition Survey. *Front Nutr*, 5, 55.
- DESCOTEAUX, M., DERICHE, R., KNÖSCHE, T. R. & ANWANDER, A. 2009. Deterministic and probabilistic tractography based on complex fibre orientation distributions. *IEEE Trans Med Imaging*, 28, 269-86.
- DEVI, C. N., CHANDRASEKHARAN, A., SUNDARARAMAN, V. K. & ALEX, Z. C. 2015. Neonatal brain MRI segmentation: A review. *Computers in Biology and Medicine*, 64, 163-178.
- DI DOMENICO, M., BENEVENUTO, S. G. D. M., TOMASINI, P. P., YARIWAKE, V. Y., DE OLIVEIRA ALVES, N., RAHMEIER, F. L., DA CRUZ FERNANDES, M., MOURA, D. J., NASCIMENTO SALDIVA, P. H. & VERAS, M. M. 2020. Concentrated ambient fine particulate matter (PM_{2.5}) exposure induce brain damage in pre and postnatal exposed mice. *NeuroToxicology*, 79, 127-141.
- DICKIE, D. A., SHENKIN, S. D., ANBLAGAN, D., LEE, J., BLESÁ CABEZ, M., RODRIGUEZ, D., BOARDMAN, J. P., WALDMAN, A., JOB, D. E. & WARDLAW, J. M. 2017. Whole Brain Magnetic Resonance Image Atlases: A Systematic Review of Existing Atlases and Caveats for Use in Population Imaging. *Front Neuroinform*, 11, 1.

- DIGGS, D. L., HARRIS, K. L., REKHADEVI, P. V. & RAMESH, A. 2012. Tumor microsomal metabolism of the food toxicant, benzo(a)pyrene, in ApcMin mouse model of colon cancer. *Tumor Biology*, 33, 1255-1260.
- DOCKERY, D. W., POPE, C. A., XU, X., SPENGLER, J. D., WARE, J. H., FAY, M. E., FERRIS, B. G. & SPEIZER, F. E. 1993. An Association between Air Pollution and Mortality in Six U.S. Cities. *New England Journal of Medicine*, 329, 1753-1759.
- DONS, E., INT PANIS, L., VAN POPPEL, M., THEUNIS, J. & WETS, G. 2012. Personal exposure to Black Carbon in transport microenvironments. *Atmospheric Environment*, 55, 392-398.
- DONS, E., TEMMERMAN, P., VAN POPPEL, M., BELLEMANS, T., WETS, G. & INT PANIS, L. 2013. Street characteristics and traffic factors determining road users' exposure to black carbon. *Science of The Total Environment*, 447, 72-79.
- DOWNWARD, G. S., VAN NUNEN, E., KERCKHOFFS, J., VINEIS, P., BRUNEKREEF, B., BOER, J. M. A., MESSIER, K. P., ROY, A., VERSCHUREN, W. M. M., VAN DER SCHOUW, Y. T., SLUIJS, I., GULLIVER, J., HOEK, G. & VERMEULEN, R. 2018. Long-Term Exposure to Ultrafine Particles and Incidence of Cardiovascular and Cerebrovascular Disease in a Prospective Study of a Dutch Cohort. *Environ Health Perspect*, 126, 127007.
- DUBOIS, J., BENDERS, M., BORRADORI-TOLSA, C., CACHIA, A., LAZEYRAS, F., HA-VINH LEUCHTER, R., SIZONENKO, S. V., WARFIELD, S. K., MANGIN, J. F. & HÜPPI, P. S. 2008. Primary cortical folding in the human newborn: an early marker of later functional development. *Brain*, 131, 2028-2041.
- EDWARDS, A. D., REDSHAW, M. E., KENNEA, N., RIVERO-ARIAS, O., GONZALES-CINCA, N., NONGENA, P., EDERIES, M., FALCONER, S., CHEW, A., OMAR, O., HARDY, P., HARVEY, M. E., EDDAMA, O., HAYWARD, N., WURIE, J., AZZOPARDI, D., RUTHERFORD, M. A. & COUNSELL, S. 2018. Effect of MRI on preterm infants and their families: a randomised trial with nested diagnostic and economic evaluation. *Arch Dis Child Fetal Neonatal Ed*, 103, F15-f21.
- EDWARDS, A. D., RUECKERT, D., SMITH, S. M., ABO SEADA, S., ALANSARY, A., ALMALBIS, J., ALLSOP, J., ANDERSSON, J., ARICHI, T., ARULKUMARAN, S., BASTIANI, M., BATALLE, D., BAXTER, L., BOZEK, J., BRAITHWAITE, E., BRANDON, J., CARNEY, O., CHEW, A., CHRISTIAENS, D., CHUNG, R., COLFORD, K., CORDERO-GRANDE, L., COUNSELL, S. J., CULLEN, H., CUPITT, J., CURTIS, C., DAVIDSON, A., DEPREZ, M., DILLON, L., DIMITRAKOPOULOU, K., DIMITROVA, R., DUFF, E., FALCONER, S., FARAHIBOZORG, S. R., FITZGIBBON, S. P., GAO, J., GASPAR, A., HARPER, N., HARRISON, S. J., HUGHES, E. J., HUTTER, J., JENKINSON, M., JBABDI, S., JONES, E., KAROLIS, V., KYRIAKOPOULOU, V., LENZ, G., MAKROPOULOS, A., MALIK, S., MASON, L., MORTARI, F., NOSARTI, C., NUNES, R. G., O'KEEFFE, C., O'MUIRCHARTAIGH, J., PATEL, H., PASSERAT-PALMBACH, J., PIETSCH, M., PRICE, A. N., ROBINSON, E. C., RUTHERFORD, M. A., SCHUH, A., SOTIROPOULOS, S., STEINWEG, J., TEIXEIRA, R., TENEV, T., TOURNIER, J. D., TUSOR, N., UUS, A., VECCHIATO, K., WILLIAMS, L. Z. J., WRIGHT, R., WURIE, J. & HAJNAL, J. V. 2022. The Developing Human Connectome Project Neonatal Data Release. *Front Neurosci*, 16, 886772.
- EEFTENS, M., BELEN, R., DE HOOGH, K., BELLANDER, T., CESARONI, G., CIRACH, M., DECLERCQ, C., DÉDELÉ, A., DONS, E., DE NAZELLE, A., DIMAKOPOULOU, K., ERIKSEN, K., FALQ, G., FISCHER, P., GALASSI, C., GRAŽULEVIČIENĖ, R., HEINRICH, J., HOFFMANN, B., JERRETT, M., KEIDEL, D., KOREK, M., LANKI, T., LINDLEY, S., MADSEN, C., MÖLTER, A., NÁDOR, G., NIEUWENHUIJSEN, M., NONNEMACHER, M., PEDELI, X., RAASCHOU-NIELSEN, O., PATELARO, E., QUASS, U., RANZI, A., SCHINDLER, C., STEMPELET, M., STEPHANOU, E., SUGIRI, D., TSAI, M.-Y., YLI-TUOMI, T., VARRÓ, M. J., VIENNEAU, D., KLOT, S. V., WOLF, K., BRUNEKREEF, B. & HOEK, G. 2012. Development of Land Use Regression Models for PM2.5, PM2.5 Absorbance, PM10 and PMcoarse in 20 European Study Areas; Results of the ESCAPE Project. *Environmental Science & Technology*, 46, 11195-11205.
- EKBLAD, M., KORKEILA, J. & LEHTONEN, L. 2015. Smoking during pregnancy affects foetal brain development. *Acta Paediatrica*, 104, 12-18.

- ENKHBAT, U., GOMBOJAV, E., BANZRAI, C., BATSUKH, S., BOLDBAATAR, B., ENKHTUYA, E., BELLINGER, D. C., LANPHEAR, B. P., MCCANDLESS, L. C. & ALLEN, R. W. 2022. Portable HEPA filter air cleaner use during pregnancy and children's autistic behaviors at four years of age: The UGAAR randomized controlled trial. *Environ Int*, 168, 107432.
- ENKHBAT, U., GOMBOJAV, E., BANZRAI, C., BATSUKH, S., BOLDBAATAR, B., ENKHTUYA, E., OCHIR, C., BELLINGER, D. C., LANPHEAR, B. P., MCCANDLESS, L. C. & ALLEN, R. W. 2021. Portable HEPA filter air cleaner use during pregnancy and children's behavior problem scores: a secondary analysis of the UGAAR randomized controlled trial. *Environ Health*, 20, 78.
- ESSERS, E., BINTER, A.-C., NEUMANN, A., WHITE, T., ALEMANY, S. & GUXENS, M. 2023. Air pollution exposure during pregnancy and childhood, APOE ϵ 4 status and Alzheimer polygenic risk score, and brain structural morphology in preadolescents. *Environmental Research*, 216, 114595.
- EVANGELOPOULOS, D., KATSOUYANNI, K., KEOGH, R. H., SAMOLI, E., SCHWARTZ, J., BARRATT, B., ZHANG, H. & WALTON, H. 2020. PM_{2.5} and NO₂ exposure errors using proxy measures, including derived personal exposure from outdoor sources: A systematic review and meta-analysis. *Environment International*, 137, 105500.
- FAGUNDES, L. S., FLECK ADA, S., ZANCHI, A. C., SALDIVA, P. H. & RHODEN, C. R. 2015. Direct contact with particulate matter increases oxidative stress in different brain structures. *Inhal Toxicol*, 27, 462-7.
- FAUSTINI, A., RAPP, R. & FORASTIERE, F. 2014. Nitrogen dioxide and mortality: review and meta-analysis of long-term studies. *European Respiratory Journal*, 44, 744.
- FERNANDEZ, C. G., HAMBY, M. E., MCREYNOLDS, M. L. & RAY, W. J. 2019. The Role of APOE4 in Disrupting the Homeostatic Functions of Astrocytes and Microglia in Aging and Alzheimer's Disease. *Frontiers in Aging Neuroscience*, 11.
- FIORDELISI, A., PISCITELLI, P., TRIMARCO, B., COSCIONI, E., IACCARINO, G. & SORRIENTO, D. 2017. The mechanisms of air pollution and particulate matter in cardiovascular diseases. *Heart Failure Reviews*, 22, 337-347.
- FISK, W. J. 2013. Health benefits of particle filtration. *Indoor Air*, 23, 357-368.
- FITZSIMMONS, J., KUBICKI, M. & SHENTON, M. E. 2013. Review of functional and anatomical brain connectivity findings in schizophrenia. *Current Opinion in Psychiatry*, 26, 172-187.
- FLANAGAN, E., STROH, E., OUDIN, A. & MALMQVIST, E. 2019. Connecting Air Pollution Exposure to Socioeconomic Status: A Cross-Sectional Study on Environmental Injustice among Pregnant Women in Scania, Sweden. *Int J Environ Res Public Health*, 16.
- FLOYD, C. N., SHAHED, F., UKAH, F., MCNEILL, K., O'GALLAGHER, K., MILLS, C. E., EVANGELOPOULOS, D., LIM, S., MUDWAY, I., BARRATT, B., WALTON, H. & WEBB, A. J. 2020. Acute Blood Pressure-Lowering Effects of Nitrogen Dioxide Exposure From Domestic Gas Cooking Via Elevation of Plasma Nitrite Concentration in Healthy Individuals. *Circulation Research*, 127, 847-848.
- FONT, A., GUISEPPIN, L., BLANGIARDO, M., GHERSI, V. & FULLER, G. W. 2019. A tale of two cities: is air pollution improving in Paris and London? *Environmental Pollution*, 249, 1-12.
- FORNS, J., SUNYER, J., GARCIA-ESTEBAN, R., PORTA, D., GHASSABIAN, A., GIORGIS-ALLEMAND, L., GONG, T., GEHRING, U., SØRENSEN, M., STANDL, M., SUGIRI, D., ALMQVIST, C., ANDIARENA, A., BADALONÍ, C., BEELEN, R., BERDEL, D., CESARONI, G., CHARLES, M.-A., ERIKSEN, K. T., ESTARLICH, M., FERNANDEZ, M. F., FORHAN, A., JADDOE, V. W. V., KOREK, M., LICHTENSTEIN, P., LERTXUNDI, A., LOPEZ-ESPINOSA, M.-J., MARKEVYCH, I., DE NAZELLE, A., RAASCHOU-NIELSEN, O., NIEUWENHUIJSEN, M., PÉREZ-LOBATO, R., PHILIPPAT, C., SLAMA, R., TIESLER, C. M. T., VERHULST, F. C., VON BERG, A., VRIJKOTTE, T., NYBO ANDERSEN, A.-M., HEUDE, B., KRÄMER, U., HEINRICH, J., TIEMEIER, H., FORASTIERE, F., PERSHAGEN, G., BRUNEKREEF, B. & GUXENS, M. 2018. Air Pollution Exposure During Pregnancy and Symptoms of Attention Deficit and Hyperactivity Disorder in Children in Europe. *Epidemiology*, 29, 618-626.
- FSL. 2022. FSL course [Online]. https://open.win.ox.ac.uk/pages/fslcourse/website/online_materials.html#Prep. [Accessed 11/10 2022].

- FU, P., BAI, L., CAI, Z., LI, R. & YUNG, K. K. L. 2020. Fine particulate matter aggravates intestinal and brain injury and affects bacterial community structure of intestine and feces in Alzheimer's disease transgenic mice. *Ecotoxicol Environ Saf*, 192, 110325.
- FU, P. & YUNG, K. K. L. 2020. Air Pollution and Alzheimer's Disease: A Systematic Review and Meta-Analysis. *J Alzheimers Dis*, 77, 701-714.
- FUERTE, E., STANDL, M., FORNS, J., BERDEL, D., GARCIA-AYMERICH, J., MARKEVYCH, I., SCHULTE-KOERNE, G., SUGIRI, D., SCHIKOWSKI, T., TIESLER, C. M. T. & HEINRICH, J. 2016. Traffic-related air pollution and hyperactivity/inattention, dyslexia and dyscalculia in adolescents of the German GINIplus and LISAplus birth cohorts. *Environment International*, 97, 85-92.
- FULLER, R., LANDRIGAN, P. J., BALAKRISHNAN, K., BATHAN, G., BOSE-O'REILLY, S., BRAUER, M., CARAVANOS, J., CHILES, T., COHEN, A., CORRA, L., CROPPER, M., FERRARO, G., HANNA, J., HANRAHAN, D., HU, H., HUNTER, D., JANATA, G., KUPKA, R., LANPHEAR, B., LICHTVELD, M., MARTIN, K., MUSTAPHA, A., SANCHEZ-TRIANA, E., SANDILYA, K., SCHAEFLI, L., SHAW, J., SEDDON, J., SUK, W., TÉLLEZ-ROJO, M. M. & YAN, C. 2022. Pollution and health: a progress update. *The Lancet Planetary Health*, 6, e535-e547.
- GALE-GRANT, O., FENN-MOLTU, S., FRANÇA, L. G. S., DIMITROVA, R., CHRISTIAENS, D., CORDERO-GRANDE, L., CHEW, A., FALCONER, S., HARPER, N., PRICE, A. N., HUTTER, J., HUGHES, E., O'MUIRCHEARTAIGH, J., RUTHERFORD, M., COUNSELL, S. J., RUECKERT, D., NOSARTI, C., HAJNAL, J. V., MCALONAN, G., ARICHI, T., EDWARDS, A. D. & BATALLA, D. 2022. Effects of gestational age at birth on perinatal structural brain development in healthy term-born babies. *Human Brain Mapping*, 43, 1577-1589.
- GHASSABIAN, A., AFANASYEVA, Y., YU, K., GORDON, T., LIU, M. & TRASANDE, L. 2023. Characterisation of personalised air pollution exposure in pregnant women participating in a birth cohort study. *Paediatr Perinat Epidemiol*, 37, 436-444.
- GILLES, F. H., DOOLING, E. & FULCHIERO, A. 1976. Sequence of myelination in the human fetus. *Trans Am Neurol Assoc*, 101, 244-6.
- GIRAUD, C. 2021. *Introduction to high-dimensional statistics*, CRC Press.
- GIRGUIS, M. S., STRICKLAND, M. J., HU, X., LIU, Y., CHANG, H. H., KLOOG, I., BELANOFF, C., BARTELL, S. M. & VIEIRA, V. M. 2018. Exposure to acute air pollution and risk of bronchiolitis and otitis media for preterm and term infants. *J Expo Sci Environ Epidemiol*, 28, 348-357.
- GONZÁLEZ-MARTÍN, J., KRAAKMAN, N. J. R., PÉREZ, C., LEBRERO, R. & MUÑOZ, R. 2021. A state-of-the-art review on indoor air pollution and strategies for indoor air pollution control. *Chemosphere*, 262, 128376.
- GONZÁLEZ-VILLÀ, S., OLIVER, A., VALVERDE, S., WANG, L., ZWIGGELAAR, R. & LLADÓ, X. 2016. A review on brain structures segmentation in magnetic resonance imaging. *Artificial Intelligence in Medicine*, 73, 45-69.
- GONZÁLEZ, I., DEJEAN, S., MARTIN, P. G. P. & BACCINI, A. 2008. CCA: An R package to extend canonical correlation analysis. *Journal of Statistical Software*, 23, 1-14.
- GOUSIAS, I. S., EDWARDS, A. D., RUTHERFORD, M. A., COUNSELL, S. J., HAJNAL, J. V., RUECKERT, D. & HAMMERS, A. 2012. Magnetic resonance imaging of the newborn brain: Manual segmentation of labelled atlases in term-born and preterm infants. *NeuroImage*, 62, 1499-1509.
- GRANDE-BARRETO, J. Partial Volume Segmentation in Magnetic Resonance Imaging (MRI). 2017.
- GRANDJEAN, P. & LANDRIGAN, P. J. 2014. Neurobehavioural effects of developmental toxicity. *The Lancet Neurology*, 13, 330-338.
- GREATER LONDON AUTHORITY 2019. CENTRAL LONDON ULTRA LOW EMISSION ZONE – SIX MONTH REPORT.
https://www.london.gov.uk/sites/default/files/ulez_six_month_evaluation_report_final_oct.pdf.

- GREATER LONDON AUTHORITY 2023. INNER LONDON ULTRA LOW EMISSION ZONE – ONE YEAR REPORT. <https://www.london.gov.uk/sites/default/files/2023-02/Inner%20London%20ULEZ%20One%20Year%20Report%20-%20final.pdf>.
- GROVER, V. P., TOGNARELLI, J. M., CROSSEY, M. M., COX, I. J., TAYLOR-ROBINSON, S. D. & MCPHAIL, M. J. 2015. Magnetic Resonance Imaging: Principles and Techniques: Lessons for Clinicians. *J Clin Exp Hepatol*, 5, 246-55.
- GRUSSU, F., SCHNEIDER, T., TUR, C., YATES, R. L., TACHROUNT, M., IANUŞ, A., YIANNAKAS, M. C., NEWCOMBE, J., ZHANG, H., ALEXANDER, D. C., DELUCA, G. C. & GANDINI WHEELER-KINGSHOTT, C. A. M. 2017. Neurite dispersion: a new marker of multiple sclerosis spinal cord pathology? *Annals of Clinical and Translational Neurology*, 4, 663-679.
- GRYPARIS, A., FORSBERG, B., KATSOUYANNI, K., ANALITIS, A., TOULLOUMI, G., SCHWARTZ, J., SAMOLI, E., MEDINA, S., ANDERSON, H. R., NICIU, E. M., WICHMANN, H. E., KRIZ, B., KOSNIK, M., SKORKOVSKY, J., VONK, J. M. & DÖRTBUDAK, Z. 2004. Acute effects of ozone on mortality from the "air pollution and health: a European approach" project. *Am J Respir Crit Care Med*, 170, 1080-7.
- GUENTHER, A., HEWITT, C. N., ERICKSON, D., FALL, R., GERON, C., GRAEDEL, T., HARLEY, P., KLINGER, L., LERDAU, M. & MCKAY, W. 1995. A global model of natural volatile organic compound emissions. *Journal of Geophysical Research: Atmospheres*, 100, 8873-8892.
- GUXENS, M., LUBCZYŃSKA, M. J., MUETZEL, R. L., DALMAU-BUENO, A., JADDOE, V. W. V., HOEK, G., VAN DER LUGT, A., VERHULST, F. C., WHITE, T., BRUNEKREEF, B., TIEMEIER, H. & EL MARROUN, H. 2018. Air Pollution Exposure During Fetal Life, Brain Morphology, and Cognitive Function in School-Age Children. *Biological Psychiatry*, 84, 295-303.
- GUXENS, M., MAŁGORZATA, J. L., LAURA, P. C., RYAN, L. M., HANAN, E. M., XAVIER, B., GERARD, H. & HENNING, T. 2022. Associations of Air Pollution on the Brain in Children: A Brain Imaging Study. *Res Rep Health Eff Inst*, 1-61.
- HA, S., NOBLES, C., KANNER, J., SHERMAN, S., CHO, S. H., PERKINS, N., WILLIAMS, A., GROBMAN, W., BIGGIO, J., SUBRAMANIAM, A., OUIDIR, M., CHEN, Z. & MENDOLA, P. 2020. Air Pollution Exposure Monitoring among Pregnant Women with and without Asthma. *Int J Environ Res Public Health*, 17.
- HAJAT, A., HSIA, C. & O'NEILL, M. S. 2015. Socioeconomic Disparities and Air Pollution Exposure: a Global Review. *Curr Environ Health Rep*, 2, 440-50.
- HAJMOHAMMADI, H. & HEYDECKER, B. 2022. Evaluation of air quality effects of the London ultra-low emission zone by state-space modelling. *Atmospheric Pollution Research*, 13, 101514.
- HÄRDLE, W. K. & SIMAR, L. 2015. Canonical Correlation Analysis. *Applied Multivariate Statistical Analysis*. Berlin, Heidelberg: Springer Berlin Heidelberg.
- HARDOON, D. R., SZEDMAK, S. & SHAW-TAYLOR, J. 2003. Canonical correlation analysis; An overview with application to learning methods. In: SOTON:259225 (ed.) *Canonical correlation analysis, kernel canonical correlation analysis, partial Gram-Schmidt orthogonalisation, Cholesky decomposition, incomplete Cholesky decomposition, kernel methods*. <https://eprints.soton.ac.uk/259225/>.
- HASTIE, T., TIBSHIRANI, R. & WAINWRIGHT, M. 2015. *Statistical learning with sparsity: the lasso and generalizations*, CRC press.
- HATCH, G. E., SLADE, R., HARRIS, L. P., MCDONNELL, W. F., DEVLIN, R. B., KOREN, H. S., COSTA, D. L. & MCKEE, J. 1994. Ozone dose and effect in humans and rats. A comparison using oxygen-18 labeling and bronchoalveolar lavage. *Am J Respir Crit Care Med*, 150, 676-83.
- HEALTH AND SAFETY EXECUTIVE 2020. EH40/2005 Workplace exposure limits. <https://www.hse.gov.uk/pubns/priced/eh40.pdf>.
- HEALTH EFFECTS INSTITUTE 2010. Traffic-Related Air Pollution: A Critical Review of the Literature on Emissions, Exposure, and Health Effects.
- HERNÁN, M. A. & ROBINS, J. M. 2010. Causal inference. CRC Boca Raton, FL.

- HERNANDEZ-FERNANDEZ, M., REGULY, I., JBABDI, S., GILES, M., SMITH, S. & SOTIROPOULOS, S. N. 2019. Using GPUs to accelerate computational diffusion MRI: From microstructure estimation to tractography and connectomes. *Neuroimage*, 188, 598-615.
- HERNÁNDEZ, M., GUERRERO, G. D., CECILIA, J. M., GARCÍA, J. M., INUGGI, A., JBABDI, S., BEHRENS, T. E. J. & SOTIROPOULOS, S. N. 2013. Accelerating Fibre Orientation Estimation from Diffusion Weighted Magnetic Resonance Imaging Using GPUs. *PLOS ONE*, 8, e61892.
- HERRERA-ARAUJO, D. 2016. Folic acid advisories: a public health challenge? *Health Economics*, 25, 1104-1122.
- HERTING, M. M., YOUNAN, D., CAMPBELL, C. E. & CHEN, J. C. 2019. Outdoor Air Pollution and Brain Structure and Function From Across Childhood to Young Adulthood: A Methodological Review of Brain MRI Studies. *Front Public Health*, 7, 332.
- HEYDON, J. & CHAKRABORTY, R. 2020. Can portable air quality monitors protect children from air pollution on the school run? An exploratory study. *Environ Monit Assess*, 192, 195.
- HO, J. J., SUBRAMANIAM, P. & DAVIS, P. G. 2020. Continuous positive airway pressure (CPAP) for respiratory distress in preterm infants. *Cochrane Database Syst Rev*, 10, Cd002271.
- HOEK, G. 2017. Methods for Assessing Long-Term Exposures to Outdoor Air Pollutants. *Current Environmental Health Reports*, 4, 450-462.
- HOLGATE, S. T. 2017. 'Every breath we take: the lifelong impact of air pollution'—a call for action. *Clinical Medicine*, 17, 8.
- HOLM, S. M., BALMES, J. R., GUNIER, R. B., KOGUT, K., HARLEY, K. G. & ESKENAZI, B. 2023. Cognitive Development and Prenatal Air Pollution Exposure in the CHAMACOS Cohort. *Environ Health Perspect*, 131, 37007.
- HOLMES, N. S. & MORAWSKA, L. 2006. A review of dispersion modelling and its application to the dispersion of particles: An overview of different dispersion models available. *Atmospheric Environment*, 40, 5902-5928.
- HORTON, M. K., MARGOLIS, A. E., TANG, C. & WRIGHT, R. 2014. Neuroimaging is a novel tool to understand the impact of environmental chemicals on neurodevelopment. *Curr Opin Pediatr*, 26, 230-6.
- HOTELLING, H. 1936. Relations Between Two Sets of Variates. *Biometrika*, 28, 321-377.
- HUANG, H., JEON, T., SEDMAK, G., PLETIKOS, M., VASUNG, L., XU, X., YAROWSKY, P., RICHARDS, L. J., KOSTOVIĆ, I., ŠESTAN, N. & MORI, S. 2012. Coupling Diffusion Imaging with Histological and Gene Expression Analysis to Examine the Dynamics of Cortical Areas across the Fetal Period of Human Brain Development. *Cerebral Cortex*, 23, 2620-2631.
- HUANG, W. & MORAWSKA, L. 2019. Face masks could raise pollution risks. *Nature*, 574, 29-30.
- HUDDA, N. & FRUIN, S. A. 2018. Carbon dioxide accumulation inside vehicles: The effect of ventilation and driving conditions. *Science of The Total Environment*, 610-611, 1448-1456.
- HUGHES, E. J., WINCHMAN, T., PADORMO, F., TEIXEIRA, R., WURIE, J., SHARMA, M., FOX, M., HUTTER, J., CORDERO-GRANDE, L., PRICE, A. N., ALLSOP, J., BUENO-CONDE, J., TUSOR, N., ARICHI, T., EDWARDS, A. D., RUTHERFORD, M. A., COUNSELL, S. J. & HAJNAL, J. V. 2017. A dedicated neonatal brain imaging system. *Magnetic Resonance in Medicine*, 78, 794-804.
- HUTTER, J., CHRISTIAENS, D. J., SCHNEIDER, T., CORDERO-GRANDE, L., SLATOR, P. J., DEPREZ, M., PRICE, A. N., TOURNIER, J. D., RUTHERFORD, M. & HAJNAL, J. V. 2018. Slice-level diffusion encoding for motion and distortion correction. *Medical Image Analysis*, 48, 214-229.
- JEDRYCHOWSKI, W. A., PERERA, F. P., CAMANN, D., SPENGLER, J., BUTSCHER, M., MROZ, E., MAJEWSKA, R., FLAK, E., JACEK, R. & SOWA, A. 2015. Prenatal exposure to polycyclic aromatic hydrocarbons and cognitive dysfunction in children. *Environmental Science and Pollution Research*, 22, 3631-3639.
- JENKINSON, M. & CHAPPELL, M. 2018. *Introduction to Neuroimaging Analysis*, Oxford University Press.
- JERRETT, M., ARAIN, A., KANAROGLU, P., BECKERMAN, B., POTOGLU, D., SAHSUVAROGLU, T., MORRISON, J. & GIOVIS, C. 2005. A review and evaluation of intraurban air pollution exposure models. *Journal of Exposure Science & Environmental Epidemiology*, 15, 185-204.

- JESPERSEN, S. N., BJARKAM, C. R., NYENGAARD, J. R., CHAKRAVARTY, M. M., HANSEN, B., VOSEGAARD, T., ØSTERGAARD, L., YABLONSKIY, D., NIELSEN, N. C. & VESTERGAARD-POULSEN, P. 2010. Neurite density from magnetic resonance diffusion measurements at ultrahigh field: Comparison with light microscopy and electron microscopy. *NeuroImage*, 49, 205-216.
- JEURISSEN, B., DESCOTEAUX, M., MORI, S. & LEEMANS, A. 2017. Diffusion MRI fiber tractography of the brain. *NMR in Biomedicine*, 32, e3785.
- JOHNSON, A. T. 2016. Respirator masks protect health but impact performance: a review. *J Biol Eng*, 10, 4.
- JOHNSON, D., RICCIARDI, A., BROWNEE, W., KANBER, B., PRADOS, F., COLLORONE, S., KADEN, E., TOOSY, A., ALEXANDER, D. C., GANDINI WHEELER-KINGSHOTT, C. A. M., CICCARELLI, O. & GRUSSU, F. 2021. Comparison of Neurite Orientation Dispersion and Density Imaging and Two-Compartment Spherical Mean Technique Parameter Maps in Multiple Sclerosis. *Front Neurol*, 12, 662855.
- JOHNSON, M., PILLARISSETTI, A., PIEDRAHITA, R., BALAKRISHNAN, K., PEEL, J. L., STEENLAND, K., UNDERHILL, L. J., ROSA, G., KIRBY, M. A., DÍAZ-ARTIGA, A., MCCracken, J., CLARK, M. L., WALLER, L., CHANG, H. H., WANG, J., DUSABIMANA, E., NDAGIJIMANA, F., SAMBANDAM, S., MUKHOPADHYAY, K., KEARNS, K. A., CAMPBELL, D., KREMER, J., ROSENTHAL, J. P., CHECKLEY, W., CLASEN, T. & NAEHER, L. 2022. Exposure Contrasts of Pregnant Women during the Household Air Pollution Intervention Network Randomized Controlled Trial. *Environ Health Perspect*, 130, 97005.
- JOHNSON, M. H. 2001. Functional brain development in humans. *Nature Reviews Neuroscience*, 2, 475-483.
- JOHNSON, S. & MARLOW, N. 2017. Early and long-term outcome of infants born extremely preterm. *Arch Dis Child*, 102, 97-102.
- JONES, D. K. 2008. Studying connections in the living human brain with diffusion MRI. *Cortex*, 44, 936-52.
- JONES, D. K. & CERCIGNANI, M. 2010. Twenty-five pitfalls in the analysis of diffusion MRI data. *NMR in Biomedicine*, 23, 803-820.
- JONES, D. K., KNÖSCHE, T. R. & TURNER, R. 2013. White matter integrity, fiber count, and other fallacies: The do's and don'ts of diffusion MRI. *NeuroImage*, 73, 239-254.
- JONES, R. R., HOEK, G., FISHER, J. A., HASHEMINASSAB, S., WANG, D., WARD, M. H., SIOUTAS, C., VERMEULEN, R. & SILVERMAN, D. T. 2020. Land use regression models for ultrafine particles, fine particles, and black carbon in Southern California. *Science of The Total Environment*, 699, 134234.
- JONES, S. R., CARLEY, S. & HARRISON, M. 2003. An introduction to power and sample size estimation. *Emergency Medicine Journal*, 20, 453.
- KAMIYA, K., HORI, M. & AOKI, S. 2020. NODDI in clinical research. *Journal of Neuroscience Methods*, 346, 108908.
- KANAROGLOU, P. S., JERRETT, M., MORRISON, J., BECKERMAN, B., ARAIN, M. A., GILBERT, N. L. & BROOK, J. R. 2005. Establishing an air pollution monitoring network for intra-urban population exposure assessment: A location-allocation approach. *Atmospheric Environment*, 39, 2399-2409.
- KANCHAN, K., GORAI, A. K. & GOYAL, P. 2015. A review on air quality indexing system. *Asian Journal of Atmospheric Environment*, 9, 101-113.
- KARMACHARYA, S., GAGOSKI, B., NING, L., VYAS, R., CHENG, H. H., SOUL, J., NEWBERGER, J. W., SHENTON, M. E., RATHI, Y. & GRANT, P. E. 2018. Advanced diffusion imaging for assessing normal white matter development in neonates and characterizing aberrant development in congenital heart disease. *NeuroImage: Clinical*, 19, 360-373.
- KAUR, S., NIEUWENHUIJSEN, M. J. & COLVILE, R. N. 2007. Fine particulate matter and carbon monoxide exposure concentrations in urban street transport microenvironments. *Atmospheric Environment*, 41, 4781-4810.

- KEIL, B., ALAGAPPAN, V., MAREYAM, A., MCNAB, J. A., FUJIMOTO, K., TOUNTCHEVA, V., TRIANTAFYLLOU, C., DILKS, D. D., KANWISHER, N., LIN, W., GRANT, P. E. & WALD, L. L. 2011. Size-optimized 32-channel brain arrays for 3 T pediatric imaging. *Magnetic Resonance in Medicine*, 66, 1777-1787.
- KELLY, C. J., HUGHES, E. J., RUTHERFORD, M. A. & COUNSELL, S. J. 2019. Advances in neonatal MRI of the brain: from research to practice. *Archives of disease in childhood - Education & practice edition*, 104, 106.
- KELLY, F., ARMSTRONG, B., ATKINSON, R., ANDERSON, H. R., BARRATT, B., BEEVERS, S., COOK, D., GREEN, D., DERWENT, D., MUDWAY, I. & WILKINSON, P. 2011. The London low emission zone baseline study; Appendix B. *Res Rep Health Eff Inst*, 3-79.
- KELLY, F. J. & FUSSELL, J. C. 2018. Improving indoor air quality, health and performance within environments where people live, travel, learn and work. *ATMOSPHERIC ENVIRONMENT*.
- KERSBERGEN, K. J., MAKROPOULOS, A., ALJABAR, P., GROENENDAAL, F., DE VRIES, L. S., COUNSELL, S. J. & BENDERS, M. J. N. L. 2016. Longitudinal Regional Brain Development and Clinical Risk Factors in Extremely Preterm Infants. *The Journal of Pediatrics*, 178, 93-100.e6.
- KIERS, H. A. L. & SMILDE, A. K. 2007. A comparison of various methods for multivariate regression with highly collinear variables. *Statistical Methods and Applications*, 16, 193-228.
- KIM, E., PARK, H., HONG, Y.-C., HA, M., KIM, Y., KIM, B.-N., KIM, Y., ROH, Y.-M., LEE, B.-E., RYU, J.-M., KIM, B.-M. & HA, E.-H. 2014. Prenatal exposure to PM10 and NO2 and children's neurodevelopment from birth to 24months of age: Mothers and Children's Environmental Health (MOCEH) study. *Science of The Total Environment*, 481, 439-445.
- KIM, S. Y., KIM, J. K., PARK, S. H., KIM, B. G., JANG, A. S., OH, S. H., LEE, J. H., SUH, M. W. & PARK, M. K. 2018. Effects of inhaled particulate matter on the central nervous system in mice. *Neurotoxicology*, 67, 169-177.
- KLOCKE, C., ALLEN, J. L., SOBOLEWSKI, M., BLUM, J. L., ZELIKOFF, J. T. & CORY-SLECHTA, D. A. 2018a. Exposure to fine and ultrafine particulate matter during gestation alters postnatal oligodendrocyte maturation, proliferation capacity, and myelination. *Neurotoxicology*, 65, 196-206.
- KLOCKE, C., ALLEN, J. L., SOBOLEWSKI, M., MAYER-PROSCHEL, M., BLUM, J. L., LAUTERSTEIN, D., ZELIKOFF, J. T. & CORY-SLECHTA, D. A. 2017. Neuropathological Consequences of Gestational Exposure to Concentrated Ambient Fine and Ultrafine Particles in the Mouse. *Toxicol Sci*, 156, 492-508.
- KLOCKE, C., SHERINA, V., GRAHAM, U. M., GUNDERSON, J., ALLEN, J. L., SOBOLEWSKI, M., BLUM, J. L., ZELIKOFF, J. T. & CORY-SLECHTA, D. A. 2018b. Enhanced cerebellar myelination with concomitant iron elevation and ultrastructural irregularities following prenatal exposure to ambient particulate matter in the mouse. *Inhalation toxicology*, 30, 381-396.
- KLOOG, I., RIDGWAY, B., KOUTRAKIS, P., COULL, B. A. & SCHWARTZ, J. D. 2013. Long- and short-term exposure to PM2.5 and mortality: using novel exposure models. *Epidemiology*, 24, 555-61.
- KLOSKE, C. M. & WILCOCK, D. M. 2020. The Important Interface Between Apolipoprotein E and Neuroinflammation in Alzheimer's Disease. *Frontiers in Immunology*, 11.
- KNIBBS, L. D., COLE-HUNTER, T. & MORAWSKA, L. 2011. A review of commuter exposure to ultrafine particles and its health effects. *Atmospheric Environment*, 45, 2611-2622.
- KOSTOVIĆ, I. & JOVANOVIĆ-MILOSEVIĆ, N. 2006. The development of cerebral connections during the first 20-45 weeks' gestation. *Semin Fetal Neonatal Med*, 11, 415-22.
- KROENKE, C. D. 2018. Using diffusion anisotropy to study cerebral cortical gray matter development. *Journal of Magnetic Resonance*, 292, 106-116.
- KRZANOWSKI, W. J. 1988. *Principles of multivariate analysis: a user's perspective*, Oxford University Press, Inc.
- KUKLISOVA-MURGASOVA, M., QUAGHEBEUR, G., RUTHERFORD, M. A., HAJNAL, J. V. & SCHNABEL, J. A. 2012. Reconstruction of fetal brain MRI with intensity matching and complete outlier removal. *Med Image Anal*, 16, 1550-64.

- KULAS, J. A., HETTER, J. V., SOHRABI, M., MELVIN, J. E., MANOCHA, G. D., PUIG, K. L., GORR, M. W., TANWAR, V., MCDONALD, M. P., WOLD, L. E. & COMBS, C. K. 2018. In utero exposure to fine particulate matter results in an altered neuroimmune phenotype in adult mice. *Environmental Pollution*, 241, 279-288.
- KUMAR, A., SINGH, B. P., PUNIA, M., SINGH, D., KUMAR, K. & JAIN, V. K. 2014. Assessment of indoor air concentrations of VOCs and their associated health risks in the library of Jawaharlal Nehru University, New Delhi. *Environ Sci Pollut Res Int*, 21, 2240-2248.
- KUNDU, S. & STONE, E. A. 2014. Composition and sources of fine particulate matter across urban and rural sites in the Midwestern United States. *Environ Sci Process Impacts*, 16, 1360-70.
- KUNZ, N., ZHANG, H., VASUNG, L., O'BRIEN, K. R., ASSAF, Y., LAZEYRAS, F., ALEXANDER, D. C. & HÜPPI, P. S. 2014. Assessing white matter microstructure of the newborn with multi-shell diffusion MRI and biophysical compartment models. *Neuroimage*, 96, 288-99.
- LAMOUREUX, P. 2005. Campagnes de communication en santé publique et éducation à la santé. *Les Tribunes de la santé*, 9, 35-42.
- LANGRISH, J. P., LI, X., WANG, S., LEE, M. M., BARNES, G. D., MILLER, M. R., CASSEE, F. R., BOON, N. A., DONALDSON, K., LI, J., LI, L., MILLS, N. L., NEWBY, D. E. & JIANG, L. 2012. Reducing personal exposure to particulate air pollution improves cardiovascular health in patients with coronary heart disease. *Environ Health Perspect*, 120, 367-72.
- LANGRISH, J. P., MILLS, N. L., CHAN, J. K., LESEMAN, D. L., AITKEN, R. J., FOKKENS, P. H., CASSEE, F. R., LI, J., DONALDSON, K., NEWBY, D. E. & JIANG, L. 2009. Beneficial cardiovascular effects of reducing exposure to particulate air pollution with a simple facemask. *Part Fibre Toxicol*, 6, 8.
- LAQN 2018. London Air Quality Network - Monitoring sites classification. https://www.londonair.org.uk/london/asp/classification.asp?region=13&site=SK2&details=general&mapview=all&la_id=&network=All&MapType=Static.
- LAULE, C., VAVASOUR, I. M., KOLIND, S. H., LI, D. K., TRABOULSEE, T. L., MOORE, G. R. & MACKAY, A. L. 2007. Magnetic resonance imaging of myelin. *Neurotherapeutics*, 4, 460-84.
- LAUMBACH, R. J. & CROMAR, K. R. 2022. Personal Interventions to Reduce Exposure to Outdoor Air Pollution. *Annu Rev Public Health*, 43, 293-309.
- LAUMBACH, R. J., CROMAR, K. R., ADAMKIEWICZ, G., CARLSTEN, C., CHARPIN, D., CHAN, W. R., DE NAZELLE, A., FORASTIERE, F., GOLDSTEIN, J., GUMY, S., HALLMAN, W. K., JERRETT, M., KIPEN, H. M., PIROZZI, C. S., POLIVKA, B. J., RADBEL, J., SHAFFER, R. E., SIN, D. D. & VIEGI, G. 2021. Personal Interventions for Reducing Exposure and Risk for Outdoor Air Pollution: An Official American Thoracic Society Workshop Report. *Ann Am Thorac Soc*, 18, 1435-1443.
- LEE, J., KALIA, V., PERERA, F., HERBSTMAN, J., LI, T., NIE, J., QU, L. R., YU, J. & TANG, D. 2017. Prenatal airborne polycyclic aromatic hydrocarbon exposure, LINE1 methylation and child development in a Chinese cohort. *Environment International*, 99, 315-320.
- LEE, K. K., BING, R., KIANG, J., BASHIR, S., SPATH, N., STELZLE, D., MORTIMER, K., BULARGA, A., DOUDESIS, D., JOSHI, S. S., STRACHAN, F., GUMY, S., ADAIR-ROHANI, H., ATTIA, E. F., CHUNG, M. H., MILLER, M. R., NEWBY, D. E., MILLS, N. L., MCALLISTER, D. A. & SHAH, A. S. V. 2020a. Adverse health effects associated with household air pollution: a systematic review, meta-analysis, and burden estimation study. *The Lancet Global Health*, 8, e1427-e1434.
- LEE, K. K., SPATH, N., MILLER, M. R., MILLS, N. L. & SHAH, A. S. V. 2020b. Short-term exposure to carbon monoxide and myocardial infarction: A systematic review and meta-analysis. *Environment International*, 143, 105901.
- LEMKADDEM, A., DADUCCI, A., KUNZ, N., LAZEYRAS, F., SEECK, M., THIRAN, J.-P. & VULLIÉMOZ, S. 2014. Connectivity and tissue microstructural alterations in right and left temporal lobe epilepsy revealed by diffusion spectrum imaging. *NeuroImage: Clinical*, 5, 349-358.
- LEVITON, A. & GILLES, F. 1996. Ventriculomegaly, delayed myelination, white matter hypoplasia, and "periventricular" leukomalacia: how are they related? *Pediatr Neurol*, 15, 127-36.
- LEWIS, A. & EDWARDS, P. 2016. Validate personal air-pollution sensors. *Nature*, 535, 29-31.

- LEWIS, A. C., LEE, J. D., EDWARDS, P. M., SHAW, M. D., EVANS, M. J., MOLLER, S. J., SMITH, K. R., BUCKLEY, J. W., ELLIS, M., GILLOT, S. R. & WHITE, A. 2016. Evaluating the performance of low cost chemical sensors for air pollution research. *Faraday Discussions*, 189, 85-103.
- LIM, S., BARRATT, B., HOLLIDAY, L., GRIFFITHS, C. J. & MUDWAY, I. S. 2021. Characterising professional drivers' exposure to traffic-related air pollution: Evidence for reduction strategies from in-vehicle personal exposure monitoring. *Environ Int*, 153, 106532.
- LIU, W., HUANG, J., LIN, Y., CAI, C., ZHAO, Y., TENG, Y., MO, J., XUE, L., LIU, L., XU, W., GUO, X., ZHANG, Y. & ZHANG, J. 2021. Negative ions offset cardiorespiratory benefits of PM_{2.5} reduction from residential use of negative ion air purifiers. *Indoor Air*, 31, 220-228.
- LIVERANI, M. C., LOUKAS, S., GUI, L., PITTET, M. P., PEREIRA, M., TRUTTMANN, A. C., BRUNNER, P., BICKLE-GRAZ, M., HÜPPI, P. S., MESKALDJI, D. E. & BORRADORI-TOLSA, C. 2023. Behavioral outcome of very preterm children at 5 years of age: Prognostic utility of brain tissue volumes at term-equivalent-age, perinatal, and environmental factors. *Brain Behav*, 13, e2818.
- LOPUSZANSKA, U. & SAMARDAKIEWICZ, M. 2020. The Relationship Between Air Pollution and Cognitive Functions in Children and Adolescents: A Systematic Review. *Cognitive and Behavioral Neurology*, 33.
- LOZANO, M., MURCIA, M., SOLER-BLASCO, R., CASAS, M., ZUBERO, B., RIUTORT-MAYOL, G., GIL, F., OLMEDO, P., GRIMALT, J. O., AMORÓS, R., LERTXUNDI, A., VRIJHEID, M., BALLESTER, F. & LLOP, S. 2022. Exposure to metals and metalloids among pregnant women from Spain: Levels and associated factors. *Chemosphere*, 286, 131809.
- LU, F., XU, D., CHENG, Y., DONG, S., GUO, C., JIANG, X. & ZHENG, X. 2015. Systematic review and meta-analysis of the adverse health effects of ambient PM_{2.5} and PM₁₀ pollution in the Chinese population. *Environ Res*, 136, 196-204.
- LUBCZYŃSKA, M. J., MUETZEL, R. L., EL MARROUN, H., HOEK, G., KOOTER, I. M., THOMSON, E. M., HILLEGERS, M., VERNOOIJ, M. W., WHITE, T., TIEMEIER, H. & GUXENS, M. 2021. Air pollution exposure during pregnancy and childhood and brain morphology in preadolescents. *Environmental Research*, 198, 110446.
- LUBCZYŃSKA, M. J., MUETZEL RYAN, L., EL MARROUN, H., BASAGAÑA, X., STRAK, M., DENAULT, W., JADDOE VINCENT, W. V., HILLEGERS, M., VERNOOIJ MEIKE, W., HOEK, G., WHITE, T., BRUNEKREEF, B., TIEMEIER, H. & GUXENS, M. 2020. Exposure to Air Pollution during Pregnancy and Childhood, and White Matter Microstructure in Preadolescents. *Environmental Health Perspectives*, 128, 027005.
- MAHER, B. A., AHMED, I. A. M., KARLOUKOVSKI, V., MACLAREN, D. A., FOULDS, P. G., ALLSOP, D., MANN, D. M. A., TORRES-JARDÓN, R. & CALDERON-GARCIDUENAS, L. 2016. Magnetite pollution nanoparticles in the human brain. *Proceedings of the National Academy of Sciences*, 113, 10797.
- MAHER, G. M., O'KEEFFE, G. W., KEARNEY, P. M., KENNY, L. C., DINAN, T. G., MATTSSON, M. & KHASHAN, A. S. 2018. Association of Hypertensive Disorders of Pregnancy With Risk of Neurodevelopmental Disorders in Offspring: A Systematic Review and Meta-analysis. *JAMA Psychiatry*, 75, 809-819.
- MAKROPOULOS, A., ALJABAR, P., WRIGHT, R., HÜNING, B., MERCHANT, N., ARICHI, T., TUSOR, N., HAJNAL, J. V., EDWARDS, A. D., COUNSELL, S. J. & RUECKERT, D. 2016. Regional growth and atlasing of the developing human brain. *NeuroImage*, 125, 456-478.
- MAKROPOULOS, A., GOUSIAS, I. S., LEDIG, C., ALJABAR, P., SERAG, A., HAJNAL, J. V., EDWARDS, A. D., COUNSELL, S. J. & RUECKERT, D. 2014. Automatic Whole Brain MRI Segmentation of the Developing Neonatal Brain. *IEEE Transactions on Medical Imaging*, 33, 1818-1831.
- MAKROPOULOS, A., ROBINSON, E. C., SCHUH, A., WRIGHT, R., FITZGIBBON, S., BOZEK, J., COUNSELL, S. J., STEINWEG, J., VECCHIATO, K., PASSERAT-PALMBACH, J., LENZ, G., MORTARI, F., TENEV, T., DUFF, E. P., BASTIANI, M., CORDERO-GRANDE, L., HUGHES, E., TUSOR, N., TOURNIER, J.-D., HUTTER, J., PRICE, A. N., TEIXEIRA, R. P. A. G., MURGASOVA, M., VICTOR, S., KELLY, C., RUTHERFORD, M. A., SMITH, S. M., EDWARDS, A. D., HAJNAL, J. V., JENKINSON, M. &

- RUECKERT, D. 2018. The developing human connectome project: A minimal processing pipeline for neonatal cortical surface reconstruction. *NeuroImage*, 173, 88-112.
- MANISALIDIS, I., STAVROPOULOU, E., STAVROPOULOS, A. & BEZIRTZOGLU, E. 2020. Environmental and Health Impacts of Air Pollution: A Review. *Front Public Health*, 8, 14.
- MARSHALL, J. D., GRANVOLD, P. W., HOATS, A. S., MCKONE, T. E., DEAKIN, E. & W NAZAROFF, W. 2006. Inhalation intake of ambient air pollution in California's South Coast Air Basin. *Atmospheric Environment*, 40, 4381-4392.
- MARTINEZ-HERAS, E., GRUSSU, F., PRADOS, F., SOLANA, E. & LLUFRIU, S. 2021. Diffusion-Weighted Imaging: Recent Advances and Applications. *Seminars in Ultrasound, CT and MRI*, 42, 490-506.
- MASEKELA, R., MORTIMER, K. J., FEARY, J. & BINEGDIE, A. B. 2023. Stop normalizing poverty: How can African children achieve their true lung health potential? *Journal of the Pan African Thoracic Society*, 4.
- MAUNG, T. Z., BISHOP, J. E., HOLT, E., TURNER, A. M. & PFRANG, C. 2022. Indoor Air Pollution and the Health of Vulnerable Groups: A Systematic Review Focused on Particulate Matter (PM), Volatile Organic Compounds (VOCs) and Their Effects on Children and People with Pre-Existing Lung Disease. *Int J Environ Res Public Health*, 19.
- MCCARRON, A., SEMPLE, S., BRABAN, C. F., SWANSON, V., GILLESPIE, C. & PRICE, H. D. 2023. Public engagement with air quality data: using health behaviour change theory to support exposure-minimising behaviours. *Journal of Exposure Science & Environmental Epidemiology*, 33, 321-331.
- MICHANOWICZ, D. R., SHMOOL, J. L. C., TUNNO, B. J., TRIPATHY, S., GILLOOLY, S., KINNEE, E. & CLOUGHERTY, J. E. 2016. A hybrid land use regression/AERMOD model for predicting intra-urban variation in PM_{2.5}. *Atmospheric Environment*, 131, 307-315.
- MICHIELIN, F. & MULDER, C. H. 2008. Family Events and the Residential Mobility of Couples. *Environment and Planning A: Economy and Space*, 40, 2770-2790.
- MILLER, J. H., BARDO, D. M. E. & CORNEJO, P. 2020. Neonatal Neuroimaging. *Seminars in Pediatric Neurology*, 33, 100796.
- MITSAKOU, C., ADAMSON, J. P., DOUTSI, A., BRUNT, H., JONES, S. J., GOWERS, A. M. & EXLEY, K. S. 2021. Assessing the exposure to air pollution during transport in urban areas – Evidence review. *Journal of Transport & Health*, 21, 101064.
- MORI, S., CRAIN, B. J., CHACKO, V. P. & VAN ZIJL, P. C. M. 1999. Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. *Annals of Neurology*, 45, 265-269.
- MORISHITA, M., WANG, L., SPETH, K., ZHOU, N., BARD, R. L., LI, F., BROOK, J. R., RAJAGOPALAN, S. & BROOK, R. D. 2019. Acute Blood Pressure and Cardiovascular Effects of Near-Roadway Exposures With and Without N95 Respirators. *Am J Hypertens*, 32, 1054-1065.
- MORRIS-SCHAFFER, K., MERRILL, A. K., WONG, C., JEW, K., SOBOLEWSKI, M. & CORY-SLECHTA, D. A. 2019. Limited developmental neurotoxicity from neonatal inhalation exposure to diesel exhaust particles in C57BL/6 mice. *Particle and Fibre Toxicology*, 16, 1-14.
- MORTAMAI, M., PUJOL, J., MARTÍNEZ-VILAVELLA, G., FENOLL, R., REYNES, C., SABATIER, R., RIVAS, I., FORNS, J., VILOR-TEJEDOR, N., ALEMANY, S., CIRACH, M., ALVAREZ-PEDREROL, M., NIEUWENHUIJSEN, M. & SUNYER, J. 2019. Effects of prenatal exposure to particulate matter air pollution on corpus callosum and behavioral problems in children. *Environmental Research*, 178, 108734.
- MORTAMAI, M., PUJOL, J., VAN DROOGE, B. L., MACIÀ, D., MARTÍNEZ-VILAVELLA, G., REYNES, C., SABATIER, R., RIVAS, I., GRIMALT, J., FORNS, J., ALVAREZ-PEDREROL, M., QUEROL, X. & SUNYER, J. 2017. Effect of exposure to polycyclic aromatic hydrocarbons on basal ganglia and attention-deficit hyperactivity disorder symptoms in primary school children. *Environ Int*, 105, 12-19.
- MURATA, H., BARNHILL, L. M. & BRONSTEIN, J. M. 2022. Air Pollution and the Risk of Parkinson's Disease: A Review. *Mov Disord*, 37, 894-904.

- MURRAY, C. J., ARAVKIN, A. Y., ZHENG, P., ABBAFATI, C., ABBAS, K. M., ABBASI-KANGEVARI, M., ABD-ALLAH, F., ABDELALIM, A., ABDOLLAHI, M. & ABDOLLAHPOUR, I. 2020. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *The lancet*, 396, 1223-1249.
- MURRELLS, T., PASSANT, N., THISTLETHWAITE, G., WAGNER, A., LI, Y., BUSH, T., NORRIS, J., WALKER, C., STEWART, R. & TSAGATAKIS, I. 2010. *UK Emissions of Air Pollutants 1970-2008*, AEA Technology plc.
- NATIONAL ATMOSPHERIC EMISSIONS INVENTORY 2020. Air Quality Pollutant Inventories for England, Scotland, Wales and Northern Ireland: 2005-2019.
- NATIONAL ATMOSPHERIC EMISSIONS INVENTORY 2022. Overview of Air Pollutants. <https://naei.beis.gov.uk/>.
- NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE 2014. Maternal and child nutrition [PH11]. <https://www.nice.org.uk/guidance/ph11>.
- NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE 2021. Antenatal care, NICE guideline [NG201]. <https://www.nice.org.uk/guidance/ng201>.
- NAZAROFF, W. W. 2021. Residential air-change rates: A critical review. *Indoor Air*, 31, 282-313.
- NEPHEW, B. C., NEMETH, A., HUDDA, N., BEAMER, G., MANN, P., PETITTO, J., CALI, R., FEBO, M., KULKARNI, P., POIRIER, G., KING, J., DURANT, J. L. & BRUGGE, D. 2020. Traffic-related particulate matter affects behavior, inflammation, and neural integrity in a developmental rodent model. *Environ Res*, 183, 109242.
- NETHERY, E., BRAUER, M. & JANSSEN, P. 2009. Time–activity patterns of pregnant women and changes during the course of pregnancy. *Journal of Exposure Science & Environmental Epidemiology*, 19, 317-324.
- NETHERY, E., LECKIE, S. E., TESCHKE, K. & BRAUER, M. 2008. From measures to models: an evaluation of air pollution exposure assessment for epidemiological studies of pregnant women. *Occupational and Environmental Medicine*, 65, 579.
- NICHOLS, T. E. & HOLMES, A. P. 2002. Nonparametric permutation tests for functional neuroimaging: a primer with examples. *Hum Brain Mapp*, 15, 1-25.
- NOONAN, D. S. 2014. Smoggy with a Chance of Altruism: The Effects of Ozone Alerts on Outdoor Recreation and Driving in Atlanta. *Policy Studies Journal*, 42, 122-145.
- NYADANU, S. D., DUNNE, J., TESSEMA, G. A., MULLINS, B., KUMI-BOATENG, B., LEE BELL, M., DUKO, B. & PEREIRA, G. 2022. Prenatal exposure to ambient air pollution and adverse birth outcomes: An umbrella review of 36 systematic reviews and meta-analyses. *Environmental Pollution*, 306, 119465.
- NYHAN, M., MCNABOLA, A. & MISSTEAR, B. 2014. Comparison of particulate matter dose and acute heart rate variability response in cyclists, pedestrians, bus and train passengers. *Science of The Total Environment*, 468-469, 821-831.
- OBERDÖRSTER, G., SHARP, Z., ATUDOREI, V., ELDER, A., GELEIN, R., KREYLING, W. & COX, C. 2004. Translocation of Inhaled Ultrafine Particles to the Brain. *Inhalation Toxicology*, 16, 437-445.
- OISHI, K., FARIA, A. V., YOSHIDA, S., CHANG, L. & MORI, S. 2013. Quantitative evaluation of brain development using anatomical MRI and diffusion tensor imaging. *International Journal of Developmental Neuroscience*, 31, 512-524.
- OLSEN, Y., KAROTTKI, D. G., JENSEN, D. M., BEKÖ, G., KJELDSSEN, B. U., CLAUSEN, G., HERSOUG, L. G., HOLST, G. J., WIERZBICKA, A., SIGSGAARD, T., LINNEBERG, A., MØLLER, P. & LOFT, S. 2014. Vascular and lung function related to ultrafine and fine particles exposure assessed by personal and indoor monitoring: a cross-sectional study. *Environ Health*, 13, 112.
- OLTRA, C., SALA, R., BOSO, À. & ASENSIO, S. L. 2017. Public engagement on urban air pollution: an exploratory study of two interventions. *Environ Monit Assess*, 189, 296.
- OPENAQ 2020. Open Air Quality Data: The Global State of Play. <https://documents.openaq.org/reports/Open+Air+Quality+Data+Global+State+of+Play+2020.pdf>.

- OPHELDERS, D. R. M. G., GUSSENHOVEN, R., KLEIN, L., JELLEMA, R. K., WESTERLAKEN, R. J. J., HÜTTEN, M. C., VERMEULEN, J., WASSINK, G., GUNN, A. J. & WOLFS, T. G. A. M. 2020. Preterm Brain Injury, Antenatal Triggers, and Therapeutics: Timing Is Key. *Cells*, 9, 1871.
- PAGALAN, L., BICKFORD, C., WEIKUM, W., LANPHEAR, B., BRAUER, M., LANPHEAR, N., HANLEY, G. E., OBERLANDER, T. F. & WINTERS, M. 2019. Association of Prenatal Exposure to Air Pollution With Autism Spectrum Disorder. *JAMA pediatrics*, 173, 86-92.
- PAGNOZZI, A. M., VAN EIJK, L., PANNEK, K., BOYD, R. N., SAHA, S., GEORGE, J., BORA, S., BRADFORD, D., FAHEY, M., DITCHFIELD, M., MALHOTRA, A., LILEY, H., COLDITZ, P. B., ROSE, S. & FRIPP, J. 2023. Early brain morphometrics from neonatal MRI predict motor and cognitive outcomes at 2-years corrected age in very preterm infants. *Neuroimage*, 267, 119815.
- PANDIT, A. S., BALL, G., EDWARDS, A. D. & COUNSELL, S. J. 2013. Diffusion magnetic resonance imaging in preterm brain injury. *Neuroradiology*, 55 Suppl 2, 65-95.
- PANNEK, K., SCHECK, S. M., COLDITZ, P. B., BOYD, R. N. & ROSE, S. E. 2014. Magnetic resonance diffusion tractography of the preterm infant brain: a systematic review. *Developmental Medicine & Child Neurology*, 56, 113-124.
- PARK, Y. M. & KWAN, M.-P. 2017. Individual exposure estimates may be erroneous when spatiotemporal variability of air pollution and human mobility are ignored. *Health & Place*, 43, 85-94.
- PARTRIDGE, S. C., MUKHERJEE, P., HENRY, R. G., MILLER, S. P., BERMAN, J. I., JIN, H., LU, Y., GLENN, O. A., FERRIERO, D. M., BARKOVICH, A. J. & VIGNERON, D. B. 2004. Diffusion tensor imaging: serial quantitation of white matter tract maturity in premature newborns. *Neuroimage*, 22, 1302-14.
- PATTEN, K. T., GONZÁLEZ, E. A., VALENZUELA, A., BERG, E., WALLIS, C., GARBOW, J. R., SILVERMAN, J. L., BEIN, K. J., WEXLER, A. S. & LEIN, P. J. 2020. Effects of early life exposure to traffic-related air pollution on brain development in juvenile Sprague-Dawley rats. *Translational psychiatry*, 10, 166-166.
- PEARCE, A., ELLIMAN, D., BEDFORD, H. & LAW, C. 2008. Residential mobility and uptake of childhood immunisations: Findings from the UK Millennium Cohort Study. *Vaccine*, 26, 1675-1680.
- PECHEVA, D., YUSHKEVICH, P., BATALLE, D., HUGHES, E., ALJABAR, P., WURIE, J., HAJNAL, J. V., EDWARDS, A. D., ALEXANDER, D. C., COUNSELL, S. J. & ZHANG, H. 2017. A tract-specific approach to assessing white matter in preterm infants. *NeuroImage*, 157, 675-694.
- PERERA, F., RAUH, V., WHYATT ROBIN, M., TSAI, W.-Y., TANG, D., DIAZ, D., HOEPNER, L., BARR, D., TU, Y.-H., CAMANN, D. & KINNEY, P. 2006. Effect of Prenatal Exposure to Airborne Polycyclic Aromatic Hydrocarbons on Neurodevelopment in the First 3 Years of Life among Inner-City Children. *Environmental Health Perspectives*, 114, 1287-1292.
- PERERA, F. P., LI, Z., WHYATT, R., HOEPNER, L., WANG, S., CAMANN, D. & RAUH, V. 2009. Prenatal airborne polycyclic aromatic hydrocarbon exposure and child IQ at age 5 years. *Pediatrics*, 124, e195-e202.
- PETERS, A., VERONESI, B., CALDERÓN-GARCIDUEÑAS, L., GEHR, P., CHEN, L. C., GEISER, M., REED, W., ROTHEN-RUTISHAUSER, B., SCHÜRCH, S. & SCHULZ, H. 2006. Translocation and potential neurological effects of fine and ultrafine particles a critical update. *Particle and Fibre Toxicology*, 3, 13.
- PETERSON, B. S., BANSAL, R., SAWARDEKAR, S., NATI, C., ELGABALAWY, E. R., HOEPNER, L. A., GARCIA, W., HAO, X., MARGOLIS, A., PERERA, F. & RAUH, V. 2022. Prenatal exposure to air pollution is associated with altered brain structure, function, and metabolism in childhood. *J Child Psychol Psychiatry*.
- PETERSON, B. S., RAUH, V. A., BANSAL, R., HAO, X., TOTH, Z., NATI, G., WALSH, K., MILLER, R. L., ARIAS, F., SEMANEK, D. & PERERA, F. 2015. Effects of Prenatal Exposure to Air Pollutants (Polycyclic Aromatic Hydrocarbons) on the Development of Brain White Matter, Cognition, and Behavior in Later Childhood. *JAMA Psychiatry*, 72, 531-540.

- PIERS, R. J. 2018. Structural brain volume differences between cognitively intact ApoE4 carriers and non-carriers across the lifespan. *Neural Regeneration Research*, 13.
- PIETERMAN, K., PLAISIER, A., GOVAERT, P., LEEMANS, A., LEQUIN, M. H. & DUDINK, J. 2015. Data quality in diffusion tensor imaging studies of the preterm brain: a systematic review. *Pediatr Radiol*, 45, 1372-81.
- PLATT, M. J. 2014. Outcomes in preterm infants. *Public Health*, 128, 399-403.
- POOLEY, R. A. 2005. Fundamental Physics of MR Imaging. *RadioGraphics*, 25, 1087-1099.
- POPE, C. A., CROPPER, M., COGGINS, J. & COHEN, A. 2015. Health benefits of air pollution abatement policy: Role of the shape of the concentration–response function. *Journal of the Air & Waste Management Association*, 65, 516-522.
- POWER, M. C., ADAR, S. D., YANOSKY, J. D. & WEUVE, J. 2016. Exposure to air pollution as a potential contributor to cognitive function, cognitive decline, brain imaging, and dementia: A systematic review of epidemiologic research. *Neurotoxicology*, 56, 235-253.
- PUJOL, J., FENOLL, R., MACIÀ, D., MARTÍNEZ-VILAVELLA, G., ALVAREZ-PEDREROL, M., RIVAS, I., FORNS, J., DEUS, J., BLANCO-HINOJO, L., QUEROL, X. & SUNYER, J. 2016a. Airborne copper exposure in school environments associated with poorer motor performance and altered basal ganglia. *Brain Behav*, 6, e00467.
- PUJOL, J., MARTÍNEZ-VILAVELLA, G., MACIÀ, D., FENOLL, R., ALVAREZ-PEDREROL, M., RIVAS, I., FORNS, J., BLANCO-HINOJO, L., CAPELLADES, J., QUEROL, X., DEUS, J. & SUNYER, J. 2016b. Traffic pollution exposure is associated with altered brain connectivity in school children. *NeuroImage*, 129, 175-184.
- RAMÍREZ, A. S., RAMONDT, S., VAN BOGART, K. & PEREZ-ZUNIGA, R. 2019. Public Awareness of Air Pollution and Health Threats: Challenges and Opportunities for Communication Strategies To Improve Environmental Health Literacy. *J Health Commun*, 24, 75-83.
- RAZ, R., ROBERTS, A. L., LYALL, K., HART, J. E., JUST, A. C., LADEN, F. & WEISSKOPF, M. G. 2015. Autism spectrum disorder and particulate matter air pollution before, during, and after pregnancy: a nested case-control analysis within the Nurses' Health Study II Cohort. *Environmental health perspectives*, 123, 264-270.
- REIS, S., LIŠKA, T., VIENO, M., CARNELL, E. J., BECK, R., CLEMENS, T., DRAGOSITS, U., TOMLINSON, S. J., LEAVER, D. & HEAL, M. R. 2018. The influence of residential and workday population mobility on exposure to air pollution in the UK. *Environment International*, 121, 803-813.
- RENGASAMY, S. & EIMER, B. C. 2011. Total inward leakage of nanoparticles through filtering facepiece respirators. *Ann Occup Hyg*, 55, 253-63.
- RHODES, A., SMITH, A. D., CHADWICK, P., CROKER, H. & LLEWELLYN, C. H. 2020. Exclusively Digital Health Interventions Targeting Diet, Physical Activity, and Weight Gain in Pregnant Women: Systematic Review and Meta-Analysis. *JMIR Mhealth Uhealth*, 8, e18255.
- RIBEIRO, M. M., ANDRADE, A. & NUNES, I. 2022. Physical exercise in pregnancy: benefits, risks and prescription. *J Perinat Med*, 50, 4-17.
- RIVAS, I., BASAGAÑA, X., CIRACH, M., LÓPEZ-VICENTE, M., SUADES-GONZÁLEZ, E., GARCIA-ESTEBAN, R., ÁLVAREZ-PEDREROL, M., DADVAND, P. & SUNYER, J. 2019. Association between Early Life Exposure to Air Pollution and Working Memory and Attention. *Environmental Health Perspectives*, 127, 057002.
- ROBERGE, R. J., KIM, J. H. & POWELL, J. B. 2014. N95 respirator use during advanced pregnancy. *Am J Infect Control*, 42, 1097-100.
- ROCKLIFFE, L., PETERS, S., HEAZELL, A. E. P. & SMITH, D. M. 2021. Factors influencing health behaviour change during pregnancy: a systematic review and meta-synthesis. *Health Psychology Review*, 15, 613-632.
- RODULFO-CÁRDENAS, R., RUIZ-SOBREMAZAS, D., BIOSCA-BRULL, J., CABRÉ, M., BLANCO, J., LÓPEZ-GRANERO, C., SÁNCHEZ-SANTED, F. & COLOMINA, M. T. 2023. The influence of environmental particulate matter exposure during late gestation and early life on the risk of

- neurodevelopmental disorders: A systematic review of experimental evidences. *Environ Res*, 236, 116792.
- ROGNE, T., TIELEMANS, M. J., CHONG, M. F., YAJNIK, C. S., KRISHNAVENI, G. V., POSTON, L., JADDOE, V. W., STEEGERS, E. A., JOSHI, S., CHONG, Y. S., GODFREY, K. M., YAP, F., YAHYAOU, R., THOMAS, T., HAY, G., HOGEVEEN, M., DEMIR, A., SARAVANAN, P., SKOVLUND, E., MARTINUSSEN, M. P., JACOBSEN, G. W., FRANCO, O. H., BRACKEN, M. B. & RISNES, K. R. 2017. Associations of Maternal Vitamin B12 Concentration in Pregnancy With the Risks of Preterm Birth and Low Birth Weight: A Systematic Review and Meta-Analysis of Individual Participant Data. *Am J Epidemiol*, 185, 212-223.
- ROOSBROECK, S. V., HOEK, G., MELIEFSTE, K., JANSSEN, N. A. H. & BRUNEKREEF, B. 2008. Validity of Residential Traffic Intensity as an Estimate of Long-Term Personal Exposure to Traffic-Related Air Pollution among Adults. *Environmental Science & Technology*, 42, 1337-1344.
- ROSÁRIO FILHO, N. A., URRUTIA-PEREIRA, M., D'AMATO, G., CECCHI, L., ANSOTEGUI, I. J., GALÁN, C., POMÉS, A., MURRIETA-AGUTTES, M., CARABALLO, L., ROUADI, P., CHONG-NETO, H. J. & PEDEN, D. B. 2021. Air pollution and indoor settings. *World Allergy Organ J*, 14, 100499.
- SANDERSON, M. G. 2002. *Emission of isoprene, monoterpenes, ethene and propene by vegetation*, Hadley Centre for Climate Prediction and Research.
- SARWAR, T., RAMAMOCHANARAO, K. & ZALESKY, A. 2019. Mapping connectomes with diffusion MRI: deterministic or probabilistic tractography? *Magn Reson Med*, 81, 1368-1384.
- SCHILLING, K. G., JANVE, V., GAO, Y., STEPNIEWSKA, I., LANDMAN, B. A. & ANDERSON, A. W. 2018. Histological validation of diffusion MRI fiber orientation distributions and dispersion. *NeuroImage*, 165, 200-221.
- SCHRAUFNAGEL, D. E. 2020. The health effects of ultrafine particles. *Experimental & Molecular Medicine*, 52, 311-317.
- SCHUH, A., MAKROPOULOS, A., ROBINSON, E. C., CORDERO-GRANDE, L., HUGHES, E., HUTTER, J., PRICE, A. N., MURGASOVA, M., TEIXEIRA, R. P. A. G., TUSOR, N., STEINWEG, J. K., VICTOR, S., RUTHERFORD, M. A., HAJNAL, J. V., EDWARDS, A. D. & RUECKERT, D. 2018. Unbiased construction of a temporally consistent morphological atlas of neonatal brain development. *bioRxiv*, 251512.
- SENTÍS, A., SUNYER, J., DALMAU-BUENO, A., ANDIARENA, A., BALLESTER, F., CIRACH, M., ESTARLICH, M., FERNÁNDEZ-SOMOANO, A., IBARLUZEA, J., ÍÑIGUEZ, C., LERTXUNDI, A., TARDÓN, A., NIEUWENHUIJSEN, M., VRIJHEID, M. & GUXENS, M. 2017a. Prenatal and postnatal exposure to NO₂ and child attentional function at 4–5years of age. *Environment International*, 106, 170-177.
- SENTÍS, A., SUNYER, J., DALMAU-BUENO, A., ANDIARENA, A., BALLESTER, F., CIRACH, M., ESTARLICH, M., FERNÁNDEZ-SOMOANO, A., IBARLUZEA, J., ÍÑIGUEZ, C., LERTXUNDI, A., TARDÓN, A., NIEUWENHUIJSEN, M., VRIJHEID, M. & GUXENS, M. 2017b. Prenatal and postnatal exposure to NO₂ and child attentional function at 4-5years of age. *Environ Int*, 106, 170-177.
- SERAG, A., ALJABAR, P., BALL, G., COUNSELL, S. J., BOARDMAN, J. P., RUTHERFORD, M. A., EDWARDS, A. D., HAJNAL, J. V. & RUECKERT, D. 2012. Construction of a consistent high-definition spatio-temporal atlas of the developing brain using adaptive kernel regression. *NeuroImage*, 59, 2255-2265.
- SERDAR, C. C., CIHAN, M., YÜCEL, D. & SERDAR, M. A. 2021. Sample size, power and effect size revisited: simplified and practical approaches in pre-clinical, clinical and laboratory studies. *Biochem Med (Zagreb)*, 31, 010502.
- SHANG, L., YANG, L., YANG, W., HUANG, L., QI, C., YANG, Z., FU, Z. & CHUNG, M. C. 2020. Effects of prenatal exposure to NO₂ on children's neurodevelopment: a systematic review and meta-analysis. *Environmental science and pollution research international*, 27, 24786-24798.
- SHAPIRO, S. S. & WILK, M. B. 1965. An Analysis of Variance Test for Normality (Complete Samples). *Biometrika*, 52, 591-611.

- SHARMA, N. & AGGARWAL, L. M. 2010. Automated medical image segmentation techniques. *J Med Phys*, 35, 3-14.
- SHI, F., YAP, P.-T., WU, G., JIA, H., GILMORE, J. H., LIN, W. & SHEN, D. 2011. Infant Brain Atlases from Neonates to 1- and 2-Year-Olds. *PLOS ONE*, 6, e18746.
- SHI, J., LIN, Z., CHEN, R., WANG, C., YANG, C., CAI, J., LIN, J., XU, X., ROSS, J. A., ZHAO, Z. & KAN, H. 2017. Cardiovascular Benefits of Wearing Particulate-Filtering Respirators: A Randomized Crossover Trial. *Environ Health Perspect*, 125, 175-180.
- SHIGEMOTO-MOGAMI, Y., HOSHIKAWA, K., GOLDMAN, J. E., SEKINO, Y. & SATO, K. 2014. Microglia Enhance Neurogenesis and Oligodendrogenesis in the Early Postnatal Subventricular Zone. *The Journal of Neuroscience*, 34, 2231.
- SINHARAY, R., GONG, J., BARRATT, B., OHMAN-STRICKLAND, P., ERNST, S., KELLY, F. J., ZHANG, J., COLLINS, P., CULLINAN, P. & CHUNG, K. F. 2018. Respiratory and cardiovascular responses to walking down a traffic-polluted road compared with walking in a traffic-free area in participants aged 60 years and older with chronic lung or heart disease and age-matched healthy controls: a randomised, crossover study. *The Lancet*, 391, 339-349.
- SMITH, J. D., MITSAKOU, C., KITWIROON, N., BARRATT, B. M., WALTON, H. A., TAYLOR, J. G., ANDERSON, H. R., KELLY, F. J. & BEEVERS, S. D. 2016. London Hybrid Exposure Model: Improving Human Exposure Estimates to NO₂ and PM_{2.5} in an Urban Setting. *Environmental Science & Technology*, 50, 11760-11768.
- SMITH, R. B., BEEVERS, S. D., GULLIVER, J., DAJNAK, D., FECHT, D., BLANGIARDO, M., DOUGLASS, M., HANSELL, A. L., ANDERSON, H. R., KELLY, F. J. & TOLEDANO, M. B. 2020. Impacts of air pollution and noise on risk of preterm birth and stillbirth in London. *Environ Int*, 134, 105290.
- SMITH, R. B., FECHT, D., GULLIVER, J., BEEVERS, S. D., DAJNAK, D., BLANGIARDO, M., GHOSH, R. E., HANSELL, A. L., KELLY, F. J., ANDERSON, H. R. & TOLEDANO, M. B. 2017. Impact of London's road traffic air and noise pollution on birth weight: retrospective population based cohort study. *BMJ*, 359, j5299.
- SMITH, S. M., JENKINSON, M., JOHANSEN-BERG, H., RUECKERT, D., NICHOLS, T. E., MACKAY, C. E., WATKINS, K. E., CICCARELLI, O., CADER, M. Z., MATTHEWS, P. M. & BEHRENS, T. E. J. 2006. Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. *NeuroImage*, 31, 1487-1505.
- SMITH, S. M., NICHOLS, T. E., VIDAURRE, D., WINKLER, A. M., BEHRENS, T. E., GLASSER, M. F., UGURBIL, K., BARCH, D. M., VAN ESSEN, D. C. & MILLER, K. L. 2015. A positive-negative mode of population covariation links brain connectivity, demographics and behavior. *Nat Neurosci*, 18, 1565-7.
- SNYDER, E. G., WATKINS, T. H., SOLOMON, P. A., THOMA, E. D., WILLIAMS, R. W., HAGLER, G. S. W., SHELOW, D., HINDIN, D. A., KILARU, V. J. & PREUSS, P. W. 2013. The Changing Paradigm of Air Pollution Monitoring. *Environmental Science & Technology*, 47, 11369-11377.
- SONG, G., HAN, J., ZHAO, Y., WANG, Z. & DU, H. 2017. A Review on Medical Image Registration as an Optimization Problem. *Curr Med Imaging Rev*, 13, 274-283.
- SOTIROPOULOS, S. N., HERNÁNDEZ-FERNÁNDEZ, M., VU, A. T., ANDERSSON, J. L., MOELLER, S., YACOUB, E., LENGLET, C., UGURBIL, K., BEHRENS, T. E. J. & JBABDI, S. 2016. Fusion in diffusion MRI for improved fibre orientation estimation: An application to the 3T and 7T data of the Human Connectome Project. *NeuroImage*, 134, 396-409.
- STAFOGGIA, M., CESARONI, G., PETERS, A., ANDERSEN ZORANA, J., BADALONI, C., BEELEN, R., CARACCILO, B., CYRYS, J., DE FAIRE, U., DE HOOGH, K., ERIKSEN KIRSTEN, T., FRATIGLIONI, L., GALASSI, C., GIGANTE, B., HAVULINNA AKI, S., HENNIG, F., HILDING, A., HOEK, G., HOFFMANN, B., HOUTHUIJS, D., KOREK, M., LANKI, T., LEANDER, K., MAGNUSSON PATRIK, K., MEISINGER, C., MIGLIORE, E., OVERVAD, K., ÖSTENSON, C.-G., PEDERSEN NANCY, L., PEKKANEN, J., PENELL, J., PERSHAGEN, G., PUNDT, N., PYKO, A., RAASCHOU-NIELSEN, O., RANZI, A., RICCI, F., SACERDOTE, C., SWART WIM, J. R., TURUNEN ANU, W., VINEIS, P., WEIMAR, C., WEINMAYR, G., WOLF, K., BRUNEKREEF, B. & FORASTIERE, F. 2014. Long-Term Exposure to Ambient Air

- Pollution and Incidence of Cerebrovascular Events: Results from 11 European Cohorts within the ESCAPE Project. *Environmental Health Perspectives*, 122, 919-925.
- SYMMS, M., JÄGER, H. R., SCHMIERER, K. & YOUSRY, T. A. 2004. A review of structural magnetic resonance neuroimaging. *Journal of Neurology, Neurosurgery & Psychiatry*, 75, 1235.
- TAINIO, M., JOVANOVIĆ ANDERSEN, Z., NIEUWENHUIJSEN, M. J., HU, L., DE NAZELLE, A., AN, R., GARCIA, L. M. T., GOENKA, S., ZAPATA-DIOMEDI, B., BULL, F. & SÁ, T. H. D. 2021. Air pollution, physical activity and health: A mapping review of the evidence. *Environment International*, 147, 105954.
- TAMANA, S. K., GOMBOJAV, E., KANLIC, A., BANZRAI, C., BATSUKH, S., ENKHTUYA, E., BOLDBAATAR, B., LANPHEAR, B. P., LEAR, S. A., MCCANDLESS, L. C., VENNERS, S. A. & ALLEN, R. W. 2021. Portable HEPA filter air cleaner use during pregnancy and children's body mass index at two years of age: The UGAAR randomized controlled trial. *Environ Int*, 156, 106728.
- TANG, R., TIAN, L., THACH, T.-Q., TSUI, T. H., BRAUER, M., LEE, M., ALLEN, R., YUCHI, W., LAI, P.-C., WONG, P. & BARRATT, B. 2018. Integrating travel behavior with land use regression to estimate dynamic air pollution exposure in Hong Kong. *Environment International*, 113, 100-108.
- TAYLOR, R. M., FEALY, S. M., BISQUERA, A., SMITH, R., COLLINS, C. E., EVANS, T. J. & HURE, A. J. 2017. Effects of Nutritional Interventions during Pregnancy on Infant and Child Cognitive Outcomes: A Systematic Review and Meta-Analysis. *Nutrients*, 9.
- THAKUR, M., NUYTS, P. A. W., BOUDEWIJNS, E. A., FLORES KIM, J., FABER, T., BABU, G. R., VAN SCHAYCK, O. C. P. & BEEN, J. V. 2018. Impact of improved cookstoves on women's and child health in low and middle income countries: a systematic review and meta-analysis. *Thorax*, 73, 1026-1040.
- THOMAS, E., WICKRAMASINGHE, K., MENDIS, S., ROBERTS, N. & FOSTER, C. 2015. Improved stove interventions to reduce household air pollution in low and middle income countries: a descriptive systematic review. *BMC Public Health*, 15, 650.
- TOCCHIO, S., KLINE-FATH, B., KANAL, E., SCHMITHORST, V. J. & PANIGRAHY, A. 2015. MRI evaluation and safety in the developing brain. *Seminars in Perinatology*, 39, 73-104.
- TRATTNIG, S., SPRINGER, E., BOGNER, W., HANGEL, G., STRASSER, B., DYMERKA, B., CARDOSO, P. L. & ROBINSON, S. D. 2018. Key clinical benefits of neuroimaging at 7T. *Neuroimage*, 168, 477-489.
- TUCH, D. S., REESE, T. G., WIEGELL, M. R., MAKRI, N., BELLIVEAU, J. W. & WEDEEN, V. J. 2002. High angular resolution diffusion imaging reveals intravoxel white matter fiber heterogeneity. *Magnetic Resonance in Medicine*, 48, 577-582.
- TULARAM, H., RAMSAY, L. F., MUTTOO, S., BRUNEKREEF, B., MELIEFSTE, K., DE HOOGH, K. & NAIDOO, R. N. 2021. A hybrid air pollution / land use regression model for predicting air pollution concentrations in Durban, South Africa. *Environmental Pollution*, 274, 116513.
- TUNSTALL, H., PICKETT, K. & JOHNSEN, S. 2010. Residential mobility in the UK during pregnancy and infancy: Are pregnant women, new mothers and infants 'unhealthy migrants'? *Social Science & Medicine*, 71, 786-798.
- TUSOR, N., ARICHI, T., COUNSELL, S. J. & EDWARDS, A. D. 2014. Brain Development in Preterm Infants Assessed Using Advanced MRI Techniques. *Clinics in Perinatology*, 41, 25-45.
- ULZIKHUU, B., GOMBOJAV, E., BANZRAI, C., BATSUKH, S., ENKHTUYA, E., BOLDBAATAR, B., BELLINGER, D. C., LANPHEAR, B. P., MCCANDLESS, L. C., TAMANA, S. K. & ALLEN, R. W. 2022. Portable HEPA Filter Air Cleaner Use during Pregnancy and Children's Cognitive Performance at Four Years of Age: The UGAAR Randomized Controlled Trial. *Environ Health Perspect*, 130, 67006.
- UNITED STATES CENSUS BUREAU 2011. Maternity Leave and Employment Patterns of First-Time Mothers: 1961–2008. In: LAUGHLIN, L. (ed.) *Household Economic Studies*.

- US EPA 2018. Residential air cleaners: a technical summary. [https://www.epa.gov/sites/default/files/2018-07/documents/residential air cleaners - a technical summary 3rd edition.pdf](https://www.epa.gov/sites/default/files/2018-07/documents/residential_air_cleaners_-_a_technical_summary_3rd_edition.pdf): EPA 402-F09-002, US EPA, Washington, DC.
- VAN ROOSBROECK, S., LI, R., HOEK, G., LEBRET, E., BRUNEKREEF, B. & SPIEGELMAN, D. 2008. Traffic-Related Outdoor Air Pollution and Respiratory Symptoms in Children: The Impact of Adjustment for Exposure Measurement Error. *Epidemiology*, 19.
- VANDE LOOCK, K., CIARDELLI, R., DECORDIER, I., PLAS, G., HAUMONT, D. & KIRSCH-VOLDERS, M. 2012. Preterm newborns show slower repair of oxidative damage and paternal smoking associated DNA damage. *Mutagenesis*, 27, 573-80.
- VANES, L., FENN-MOLTU, S., HADAYA, L., FITZGIBBON, S., CORDERO-GRANDE, L., PRICE, A., CHEW, A., FALCONER, S., ARICHI, T., COUNSELL, S. J., HAJNAL, J. V., BATALLE, D., EDWARDS, A. D. & NOSARTI, C. 2023. Longitudinal neonatal brain development and socio-demographic correlates of infant outcomes following preterm birth. *Dev Cogn Neurosci*, 61, 101250.
- VARADEN, D., LEIDLAND, E., LIM, S. & BARRATT, B. 2021. "I am an air quality scientist" – Using citizen science to characterise school children's exposure to air pollution. *Environmental Research*, 201, 111536.
- VASUNG, L., ABACI TURK, E., FERRADAL, S. L., SUTIN, J., STOUT, J. N., AHTAM, B., LIN, P.-Y. & GRANT, P. E. 2019. Exploring early human brain development with structural and physiological neuroimaging. *NeuroImage*, 187, 226-254.
- VEDAL, S., BRAUER, M., WHITE, R. & PETKAU, J. 2003. Air pollution and daily mortality in a city with low levels of pollution. *Environmental health perspectives*, 111, 45-52.
- VENTURA-ANTUNES, L., MOTA, B. & HERCULANO-HOUZEL, S. 2013. Different scaling of white matter volume, cortical connectivity, and gyrification across rodent and primate brains. *Frontiers in neuroanatomy*, 7, 3.
- VISSER, G. H. A., EILERS, P. H. C., ELFERINK-STINKENS, P. M., MERKUS, H. M. W. M. & WIT, J. M. 2009. New Dutch reference curves for birthweight by gestational age. *Early Human Development*, 85, 737-744.
- VOLK, H. E., PERERA, F., BRAUN, J. M., KINGSLEY, S. L., GRAY, K., BUCKLEY, J., CLOUGHERTY, J. E., CROEN, L. A., ESKENAZI, B., HERTING, M., JUST, A. C., KLOOG, I., MARGOLIS, A., MCCLURE, L. A., MILLER, R., LEVINE, S. & WRIGHT, R. 2021. Prenatal air pollution exposure and neurodevelopment: A review and blueprint for a harmonized approach within ECHO. *Environ Res*, 196, 110320.
- WAKANA, S., CAPRIHAN, A., PANZENBOECK, M. M., FALLON, J. H., PERRY, M., GOLLUB, R. L., HUA, K., ZHANG, J., JIANG, H., DUBEY, P., BLITZ, A., VAN ZIJL, P. & MORI, S. 2007. Reproducibility of quantitative tractography methods applied to cerebral white matter. *NeuroImage*, 36, 630-644.
- WALANI, S. R. 2020. Global burden of preterm birth. *International Journal of Gynecology & Obstetrics*, 150, 31-33.
- WALTON, R. T., MUDWAY, I. S., DUNDAS, I., MARLIN, N., KOH, L. C., AITLHADJ, L., VULLIAMY, T., JAMALUDIN, J. B., WOOD, H. E., BARRATT, B. M., BEEVERS, S., DAJNAK, D., SHEIKH, A., KELLY, F. J., GRIFFITHS, C. J. & GRIGG, J. 2016. Air pollution, ethnicity and telomere length in east London schoolchildren: An observational study. *Environment International*, 96, 41-47.
- WANG, H.-T., SMALLWOOD, J., MOURAO-MIRANDA, J., XIA, C. H., SATTERTHWAIT, T. D., BASSETT, D. S. & BZDOK, D. 2020. Finding the needle in a high-dimensional haystack: Canonical correlation analysis for neuroscientists. *NeuroImage*, 216, 116745.
- WANG, S., LEDIG, C., HAJNAL, J. V., COUNSELL, S. J., SCHNABEL, J. A. & DEPREZ, M. 2019. Quantitative assessment of myelination patterns in preterm neonates using T2-weighted MRI. *Sci Rep*, 9, 12938.
- WARRINGTON, S., BRYANT, K. L., KHRAPITCHEV, A. A., SALLET, J., CHARQUERO-BALLESTER, M., DOUAUD, G., JBABDI, S., MARS, R. B. & SOTIROPOULOS, S. N. 2020. XTRACT - Standardised

- protocols for automated tractography in the human and macaque brain. *NeuroImage*, 217, 116923.
- WEISSKOPF, M. G. & WEBSTER, T. F. 2017. Trade-offs of Personal Versus More Proxy Exposure Measures in Environmental Epidemiology. *Epidemiology*, 28, 635-643.
- WELLS, P. G., MCCALLUM, G. P., LAM, K. C. H., HENDERSON, J. T. & ONDOVCIK, S. L. 2010. Oxidative DNA damage and repair in teratogenesis and neurodevelopmental deficits. *Birth Defects Research Part C: Embryo Today: Reviews*, 90, 103-109.
- WEST, S. E., BOWYER, C. J., APONDO, W., BÜKER, P., CINDERBY, S., GRAY, C. M., HAHN, M., LAMBE, F., LOH, M. & MEDCALF, A. 2021. Using a co-created transdisciplinary approach to explore the complexity of air pollution in informal settlements. *Humanities and Social Sciences Communications*, 8, 1-13.
- WILSON, A., HSU, H.-H. L., MATHILDA CHIU, Y.-H., WRIGHT, R. O., WRIGHT, R. J. & COULL, B. A. 2019. Kernel Machine and Distributed Lag Models for Assessing Windows of Susceptibility to Environmental Mixtures in Children's Health Studies. Available: <https://ui.adsabs.harvard.edu/abs/2019arXiv190412417W> [Accessed April 01, 2019].
- WILSON, S., PIETSCH, M., CORDERO-GRANDE, L., PRICE, A. N., HUTTER, J., XIAO, J., MCCABE, L., RUTHERFORD, M. A., HUGHES, E. J., COUNSELL, S. J., TOURNIER, J. D., ARICHI, T., HAJNAL, J. V., EDWARDS, A. D., CHRISTIAENS, D. & O'MUIRCHARTAIGH, J. 2021. Development of human white matter pathways in utero over the second and third trimester. *Proc Natl Acad Sci U S A*, 118.
- WILSON, W. E. & SUH, H. H. 1997. Fine particles and coarse particles: concentration relationships relevant to epidemiologic studies. *J Air Waste Manag Assoc*, 47, 1238-49.
- WONG-PARODI, G., DIAS, M. B. & TAYLOR, M. 2018. Effect of Using an Indoor Air Quality Sensor on Perceptions of and Behaviors Toward Air Pollution (Pittsburgh Empowerment Library Study): Online Survey and Interviews. *JMIR Mhealth Uhealth*, 6, e48.
- WOODWARD, N. C., HAGHANI, A., JOHNSON, R. G., HSU, T. M., SAFFARI, A., SIOUTAS, C., KANOSKI, S. E., FINCH, C. E. & MORGAN, T. E. 2018. Prenatal and early life exposure to air pollution induced hippocampal vascular leakage and impaired neurogenesis in association with behavioral deficits. *Translational Psychiatry*, 8, 261.
- WOOLLEY, K. E., DICKINSON-CRAIG, E., LAWSON, H. L., SHEIKH, J., DAY, R., POPE, F. D., GREENFIELD, S. M., BARTINGTON, S. E., WARBURTON, D., MANASEKI-HOLLAND, S., PRICE, M. J., MOORE, D. J. & THOMAS, G. N. 2022. Effectiveness of interventions to reduce household air pollution from solid biomass fuels and improve maternal and child health outcomes in low- and middle-income countries: A systematic review and meta-analysis. *Indoor Air*, 32, e12958.
- WORLD HEALTH ORGANIZATION 1977. WHO: recommended definitions, terminology and format for statistical tables related to the perinatal period and use of a new certificate for cause of perinatal deaths. Modifications recommended by FIGO as amended October 14, 1976. *Acta Obstet Gynecol Scand*, 56, 247-53.
- WORLD HEALTH ORGANIZATION 2015. Nurses and midwives: a vital resource for health. European compendium of good practices in nursing and midwifery towards Health 2020 goals. Copenhagen: World Health Organization. Regional Office for Europe.
- WORLD HEALTH ORGANIZATION 2020. *Personal interventions and risk communication on air pollution: summary report of WHO expert consultation, 12-14 February 2019, Geneva, Switzerland*, Geneva, World Health Organization.
- WORLD HEALTH ORGANIZATION 2021. *WHO global air quality guidelines: particulate matter (PM_{2.5} and PM₁₀), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide*, Geneva, World Health Organization.
- WYLIE BLAIR, J., MATECHI, E., KISHASHU, Y., FAWZI, W., PREMJI, Z., COULL BRENT, A., HAUSER, R., EZZATI, M. & ROBERTS DRUCILLA, J. 2017. Placental Pathology Associated with Household Air Pollution in a Cohort of Pregnant Women from Dar es Salaam, Tanzania. *Environmental Health Perspectives*, 125, 134-140.

- XING, Y. F., XU, Y. H., SHI, M. H. & LIAN, Y. X. 2016. The impact of PM_{2.5} on the human respiratory system. *J Thorac Dis*, 8, E69-74.
- YLIJOKI, M. K., EKHOLM, E., EKBLAD, M. & LEHTONEN, L. 2019. Prenatal Risk Factors for Adverse Developmental Outcome in Preterm Infants-Systematic Review. *Front Psychol*, 10, 595.
- YOUNG, J. M., VANDEWOUW, M. M., MORGAN, B. R., SMITH, M. L., SLED, J. G. & TAYLOR, M. J. 2018. Altered white matter development in children born very preterm. *Brain Structure and Function*, 223, 2129-2141.
- YU, H., RUSSELL, A., MULHOLLAND, J. & HUANG, Z. 2018. Using cell phone location to assess misclassification errors in air pollution exposure estimation. *Environmental Pollution*, 233, 261-266.
- YU, M., LINN, K. A., SHINOHARA, R. T., OATHES, D. J., COOK, P. A., DUPRAT, R., MOORE, T. M., OQUENDO, M. A., PHILLIPS, M. L., MCINNIS, M., FAVA, M., TRIVEDI, M. H., MCGRATH, P., PARSEY, R., WEISSMAN, M. M. & SHELINE, Y. I. 2019. Childhood trauma history is linked to abnormal brain connectivity in major depression. *Proceedings of the National Academy of Sciences*, 116, 8582-8590.
- YU, Z., ZHANG, X., ZHANG, J., FENG, Y., ZHANG, H., WAN, Z., XIAO, C., ZHANG, H., WANG, Q. & HUANG, C. 2022. Gestational exposure to ambient particulate matter and preterm birth: An updated systematic review and meta-analysis. *Environ Res*, 212, 113381.
- YUAN, L., ZHANG, Y., WANG, W., CHEN, R., LIU, Y., LIU, C., KAN, H., GAO, Y. & TIAN, Y. 2020. Critical windows for maternal fine particulate matter exposure and adverse birth outcomes: The Shanghai birth cohort study. *Chemosphere*, 240, 124904.
- ZEGER, S. L., THOMAS, D., DOMINICI, F., SAMET, J. M., SCHWARTZ, J., DOCKERY, D. & COHEN, A. 2000. Exposure measurement error in time-series studies of air pollution: concepts and consequences. *Environ Health Perspect*, 108, 419-26.
- ZHANG, H., SCHNEIDER, T., WHEELER-KINGSHOTT, C. A. & ALEXANDER, D. C. 2012. NODDI: Practical in vivo neurite orientation dispersion and density imaging of the human brain. *NeuroImage*, 61, 1000-1016.
- ZHANG, H., YUSHKEVICH, P. A., ALEXANDER, D. C. & GEE, J. C. 2006. Deformable registration of diffusion tensor MR images with explicit orientation optimization. *Medical Image Analysis*, 10, 764-785.
- ZHANG, K. & SEJNOWSKI, T. J. 2000. A universal scaling law between gray matter and white matter of cerebral cortex. *Proceedings of the National Academy of Sciences*, 97, 5621-5626.
- ZHANG, M., MUELLER, N. T., WANG, H., HONG, X., APPEL, L. J. & WANG, X. 2018a. Maternal Exposure to Ambient Particulate Matter $\leq 2.5 \mu\text{m}$ During Pregnancy and the Risk for High Blood Pressure in Childhood. *Hypertension*, 72, 194-201.
- ZHANG, T., ZHENG, X., WANG, X., ZHAO, H., WANG, T., ZHANG, H., LI, W., SHEN, H. & YU, L. 2018b. Maternal Exposure to PM_{2.5} during Pregnancy Induces Impaired Development of Cerebral Cortex in Mice Offspring. *International Journal of Molecular Sciences* [Online], 19.
- ZHANG, X., LIU, S. H., GERON, M., MATHILDA CHIU, Y.-H., GERSHON, R., HO, E., HUDDLESTON, K., JUST, A. C., KLOOG, I., COULL, B. A., ENLOW, M. B., WRIGHT, R. O. & WRIGHT, R. J. 2022. Prenatal exposure to PM_{2.5} and childhood cognition: Accounting for between-site heterogeneity in a pooled analysis of ECHO cohorts in the Northeastern United States. *Environmental Research*, 214, 114163.
- ZHANG, X., SPEAR, E., GENNINGS, C., CURTIN, P. C., JUST, A. C., BRAGG, J. B. & STROUSTRUP, A. 2020. The association of prenatal exposure to intensive traffic with early preterm infant neurobehavioral development as reflected by the NICU Network Neurobehavioral Scale (NNNS). *Environmental Research*, 183, 109204.
- ZHAO, Y., HU, J., TAN, Z., LIU, T., ZENG, W., LI, X., HUANG, C., WANG, S., HUANG, Z. & MA, W. 2019. Ambient carbon monoxide and increased risk of daily hospital outpatient visits for respiratory diseases in Dongguan, China. *Science of The Total Environment*, 668, 254-260.

- ZHENG, X., WANG, X., WANG, T., ZHANG, H., WU, H., ZHANG, C., YU, L. & GUAN, Y. 2019. Gestational exposure to particulate matter 2.5 (PM_{2.5}) leads to spatial memory dysfunction and neurodevelopmental impairment in hippocampus of mice offspring. *Frontiers in neuroscience*, 12, 1000.
- ZHOU, S., LI, T., HAN, N., ZHANG, Y., CHEN, G., JI, Y., LI, Q., LIU, J., WANG, H., HU, J., LIU, T., GUO, Y. & WANG, H.-J. 2022. The associations of prenatal exposure to PM_{2.5} and its constituents with fetal growth: A prospective birth cohort in Beijing, China. *Environmental Research*, 214, 114196.
- ZHU, K., KAWYN, M. N., KORDAS, K., MU, L., YOO, E. H., SEIBERT, R. & SMITH, L. E. 2022. Assessing exposure to household air pollution in children under five: A scoping review. *Environ Pollut*, 311, 119917.
- ZHUANG, X., YANG, Z. & CORDES, D. 2020. A technical review of canonical correlation analysis for neuroscience applications. *Hum Brain Mapp*, 41, 3807-3833.
- ZINSSER, L. A., STOLL, K., WIEBER, F., PEHLKE-MILDE, J. & GROSS, M. M. 2020. Changing behaviour in pregnant women: A scoping review. *Midwifery*, 85, 102680.
- ZUNDEL, C. G., RYAN, P., BROKAMP, C., HEETER, A., HUANG, Y., STRAWN, J. R. & MARUSAK, H. A. 2022. Air pollution, depressive and anxiety disorders, and brain effects: A systematic review. *Neurotoxicology*, 93, 272-300.

Appendix

Table A1: Single linear regression results between pollution exposure over the entire gestational period and dMRI measures in all tracts, adjusted for sex, IMD, PMA at scan, and GA at birth. Beta = effect size; CI = Confidence interval (95%); q-value = p-value after FDR correction. Significant p-values are marked in red. WM microstructure metrics are coded as follows: First the type of metric, followed by the tract, and l = left, or r = right hemisphere, respectively. FA = fractional anisotropy; MD = mean diffusivity; fintra = neurite density index (NDI); OD = orientation dispersion index (ODI). Tract abbreviations: ac = anterior commissure; af = arcuate fasciculus; ar = acoustic radiation; atr = anterior thalamic radiations; cbd = dorsal cingulum; cbp = peri-genual cingulum tract; cbt = temporal cingulum; cst = corticospinal tract; fa = arcuate fasciculus; fma = forceps major; fmi = forceps minor; fx = fornix; ifo = inferior fronto-occipital fasciculus; ilf = inferior longitudinal fasciculus; mcp = middle cerebellar peduncle; mdlf = middle longitudinal fasciculus; or = optic radiation; slf(1,2,3) = superior longitudinal fasciculi; str = superior thalamic radiation; uf = uncinate fasciculus; vof = vertical occipital fasciculus.

WM microstructure metric	Pollutant	beta (in 10 ⁻³)	Std. error (in 10 ⁻³)	Lower CI (in 10 ⁻³)	Upper CI (in 10 ⁻³)	p-value	q-value
FA_ac	PM _{2.5}	-0.075	0.499	-1.057	0.907	0.881	0.986
FA_ac	PM ₁₀	0.237	0.463	-0.675	1.149	0.609	0.92
FA_ac	NO ₂	0.076	0.154	-0.227	0.379	0.623	0.929
FA_af_l	PM _{2.5}	-0.520	0.555	-1.614	0.573	0.349	0.826
FA_af_l	PM ₁₀	-0.470	0.516	-1.486	0.545	0.363	0.826
FA_af_l	NO ₂	-0.025	0.172	-0.363	0.313	0.886	0.986
FA_af_r	PM _{2.5}	-1.313	0.549	-2.394	-0.232	0.017	0.65
FA_af_r	PM ₁₀	-1.068	0.511	-2.074	-0.061	0.038	0.65
FA_af_r	NO ₂	-0.169	0.171	-0.506	0.168	0.325	0.806
FA_ar_l	PM _{2.5}	-0.478	0.518	-1.498	0.542	0.357	0.826
FA_ar_l	PM ₁₀	-0.598	0.480	-1.544	0.348	0.214	0.806
FA_ar_l	NO ₂	-0.096	0.160	-0.411	0.219	0.549	0.898
FA_ar_r	PM _{2.5}	-0.397	0.528	-1.438	0.644	0.453	0.871
FA_ar_r	PM ₁₀	-0.166	0.491	-1.133	0.802	0.737	0.955
FA_ar_r	NO ₂	0.058	0.163	-0.264	0.38	0.722	0.955
FA_atr_l	PM _{2.5}	-1.354	0.618	-2.571	-0.138	0.029	0.65
FA_atr_l	PM ₁₀	-1.261	0.574	-2.391	-0.131	0.029	0.65

FA_atr_l	NO ₂	-0.314	0.192	-0.691	0.064	0.103	0.737
FA_atr_r	PM _{2.5}	-1.430	0.609	-2.630	-0.23	0.020	0.65
FA_atr_r	PM ₁₀	-1.100	0.568	-2.218	0.019	0.054	0.65
FA_atr_r	NO ₂	-0.244	0.190	-0.617	0.129	0.199	0.806
FA_cbd_l	PM _{2.5}	-1.011	0.603	-2.198	0.176	0.095	0.737
FA_cbd_l	PM ₁₀	-0.702	0.561	-1.807	0.404	0.212	0.806
FA_cbd_l	NO ₂	-0.181	0.187	-0.549	0.187	0.333	0.807
FA_cbd_r	PM _{2.5}	-1.052	0.620	-2.274	0.171	0.091	0.72
FA_cbd_r	PM ₁₀	-0.537	0.579	-1.676	0.604	0.355	0.826
FA_cbd_r	NO ₂	-0.066	0.193	-0.446	0.313	0.732	0.955
FA_cbp_l	PM _{2.5}	0.485	0.895	-1.279	2.248	0.589	0.909
FA_cbp_l	PM ₁₀	0.628	0.831	-1.010	2.265	0.451	0.871
FA_cbp_l	NO ₂	0.123	0.277	-0.421	0.668	0.656	0.932
FA_cbp_r	PM _{2.5}	0.048	0.899	-1.722	1.818	0.958	0.994
FA_cbp_r	PM ₁₀	0.405	0.834	-1.239	2.048	0.628	0.932
FA_cbp_r	NO ₂	0.133	0.277	-0.414	0.679	0.633	0.932
FA_cbt_l	PM _{2.5}	-0.466	0.389	-1.232	0.299	0.231	0.806
FA_cbt_l	PM ₁₀	-0.371	0.361	-1.083	0.34	0.305	0.806
FA_cbt_l	NO ₂	-0.041	0.120	-0.278	0.196	0.734	0.955
FA_cbt_r	PM _{2.5}	-1.110	0.447	-1.990	-0.23	0.014	0.65
FA_cbt_r	PM ₁₀	-0.680	0.418	-1.503	0.144	0.105	0.737
FA_cbt_r	NO ₂	-0.139	0.139	-0.414	0.135	0.318	0.806
FA_cst_l	PM _{2.5}	-0.684	0.795	-2.250	0.883	0.391	0.838
FA_cst_l	PM ₁₀	-0.665	0.739	-2.120	0.789	0.368	0.826
FA_cst_l	NO ₂	-0.080	0.246	-0.564	0.404	0.746	0.959
FA_cst_r	PM _{2.5}	-1.527	0.764	-3.031	-0.022	0.047	0.65
FA_cst_r	PM ₁₀	-0.952	0.713	-2.355	0.452	0.183	0.806
FA_cst_r	NO ₂	-0.114	0.238	-0.582	0.354	0.631	0.932
FA_fa_l	PM _{2.5}	-0.099	0.537	-1.156	0.958	0.854	0.985
FA_fa_l	PM ₁₀	0.115	0.498	-0.867	1.097	0.818	0.977
FA_fa_l	NO ₂	0.227	0.165	-0.098	0.552	0.171	0.806
FA_fa_r	PM _{2.5}	-0.802	0.505	-1.796	0.193	0.114	0.737
FA_fa_r	PM ₁₀	-0.383	0.471	-1.310	0.544	0.417	0.856

FA_fa_r	NO ₂	0.078	0.157	-0.231	0.386	0.621	0.929
FA_fma	PM _{2.5}	-0.261	0.610	-1.463	0.941	0.669	0.934
FA_fma	PM ₁₀	0.128	0.567	-0.989	1.245	0.821	0.977
FA_fma	NO ₂	0.228	0.188	-0.142	0.598	0.226	0.806
FA_fmi	PM _{2.5}	-1.607	0.820	-3.222	0.008	0.051	0.65
FA_fmi	PM ₁₀	-1.358	0.763	-2.860	0.144	0.076	0.668
FA_fmi	NO ₂	-0.373	0.254	-0.873	0.128	0.144	0.775
FA_fx_l	PM _{2.5}	-0.596	0.472	-1.526	0.334	0.208	0.806
FA_fx_l	PM ₁₀	-0.555	0.439	-1.419	0.309	0.207	0.806
FA_fx_l	NO ₂	-0.024	0.146	-0.312	0.265	0.872	0.985
FA_fx_r	PM _{2.5}	-0.967	0.491	-1.934	0	0.050	0.65
FA_fx_r	PM ₁₀	-0.539	0.458	-1.442	0.364	0.241	0.806
FA_fx_r	NO ₂	-0.023	0.153	-0.324	0.278	0.879	0.985
FA_ifo_l	PM _{2.5}	-1.327	0.668	-2.642	-0.011	0.048	0.65
FA_ifo_l	PM ₁₀	-0.977	0.622	-2.203	0.248	0.118	0.737
FA_ifo_l	NO ₂	-0.156	0.208	-0.565	0.253	0.453	0.871
FA_ifo_r	PM _{2.5}	-1.201	0.652	-2.485	0.082	0.066	0.65
FA_ifo_r	PM ₁₀	-0.772	0.607	-1.968	0.425	0.205	0.806
FA_ifo_r	NO ₂	-0.144	0.202	-0.543	0.254	0.477	0.875
FA_ilf_l	PM _{2.5}	-0.339	0.521	-1.365	0.688	0.517	0.894
FA_ilf_l	PM ₁₀	-0.221	0.484	-1.175	0.733	0.649	0.932
FA_ilf_l	NO ₂	0.006	0.161	-0.311	0.324	0.968	0.994
FA_ilf_r	PM _{2.5}	-0.894	0.557	-1.991	0.203	0.110	0.737
FA_ilf_r	PM ₁₀	-0.592	0.519	-1.614	0.43	0.255	0.806
FA_ilf_r	NO ₂	-0.079	0.173	-0.419	0.262	0.650	0.932
FA_mcp	PM _{2.5}	-0.288	0.504	-1.280	0.705	0.569	0.902
FA_mcp	PM ₁₀	-0.301	0.468	-1.223	0.621	0.520	0.894
FA_mcp	NO ₂	0.094	0.156	-0.212	0.401	0.545	0.898
FA_mdif_l	PM _{2.5}	-1.279	0.672	-2.603	0.045	0.058	0.65
FA_mdif_l	PM ₁₀	-1.024	0.626	-2.256	0.208	0.103	0.737
FA_mdif_l	NO ₂	-0.154	0.209	-0.565	0.258	0.463	0.871
FA_mdif_r	PM _{2.5}	-1.268	0.650	-2.548	0.012	0.052	0.65
FA_mdif_r	PM ₁₀	-0.877	0.606	-2.071	0.316	0.149	0.775

FA_mdIf_r	NO ₂	-0.153	0.202	-0.550	0.245	0.450	0.871
FA_or_l	PM _{2.5}	-1.239	0.730	-2.676	0.199	0.091	0.72
FA_or_l	PM ₁₀	-0.720	0.680	-2.060	0.62	0.291	0.806
FA_or_l	NO ₂	0.007	0.227	-0.440	0.453	0.977	0.995
FA_or_r	PM _{2.5}	-1.422	0.751	-2.901	0.056	0.059	0.65
FA_or_r	PM ₁₀	-0.919	0.700	-2.297	0.46	0.190	0.806
FA_or_r	NO ₂	-0.145	0.233	-0.604	0.315	0.535	0.898
FA_slf1_l	PM _{2.5}	-0.676	0.615	-1.886	0.535	0.273	0.806
FA_slf1_l	PM ₁₀	-0.462	0.572	-1.588	0.664	0.420	0.859
FA_slf1_l	NO ₂	0.085	0.190	-0.290	0.46	0.656	0.932
FA_slf1_r	PM _{2.5}	-1.168	0.624	-2.398	0.062	0.063	0.65
FA_slf1_r	PM ₁₀	-0.887	0.581	-2.032	0.258	0.128	0.737
FA_slf1_r	NO ₂	-0.025	0.194	-0.408	0.357	0.897	0.986
FA_slf2_l	PM _{2.5}	-0.782	0.628	-2.019	0.455	0.214	0.806
FA_slf2_l	PM ₁₀	-0.606	0.584	-1.756	0.544	0.300	0.806
FA_slf2_l	NO ₂	-0.043	0.195	-0.426	0.34	0.825	0.977
FA_slf2_r	PM _{2.5}	-1.376	0.575	-2.508	-0.244	0.017	0.65
FA_slf2_r	PM ₁₀	-1.012	0.536	-2.068	0.045	0.060	0.65
FA_slf2_r	NO ₂	-0.153	0.179	-0.506	0.2	0.394	0.838
FA_slf3_l	PM _{2.5}	-0.240	0.540	-1.304	0.824	0.657	0.932
FA_slf3_l	PM ₁₀	-0.031	0.502	-1.020	0.958	0.951	0.994
FA_slf3_l	NO ₂	0.178	0.167	-0.150	0.506	0.285	0.806
FA_slf3_r	PM _{2.5}	-1.011	0.503	-2.002	-0.019	0.046	0.65
FA_slf3_r	PM ₁₀	-0.749	0.469	-1.673	0.175	0.112	0.737
FA_slf3_r	NO ₂	-0.101	0.157	-0.409	0.208	0.521	0.894
FA_str_l	PM _{2.5}	-0.570	0.578	-1.709	0.568	0.325	0.806
FA_str_l	PM ₁₀	-0.562	0.537	-1.619	0.495	0.296	0.806
FA_str_l	NO ₂	-0.063	0.179	-0.415	0.289	0.726	0.955
FA_str_r	PM _{2.5}	-0.927	0.526	-1.964	0.11	0.079	0.677
FA_str_r	PM ₁₀	-0.541	0.491	-1.507	0.426	0.272	0.806
FA_str_r	NO ₂	0.016	0.164	-0.306	0.338	0.922	0.986
FA_uf_l	PM _{2.5}	-1.314	0.600	-2.496	-0.132	0.030	0.65
FA_uf_l	PM ₁₀	-1.089	0.559	-2.190	0.011	0.052	0.65

FA_uf_l	NO ₂	-0.230	0.187	-0.598	0.137	0.219	0.806
FA_uf_r	PM _{2.5}	-1.255	0.552	-2.342	-0.169	0.024	0.65
FA_uf_r	PM ₁₀	-0.927	0.515	-1.941	0.086	0.073	0.668
FA_uf_r	NO ₂	-0.194	0.172	-0.532	0.144	0.259	0.806
FA_vof_l	PM _{2.5}	0.112	0.362	-0.601	0.825	0.756	0.965
FA_vof_l	PM ₁₀	0.151	0.336	-0.511	0.814	0.653	0.932
FA_vof_l	NO ₂	0.179	0.111	-0.040	0.398	0.109	0.737
FA_vof_r	PM _{2.5}	-0.372	0.373	-1.106	0.362	0.319	0.806
FA_vof_r	PM ₁₀	-0.196	0.347	-0.879	0.486	0.572	0.903
FA_vof_r	NO ₂	0.100	0.115	-0.127	0.326	0.387	0.838
fintra_ac	PM _{2.5}	-1.398	0.597	-2.575	-0.222	0.020	0.65
fintra_ac	PM ₁₀	-0.847	0.558	-1.946	0.253	0.131	0.737
fintra_ac	NO ₂	-0.143	0.186	-0.509	0.224	0.444	0.871
fintra_af_l	PM _{2.5}	-0.029	0.778	-1.561	1.503	0.970	0.994
fintra_af_l	PM ₁₀	-0.047	0.723	-1.470	1.376	0.948	0.994
fintra_af_l	NO ₂	0.080	0.240	-0.393	0.553	0.740	0.955
fintra_af_r	PM _{2.5}	-0.943	0.741	-2.403	0.517	0.204	0.806
fintra_af_r	PM ₁₀	-0.623	0.690	-1.981	0.736	0.368	0.826
fintra_af_r	NO ₂	-0.028	0.230	-0.480	0.425	0.904	0.986
fintra_ar_l	PM _{2.5}	0.642	0.573	-0.486	1.771	0.263	0.806
fintra_ar_l	PM ₁₀	0.570	0.532	-0.478	1.619	0.285	0.806
fintra_ar_l	NO ₂	0.269	0.177	-0.079	0.617	0.129	0.737
fintra_ar_r	PM _{2.5}	-0.060	0.561	-1.165	1.045	0.915	0.986
fintra_ar_r	PM ₁₀	0.081	0.521	-0.946	1.108	0.877	0.985
fintra_ar_r	NO ₂	0.182	0.173	-0.159	0.522	0.295	0.806
fintra_atr_l	PM _{2.5}	-1.276	0.729	-2.711	0.16	0.081	0.678
fintra_atr_l	PM ₁₀	-1.091	0.678	-2.426	0.244	0.109	0.737
fintra_atr_l	NO ₂	-0.230	0.226	-0.675	0.215	0.309	0.806
fintra_atr_r	PM _{2.5}	-1.978	0.726	-3.407	-0.549	0.007	0.65
fintra_atr_r	PM ₁₀	-1.429	0.678	-2.764	-0.093	0.036	0.65
fintra_atr_r	NO ₂	-0.266	0.227	-0.713	0.18	0.241	0.806
fintra_cbd_l	PM _{2.5}	-0.713	0.696	-2.084	0.659	0.307	0.806
fintra_cbd_l	PM ₁₀	-0.637	0.647	-1.911	0.637	0.326	0.806

fintra_cbd_l	NO ₂	-0.098	0.215	-0.522	0.326	0.650	0.932
fintra_cbd_r	PM _{2.5}	-1.063	0.731	-2.502	0.377	0.147	0.775
fintra_cbd_r	PM ₁₀	-0.809	0.680	-2.149	0.53	0.235	0.806
fintra_cbd_r	NO ₂	-0.133	0.227	-0.579	0.313	0.557	0.899
fintra_cbp_l	PM _{2.5}	-0.149	0.798	-1.720	1.423	0.852	0.985
fintra_cbp_l	PM ₁₀	-0.070	0.741	-1.529	1.39	0.925	0.986
fintra_cbp_l	NO ₂	0.023	0.246	-0.462	0.508	0.925	0.986
fintra_cbp_r	PM _{2.5}	-1.471	0.798	-3.043	0.1	0.066	0.65
fintra_cbp_r	PM ₁₀	-1.142	0.743	-2.605	0.322	0.126	0.737
fintra_cbp_r	NO ₂	-0.197	0.248	-0.685	0.291	0.427	0.865
fintra_cbt_l	PM _{2.5}	-0.193	0.463	-1.104	0.719	0.678	0.938
fintra_cbt_l	PM ₁₀	-0.307	0.429	-1.153	0.539	0.476	0.875
fintra_cbt_l	NO ₂	-0.178	0.142	-0.458	0.103	0.213	0.806
fintra_cbt_r	PM _{2.5}	-0.462	0.431	-1.311	0.387	0.284	0.806
fintra_cbt_r	PM ₁₀	-0.269	0.401	-1.059	0.521	0.503	0.892
fintra_cbt_r	NO ₂	-0.101	0.133	-0.364	0.161	0.449	0.871
fintra_cst_l	PM _{2.5}	0.117	0.687	-1.236	1.47	0.865	0.985
fintra_cst_l	PM ₁₀	0.327	0.638	-0.930	1.584	0.609	0.92
fintra_cst_l	NO ₂	0.218	0.212	-0.199	0.635	0.304	0.806
fintra_cst_r	PM _{2.5}	-0.661	0.656	-1.953	0.631	0.315	0.806
fintra_cst_r	PM ₁₀	-0.375	0.610	-1.577	0.827	0.539	0.898
fintra_cst_r	NO ₂	0.025	0.203	-0.374	0.425	0.900	0.986
fintra_fa_l	PM _{2.5}	-0.195	0.760	-1.691	1.301	0.798	0.977
fintra_fa_l	PM ₁₀	-0.060	0.706	-1.450	1.33	0.933	0.986
fintra_fa_l	NO ₂	0.111	0.234	-0.350	0.573	0.635	0.932
fintra_fa_r	PM _{2.5}	-0.915	0.728	-2.348	0.518	0.210	0.806
fintra_fa_r	PM ₁₀	-0.589	0.677	-1.923	0.744	0.385	0.838
fintra_fa_r	NO ₂	0.027	0.225	-0.417	0.471	0.905	0.986
fintra_fma	PM _{2.5}	0.504	0.690	-0.855	1.864	0.466	0.871
fintra_fma	PM ₁₀	0.433	0.641	-0.831	1.696	0.501	0.892
fintra_fma	NO ₂	0.226	0.213	-0.194	0.645	0.290	0.806
fintra_fmi	PM _{2.5}	-1.445	0.790	-3.002	0.111	0.069	0.655
fintra_fmi	PM ₁₀	-1.154	0.735	-2.602	0.295	0.118	0.737

fintra_fmi	NO ₂	-0.284	0.245	-0.767	0.199	0.248	0.806
fintra_fx_l	PM _{2.5}	-0.568	0.722	-1.990	0.855	0.432	0.865
fintra_fx_l	PM ₁₀	-0.570	0.671	-1.891	0.751	0.396	0.838
fintra_fx_l	NO ₂	-0.466	0.221	-0.902	-0.03	0.036	0.65
fintra_fx_r	PM _{2.5}	-0.740	0.558	-1.839	0.358	0.186	0.806
fintra_fx_r	PM ₁₀	-0.581	0.519	-1.602	0.441	0.264	0.806
fintra_fx_r	NO ₂	-0.308	0.172	-0.646	0.03	0.074	0.668
fintra_ifo_l	PM _{2.5}	-0.662	0.681	-2.003	0.678	0.331	0.807
fintra_ifo_l	PM ₁₀	-0.542	0.633	-1.788	0.704	0.392	0.838
fintra_ifo_l	NO ₂	-0.124	0.210	-0.538	0.291	0.557	0.899
fintra_ifo_r	PM _{2.5}	-1.064	0.668	-2.380	0.252	0.113	0.737
fintra_ifo_r	PM ₁₀	-0.764	0.622	-1.989	0.461	0.220	0.806
fintra_ifo_r	NO ₂	-0.120	0.207	-0.528	0.288	0.562	0.899
fintra_ilf_l	PM _{2.5}	-0.489	0.618	-1.706	0.728	0.429	0.865
fintra_ilf_l	PM ₁₀	-0.424	0.574	-1.555	0.707	0.461	0.871
fintra_ilf_l	NO ₂	-0.118	0.191	-0.494	0.258	0.536	0.898
fintra_ilf_r	PM _{2.5}	-0.707	0.591	-1.871	0.458	0.233	0.806
fintra_ilf_r	PM ₁₀	-0.397	0.550	-1.480	0.687	0.472	0.875
fintra_ilf_r	NO ₂	-0.074	0.183	-0.434	0.287	0.688	0.939
fintra_mcp	PM _{2.5}	-0.723	0.722	-2.145	0.699	0.318	0.806
fintra_mcp	PM ₁₀	-0.700	0.671	-2.020	0.621	0.298	0.806
fintra_mcp	NO ₂	-0.229	0.223	-0.668	0.21	0.305	0.806
fintra_mdif_l	PM _{2.5}	-0.283	0.714	-1.689	1.123	0.692	0.939
fintra_mdif_l	PM ₁₀	-0.213	0.663	-1.519	1.093	0.748	0.96
fintra_mdif_l	NO ₂	0.011	0.220	-0.423	0.445	0.960	0.994
fintra_mdif_r	PM _{2.5}	-0.780	0.658	-2.077	0.517	0.237	0.806
fintra_mdif_r	PM ₁₀	-0.564	0.612	-1.770	0.642	0.358	0.826
fintra_mdif_r	NO ₂	-0.032	0.204	-0.434	0.369	0.875	0.985
fintra_or_l	PM _{2.5}	-0.459	0.791	-2.016	1.099	0.562	0.899
fintra_or_l	PM ₁₀	-0.547	0.734	-1.993	0.899	0.457	0.871
fintra_or_l	NO ₂	-0.176	0.244	-0.656	0.305	0.472	0.875
fintra_or_r	PM _{2.5}	-0.799	0.722	-2.221	0.622	0.269	0.806
fintra_or_r	PM ₁₀	-0.565	0.671	-1.887	0.757	0.400	0.838

fintra_or_r	NO ₂	-0.026	0.223	-0.465	0.414	0.909	0.986
fintra_slf1_l	PM _{2.5}	0.078	0.764	-1.428	1.583	0.919	0.986
fintra_slf1_l	PM ₁₀	0.172	0.710	-1.227	1.57	0.809	0.977
fintra_slf1_l	NO ₂	0.237	0.236	-0.227	0.701	0.316	0.806
fintra_slf1_r	PM _{2.5}	-0.770	0.762	-2.271	0.731	0.313	0.806
fintra_slf1_r	PM ₁₀	-0.422	0.709	-1.818	0.975	0.553	0.898
fintra_slf1_r	NO ₂	0.057	0.236	-0.407	0.522	0.808	0.977
fintra_slf2_l	PM _{2.5}	-0.164	0.830	-1.799	1.471	0.843	0.984
fintra_slf2_l	PM ₁₀	0.030	0.771	-1.489	1.549	0.969	0.994
fintra_slf2_l	NO ₂	0.144	0.256	-0.361	0.648	0.575	0.903
fintra_slf2_r	PM _{2.5}	-0.919	0.784	-2.463	0.625	0.242	0.806
fintra_slf2_r	PM ₁₀	-0.660	0.729	-2.096	0.776	0.366	0.826
fintra_slf2_r	NO ₂	-0.044	0.243	-0.522	0.434	0.858	0.985
fintra_slf3_l	PM _{2.5}	-0.189	0.787	-1.740	1.362	0.810	0.977
fintra_slf3_l	PM ₁₀	-0.159	0.731	-1.599	1.282	0.828	0.977
fintra_slf3_l	NO ₂	0.083	0.243	-0.396	0.562	0.733	0.955
fintra_slf3_r	PM _{2.5}	-0.989	0.785	-2.535	0.556	0.209	0.806
fintra_slf3_r	PM ₁₀	-0.651	0.730	-2.089	0.787	0.374	0.826
fintra_slf3_r	NO ₂	-0.022	0.243	-0.501	0.457	0.928	0.986
fintra_str_l	PM _{2.5}	-0.187	0.627	-1.421	1.047	0.766	0.967
fintra_str_l	PM ₁₀	-0.170	0.582	-1.316	0.977	0.771	0.969
fintra_str_l	NO ₂	-0.016	0.193	-0.397	0.365	0.935	0.987
fintra_str_r	PM _{2.5}	-1.048	0.604	-2.237	0.142	0.084	0.678
fintra_str_r	PM ₁₀	-0.742	0.562	-1.850	0.365	0.188	0.806
fintra_str_r	NO ₂	-0.118	0.187	-0.487	0.252	0.531	0.898
fintra_uf_l	PM _{2.5}	-0.756	0.735	-2.204	0.692	0.305	0.806
fintra_uf_l	PM ₁₀	-0.459	0.684	-1.806	0.887	0.502	0.892
fintra_uf_l	NO ₂	-0.061	0.227	-0.509	0.387	0.789	0.971
fintra_uf_r	PM _{2.5}	-1.398	0.720	-2.817	0.021	0.053	0.65
fintra_uf_r	PM ₁₀	-0.874	0.672	-2.198	0.45	0.195	0.806
fintra_uf_r	NO ₂	-0.136	0.224	-0.578	0.305	0.543	0.898
fintra_vof_l	PM _{2.5}	1.125	0.609	-0.074	2.324	0.066	0.65
fintra_vof_l	PM ₁₀	1.100	0.565	-0.013	2.213	0.053	0.65

fintra_vof_l	NO ₂	0.416	0.187	0.047	0.785	0.027	0.65
fintra_vof_r	PM _{2.5}	0.599	0.617	-0.618	1.815	0.333	0.807
fintra_vof_r	PM ₁₀	0.675	0.573	-0.454	1.804	0.240	0.806
fintra_vof_r	NO ₂	0.298	0.190	-0.076	0.673	0.118	0.737
fiso_ac	PM _{2.5}	0	0	0	0	0.131	0.737
fiso_ac	PM ₁₀	0	0	0	0	0.255	0.806
fiso_ac	NO ₂	0	0	0	0	0.552	0.898
fiso_af_l	PM _{2.5}	0	0	0	0	0.059	0.65
fiso_af_l	PM ₁₀	0	0	0	0	0.025	0.65
fiso_af_l	NO ₂	0	0	0	0	0.076	0.668
fiso_af_r	PM _{2.5}	0	0	0	0	0.878	0.985
fiso_af_r	PM ₁₀	0	0	0	0	0.895	0.986
fiso_af_r	NO ₂	0	0	0	0	0.991	0.999
fiso_ar_l	PM _{2.5}	0	0	0	0	0.245	0.806
fiso_ar_l	PM ₁₀	0	0	0	0	0.067	0.65
fiso_ar_l	NO ₂	0	0	0	0	0.065	0.65
fiso_ar_r	PM _{2.5}	0	0	0	0	0.564	0.899
fiso_ar_r	PM ₁₀	0	0	0	0	0.235	0.806
fiso_ar_r	NO ₂	0	0	0	0	0.16	0.791
fiso_atr_l	PM _{2.5}	0	0	0	0	0.097	0.737
fiso_atr_l	PM ₁₀	0	0	0	0	0.22	0.806
fiso_atr_l	NO ₂	0	0	0	0	0.21	0.806
fiso_atr_r	PM _{2.5}	0	0	0	0	0.362	0.826
fiso_atr_r	PM ₁₀	0	0	0	0	0.65	0.932
fiso_atr_r	NO ₂	0	0	0	0	0.469	0.875
fiso_cbd_l	PM _{2.5}	0	0	0	0	0.598	0.917
fiso_cbd_l	PM ₁₀	0	0	0	0	0.273	0.806
fiso_cbd_l	NO ₂	0	0	0	0	0.102	0.737
fiso_cbd_r	PM _{2.5}	0	0	0	0	0.411	0.851
fiso_cbd_r	PM ₁₀	0	0	0	0	0.287	0.806
fiso_cbd_r	NO ₂	0	0	0	0	0.412	0.851
fiso_cbp_l	PM _{2.5}	0	0	0	0	0.609	0.92
fiso_cbp_l	PM ₁₀	0	0	0	0	0.832	0.977

fiso_cbp_l	NO ₂	0	0	0	0	0.859	0.985
fiso_cbp_r	PM _{2.5}	0	0	0	0	0.326	0.806
fiso_cbp_r	PM ₁₀	0	0	0	0	0.498	0.892
fiso_cbp_r	NO ₂	0	0	0	0	0.327	0.806
fiso_cbt_l	PM _{2.5}	0	0	0	0	0.171	0.806
fiso_cbt_l	PM ₁₀	0	0	0	0	0.105	0.737
fiso_cbt_l	NO ₂	0	0	0	0	0.351	0.826
fiso_cbt_r	PM _{2.5}	-0.044	0.068	-0.178	0.09	0.519	0.894
fiso_cbt_r	PM ₁₀	-0.028	0.063	-0.153	0.097	0.657	0.932
fiso_cbt_r	NO ₂	-0.006	0.021	-0.047	0.036	0.783	0.971
fiso_cst_l	PM _{2.5}	0	0	0	0	0.364	0.826
fiso_cst_l	PM ₁₀	0	0	0	0	0.369	0.826
fiso_cst_l	NO ₂	0	0	0	0	0.708	0.947
fiso_cst_r	PM _{2.5}	0	0	0	0	0.677	0.938
fiso_cst_r	PM ₁₀	0	0	0	0	0.635	0.932
fiso_cst_r	NO ₂	0	0	0	0	0.451	0.871
fiso_fa_l	PM _{2.5}	-0.075	0.084	-0.241	0.091	0.376	0.829
fiso_fa_l	PM ₁₀	-0.061	0.078	-0.215	0.094	0.439	0.87
fiso_fa_l	NO ₂	-0.014	0.026	-0.066	0.037	0.583	0.906
fiso_fa_r	PM _{2.5}	0	0	0	0	0.691	0.939
fiso_fa_r	PM ₁₀	0	0	0	0	0.996	0.999
fiso_fa_r	NO ₂	0	0	0	0	0.696	0.939
fiso_fma	PM _{2.5}	0.066	0.508	-0.934	1.066	0.897	0.986
fiso_fma	PM ₁₀	0.236	0.472	-0.693	1.165	0.617	0.928
fiso_fma	NO ₂	0.104	0.157	-0.205	0.412	0.508	0.892
fiso_fmi	PM _{2.5}	1.105	0.805	-0.48	2.691	0.171	0.806
fiso_fmi	PM ₁₀	0.81	0.749	-0.664	2.285	0.28	0.806
fiso_fmi	NO ₂	0.293	0.249	-0.197	0.783	0.24	0.806
fiso_fx_l	PM _{2.5}	0.568	3.282	-5.896	7.033	0.863	0.985
fiso_fx_l	PM ₁₀	0.297	3.049	-5.708	6.303	0.922	0.986
fiso_fx_l	NO ₂	-1.542	1.008	-3.529	0.444	0.127	0.737
fiso_fx_r	PM _{2.5}	2.003	2.692	-3.299	7.305	0.457	0.871
fiso_fx_r	PM ₁₀	1.674	2.501	-3.252	6.601	0.504	0.892

fiso_fx_r	NO ₂	-0.454	0.831	-2.092	1.184	0.585	0.908
fiso_ifo_l	PM _{2.5}	1.186	0.666	-0.126	2.497	0.076	0.668
fiso_ifo_l	PM ₁₀	1.164	0.618	-0.053	2.381	0.061	0.65
fiso_ifo_l	NO ₂	0.419	0.205	0.015	0.823	0.042	0.65
fiso_ifo_r	PM _{2.5}	0.374	0.482	-0.575	1.323	0.438	0.87
fiso_ifo_r	PM ₁₀	0.293	0.448	-0.589	1.175	0.514	0.894
fiso_ifo_r	NO ₂	0.152	0.149	-0.141	0.444	0.308	0.806
fiso_ilf_l	PM _{2.5}	1.763	0.909	-0.028	3.554	0.054	0.65
fiso_ilf_l	PM ₁₀	1.809	0.843	0.148	3.47	0.033	0.65
fiso_ilf_l	NO ₂	0.495	0.281	-0.059	1.049	0.08	0.677
fiso_ilf_r	PM _{2.5}	0.748	0.821	-0.87	2.365	0.363	0.826
fiso_ilf_r	PM ₁₀	0.72	0.763	-0.782	2.223	0.346	0.826
fiso_ilf_r	NO ₂	0.283	0.253	-0.216	0.782	0.265	0.806
fiso_mcp	PM _{2.5}	0.008	0.776	-1.521	1.537	0.992	0.999
fiso_mcp	PM ₁₀	0.48	0.721	-0.939	1.899	0.506	0.892
fiso_mcp	NO ₂	-0.096	0.24	-0.568	0.376	0.689	0.939
fiso_mdif_l	PM _{2.5}	0.619	0.398	-0.164	1.402	0.121	0.737
fiso_mdif_l	PM ₁₀	0.779	0.368	0.054	1.503	0.035	0.65
fiso_mdif_l	NO ₂	0.29	0.122	0.05	0.531	0.018	0.65
fiso_mdif_r	PM _{2.5}	0.272	0.343	-0.404	0.949	0.429	0.865
fiso_mdif_r	PM ₁₀	0.251	0.319	-0.377	0.879	0.432	0.865
fiso_mdif_r	NO ₂	0.117	0.106	-0.091	0.326	0.269	0.806
fiso_or_l	PM _{2.5}	0.396	0.832	-1.244	2.035	0.635	0.932
fiso_or_l	PM ₁₀	0.235	0.773	-1.289	1.758	0.762	0.966
fiso_or_l	NO ₂	-0.023	0.257	-0.529	0.484	0.929	0.986
fiso_or_r	PM _{2.5}	0.505	0.578	-0.634	1.644	0.383	0.838
fiso_or_r	PM ₁₀	0.314	0.538	-0.745	1.373	0.56	0.899
fiso_or_r	NO ₂	0.095	0.179	-0.258	0.447	0.597	0.917
fiso_slf1_l	PM _{2.5}	0	0	0	0	0.866	0.985
fiso_slf1_l	PM ₁₀	0	0	0	0	0.994	0.999
fiso_slf1_l	NO ₂	0	0	0	0	0.805	0.977
fiso_slf1_r	PM _{2.5}	0	0	0	0	0.845	0.984
fiso_slf1_r	PM ₁₀	0	0	0	0	0.901	0.986

fiso_slf1_r	NO ₂	0	0	0	0	0.992	0.999
fiso_slf2_l	PM _{2.5}	-0.177	0.179	-0.53	0.176	0.323	0.806
fiso_slf2_l	PM ₁₀	-0.154	0.167	-0.482	0.174	0.356	0.826
fiso_slf2_l	NO ₂	-0.036	0.055	-0.146	0.073	0.511	0.892
fiso_slf2_r	PM _{2.5}	0	0	0	0	0.236	0.806
fiso_slf2_r	PM ₁₀	0	0	0	0	0.608	0.92
fiso_slf2_r	NO ₂	0	0	0	0	0.966	0.994
fiso_slf3_l	PM _{2.5}	-0.072	0.072	-0.214	0.071	0.323	0.806
fiso_slf3_l	PM ₁₀	-0.062	0.067	-0.194	0.07	0.357	0.826
fiso_slf3_l	NO ₂	-0.015	0.022	-0.059	0.029	0.511	0.892
fiso_slf3_r	PM _{2.5}	0	0	0	0	0.915	0.986
fiso_slf3_r	PM ₁₀	0	0	0	0	0.68	0.938
fiso_slf3_r	NO ₂	0	0	0	0	0.591	0.91
fiso_str_l	PM _{2.5}	0	0	0	0	0.66	0.934
fiso_str_l	PM ₁₀	0	0	0	0	0.429	0.865
fiso_str_l	NO ₂	0	0	0	0	0.191	0.806
fiso_str_r	PM _{2.5}	0	0	0	0	0.119	0.737
fiso_str_r	PM ₁₀	0	0	0	0	0.14	0.767
fiso_str_r	NO ₂	0	0	0	0	0.074	0.668
fiso_uf_l	PM _{2.5}	0.018	0.146	-0.27	0.307	0.9	0.986
fiso_uf_l	PM ₁₀	0.077	0.136	-0.191	0.344	0.573	0.903
fiso_uf_l	NO ₂	0.048	0.045	-0.041	0.137	0.289	0.806
fiso_uf_r	PM _{2.5}	-0.009	0.19	-0.383	0.366	0.965	0.994
fiso_uf_r	PM ₁₀	-0.06	0.176	-0.407	0.287	0.734	0.955
fiso_uf_r	NO ₂	-0.002	0.059	-0.117	0.114	0.975	0.995
fiso_vof_l	PM _{2.5}	0.045	0.914	-1.756	1.846	0.961	0.994
fiso_vof_l	PM ₁₀	0.818	0.848	-0.852	2.487	0.336	0.81
fiso_vof_l	NO ₂	0.383	0.281	-0.171	0.936	0.175	0.806
fiso_vof_r	PM _{2.5}	-0.218	0.366	-0.939	0.503	0.552	0.898
fiso_vof_r	PM ₁₀	0.034	0.34	-0.637	0.704	0.921	0.986
fiso_vof_r	NO ₂	0.053	0.113	-0.169	0.276	0.638	0.932
MD_ac	PM _{2.5}	0.002	0.001	0.000	0.004	0.032	0.65
MD_ac	PM ₁₀	0.001	0.001	-0.001	0.003	0.235	0.806

MD_ac	NO ₂	0.000	0.000	-0.001	0.001	0.686	0.939
MD_af_l	PM _{2.5}	0.000	0.002	-0.003	0.004	0.825	0.977
MD_af_l	PM ₁₀	0.001	0.002	-0.003	0.004	0.787	0.971
MD_af_l	NO ₂	0.000	0.001	-0.001	0.001	0.819	0.977
MD_af_r	PM _{2.5}	0.002	0.002	-0.002	0.006	0.314	0.806
MD_af_r	PM ₁₀	0.001	0.002	-0.002	0.005	0.490	0.886
MD_af_r	NO ₂	0.000	0.001	-0.001	0.001	0.963	0.994
MD_ar_l	PM _{2.5}	-0.001	0.002	-0.004	0.003	0.669	0.934
MD_ar_l	PM ₁₀	-0.001	0.002	-0.004	0.003	0.779	0.971
MD_ar_l	NO ₂	-0.001	0.001	-0.002	0.001	0.318	0.806
MD_ar_r	PM _{2.5}	0.001	0.002	-0.003	0.004	0.665	0.934
MD_ar_r	PM ₁₀	0.000	0.002	-0.003	0.003	0.944	0.994
MD_ar_r	NO ₂	0.000	0.001	-0.001	0.001	0.431	0.865
MD_atr_l	PM _{2.5}	0.002	0.002	-0.001	0.006	0.161	0.791
MD_atr_l	PM ₁₀	0.002	0.002	-0.001	0.005	0.299	0.806
MD_atr_l	NO ₂	0.000	0.001	-0.001	0.001	0.668	0.934
MD_atr_r	PM _{2.5}	0.003	0.002	0.000	0.006	0.051	0.65
MD_atr_r	PM ₁₀	0.002	0.001	-0.001	0.005	0.193	0.806
MD_atr_r	NO ₂	0.000	0.001	-0.001	0.001	0.696	0.939
MD_cbd_l	PM _{2.5}	0.002	0.002	-0.002	0.005	0.384	0.838
MD_cbd_l	PM ₁₀	0.002	0.002	-0.002	0.005	0.307	0.806
MD_cbd_l	NO ₂	0.000	0.001	-0.001	0.001	0.639	0.932
MD_cbd_r	PM _{2.5}	0.002	0.002	-0.002	0.006	0.282	0.806
MD_cbd_r	PM ₁₀	0.002	0.002	-0.002	0.005	0.348	0.826
MD_cbd_r	NO ₂	0.000	0.001	-0.001	0.001	0.750	0.96
MD_cbp_l	PM _{2.5}	0.000	0.002	-0.004	0.004	0.922	0.986
MD_cbp_l	PM ₁₀	0.000	0.002	-0.003	0.004	0.907	0.986
MD_cbp_l	NO ₂	0.000	0.001	-0.001	0.001	0.827	0.977
MD_cbp_r	PM _{2.5}	0.002	0.002	-0.002	0.006	0.235	0.806
MD_cbp_r	PM ₁₀	0.002	0.002	-0.002	0.005	0.327	0.806
MD_cbp_r	NO ₂	0.000	0.001	-0.001	0.001	0.864	0.985
MD_cbt_l	PM _{2.5}	0.000	0.001	-0.002	0.003	0.898	0.986
MD_cbt_l	PM ₁₀	0.001	0.001	-0.002	0.003	0.574	0.903

MD_cbt_l	NO ₂	0.000	0.000	-0.001	0.001	0.736	0.955
MD_cbt_r	PM _{2.5}	0.000	0.001	-0.002	0.003	0.805	0.977
MD_cbt_r	PM ₁₀	0.000	0.001	-0.002	0.003	0.786	0.971
MD_cbt_r	NO ₂	0.000	0.000	-0.001	0.001	0.734	0.955
MD_cst_l	PM _{2.5}	0.001	0.002	-0.003	0.004	0.720	0.955
MD_cst_l	PM ₁₀	0.000	0.002	-0.004	0.003	0.917	0.986
MD_cst_l	NO ₂	-0.001	0.001	-0.002	0.001	0.366	0.826
MD_cst_r	PM _{2.5}	0.002	0.002	-0.001	0.006	0.212	0.806
MD_cst_r	PM ₁₀	0.001	0.002	-0.002	0.004	0.446	0.871
MD_cst_r	NO ₂	0.000	0.001	-0.001	0.001	0.810	0.977
MD_fa_l	PM _{2.5}	0.001	0.002	-0.004	0.005	0.757	0.965
MD_fa_l	PM ₁₀	0.000	0.002	-0.004	0.004	0.963	0.994
MD_fa_l	NO ₂	0.000	0.001	-0.002	0.001	0.641	0.932
MD_fa_r	PM _{2.5}	0.002	0.002	-0.002	0.006	0.370	0.826
MD_fa_r	PM ₁₀	0.001	0.002	-0.003	0.005	0.712	0.951
MD_fa_r	NO ₂	0.000	0.001	-0.002	0.001	0.547	0.898
MD_fma	PM _{2.5}	0.000	0.002	-0.005	0.004	0.863	0.985
MD_fma	PM ₁₀	-0.001	0.002	-0.005	0.004	0.762	0.966
MD_fma	NO ₂	-0.001	0.001	-0.002	0	0.150	0.775
MD_fmi	PM _{2.5}	0.004	0.003	-0.001	0.01	0.129	0.737
MD_fmi	PM ₁₀	0.004	0.003	-0.002	0.009	0.177	0.806
MD_fmi	NO ₂	0.001	0.001	-0.001	0.003	0.311	0.806
MD_fx_l	PM _{2.5}	0.001	0.003	-0.005	0.007	0.716	0.952
MD_fx_l	PM ₁₀	0.000	0.003	-0.005	0.005	0.961	0.994
MD_fx_l	NO ₂	-0.001	0.001	-0.003	0.001	0.158	0.791
MD_fx_r	PM _{2.5}	0.004	0.003	-0.002	0.009	0.180	0.806
MD_fx_r	PM ₁₀	0.003	0.003	-0.002	0.008	0.270	0.806
MD_fx_r	NO ₂	0.000	0.001	-0.002	0.002	0.897	0.986
MD_ifo_l	PM _{2.5}	0.002	0.002	-0.003	0.007	0.374	0.826
MD_ifo_l	PM ₁₀	0.001	0.002	-0.003	0.006	0.526	0.898
MD_ifo_l	NO ₂	0.000	0.001	-0.002	0.002	0.980	0.995
MD_ifo_r	PM _{2.5}	0.004	0.002	-0.001	0.008	0.136	0.753
MD_ifo_r	PM ₁₀	0.002	0.002	-0.002	0.006	0.319	0.806

MD_ifo_r	NO ₂	0.000	0.001	-0.001	0.002	0.827	0.977
MD_ilf_l	PM _{2.5}	0.003	0.002	-0.002	0.007	0.251	0.806
MD_ilf_l	PM ₁₀	0.002	0.002	-0.002	0.006	0.333	0.807
MD_ilf_l	NO ₂	0.000	0.001	-0.001	0.002	0.776	0.971
MD_ilf_r	PM _{2.5}	0.002	0.002	-0.002	0.007	0.300	0.806
MD_ilf_r	PM ₁₀	0.001	0.002	-0.003	0.005	0.540	0.898
MD_ilf_r	NO ₂	0.000	0.001	-0.001	0.001	0.978	0.995
MD_mcp	PM _{2.5}	0.001	0.002	-0.003	0.004	0.743	0.957
MD_mcp	PM ₁₀	0.001	0.002	-0.002	0.004	0.466	0.871
MD_mcp	NO ₂	0.000	0.001	-0.001	0.001	0.819	0.977
MD_mdif_l	PM _{2.5}	0.002	0.002	-0.003	0.006	0.507	0.892
MD_mdif_l	PM ₁₀	0.001	0.002	-0.003	0.005	0.613	0.924
MD_mdif_l	NO ₂	0.000	0.001	-0.002	0.001	0.888	0.986
MD_mdif_r	PM _{2.5}	0.003	0.002	-0.001	0.008	0.149	0.775
MD_mdif_r	PM ₁₀	0.002	0.002	-0.002	0.006	0.306	0.806
MD_mdif_r	NO ₂	0.000	0.001	-0.001	0.002	0.831	0.977
MD_or_l	PM _{2.5}	0.000	0.003	-0.005	0.005	0.919	0.986
MD_or_l	PM ₁₀	0.000	0.002	-0.005	0.004	0.873	0.985
MD_or_l	NO ₂	-0.001	0.001	-0.002	0.001	0.271	0.806
MD_or_r	PM _{2.5}	0.003	0.002	-0.002	0.008	0.271	0.806
MD_or_r	PM ₁₀	0.002	0.002	-0.003	0.006	0.484	0.88
MD_or_r	NO ₂	0.000	0.001	-0.002	0.001	0.829	0.977
MD_slf1_l	PM _{2.5}	0.001	0.002	-0.004	0.005	0.788	0.971
MD_slf1_l	PM ₁₀	0.000	0.002	-0.004	0.004	0.998	1
MD_slf1_l	NO ₂	-0.001	0.001	-0.002	0.001	0.348	0.826
MD_slf1_r	PM _{2.5}	0.002	0.002	-0.002	0.006	0.266	0.806
MD_slf1_r	PM ₁₀	0.001	0.002	-0.003	0.005	0.529	0.898
MD_slf1_r	NO ₂	0.000	0.001	-0.002	0.001	0.701	0.943
MD_slf2_l	PM _{2.5}	0.001	0.003	-0.004	0.005	0.822	0.977
MD_slf2_l	PM ₁₀	0.000	0.002	-0.004	0.005	0.932	0.986
MD_slf2_l	NO ₂	0.000	0.001	-0.002	0.001	0.665	0.934
MD_slf2_r	PM _{2.5}	0.003	0.002	-0.002	0.007	0.253	0.806
MD_slf2_r	PM ₁₀	0.002	0.002	-0.003	0.006	0.454	0.871

MD_slf2_r	NO ₂	0.000	0.001	-0.001	0.001	0.990	1
MD_slf3_l	PM _{2.5}	0.001	0.002	-0.004	0.005	0.814	0.977
MD_slf3_l	PM ₁₀	0.001	0.002	-0.004	0.005	0.782	0.971
MD_slf3_l	NO ₂	0.000	0.001	-0.002	0.001	0.869	0.985
MD_slf3_r	PM _{2.5}	0.002	0.002	-0.003	0.006	0.396	0.838
MD_slf3_r	PM ₁₀	0.001	0.002	-0.003	0.005	0.578	0.903
MD_slf3_r	NO ₂	0.000	0.001	-0.001	0.001	0.916	0.986
MD_str_l	PM _{2.5}	0.001	0.001	-0.002	0.003	0.552	0.898
MD_str_l	PM ₁₀	0.000	0.001	-0.002	0.003	0.845	0.984
MD_str_l	NO ₂	0.000	0.000	-0.001	0.001	0.702	0.943
MD_str_r	PM _{2.5}	0.002	0.001	-0.001	0.004	0.158	0.791
MD_str_r	PM ₁₀	0.001	0.001	-0.001	0.003	0.406	0.844
MD_str_r	NO ₂	0.000	0.000	-0.001	0.001	0.914	0.986
MD_uf_l	PM _{2.5}	0.002	0.002	-0.002	0.006	0.301	0.806
MD_uf_l	PM ₁₀	0.002	0.002	-0.002	0.005	0.462	0.871
MD_uf_l	NO ₂	0.000	0.001	-0.001	0.002	0.794	0.975
MD_uf_r	PM _{2.5}	0.003	0.002	-0.001	0.007	0.119	0.737
MD_uf_r	PM ₁₀	0.002	0.002	-0.002	0.006	0.306	0.806
MD_uf_r	NO ₂	0.000	0.001	-0.001	0.002	0.739	0.955
MD_vof_l	PM _{2.5}	-0.002	0.002	-0.006	0.002	0.393	0.838
MD_vof_l	PM ₁₀	-0.001	0.002	-0.005	0.002	0.464	0.871
MD_vof_l	NO ₂	-0.001	0.001	-0.002	0.001	0.124	0.737
MD_vof_r	PM _{2.5}	0.000	0.002	-0.004	0.004	0.827	0.977
MD_vof_r	PM ₁₀	-0.001	0.002	-0.004	0.003	0.707	0.947
MD_vof_r	NO ₂	-0.001	0.001	-0.002	0.001	0.265	0.806
OD_ac	PM _{2.5}	-1.534	0.631	-2.777	-0.291	0.016	0.65
OD_ac	PM ₁₀	-1.452	0.586	-2.606	-0.298	0.014	0.65
OD_ac	NO ₂	-0.385	0.196	-0.771	0.001	0.050	0.65
OD_af_l	PM _{2.5}	0.215	0.765	-1.293	1.722	0.779	0.971
OD_af_l	PM ₁₀	0.046	0.711	-1.354	1.447	0.948	0.994
OD_af_l	NO ₂	-0.003	0.236	-0.468	0.463	0.991	1
OD_af_r	PM _{2.5}	-0.222	0.755	-1.708	1.265	0.769	0.969
OD_af_r	PM ₁₀	-0.171	0.701	-1.551	1.21	0.808	0.977

OD_af_r	NO ₂	-0.020	0.233	-0.479	0.439	0.931	0.986
OD_ar_l	PM _{2.5}	0.449	0.718	-0.965	1.863	0.532	0.898
OD_ar_l	PM ₁₀	0.415	0.667	-0.899	1.728	0.535	0.898
OD_ar_l	NO ₂	0.188	0.222	-0.249	0.624	0.398	0.838
OD_ar_r	PM _{2.5}	-0.280	0.652	-1.563	1.004	0.668	0.934
OD_ar_r	PM ₁₀	-0.417	0.605	-1.608	0.775	0.492	0.886
OD_ar_r	NO ₂	-0.040	0.201	-0.436	0.356	0.843	0.984
OD_atr_l	PM _{2.5}	-1.864	0.768	-3.376	-0.352	0.016	0.65
OD_atr_l	PM ₁₀	-1.251	0.717	-2.663	0.162	0.082	0.678
OD_atr_l	NO ₂	-0.326	0.239	-0.796	0.145	0.174	0.806
OD_atr_r	PM _{2.5}	-2.630	0.804	-4.214	-1.047	0.001	0.65
OD_atr_r	PM ₁₀	-1.970	0.753	-3.452	-0.487	0.009	0.65
OD_atr_r	NO ₂	-0.535	0.251	-1.030	-0.04	0.034	0.65
OD_cbd_l	PM _{2.5}	-1.041	0.805	-2.627	0.544	0.197	0.806
OD_cbd_l	PM ₁₀	-1.148	0.747	-2.619	0.323	0.126	0.737
OD_cbd_l	NO ₂	-0.316	0.249	-0.805	0.174	0.205	0.806
OD_cbd_r	PM _{2.5}	-1.972	0.813	-3.574	-0.371	0.016	0.65
OD_cbd_r	PM ₁₀	-2.003	0.754	-3.488	-0.519	0.008	0.65
OD_cbd_r	NO ₂	-0.585	0.251	-1.079	-0.09	0.021	0.65
OD_cbp_l	PM _{2.5}	-1.231	1.144	-3.485	1.023	0.283	0.806
OD_cbp_l	PM ₁₀	-1.084	1.063	-3.179	1.01	0.309	0.806
OD_cbp_l	NO ₂	-0.210	0.354	-0.907	0.487	0.553	0.898
OD_cbp_r	PM _{2.5}	-3.459	1.381	-6.178	-0.739	0.013	0.65
OD_cbp_r	PM ₁₀	-3.226	1.282	-5.752	-0.7	0.013	0.65
OD_cbp_r	NO ₂	-0.842	0.428	-1.685	0.002	0.050	0.65
OD_cbt_l	PM _{2.5}	0.219	0.733	-1.224	1.663	0.765	0.967
OD_cbt_l	PM ₁₀	-0.277	0.681	-1.618	1.064	0.684	0.939
OD_cbt_l	NO ₂	-0.292	0.226	-0.736	0.153	0.197	0.806
OD_cbt_r	PM _{2.5}	-0.447	0.806	-2.034	1.141	0.580	0.905
OD_cbt_r	PM ₁₀	-0.840	0.747	-2.311	0.632	0.262	0.806
OD_cbt_r	NO ₂	-0.358	0.248	-0.846	0.13	0.150	0.775
OD_cst_l	PM _{2.5}	0.018	0.676	-1.314	1.349	0.979	0.995
OD_cst_l	PM ₁₀	0.259	0.628	-0.978	1.495	0.681	0.938

OD_cst_l	NO ₂	0.143	0.208	-0.267	0.554	0.492	0.886
OD_cst_r	PM _{2.5}	-0.346	0.659	-1.644	0.953	0.600	0.918
OD_cst_r	PM ₁₀	-0.177	0.613	-1.383	1.03	0.773	0.97
OD_cst_r	NO ₂	0.012	0.204	-0.389	0.413	0.953	0.994
OD_fa_l	PM _{2.5}	-0.710	0.964	-2.609	1.189	0.462	0.871
OD_fa_l	PM ₁₀	-0.752	0.895	-2.516	1.012	0.402	0.838
OD_fa_l	NO ₂	-0.293	0.297	-0.878	0.293	0.326	0.806
OD_fa_r	PM _{2.5}	-1.437	0.898	-3.205	0.331	0.111	0.737
OD_fa_r	PM ₁₀	-1.192	0.835	-2.836	0.452	0.155	0.791
OD_fa_r	NO ₂	-0.306	0.278	-0.853	0.242	0.273	0.806
OD_fma	PM _{2.5}	0.887	1.026	-1.133	2.907	0.388	0.838
OD_fma	PM ₁₀	0.550	0.954	-1.328	2.429	0.564	0.899
OD_fma	NO ₂	0.286	0.317	-0.338	0.909	0.368	0.826
OD_fmi	PM _{2.5}	-2.247	0.978	-4.172	-0.321	0.022	0.65
OD_fmi	PM ₁₀	-1.743	0.911	-3.537	0.052	0.057	0.65
OD_fmi	NO ₂	-0.457	0.304	-1.055	0.141	0.133	0.743
OD_fx_l	PM _{2.5}	-1.125	0.686	-2.476	0.227	0.103	0.737
OD_fx_l	PM ₁₀	-0.834	0.639	-2.092	0.424	0.193	0.806
OD_fx_l	NO ₂	-0.244	0.213	-0.663	0.174	0.251	0.806
OD_fx_r	PM _{2.5}	-2.045	0.682	-3.387	-0.702	0.003	0.65
OD_fx_r	PM ₁₀	-1.617	0.636	-2.871	-0.364	0.012	0.65
OD_fx_r	NO ₂	-0.462	0.212	-0.880	-0.044	0.031	0.65
OD_ifo_l	PM _{2.5}	-0.125	0.671	-1.446	1.195	0.852	0.985
OD_ifo_l	PM ₁₀	-0.098	0.623	-1.325	1.129	0.876	0.985
OD_ifo_l	NO ₂	-0.018	0.207	-0.426	0.39	0.932	0.986
OD_ifo_r	PM _{2.5}	-1.134	0.708	-2.527	0.26	0.110	0.737
OD_ifo_r	PM ₁₀	-0.808	0.659	-2.106	0.489	0.221	0.806
OD_ifo_r	NO ₂	-0.086	0.220	-0.519	0.346	0.694	0.939
OD_ilf_l	PM _{2.5}	-0.546	0.977	-2.471	1.38	0.577	0.903
OD_ilf_l	PM ₁₀	-0.635	0.908	-2.423	1.153	0.485	0.88
OD_ilf_l	NO ₂	-0.229	0.302	-0.823	0.365	0.448	0.871
OD_ilf_r	PM _{2.5}	-1.383	0.903	-3.162	0.395	0.127	0.737
OD_ilf_r	PM ₁₀	-0.834	0.841	-2.491	0.823	0.322	0.806

OD_ilf_r	NO ₂	-0.200	0.280	-0.751	0.351	0.476	0.875
OD_mcp	PM _{2.5}	-0.399	0.812	-1.997	1.2	0.624	0.929
OD_mcp	PM ₁₀	-0.496	0.754	-1.981	0.988	0.511	0.892
OD_mcp	NO ₂	-0.458	0.249	-0.948	0.032	0.067	0.65
OD_mdif_l	PM _{2.5}	0.477	0.739	-0.979	1.933	0.519	0.894
OD_mdif_l	PM ₁₀	0.278	0.687	-1.075	1.631	0.686	0.939
OD_mdif_l	NO ₂	0.118	0.228	-0.332	0.568	0.605	0.92
OD_mdif_r	PM _{2.5}	-0.863	0.713	-2.268	0.542	0.227	0.806
OD_mdif_r	PM ₁₀	-0.717	0.663	-2.023	0.588	0.280	0.806
OD_mdif_r	NO ₂	-0.047	0.221	-0.482	0.389	0.833	0.978
OD_or_l	PM _{2.5}	0.636	0.709	-0.761	2.033	0.371	0.826
OD_or_l	PM ₁₀	0.311	0.660	-0.988	1.611	0.638	0.932
OD_or_l	NO ₂	0.126	0.219	-0.306	0.558	0.565	0.899
OD_or_r	PM _{2.5}	-0.365	0.672	-1.688	0.958	0.588	0.909
OD_or_r	PM ₁₀	-0.287	0.624	-1.516	0.942	0.646	0.932
OD_or_r	NO ₂	0.088	0.207	-0.320	0.497	0.670	0.934
OD_slf1_l	PM _{2.5}	0.709	0.835	-0.935	2.352	0.397	0.838
OD_slf1_l	PM ₁₀	0.632	0.775	-0.895	2.159	0.416	0.856
OD_slf1_l	NO ₂	0.157	0.258	-0.350	0.665	0.542	0.898
OD_slf1_r	PM _{2.5}	-0.677	0.802	-2.257	0.904	0.400	0.838
OD_slf1_r	PM ₁₀	-0.344	0.746	-1.813	1.126	0.645	0.932
OD_slf1_r	NO ₂	-0.076	0.248	-0.564	0.413	0.761	0.966
OD_slf2_l	PM _{2.5}	0.146	0.823	-1.475	1.767	0.859	0.985
OD_slf2_l	PM ₁₀	0.003	0.765	-1.503	1.509	0.997	1
OD_slf2_l	NO ₂	0.000	0.254	-0.501	0.5	1.000	1
OD_slf2_r	PM _{2.5}	-0.470	0.768	-1.983	1.044	0.541	0.898
OD_slf2_r	PM ₁₀	-0.501	0.714	-1.907	0.905	0.483	0.88
OD_slf2_r	NO ₂	-0.100	0.237	-0.568	0.367	0.674	0.937
OD_slf3_l	PM _{2.5}	-0.049	0.891	-1.803	1.705	0.956	0.994
OD_slf3_l	PM ₁₀	-0.409	0.827	-2.037	1.22	0.621	0.929
OD_slf3_l	NO ₂	-0.194	0.275	-0.735	0.347	0.480	0.879
OD_slf3_r	PM _{2.5}	-0.308	0.878	-2.038	1.422	0.726	0.955
OD_slf3_r	PM ₁₀	-0.299	0.816	-1.906	1.308	0.714	0.951

OD_slf3_r	NO ₂	-0.042	0.271	-0.576	0.492	0.877	0.985
OD_str_l	PM _{2.5}	-0.168	0.616	-1.380	1.045	0.786	0.971
OD_str_l	PM ₁₀	0.091	0.572	-1.035	1.218	0.873	0.985
OD_str_l	NO ₂	0.008	0.190	-0.366	0.383	0.966	0.994
OD_str_r	PM _{2.5}	-0.778	0.602	-1.964	0.408	0.197	0.806
OD_str_r	PM ₁₀	-0.564	0.560	-1.667	0.539	0.315	0.806
OD_str_r	NO ₂	-0.200	0.186	-0.567	0.166	0.283	0.806
OD_uf_l	PM _{2.5}	-0.594	0.763	-2.097	0.91	0.437	0.87
OD_uf_l	PM ₁₀	-0.438	0.709	-1.835	0.96	0.538	0.898
OD_uf_l	NO ₂	-0.084	0.236	-0.548	0.381	0.723	0.955
OD_uf_r	PM _{2.5}	-1.804	0.822	-3.422	-0.185	0.029	0.65
OD_uf_r	PM ₁₀	-1.334	0.766	-2.843	0.176	0.083	0.678
OD_uf_r	NO ₂	-0.315	0.255	-0.818	0.188	0.218	0.806
OD_vof_l	PM _{2.5}	2.440	1.067	0.339	4.541	0.023	0.65
OD_vof_l	PM ₁₀	1.928	0.994	-0.030	3.885	0.054	0.65
OD_vof_l	NO ₂	0.486	0.331	-0.167	1.138	0.144	0.775
OD_vof_r	PM _{2.5}	1.525	1.074	-0.590	3.64	0.157	0.791
OD_vof_r	PM ₁₀	1.334	0.998	-0.631	3.3	0.182	0.806
OD_vof_r	NO ₂	0.337	0.332	-0.317	0.992	0.311	0.806

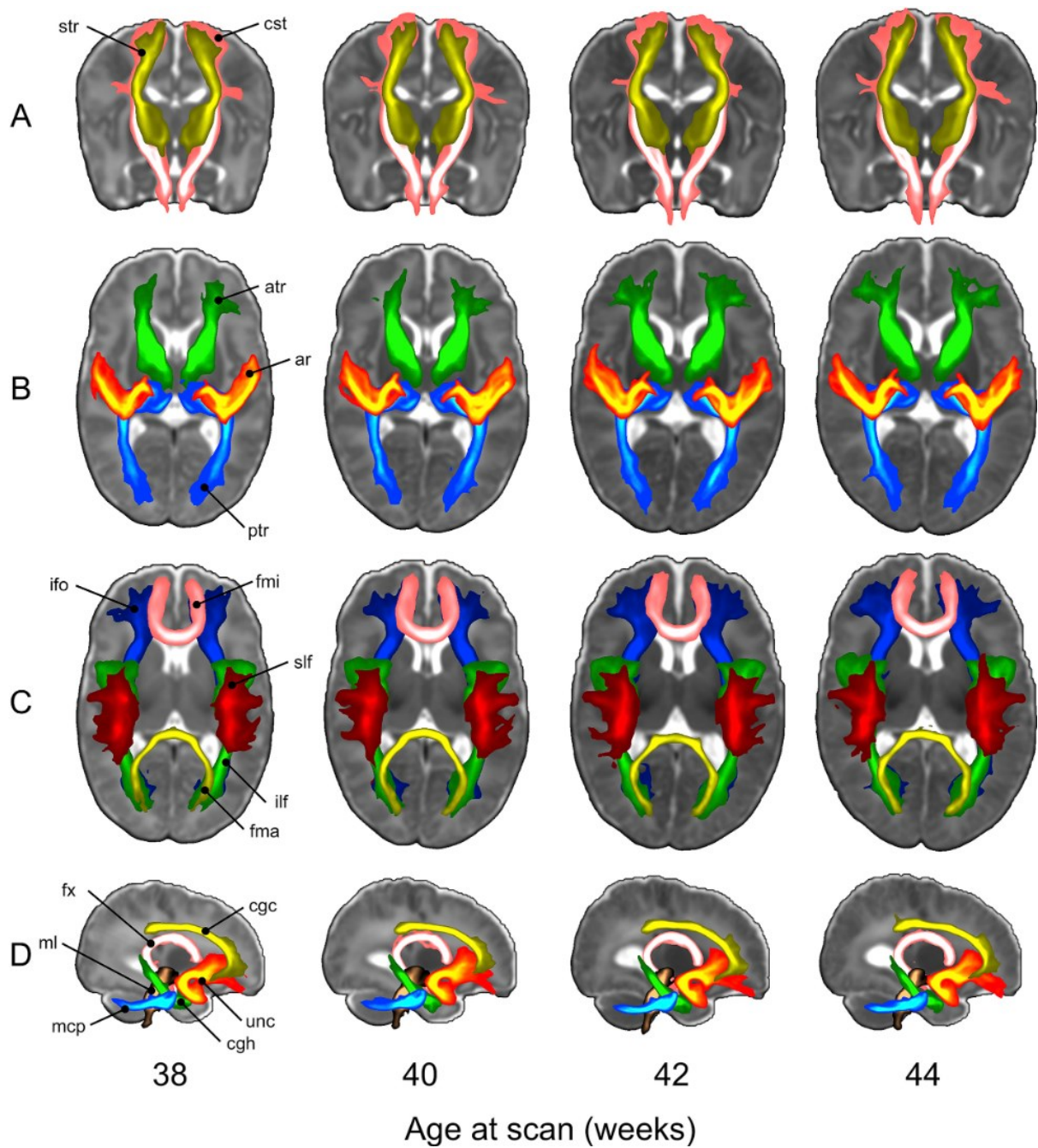


Figure A1: Output of the dMRI processing pipeline from 38 to 44 weeks post-menstrual age (20 subjects per bin) showing maximum intensity projections of the automated probabilistic tractography results averaged across 80 dHCP subjects (20 per age bin). All tracts are visualized using the same thresholds (0.005, 0.05). These thresholds extract the main body of the tracts and might remove lateral projections due to the variable and low number of crossings that can be estimated especially at the very young age. A) Sensory-motor projection fibres: corticospinal tract (pink) and superior thalamic radiation (yellow) B) Thalamic projection fibres: anterior thalamic radiation (green), acoustic radiation (red-yellow), posterior thalamic radiation (blue-light blue); C) Callosal and association fibres: forceps minor (pink), forceps major (yellow), superior longitudinal fasciculus (red), inferior longitudinal

fasciculus (green), inferior fronto-occipital fasciculus (blue). D) Brainstem tracts and association fibres in the left hemisphere: middle cerebellar peduncle (blue-light blue), medial lemniscus (brown), cingulate gyrus part of the cingulum (yellow), parahippocampal part of the cingulum (green), fornix (pink), uncinate fasciculus (red-yellow) (reproduced from Bastiani et al., (2019)).

Table A2: Single pollutant linear regression results for each relative brain volume and pollutant, for the first trimester, adjusted for sex, IMD, PMA at scan, and GA at birth; beta = effect size; CI = Confidence interval (95%); q-value = p-value after FDR correction. Significant p-values are marked in red.

Brain Region	Pollutant	<i>beta</i> (in 10 ⁻³)	Std. error (in 10 ⁻³)	Lower CI (in 10 ⁻³)	Upper CI (in 10 ⁻³)	p-value	q-value
Relative White Matter	PM _{2.5}	0.061	0.246	-0.422	0.545	0.803	0.918
	PM ₁₀	-0.072	0.204	-0.473	0.329	0.724	0.918
	NO ₂	-0.055	0.099	-0.249	0.139	0.578	0.918
Relative Grey Matter	PM _{2.5}	-0.113	0.256	-0.616	0.391	0.661	0.918
	PM ₁₀	0.059	0.212	-0.358	0.476	0.78	0.918
	NO ₂	0.075	0.103	-0.127	0.277	0.468	0.918
Relative Amygdala	PM _{2.5}	-0.002	0.011	-0.023	0.019	0.855	0.932
	PM ₁₀	-0.01	0.009	-0.028	0.007	0.246	0.844
	NO ₂	-0.001	0.004	-0.009	0.008	0.902	0.941
Relative Cerebellum	PM _{2.5}	0.038	0.111	-0.18	0.256	0.732	0.918
	PM ₁₀	0.036	0.092	-0.145	0.216	0.699	0.918
	NO ₂	-0.038	0.045	-0.126	0.049	0.391	0.918
Relative Basal Ganglia	PM _{2.5}	-0.02	0.074	-0.165	0.126	0.79	0.918
	PM ₁₀	-0.041	0.061	-0.162	0.079	0.502	0.918
	NO ₂	0.01	0.03	-0.049	0.068	0.744	0.918
Relative Ventricles	PM _{2.5}	0.224	0.087	0.054	0.394	0.01	0.121
	PM ₁₀	0.196	0.072	0.055	0.337	0.006	0.121
	NO ₂	-0.001	0.035	-0.07	0.068	0.977	0.977
Relative Brainstem	PM _{2.5}	0.033	0.022	-0.011	0.076	0.138	0.664
	PM ₁₀	0.018	0.018	-0.018	0.054	0.32	0.871

	NO ₂	0.009	0.009	-0.009	0.026	0.327	0.871
Relative Extracerebral CSF	PM _{2.5}	0.805	0.434	-0.049	1.659	0.064	0.516
	PM ₁₀	0.571	0.36	-0.138	1.279	0.114	0.664
	NO ₂	0.228	0.175	-0.116	0.571	0.194	0.777

Table A3: Single pollutant linear regression results for each relative brain volume and pollutant, for the second trimester, adjusted for sex, IMD, PMA at scan, and GA at birth; beta = effect size; CI = Confidence interval (95%); q-value = p-value after FDR correction. Significant p-values are marked in red.

Brain Region	Pollutant	beta (in 10 ⁻³)	Std. error (in 10 ⁻³)	Lower CI (in 10 ⁻³)	Upper CI (in 10 ⁻³)	p-value	q-value
Relative White Matter	PM _{2.5}	-0.242	0.222	-0.679	0.195	0.276	0.829
	PM ₁₀	-0.170	0.189	-0.540	0.201	0.368	0.829
	NO ₂	-0.061	0.093	-0.245	0.122	0.512	0.829
Relative Grey Matter	PM _{2.5}	0.172	0.232	-0.283	0.627	0.458	0.829
	PM ₁₀	0.101	0.196	-0.285	0.487	0.607	0.829
	NO ₂	0.092	0.097	-0.099	0.283	0.343	0.829
Relative Amygdala	PM _{2.5}	-0.006	0.010	-0.025	0.014	0.572	0.829
	PM ₁₀	-0.007	0.008	-0.023	0.010	0.423	0.829
	NO ₂	-0.001	0.004	-0.009	0.007	0.841	0.915
Relative Cerebellum	PM _{2.5}	0.014	0.100	-0.183	0.211	0.889	0.915
	PM ₁₀	0.009	0.085	-0.158	0.176	0.915	0.915
	NO ₂	-0.038	0.042	-0.121	0.044	0.363	0.829
Relative Basal Ganglia	PM _{2.5}	0.046	0.067	-0.086	0.178	0.492	0.829
	PM ₁₀	0.042	0.057	-0.069	0.154	0.458	0.829
	NO ₂	0.003	0.028	-0.052	0.059	0.907	0.915
Relative Ventricles	PM _{2.5}	-0.063	0.079	-0.218	0.092	0.428	0.829
	PM ₁₀	-0.011	0.067	-0.143	0.120	0.864	0.915
	NO ₂	-0.057	0.033	-0.122	0.008	0.086	0.829
Relative Brainstem	PM _{2.5}	0.011	0.020	-0.029	0.050	0.602	0.829
	PM ₁₀	0.018	0.017	-0.016	0.051	0.304	0.829

	NO ₂	0.004	0.008	-0.012	0.021	0.622	0.829
Relative Extracerebral CSF	PM _{2.5}	0.320	0.394	-0.455	1.094	0.418	0.829
	PM ₁₀	0.488	0.334	-0.168	1.143	0.144	0.829
	NO ₂	0.059	0.166	-0.266	0.384	0.721	0.911

Table A4: Single pollutant linear regression results for each relative brain volume and pollutant, for the third trimester, adjusted for sex, IMD, PMA at scan, and GA at birth; beta = effect size; CI = Confidence interval (95%); q-value = p-value after FDR correction. Significant p-values are marked in red.

Brain Region	Pollutant	beta (in 10 ⁻³)	Std. error (in 10 ⁻³)	Lower CI (in 10 ⁻³)	Upper CI (in 10 ⁻³)	p-value	q-value
Relative White Matter	PM _{2.5}	-0.049	0.247	-0.533	-0.533	0.844	0.97
	PM ₁₀	-0.047	0.196	-0.432	-0.432	0.812	0.97
	NO ₂	-0.043	0.097	-0.233	-0.233	0.658	0.97
Relative Grey Matter	PM _{2.5}	0.061	0.257	-0.444	-0.444	0.814	0.97
	PM ₁₀	0.086	0.204	-0.315	-0.315	0.675	0.97
	NO ₂	0.086	0.101	-0.111	-0.111	0.391	0.97
Relative Amygdala	PM _{2.5}	0.009	0.011	-0.012	-0.012	0.389	0.97
	PM ₁₀	0.010	0.009	-0.007	-0.007	0.243	0.97
	NO ₂	0.005	0.004	-0.003	-0.003	0.204	0.97
Relative Cerebellum	PM _{2.5}	-0.058	0.111	-0.277	-0.277	0.603	0.97
	PM ₁₀	-0.063	0.088	-0.237	-0.237	0.473	0.97
	NO ₂	-0.057	0.044	-0.143	-0.143	0.190	0.97
Relative Basal Ganglia	PM _{2.5}	0.030	0.074	-0.116	-0.116	0.691	0.97
	PM ₁₀	0.010	0.059	-0.106	-0.106	0.860	0.97
	NO ₂	0.004	0.029	-0.054	-0.054	0.902	0.97
Relative Ventricles	PM _{2.5}	0.003	0.087	-0.169	-0.169	0.970	0.97
	PM ₁₀	0.003	0.069	-0.133	-0.133	0.963	0.97
	NO ₂	-0.035	0.034	-0.102	-0.102	0.308	0.97
Relative Brainstem	PM _{2.5}	0.016	0.022	-0.027	-0.027	0.462	0.97
	PM ₁₀	0.014	0.018	-0.021	-0.021	0.425	0.97

	NO ₂	0.010	0.009	-0.007	-0.007	0.256	0.97
Relative Extracerebral CSF	PM _{2.5}	0.289	0.437	-0.570	-0.570	0.509	0.97
	PM ₁₀	0.096	0.347	-0.587	-0.587	0.783	0.97
	NO ₂	0.118	0.171	-0.219	-0.219	0.492	0.97

Table A5: Descriptive statistics of the absolute brain volumes of the dHCP subjects included in this study.

Brain region	Median (in mm³)	Range (in mm³)
Intracranial Volume	439103	273073 – 664283
Cortical Grey Matter	149824	96600 – 202719
White Matter	151371	86492 – 245847
Cerebellum	25215	13785 – 41752
Ventricles	4553	2052 – 15975
Deep Grey Nuclei	27170	19253 – 35574
Brainstem	6558	4616 – 8603
Amygdala & Hippocampus	2560	1673 – 3462
Extracerebral CSF	73780	42251 – 126000

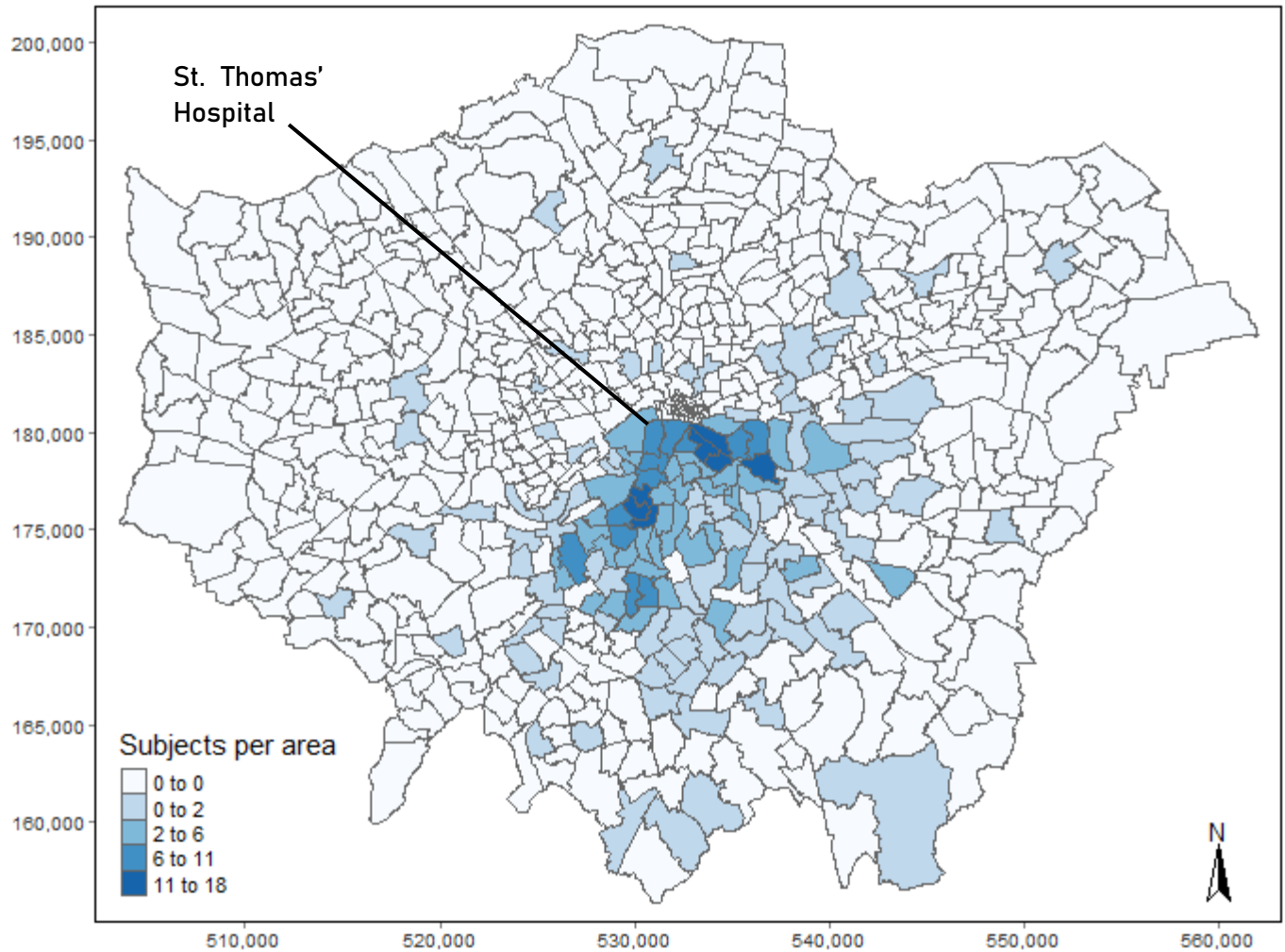


Figure A2: Subject distribution of my subjects from the developing human connectome project (dHCP) per lower super output area (LSOA) in Greater London. The subjects were scanned at St. Thomas' Hospital in central London, which is indicated on the map.

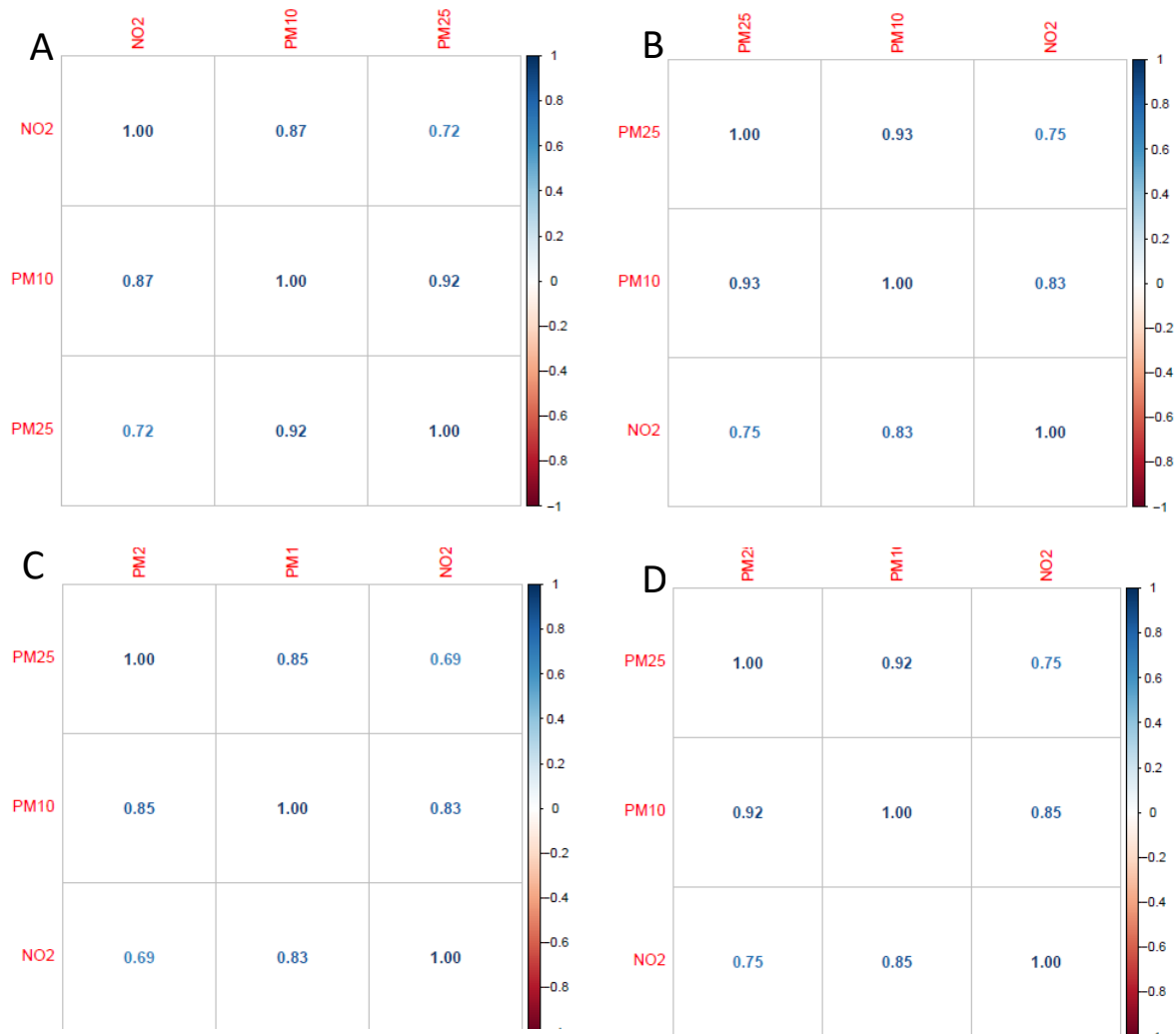


Figure A3: Correlation between $PM_{2.5}$, PM_{10} , and NO_2 . Modelled over the entire gestational period (A), the first trimester (B), the second trimester (C), and the third trimester (D).

Table A6: Additional descriptive statistics of the ePrime subjects.

ePrime cohort	Subjects	Range	Mean
Total Parenteral Nutrition (TPN)	147 (51.6%)	0 – 59 days	6.8 days
Ventilation	105 (36.8%)	0 – 33 days	1.8 days
Major lesions	34 (11.9%)		
Birthweight z-score		-3.1 – 2.76	-0.51

Table A7: Absolute brain volumes of the ePrime subjects.

Brain region (in mm ³)	Median	Range
Total Brain Volume	377090	271017 – 529459
Cortical Grey Matter	187317	111794 – 285434
White Matter	121358	81437 – 156829
Cerebellum	33016	22176 – 47425
Ventricles	8327	4551 – 21215
Deep Grey Nuclei	32124	24475 – 41471
Brainstem	5879	4543 – 7511
Amygdala	941	696 – 1235
Thalamus	9049	6109 – 11761
Hippocampus	1412	916 – 1940

Table A8: Single linear regression results between pollution exposure over the entire gestational period and dMRI measures in all tracts, adjusted for sex, IMD, PMA at scan, GA at birth, birth weight z-score (BWZ), and days ventilated. Beta = effect size; CI = Confidence interval (95%); q-value = p-value after FDR correction. WM microstructure metrics are coded as follows: First the hemisphere L = left, and R = right, followed by the tract, and the type of metric, respectively. FA = fractional anisotropy; MD = mean diffusivity; AD = axial diffusivity; RD = radial diffusivity. Tract abbreviations: CC = corpus callosum; CST = corticospinal tract; IFO = inferior fronto-occipital fasciculus; ILF = inferior longitudinal fasciculus; UNC = uncinate fasciculus.

Tract	Pollutant	beta (in 10 ⁻³)	Std. error (in 10 ⁻³)	Lower CI (in 10 ⁻³)	Upper CI (in 10 ⁻³)	p-value	q-value
LILF_FA	PM _{2.5}	-0.233	0.580	-1.375	0.909	0.688	0.991

LILF_FA	PM ₁₀	-0.153	0.445	-1.031	0.724	0.731	0.991
LILF_FA	NO ₂	0.241	0.205	-0.163	0.645	0.241	0.991
LILF_MD	PM _{2.5}	1.668	1.882	-2.038	5.375	0.376	0.991
LILF_MD	PM ₁₀	1.178	1.446	-1.671	4.027	0.416	0.991
LILF_MD	NO ₂	-0.275	0.668	-1.591	1.042	0.682	0.991
LILF_AD	PM _{2.5}	1.972	1.861	-1.695	5.638	0.290	0.991
LILF_AD	PM ₁₀	1.436	1.431	-1.382	4.254	0.316	0.991
LILF_AD	NO ₂	0.028	0.661	-1.275	1.331	0.967	0.991
LILF_RD	PM _{2.5}	1.517	1.976	-2.377	5.410	0.444	0.991
LILF_RD	PM ₁₀	1.049	1.519	-1.944	4.041	0.491	0.991
LILF_RD	NO ₂	-0.426	0.701	-1.807	0.956	0.544	0.991
RILF_FA	PM _{2.5}	0.249	0.556	-0.846	1.345	0.654	0.991
RILF_FA	PM ₁₀	0.123	0.427	-0.719	0.966	0.773	0.991
RILF_FA	NO ₂	0.379	0.196	-0.006	0.765	0.054	0.991
RILF_MD	PM _{2.5}	-1.629	2.280	-6.121	2.863	0.476	0.991
RILF_MD	PM ₁₀	-0.695	1.754	-4.150	2.759	0.692	0.991
RILF_MD	NO ₂	-0.727	0.808	-2.318	0.865	0.369	0.991
RILF_AD	PM _{2.5}	-1.689	2.329	-6.277	2.900	0.469	0.991
RILF_AD	PM ₁₀	-0.676	1.791	-4.205	2.853	0.706	0.991
RILF_AD	NO ₂	-0.298	0.827	-1.927	1.330	0.718	0.991
RILF_RD	PM _{2.5}	-1.599	2.326	-6.182	2.984	0.492	0.991
RILF_RD	PM ₁₀	-0.705	1.789	-4.229	2.819	0.694	0.991
RILF_RD	NO ₂	-0.941	0.823	-2.563	0.682	0.254	0.991
LUNC_FA	PM _{2.5}	0.665	0.387	-0.098	1.428	0.087	0.991
LUNC_FA	PM ₁₀	0.349	0.299	-0.239	0.937	0.244	0.991
LUNC_FA	NO ₂	0.127	0.138	-0.145	0.399	0.358	0.991
LUNC_MD	PM _{2.5}	1.541	1.508	-1.430	4.512	0.308	0.991
LUNC_MD	PM ₁₀	1.590	1.157	-0.689	3.869	0.171	0.991
LUNC_MD	NO ₂	0.766	0.534	-0.285	1.817	0.152	0.991

LUNC_AD	PM _{2.5}	2.492	1.516	-0.494	5.479	0.101	0.991
LUNC_AD	PM ₁₀	2.211	1.163	-0.079	4.502	0.058	0.991
LUNC_AD	NO ₂	1.023	0.536	-0.034	2.080	0.058	0.991
LUNC_RD	PM _{2.5}	1.066	1.547	-1.983	4.114	0.492	0.991
LUNC_RD	PM ₁₀	1.279	1.187	-1.060	3.618	0.282	0.991
LUNC_RD	NO ₂	0.638	0.548	-0.441	1.717	0.245	0.991
RUNC_FA	PM _{2.5}	-0.401	0.406	-1.201	0.400	0.325	0.991
RUNC_FA	PM ₁₀	-0.436	0.312	-1.049	0.178	0.163	0.991
RUNC_FA	NO ₂	-0.063	0.144	-0.347	0.222	0.664	0.991
RUNC_MD	PM _{2.5}	1.979	1.494	-0.965	4.923	0.187	0.991
RUNC_MD	PM ₁₀	1.979	1.145	-0.278	4.235	0.085	0.991
RUNC_MD	NO ₂	0.907	0.529	-0.134	1.948	0.088	0.991
RUNC_AD	PM _{2.5}	1.630	1.485	-1.296	4.556	0.274	0.991
RUNC_AD	PM ₁₀	1.685	1.139	-0.559	3.928	0.140	0.991
RUNC_AD	NO ₂	0.900	0.525	-0.133	1.934	0.087	0.991
RUNC_RD	PM _{2.5}	2.154	1.553	-0.907	5.213	0.167	0.991
RUNC_RD	PM ₁₀	2.126	1.190	-0.220	4.471	0.075	0.991
RUNC_RD	NO ₂	0.910	0.550	-0.173	1.993	0.099	0.991
LIFO_FA	PM _{2.5}	0.392	0.483	-0.559	1.344	0.417	0.991
LIFO_FA	PM ₁₀	0.196	0.372	-0.535	0.928	0.597	0.991
LIFO_FA	NO ₂	0.219	0.171	-0.117	0.556	0.201	0.991
LIFO_MD	PM _{2.5}	0.485	1.549	-2.568	3.537	0.755	0.991
LIFO_MD	PM ₁₀	0.629	1.190	-1.716	2.973	0.598	0.991
LIFO_MD	NO ₂	0.258	0.549	-0.824	1.340	0.639	0.991
LIFO_AD	PM _{2.5}	1.014	1.526	-1.993	4.021	0.507	0.991
LIFO_AD	PM ₁₀	0.973	1.172	-1.337	3.282	0.408	0.991
LIFO_AD	NO ₂	0.578	0.540	-0.487	1.642	0.286	0.991
LIFO_RD	PM _{2.5}	0.220	1.621	-2.973	3.413	0.892	0.991
LIFO_RD	PM ₁₀	0.457	1.245	-1.996	2.910	0.714	0.991

LIFO_RD	NO ₂	0.098	0.575	-1.034	1.230	0.865	0.991
RIFO_FA	PM _{2.5}	0.415	0.428	-0.428	1.258	0.333	0.991
RIFO_FA	PM ₁₀	0.208	0.329	-0.441	0.856	0.529	0.991
RIFO_FA	NO ₂	0.295	0.151	-0.002	0.592	0.052	0.991
RIFO_MD	PM _{2.5}	-0.344	1.520	-3.338	2.649	0.821	0.991
RIFO_MD	PM ₁₀	0.104	1.168	-2.197	2.404	0.929	0.991
RIFO_MD	NO ₂	-0.138	0.539	-1.200	0.923	0.798	0.991
RIFO_AD	PM _{2.5}	0.128	1.489	-2.804	3.061	0.931	0.991
RIFO_AD	PM ₁₀	0.425	1.144	-1.828	2.678	0.711	0.991
RIFO_AD	NO ₂	0.226	0.528	-0.814	1.265	0.669	0.991
RIFO_RD	PM _{2.5}	-0.581	1.591	-3.715	2.554	0.715	0.991
RIFO_RD	PM ₁₀	-0.057	1.223	-2.466	2.352	0.963	0.991
RIFO_RD	NO ₂	-0.320	0.564	-1.431	0.791	0.571	0.991
LSLF_FA	PM _{2.5}	-0.167	0.400	-0.956	0.621	0.676	0.991
LSLF_FA	PM ₁₀	-0.202	0.308	-0.808	0.404	0.512	0.991
LSLF_FA	NO ₂	0.036	0.142	-0.244	0.315	0.802	0.991
LSLF_MD	PM _{2.5}	1.341	1.673	-1.955	4.636	0.424	0.991
LSLF_MD	PM ₁₀	0.800	1.286	-1.733	3.334	0.534	0.991
LSLF_MD	NO ₂	0.020	0.594	-1.150	1.190	0.973	0.991
LSLF_AD	PM _{2.5}	1.062	1.647	-2.184	4.307	0.520	0.991
LSLF_AD	PM ₁₀	0.433	1.267	-2.062	2.929	0.733	0.991
LSLF_AD	NO ₂	-0.008	0.585	-1.160	1.144	0.989	0.991
LSLF_RD	PM _{2.5}	1.480	1.732	-1.931	4.892	0.394	0.991
LSLF_RD	PM ₁₀	0.984	1.331	-1.639	3.607	0.461	0.991
LSLF_RD	NO ₂	0.034	0.615	-1.178	1.245	0.956	0.991
RSLF_FA	PM _{2.5}	0.097	0.434	-0.757	0.952	0.822	0.991
RSLF_FA	PM ₁₀	0.103	0.333	-0.553	0.759	0.758	0.991
RSLF_FA	NO ₂	0.096	0.154	-0.206	0.399	0.532	0.991
RSLF_MD	PM _{2.5}	0.343	1.748	-3.101	3.788	0.845	0.991

RSLF_MD	PM ₁₀	0.015	1.344	-2.632	2.662	0.991	0.991
RSLF_MD	NO ₂	0.135	0.620	-1.087	1.356	0.828	0.991
RSLF_AD	PM _{2.5}	-0.233	0.580	-1.375	0.909	0.770	0.991
RSLF_AD	PM ₁₀	-0.153	0.445	-1.031	0.724	0.898	0.991
RSLF_AD	NO ₂	0.241	0.205	-0.163	0.645	0.583	0.991
RSLF_RD	PM _{2.5}	1.668	1.882	-2.038	5.375	0.883	0.991
RSLF_RD	PM ₁₀	1.178	1.446	-1.671	4.027	0.966	0.991
RSLF_RD	NO ₂	-0.275	0.668	-1.591	1.042	0.952	0.991
LCST_FA	PM _{2.5}	1.972	1.861	-1.695	5.638	0.941	0.991
LCST_FA	PM ₁₀	1.436	1.431	-1.382	4.254	0.913	0.991
LCST_FA	NO ₂	0.028	0.661	-1.275	1.331	0.801	0.991
LCST_MD	PM _{2.5}	1.517	1.976	-2.377	5.410	0.303	0.991
LCST_MD	PM ₁₀	1.049	1.519	-1.944	4.041	0.345	0.991
LCST_MD	NO ₂	-0.426	0.701	-1.807	0.956	0.607	0.991
LCST_AD	PM _{2.5}	0.249	0.556	-0.846	1.345	0.230	0.991
LCST_AD	PM ₁₀	0.123	0.427	-0.719	0.966	0.279	0.991
LCST_AD	NO ₂	0.379	0.196	-0.006	0.765	0.628	0.991
LCST_RD	PM _{2.5}	-1.629	2.280	-6.121	2.863	0.355	0.991
LCST_RD	PM ₁₀	-0.695	1.754	-4.150	2.759	0.392	0.991
LCST_RD	NO ₂	-0.727	0.808	-2.318	0.865	0.608	0.991
RCST_FA	PM _{2.5}	-1.689	2.329	-6.277	2.900	0.289	0.991
RCST_FA	PM ₁₀	-0.676	1.791	-4.205	2.853	0.274	0.991
RCST_FA	NO ₂	-0.298	0.827	-1.927	1.330	0.602	0.991
RCST_MD	PM _{2.5}	-1.599	2.326	-6.182	2.984	0.804	0.991
RCST_MD	PM ₁₀	-0.705	1.789	-4.229	2.819	0.972	0.991
RCST_MD	NO ₂	-0.941	0.823	-2.563	0.682	0.891	0.991
RCST_AD	PM _{2.5}	0.665	0.387	-0.098	1.428	0.414	0.991
RCST_AD	PM ₁₀	0.349	0.299	-0.239	0.937	0.566	0.991
RCST_AD	NO ₂	0.127	0.138	-0.145	0.399	0.935	0.991

RCST_RD	PM _{2.5}	1.541	1.508	-1.430	4.512	0.985	0.991
RCST_RD	PM ₁₀	1.590	1.157	-0.689	3.869	0.833	0.991
RCST_RD	NO ₂	0.766	0.534	-0.285	1.817	0.875	0.991
CC_FA	PM _{2.5}	2.492	1.516	-0.494	5.479	0.395	0.991
CC_FA	PM ₁₀	2.211	1.163	-0.079	4.502	0.770	0.991
CC_FA	NO ₂	1.023	0.536	-0.034	2.080	0.774	0.991
CC_MD	PM _{2.5}	1.066	1.547	-1.983	4.114	0.957	0.991
CC_MD	PM ₁₀	1.279	1.187	-1.060	3.618	0.816	0.991
CC_MD	NO ₂	0.638	0.548	-0.441	1.717	0.647	0.991
CC_AD	PM _{2.5}	-0.401	0.406	-1.201	0.400	0.694	0.991
CC_AD	PM ₁₀	-0.436	0.312	-1.049	0.178	0.662	0.991
CC_AD	NO ₂	-0.063	0.144	-0.347	0.222	0.515	0.991
CC_RD	PM _{2.5}	1.979	1.494	-0.965	4.923	0.927	0.991
CC_RD	PM ₁₀	1.979	1.145	-0.278	4.235	0.888	0.991
CC_RD	NO ₂	0.907	0.529	-0.134	1.948	0.713	0.991

Table A9: Single linear regression results between pollution exposure over the first trimester and dMRI measures in all tracts for all subjects in the ePrime cohort, adjusted for sex, IMD, PMA at scan, GA at birth, birth weight z-score (BWZ), and days ventilated. Beta = effect size; CI = Confidence interval (95%); q-value = p-value after FDR correction. WM microstructure metrics are coded as follows: First the hemisphere L = left, and R = right, followed by the tract, and the type of metric, respectively. FA = fractional anisotropy; MD = mean diffusivity; AD = axial diffusivity; RD = radial diffusivity. Tract abbreviations: CC = corpus callosum; CST = corticospinal tract; IFO = inferior fronto-occipital fasciculus; ILF = inferior longitudinal fasciculus; UNC = uncinate fasciculus.

Tract	Pollutant	<i>b</i> (in 10 ⁻³)	Std. error (in 10 ⁻³)	Lower CI (in 10 ⁻³)	Upper CI (in 10 ⁻³)	p-value	q-value
LILF_FA	PM _{2.5}	-0.009	0.426	-0.849	0.831	0.983	0.993
LILF_FA	PM ₁₀	0.013	0.335	-0.649	0.674	0.970	0.993
LILF_FA	NO ₂	0.141	0.176	-0.207	0.489	0.426	0.911
LILF_MD	PM _{2.5}	1.083	1.369	-1.617	3.782	0.430	0.911

LILF_MD	PM ₁₀	0.637	1.079	-1.490	2.765	0.555	0.911
LILF_MD	NO ₂	0.388	0.568	-0.732	1.508	0.495	0.911
LILF_AD	PM _{2.5}	1.554	1.368	-1.145	4.252	0.258	0.911
LILF_AD	PM ₁₀	0.984	1.079	-1.145	3.112	0.363	0.911
LILF_AD	NO ₂	0.737	0.567	-0.381	1.856	0.195	0.911
LILF_RD	PM _{2.5}	0.847	1.432	-1.976	3.670	0.555	0.911
LILF_RD	PM ₁₀	0.464	1.128	-1.761	2.689	0.681	0.948
LILF_RD	NO ₂	0.214	0.594	-0.958	1.386	0.719	0.948
RILF_FA	PM _{2.5}	-0.125	0.413	-0.940	0.689	0.762	0.948
RILF_FA	PM ₁₀	-0.083	0.325	-0.724	0.559	0.800	0.948
RILF_FA	NO ₂	0.181	0.171	-0.156	0.518	0.292	0.911
RILF_MD	PM _{2.5}	-0.102	1.654	-3.364	3.159	0.951	0.993
RILF_MD	PM ₁₀	0.024	1.303	-2.545	2.594	0.985	0.993
RILF_MD	NO ₂	0.196	0.686	-1.157	1.548	0.776	0.948
RILF_AD	PM _{2.5}	-0.295	1.693	-3.634	3.044	0.862	0.989
RILF_AD	PM ₁₀	-0.051	1.334	-2.682	2.579	0.969	0.993
RILF_AD	NO ₂	0.521	0.701	-0.862	1.904	0.458	0.911
RILF_RD	PM _{2.5}	-0.006	1.685	-3.329	3.318	0.997	0.997
RILF_RD	PM ₁₀	0.062	1.327	-2.555	2.680	0.963	0.993
RILF_RD	NO ₂	0.033	0.699	-1.346	1.412	0.962	0.993
LUNC_FA	PM _{2.5}	-0.064	0.285	-0.626	0.498	0.823	0.961
LUNC_FA	PM ₁₀	-0.132	0.224	-0.574	0.310	0.557	0.911
LUNC_FA	NO ₂	0.053	0.118	-0.180	0.287	0.652	0.948
LUNC_MD	PM _{2.5}	1.253	1.110	-0.937	3.442	0.261	0.911
LUNC_MD	PM ₁₀	1.071	0.874	-0.653	2.795	0.222	0.911
LUNC_MD	NO ₂	0.887	0.458	-0.016	1.790	0.054	0.893
LUNC_AD	PM _{2.5}	1.351	1.120	-0.859	3.560	0.229	0.911
LUNC_AD	PM ₁₀	1.081	0.882	-0.659	2.821	0.222	0.911
LUNC_AD	NO ₂	1.051	0.460	0.143	1.959	0.024	0.621

LUNC_RD	PM _{2.5}	1.204	1.136	-1.036	3.444	0.291	0.911
LUNC_RD	PM ₁₀	1.066	0.894	-0.697	2.829	0.235	0.911
LUNC_RD	NO ₂	0.805	0.469	-0.120	1.730	0.088	0.911
RUNC_FA	PM _{2.5}	-0.718	0.289	-1.288	-0.149	0.014	0.621
RUNC_FA	PM ₁₀	-0.593	0.227	-1.041	-0.145	0.010	0.621
RUNC_FA	NO ₂	-0.211	0.121	-0.449	0.027	0.082	0.911
RUNC_MD	PM _{2.5}	1.488	1.089	-0.659	3.635	0.173	0.911
RUNC_MD	PM ₁₀	1.257	0.857	-0.433	2.947	0.144	0.911
RUNC_MD	NO ₂	1.042	0.448	0.159	1.925	0.021	0.621
RUNC_AD	PM _{2.5}	0.805	1.091	-1.347	2.958	0.461	0.911
RUNC_AD	PM ₁₀	0.750	0.859	-0.944	2.445	0.384	0.911
RUNC_AD	NO ₂	0.877	0.449	-0.009	1.762	0.052	0.893
RUNC_RD	PM _{2.5}	1.829	1.126	-0.391	4.049	0.106	0.911
RUNC_RD	PM ₁₀	1.511	0.886	-0.237	3.258	0.090	0.911
RUNC_RD	NO ₂	1.125	0.463	0.211	2.038	0.016	0.621
LIFO_FA	PM _{2.5}	-0.087	0.351	-0.780	0.606	0.804	0.948
LIFO_FA	PM ₁₀	-0.113	0.277	-0.659	0.433	0.684	0.948
LIFO_FA	NO ₂	0.097	0.146	-0.190	0.384	0.507	0.911
LIFO_MD	PM _{2.5}	0.778	1.128	-1.447	3.003	0.491	0.911
LIFO_MD	PM ₁₀	0.612	0.889	-1.141	2.364	0.492	0.911
LIFO_MD	NO ₂	0.658	0.466	-0.262	1.577	0.160	0.911
LIFO_AD	PM _{2.5}	0.813	1.123	-1.402	3.029	0.470	0.911
LIFO_AD	PM ₁₀	0.586	0.885	-1.159	2.332	0.509	0.911
LIFO_AD	NO ₂	0.896	0.462	-0.016	1.807	0.054	0.893
LIFO_RD	PM _{2.5}	0.760	1.175	-1.556	3.077	0.518	0.911
LIFO_RD	PM ₁₀	0.625	0.925	-1.200	2.449	0.500	0.911
LIFO_RD	NO ₂	0.539	0.486	-0.420	1.497	0.269	0.911
RIFO_FA	PM _{2.5}	-0.312	0.313	-0.929	0.304	0.319	0.911
RIFO_FA	PM ₁₀	-0.251	0.246	-0.736	0.235	0.310	0.911

RIFO_FA	NO ₂	0.089	0.130	-0.167	0.345	0.492	0.911
RIFO_MD	PM _{2.5}	0.852	1.117	-1.352	3.055	0.447	0.911
RIFO_MD	PM ₁₀	0.621	0.880	-1.115	2.358	0.481	0.911
RIFO_MD	NO ₂	0.477	0.463	-0.436	1.390	0.304	0.911
RIFO_AD	PM _{2.5}	0.592	1.108	-1.594	2.777	0.594	0.945
RIFO_AD	PM ₁₀	0.443	0.873	-1.278	2.165	0.612	0.948
RIFO_AD	NO ₂	0.687	0.457	-0.215	1.589	0.135	0.911
RIFO_RD	PM _{2.5}	0.982	1.163	-1.312	3.275	0.400	0.911
RIFO_RD	PM ₁₀	0.710	0.916	-1.096	2.517	0.439	0.911
RIFO_RD	NO ₂	0.372	0.483	-0.579	1.324	0.441	0.911
LSLF_FA	PM _{2.5}	-0.076	0.302	-0.671	0.519	0.802	0.948
LSLF_FA	PM ₁₀	-0.091	0.238	-0.559	0.378	0.703	0.948
LSLF_FA	NO ₂	0.003	0.125	-0.244	0.249	0.984	0.993
LSLF_MD	PM _{2.5}	0.849	1.237	-1.589	3.288	0.493	0.911
LSLF_MD	PM ₁₀	0.316	0.975	-1.607	2.238	0.746	0.948
LSLF_MD	NO ₂	0.425	0.513	-0.586	1.436	0.408	0.911
LSLF_AD	PM _{2.5}	0.963	1.213	-1.428	3.355	0.428	0.911
LSLF_AD	PM ₁₀	0.298	0.956	-1.588	2.184	0.756	0.948
LSLF_AD	NO ₂	0.457	0.503	-0.534	1.449	0.364	0.911
LSLF_RD	PM _{2.5}	0.792	1.284	-1.739	3.324	0.538	0.911
LSLF_RD	PM ₁₀	0.325	1.012	-1.671	2.320	0.749	0.948
LSLF_RD	NO ₂	0.409	0.532	-0.641	1.459	0.443	0.911
RSLF_FA	PM _{2.5}	0.018	0.324	-0.621	0.657	0.955	0.993
RSLF_FA	PM ₁₀	0.027	0.255	-0.476	0.530	0.916	0.993
RSLF_FA	NO ₂	0.059	0.134	-0.206	0.324	0.661	0.948
RSLF_MD	PM _{2.5}	0.564	1.320	-2.039	3.166	0.670	0.948
RSLF_MD	PM ₁₀	0.116	1.040	-1.934	2.167	0.911	0.993
RSLF_MD	NO ₂	0.479	0.547	-0.599	1.557	0.382	0.911
RSLF_AD	PM _{2.5}	0.681	1.263	-1.810	3.172	0.591	0.945

RSLF_AD	PM ₁₀	0.200	0.996	-1.764	2.163	0.841	0.974
RSLF_AD	NO ₂	0.661	0.522	-0.370	1.691	0.208	0.911
RSLF_RD	PM _{2.5}	0.505	1.380	-2.217	3.227	0.715	0.948
RSLF_RD	PM ₁₀	0.075	1.088	-2.070	2.219	0.945	0.993
RSLF_RD	NO ₂	0.388	0.572	-0.740	1.516	0.498	0.911
LCST_FA	PM _{2.5}	0.168	0.349	-0.521	0.857	0.632	0.948
LCST_FA	PM ₁₀	0.167	0.275	-0.375	0.710	0.544	0.911
LCST_FA	NO ₂	0.019	0.145	-0.267	0.305	0.896	0.993
LCST_MD	PM _{2.5}	1.013	1.134	-1.224	3.250	0.373	0.911
LCST_MD	PM ₁₀	0.424	0.895	-1.341	2.189	0.636	0.948
LCST_MD	NO ₂	0.626	0.469	-0.300	1.552	0.184	0.911
LCST_AD	PM _{2.5}	1.377	1.048	-0.690	3.443	0.190	0.911
LCST_AD	PM ₁₀	0.710	0.827	-0.922	2.342	0.392	0.911
LCST_AD	NO ₂	0.722	0.434	-0.133	1.577	0.097	0.911
LCST_RD	PM _{2.5}	0.831	1.212	-1.559	3.221	0.494	0.911
LCST_RD	PM ₁₀	0.281	0.955	-1.603	2.166	0.769	0.948
LCST_RD	NO ₂	0.578	0.502	-0.411	1.568	0.250	0.911
RCST_FA	PM _{2.5}	0.395	0.300	-0.196	0.986	0.189	0.911
RCST_FA	PM ₁₀	0.316	0.236	-0.150	0.782	0.182	0.911
RCST_FA	NO ₂	0.169	0.124	-0.076	0.415	0.175	0.911
RCST_MD	PM _{2.5}	0.308	0.928	-1.522	2.137	0.741	0.948
RCST_MD	PM ₁₀	-0.108	0.731	-1.549	1.334	0.883	0.993
RCST_MD	NO ₂	0.293	0.384	-0.466	1.051	0.448	0.911
RCST_AD	PM _{2.5}	1.016	0.876	-0.711	2.742	0.248	0.911
RCST_AD	PM ₁₀	0.405	0.691	-0.959	1.768	0.559	0.911
RCST_AD	NO ₂	0.551	0.362	-0.164	1.265	0.130	0.911
RCST_RD	PM _{2.5}	-0.046	0.984	-1.987	1.894	0.962	0.993
RCST_RD	PM ₁₀	-0.364	0.775	-1.891	1.164	0.639	0.948
RCST_RD	NO ₂	0.163	0.408	-0.641	0.968	0.689	0.948

CC_FA	PM _{2.5}	-0.092	0.331	-0.745	0.561	0.781	0.948
CC_FA	PM ₁₀	-0.195	0.261	-0.709	0.319	0.455	0.911
CC_FA	NO ₂	0.007	0.137	-0.264	0.278	0.959	0.993
CC_MD	PM _{2.5}	0.570	1.187	-1.771	2.910	0.632	0.948
CC_MD	PM ₁₀	0.285	0.935	-1.559	2.129	0.761	0.948
CC_MD	NO ₂	0.583	0.491	-0.385	1.551	0.237	0.911
CC_AD	PM _{2.5}	0.686	1.068	-1.420	2.792	0.521	0.911
CC_AD	PM ₁₀	0.215	0.842	-1.445	1.875	0.799	0.948
CC_AD	NO ₂	0.703	0.441	-0.166	1.572	0.112	0.911
CC_RD	PM _{2.5}	0.511	1.268	-1.990	3.013	0.687	0.948
CC_RD	PM ₁₀	0.320	0.999	-1.651	2.291	0.749	0.948
CC_RD	NO ₂	0.523	0.525	-0.513	1.558	0.321	0.911

Table A10: Single linear regression results between pollution exposure over the second trimester and dMRI measures in all tracts for all subjects in the ePrime cohort, adjusted for sex, IMD, PMA at scan, GA at birth, birth weight z-score (BWZ), and days ventilated. Beta = effect size; CI = Confidence interval (95%); q-value = p-value after FDR correction. WM microstructure metrics are coded as follows: First the hemisphere L = left, and R = right, followed by the tract, and the type of metric, respectively. FA = fractional anisotropy; MD = mean diffusivity; AD = axial diffusivity; RD = radial diffusivity. Tract abbreviations: CC = corpus callosum; CST = corticospinal tract; IFO = inferior fronto-occipital fasciculus; ILF = inferior longitudinal fasciculus; UNC = uncinate fasciculus.

Tract	Pollutant	<i>beta (in 10⁻³)</i>	<i>Std. error (in 10⁻³)</i>	<i>Lower CI (in 10⁻³)</i>	<i>Upper CI (in 10⁻³)</i>	<i>p-value</i>	<i>q-value</i>
LILF_FA	PM _{2.5}	-0.094	0.384	-0.852	0.663	0.806	0.972
LILF_FA	PM ₁₀	-0.049	0.309	-0.657	0.56	0.875	0.972
LILF_FA	NO ₂	0.108	0.18	-0.246	0.462	0.549	0.969
LILF_MD	PM _{2.5}	1.271	1.234	-1.163	3.704	0.304	0.969
LILF_MD	PM ₁₀	0.791	0.992	-1.166	2.748	0.426	0.969
LILF_MD	NO ₂	0.136	0.579	-1.005	1.277	0.815	0.972
LILF_AD	PM _{2.5}	1.442	1.235	-0.993	3.877	0.244	0.969
LILF_AD	PM ₁₀	0.92	0.993	-1.039	2.879	0.356	0.969

LILF_AD	NO ₂	0.29	0.579	-0.852	1.432	0.617	0.969
LILF_RD	PM _{2.5}	1.185	1.291	-1.36	3.73	0.36	0.969
LILF_RD	PM ₁₀	0.727	1.038	-1.319	2.774	0.484	0.969
LILF_RD	NO ₂	0.059	0.605	-1.134	1.251	0.923	0.972
RILF_FA	PM _{2.5}	-0.066	0.373	-0.801	0.669	0.859	0.972
RILF_FA	PM ₁₀	-0.01	0.299	-0.6	0.581	0.975	0.975
RILF_FA	NO ₂	0.16	0.174	-0.183	0.503	0.359	0.969
RILF_MD	PM _{2.5}	0.954	1.491	-1.987	3.895	0.523	0.969
RILF_MD	PM ₁₀	0.527	1.199	-1.837	2.891	0.661	0.969
RILF_MD	NO ₂	0.066	0.698	-1.311	1.443	0.925	0.972
RILF_AD	PM _{2.5}	0.911	1.527	-2.1	3.922	0.551	0.969
RILF_AD	PM ₁₀	0.539	1.227	-1.881	2.959	0.661	0.969
RILF_AD	NO ₂	0.267	0.714	-1.142	1.676	0.709	0.969
RILF_RD	PM _{2.5}	0.976	1.519	-2.021	3.972	0.521	0.969
RILF_RD	PM ₁₀	0.521	1.221	-1.888	2.929	0.67	0.969
RILF_RD	NO ₂	-0.034	0.711	-1.437	1.368	0.962	0.972
LUNC_FA	PM _{2.5}	0.303	0.256	-0.202	0.809	0.238	0.969
LUNC_FA	PM ₁₀	0.201	0.206	-0.205	0.608	0.33	0.969
LUNC_FA	NO ₂	0.146	0.12	-0.09	0.383	0.224	0.969
LUNC_MD	PM _{2.5}	1.46	1	-0.512	3.433	0.146	0.969
LUNC_MD	PM ₁₀	1.096	0.804	-0.489	2.682	0.174	0.969
LUNC_MD	NO ₂	0.9	0.466	-0.018	1.819	0.055	0.969
LUNC_AD	PM _{2.5}	1.939	1.005	-0.044	3.921	0.055	0.969
LUNC_AD	PM ₁₀	1.427	0.809	-0.168	3.022	0.079	0.969
LUNC_AD	NO ₂	1.203	0.467	0.283	2.123	0.011	0.969
LUNC_RD	PM _{2.5}	1.221	1.025	-0.799	3.242	0.235	0.969
LUNC_RD	PM ₁₀	0.931	0.823	-0.693	2.555	0.26	0.969
LUNC_RD	NO ₂	0.749	0.478	-0.194	1.691	0.119	0.969
RUNC_FA	PM _{2.5}	-0.178	0.265	-0.7	0.343	0.501	0.969
RUNC_FA	PM ₁₀	-0.183	0.212	-0.602	0.235	0.389	0.969
RUNC_FA	NO ₂	0.08	0.124	-0.164	0.324	0.517	0.969
RUNC_MD	PM _{2.5}	1.475	0.982	-0.461	3.411	0.135	0.969
RUNC_MD	PM ₁₀	1.255	0.788	-0.299	2.809	0.113	0.969

RUNC_MD	NO ₂	0.769	0.458	-0.135	1.673	0.095	0.969
RUNC_AD	PM _{2.5}	1.287	0.982	-0.65	3.223	0.192	0.969
RUNC_AD	PM ₁₀	1.088	0.789	-0.467	2.643	0.169	0.969
RUNC_AD	NO ₂	0.926	0.457	0.025	1.826	0.044	0.969
RUNC_RD	PM _{2.5}	1.569	1.017	-0.436	3.574	0.124	0.969
RUNC_RD	PM ₁₀	1.338	0.816	-0.271	2.947	0.103	0.969
RUNC_RD	NO ₂	0.69	0.476	-0.248	1.629	0.148	0.969
LIFO_FA	PM _{2.5}	0.165	0.317	-0.46	0.79	0.604	0.969
LIFO_FA	PM ₁₀	0.107	0.255	-0.395	0.61	0.674	0.969
LIFO_FA	NO ₂	0.167	0.148	-0.124	0.459	0.259	0.969
LIFO_MD	PM _{2.5}	0.516	1.019	-1.494	2.525	0.613	0.969
LIFO_MD	PM ₁₀	0.291	0.819	-1.324	1.905	0.723	0.969
LIFO_MD	NO ₂	0.442	0.476	-0.496	1.38	0.354	0.969
LIFO_AD	PM _{2.5}	0.673	1.014	-1.328	2.673	0.508	0.969
LIFO_AD	PM ₁₀	0.368	0.815	-1.24	1.975	0.653	0.969
LIFO_AD	NO ₂	0.728	0.472	-0.203	1.658	0.125	0.969
LIFO_RD	PM _{2.5}	0.437	1.061	-1.655	2.529	0.681	0.969
LIFO_RD	PM ₁₀	0.253	0.852	-1.428	1.934	0.767	0.972
LIFO_RD	NO ₂	0.299	0.496	-0.679	1.277	0.547	0.969
RIFO_FA	PM _{2.5}	0.236	0.282	-0.321	0.792	0.405	0.969
RIFO_FA	PM ₁₀	0.191	0.227	-0.256	0.638	0.401	0.969
RIFO_FA	NO ₂	0.254	0.131	-0.004	0.513	0.054	0.969
RIFO_MD	PM _{2.5}	0.044	1.01	-1.948	2.036	0.965	0.972
RIFO_MD	PM ₁₀	-0.098	0.811	-1.698	1.503	0.905	0.972
RIFO_MD	NO ₂	-0.041	0.472	-0.972	0.891	0.932	0.972
RIFO_AD	PM _{2.5}	0.323	1.001	-1.65	2.297	0.747	0.969
RIFO_AD	PM ₁₀	0.118	0.804	-1.467	1.704	0.883	0.972
RIFO_AD	NO ₂	0.279	0.468	-0.644	1.201	0.552	0.969
RIFO_RD	PM _{2.5}	-0.095	1.051	-2.169	1.978	0.928	0.972
RIFO_RD	PM ₁₀	-0.205	0.845	-1.871	1.46	0.808	0.972
RIFO_RD	NO ₂	-0.2	0.491	-1.17	0.769	0.684	0.969
LSLF_FA	PM _{2.5}	0.118	0.272	-0.419	0.654	0.666	0.969
LSLF_FA	PM ₁₀	0.086	0.219	-0.346	0.517	0.696	0.969

LSLF_FA	NO ₂	0.101	0.127	-0.15	0.352	0.427	0.969
LSLF_MD	PM _{2.5}	0.963	1.115	-1.237	3.162	0.389	0.969
LSLF_MD	PM ₁₀	0.624	0.897	-1.144	2.392	0.487	0.969
LSLF_MD	NO ₂	0.275	0.522	-0.755	1.305	0.599	0.969
LSLF_AD	PM _{2.5}	1.263	1.093	-0.892	3.417	0.249	0.969
LSLF_AD	PM ₁₀	0.833	0.879	-0.9	2.565	0.344	0.969
LSLF_AD	NO ₂	0.41	0.512	-0.6	1.419	0.424	0.969
LSLF_RD	PM _{2.5}	0.813	1.159	-1.472	3.097	0.484	0.969
LSLF_RD	PM ₁₀	0.52	0.931	-1.316	2.356	0.577	0.969
LSLF_RD	NO ₂	0.207	0.542	-0.862	1.277	0.702	0.969
RSLF_FA	PM _{2.5}	0.041	0.292	-0.536	0.617	0.89	0.972
RSLF_FA	PM ₁₀	0.046	0.235	-0.417	0.509	0.845	0.972
RSLF_FA	NO ₂	0.083	0.137	-0.187	0.352	0.545	0.969
RSLF_MD	PM _{2.5}	0.448	1.191	-1.901	2.797	0.707	0.969
RSLF_MD	PM ₁₀	0.061	0.957	-1.827	1.949	0.949	0.972
RSLF_MD	NO ₂	0.177	0.557	-0.922	1.275	0.751	0.969
RSLF_AD	PM _{2.5}	0.5	1.14	-1.749	2.749	0.662	0.969
RSLF_AD	PM ₁₀	0.062	0.917	-1.746	1.869	0.947	0.972
RSLF_AD	NO ₂	0.333	0.533	-0.718	1.385	0.532	0.969
RSLF_RD	PM _{2.5}	0.422	1.246	-2.035	2.879	0.735	0.969
RSLF_RD	PM ₁₀	0.061	1.001	-1.914	2.035	0.952	0.972
RSLF_RD	NO ₂	0.098	0.583	-1.051	1.248	0.866	0.972
LCST_FA	PM _{2.5}	-0.062	0.316	-0.684	0.561	0.846	0.972
LCST_FA	PM ₁₀	0.017	0.254	-0.483	0.517	0.946	0.972
LCST_FA	NO ₂	-0.023	0.148	-0.314	0.268	0.875	0.972
LCST_MD	PM _{2.5}	0.978	1.024	-1.041	2.996	0.341	0.969
LCST_MD	PM ₁₀	0.552	0.823	-1.072	2.175	0.504	0.969
LCST_MD	NO ₂	0.301	0.479	-0.645	1.246	0.531	0.969
LCST_AD	PM _{2.5}	0.921	0.948	-0.948	2.79	0.332	0.969
LCST_AD	PM ₁₀	0.558	0.762	-0.945	2.06	0.465	0.969
LCST_AD	NO ₂	0.29	0.444	-0.585	1.165	0.514	0.969
LCST_RD	PM _{2.5}	1.006	1.093	-1.149	3.161	0.358	0.969
LCST_RD	PM ₁₀	0.549	0.879	-1.184	2.282	0.533	0.969

LCST_RD	NO ₂	0.306	0.512	-0.703	1.315	0.551	0.969
RCST_FA	PM _{2.5}	0.094	0.272	-0.442	0.63	0.729	0.969
RCST_FA	PM ₁₀	0.143	0.218	-0.287	0.573	0.513	0.969
RCST_FA	NO ₂	0.024	0.127	-0.227	0.274	0.852	0.972
RCST_MD	PM _{2.5}	0.626	0.836	-1.023	2.275	0.455	0.969
RCST_MD	PM ₁₀	0.218	0.673	-1.109	1.544	0.747	0.969
RCST_MD	NO ₂	0.09	0.392	-0.682	0.862	0.819	0.972
RCST_AD	PM _{2.5}	0.766	0.791	-0.794	2.326	0.334	0.969
RCST_AD	PM ₁₀	0.375	0.637	-0.881	1.63	0.557	0.969
RCST_AD	NO ₂	0.055	0.371	-0.677	0.786	0.883	0.972
RCST_RD	PM _{2.5}	0.556	0.887	-1.194	2.305	0.532	0.969
RCST_RD	PM ₁₀	0.139	0.713	-1.268	1.546	0.846	0.972
RCST_RD	NO ₂	0.108	0.415	-0.711	0.926	0.796	0.972
CC_FA	PM _{2.5}	0.178	0.299	-0.411	0.767	0.552	0.969
CC_FA	PM ₁₀	0.138	0.24	-0.335	0.612	0.565	0.969
CC_FA	NO ₂	0.1	0.14	-0.176	0.375	0.477	0.969
CC_MD	PM _{2.5}	0.714	1.07	-1.397	2.825	0.505	0.969
CC_MD	PM ₁₀	0.374	0.861	-1.323	2.071	0.665	0.969
CC_MD	NO ₂	0.285	0.501	-0.702	1.273	0.57	0.969
CC_AD	PM _{2.5}	0.957	0.963	-0.941	2.855	0.321	0.969
CC_AD	PM ₁₀	0.549	0.774	-0.978	2.076	0.479	0.969
CC_AD	NO ₂	0.412	0.45	-0.476	1.3	0.361	0.969
CC_RD	PM _{2.5}	0.593	1.145	-1.664	2.85	0.605	0.969
CC_RD	PM ₁₀	0.286	0.92	-1.528	2.1	0.756	0.969
CC_RD	NO ₂	0.222	0.535	-0.834	1.278	0.679	0.969

Table A11: Single linear regression results between pollution exposure over the first trimester and dMRI measures in all tracts for all subjects in the ePrime cohort, adjusted for sex, IMD, PMA at scan, GA at birth, birth weight z-score (BWZ), and days ventilated. Beta = effect size; CI = Confidence interval (95%); q-value = p-value after FDR correction.

Brain Region	Pollutant					p-value	q-value
--------------	-----------	--	--	--	--	---------	---------

		<i>beta</i> (in 10 ⁻³)	Std. error (in 10 ⁻³)	Lower CI (in 10 ⁻³)	Upper CI (in 10 ⁻³)		
Relative White Matter	PM _{2.5}	0.662	0.43	-0.185	1.509	0.125	0.877
	PM ₁₀	0.398	0.339	-0.27	1.066	0.242	0.877
	NO ₂	0.257	0.193	-0.124	0.638	0.185	0.877
Relative Grey Matter	PM _{2.5}	-0.504	0.427	-1.345	0.337	0.238	0.877
	PM ₁₀	-0.348	0.336	-1.01	0.314	0.301	0.877
	NO ₂	-0.27	0.191	-0.647	0.107	0.16	0.877
Relative Amygdala	PM _{2.5}	-0.001	0.003	-0.008	0.006	0.81	0.984
	PM ₁₀	0.001	0.003	-0.005	0.006	0.826	0.984
	NO ₂	-0.002	0.002	-0.005	0.001	0.19	0.877
Relative Hippocampus	PM _{2.5}	0.006	0.007	-0.007	0.019	0.379	0.878
	PM ₁₀	0.007	0.005	-0.003	0.018	0.183	0.877
	NO ₂	0.002	0.003	-0.004	0.008	0.589	0.919
Relative Cerebellum	PM _{2.5}	-0.128	0.119	-0.363	0.107	0.284	0.877
	PM ₁₀	-0.057	0.094	-0.243	0.128	0.545	0.919
	NO ₂	-0.009	0.054	-0.115	0.097	0.863	0.984
Relative Deep Grey Nuclei	PM _{2.5}	-0.03	0.072	-0.172	0.113	0.684	0.972
	PM ₁₀	0.007	0.057	-0.105	0.12	0.897	0.984
	NO ₂	0.022	0.033	-0.042	0.086	0.496	0.919
Relative Ventricles	PM _{2.5}	-0.008	0.146	-0.296	0.28	0.956	0.984
	PM ₁₀	0.004	0.115	-0.222	0.231	0.97	0.984
	NO ₂	0.001	0.066	-0.128	0.131	0.984	0.984
Relative Brainstem	PM _{2.5}	-0.016	0.019	-0.052	0.021	0.39	0.878
	PM ₁₀	-0.004	0.015	-0.032	0.025	0.799	0.984
	NO ₂	-0.004	0.008	-0.021	0.012	0.613	0.919
Relative Thalamus	PM _{2.5}	0.016	0.03	-0.044	0.076	0.598	0.919
	PM ₁₀	0.018	0.024	-0.029	0.065	0.445	0.919
	NO ₂	0.013	0.014	-0.013	0.04	0.325	0.877

Table A12: Single linear regression results between pollution exposure over the second trimester and dMRI measures in all tracts for all subjects in the ePrime cohort, adjusted for sex, IMD, PMA at scan, GA at birth, birth weight z-score (BWZ), and days ventilated. Beta = effect size; CI = Confidence interval (95%); q-value = p-value after FDR correction.

Brain Region	Pollutant	<i>beta</i> (in 10^{-3})	Std. error (in 10^{-3})	Lower CI (in 10^{-3})	Upper CI (in 10^{-3})	p-value	q-value
Relative White Matter	PM _{2.5}	0.31	0.427	-0.532	1.152	0.469	0.969
	PM ₁₀	0.17	0.346	-0.511	0.852	0.623	0.969
	NO ₂	0.032	0.199	-0.36	0.424	0.872	0.969
Relative Grey Matter	PM _{2.5}	-0.314	0.423	-1.148	0.52	0.459	0.969
	PM ₁₀	-0.154	0.343	-0.829	0.521	0.653	0.969
	NO ₂	-0.067	0.197	-0.455	0.321	0.735	0.969
Relative Amygdala	PM _{2.5}	-0.003	0.003	-0.01	0.004	0.391	0.969
	PM ₁₀	-0.004	0.003	-0.009	0.002	0.207	0.969
	NO ₂	-0.001	0.002	-0.004	0.002	0.408	0.969
Relative Hippocampus	PM _{2.5}	0.003	0.007	-0.01	0.016	0.682	0.969
	PM ₁₀	0.002	0.005	-0.009	0.013	0.735	0.969
	NO ₂	0.002	0.003	-0.004	0.008	0.463	0.969
Relative Cerebellum	PM _{2.5}	-0.007	0.118	-0.24	0.226	0.952	0.989
	PM ₁₀	-0.029	0.096	-0.218	0.16	0.764	0.969
	NO ₂	0.016	0.055	-0.092	0.125	0.768	0.969
Relative Deep Grey Nuclei	PM _{2.5}	0.011	0.072	-0.131	0.152	0.882	0.969
	PM ₁₀	0.013	0.058	-0.101	0.127	0.824	0.969
	NO ₂	0.019	0.033	-0.047	0.084	0.579	0.969
Relative Ventricles	PM _{2.5}	0.232	0.144	-0.051	0.516	0.108	0.969
	PM ₁₀	0.213	0.116	-0.016	0.442	0.068	0.969
	NO ₂	0.033	0.067	-0.099	0.166	0.62	0.969
Relative Brainstem	PM _{2.5}	-0.014	0.018	-0.05	0.022	0.443	0.969
	PM ₁₀	-0.013	0.015	-0.042	0.016	0.389	0.969
	NO ₂	-0.003	0.009	-0.02	0.014	0.736	0.969
Relative Thalamus	PM _{2.5}	0	0.03	-0.059	0.059	0.994	0.994

	PM ₁₀	0.006	0.024	-0.042	0.053	0.821	0.969
	NO ₂	0.002	0.014	-0.026	0.029	0.897	0.969